

What are the 100 most cited fungal genera?

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Abstract: The global diversity of fungi has been estimated between 2 to 11 million species, of which only about 155 000 have been named. Most fungi are invisible to the unaided eye, but they represent a major component of biodiversity on our planet, and play essential ecological roles, supporting life as we know it. Although approximately 20 000 fungal genera are presently recognised, the ecology of most remains undetermined. Despite all this diversity, the mycological community actively researches some fungal genera more commonly than others. This poses an interesting question: why have some fungal genera impacted mycology and related fields more than others? To address this issue, we conducted a bibliometric analysis to identify the top 100 most cited fungal genera. A thorough database search of the Web of Science, Google Scholar, and PubMed was performed to establish which genera are most cited. The most cited 10 genera are *Saccharomyces*, *Candida*, *Aspergillus*, *Fusarium*, *Penicillium*, *Trichoderma*, *Botrytis*, *Pichia*, *Cryptococcus* and *Alternaria*. Case studies are presented for the 100 most cited genera with general background, notes on their ecology and economic significance and important research advances. This paper provides a historic overview of scientific research of these genera and the prospect for further research.

Key words: Bibliometric analysis, fungi, highly-cited, Web of Science.

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INTRODUCTION

Fungi are a diverse group of eukaryotic organisms that play important roles in numerous biological processes (Pawlowski *et al.* 2012, Antonelli *et al.* 2020). Fungi can be found in a wide range of habitats (Hyde *et al.* 2020c, Apurillo *et al.* 2023, Asghari *et al.* 2023, Gunarathne *et al.* 2024, Thakshila *et al.* 2024), but their actual number is poorly understood. There are estimated to exist between 2 to 11 million species (Tedersoo *et al.* 2010b, Hawksworth & Lücking 2017, Baldrian *et al.* 2021, Lücking *et al.* 2021), but only about 155 000 species have been formally described (Bánki *et al.* 2023). There are approximately 20 000 fungal genera that have been described since the 1690s (Phukhamsakda *et al.* 2022) and about 2 000 new species have been described each year in the past two decades (Cheek *et al.* 2020, Bhunjun *et al.* 2022). Over the years several genera have emerged as being more commonly researched than others, with numerous studies on their biology, ecology, and pathogenicity. This raises the question why some genera have impacted mycology and related fields more than others. Are these genera important pathogens with a large number of studies aiming to better understand the underlying mechanisms of pathogenicity? Are these genera used in the production of various foods and beverages and a better understanding of their physiology and ecology can be vital in the development of new products? Or are these genera more commonly studied as they are a rich source of bioactive compounds with numerous biotechnological applications? Or are they simply occurring on many substrates across the globe? Therefore, there is a need to determine the most researched genera as well as provide insights into various aspects of their biology, ecology, and pathogenicity with prospects for future research.

In this study, the Web of Science database was used to establish which genera are most cited as of December 2021 (Table 1). The 100 most cited genera are presented as case studies with general background, notes on their ecology and economic significance and important research advances. This study provides a valuable resource by highlighting the importance and research trends associated with these genera.

METHODS

The list of fungal genera was selected from Wijayawardene *et al.* (2022) and the 100 most cited genera were determined by searching the Web of Science Core Collection database (<http://apps.webofknowledge.com/>). The taxon name was used as a query under “Topic” on Web of Science and the genera were ranked according to the summary of citation numbers obtained from the citation report of Web of Science. There were no restrictions on publication type or language, but the period of 2011 to 2021 was selected. All the searches were performed in December 2021.

The number of publications and summary of times cited of each genus were retrieved from the citation report. When compiling the list of the top 10 cited articles, publications that only refer to the coincidental use of the name of the genus or species epithet were excluded as well as publications that refer to fungi now placed in other genera. The publication titles, number of publications and number of citations were retrieved and analysed by Excel (2016) and VOSviewer v. 1.6.15 software. The VOSviewer software was also used to retrieve high-frequency words or terms to map the network of keywords for the 25 most cited genera.

CASE STUDIES

In this section, we provide a review of the 100 most cited genera with a general background, ecology, economic significance and important research advances. The genera are listed according to the number of citations, starting from the highest cited genus.

1. *Saccharomyces* Meyen, Arch. Naturgesch. 4 (2): 100. 1838.

Type species: *Saccharomyces cerevisiae* Meyen

Classification: Ascomycota, Saccharomycotina, Saccharomycetes, Saccharomycetales, Saccharomycetaceae.

Background

Saccharomyces was introduced in 1838 by F.J.F. Meyen for T. Schwann's “Zuckerpilz”, which was a sugar fungus responsible for fermentation as demonstrated by the fermentation experiments Schwann performed in 1837 (Barnett 1998). Three species, *S. cerevisiae*, *S. pomorum* and *S. vini* were initially proposed by Meyen, with the specific epithets indicating their sources of beer, fermenting apple juice and wine, respectively (Barnett 2004). Reess (1870) described the morphology of *S. cerevisiae* with accurate drawings of the cells, asci and ascospores. Hansen (1883) described the formation and germination of ascospores of *S. cerevisiae* based on the study of pure cultures that he developed in the early 1880s (Barnett 2004).

At present, eight natural species, *S. arboricola*, *S. cerevisiae*, *S. eubayanus*, *S. jurei*, *S. kudriavzevii*, *S. mikatae*, *S. paradoxus*, and *S. uvarum*; and two natural hybrids, *S. pastorianus* (syn. *S. carlsbergensis*) and *S. bayanus*, are included in the genus *Saccharomyces* (Alsammar & Delneri 2020) (Fig. 1). *Saccharomyces pastorianus* is an allopolyploid hybrid formed by *S. cerevisiae* and *S. eubayanus*, while *S. bayanus* is a triple-hybrid with a genome composed of mainly *S. uvarum* and *S. eubayanus* sequences with introgressions from *S. cerevisiae* (Libkind *et al.* 2011). The hybrid species are sexually infertile and their ascospores are mostly inviable, while the natural species

Table 1. Top 100 cited genera starting with the most cited genus and the number of citations from the Web of Science (WoS) from the period of 2011 to 2021.

Rank	Genera	WoS Citation	Rank	Genera	WoS Citation
1	<i>Saccharomyces</i>	>1 000 000	51	<i>Microsporum</i>	11 474
2	<i>Candida</i>	>500 000	52	<i>Curvularia</i>	11 008
3	<i>Aspergillus</i>	>400 000	53	<i>Rhizomucor</i>	10 915
4	<i>Fusarium</i>	363 128	54	<i>Pyricularia</i>	10 856
5	<i>Penicillium</i>	130 850	55	<i>Parastagonospora</i>	10 146
6	<i>Trichoderma</i>	117 855	56	<i>Monascus</i>	10 083
7	<i>Botrytis</i>	103 497	57	<i>Hanseniaspora</i>	9 891
8	<i>Pichia</i>	102 697	58	<i>Paracoccidioides</i>	9 763
9	<i>Cryptococcus</i>	95 586	59	<i>Schizophyllum</i>	9 725
10	<i>Alternaria</i>	73 134	60	<i>Plasmopara</i>	9 535
11	<i>Phytophthora</i>	69 739	61	<i>Auricularia</i>	9 237
12	<i>Rhizopus</i>	51 691	62	<i>Russula</i>	9 156
13	<i>Phanerochaete</i>	50 545	63	<i>Zygosaccharomyces</i>	9 140
14	<i>Colletotrichum</i>	46 970	64	<i>Torulaspora</i>	9 132
15	<i>Trametes</i>	46 427	65	<i>Boletus</i>	9 078
16	<i>Rhizoctonia</i>	46 317	66	<i>Botryosphaeria</i>	9 058
17	<i>Pleurotus</i>	45 475	67	<i>Cunninghamella</i>	8 997
18	<i>Ganoderma</i>	44 643	68	<i>Diaporthe</i>	8 987
19	<i>Neurospora</i>	44 091	69	<i>Bipolaris</i>	8 933
20	<i>Cladosporium</i>	38 580	70	<i>Lentinula</i>	8 733
21	<i>Yarrowia</i>	37 460	71	<i>Erysiphe</i>	8 683
22	<i>Agaricus</i>	34 079	72	<i>Scedosporium</i>	8 662
23	<i>Kluyveromyces</i>	33 194	73	<i>Zymoseptoria</i>	8 661
24	<i>Mucor</i>	30 923	74	<i>Phellinus</i>	8 392
25	<i>Verticillium</i>	30 674	75	<i>Sporothrix</i>	8 267
26	<i>Sclerotinia</i>	27 698	76	<i>Macrophomina</i>	8 240
27	<i>Rhodotorula</i>	26 581	77	<i>Flammulina</i>	8 218
28	<i>Beauveria</i>	26 077	78	<i>Pseudogymnoascus</i>	7 988
29	<i>Puccinia</i>	25 970	79	<i>Podospora</i>	7 890
30	<i>Cordyceps</i>	23 831	80	<i>Amanita</i>	7 672
31	<i>Trichophyton</i>	21 756	81	<i>Cercospora</i>	7 493
32	<i>Metarhizium</i>	21 615	82	<i>Lactarius</i>	7 481
33	<i>Pythium</i>	20 902	83	<i>Lasiodiplodia</i>	7 394
34	<i>Funnelliformis</i>	20 832	84	<i>Exophiala</i>	7 344
35	<i>Ustilago</i>	20 809	85	<i>Monilinia</i>	7 268
36	<i>Rhizoglyphus</i>	17 651	86	<i>Coccidioides</i>	6 936
37	<i>Acremonium</i>	17 481	87	<i>Melampsora</i>	6 915
38	<i>Chaetomium</i>	16 519	88	<i>Antrodia</i>	6 910
39	<i>Paecilomyces</i>	16 324	89	<i>Brettanomyces</i>	6 693
40	<i>Trichosporon</i>	15 922	90	<i>Ascochyta</i>	6 690
41	<i>Malassezia</i>	15 632	91	<i>Epichloe</i>	6 496
42	<i>Phoma</i>	15 402	92	<i>Pyrenophora</i>	6 439
43	<i>Thermomyces</i>	15 013	93	<i>Hymenoscyphus</i>	6 420
44	<i>Lentinus</i>	13 964	94	<i>Diplodia</i>	6 337
45	<i>Mortierella</i>	12 787	95	<i>Inonotus</i>	6 331
46	<i>Debaryomyces</i>	12 476	96	<i>Ophiostoma</i>	5 912
47	<i>Metschnikowia</i>	11 995	97	<i>Neofusicoccum</i>	5 591
48	<i>Talaromyces</i>	11 976	98	<i>Hericium</i>	5 458
49	<i>Geotrichum</i>	11 900	99	<i>Phakopsora</i>	5 143
50	<i>Pestalotiopsis</i>	11 758	100	<i>Leptosphaeria</i>	5 133

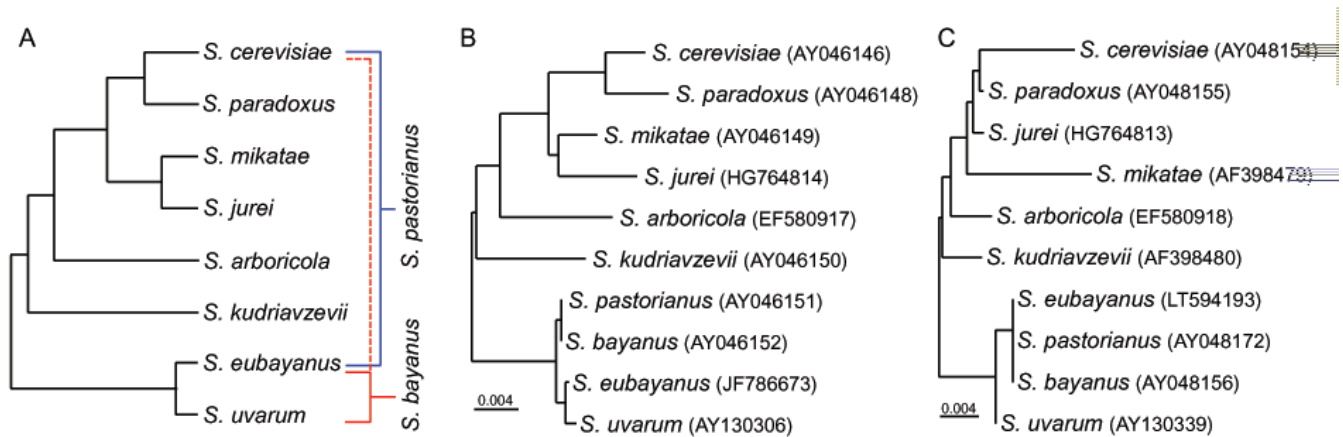


Fig. 1. Phylogenetic relationships of the currently recognised *Saccharomyces* species inferred from the **A.** maximum likelihood of whole genome, **B.** neighbour joining tree of internal transcribed spacer (ITS) region of the rRNA gene, and **C.** neighbour joining tree of D1/D2 domain of the large subunit (LSU) of the rRNA gene sequences. The parents of the two hybrid species are marked in A. and the parent that donates only minor genome sequences is marked by a dashed line. GenBank accession numbers for the ITS and D1/D2 sequences of type strains are shown in parentheses.

can mate with each other (Naumov 1996). Thus, the species exhibit post-zygotic isolation and the biological species concept combined with consideration of genome sequence divergence is used to define species in the genus (Liti *et al.* 2006). The species are morphologically and physiologically similar (Vaughan-Martini & Martini 2011), but the eight natural species can be identified using ITS and D1/D2 sequence analyses (Fig. 1B, C). The two hybrid species, which usually occur in fermentation associated environments, can be differentiated further using specific markers targeting the genome sequences of the parental species of the hybrids (Bing & Bai 2018).

Ecologically, *Saccharomyces* species occur broadly in nature associated with bark, rotten wood of broad-leaved trees, especially *Fagales*, and nearby soil (Sampaio & Gonçalves 2008, Wang *et al.* 2012d, Hittinger 2013, Alsammar & Delneri 2020, Bai *et al.* 2022). In contrast to the expectation that these yeasts may distribute commonly in sugar-rich environments, as implied by the etymology of the genus name (sugar fungus), they have rarely been isolated from fruit and orchards, except for *S. cerevisiae*. Though *S. cerevisiae* exists on fruit, the success rate of *S. cerevisiae* isolation from fruit is generally lower than that from broad-leaved tree bark (Wang *et al.* 2012d, Bai *et al.* 2022). Geographically, some *Saccharomyces* species are cosmopolitan while others occur in only limited regions (Table 2). *Saccharomyces cerevisiae* and *S. paradoxus* usually coexist in nature globally, but the former distributes ubiquitously from tropical

to temperate climate zones, while the latter has rarely been found in tropical areas (He *et al.* 2022b). *Saccharomyces eubayanus*, *S. uvarum* and *S. kudriavzevii* are usually cryophilic or cryotolerant species since they are more easily isolated at low temperatures (Sampaio & Gonçalves 2008) or occur more commonly at high altitudes. The hybrid species *S. pastorianus* and *S. bayanus* are also considered cryophilic because they are usually associated with low-temperature fermentation processes.

Saccharomyces species usually grow as diploids in nature. Their life cycles are illustrated using *S. cerevisiae* as an example (Fig. 2), which has been well documented in the laboratory (Herskowitz 1988). The diploid cells usually reproduce asexually by budding and undergo meiosis and sporulation in response to nutrition depletion, especially nitrogen starvation. Four haploid spores are usually formed in an ascus with two of the spores having mating type a (*MATa*) and the other two *MATα*. Intratetrad mating can occur between a pair of spores with opposite mating types within the ascus upon germination and form a diploid cell. Ascospores can also germinate and reproduce asexually by budding to form *MATa* and *MATα* haploid cell lines. A haploid cell can mate with another haploid with an opposite mating type either from an ascospore of the same strain (selfing) or from an ascospore of a different strain (outcrossing). Haploid cells can also restore the diploid state through a haplo-selfing or autodiploidisation process regulated by a mating-type switch mechanism (Lee & Haber 2015).

Table 2. Ecological and geographical distributions of the wild *Saccharomyces* species.

Species	Observed habitats in nature	Geographical distribution
<i>S. arboricola</i>	Bark and exudates of <i>Quercus</i> , <i>Cyclobalanopsis</i> , <i>Juglans</i> , and <i>Castanea</i> ; soil; insects; mushrooms; fruit	Asia (China), Oceania (New Zealand)
<i>S. cerevisiae</i>	Bark, rotten wood, and nearby soil of broad-leaved trees, fruit	Cosmopolitan in tropical to temperate climate zones
<i>S. eubayanus</i>	Bark, leaves, exudates and seeds of <i>Quercus</i> , <i>Nothofagus</i> , <i>Araucaria</i> ; rotten wood; sporocarps of <i>Cyttaria</i> ; soil	Asia (China), North America, South America (Argentina, Chile), Oceania (New Zealand)
<i>S. jurei</i>	Bark of <i>Quercus</i>	Europe
<i>S. kudriavzevii</i>	Bark of <i>Quercus</i> , <i>Cyclobalanopsis</i> , and <i>Castanea</i> ; soil; decayed leaves	Asia, Europe
<i>S. mikatae</i>	Bark of <i>Quercus</i> , <i>Ulmus</i> , <i>Juglans</i> , <i>Diospyros</i> , <i>Betula</i> ; soil; fruit	Asia
<i>S. paradoxus</i>	Bark, rotten wood, and nearby soil of broad-leaved trees, mostly <i>Fagales</i>	Cosmopolitan in subtropical (rare) to temperate climate zones
<i>S. uvarum</i>	Bark or seed of <i>Nothofagus</i> , <i>Quercus</i> , <i>Fagus</i> , <i>Araucaria</i> ; sporocarps of <i>Cyttaria</i> ; soil; wine; beer; fruit; juice	Asia, Europe, North America, South America, Oceania

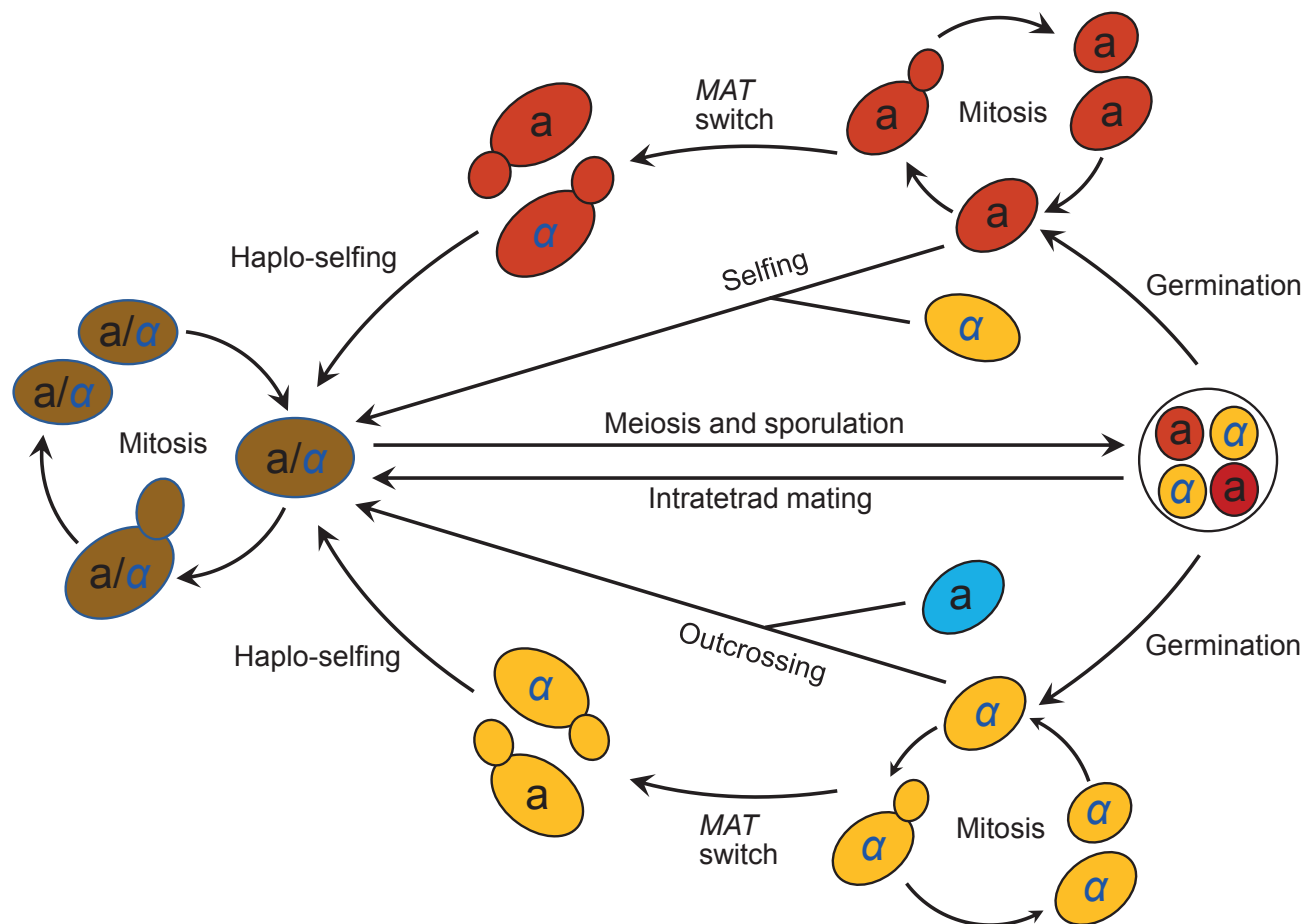


Fig. 2. Life cycle of *S. cerevisiae*. *Saccharomyces cerevisiae* usually grows in nature as a diploid microbe. Diploid cells (a/a) either reproduce asexually by budding (mitosis) or undergo meiosis and sporulation in response to nutrition depletion, resulting in the formation of tetrads with four ascospores each. Ascospores either undergo intratetrad mating to form a diploid cell or germinate to form haploid cells (a or α). A haploid cell either reproduces by budding (selfing) or mates with a sibling (selfing) or non-sibling (outcrossing) haploid with an opposite mating type to form a diploid cell or undergoes haplo-selfing or autodiploidization through a process known as mating-type (*MAT*) switch to restore the diploid phase.

Economic and scientific significance

A unique trait of *Saccharomyces* species is that they preferentially metabolise sugars through an anaerobic fermentation pathway to produce ethanol and CO_2 , even in the presence of oxygen for aerobic respiration. This aerobic fermentative trait is known as the Crabtree effect (Dedeken 1966), which shares several features with the Warburg effect (enhanced glycolytic activity and reduced oxidative phosphorylation) of tumour cells (Diaz-Ruiz *et al.* 2009). This trait is usually thought of as an outcome of adaptative evolution which endows *Saccharomyces* species with an enhanced ability of fast sugar consumption and ethanol production and thus a strong ability to outcompete other microbes in sugar-rich niches (Piškur *et al.* 2006). The fast and strong CO_2 and ethanol production abilities of the yeasts have been explored by humans for bread and alcoholic beverage production worldwide for thousands of years. The earliest archaeological evidence for wine-like beverage production in about 7 000 BC was found in a Neolithic village in China (McGovern *et al.* 2004).

The role of yeast as the agent of fermentation was revealed 150 years ago by pioneering scientists, including Theodor Schwann and Louis Pasteur (Barnett 1998, 2000). In the early 1880s, Emil Christian Hansen developed an effective technique for isolating pure yeast cultures and paved the way for their use in standardised industrial fermentation (Barnett & Lichtenhaler 2001). Although ancient practices employing spontaneous fermentation by natural

microbial communities dominated by *Saccharomyces* yeasts are still used in traditional fermented food production worldwide, elaborately selected or bred *S. cerevisiae* or *S. pastorianus* strains are usually used in large-scale industrial production of bread, beer, wine, and spirits. The current worldwide market of alcoholic drinks is estimated to be over 1 600 billion US dollars. Beer contributes the largest market segment at nearly 640 billion US dollars, while spirits and wine amount to approximately 520 and 360 billion US dollars, respectively (data from <https://www.statista.com/outlook/cmo/alcoholic-drinks/worldwide>).

Saccharomyces cerevisiae is also used for bioethanol production (Elidório *et al.* 2019). There is an increasing demand for clean renewable biofuels to cope with climate change (Liu *et al.* 2021a). Among such biofuels, bioethanol is currently the largest product from crops and other feedstock biomass (Elidório *et al.* 2019). *Saccharomyces cerevisiae* is the dominant species in industrial bioethanol production due to its ability to efficiently and completely ferment sugars from hydrolysates of feedstock biomass into ethanol (Walker & Walker 2018). The annual world bioethanol production from 2016 to 2021 ranged from 26 to 29 billion gallons (Renewable Fuels Association 2022).

With the advantages of easy cultivation, a fast growth rate, a simple single-celled life cycle with clear vegetative and sexual reproduction states, sharing with multicellular eukaryotes many fundamental cellular structures and biological properties, and a relatively small eukaryotic genome, *S. cerevisiae* has become one

of the most powerful eukaryotic models in virtually every discipline of biology (Botstein & Fink 1988, 2011, Duina *et al.* 2014). The first evidence of enzymatic activities outside of a living cell was obtained using yeast extracts by Edward Buchner in the early 1900s, which founded the groundwork for biochemistry and metabolism research (Barnett & Lichtenthaler 2001). In the 1930s, Øjvind Winge and Carl Lindegren began to use yeast as an experimental organism in genetic studies (Mortimer 2000). The genetic and biochemical experiments performed by Fred Sherman in the 1960s and 1970s attracted broad attention to the yeast system from the scientific community (Liebman & Haber 2013). Then, the successful transformation of yeast with a plasmid replicable in *Escherichia coli* in 1978 (Hinnen *et al.* 1978) established the central role of *S. cerevisiae* as a model in molecular biology.

A milestone in the history of biology is the sequencing of the first eukaryotic genome of *S. cerevisiae* in 1996, which was the outcome of a worldwide collaboration of hundreds of researchers (Goffeau *et al.* 1996). Approximately 6 000 genes were recognised in the genome of the yeast strain S288C with a total size of 12 000 kb and 16 chromosomes. The high-quality genome sequence of *S. cerevisiae*, which is comprehensively annotated in the *Saccharomyces* Genome Database (SGD, <http://www.yeastgenome.org/>) has provided a wealth of information for intensive studies on genomics and many other disciplines of biology (Cherry *et al.* 2012, Engel *et al.* 2014). Based on the genomic sequence and efficient tools for homologous recombination in yeast, a budding yeast deletion library has been generated through a cooperative effort of the international yeast community (Winzeler *et al.* 1999, Giaever *et al.* 2002). These resources together with the Gene Ontology Consortium (GO) database (Ashburner *et al.* 2000; <http://www.geneontology.org/>) and a series of other resources available to the scientific community (Botstein & Fink 2011, Duina *et al.* 2014) have greatly improved the studies on the functions of genes and proteins and laid the groundwork for the fields of functional genomics and systems biology, which focus on how genes and proteins interact and work together to determine the traits of organisms.

The budding yeast system has facilitated many landmark discoveries in biology. Since the beginning of the 21st century, at least five Nobel Prizes have been awarded to scientists for their breakthrough work mainly using *S. cerevisiae* as a model organism. Lee Hartwell revealed the foundations of regulated cell division in budding yeast and was awarded a Nobel Prize in Physiology or Medicine in 2001. Roger Kornberg deciphered the structure of the components critical for transcription using the budding yeast toolkit and was awarded a Nobel Prize in Chemistry in 2006. Jack Szostak, Elizabeth Blackburn, and Carol Greider were awarded the 2009 Nobel Prize in Physiology or Medicine for their work in eukaryotic telomere structure involving budding yeast. Two other excellent discoveries that took advantage of the yeast system are Randy Schekman's work on eukaryotic vesicle trafficking (2013 Nobel Prize in Physiology or Medicine) and Yoshinori Ohsumi's work on mechanisms of autophagy (2016 Nobel Prize in Physiology or Medicine). These examples highlight the far-reaching impact that the yeast system has had on our understanding of basic biological processes relevant to all eukaryotes, including humans.

Research interests

There are over 50 000 publications and over 1 000 000 citations from 2011–2021 in the Web of Science (Fig. 3), with numerous publications involving *S. cerevisiae* every year. It is not easy to figure out the exact number because of the extremely broad application of the model organism as an experimental tool and the use of the huge amount of genomic, proteomic and metabolomic data generated from yeast in biological research, as shown by the top cited articles in the Web of Science (Table 3). Several notable hotspots of research directly on *Saccharomyces* species or exclusively using the species as a model or tool are discussed here based on highly cited publications in the past decade (Fig. 4).

Speciation and evolution

Saccharomyces species usually exhibit post-zygotic reproductive isolation and it is easy to test the degree of isolation by examining

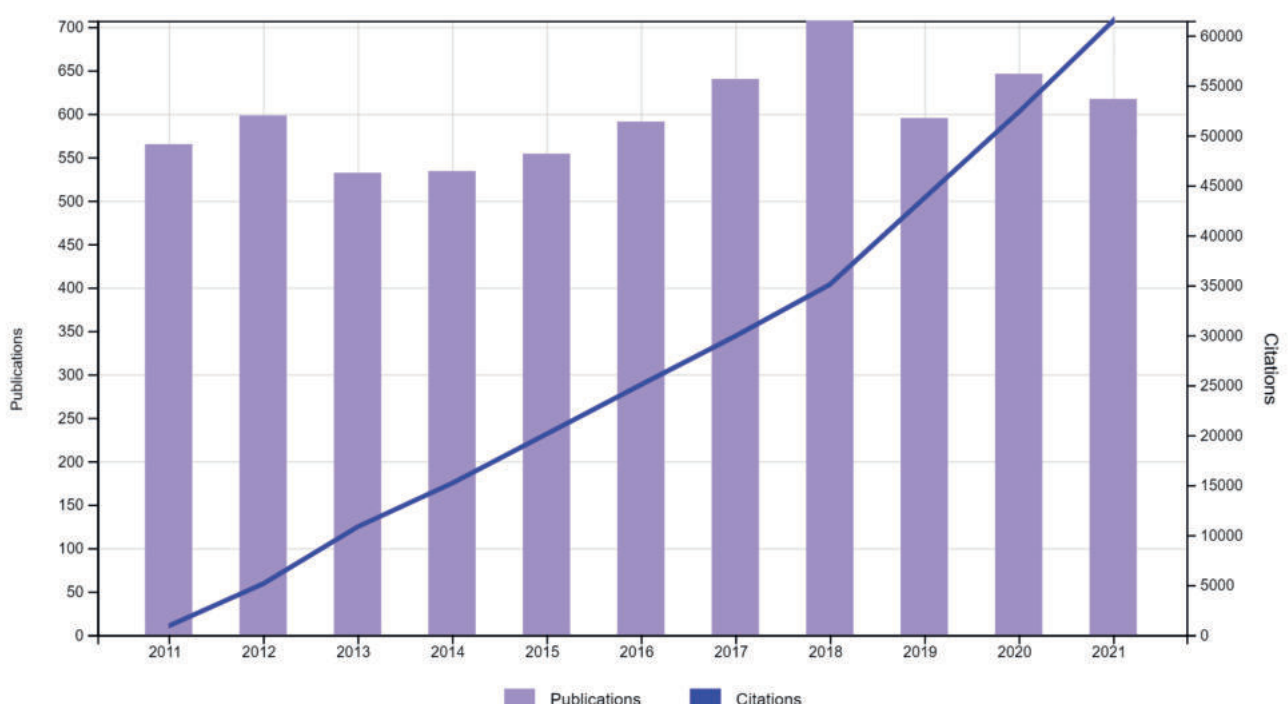


Fig. 3. Trends in research of *Saccharomyces* in the period 2011–2021. The figure shows citations for only 10 000 records.

Table 3. Top 10 cited articles related to *Saccharomyces* published in the period 2011–2021.

Rank	Article title	No. of citations	References
1	<i>Saccharomyces</i> genome database: the genomics resource of budding yeast	1 044	Cherry <i>et al.</i> (2012)
2	Search-and-replace genome editing without double-strand breaks or donor DNA	985	Anzalone <i>et al.</i> (2019)
3	Genome engineering in <i>Saccharomyces cerevisiae</i> using CRISPR-Cas systems	939	DiCarlo <i>et al.</i> (2013)
4	A global genetic interaction network maps a wiring diagram of cellular function	617	Costanzo <i>et al.</i> (2016)
5	Production of amorphadiene in yeast, and its conversion to dihydroartemisinic acid, precursor to the antimalarial agent artemisinin	454	Westfall <i>et al.</i> (2012)
6	Genome evolution across 1,011 <i>Saccharomyces cerevisiae</i> isolates	435	Peter <i>et al.</i> (2018)
7	High-resolution mapping reveals a conserved, widespread, dynamic mRNA methylation program in yeast meiosis	415	Schwartz <i>et al.</i> (2013)
8	Structure of the yeast mitochondrial large ribosomal subunit	397	Amunts <i>et al.</i> (2014)
9	The one hour yeast proteome	386	Hebert <i>et al.</i> (2014)
10	The reference genome sequence of <i>Saccharomyces cerevisiae</i> : Then and now	202	Engel <i>et al.</i> (2014)

spore viability of the crosses between strains from the same or different species. Thus, the genus has become a powerful model in research on the mechanism of speciation (Chou & Leu 2010, Ono *et al.* 2020). Typically, intra- and inter-specific crosses usually result in ~1 % or less and above 50 % spore viability, respectively (Liti *et al.* 2006, Dujon & Louis 2017). Several mechanisms underlying post-zygotic reproductive isolation between *Saccharomyces* species have been identified. Chromosomal translocations or

rearrangements can lead to unbalanced chromosomal segments and lethality in the meiotic spores lacking the translocated segments harbouring essential genes (Liti *et al.* 2006, 2009, Hou *et al.* 2014, 2015, Dujon & Louis 2017). Genetic incompatibility or Bateson-Dobzhansky-Muller incompatibility is another mechanism, which leads to improper interactions of genes from different parents in an offspring of a hybrid and thus causes sterility of the hybrid. Such incompatible genes causing reproductive isolation are usually

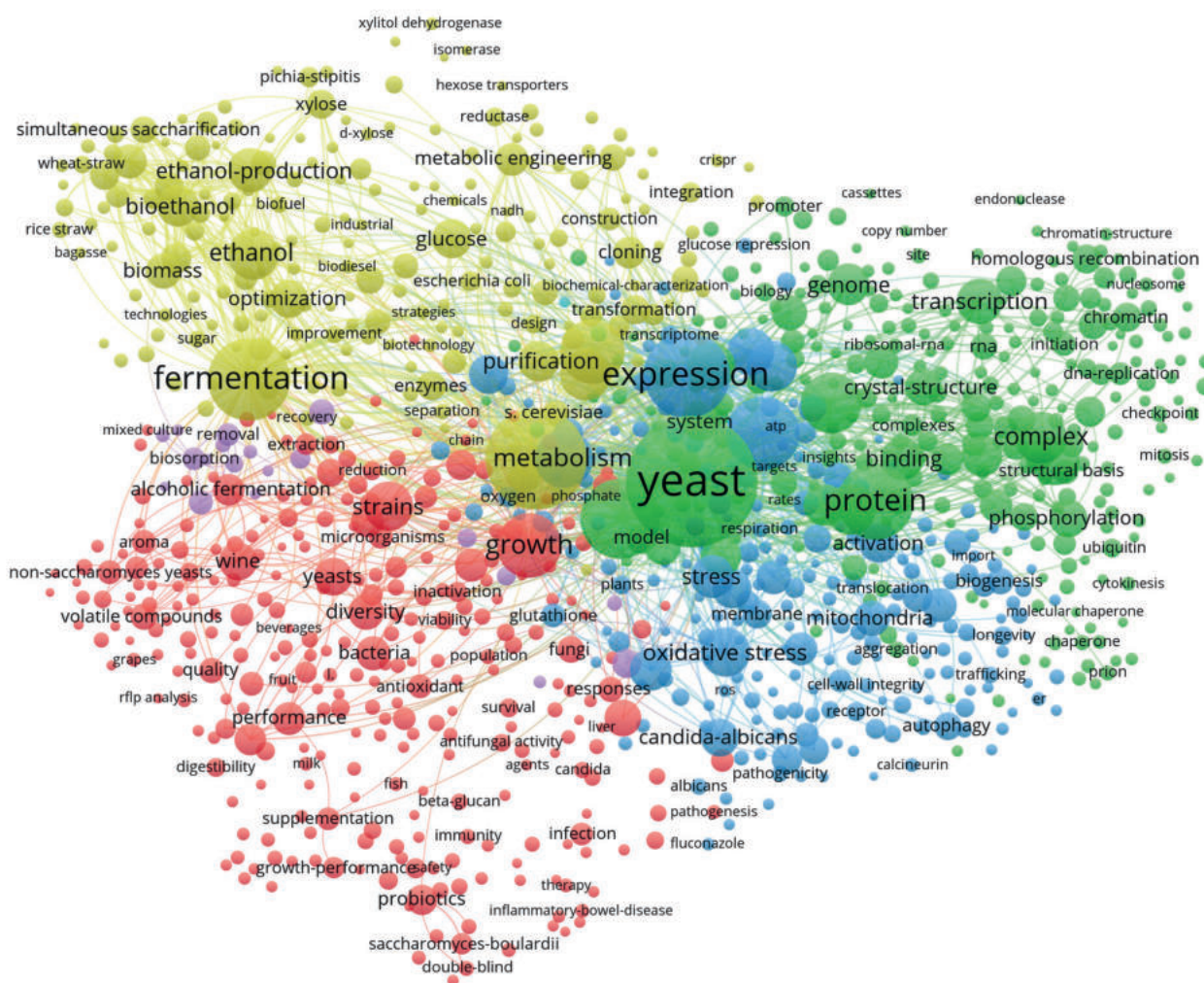


Fig. 4. Network visualisation of keywords of the publications related to *Saccharomyces*. The larger the text and the circle the more often the subject has been cited.

called “speciation genes”. A few examples of genetic incompatibility, particularly between nuclear and mitochondrial genes, have been characterised in *Saccharomyces* species (Lee *et al.* 2008, Chou & Leu 2010, Chou *et al.* 2010). However, it is not clear whether the incompatibility occurred prior to or after speciation (Louis 2009, 2011). The third mechanism is anti-recombination due to sequence divergence, which acts to prevent recombination between nonidentical sequences mediated by the mismatch repair system during meiosis, resulting in the failure of meiotic crossovers required for proper chromosome segregation (Ono *et al.* 2020).

Saccharomyces has also become a model genus in evolutionary genetics and genomics (Hittinger 2013). The genomes of 2 478 *S. cerevisiae*, 409 *S. paradoxus*, 303 *S. eubayanus*, 82 *S. uvarum*, 30 *S. kudriavzevii*, 10 *S. arboricola*, two *S. jurei*, and two *S. mikatae* strains have been sequenced and released in GenBank. Population genetics and genomic studies have shown that the wild and domesticated populations of *S. cerevisiae* are separated in phylogeny and show hallmark differences in heterozygosity and sexuality (Fay & Benavides 2005, Liti *et al.* 2009, Duan *et al.* 2018, Peter *et al.* 2018). The global genetic diversity of *S. cerevisiae* is mainly contributed by strains from Far East Asia, and the ancient basal lineages of the species have been found only in primeval forests in China, supporting an “out-of-China” origin hypothesis of the species (Wang *et al.* 2012d, Liti 2015, Duan *et al.* 2018, Peter *et al.* 2018, Bai *et al.* 2022). In addition to *S. cerevisiae*, the wild species *S. paradoxus* is a promising alternative model in ecology and evolutionary biology (Boynton & Greig 2014, Leducq *et al.* 2016). The genetic diversity of *S. paradoxus* is much higher than that of *S. cerevisiae* and the population structure of the former is well delineated along with geographical boundaries (Liti *et al.* 2009, Xia *et al.* 2017). A highly diverged ancient lineage of *S. paradoxus* has been identified in China (He *et al.* 2022b).

Another interesting progress in the evolution of *Saccharomyces* species is the identification of *S. eubayanus* as the wild ancestor of lager beer yeast *S. pastorianus* (Libkind *et al.* 2011, Bing *et al.* 2014). *Saccharomyces eubayanus*, contributing to the non-ale subgenome of the hybrid *S. pastorianus*, was first discovered from native forests in Patagonia, Argentina (Libkind *et al.* 2011) and was then isolated from the Tibetan Plateau (Bing *et al.* 2014). Population genetics and genomics analyses have shown that the genetic diversity of *S. eubayanus* is much higher in Far East Asia than in America, suggesting that *S. eubayanus* is native to Far East Asia. One of the Tibetan lineages of the species exhibited closer affinity with lager yeast than the Patagonian lineage (Bing *et al.* 2014, Okuno *et al.* 2016). Thus, a Tibetan origin hypothesis of lager yeast has been proposed (Bing *et al.* 2014), which is supported by the finding that the mitochondrial genome of *S. pastorianus* originates exclusively from the Tibetan lineage of *S. eubayanus* (Okuno *et al.* 2016).

Synthetic biology

A post-genomic global collaboration of the yeast community is the synthetic yeast genome project Sc2.0, aiming to build a functional synthetic genome of an eukaryote and to answer fundamental biological questions relating to properties of chromosomes, genome structure and evolution, gene content, function of RNA splicing, and the distinction between prokaryotes and eukaryotes, and to establish a platform for the development of biotechnology (Dymond *et al.* 2011, Richardson *et al.* 2017). Six chromosomes (synII, synIII, synV, synVI, synX, and synXII) and the right arm of chromosome IX (synIXR) have been successfully synthesised (Richardson *et al.* 2017, Pretorius & Boeke 2018). Then, a functional single-

chromosome yeast from a haploid cell of *S. cerevisiae* containing 16 linear chromosomes has been created by successive end-to-end chromosome fusions and centromere deletions (Shao *et al.* 2018).

Benefiting from the rapid developments of synthetic biology and genome editing tools, especially the CRISPR-Cas9 system (DiCarlo *et al.* 2013), *S. cerevisiae* has been developed as a cell factory to produce many chemicals, bioactive secondary metabolites, and pharmaceuticals (Nielsen *et al.* 2019). For example, amorphaadiene, which is the precursor to the antimalarial agent artemisinin, was produced by fermentation from engineered *S. cerevisiae* (Westfall *et al.* 2012). *Saccharomyces cerevisiae* was also engineered to produce opioid compounds thebaine and hydrocodone starting from sugar by reconstructing the full biosynthesis pathway required for the expression of 21 (thebaine) and 23 (hydrocodone) enzymes from plants, mammals, bacteria, and yeast itself (Galanie *et al.* 2015). Through metabolic rewiring, directed evolution, and bioprocess optimisation, *S. cerevisiae* was reprogrammed from ethanol fermentation to a pure lipogenesis metabolism for high-level production of free fatty acids (Yu *et al.* 2018).

Structural biology

Because of the high-level conservation between yeast and human in protein sequences and cell organelle structures and their functions, *S. cerevisiae* has been used as a powerful model in structural biology. Due to the application of yeast as a model system in the study of human mitochondrial disorders (Barrientos 2003), the structure of yeast mitochondrial ribosomal large subunit was solved using single-particle cryo-electron microscopy. A nearly complete atomic model with a resolution of 3.2 angstroms was built *de novo*, including 39 proteins and expansion segments of mitoribosomal RNA (Amunts *et al.* 2014). The structure of the intact spliceosome of *S. cerevisiae*, which mediates splicing of the precursor messenger RNA (pre-mRNA) involving intron removal and exon ligation, was resolved at atomic resolution through a series of structural studies since 2016 (Wan *et al.* 2020). The molecular mechanism of pre-mRNA splicing was elucidated based on structural studies together with biochemical and genetic investigations (Wan *et al.* 2020). The structural studies on human spliceosomes performed simultaneously revealed strict conservation between humans and yeast in the overall organisation of the spliceosome and the configuration of the splicing active site (Wan *et al.* 2020).

Epigenetics

Post-synthesis modifications of DNA, RNA, and proteins all potentially impact their function and are the main targets of epigenetics, which focuses on heritable changes in gene function that are not attributed to alterations of the DNA sequence. Previous studies have shown that DNA methylation and RNA interference (RNAi) machinery are absent from *S. cerevisiae* (O’Kane & Hyland 2019). The lack of these processes simplifies the examination of the remaining epigenetic marks. The lack of potential complications caused by the cross-talk between the DNA methylation and histone modification pathways as observed in animal cells (Cedar & Bergman 2009) and the limited functionally redundant copies of the genes encoding core histone proteins make *S. cerevisiae* one of the best models available for studying the inheritance of histone modification-dependent chromatin states. Epigenetic mechanisms involving heritable silent chromatin in *S. cerevisiae*, including telomere silencing, mating type silencing, and rDNA silencing, have been extensively studied (Rusche *et al.* 2003, Grunstein & Gasser 2013, Gartenberg & Smith 2016, O’Kane & Hyland 2019).

Messenger RNA (mRNA) methylation has been revealed as a key player in eukaryotic gene expression regulation, and N⁶-methyladenosine (m⁶A) is among the most abundant internal mRNA modification known in eukaryotic mRNA (Covelo-Molares *et al.* 2018). In *S. cerevisiae* mRNA methylation occurs only during meiosis. Deletion of the core RNA methyltransferase components delays meiotic entry but is not lethal to yeast. Therefore, *S. cerevisiae* is a promising tool in the study of mRNA methylation (Schwartz *et al.* 2013). Genomic maps of m⁶A sites in meiotic yeast transcripts at nearly single-nucleotide resolution were generated using a high-resolution assay coupled with mutants defective in methylation, resulting in the identification of 1 308 putatively methylated sites within 1 183 transcripts (Schwartz *et al.* 2013). The study also showed a striking similarity in methylation profiles and components between yeast and mammals, enhancing the value of yeast as a compelling model system for studying the role of methylations (Schwartz *et al.* 2013).

Proteomics

Expression and interactions of proteins are essential for understanding biological phenomena. Technologies for large-scale quantitative measurement of proteins have been developed and improved substantially in recent decades. With its unmatched resources in genomics and transcriptomics, *S. cerevisiae* has been a preferred platform for proteomic studies. The first large-scale yeast proteome study using two-dimensional chromatography coupled with tandem mass spectrometry identified 1 483 proteins (Washburn *et al.* 2001). Ghaemmaghami *et al.* (2003) created a *S. cerevisiae* fusion library where each annotated ORF was fused to a TAP tag. They measured approximate expression levels of the tagged ORFs and found that about 4 500 proteins (80 % of the proteome) were expressed during normal growth conditions. Huh *et al.* (2003) fused more than 4 100 proteins to GFP and identified their subcellular locations, providing information about what their function might be.

Picotti *et al.* (2013) generated an almost complete reference map (97 % of the genome-predicted proteins) of the *S. cerevisiae* proteome using a strategy based on high-throughput peptide synthesis and mass spectrometry and applied the maps to a protein quantitative trait locus (QTL) analysis. Hebert *et al.* (2014) developed a protocol for comprehensive analysis of the yeast proteome in just over one hour with improved sample preparation and chromatographic separations, and by using a new Orbitrap hybrid mass spectrometer. On average, each 1 h analysis achieved the detection of 3 977 proteins (1 % false discovery rate). Ho *et al.* (2018) generated a unified protein abundance data set, covering about 5 400 proteins by combining 21 quantitative yeast proteome data sets, including MS-, GFP-, and western blotting-based methods. Recently, Gao *et al.* (2021b) generated the largest yeast proteome data set, including 5 610 identified proteins, using a strategy based on optimised sample preparation and high-resolution mass spectrometry. These yeast proteome data sets are important resources for further systematic studies.

Author: F.Y. Bai

2. *Candida* Berkhout, Schimmeligsl. Monilia: 41. 1923.

Type species: *Candida vulgaris* Berkhout [(syn. *Candida tropicalis* (Castellani) Berkhout)]

Classification: Ascomycota, Saccharomycotina, Pichiomyces, Seriales, Debaryomycetaceae.

Background

Candida was introduced by C.M. Berkhout (1923) in her PhD thesis to accommodate asexually reproducing yeasts that form hyphae that may disarticulate and form blastoconidia by budding from the hyphae or each other. Berkhout's translated diagnosis of the genus reads as "Few hyphae, sessile, disarticulating into shorter or longer fragments. Conidia formed budding from hypha or each other; they are small and colourless (hyaline)". *Candida vulgaris*, currently a synonym under *C. tropicalis* (Lachance *et al.* 2011), was selected by Berkhout as the generic type. The expansion of the genus *Candida* over the years is clearly illustrated by the number of species listed in the first monograph on asexual yeasts (Diddens & Lodder 1942) and all subsequent five editions of "The Yeasts, a Taxonomic study" (TYTS, Lodder & Kreger-van Rij 1952, Lodder 1970, Kreger-van Rij 1984, Kurtzman & Fell 1998, Kurtzman *et al.* 2011) that contained 26, 30, 81, 196, 163, and 314 species, respectively. *Candida* contains asexually reproducing Saccharomycotina budding yeasts with white, moist colonies that may or may not form pseudohyphae or true hyphae, and produces yeast cells by blastoconidiogenesis. For a long time, morphologically similar yeasts belonging to both Basidiomycota and Ascomycota were included in the genus. Yarrow & Meyer (1978) changed the generic concept by including yeasts that do not form hyphae. Thus, they merged *Torulopsis* (with no hyphae) with *Candida* (with hyphae) giving nomenclatural priority. *Torulopsis* was described by Berlese (1895) with *T. rosea* as the type species. However, the taxonomic concept of *Torulopsis* remained doubtful as its true identity could not be verified because no strain was available. Yarrow and Meyer recombined *Torulopsis glabrata*, originally described as *Cryptococcus glabratus* Anderson, in *Candida* as *C. glabrata* (Anderson) Yarrow & Meyer (1978). This merging of *Candida* and *Torulopsis* has contributed to the present highly polyphyletic nature of the genus (see below).

This expansion of *Candida* was followed by a taxonomic clean-up by the removal of yeasts with basidiomycetous affinity (Weijman *et al.* 1988), thus restricting *Candida* to ascomycetous yeasts with the following characteristics: *Candida* Berkhout char. *emend.* Weijman, Rodrigues de Miranda & Van der Walt: Cells globose, ellipsoid, ovoid, cylindrical, elongate, rarely oval, triangular, apiculate or ampulliform. Cell wall by TEM ascomycetous, two-layered. Vegetative reproduction is holoblastic and as a rule multilateral budding. Pseudohyphae and as a rule non-disarticulating hyphae may occur, the latter if septate, non-porate or with closure lines or disjunctives (micropores plasmodesmata). Chlamydospores may occur. Pigmentation, when manifest, due to non-carotenoids. Amyloid compounds giving a positive starch reaction absent. Xylose, rhamnose and fucose are absent in cell wall hydrolysates. The presence of disarticulating hyphae is considered by these authors a key feature.

With the advent of molecular phylogeny, it became clear that *Candida*, as defined above, belongs to many phylogenetic lineages within Saccharomycotina (Kurtzman 1987, 1990, 1993a, 1993b, 1993c, Kuramae *et al.* 2006, Lachance *et al.* 2011, Gabaldón *et al.* 2013, Daniel *et al.* 2014, Hittinger *et al.* 2015, Shen *et al.* 2018). Barns *et al.* (1991) using sequence analysis of the small subunit (SSU or 18S) ribosomal RNA (rRNA) gene had already noticed that *C. glabrata* clustered distinctly from *C. albicans* and *C. tropicalis*, and was more closely related to *Saccharomyces cerevisiae*. This was confirmed by Kurtzman & Robnett (1997, 1998) who in several studies using partial sequence (D1/D2 regions) of LSU showed that *C. glabrata* belongs to a different lineage than *C. tropicalis*, but also from *C. albicans* (Kurtzman &

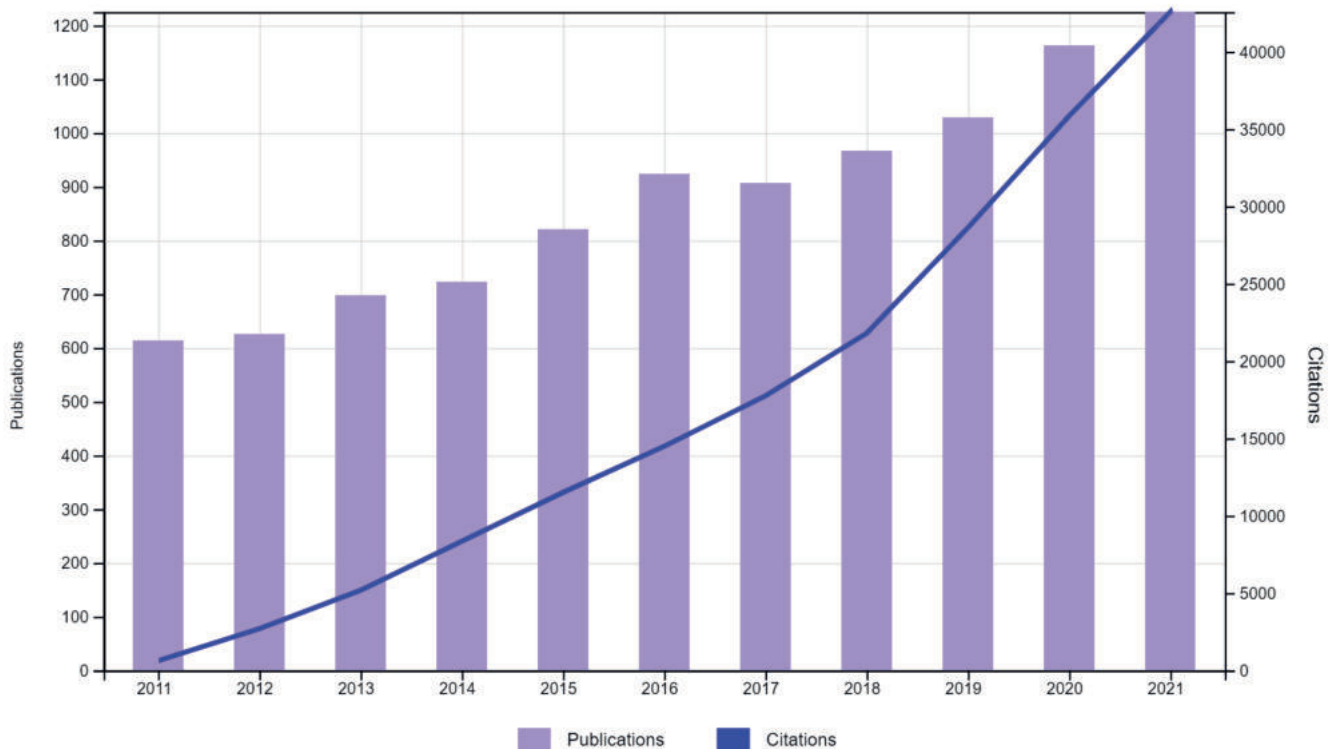


Fig. 5. Trends in research of *Candida* in the period 2011–2021. The figure shows citations for only 10 000 records.

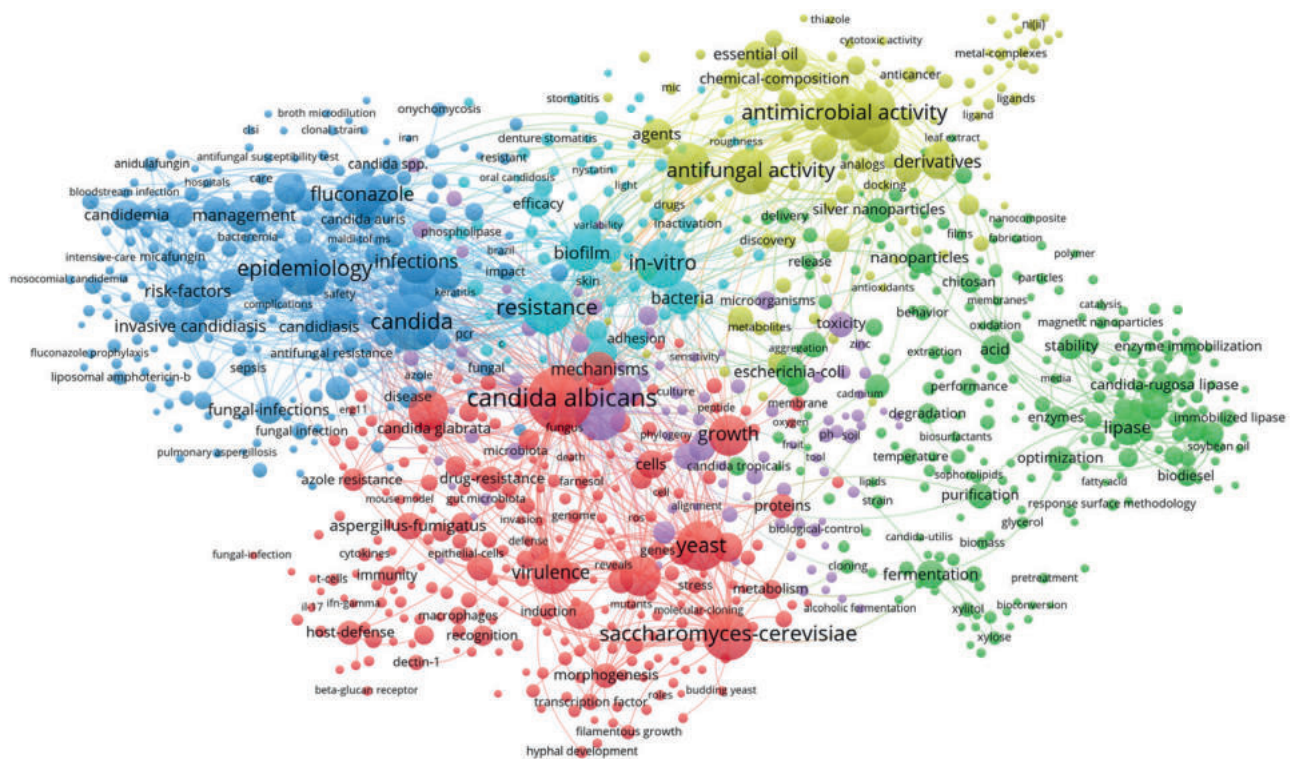


Fig. 6. Network visualisation of keywords of the publications related to *Candida*. The larger the text and the circle the more often the subject has been cited.

Robnett 1998). This was later confirmed by phylogenetic analyses using whole genome-based data (Fitzpatrick *et al.* 2006, Kuramae *et al.* 2006, Robertse *et al.* 2006, Gabaldón 2013, Pryszcz *et al.* 2014, 2015, Hittinger *et al.* 2015). All these studies confirmed the large phylogenetic distances between various lineages of ascomycetous budding yeasts (Kurtzman & Robnett 1998, Dujon 2006). As a result, the 314 described species, plus the 51 species that were not yet included in the 5th edition of TYTS, belonged to at least 28 clades (Lachance *et al.* 2011). Daniel *et al.* (2014) listed 12 sexually defined ascomycetous genera that contain *Candida*

species. *Candida glabrata* clustered in *Saccharomycetaceae* and *C. albicans* and *C. tropicalis* in the so-called Lodderomyces clade of *Debaryomycetaceae*. The website “theyeasts.org”, the electronic successor of TYTS, still lists 288 species in *Candida*, while the remaining species have been reclassified in a large number of genera: *Ambrosiozyma*, *Blastobotrys*, *Clavispora*, *Danielozyma*, *Diddensiella*, *Diutina*, *Groenewaldozyma*, *Hemisphaericaspora*, *Hyphopichia*, *Kazachstania*, *Kuraishia*, *Kurtzmaniella*, *Martiniozyma*, *Metschnikowia*, *Metahyphopichia*, *Meyerozyma*, *Middelhovenomyces*, *Nakazawaea*, *Ogataea*, *Priceomyces*,

Table 4. Top 10 cited articles related to *Candida* published in the period 2011–2021.

Rank	Article title	No. of citations	References
1	Tryptophan catabolites from microbiota engage aryl hydrocarbon receptor and balance mucosal reactivity via interleukin-22	1 134	Zelante <i>et al.</i> (2013)
2	<i>Candida albicans</i> pathogenicity mechanisms	973	Mayer <i>et al.</i> (2013)
3	Fate mapping of IL-17-producing T cells in inflammatory responses	799	Hirota <i>et al.</i> (2011)
4	ESCMID* guideline for the diagnosis and management of <i>Candida</i> diseases 2012: non-neutropenic adult patients	791	Cornely <i>et al.</i> (2012)
5	Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity	708	Puel <i>et al.</i> (2011)
6	<i>Candida</i> species: current epidemiology, pathogenicity, biofilm formation, natural antifungal products and new therapeutic options	686	Sardi <i>et al.</i> (2013)
7	Growth of <i>Candida albicans</i> hyphae	665	Sudbery (2011)
8	Invasive candidiasis	650	Kullberg & Arendrup (2015)
9	Type I interferon inhibits interleukin-1 production and inflammasome activation	648	Guarda <i>et al.</i> (2011)
10	Antifungal drug resistance: mechanisms, epidemiology, and consequences for treatment	624	Pfaller (2012)

Saccharomycopsis, *Saturnispora*, *Scheffersomyces*, *Spathaspora*, *Spencermartinsiella*, *Starmerella*, *Sugiyamaella*, *Suhomyces*, *Teunomyces*, *Tortispora*, *Wickerhamiella*, *Yamadazyma*, and *Zygoascus*. To further complicate the current polyphyly of the genus, the 288 species retained in *Candida* are distributed into at least 25 clades or families: namely clades *Ambrosiozyma*, *Barnettozyma*, *Candida glaeboa*, *Cyberlindnera*, *Dipodascaceae*, *Kazachstania*, *Kodamaea*, *Kurtzmaniella*, *Lodderomyces*/*Spathaspora*, *Metschnikowia*/*Clavispora*, *Meyerozyma*, *Nakaseomyces*, *Nakazawaea*, *Ogataea*, *Phaffia*/*Komagataella*, *Phaffozyma*, *Pichia*, *Priceomyces*, *Scheffersomyces*, *Starmera*, *Sugiyamaella*, *Suhomyces*, *Wickerhamomyces*, *Yamadazyma*, *Yarrowia*, *Zygoascus*, and, in addition, 13 unaffiliated clades. As the generic type *C. vulgaris*, a current synonym under *C. tropicalis* belongs to the *Lodderomyces* clade, it is clear that this clade will form the core of the *s. str.* circumscription of the genus *Candida* after this has been fully revised. Even the *Lodderomyces* clade might host a number of genera. To link the name *Candida* to that of the infectious disease candidiasis, the most common fungal infection in man/animals, and *C. albicans* its main causative agent, it might be needed to reconsider the typification of the genus and select *C. albicans* as a neotype. Proper actions to realise this have to be taken by yeast taxonomists and nomenclatural experts. With the global emergence of *Candida auris* as a human pathogen (Rhodes & Fisher 2019, Chow *et al.* 2020, Chakrabarti & Sood 2021), a species that belongs to the *Metschnikowia* clade, such typification issues should be convincing for the nomenclature purists, and also for the broader community of clinicians. Clinical arguments for such restriction of the genus *Candida* can be found in the extensive differences in antifungal susceptibility patterns and clinical aspects by species belonging to the various clades (Schmalreck *et al.* 2014, Stavrou *et al.* 2019, 2020). Restriction of *Candida* to the clade that contains *C. albicans* will also be beneficial for the acceptance of other species that are currently classified in the polyphyletic genus *Candida*, for use in biotechnology, fermentation and biocontrol.

Ecological and economic significance

Candida ranks number two in the list of most cited fungal genera, which is mainly due to the large number of opportunistic infections caused by species hitherto classified in the genus. Candidiasis occurs globally with an estimated > 400 000 cases per year (Brown *et al.* 2012). Fifty to 75 percent of fertile women suffer from at least

one episode of vulvovaginal candidiasis and five to eight percent suffer from four episodes annually (Brown *et al.* 2012). Among the top five clinically most important yeasts are *C. albicans*, *C. tropicalis*, *C. glabrata* and *C. parapsilosis* (*s. lat.*), whereas others, such as *Pichia kudriavzevii* (Boidin *et al.* 1965) and *Meyerozyma* (*Pichia*) *guilliermondii* are in medical literature commonly referred as *C. krusei* and *C. guilliermondii*, respectively (Cleveland *et al.* 2012, Guinea 2014, Pfaller *et al.* 2014, Schmalreck *et al.* 2014, Da Matta *et al.* 2017, Stavrou *et al.* 2019, Kmeid *et al.* 2020).

Invasive candidiasis comprises bloodstream infections or candidemia, and also deep-seated infections (Kullberg & Arendrup 2015). The latter have a mortality of 40 % even when treated with antifungals (Kullberg & Arendrup 2015). Another ongoing process, with an increased risk for patients, is the shift from infections caused by *C. albicans* to those caused by non-*albicans* *Candida* species (Kullberg & Arendrup 2015, Stavrou *et al.* 2019). Recently, *Candida auris*, has emerged as a global threat in human invasive infection exhibiting mortality rates ranging from 30 to 60 % (Calvo *et al.* 2016, Chowdhary *et al.* 2016, De Almeida *et al.* 2021, Chakrabarti & Sood 2021). Since its description in 2009, the species is associated with hospital-acquired infection causing outbreaks worldwide. *Candida auris* infections are challenging to treat as the species exhibits a resistant profile to fluconazole and variable susceptibility to other triazoles, echinocandins, and polyenes drug classes (Satoh *et al.* 2009, Chowdhary *et al.* 2014b, 2018, Chow *et al.* 2018, 2020). *Candida auris* is commonly misidentified as *C. haemulonii*, *C. famata*, *C. sake*, and even *Saccharomyces cerevisiae* by phenotypical identification methods, and accurate species characterisation requires molecular sequencing (ITS region) or MALDI-TOF MS (Kathuria *et al.* 2015, Girard *et al.* 2016, Ruiz Gaitán *et al.* 2017, Das *et al.* 2019, Ding *et al.* 2019). Due to the clinical challenges posed by *C. auris*, several public health authorities have released clinical guidelines for use in healthcare facilities on infection prevention in order to control this emerging pathogen, also highlighting the importance of notifying the cases to health authorities. As species belonging to the various *Candida* clades show differences in their susceptibility to antifungals, species identity may give a clue for the treatment of patients suffering from infections by such non-conventional *Candida* species (Schmalreck *et al.* 2014, Stavrou *et al.* 2019).

Virulence factors, such as differences in adhesion to epithelial cells, secretion of hydrolytic enzymes, yeast-hyphal dimorphism, the extent of biofilm formation, and phenotypic switching determine the

pathogenic potential of *Candida* species and their isolates (Mayer *et al.* 2013, Sardi *et al.* 2013, Nobile & Johnson 2015, Ramos *et al.* 2015, Wakade *et al.* 2020). Risk factors for invasive candidiasis include a long stay at intensive care units/critical illness, abdominal surgery, pancreatitis, hematologic malignant diseases, solid organ transplantation, solid organ tumours, use of broad-spectrum antibiotics, use of catheters, use of chemotherapy, and neonatal state or being colonised by *Candida* yeasts (Nucci *et al.* 1998, Pasqualotto *et al.* 2007, Pfaller *et al.* 2014, Kullberg & Arendrup 2015, Da Matta *et al.* 2017, Warris *et al.* 2020). The secretion of candidalysin, a recently found cytolytic peptide (Moyes *et al.* 2016), modulates innate immunity thus impacting immune regulation (Ho *et al.* 2020). For instance, candidalysin induces early and robust early and innate Th17 cell-derived interleukin 17A (IL-17A) (Verma *et al.* 2017, Ho *et al.* 2020). Complex immunomodulatory mechanisms increase or decrease the susceptibility of the host to *C. albicans*, e.g., mechanisms that enhance colonisation resistance of the gut and reduce colonisation by *C. albicans* relate to the effect of tryptophan metabolites that expand lactobacilli via aryl hydrocarbon receptor-dependent transcription of interleukin 22 (IL-22). The resulting IL22-dependent mucosal balance enhances the survival of microbial communities, and also reduced colonisation by *C. albicans* and protection against inflammation (Zelante *et al.* 2013). Other immune active molecules, such as interleukin-17 (IL-17), relate to mucocutaneous immunity against *C. albicans* (Hirota *et al.* 2011, Puel *et al.* 2011), whereas Type I interferon inhibited the production of interleukin-1 (IL-1) also impacts susceptibility of the host to the yeast (Guarda *et al.* 2011).

Clinically relevant is the observation that many *Candida* species or strains show reduced susceptibility to one or several of the major classes of antifungals (Pfaller 2012, Schmalreck *et al.* 2014, Arendrup & Patterson 2017, Cortegiani *et al.* 2019, Stavrou *et al.* 2019). Treatment options are presented in a large series of clinical guidelines, e.g., dealing with neonates, non-neutropenic patients, patients suffering from haematological malignancies, HIV infections and AIDS, patients at intensive care units, etc. (Papas *et al.* 2004, Cornely *et al.* 2012, Hope *et al.* 2012a, Lortholary *et al.* 2012, Ullmann *et al.* 2012a, b, Chaves *et al.* 2018), and also for infections caused by non-*albicans* *Candida* species (Mermel *et al.* 2011, Arendrup *et al.* 2014).

Genetic processes, such as hybridisation, either or not followed by processes of post-hybridisation genetic diversification resulting in (massive) loss of heterozygosity are considered to have played a role in the evolution of virulence of human opportunists in species (complexes), such as the *C. albicans*, *C. inconspicua*, and *C. parapsilosis* complex (Pryszcz *et al.* 2015, 2014, Mixão & Gabaldón 2018, Mixão *et al.* 2021).

Beyond the clinical importance of *Candida* species, others are also biotechnologically important. For example, *C. rugosa* produces lipases and sterol esterases that are important for application in the food industry, production of pharmaceuticals, biosurfactants, biofuels, bio-sensor, cosmetics, etc. (Benjamin & Pandye 1998, Barriuso *et al.* 2016). *Candida tropicalis* and *C. maltosa* are utilised for the production of xylitol (Guo *et al.* 2006, Kumar *et al.* 2022). Several species that were previously classified in *Candida* and that are now in genera like *Kluyveromyces*, *Scheffersomyces* and *Yarrowia* are also highly important from fermentation and biotechnological perspectives, but outside the scope of this text. *Candida parapsilosis* has been used as a biocatalyst for organic transformations, i.e., deracemisation, enantioselective reductions, and kinetic resolutions (Chadha *et al.* 2016). *Candida tropicalis* has been associated as a

relevant metaboliser of hydrophobic substrates, such as fatty acids or alkanes, to produce long-chain dicarboxylic acid, and modulation in the copy number of the *ctfat1p* gene plays an important role to improve the production of this compound (Lebeault *et al.* 1970, Zhang *et al.* 2021c). The species can successfully decontaminate phenol wastewater and soil under salt or no-salt conditions within pH and temperatures ranging from 3.0 to 9.0, and to 20 °C, respectively (Wang *et al.* 2011a, Basak *et al.* 2014, Gong *et al.* 2021). *Meyerozyma* (*Candida*) *guilliermondii* is an effective yeast for bioconversion of xylose into xylitol, a promising product of ethanol and aromas which is able to reduce the content of patulin in culture medium, and use hydrocarbons as a sole carbon source on minimal salts medium (Schirmer-Michel *et al.* 2008, Guo *et al.* 2009, Wah *et al.* 2013, Chen *et al.* 2017e, Hashem *et al.* 2018).

Research interests

There are over 40 000 publications and over 500 000 citations from 2011–2021 in the Web of Science (Fig. 5). The research interests of *Candida* yeasts focus on improving the taxonomy, epidemiology and diagnostics of *Candida*-related infections, understanding the regulation of virulence, interaction with the host immune system, fundamental cell biology and biochemistry, comparative and functional genomics, and role in human (and animal) microbiomes (Fig. 6). This is clearly reflected in the highly cited papers (Table 4). Beyond this, the use of specific *Candida* species and strains for use in biotechnology, fermentations, and biocontrol is also important. Immune response mediated by interferons and interleukins in *C. albicans* infections is also a highly cited topic. The main aspects addressed in the top-cited papers include conservative cytokines production of T_H17 cells in an acute cutaneous infection caused by *C. albicans*; the role of interleukin-17A and interleukin-17F in the mucocutaneous immunity against chronic mucocutaneous candidiasis; pro-interleukin-1 β induced by aluminium salts, and *C. albicans* suppressed by type I interferon role to develop *Candida* infections.

In the top-cited review papers, aspects include data regarding epidemiology, antifungal susceptibility profile by the manufacturer, and natural options of *Candida* species added to the integrative analysis of classical and novel pathogenic mechanisms of *C. albicans* involved in host infection highlighting molecules related to adhesion and invasion of tissues, enzymes profiles, fitness attributes, and yeast morphology switching; consensus recommendations to the diagnosis and management options for non-neutropenic adult patients with *Candida* infections intended to provide practical assistance in the laboratory and clinical decisions in different hospitalised populations, as critically ill individuals under risk factors for invasive candidemia, surgical intensive care units patients, and others; transduction pathways and the molecular processes to activate a program of hypha-specific gene transcription; and trends and strategies in invasive candidiasis.

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3. *Aspergillus* P. Micheli ex Haller, Hist. stirp. Helv. (Bernae) 3: 113. 1768.

Type species: *Aspergillus glaucus* (L.) Link

Classification: Ascomycota, Pezizomycotina, Eurotiomycetes, Eurotiales, Aspergillaceae.

Background

Aspergillus was introduced by Micheli (1729) who considered the characteristic vesiculated conidiophores to resemble an aspergillum, also called a holy water sprinkler. The name was later validated by Von Haller (1768) and sanctioned in Fries (1832). The genus is typified by *A. glaucus* [IMI 211383 (neotype); CBS 516.65 = NRRL 116 = ATCC 16469 = IMI 211383 (ex-neotype)]. Several sexual morphs (teleomorphs) like *Eurotium*, *Emericella*, *Neosartorya*, etc. are associated with *Aspergillus*, with phylogenetic analyses resolving these in a large clade, within which sexual morphs typically also resolved as distinct subclades (Houbraken & Samson 2011). Following the concept of single nomenclature (One Fungus = One Name) (McNeill *et al.* 2012), a debate followed on whether to use a broad concept of *Aspergillus* or split the genus based on the smaller clades typically represented by sexual generic names (Pitt & Samson 2007, Houbraken & Samson 2011, Pitt & Taylor 2014, 2016, Samson *et al.* 2014, 2017, Kocsube *et al.* 2016, Taylor *et al.* 2016, Houbraken *et al.* 2020). *Aspergillus* was eventually chosen by the community with several sexual and asexual genera synonymised with the former (Samson *et al.* 2014). A review of the genus resulted in Samson *et al.* (2014) publishing an accepted species list, providing guidelines to work with and identify *Aspergillus* strains, and proposing calmodulin as an alternative identification marker. Many new species were subsequently described which necessitated a review by Houbraken *et al.* (2020) who accepted 446 species (currently 454) and classified them into 6 subgenera, 27 sections and 75 series. More recently, Visagie *et al.* (2024) provided an update on taxonomic revisions and new species published since Houbraken *et al.* (2020), which brought the number of accepted species in *Aspergillus* to 453 (currently 467).

Ecological and economic significance

Food mycology and ecology

Aspergillus represents one of the most economically important fungal genera (Samson *et al.* 2014). *Aspergillus* spp. are widespread geographically and can be either beneficial or harmful microorganisms, however, they mainly have a saprophytic lifestyle and predominantly grow on decaying plant material (Perrone & Gallo 2017). They are among the most successful groups of moulds with important roles in natural ecosystems and the human economy.

Aspergilli are important in fermented food of Asian cuisines by enhancing nutrients, textures, and flavours (Bennett 2010). In particular, important in food mycology as beneficial are the three koji moulds *A. oryzae*, *A. sojae*, and *A. luchuensis*, the Koku-kin (national fungi) that are certified by the Brewing Society of Japan (Ichishima 2016). These koji moulds can be classified as yellow-, black-, and white-koji moulds (Hong *et al.* 2014). For example, *A. oryzae* is used for the production of sake, shochu (distilled sake), amazake (a sweet beverage), and mirin (sweet alcoholic seasoning) in Japan and for Huang-chiu (yellow wine) in China (Kitagaki & Kitamoto 2013, Ashu *et al.* 2016). The Black-koji moulds are used in Japan to produce shochu (*A. kawachii* = *A. luchuensis*) and awamori (*A. luchuensis*) (Hong *et al.* 2014). Many additional uses in food mycology are also known for *Aspergillus*: i.e., *A. chevalieri* and *A. pseudoglaucus* in traditional fermentation and ripening of katsuobushi (Takenaka *et al.* 2020); various species of sections *Aspergillus*, *Flavi* and *Nigri* are commonly isolated from meju, a brick of dried fermented soybeans popular in Korean cuisine (Hong

et al. 2015); and also, from fermented tea including Pu-erh tea and Fuzhuan Cha (Fu brick tea) (Park *et al.* 2017).

Unfortunately, Aspergilli are one of the major causes of degradation of agricultural products, as they can contaminate foods and feeds at different stages including pre- and postharvest, processing and handling (Perrone & Gallo 2017). So, although important in fermented foods, they can cause undesirable changes of sensorial, nutritional and qualitative nature like pigmentation, discoloration, rotting, and development of off-odours and off-flavours, but most importantly they can produce dangerous mycotoxins that contaminate food, agricultural and food products (Perrone *et al.* 2007, Bennet 2010, Taniwaki *et al.* 2018). However, only a handful of species are significant mycotoxin producers in agricultural products and food and mainly belong within the subgenus *Circumdati*. In particular, three species groups are represented: *A. flavus* - *A. parasiticus* and their close relatives; *A. westerdijkiae* - *A. steynii* and their close relatives; *A. carbonarius* and the closely related species in series (Visagie *et al.* 2014b, Frisvad *et al.* 2019, Houbraken *et al.* 2020). Most *Aspergillus* species are saprophytic, but in some cases can be pathogenic like in the *Flavi* group producing aflatoxins on peanuts and maize. These species can grow in these plants under unfavourable growth conditions for the plants, such as drought stress, which permits infection of developing nuts or grains, and hence the production of aflatoxins before harvest (Saori & Keller 2011). Subgenera *Circumdati* and *Nigri* species occur mainly as postharvest infections having no affinity with crop plants, with some exceptions like *A. carbonarius* and closely related species on grapes (Perrone *et al.* 2008, Perrone & Gallo 2017). *Aspergillus* species can grow at a very wide range of temperatures, water activities and pH, so its species are cosmopolitan and prevalent components of different ecosystems in a wide range of environmental and climatic zones (Klich 2002, Abdel-Azeem *et al.* 2016). They are widely present in soils (Klich 2002, Jaime-Garcia & Cotty 2010), salt marshes (Butinar *et al.* 2011), agricultural ecosystems (Perrone *et al.* 2007, Taniwaki *et al.* 2018), arctic (Arenz *et al.* 2014), stones, fossils, water, animal and humans, etc. (Abdel-Azeem *et al.* 2019). They are very important in decomposition processes driving the natural cycling of chemical elements, particularly in the carbon cycle; they are part of a consortia of organisms from different kingdoms that recycle starches, hemicelluloses, celluloses, pectins and other sugar polymers. Some aspergilli are capable of degrading more refractory compounds such as fats, oils, chitin, and keratin (Bennet 2007). Recently the beneficial impact of *Aspergillus* species in soil and environment has been reviewed (Nayak *et al.* 2020), and also, its protective role as plant growth-promoting fungi has been evidenced (Daigham *et al.* 2023).

Their ability to disperse spores globally in air, to survive and grow in different environmental and geographical habitats, together with high reproductive and competitive capabilities means that “ubiquitous” is among the most common adjectives used to describe these moulds (Horn & Dörner 2002, Bennet 2007, Mehl & Cotty 2013).

Research interests

There are over 35 000 publications and over 400 000 citations from 2011–2021 in the Web of Science (Fig. 7) with the top 10 most cited articles listed in Table 5. Most publications focused on secondary metabolites and diseases associated with *Aspergillus* (Fig. 8).

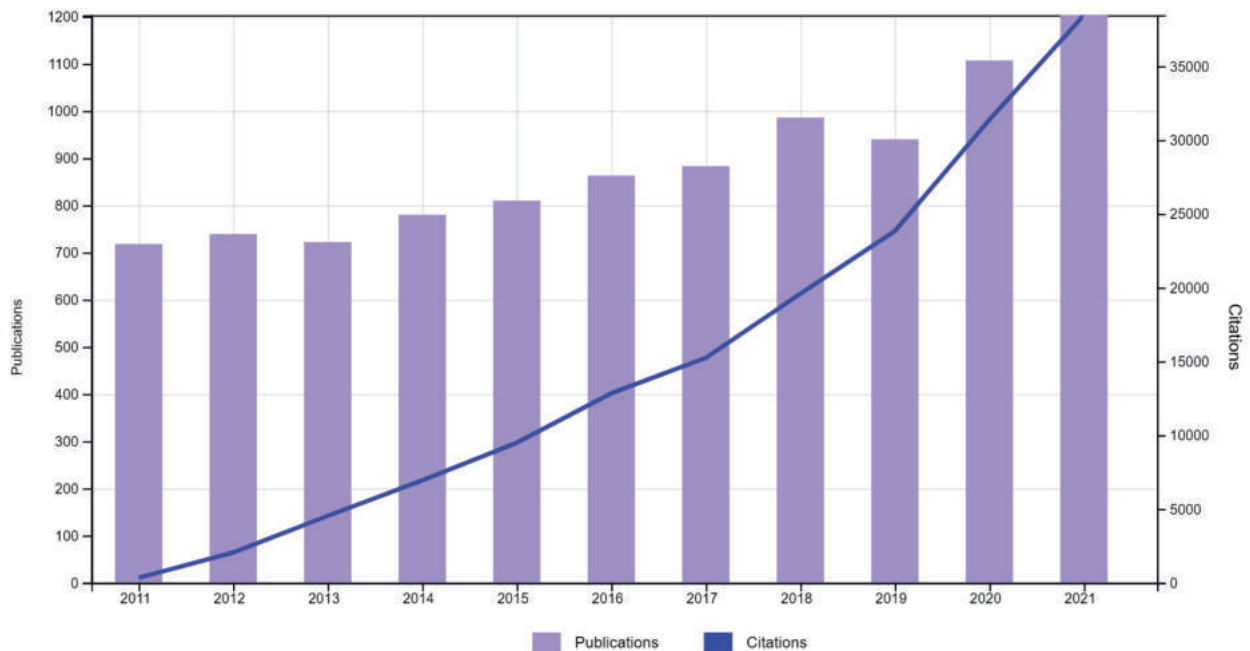


Fig. 7. Trends in research of *Aspergillus* in the period 2011–2021. The figure shows citations for only 10 000 records.

Table 5. Top 10 cited articles related to *Aspergillus* published in the period 2011–2021.

Rank	Article title	No. of citations	References
1	Hidden killers: human fungal infections	2 175	Brown <i>et al.</i> (2012)
2	Practice guidelines for the diagnosis and management of Aspergillosis: 2016 update by the infectious diseases society of America	1 079	Patterson <i>et al.</i> (2016)
3	Immunity to fungal infections	729	Romani (2011)
4	A comprehensive evaluation of normalization methods for Illumina high-throughput RNA sequencing data analysis	655	Dillies <i>et al.</i> (2011)
5	Antifungal drug resistance: mechanisms, epidemiology, and consequences for treatment	624	Pfaller (2012)
6	Impact of mycotoxins on humans and animals	608	Zain (2011)
7	Epidemiology and clinical manifestations of mucormycosis	604	Petrikos <i>et al.</i> (2012)
8	Regulation of fungal secondary metabolism	569	Brakhage (2013)
9	Phylogeny, identification and nomenclature of the genus <i>Aspergillus</i>	557	Samson <i>et al.</i> (2014)
10	Diagnosis and management of <i>Aspergillus</i> diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline	529	Ullmann <i>et al.</i> (2018)

Extrolites

The 467 species described and accepted in *Aspergillus* can produce a very large number of small molecule extrolites, also called secondary metabolites, specialised metabolites or natural products (Samson *et al.* 2014, Frisvad 2015, Frisvad & Larsen 2015, Houbraken *et al.* 2020). While *Aspergillus* spp. share many secondary metabolites (SMs) with *Penicillium* spp., these two genera share many secondary metabolites with *Talaromyces* spp. (Yilmaz *et al.* 2014). Like in other filamentous fungi, the SMs produced by *Aspergillus* species are produced in species specific profiles (Frisvad 2015), and recently it has been shown that profiles of carbohydrate active enzymes (CAZymes) are also species specific in *Aspergillus* and *Penicillium* (Barrett *et al.* 2020).

Important drugs or promising drugs in clinical trials produced by isolates of *Aspergillus* species include lovastatin (= mevinolin = monacolin K) produced by *A. terreus* (Huang *et al.* 2021d), fumagillin produced by *A. fumigatus* (Kornienko *et al.* 2015, Frisvad & Larsen 2016), and the anticancer halimide (= phenylhistin)

produced by *A. calidoustus* (Komieno *et al.* 2015, Aldholmi *et al.* 2020). Many other bioactive potential drug candidates have been found in species of *Aspergillus* (Lee *et al.* 2013).

The most important mycotoxin from *Aspergillus* is the most carcinogenic secondary metabolite known, aflatoxin B₁, and this toxin is produced foremost by species in section *Flavi*: *A. aflatoxiformans*, *A. austwickii*, *A. cerealis*, *A. flavus*, *A. minisclerotigenes*, *A. luteovirescens* (syn. *A. bombycis*), *A. mottae*, *A. nomiae*, *A. novoparasiticus*, *A. parasiticus*, *A. pipericola*, *A. pseudocaelatus*, *A. pseudonomiae*, *A. pseudotamarii*, *A. togoensis* and *A. transmontanensis*, and aflatoxin is of serious consequence for food safety (Varga *et al.* 2011, Frisvad *et al.* 2019, Kjærboelling *et al.* 2020). Aflatoxins and sterigmatocystins are also produced by *Aspergillus* species from other sections that rarely occur in foods, feeds or the built environment (Rank *et al.* 2011). In addition to aflatoxins, many species in section *Flavi* also produce the mycotoxins 3-nitropropionic acid and cyclopiazonic acid, adding to the high toxicity of *A. flavus* and similar species. Many species

in *Aspergillus* subgenus *Nidulantes*, section *Nidulantes* series *Versicolores* can produce sterigmatocystin and these species are common in the built environment. Other important mycotoxins from *Aspergillus* species include ochratoxin A, produced by *A. westerdijkiae*, *A. steynii*, *A. ochraceus* and other species in section *Circumdati* (Visagie *et al.* 2014c), by *A. alliaceus* in section *Flavi* and *A. niger*, *A. welwitschiae* and *A. carbonarius* in section *Nigri* (Abarca *et al.* 1994, Samson *et al.* 2004). *Aspergillus niger* and the closely related *A. welwitschiae*, can in addition, produce fumonisin B₂, B₄ and B₆ (Frisvad *et al.* 2007, 2011, Logrieco *et al.* 2014). The mycotoxin patulin is produced by members of section *Clavati*, most importantly *A. clavatus* (Bergel *et al.* 1943) that can occur in breweries and produce both patulin and cytochalasin E in the barley (LopezDiaz & Flannigan 1997). In addition to ochratoxins, species in *Aspergillus* section *Circumdati* can also produce the mycotoxins penicillic acid, xanthomegnin, viomellein, vioxanthin, avrainvillamide and stephacidin A (Visagie *et al.* 2014c, Mikkola *et al.* 2015).

4. ***Fusarium*** Link, Mag. Ges. Naturf. Freunde Berlin 3: 10. 1809.
Synonyms: Fusisporium Link, Mag. Ges. Naturf. Freunde Berlin 3: 19. 1809.
Selenosporium Corda, Icon. Fung. 1: 7. 1837.
Gibberella Sacc., *Michelia* 1: 43. 1877.
Lisea Sacc., *Michelia* 1: 43. 1877.
Sporotrichella P. Karst., Meddel. Soc. Fauna Fl. Fenn. 14: 96. 1887.
Gibberella subgen. *Lisiella* Cooke & Massee, *Grevillea* 16: 5. 1887.
Lisiella (Cooke & Massee) Sacc., *Syll. Fung.* 9: 945. 1891.
Septorella Allesch., *Hedwigia* 36: 241. 1897.
Ustilaginoidella Essed, *Ann. Bot.* 25: 351. 1911.
Rachisia Linder, *Deutsche Essigind.* 17: 467. 1913.
Stagonostroma Died., *Krypt.-Fl. Mark Brandenb.* 9: 561. 1914.

Classification: Ascomycota, Pezizomycotina, Sordariomycetes, Hypocreales, Nectriaceae.

For decades the genus *Fusarium* has attracted significant attention from researchers from different disciplines, resulting in a long and rather conflictive taxonomic history. Its high relevance derives from its diverse ecology, worldwide distribution, and species richness. It includes some of the most important plant pathogens (Dean *et al.* 2012), common endophytes and occasionally saprobes (Zhang *et al.* 2023a), opportunistic animal and human pathogens (Al-Hatmi *et al.* 2019, Lombard *et al.* 2019b, Song *et al.* 2023), and producers of bioactive secondary metabolites, including mycotoxins (Ibrahim *et al.* 2021).

Fusarium was first described by Link (1809), and characterised by forming elongated, fusoid, multiseptate conidia. Currently, 18 species complexes are recognised in *Fusarium* s. str. using multigenic genealogy, morphology, secondary metabolite data, sexual reproduction and host diversity. Among these, the *Fu. fujikuroi* species complex (SC) (FFSC), *Fu. chlamydosporum* SC (FCSC), *Fu. incarnatum-equiseti* SC (FIESC), *Fu. oxysporum* SC (FOSC), and *Fu. sambucinum* SC (FSAMSC, including the internal *Fu. graminearum* clade) encompass the most relevant species for agriculture, animal and human health, and biotechnology (Crous *et al.* 2021a, 2022).

Laboratory identification of *Fusarium* s. lat. (including the genera *Albonectria*, *Bisifusarium*, *Cyanonectria*, *Fusarium* s. str.,

Geejayessia, *Luteonectria*, *Neocosmospora*, *Nothofusarium*, and *Setofusarium*), mostly rely on molecular characterisation using translation elongation factor (*tef1*) and RNA polymerase II second largest subunit (*rpb2*) markers. Morphological data, such as culture features (colony texture, pigmentation, type of aerial mycelium, presence of sporodochia), sexual morph (ascomata colour, wall thickness, ornamentation, presence and nature of basal stroma), and asexual morph (nature of conidiophores, conidiogenous cells, conidia and chlamydospores), as well as host preference, can be used for species identification (Leslie & Summerell 2006, Crous *et al.* 2021b). Mycotoxin profiling may also be helpful to separate *Fusarium s. str.* from other closely related fusarioid genera as, for instance, trichothecenes, known to be produced by species of *Fusarium s. str.* are generally not detected from other fusarioid genera; while cyclosporins, dihydrofusarin, polyketides neovasipyrone and vasinfectin A have been reported only from *Neocosmospora* species but not from *Fusarium s. str.* (Crous *et al.* 2021a).

Ecological and economic significance

Species of *Fusarium s. lat.* can cause diseases in numerous economically important crops (Afroz *et al.* 2020, Paul *et al.* 2020, Lombard *et al.* 2022), in forests (Hyde *et al.* 2023b), and also infect animals and humans (Chang *et al.* 2006, O'Donnell *et al.* 2009). Plant diseases cause significant economic losses and threaten global food security. They are difficult to eradicate due to elevated resistance or tolerance to fungicides. Similarly, most of the clinically relevant *Fusarium* species are also resistant to currently available antifungal agents and such diseases can be fatal (Al-Hatmi *et al.* 2016). Some of these diseases and infections are summarised below.

Plant diseases

Two main plant diseases, wilt and root rot caused by *Fusarium s. lat.*, result from fungal spores that can remain dormant in the soil or an alternative host for a prolonged period (Dita *et al.* 2018). When a suitable host is introduced to the environment, spores germinate and penetrate the roots. The mycelium invades the plant vascular system by growing through the cortex to the epidermis. Constant production of fungal spores occurs in vascular tissues from where they spread throughout the plant. As a result of vascular tissue blockage, leaves may turn yellow (Dita *et al.* 2018, Arie 2019). In the case of pitch canker and malformation, air-borne spores enter the host through a fresh wound, or the fungus can be transmitted via insects (Fox *et al.* 1991, Dwinell *et al.* 2001). Stress factors such as drought might increase the incidence and severity of diseases as shown in the crown and root rot diseases in asparagus and citrus species (Nigh 1990, Sandoval-Denis *et al.* 2018).

Crown rot is a disease caused mainly by *Fu. culmorum* and *Fu. pseudograminearum*. These species can infect barley, oats, rye and wheat (Kazan & Gardiner 2018, Hagerty *et al.* 2021). *Fusarium* crown rot (and root rot) disease in *Asparagus officinalis* (Elmer 2001) is caused by *Fu. oxysporum s. lat.* and *Fu. annulatum*.

Ear rot disease affects maize ears and kernels, and is one of the most important maize diseases, due to yield decrease and mycotoxin contamination of the grain. It is mainly associated with *Fu. annulatum*, *Fu. subglutinans*, *Fu. verticillioides*, and less frequently with *Fu. culmorum* and *Fu. graminearum* (Duncan & Howard 2010, Oldenburg & Ellner 2015, Lanubile *et al.* 2017).

Wilt disease affects tomato and sweet potato (caused by *Fu. oxysporum s. lat.*), cabbage (*Fu. equiseti* and *Fu. oxysporum s.*

lat.), date palms (by *Fu. oxysporum f. sp. canariensis* and *Fu. oxysporum s. lat.*), oil palms (by *Fu. oxysporum f. sp. elaidis*), and banana (also called Panama disease, by *Fu. odoratissimum*), the latter is considered one of the most destructive banana diseases (Ploetz 2001, Song *et al.* 2004, Liu *et al.* 2017e, Dita *et al.* 2018, Maryani *et al.* 2019, Afroz *et al.* 2020, Paul *et al.* 2020).

Stalk rot and grain mould in sorghum are mainly induced by *Fu. andiyazi*, *Fu. annulatum*, *Fu. beomiforme*, *Fu. nygamai*, *Fu. sacchari*, *Fu. thapsinum* and *Fu. verticillioides*. In stalk rot, *Fusarium* mainly colonises the plant stem, causing tipping and breaking, but it can also interfere with grain formation. In grain mould, *Fusarium* species infect and colonise the grains, causing a reduction in grain size and weight (Leslie *et al.* 2005, Petrovic *et al.* 2009, Mohamed Nor *et al.* 2019).

Bakanae disease is the most important disease of rice caused by *Fusarium* species. *Fusarium fujikuroi* is the main causal agent, but other species of the FFSC, such as *Fu. andiyazi*, *Fu. annulatum*, *Fu. sacchari*, *Fu. subglutinans* and *Fu. verticillioides* have also been reported to be associated with Bakanae symptoms (Ploetz 2001, Amatulli *et al.* 2010, Wulff *et al.* 2010, Hsuan *et al.* 2011, Kim *et al.* 2014). The disease causes abnormal plant development and infected plants either eventually die or lose the ability to produce grain (Kim *et al.* 2014).

Head blight disease, scab or tombstone occurs in wheat and barley heads, and is induced predominantly by *Fu. graminearum*. The disease disrupts the development of kernels and causes discolouration and grain weight loss (McMullen *et al.* 2012).

Pitch canker affects *Pinus* species and is caused by *Fu. circinatum* (Steenkamp *et al.* 2012, Pfenning *et al.* 2014). The fungus can infect the vegetative and reproductive parts of plants. Disease symptoms include wilting and discolouration of leaves, branch dieback, mortality of female flowers and mature cones, damping-off of seedlings and seed deterioration (Wingfield *et al.* 2008).

Malformation of mango refers to abnormal growth of vegetative and reproductive parts of the mango plant caused by *Fu. mangiferae*, *Fu. mexicanum*, *Fu. sterilihyphosum* and *Fu. tuiense* (Britz *et al.* 2002, Otero-Colina *et al.* 2010, Lima *et al.* 2012).

Pokkah boeng occurs in sugarcane and is caused by species of the FFSC, such as *Fu. sacchari*, *Fu. proliferatum* and *Fu. madaense*. Disease symptoms include chlorosis and necrosis of leaves, death of the top of the plant and stalk rot (Costa *et al.* 2019).

Human and animal infections

Fusarium s. lat. contains highly relevant species in human and veterinary medicine, mostly opportunistic agents affecting immunocompromised hosts, commonly involved in keratitis, skin infections, and onychomycosis, and also associated with deep-seated and disseminated, often fatal infections. Clinically relevant fusarioid fungi are distributed in several *Fusarium* species complexes *i.e.*, FCSC, FFSC, FIESC, FOSC, FSAMSC, and also in the closely related genera *Bisifusarium* and *Neocosmospora* (Dignani & Anaissie 2004, Chang *et al.* 2006, O'Donnell *et al.* 2009, 2010).

Mycotic keratitis can be caused by *Fu. fujikuroi*, *Fu. oxysporum s. lat.*, and several species of *Neocosmospora* (*N. falciformis*, *N. gamsii*, *N. keratoplastica*, *N. lichenicola*, *N. metavorans*, *N. petrophila*, *N. solani*, *N. suttoniana* and *N. tonkinensis*) (Chang *et al.* 2006, Walther *et al.* 2021, Boral *et al.* 2018, Oliveira dos Santos *et al.* 2020). A history of ocular trauma is the major predisposing factor for mycotic keratitis caused by these fungi. However, contact lens usage and the presence of primary viral or bacterial eye

infections are also linked to mycotic keratitis (Oliveira Dos Santos *et al.* 2020, Harbiyeli *et al.* 2021, Walther *et al.* 2021). Successful treatment of mycotic keratitis depends on timely diagnosis and appropriate initial therapy. However, in the case of mycotic keratitis and endophthalmitis caused by filamentous fungi, diagnosis may be prolonged and keratoplasty or even enucleation of the infected eye is required (Erdem *et al.* 2018, Hof 2020).

Disseminated fusariosis is mainly caused by species of *Neocosmospora* and *Fu. oxysporum* s. lat. (Hoenigl *et al.* 2021). Immunocompromised individuals are mostly infected through physical trauma or by inhalation of microconidia. The fungi disseminate hematogenously and affect different parts of the body, especially the lungs and sinuses (Nucci *et al.* 2018). These infections are often fatal (Guarro 2013).

Skin infections caused by species of *Bisifusarium*, *Fusarium* s. str., and *Neocosmospora*, can be seen as subcutaneous nodules or necrotic, ulcerated lesions (Gupta *et al.* 2000b). Immunosuppression and traumatic injury are the main predisposing factors for these infections (Tram *et al.* 2020, Khalid *et al.* 2021). Even though these infections can be resolved by applying appropriate antifungal therapy, surgical debridement, skin transplantation and even amputation may be required to prevent further dissemination (Goussous *et al.* 2019). In some cases, patients do not survive due to septicemia or secondary infections (Tram *et al.* 2020, Khalid *et al.* 2021).

Onychomycosis is rarely caused by species of *Bisifusarium*, *Fusarium* s. str. or *Neocosmospora* (Uemura *et al.* 2022). Risk factors for onychomycosis can include climate, age, chronic skin illness, footwear, history of peripheral vascular diseases, diabetes and immunosuppression. Onychomycosis caused by non-dermatophyte species might make systemic dissemination of the fungus easier in case of immunosuppression (Girmeria *et al.* 1992, Gupta *et al.* 2000a).

Species of *Fusarium* s. lat. occasionally cause infections in animals. They can cause opportunistic infections in aquatic animals (Smyth *et al.* 2019, Cafarchia *et al.* 2020, Mallik *et al.* 2020), and insects (O'Donnell *et al.* 2012), keratitis in horses (O'Donnell *et al.* 2016), meningoencephalitis, invasive sinusitis and facial mycetoma

in dogs (Evans *et al.* 2004, O'Donnell *et al.* 2010). Animal diseases associated with toxigenic *Fusarium* species were summarised by Nelson *et al.* (1994). Soil and sand are thought to be the main sources of infections as well as mycotoxins obtained from animal feed (Wu 2007, Sáenz *et al.* 2020).

Research interests

There are 25 152 publications and 363 128 citations from 2011–2021 related to *Fusarium* s. lat. in the Web of Science (Fig. 9) with the top 10 most cited articles listed in Table 6. Most of the publications focused on the impact of mycotoxins on plants, humans and animals, as well as epidemiology, diagnosis and management of infections caused by *Fusarium* species (Fig. 10).

Disease management

Species of *Fusarium* s. lat. that are involved in plant diseases are mostly resistant to fungicides and fumigants. Additionally, many *Fusarium* species are facultative pathogens with a saprobic phase and can survive for long periods in soil and plant debris. Therefore, the main approach to preventing diseases is to increase host resistance. Breeding programs to obtain resistant cultivars, eradication of infected plants and local quarantine procedures to prevent the spread of the disease to unaffected areas are recommended. Farm hygiene procedures such as using disease-free planting materials, and improving soil health to suppress fungal growth and reduce the intensity of the disease are recommended for disease control (Moore *et al.* 2001, Dita *et al.* 2018).

Clinical aspects

Treatment of mycotic keratitis caused by *Fusarium* s. lat. mainly relies on the use of natamycin (5 %) and voriconazole (1 %) (Jiang *et al.* 2020). In the case of unavailability of natamycin, a combination of liposomal amphotericin B and voriconazole has also been shown to be effective (Boral *et al.* 2018). Alternative treatments such as chlorhexidine (0.02 %) eye drops, and collagen cross-linking gave promising results (Zhu *et al.* 2018, Kunt *et al.* 2020, Oliveira Dos Santos *et al.* 2021). High-dose intravenous

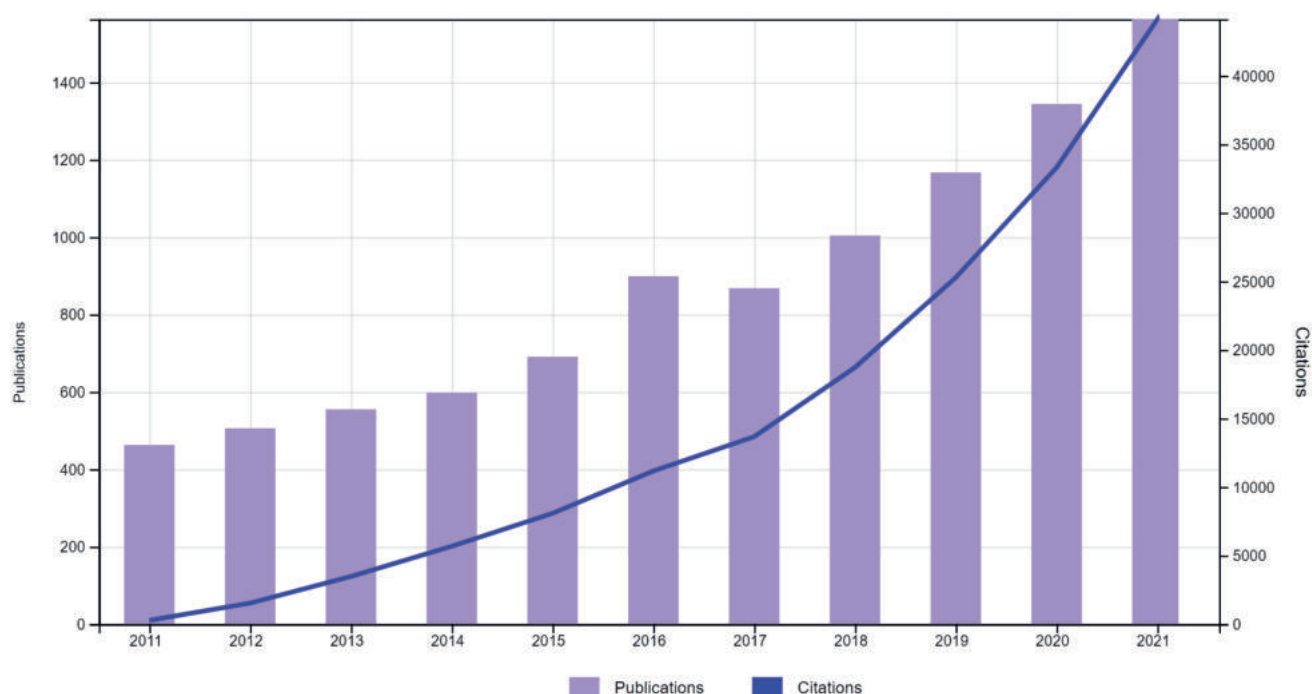


Fig. 9. Trends in research of *Fusarium* in the period 2011–2021. The figure shows citations for only 10 000 records.

Table 6. Top 10 cited articles related to *Fusarium* published in the period 2011–2021.

Rank	Article title	No. of citations	References
1	The top 10 fungal pathogens in molecular plant pathology	1 769	Dean <i>et al.</i> (2012)
2	Mycotoxins: Occurrence, toxicology, and exposure assessment	785	Marin <i>et al.</i> (2013)
3	Impact of mycotoxins on humans and animals	608	Zain (2011)
4	A polycationic antimicrobial and biocompatible hydrogel with microbe membrane suctioning ability	552	Li <i>et al.</i> (2011c)
5	Masked mycotoxins: A review	512	Berthiller <i>et al.</i> (2013)
6	Climate change, plant diseases and food security: an overview	420	Chakraborty & Newton (2011)
7	A unified effort to fight an enemy of wheat and barley: <i>Fusarium</i> head blight	399	McMullen <i>et al.</i> (2012)
8	Occurrence, toxicity, and analysis of major mycotoxins in food	392	Alshannaq & Yu (2017)
9	Current situation of mycotoxin contamination and co-occurrence in animal feed-focus on Europe	392	Streit <i>et al.</i> (2012)
10	Production and characterization of antifungal compounds produced by <i>Lactobacillus plantarum</i> IMAU10014	365	Wang <i>et al.</i> (2012b)

amphotericin B, voriconazole or posaconazole are recommended for the treatment of invasive fusariosis (Pound *et al.* 2011, Hoenigl *et al.* 2021, Khalid *et al.* 2021). Combined therapy is widely used primarily because of the severe nature of infections (Hoenigl *et al.* 2021). Onychomycosis by *Fusarium s. lat.* can be treated with terbinafine and itraconazole, however, recurrence may happen

(Tosti *et al.* 2003). The wide range of antifungal drug resistance among *Fusarium s. str.* and *Neocosmospora* species is one of the main difficulties to control infections by these agents. To overcome this problem, the efficiency of novel antifungal agents, host-pathogen interactions, as well as drug-drug interactions remain relevant for future investigations.

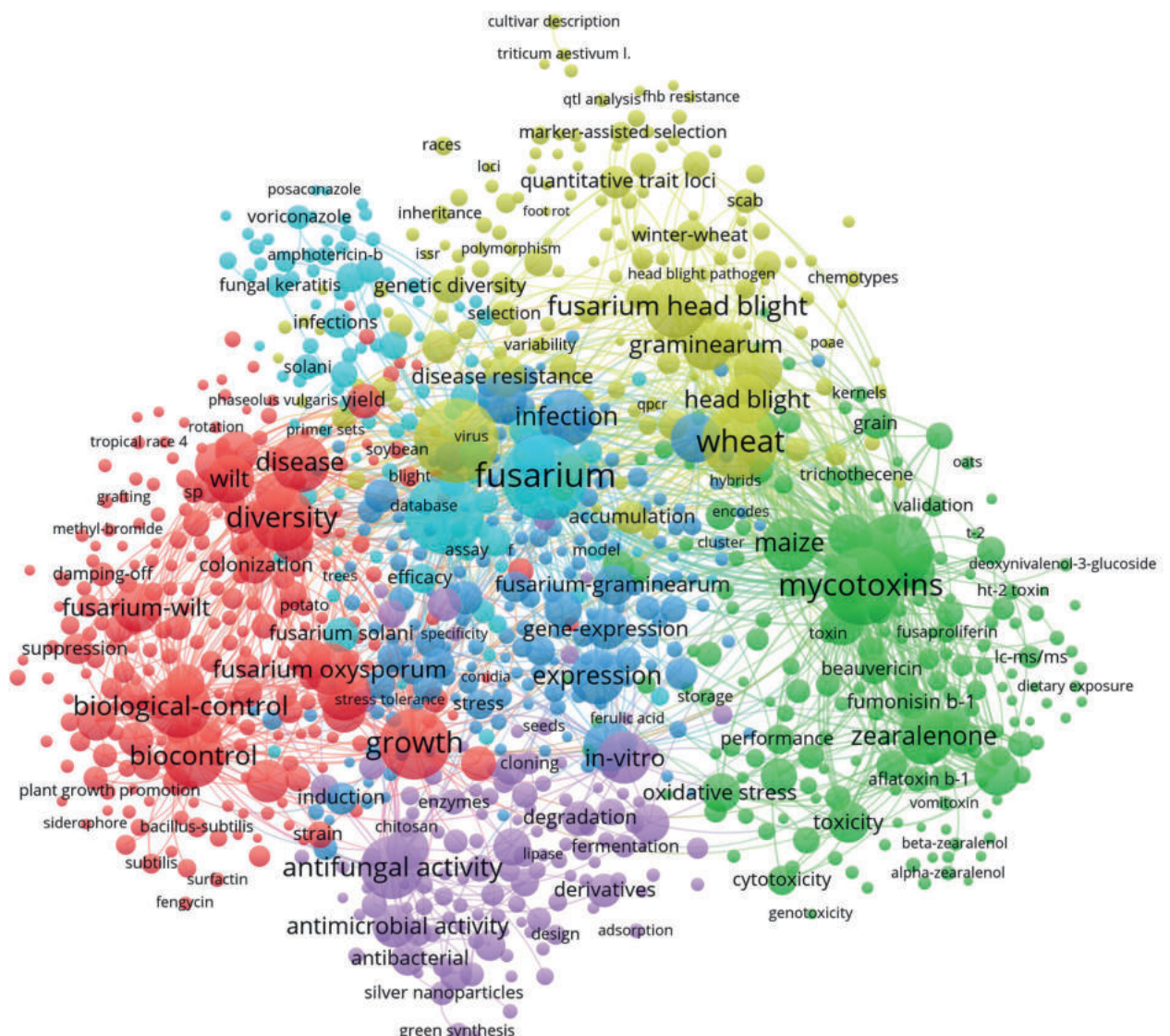


Fig. 10. Network visualisation of keywords of the publications related to *Fusarium*. The larger the text and the circle the more often the subject has been cited.

Toxins

Secondary metabolites of fungi can play a role in fungal pathogenesis, but in the case of mycotoxins, they might also contaminate food and feed produced by these plants. A variety of mycotoxins *i.e.*, trichothecenes, fumonisins, beauvericin, enniatin, fusaric acid, fusarin and moniliformin are known to be produced by species of different *Fusarium* complexes, mainly species from the FFSC, FSAMSC and FIESC (Desjardins 2006, Sy-Cordero *et al.* 2012, Wang & Xu 2012, Proctor *et al.* 2020). Among these mycotoxins, trichothecenes can be produced by many species of the FSAMSC and FIESC. This mycotoxin class includes diacetoxyscirpenol (DAS), T-2 toxin, deoxynivalenol (DON), 3-acetyl-deoxynivalenol (3-ADON), 15-acetyl-deoxynivalenol (15-ADON), and nivalenol (NIV). Trichothecenes were shown to be toxic to animals and humans (Bertero *et al.* 2018, Ji *et al.* 2019, Proctor *et al.* 2020), and can act as virulence factors in the development of plant diseases, such as wheat head blight by *Fu. graminearum* (Proctor *et al.* 1997). The trichothecenes NIV and T-2 have an immunosuppressive effect on humans and animals (Zain 2011, Ji *et al.* 2019). A correlation was found between DON and *Fusarium* head blight disease caused by *Fu. pseudograminearum* (Kazan & Gardiner 2017). Nivalenol is produced mainly by *Fu. graminearum* and *Fu. cerealis* (syn. *Fu. crookwellense*). It can be detected in barley, maize, rice, wheat, and cereal products (Ji *et al.* 2019). Several types of grains have been found to contain T-2 toxin, one of the most acutely toxic trichothecenes. Major producers of the T-2 toxin are *Fu. langsethiae* followed by *Fu. poae* and *Fu. sporotrichioides* (Ji *et al.* 2019). Another important group of mycotoxins are the fumonisins, mainly produced by species of the FFSC, such as *Fu. annulatum* (as *Fu. proliferatum*) and *Fu. verticillioides* (Pitt 2014). Fumonisins have often been isolated from corn and its products and they have severe effects both in humans and animals (Summerell & Leslie 2011). Zearalenone is produced by *Fu. culmorum*, *Fu. graminearum*, and *Fu. sporotrichioides* and can cause estrogenic effects in farm animals (Zain *et al.* 2011). For further reading about the effects of other mycotoxins produced by fusarioid taxa (*e.g.*, fusarins, fusaric acid, moniliformin, enniatins, beauvericins, cyclosporins, vasinfectin-A) see Zain (2011), Bertero *et al.* (2018) and Ji *et al.* (2019).

Taxonomy and phylogeny

As in many other fungal groups, *Fusarium* taxonomy has not been exempted from conflicts and disputes, and also required revision, especially after the wide use of molecular techniques and the One Fungus = One Name declaration (Hawksworth *et al.* 2011, Taylor 2011). Currently, two opposing systems exist, one that argues for a purely cladistic, comprehensive generic definition, without acknowledging any synapomorphies for morphological recognition (Geiser *et al.* 2013, 2021, O'Donnell *et al.* 2020); and a second alternative (as applied here) based on the combination of available genetic, morphological and physiological data to define narrower, morphologically recognisable taxonomic units (Lombard *et al.* 2015, Crous *et al.* 2021a). According to the latter treatment, species previously described in the *Fu. dimerum* SC, *Fu. buxicola* SC, *Fu. staphyleae* SC, *Fu. solani* SC and *Fu. ventricosum* SC were reclassified in the genera *Bisifusarium*, *Cyanonectria*, *Geejayessia*, *Neocosmospora*, and *Rectifusarium*, respectively. Furthermore, three additional genera were recognised within *Fusarium* s. lat., namely *Luteonectria*, *Nothofusarium*, and *Setofusarium*. Further studies using whole genome data and typifying the described taxa will further improve the delimitation of genera in *Fusarium* s. lat. and provide a more stable nomenclature for taxonomists,

plant pathologists, medical mycologists, students, and regulatory authorities.

Despite the divergent and conflicting generic taxonomic approaches, species-level taxonomy has remained more or less stable, with several novelties proposed in later years, mostly helped by the proliferation of molecular phylogenetic studies and recent monographic treatments (O'Donnell *et al.* 2004, 2009, 2010, Lombard *et al.* 2019a, b, Sandoval-Denis *et al.* 2019, Xia *et al.* 2019, Yilmaz *et al.* 2021).

Authors: H. Kandemir, M.M. Costa and M. Sandoval-Denis

5. ***Penicillium*** Link, Mag. Gesell. naturf. Freunde, Berlin 3(1–2): 16. 1809.

Type species: *Penicillium expansum* Link

Classification: Ascomycota, Pezizomycotina, Eurotiomycetes, Eurotiales, Aspergillaceae.

Background

Penicillium was introduced by Link (1809) with three species, *P. expansum*, *P. glaucum* and *P. candidum*. *Penicillium expansum* [CBS H-7082 (neotype); CBS 325.48 = ATCC 7861 = ATHUM 2891 = CCRC 30566 = FRR 976 = IBT 3486 = IBT 5101 = IMI 039761 = IMI 039761ii = MUCL 29192 = NRRL 976 = VKMF-275 (ex-neotype)] For much of its history, classification and identifications were based on morphology, which is notoriously difficult to interpret. Monographic treatments on the genus and its associated sexual morph (teleomorphic) genera *Eupenicillium* and *Talaromyces* included Thom (1930), Raper & Thom (1949), Pitt (1980) and Ramírez (1982). These works typically emphasised the need for standard working methods to delineate and classify species more accurately.

The early days of DNA sequencing and phylogenetic analyses revealed that *Penicillium* was polyphyletic, segregating into two clades defined by *Eupenicillium* and *Talaromyces* (LoBuglio *et al.* 1993, Berbee *et al.* 1995). Peterson (2000) noted that subgeneric classifications based on conidiophore branching patterns were not consistent with phylogenetic clades. Frisvad & Samson (2004) stabilised the taxonomy of *Penicillium* subgenus *Penicillium* in their revision where they introduced the polyphasic species concept characterising species based on morphological, extrolite and DNA sequence data.

The move to single-name nomenclature in the International Code of Nomenclature for algae, fungi, and plants (ICNafp; McNeill *et al.* 2012) allowed the opportunity for Houbraken & Samson (2011) to redefine *Penicillium*. Based on a four-gene phylogeny, they reviewed generic concepts in *Trichocomaceae*, redefined *Penicillium* to include several other genera like *Chromocleista*, *Eupenicillium*, *Eladia*, *Hemicarpaceles*, *Torulomyces*, and *Thysanophora*, adding to already synonymised genera *Aspergillopsis*, *Carpenteles*, *Citromyces*, *Coremium*, *Floccaria*, *Pritzeliiella*, *Hormodendrum* and *Walzia*, and introduced the family *Aspergillaceae* to accommodate for example *Aspergillus* and *Penicillium*. In addition, they showed that *Talaromyces* formed a monophyletic clade with most *Penicillium* subgenus *Biverticillium* species in *Trichocomaceae*. These *Penicillium* names were subsequently transferred to *Talaromyces* by Samson *et al.* (2011). Finally, Houbraken & Samson (2011) introduced a new subgeneric classification dividing *Penicillium* into two subgenera and 25 sections. Visagie *et al.* (2014b) updated the “accepted species

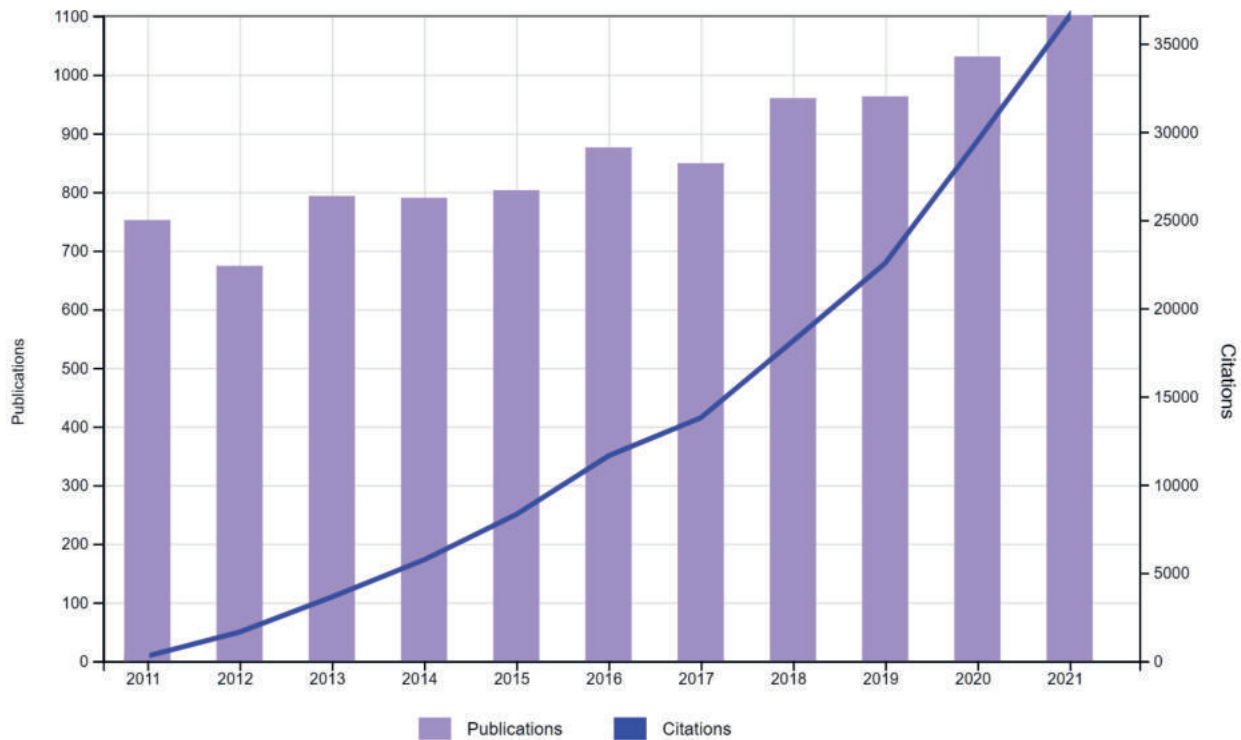


Fig. 11. Trends in research of *Penicillium* in the period 2011–2021.

Table 7. Top 10 cited articles related to *Penicillium* published in the period 2011–2021.

Rank	Article title	No. of citations	References
1	Thoughts and facts about antibiotics: where we are now and where we are heading	555	Bérdy <i>et al.</i> (2012)
2	Curcumin nanoparticles: preparation, characterization, and antimicrobial study	467	Basniwal <i>et al.</i> (2011)
3	Antifungal activity of zinc oxide nanoparticles against <i>Botrytis cinerea</i> and <i>Penicillium expansum</i>	420	He <i>et al.</i> (2011)
4	Identification and nomenclature of the genus <i>Penicillium</i>	393	Visagie <i>et al.</i> (2014b)
5	Occurrence, toxicity, and analysis of major mycotoxins in food	392	Alshannaq & Yu (2017)
6	Current situation of mycotoxin contamination and co-occurrence in animal feed-focus on Europe	392	Streit <i>et al.</i> (2012)
7	Food fermentations: microorganisms with technological beneficial use	377	Bourdichon <i>et al.</i> (2012)
8	Production and characterization of antifungal compounds produced by <i>Lactobacillus plantarum</i> IMAU10014	365	Wang <i>et al.</i> (2012b)
9	Phylogeny of <i>Penicillium</i> and the segregation of <i>Trichocomaceae</i> into three families	316	Houbraken & Samson (2011)
10	50-plus years of fungal viruses	312	Ghabrial <i>et al.</i> (2015)

list”, becoming the first of its kind that incorporated DNA reference sequences. It followed on from previous lists published by Pitt & Samson (1993) and Pitt *et al.* (2000), but in principle, the 354 species accepted all had reference sequences available needed for their identification. This review also proposed standardised working methods specifying growth medium formulations, incubation conditions, PCR and sequencing protocols and suggested the use of *tub* as a secondary identification marker for species identifications. In the following years, many new species were introduced and necessitated an update to the species list in which Houbraken *et al.* (2020) accepted 483 *Penicillium* species (501 accepted on 14 April 2022). A large sequencing effort also means that an almost complete dataset for ITS, *tub*, *cal* and *rpb2* is available for at least the ex-type strain of each species. Building on the proposed subgeneric and sectional classification (Houbraken & Samson 2011), a new series classification was proposed resulting

in *Penicillium* now containing two subgenera, 32 sections and 89 series. More recently, Visagie *et al.* (2024) provided an update on taxonomic revisions and new species published since Houbraken *et al.* (2020), which brought the number of accepted species in *Penicillium* to 535 until 31 December 2022 (currently 598)..

Ecological and economic significance

Food mycology and ecology

Penicillium is one of the most common fungal genera occurring worldwide in a diverse range of habitats, from soil to vegetation, air, indoor environments and various food products. Its species play important and various roles, such as the production of specialty cheeses, Camembert or Roquefort (Thom 1906, Nelson 1970, Giraud *et al.* 2010), and fermented sausages (Ludeman *et al.* 2010, Magistà *et al.* 2017), decomposition of organic materials, causing devastating

rots as pre- and postharvest pathogens on food crops (Samson *et al.* 2010), production of a diverse range of mycotoxins (Frisvad *et al.* 2004). The biggest claim for the genus is the production of penicillin, which revolutionised medical approaches to treating bacterial diseases (Fleming 1929, Thom 1945).

Gorgonzola, it is an important spoilage microorganism of airtight-stored grain and relevant accumulation of roquefortine C in grains (Petersson & Shnürer 1999). Recently five different domesticated populations have been identified by genomic studies in *P. roqueforti* (Dumas *et al.* 2020, Crequer *et al.* 2023). The emblematic species *P. camemberti*, used as a starter species in the production of many cheeses, is regarded as a domesticated species derived from the contaminant species *P. commune* (Giraud *et al.* 2010, Panelli *et al.* 2012). *Penicillia* represents 50 to 90 % of fungal species occurring on dry-cured meat, especially on the surface of ripening products, such as dry-fermented traditional sausages, with the prevalence of *P. nalgioense*, followed by *P. olsonii*, *P. chrysogenum*, *P. commune*, *P. solitum* and a recently described species *P. salami* (Perrone *et al.* 2015, Magistà *et al.* 2017). The halotolerant *P. chrysogenum* was shown in some studies to improve the quality of ham by promoting proteolysis and contributing to the development of the typical ham flavour (Comi & Iacumin 2013), while *P. commune* has been cited as responsible for the phenol acid defect (off-odour). Although most moulds found on cured meat products are non-toxicogenic, strains of *P. nordicum* and *P. verrucosum* are reported for ochratoxin A (OTA) risk in these products, especially *P. nordicum* as a well-adapted species of NaCl-rich and protein-rich food, and represent the most commonly occurring ochratoxigenic species on dry-cured meat products (Iacumin *et al.* 2009, Scaramuzza *et al.* 2015). In addition,

Penicillium species with interesting technological properties were also observed in the fermentation of various table olives products (Bavaro *et al.* 2017). Although the detected level of toxic metabolites of fungi in table olives was very low, they are a potential source of fungal toxic metabolites due to *Penicillium* spoilage (Medina-Pradas & Arroyo-López 2015). Recently, a new species *P. gravinicaei* in sect. *Cinnamopurpurea*, has been reported as being involved in the seasoning of cheese in caves (Anelli *et al.* 2018). Recently *P. brevicompactum* was studied for the first time as a potential pigment producer using submerged fermentation, and it was demonstrated to be a safe source of natural pigments with interesting properties for the food industry (Fonseca *et al.* 2022a).

Research interests

There are 9 592 publications and 130 850 citations from 2011–2021 in the Web of Science (Fig. 11), with the top 10 most cited articles included in Table 7. Most publications focused on taxonomy and secondary metabolites from *Penicillium* (Fig. 12).

Extrolites

Penicillium can produce many small molecule extrolites (Frisvad 2015). Despite this, genome sequencing has shown that it is only 10–20 % of the SMs that can potentially be produced on common laboratory media (Grijseels *et al.* 2016, Nielsen *et al.* 2017).

Important drugs produced by *Penicillium* species include the cholesterol-lowering compactin (= mevistatin) produced primarily by *P. solitum* (Frisvad & Filtenborg 1989, Chakravari & Sahal 2004; under the incorrect producer-name *P. citrinum*), the antifungal griseofulvin produced by *P. janczewskii* and *P. griseofulvum* (Petersen *et al.* 2014), the immunosuppressive mycophenolic acid produced industrially by *P. brevicompactum* (Wu *et al.* 2020b), adenophostin produced by *P. brevicompactum* (Takahashi *et al.* 1993), the antibiotic penicillin produced industrially by *P. rubens* (Houbraken *et al.* 2011a), and the immunosuppressive bredinin produced by *P. brefeldianum* (Iwata *et al.* 1977, Ishikawa *et al.* 1980). Many other bioactive compounds have been isolated from *Penicillium* species (Frisvad & Samson 2004, Frisvad *et al.* 2004, Nicoletti & Trincone 2016) and some may be important future drugs.

Important mycotoxins produced by *Penicillium* species include the nephrotoxin ochratoxin A produced by *P. verrucosum* (Frisvad 1985, Pitt 1987) and *P. nordicum* (Larsen *et al.* 2001), the nephrotoxin citrinin produced by *P. verrucosum*, *P. expansum* and *P. citrinum* (and many other species) (Hetherington & Raistrick 1931, Harwig *et al.* 1973, Houbraken *et al.* 2011b), penicillic acid produced primarily in cereals by species in series *Viridicata* (Frisvad 2018), and patulin produced primarily by *P. expansum* in pomaceous fruits but also by many other species (Frisvad 2018).

Authors: G. Perrone, C.M. Visagie and J.C. Frisvad

6. *Trichoderma* Pers., Neues Mag. Bot. 1: 92. 1794.

Type species: *Trichoderma viride* Pers.

Classification: Ascomycota, Pezizomycotina, Sordariomycetes, Hypocreales, Hypocreaceae.

Background

Trichoderma is a hyperdiverse and cosmopolitan genus with the number of species exponentially increasing since it was first

described in 1794, from one species in 1930, five in 1960, 25 in 1990, 120 in 2010, to ca. 460 in 2022 (Index Fungorum and MycoBank). *Trichoderma* species are most known for biological control properties against phytopathogens and used in biotechnology (e.g., enzyme production) (Fig. 13). In agriculture, *Trichoderma* has also been utilised to promote plant growth, protect and alleviate plants from abiotic stressors (e.g., drought or extreme salinity), and even bioremediate or remove contaminants from soils (Harman *et al.* 2004, Hermosa *et al.* 2012, Khan & Mohiddin 2018). In biotechnology, its applications range from biofuel/bioethanol production, animal feed and textile manufacturing, to nanotechnology (Bhat 2000, Polizeli *et al.* 2005, Dhawan & Kaur 2007, Gajbhiye *et al.* 2009, Fayaz *et al.* 2010, Elamawi *et al.* 2018). The efficacy of this genus comes from the diversity of enzymes and secondary metabolites that it produces. For example, more than 600 enzymes are in BRENDA, The Comprehensive Enzyme Information System (as of April 2022), compared to ca. 1 500 in *Aspergillus*, ca. 900 in *Fusarium*, and 80 in *Cercospora*. In addition, more than 1 000 compounds, including secondary metabolites, have been identified in *Trichoderma* (Zeilinger *et al.* 2016, Zhang *et al.* 2021b).

The number of enzymes and secondary metabolites produced by *Trichoderma* is possibly a result of its ability to colonise different types of substrata and compete against other microorganisms in a variety of natural habitats and ecosystems (Samuels 1996, 2006, Druzhinina *et al.* 2011, Chaverri & Samuels 2013, Contreras-Cornejo *et al.* 2016). For example, *Trichoderma* has been found inhabiting terrestrial and marine/aquatic soils, travelling in air, decomposing plant material, parasitising nematodes and other fungi, growing endophytically in living plant tissues, and, less commonly, causing infections in immunocompromised humans (Garo *et al.* 2003, Rubini *et al.* 2005, Andersen *et al.* 2011, Gazis & Chaverri 2015, Hatvani *et al.* 2019, Ogaki *et al.* 2020, Nafady *et al.* 2022). In addition, *Trichoderma* species have been found in most parts of the world, even in extreme northern and southern latitudes, and from moist tropical or subtropical forests to arid, temperate or boreal ecosystems (Samuels 2006, Kubicek *et al.* 2008, Gazis & Chaverri 2015, Cummings *et al.* 2016, Ogaki *et al.* 2020).

Until recently, it was thought that the majority of *Trichoderma* spp. were saprobes because they were typically found in soils or decaying plant material. However, it is now accepted that its main nutritional mode is mycotrophy, cryptically parasitising or antagonising e.g., fungi in the soil or immersed in decomposing wood, in addition to growing directly on other fungal sporocarps (Kubicek *et al.* 2011, Atanasova *et al.* 2013, Chaverri & Samuels 2013). It has been hypothesised that endophytically, *Trichoderma* acts with similar mechanisms, providing potential benefits to the plant (e.g., abiotic and biotic stress protection and alleviation) (Bailey *et al.* 2006, Qin *et al.* 2016, De Silva *et al.* 2019b) or waiting as latent saprobes for the plant to die (Parfitt *et al.* 2010).

Morphologically, the asexual morph of *Trichoderma* is characterised by complex conidiophores that generally branch in a pyramidal fashion (i.e., the basal branches are longer than those at the tips), with hyaline phialides formed on the exposed fertile branches, and conidia that are usually smooth, rarely ornamented, typically ellipsoidal to nearly oblong, rarely globose, and mostly green or hyaline, rarely yellow. If chlamydospores are formed, they are typically globose to subglobose and are terminal or intercalary. There are some exceptions where the morphology of the conidiophores is much simpler, i.e., acremonium-, gliocladium-, or verticillium-like (e.g., *T. pulvinatum*, *T. virens*, or *T. citrinum*, respectively).

Relatively few species of *Trichoderma* have a known sexual morph (previously known as *Hypocrea*). When known, they form cushion-shaped, brightly or lightly coloured (e.g., whitish, yellowish, ochre to reddish brown, dark green to almost black), fleshy stromata composed of pseudoparenchymatous tissue or highly compacted hyphae, generally up to 5 mm diam, although stromata of some species may be several centimetres wide. Perithecia are fully immersed in the stroma and paraphyses are absent. Asci are cylindrical, normally containing eight, 1-septate ascospores that disarticulate at the septum early in their development, producing 16 part-ascospores. Part-ascospores may be smooth to ornamented (spinulose or warted), generally dimorphic, green or hyaline, and rarely yellowish.

Persoon (1794) originally described *Trichoderma* as a “gasteromycete” and Fries erected *Hypocrea* in 1825. It was several years later that Tulasne & Tulasne (1860) and Brefeld (1891) proved the link between *Trichoderma* and *Hypocrea* by following *Trichoderma* hyphae to the stroma and by isolating ascospores into pure cultures, respectively. Bisby (1939) recognised only one species, *T. viride*. Rifai (1969) was one of the first to suggest the complex taxonomy of the genus, dividing it into nine “species aggregates,” i.e., *T. aureoviride*, *T. hamatum*, *T. harzianum*, *T. koningii*, *T. longibrachiatum*, *T. piluliferum*, *T. polysporum*, *T. pseudokoningii*, and *T. viride*. He regarded each species aggregate as comprising more than one morphologically cryptic species. Rifai also concluded that asexual characters alone might not be useful in its taxonomy.

Before Rifai's critical taxonomic revision, Dingley (1952, 1957) had already published the first “modern” treatments of *Hypocrea* when she described, characterised, and illustrated several species including their asexual morphs. Dingley identified all the *Hypocrea* asexual morphs as being typical of *T. viride*, despite their differences which were evident in her illustrations. Some years later, Doi produced substantial *Hypocrea* monographs, and described many more species from Japan, Papua New Guinea, and South America (e.g., Doi 1966, 1969, 1972, 1975, 1976). In his works, Doi described and illustrated sexual and asexual morphs. By the early 1990s, Bissett was discussing the implications of basing a *Trichoderma* classification on Rifai's species aggregates (Bissett 1991a) because some were narrowly defined species, whereas others could be interpreted as having relatively large numbers of species. For example, he suggested that more than 20 distinct species could be assigned to each of the morphological species *T. hamatum*, *T. koningii*, and *T. viride* (Bissett 1984, 1991a, b, c, 1992). He then revised the taxonomy and recognised five sections: sect. *Hypocreanum*, sect. *Longibrachiatum*, and sect. *Pachybasium*; sect. *Saturnisporium*, and sect. *Trichoderma* (Bissett 1984, 1991a, b, c, 1992). These sections are still used (e.g., Vizcaino et al. 2005, Samuels et al. 2012, Qin & Zhuang 2016, Zhang et al. 2022). More recent significant *Trichoderma* taxonomic treatments include Samuels et al. (1998, 2012), Chaverri & Samuels (2003), Chaverri et al. (2003a), Lu et al. (2004), Overton et al. (2006), Jaklitsch et al. (2006, 2008), Jaklitsch (2009, 2011) and Jaklitsch & Voglmayr (2015). In addition, smaller studies added many new species (e.g., Chaverri et al. 2002, 2003a, 2011, 2015, Chaverri & Samuels 2003, Zhu & Zhuang 2015, Qin & Zhuang 2016b, c, Zhang & Zhuang 2017).

The introduction of DNA sequencing and phylogenetics revolutionised the study of *Trichoderma* systematics. The ITS nrDNA region was the first marker to be used in the late 1990s (Kuhls et al. 1997, Ospina-Giraldo et al. 1998, 1999, Lieckfeldt et al. 1999, Dodd et al. 2000, Lieckfeldt & Seifert 2000, Lee & Hseu

2002). Then, in the mid to late 2000s, additional markers/genes were added (e.g., endochitinase, ECH42; translation elongation factor 1- α , *tef1*; mitochondrial small subunit rDNA; actin, *act*; DNA-directed RNA polymerase second largest subunit, *rpb2*; and calmodulin, *cal*) (Kullnig et al. 2001, Kullnig-Gradinger et al. 2002, Chaverri & Samuels 2003, Chaverri et al. 2003b). This decade was the beginning of the exponential growth in the number of new species described. Still today, the suggested secondary barcodes for *Trichoderma* taxonomy are *tef1* and *rpb2* (Chaverri et al. 2015, Cai & Druzhinina 2021), as it is well-accepted among *Trichoderma* taxonomists that the ITS region is not able to distinguish species. In general, *tef1* gives support to terminal clades and *rpb2* to the backbone of the genus phylogeny (Chaverri & Samuels 2013, Chaverri et al. 2015, Robbertse et al. 2017, Cai & Druzhinina 2021). However, *Trichoderma* systematists still recommend the use of several genes (Chaverri et al. 2015, Cai & Druzhinina 2021). GenBank's database of DNA sequences from *Trichoderma* types is well curated, containing most of the described species (Robbertse et al. 2017, Cai & Druzhinina 2021). A decrease in the cost of genome sequencing has made it possible to produce many *Trichoderma* genomes, with about 85 genomes on the Joint Genome Institute's MycoCosm website (<https://mycocosm.jgi.doe.gov>) and 32 on GenBank. This new genomic data pave the way to discover novel and improved markers for taxonomy and species circumscription. For additional information on taxonomic history and resources for *Trichoderma*, see reviews in Samuels (1996, 2006), Samuels & Hebbbar (2015), and Cai & Druzhinina (2021).

Ecological and economic significance

Trichoderma is ubiquitous and was thought to only inhabit the soil and decomposing plant material (Kubicek et al. 2011, Atanasova et al. 2013, Chaverri & Samuels 2013). In the soil, species of *Trichoderma* may be found as chlamydospores or may be actively parasitising nematodes, oomycetes, or other fungi (Samuels et al. 2002, Rubini et al. 2005, Samuels 2006, Gazis & Chaverri 2015, Nafady et al. 2022). In rotting wood, they may be saprobic or mycotrophic on other fungi immersed in the wood. However, *Trichoderma* spp. have also been found as endophytes in roots, and more recently in stems of some tropical trees in natural forests such as *Coffea*, *Hevea*, *Micrandra*, and *Theobroma* (Samuels et al. 2006, Gazis & Chaverri 2010, Yu et al. 2015c, Kwasna et al. 2016, Skaltsas et al. 2019, Rodriguez et al. 2021). In most cases, the nutritional mode is cryptic because the species are not obviously growing on other fungal sporocarps, and thus, it is challenging to determine if they are mycotrophs or saprotrophs. The ability of some *Trichoderma* species to colonise almost systemically in plant tissues has been demonstrated experimentally *in planta*. For example, Bailey et al. (2006, 2008) and Pujade-Renaud et al. (2019) inoculated planting soil and seeds with endophytic *Trichoderma* spp., i.e., *T. lentiforme*, *T. hamatum*, *T. neotropicale*, and *T. koningiopsis*, and demonstrated that the fungi were able to colonise seedling roots, stems and, in some cases, leaves.

The mycotrophic ability of many *Trichoderma* spp. has made this group one of the most used in the biological control of phytopathogens. The *T. harzianum* complex possibly contains most species used as bio fungicides (Chaverri et al. 2015). Members of this complex have been used to control fungi, e.g., *Alternaria*, *Botrytis*, *Corynespora*, *Curvularia*, *Fusarium*, *Moniliophthora*, *Phyllosticta*, *Rhizoctonia*, *Sclerotinia*, *Sclerotium*, and *Zymoseptoria* (Sempere & Santamarina 2007, John et al. 2010, Crozier et al. 2015, You et al. 2016, Soto et al. 2018, Baiyee et al. 2019,

Kerdraon *et al.* 2019, Silva *et al.* 2021, Navarro *et al.* 2022, Yadav & Ghasolia 2022); oomycetes, *e.g.*, *Pythium* and *Phytophthora* (Benhamou & Chet 1997, Ahmed *et al.* 1999, Chowdappa *et al.* 2013); *Spongopora* (O'Brien & Milroy 2017); and nematodes, *e.g.*, *Meloidogyne* (Sharon *et al.* 2007). The antifungal mechanisms in *Trichoderma* can be divided mainly into direct parasitism, where *e.g.*, fungal cell-wall degrading enzymes are produced; and antibiosis due to the secretion of secondary metabolites (SMs), including volatile organic compounds (VOCs) (Ghorbanpour *et al.* 2018, Köhl *et al.* 2019). Examples of wall-degrading enzymes are proteases, endochitinases, β -1,3-glucanases, polygalacturonases, xylanases, and cellulases (Hermosa *et al.* 2013, Ghorbanpour *et al.* 2018). Secondary metabolites include polyketides, pyrones, terpenes, metabolites derived from amino acids, and polypeptides (Schuster & Schmoll 2010), while volatile compounds are acids, alcohols, aldehydes, esters, ethers, hydrocarbons, ketones and different classes of terpenes (Cruz-Magalhaes *et al.* 2019, Rajani *et al.* 2021).

The benefits of *Trichoderma* are not restricted to mycotrophy but also expand to other plant-beneficial effects such as induced systemic resistance (ISR), plant growth promotion, and abiotic stress protection and alleviation. For example, jasmonic acid, ethylene, hydrophobin-like SSCP orthologues, and higher expression of pathogenesis-related enzymes, such as chitinases, β -1,3-glucanase, and peroxidases, among others, are associated with ISR (Hermosa *et al.* 2012). Additional information on *Trichoderma* and ISR can be found in reviews by Harman *et al.* (2004), Shores *et al.* (2010), Hermosa *et al.* (2012), and Mendoza-Mendoza *et al.* (2018). Some mechanisms involved in plant growth promotion by *Trichoderma* are auxin signalling (Contreras-Cornejo *et al.* 2009) and production and activity of indole acetic acid and ACC deaminase which then manipulate the phytohormone regulatory network (Gravel *et al.* 2007, Hermosa *et al.* 2013). Reviews by Harman *et al.* (2004), Hermosa *et al.* (2012) and Mendoza-Mendoza *et al.* (2018) contain additional information. Involvement of *Trichoderma* in plant resistance to heat, salinity, and drought has been attributed to the production of heat-shock proteins, *n*-acetyl- β -hexosaminidase, Kelch-repeat domain protein related to protein-protein interactions, and alleviation of damage by reactive oxygen species (ROS), water-use efficiency and secretion of phytohormonal analogues (Hermosa *et al.* 2013, Kashyap *et al.* 2017, Mona *et al.* 2017). There is also evidence that secondary metabolites play an important role in plant stress tolerance by coordinately working to bring growth regulation and protecting membranes from ROS (Mona *et al.* 2017, Phukhamsakda *et al.* 2018b, 2019, Macabeo *et al.* 2020, Garcia *et al.* 2022).

Fungal cellulases currently dominate the industrial applications of cellulases, and *T. reesei* is the main industrial source of cellulases and hemicellulases that depolymerise biomass into simple sugars that are then used in biofuels, including ethanol (Lynd *et al.* 2002, Himmel *et al.* 2007, Bischof *et al.* 2016). Cellulases from *Trichoderma* spp. have also been applied in the pulp and paper, textile, and food industries (Schuster & Schmoll 2010). Transformation techniques facilitating the genetic engineering of *T. reesei* became available in the early 1990s (see review in Bischof *et al.* 2016), making this species among the first hosts for the expression of mammalian proteins (Harkki *et al.* 1989). Currently, about 11 % of all enzyme formulations registered by the Association of Manufacturers and Formulators of Enzyme Products are produced using *T. reesei* as the expression host (see review and fig. 1 in Bischof *et al.* 2016). Additional enzymes produced by *Trichoderma* spp. are pectinases, xylanases, chitinases, lipases, proteases, amylases, manganese

peroxidases, and laccases, which are used in various industries such as animal feed, antimicrobial purposes, biorefineries, detergents, detoxification of pollutants, fruit juice clarification, leather, medicine, and waste management (Gautam & Naraian 2020).

Research interests

The number of publications and citations linked to *Trichoderma* is on an upward trend (Fig. 13). The research interests continue to be related to their plant beneficial abilities and industrial enzyme production. There are 9 380 publications and 117 855 citations from 2011–2021 in the Web of Science (Fig. 14), with the top 10 most cited articles included in Table 8. The highest cited article “Induced systemic resistance by beneficial microbes” (Pieterse *et al.* 2014) reviews the beneficial interactions between microbiomes and plants, with a focus on roots. In this review, the roles of *Trichoderma* in induced systemic resistance, modulation of root immunity, and disease-suppressive soils are discussed. The next six articles in the ranking are related to enzyme production for the biofuel and biorefinery industries (Table 8).

Future perspectives

With advances in the sequencing and availability of more than 80 *Trichoderma* genomes, it will now be possible to mine efficiently for bioactive natural products (*e.g.*, secondary metabolites and proteins) and to better understand the ecology of *Trichoderma* (Katz & Baltz 2016, Ziemert *et al.* 2016). For example, genome mining of *T. afroharzianum* T-22 (labelled as *T. harzianum* in the publication of Chen *et al.* 2019a) identified and characterised a cryptic iterative polyketide synthases (IPKS)-containing cluster that synthesises tricholignan A, which has been shown to reduce iron (III) and promote plant growth under iron-deficient conditions (Chen *et al.* 2019a). Chen *et al.* (2019a) used heterologous reconstitution and biochemical studies to unravel the biosynthetic pathway. In addition, genome mining could be used to explore how, why, or what *Trichoderma* is using to become a successful plant symbiont. For example, the detection of sets of genes encoding proteins involved in phytohormone biosynthesis and signalling (Guzmán-Guzmán *et al.* 2019).

Trichoderma could also be an important component in a strategy to produce crops more resilient to the effects of climate change, declining soil fertility, pollutants in soils, fungicide resistance, and phytopathogens (Harman *et al.* 2004, Hermosa *et al.* 2012, Kashyap *et al.* 2017, Mohapatra *et al.* 2022). Innovative research on plant-beneficial *Trichoderma* should also be geared to understand interactions with other inhabitants in the microbiome, including endophytes. For example, there is increasing evidence that *Trichoderma* is a core component in healthy endophytobiomes of some tropical trees in their natural habitats (Gaziz & Chaverri 2015, Skaltsas *et al.* 2019, Aldrich-Wolfe *et al.* 2020, Rodriguez *et al.* 2021, Fonseca *et al.* 2022b). However, little is known about how *Trichoderma* artificially inoculated in plants may interact with other fungi in the plant endo- or rhizosphere. There is evidence of non-target effects (*e.g.*, toxicity and competitive displacement) by several biocontrol species or isolates. For example, Naseby *et al.* (2000) found that the fungistatic VOCs produced by *Trichoderma* cf. *harzianum* also had a negative impact on plant growth at high doses. Szczepaniak *et al.* (2015) inoculated soils with *T. cf. viride* together with a bacterial consortium of 195 species. After one year, only 73 bacterial species were recovered from the consortium,

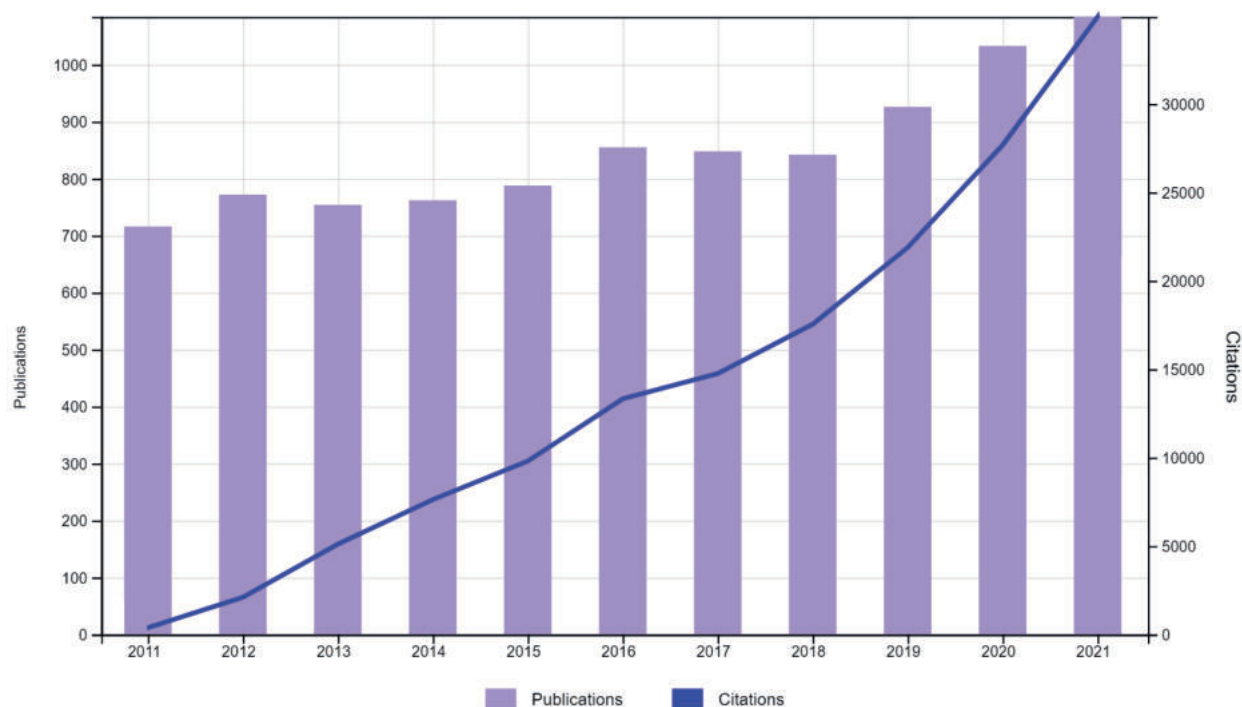


Fig. 13. Trends in research of *Trichoderma* in the period 2011–2021.

suggesting an antagonistic effect. Similarly, other species of *Trichoderma* may reduce the germination of arbuscular mycorrhizal fungal spores (McAllister *et al.* 1994, Brimner & Boland 2003). In contrast, the inoculation of *Trichoderma* spp. in natural soils significantly increased the fungal rhizospheric community (Naseby *et al.* 2000, Cordier & Alabouvette 2009). For more on this topic, see the review by Jangir *et al.* (2019).

The correct identification of *Trichoderma* continues to be problematic. In the Web of Science, more than 4 000 publications identified the species used as *T. harzianum*. It is now accepted among

Trichoderma systematists that *T. harzianum* s. str. is mostly found in temperate regions, especially Europe, and with limited biocontrol potential. Those used in biocontrol studies belong to others in the *T. harzianum* species complex, e.g., *T. afroharzianum*, *T. guizhouense*, *T. lentiforme*, and *T. simmonsii* (Chaverri *et al.* 2015). This problem is aggravated by the fact that many sequences in GenBank are incorrectly identified (pers. obs.), even though the tools for a correct identification by doing BLAST with type sequences and relatively informative secondary barcodes (*tef1* and *rpb2*) are available (Robbertse *et al.* 2017, Cai & Druzhinina 2021). Additionally, even

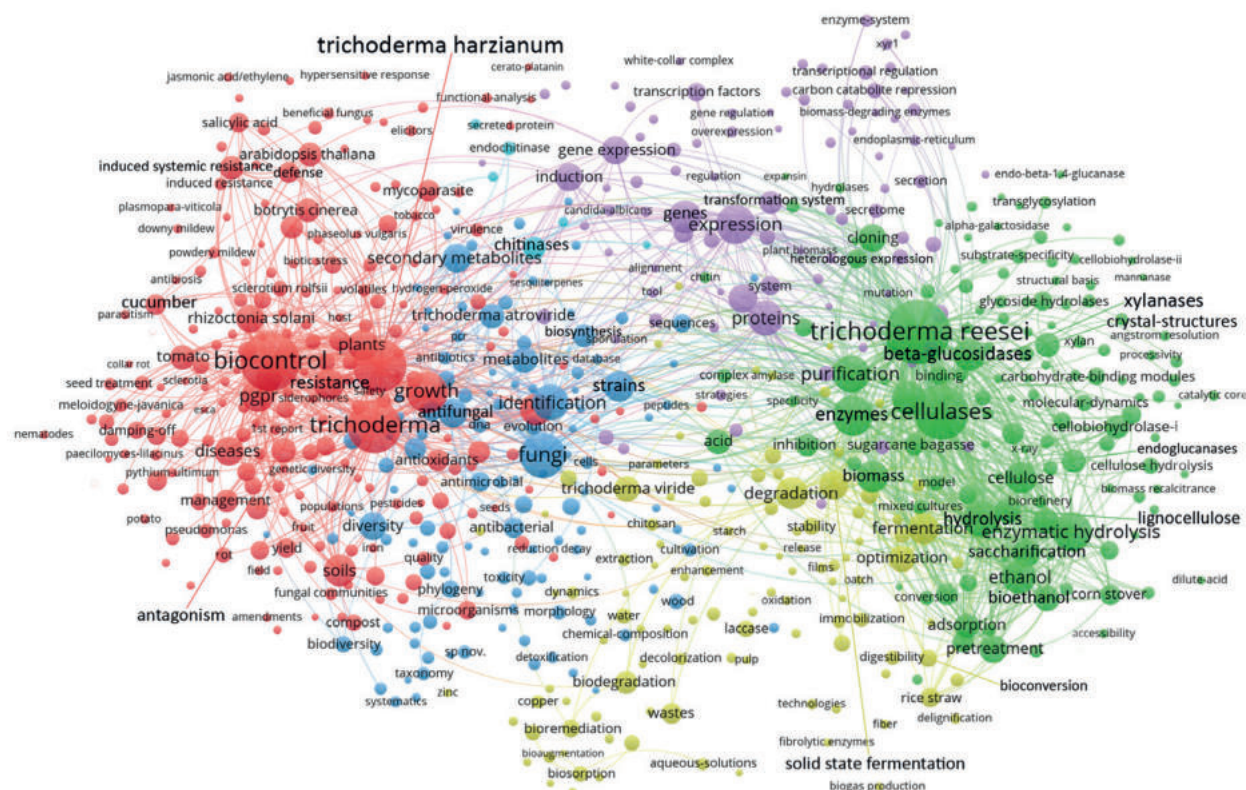


Fig. 14. Network visualisation of keywords of the publications related to *Trichoderma*. The larger the text and the circle the more often the subject has been cited.

Table 8. Top 10 cited articles related to *Trichoderma* published in the period 2011–2021.

Rank	Article title	No. of citations	References
1	Induced systemic resistance by beneficial microbes	1 089	Pieterse <i>et al.</i> (2014)
2	Bioethanol production from agricultural wastes: an overview	901	Sarkar <i>et al.</i> (2012)
3	Expansion of the enzymatic repertoire of the CAZy database to integrate auxiliary redox enzymes	681	Levasseur <i>et al.</i> (2013)
4	The challenge of enzyme cost in the production of lignocellulosic biofuels	607	Klein-Marcuschamer <i>et al.</i> (2012)
5	Novel enzymes for the degradation of cellulose	601	Horn <i>et al.</i> (2012)
6	A review of lignocellulose bioconversion using enzymatic hydrolysis and synergistic cooperation between enzymes – Factors affecting enzymes, conversion and synergy	571	Van Dyk & Pletschke (2012)
7	How does plant cell wall nanoscale architecture correlate with enzymatic digestibility?	515	Ding <i>et al.</i> (2012)
8	Mycorrhiza-induced resistance and priming of plant defenses	439	Jung <i>et al.</i> (2012)
9	Plant-beneficial effects of <i>Trichoderma</i> and of its genes	432	Hermosa <i>et al.</i> (2012a)
10	Fungal cellulases	416	Payne <i>et al.</i> (2015)

deposited whole genomes are incorrectly identified. For example, the genome of *Trichoderma* isolate T6776 was deposited with the name “*T. harzianum*” (Baroncelli *et al.* 2015). When extracting the *rpb2* and *tef1* regions from that genome, the correct identification is *T. afroharzianum* (pers. obs.). More studies on the genomics, ecology, biological control, or biotechnology of *Trichoderma* should include a robust identification. This could be advanced by, for example, increasing the number of *Trichoderma* systematists that can advocate for better taxonomy and provide more solid journal article peer reviews (see review in Cai & Druzhinina 2021, which includes a section on the taxonomy impediment facing *Trichoderma*).

Author: P. Chaverri

7. ***Botrytis*** P. Micheli ex Pers., Neues Mag. Bot. 1: 120. 1794.

Type species: *Botrytis cinerea* Pers.

Classification: Ascomycota, Pezizomycotina, Leotiomyces, Helotiales, Sclerotiniaceae.

Background

Botrytis is a large genus of plant pathogenic hyphomycetes infecting numerous host plants (Holz *et al.* 2007). *Botrytis* species have been reported to attack 596 genera of vascular plants representing over 1 400 plant species (Elad *et al.* 2016). *Botrytis* species are found ranging from tropical and subtropical to cold temperate zones or even deserts (Elad *et al.* 2007, 2016). Diseases by *Botrytis* species cause 10 to 100 billion USD in annual losses worldwide (Boddy 2015). The estimated average cost to control disease is around 18 USD/acre while management costs, depending on the importance of *Botrytis* diseases, can be up to approximately 57 USD/acre (Steiger 2007).

Botrytis was introduced in Von Haller (1768) and *Botrytis cinerea* is the type species. There are species of *Botrytis* that cause significant losses in agriculture, floriculture and horticulture but the most common and most important species is *Botr. cinerea* (Droby & Lichter 2004). *Botrytis cinerea* is responsible for considerable losses in crops, notably bulbous crops, grape vines and legume crops and it causes post-harvest spoilage of many fruits (Droby & Lichter

2004, Jackson 2014). *Botrytis cinerea* was voted by researchers and the scientific community to be the second most important plant pathogen infecting over 200 plant species (Anderson 1924, Beever & Weeds 2004, Capieau *et al.* 2004, Choquer *et al.* 2007, Mirzaei *et al.* 2007, Dean *et al.* 2012). However, *Botrytis cinerea* is also used for the production of sweet dessert wines (Sauternes) (Magyar 2011).

Botrytis species can produce both sexual and asexual morphs. The asexual morph produces copious amounts of conidia, although the survival time of conidia is normally short and depends on environmental conditions (Kerssies *et al.* 1995, Beever & Weeds 2004, Blanco *et al.* 2006, Carisse *et al.* 2012, Nassr & Bakarar 2013, Hahn 2014). The sexual morph of *Botr. cinerea* was first induced under laboratory conditions by Faretra & Antonacci (1987). Sexual morph compatibility is controlled by a single mating-type locus with *mat-1* and *mat-2* alleles (Faretra *et al.* 1988). Sclerotia, large melanised hyphal aggregates, occur with sexual reproduction and they are long-term survival structures (Hahn 2014). In addition, *Botrytis* can produce chlamydospores that can survive periods of up to 3 mo during drought (Urbach 1983).

Intensive research on *Botrytis* has been carried out by Elad *et al.* (2004) with a combination of genome sequences. A comprehensive review of *Botrytis* species diversity was published by Walker (2016) and additional information was provided by Fillinger & Elad (2016). They recognised 74 species records in Species Fungorum (2022). The type species (*Botr. cinerea*) is also an important model organism that has been used for understanding the development of fungicide resistance and plant-pathogen interactions (Staats *et al.* 2005, Amselem *et al.* 2011, Hahn 2014, Valero-Jiménez *et al.* 2019).

Ecological and economic significance

Botrytis species on bulb crops

Several *Botrytis* species are pathogens in bulb crops. *Botrytis squamosa* and *Botr. allii* are the most important fungal diseases pathogenic to onions and are causal agents of botrytis neck rot (Lorbeer 1992, 1997, Lacy & Lorbeer 1995).

Botrytis species in legume crops

Grey mould caused by *Botr. cinerea* is ubiquitously distributed and results in significant production losses. It is also a severe problem for lentils in Australia, India, Syria, and Morocco (Beniwal *et al.*

1993). When conditions are conducive *Botr. cinerea* causes grey mould that can infect the entire crop which is a serious concern in Australia, Argentina, Bangladesh, India, Nepal and Pakistan (Karki *et al.* 1993, Haware 1998, Pande *et al.* 2002). The disease occurs worldwide (Nene *et al.* 1984, Pande *et al.* 2002).

Botrytis on major crops

Botrytis cinerea is a major pathogen causing post-harvest fruit decay in table grapes with infection leading to grape decay during storage (Coertze & Holz 1999, 2002). *Botrytis cinerea* is also present at the harvest stage of tomatoes (Chastagner *et al.* 1978). *Botrytis* species cause post-harvest rots on kiwifruit, which develop mainly during cold storage (Brook 1992). Fruit rot in strawberries is a worldwide problem (Blacharski *et al.* 2001).

Research interests

There are 6 968 publications and 103 497 citations from 2011–2021 in the Web of Science (Fig. 15), with the top 10 most cited articles included in Table 9. Most publications focused on fungal disease caused by *Botrytis cinerea* and disease management (Fig. 16).

Disease management

Rapid conidial germination and infection, with mycelium growth able to occur under a wide range of microclimate conditions, leads to severe disease management problems all around the world (Elad *et al.* 2007). Disease management can use physical technologies to control *Botr. cinerea* modifying several parameters such as absolute and relative gas pressure, sonication, temperature, and UV irradiation (Crisosto *et al.* 2002, De Simone *et al.* 2020). The main physical methods investigated against grey mould decay in table grapes are listed in De Simone *et al.* (2020). Chemical technologies to control *Botr. cinerea* have been widely used but for long-term storage, there may be negative developmental effects in humans and animals (Youssef *et al.* 2015, Carter *et al.* 2015).

Sulphur dioxide (SO₂) is the main method used to control the *Botr. cinerea* spoilage of post-harvest fruit commodities (De Simone *et al.* 2020). Several succinate dehydrogenase inhibitors (SDHIs) have been introduced as chemical alternatives with inhibition rates of 80.1–94.4 % for *Botr. cinerea* in table grapes (Avenot & Michailides 2010, Vitale *et al.* 2016). Levels of CO₂ from 5–10 % failed to prevent the development of *Botr. cinerea* (Uota 1957, Laszlo 1985). The main chemical methods in both liquid and gas forms investigated against grey mould decay in table grapes are listed in De Simone *et al.* (2020). Leroux *et al.* (2002a, b) and Walker *et al.* (2013) have shown effective resistance management of *Botrytis cinerea* (grey mould) by using anti-*Botrytis* fungicides and Hahn (2014) listed major fungicides for use against *Botr. cinerea*. Multisite inhibitors have been used for long-term control but these methods now have low effectiveness when compared to active site-specific compounds (Edgington 1984). The control of *Botr. cinerea* by using microbial resources or antimicrobial compounds of biological origin has been widely accepted as an eco-friendly approach free of synthetic chemicals (Russo *et al.* 2017, Linares-Morales *et al.* 2018, Raveau *et al.* 2020). Research has proved that some raspberry cultivars can be inhibitory to *Botr. cinerea* thereby avoiding latent infections (Williamson & Jennings 1992). These findings suggest that cultivar selection will play a major role in future *Botrytis* management strategies. In addition, *Trichoderma harzianum* and *T. viride* are known for their antifungal effects and have controlled grey mould in field experiments (Mukherjee & Haware 1993, Haware 1998).

Toxins

Culture filtrates of *Botr. cinerea* can be phytotoxic when applied to plant tissue (Rebordinos *et al.* 1996). The toxic compounds were identified as botcinolide (a highly substituted lactone) and botrydial types (a tricyclic sesquiterpene) (Cutler *et al.* 1993, Colmenares *et al.* 2002).

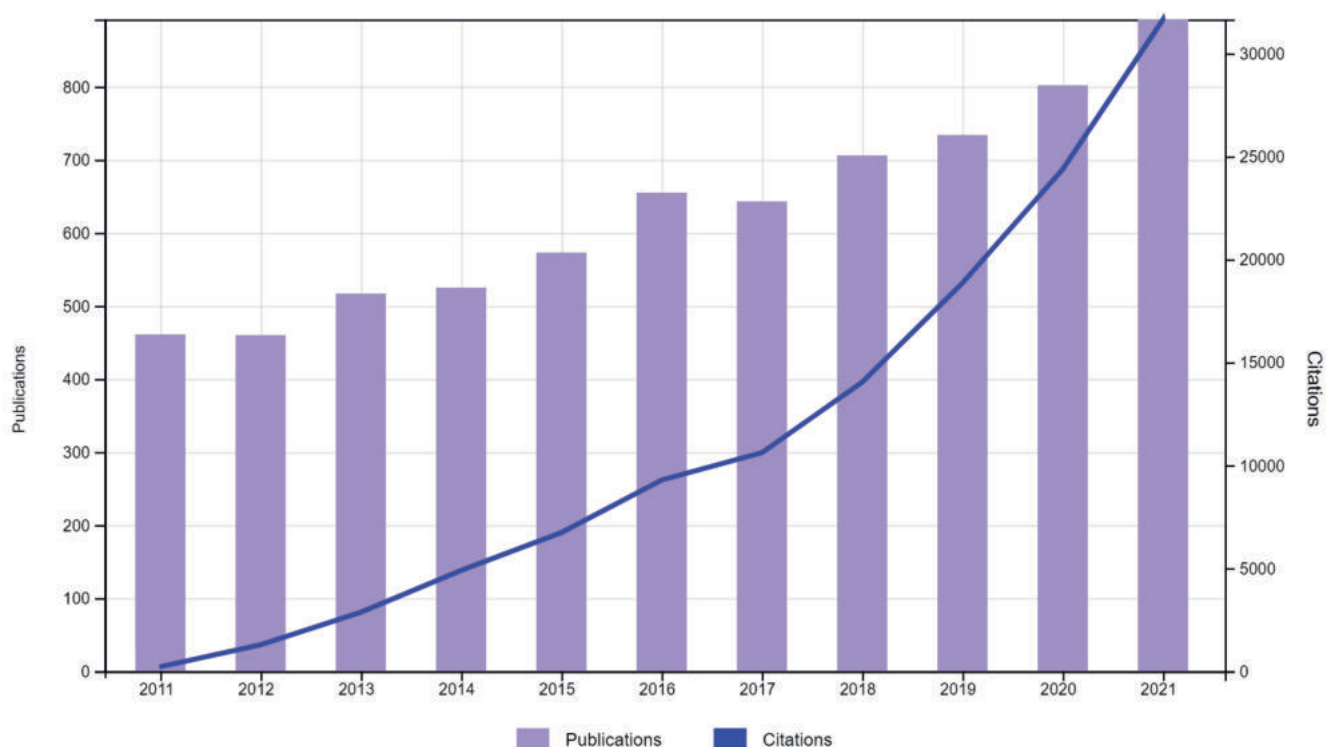


Fig. 15. Trends in research of *Botrytis* in the period 2011–2021.

Table 9. Top 10 cited articles related to *Botrytis* published in the period 2011–2021.

Rank	Article title	No. of citations	References
1	The top 10 fungal pathogens in molecular plant pathology	1 769	Dean <i>et al.</i> (2012)
2	Genomic analysis of the necrotrophic fungal pathogens <i>Sclerotinia sclerotiorum</i> and <i>Botrytis cinerea</i>	603	Amselem <i>et al.</i> (2011)
3	Fungal small RNAs suppress plant immunity by hijacking host RNA interference pathways	594	Weiberg <i>et al.</i> (2013)
4	Phosphorylation of a WRKY transcription factor by two pathogen-responsive MAPKs drives phytoalexin biosynthesis in <i>Arabidopsis</i>	444	Mao <i>et al.</i> (2011)
5	Antifungal activity of zinc oxide nanoparticles against <i>Botrytis cinerea</i> and <i>Penicillium expansum</i>	420	He <i>et al.</i> (2011)
6	Derepression of ethylene-stabilized transcription factors (EIN3/EIL1) mediates jasmonate and ethylene signaling synergy in <i>Arabidopsis</i>	404	Zhu <i>et al.</i> (2011b)
7	Production and characterization of antifungal compounds produced by <i>Lactobacillus plantarum</i> IMAU10014	365	Wang <i>et al.</i> (2012b)
8	The microbial ecology of wine grape berries	360	Barata <i>et al.</i> (2012)
9	Plants send small RNAs in extracellular vesicles to fungal pathogen to silence virulence genes	333	Cai <i>et al.</i> (2018)
10	<i>Arabidopsis</i> WRKY33 is a key transcriptional regulator of hormonal and metabolic responses toward <i>Botrytis cinerea</i> infection	291	Birkenbihl <i>et al.</i> (2012)

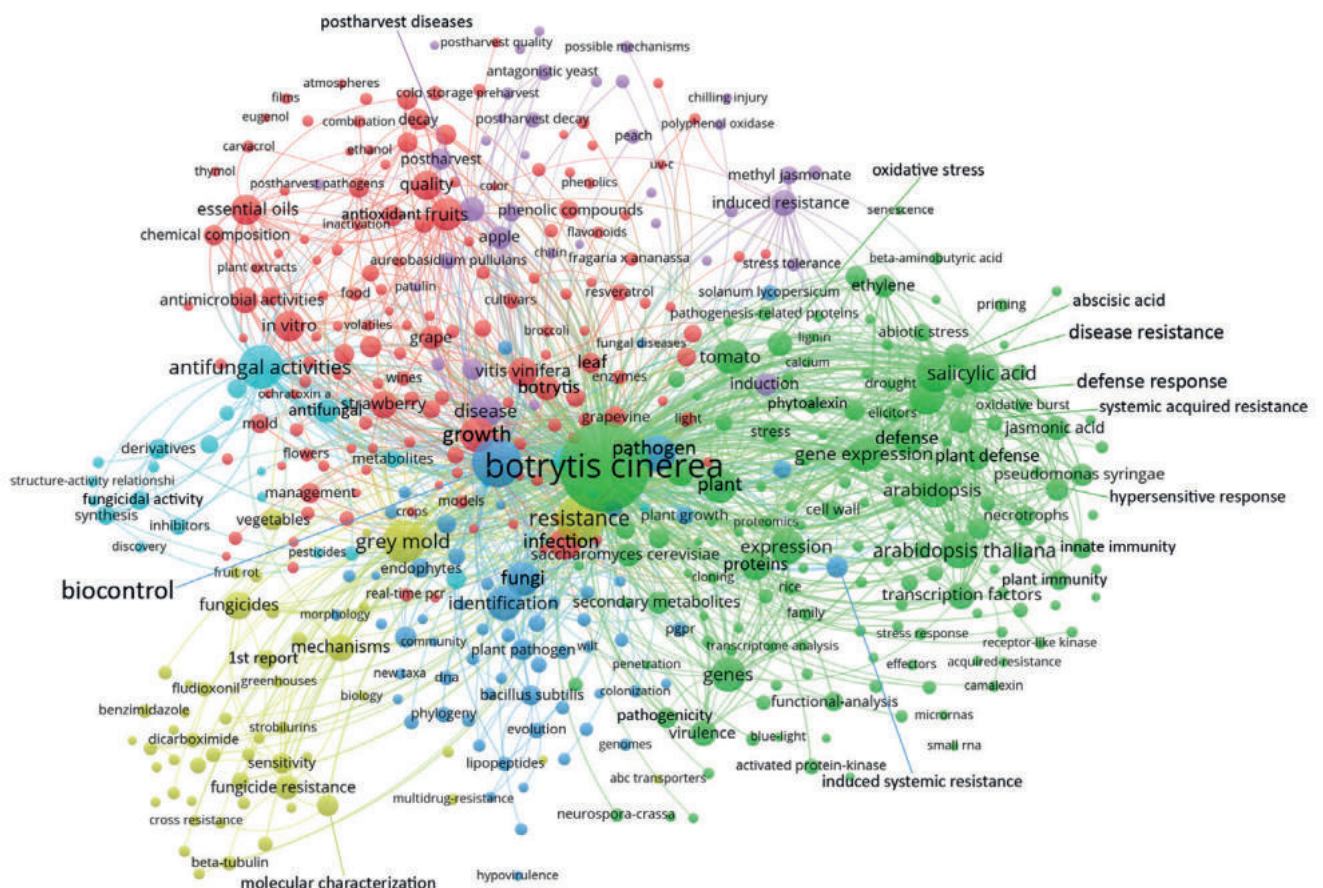


Fig. 16. Network visualisation of keywords of the publications related to *Botrytis*. The larger the text and the circle the more often the subject has been cited.

Taxonomy and phylogeny

Initially, ITS sequences were used for *Botrytis* but showed limited phylogenetic information and could not resolve relationships between species (Holst-Jensen *et al.* 1998). Staats *et al.* (2005) used glyceraldehyde-3-phosphate dehydrogenase (*gapdh*), heat shock protein 60 (*hsp60*) and *rpb2* to build a phylogenetic tree and to test congruence between different phylogenetic trees. Staats *et al.* (2007) used ethylene-inducing proteins 1 and 2 (*nep1* and *nep2*) as phylogenetically informative markers and O’Gorman *et*

al. (2008) mentioned that *gapdh* and β -tubulin (*tub*) genes helped lead to the revival of a long-lost species while *hsp60* was used for uncharacterised endophytic isolates. Khan *et al.* (2013a) used ITS, ribosomal intergenic spacer (IGS), and *gapdh* to identify *Botrytis* species infecting onions. Garfinkel (2021) stated that sequence data for the *gapdh*, *hsp60*, *rpb2*, *nep1* and *nep2* genes are necessary for identifying new species of *Botrytis*.

Author: S. Tibpromma

8. *Pichia* E.C. Hansen, Centbl. Bakt. ParasitKde, Abt. I 12(19): 538. 1904.

Type species: *Pichia membranifaciens* (E.C. Hansen) E.C. Hansen

Classification: Ascomycota, Saccharomycotina, Pichiomycetes, Pichiales, Pichiaceae.

Background

The genus *Pichia* is one of the oldest yeast genera described and studied by pioneers of yeast research. This genus was described by Hansen (1904) for a non-sugar-fermenting yeast, which he had isolated from gelatinous material on the roots of an elm tree attacked by a fungus. Hansen originally described the yeast as *Saccharomyces membranifaciens* in 1888 and later in 1904 transferred it to a newly established genus as *Pi. membranifaciens* (reviewed in Kurtzman 1998). Hansen developed techniques for obtaining and maintaining pure yeast cultures (reviewed in Barnett & Lichtenthaler 2001). The development of these techniques made studies and descriptions of new species possible because isolated pure cultures could be maintained and re-investigated (compared with potential new species). Some strains from the period of the pioneering research 1880–1900 are still available, including Hansen's strain of *Pi. membranifaciens*, which was preserved in several culture collections. In the following years, the number of species described in the genus has increased to 12 in the work by Guilliermond (1920). The authors usually examined characteristics of colony growth (colour, size and shape), growth in liquid culture and the microscopic appearance of vegetative cells and filaments, including ascospores. One peculiar micromorphological characteristic of the genus *Pichia* is the shape of ascospores with a ring or ledge, which is also visible in the light microscope. This shape of spores was called hat-shaped or galeate. The size and position of the ledge varies between species.

Since Hansen established the genus *Pichia*, the definition of this taxon has changed considerably to accommodate the ever-increasing number of new species assigned to the genus. Lodder (1972) listed 35 *Pichia* species in the second edition of the compendium "*The Yeasts, a Taxonomic Study*", whereas Kreger-van Rij (1984) included 56 species in the third edition. Physiological tests, electron microscopy, biochemical comparisons and characteristics of DNA were used to redefine *Pichia*. This resulted in a series of merging and splitting of species with members of *Debaryomyces*, *Hansenula*, *Issatchenkia*, *Komagataella*, *Williopsis*, and *Yamadazyma* (reviewed in Kurtzman 1998). For example, *Hansenula* and *Pichia* were separated from each other primarily based on a single physiological test, the ability to assimilate nitrate as a sole source of nitrogen (reviewed in Kurtzman 1998). The shape of ascospores and the position of the ledge was the characteristic of *Issatchenkia*. *Williopsis*, which was characterised by Saturn-shaped ascospores (spherical with an equatorial ring), was merged with *Hansenula* and later reinstated (reviewed in Kurtzman 1998). The type of coenzyme Q separated *Debaryomyces*, *Issatchenkia* and *Yamadazyma*. Early application of partial rRNA sequences separated several former *Hansenula* species, and new genera *Komagataella*, *Kurashia*, *Nakazawaea*, and *Ogataea* were proposed to accommodate them. Using the percentage of DNA relatedness (DNA-DNA re-association) as a taxonomic marker, Kurtzman (1984) transferred nearly all *Hansenula* species to *Pichia* and separated species with hat-shaped and Saturn-shaped spores between *Pichia* and *Williopsis*, respectively. The concept

of the large genus *Pichia* was retained until broad sequencing of the D1/D2 domains of the large subunit nrRNA gene (LSU) and subsequent analyses convincingly demonstrated that *Pichia* was polyphyletic (Kurtzman & Robnett 1998).

Subsequent multi-gene (Kurtzman *et al.* 2008) and whole-genome (Shen *et al.* 2019) phylogenetic analyses demonstrated that the core of *Pichia* (where the type species *Pi. membranifaciens* is placed) is distantly related to most of the aforementioned genera, except for *Issatchenkia*. Several biotechnologically important species were renamed following the reclassification of *Pichia*. *Hansenula* was abandoned, and the yeast known as *Hansenula anomala* was transferred to a new genus *Wickerhamomyces* (Kurtzman 2011b); *Wickerhamomyces anomalus* was conserved against older nomenclatural synonyms (Daniel *et al.* 2012). *Pichia pastoris* was renamed as *Komagataella pastoris* (Kurtzman *et al.* 2008, Kurtzman 2009, 2011a). Another biotechnologically important species *Candida utilis* appeared to be conspecific to *Pichia jadinii* and the latter was transferred to *Cyberlindnera* as *Cyberlindnera jadinii* (Kurtzman 1998, Kurtzman *et al.* 2008). Yeast genera that include former species of *Pichia* are *Ambrosiozyma*, *Barnettozyma*, *Cyberlindnera* (formerly also *Lindnera*), *Hyphopichia*, *Komagataella*, *Kregervanrija*, *Kurashia*, *Meyerozyma*, *Milleroyzyma*, *Nakazawaea*, *Ogataea*, *Peterozyma*, *Phaffomyces*, *Priceomyces*, *Saturnispora*, *Scheffersomyces*, *Starmera*, *Wickerhamomyces*, *Yamadazyma*, and *Zygoascus* (Kurtzman *et al.* 2008, Kurtzman 2011a). A few phylogenetically related to the genus *Pichia* (*Pichia* clade, Kurtzman *et al.* 2008) asexual yeasts are still classified in *Candida* (Daniel *et al.* 2014).

Ecological and economic significance

Yeasts within *Pichia* have a few remarkable phenotypic traits. Many species are thermotolerant, growing at and above 37 °C (Kurtzman 2011c). *Pichia cecembensis* and *Pi. kudriavzevii* can grow above 40 °C (Kurtzman 2011a). *Pichia kluyveri*, *Pi. kudriavzevii*, and *Pi. membranifaciens* can grow at or below pH 2 and resist high osmotic pressure (Peter *et al.* 2017, Vicente *et al.* 2021). An overview of yeasts in natural habitats is provided in the chapters of the book series *Yeasts in Natural Ecosystems* cited below (Buzzini *et al.* 2017a, b).

Like with many other ascomycetous yeasts, species of *Pichia* can be found on substrates visited or modified by insects. Many *Pichia* species have been reported to be associated with slime fluxes of trees (Phaff & Starmer 1987, Peter *et al.* 2017). However, most of these species were reclassified and transferred to other genera *Barnettozyma*, *Cyberlindnera*, *Kodamaea*, *Komagataella*, *Meyerozyma*, *Milleroyzyma*, *Ogataea*, and *Wickerhamomyces* (Peter *et al.* 2017), and only two species, *Pi. exigua* and *Pi. scutulata* remained in the genus (Kurtzman 2011c). Rotting tissues of cacti and fruits harbour a diverse community of yeasts (Ganter *et al.* 2017, Peter *et al.* 2017). *Pichia cactophila* is a ubiquitous cactophilic yeast, whereas several other species, *Pi. barkeri*, *Pi. cephalocereana*, *Pi. deserticola*, *Pi. eremophila*, *Pi. heedii*, and *Pi. insulana* have a narrow geographic (and host) distribution range (Ganter *et al.* 2017, Yurkov 2017). Several former *Pichia* species, presently classified in *Starmera* and *Yamadazyma*, also inhabit decaying cactus tissues (Ganter *et al.* 2017). Ripe and decaying fruits attract many insects that vector yeasts, including *Pi. cecembensis*, *Pi. nakasei*, *Pi. membranifaciens*, *Pi. kudriavzevii*, and *Pi. occidentalis* (Kurtzman 2011c, Ganter *et al.* 2017). Some species were also found in rotting wood (Cadete *et al.* 2017). Several previously reported insect-associated *Pichia* spp. are now classified

in the genera *Cyberlindnera*, *Kuraishia*, *Meyerozyma*, *Millerozyma*, *Ogataea*, *Scheffersomyces*, *Starmera*, and *Wickerhamomyces* (Blackwell 2017). A few species, including *Candida californica*, *C. pseudolambica*, *Pi. kluyveri*, *Pi. membranifaciens*, and *Pi. occidentalis* are associated with insect larvae (Scheidler *et al.* 2015, Steyn *et al.* 2016, Becher *et al.* 2018, Dmitrieva *et al.* 2021, Cho & Rohlf 2023). Though ascomycetous yeasts are not abundant on plant surfaces, *Pi. kudriavzevii* and *Pi. manshurica* were reported as inhabitants of this substrate (Limtong & Kaewwichian 2015, Limtong & Nasanit 2017, Opolente *et al.* 2019). Aquatic habitats, marine and freshwater, including tap water, house appliances and wastewater, harbour the following species: *Pi. fermentans*, *Pi. kluyveri*, *Pi. kudriavzevii*, and *Pi. occidentalis* (Babič *et al.* 2017, Hagler *et al.* 2017, Libkind *et al.* 2017). Two species *Pi. kudriavzevii* and *Pi. terricola* were isolated from migratory birds (Moschetti *et al.* 2017), but this is not the primary substrate for the two species. Most soil-borne yeasts are basidiomycetes (Yurkov 2018) but the ascomycetous *Pi. fermentans*, *Pi. kluyveri*, *Pi. membranifaciens*, and *Pi. terricola* were reported from soils, particularly agricultural, like orchards (Vadkertiová *et al.* 2017). Other common soil species belong to genera where former *Pichia* species have been placed, namely *Barnettozyma*, *Cyberlindnera*, *Meyerozyma*, and *Wickerhamomyces* (Yurkov 2018).

Surfaces of berries and fruits harbour ascomycetous yeasts that multiply with fruit ripening following the increasing availability of sugars coming through the cuticle. Some of these yeasts later end up in fruit juice or wine. Yeast proliferation may have a negative impact on the quality of grapes. For instance, sour rot of grapes (leaking juice from grape berries and distinctive vinegar smell) is caused by several filamentous fungi and yeasts that are transmitted to berries by insects, e.g., wasps and drosophila flies. In addition to *Metschnikowia* species that are commonly associated with sour rot, *Pi. kudriavzevii*, *Pi. membranifaciens*, and *Pi. kluyveri*, are believed to contribute to this fruit disorder (Barata *et al.* 2012).

Pichia fermentans (syn. *Candida lambica*), *Pi. kluyveri*, *Pi. manshurica*, *Pi. membranifaciens* (syn. *C. valida*), *Pi. occidentalis* (syn. *C. sorbosa*), *Pi. terricola*, and *Candida californica*, which is phylogenetically placed in the *Pichia* clade, were named among largely aerobic non-*Saccharomyces* yeasts in grape must and wine fermentations (Jolly *et al.* 2014). Formerly classified in the genus *Pichia*, *Meyerozyma guilliermondii* and *Wickerhamomyces anomalus* also occur on grapes and in wine. These yeasts are present in grape must and the initial stages of spontaneous wine fermentations. Some of these yeasts may survive in later stages of fermentation thanks to higher ethanol and acid tolerance. Because of predominantly aerobic growth and poor fermentation capabilities, these yeasts can be used in the production of low-alcoholic wines (Jolly *et al.* 2014, Vicente *et al.* 2021). *Pichia kluyveri* is one of the most frequently used species to produce beverages with reduced alcohol concentration (Vicente *et al.* 2021). This yeast has also been successfully employed in beer, cider, durian, and tequila fermentations (Gibson *et al.* 2017, Capece *et al.* 2018, Sannino *et al.* 2019, Vicente *et al.* 2021). Owing to the limited ability to ferment glucose, this yeast produces a number of flavour compounds (e.g., fruity esters and higher alcohols) through modification of hop compounds (Capece *et al.* 2018).

Yeast metabolites largely affect wine properties such as taste, aroma and colour. Co-fermentation of wine with *Saccharomyces cerevisiae* and *Meyerozyma guilliermondii* may improve colour stability (reviewed in Jolly *et al.* 2014). Ferments produced by yeasts, e.g., beta-glucosidases from *Pichia terricola* and *Wickerhamomyces anomalus*, can release bound volatile

compounds and have a positive effect on wine quality. Esters, higher alcohols, glycerol and acids produced by yeasts during wine fermentation also influence its sensory quality, either positively or negatively (off-flavour). *Pichia kluyveri* can produce substantial amounts of higher alcohols, esters (Méndez-Zamora *et al.* 2020) and volatile thiols, compounds that give a typical character to some grape varieties, like Sauvignon Blanc (reviewed in Jolly *et al.* 2014). Mixed fermentations with *Saccharomyces cerevisiae* and *Pichia fermentans* produced wines with increased concentrations of some volatile compounds and polysaccharides, improving both wine taste and body (reviewed in Jolly *et al.* 2014). Wine spoilage through the production of compounds negatively changing the taste or aroma (off-flavour) is a major concern for winemakers. Yeasts of the genus *Pichia* were reported to have both positive and negative impacts on wine spoilage. *Pichia manshurica* and *Pi. membranaefaciens* release compounds which could produce off-flavours and odours (Perpetuini *et al.* 2020).

Yeasts of the genus *Pichia* do not belong to prominent spoilage yeasts in the wine industry. On the contrary, these yeasts were used for biological control of spoilage yeasts. Several species such as *Pi. cactophila*, *Pi. eremophila*, *Pi. fermentans*, *Pi. kluyveri*, *Pi. kudriavzevii*, *Pi. manshurica*, *Pi. membranifaciens*, *Pi. occidentalis*, *Pi. scutulata*, and *Pi. terricola* produce antimicrobial compounds known as killer toxins, small proteins encoded by selfish extrachromosomal DNA or RNA virus-like particles (Klassen *et al.* 2017). The ability to secrete killer toxins is strain-specific. Not only yeasts are sensitive to killer toxins. Other target organisms include filamentous fungi, bacteria and protozoa that may compete in certain natural habitats with the killer yeast (Klassen *et al.* 2017). Toxins of *Pi. kluyveri* and *Pi. membranifaciens* have been demonstrated to be active against a wide variety of food and beverage spoilage yeasts, including *Brettanomyces bruxellensis*, but also to occasionally inhibit some *Saccharomyces* strains in wine (Klassen *et al.* 2017, Vicente *et al.* 2021). Formerly classified in *Pichia*, *Babjeviella inositovora*, *Millerozyma acaciae*, *Millerozyma farinosa*, and *Wickerhamomyces anomalus* possess well-characterised killer toxins. Other frequently mentioned in the literature as *Pichia* spp. killer yeasts include *Cyberlindnera jadinii*, *Kodamaea ohmeri* and *Komagataella pastoris* (Klassen *et al.* 2017).

Among opportunistic human pathogens, *Pichia kudriavzevii* is the fifth most common cause of candidemia (Cooper 2011) and responsible for about 1–6 % of yeast infections in humans (Stavrou *et al.* 2019). This yeast is also known under the names *Issatchenkia orientalis* and the former asexual morph name, *Candida krusei*. Treatment of infections caused by this yeast can be problematic due to the species showing intrinsic resistance to fluconazole, the most used antifungal drug (Stavrou *et al.* 2019, Jaimu *et al.* 2021). Although this dimorphic ascomycetous yeast is widespread in natural and anthropogenic sources (see above) and is found in healthy individuals (Inacio & Daniel 2017), *Pi. kudriavzevii* can cause life-threatening infections in immunocompromised patients, including persons with traumatic injuries and in surgical care (Jaimu *et al.* 2021). Genome sequences of 30 *Pi. kudriavzevii* strains were highly similar, suggesting that environmental, industrial, and clinical strains are not genetically distinct (Douglass *et al.* 2018). Another clinically relevant *Pichia* species are *Pi. norvegensis* and *Candida inconspicua*, which are phylogenetically placed in the genus *Pichia* and closely related to *Pi. cactophila* (Kurtzman 2011a, Lachance *et al.* 2011). The two species are difficult to differentiate using conventional biochemical markers and *C. inconspicua* was probably mistaken for *Pi. norvegensis* (Mixão *et al.* 2019). Although infections caused by these fluconazole-resistant yeasts are rare

(Stavrou *et al.* 2019), a 10-fold increase of *C. inconspicua* cases in HIV patients has been reported (Mixão *et al.* 2019).

Research interests

There are 7 969 publications and 102 697 citations from 2011–2021 in the Web of Science (Fig. 17), with the top 10 most cited articles included in Table 10. Fermentation (natural, industrial) and research on yeast physiology (e.g., pathways and their regulations) received substantial attention from researchers during the last decade. Yeast biotechnology remains the focus of many studies on enzymes, accumulation of lipids for biofuel production and growing yeast biomass on a variety of agricultural and industrial waste substrates (Fig. 18). The composition, dynamics and interactions of yeast communities in natural and artificial environments is an important topic for the food industry and winemaking, as reflected in the network visualisation of keywords (Fig. 18). The range of applications includes biocontrol of spoilage using antagonistic interactions of yeasts using killer toxins and co-fermentation with mixed starter cultures, and the effects on the final product.

Pichia fermentans (also known as *Candida lambica*) has been isolated from a variety of foods and fruit juices. This yeast is a spoilage organism of orange juice and brined green olives (reviewed in Kurtzman 2011c). The species has been successfully used for biocontrol of brown rot of apples. Only a few human infections caused by *Pi. fermentans* are known (Pfaller *et al.* 2004, Vervaeke *et al.* 2008).

Pichia kluyveri is common in natural fermentations of agricultural products such as coffee beans (Kurtzman 2011c). This yeast is used to produce low-alcoholic beer, wine and other beverages (see above). Some strains of the species can grow at 37 °C, but the species is not considered to be clinically relevant. A single strain of *Pi. kluyveri* was isolated from an oral lesion of a cancer patient (Aslani *et al.* 2018).

Pichia kudriavzevii (also known as *Candida krusei* and *Issatchenkia orientalis*) is widely distributed in nature (see above). This yeast is also frequently encountered in natural fermentations, like cocoa and cassava starch (e.g., Daniel *et al.* 2009). The species was reported among biotechnology-relevant oleaginous yeasts for biodiesel production from cheap substrates. As noted above, *Pi. kudriavzevii* is also a common clinical isolate.

Pichia manshurica is common in natural fermentations, including rotting plant material (Kurtzman 2011c). Kurtzman (2011b) indicated that past ecological studies that reported the occurrence of *Pi. membranifaciens* may have also included *Pi. manshurica*, due to high phenotypic similarity of the two species. The species was reported among biotechnology-relevant oleaginous yeasts for biodiesel production from cheap substrates. The clinical importance of *Pi. manshurica* is unknown but the species can grow at 37 °C. *Pichia membranifaciens* is widespread in nature (see above) but shows a limited spectrum of assimilated carbon sources (Kurtzman 2011c). This yeast is commonly found in rotted fruits and fermented beverages (e.g., Kombucha), but is also regarded as a food and beverage spoilage organism (Kurtzman 2011c). Because this species does grow at 37 °C, its clinical importance is unlikely. This yeast is promising for the conversion of biodiesel-derived waste (Chatzifragkou *et al.* 2011). Several asexual species phylogenetically related to *Pichia* are still classified as *Candida* spp. (Lachance *et al.* 2011), e.g., *C. californica* (fruits and drosophila flies), *C. ethanolica* (fodder yeast grown on ethanol), *C. inconspicua* (Italian cheese), and *C. pseudolambica* (plants, insects).

In addition to the already mentioned applications and properties of species of *Pichia*, the below-mentioned yeasts significantly contributed to the citations to the genus *Pichia*. Many publications focused on the genetic manipulation and tools for the expression of proteins in *Komagataella pastoris* and related species, also known as the *Pichia pastoris* model. This model is widely used to produce proteins of medical interest, like antibodies and antimicrobial peptides.

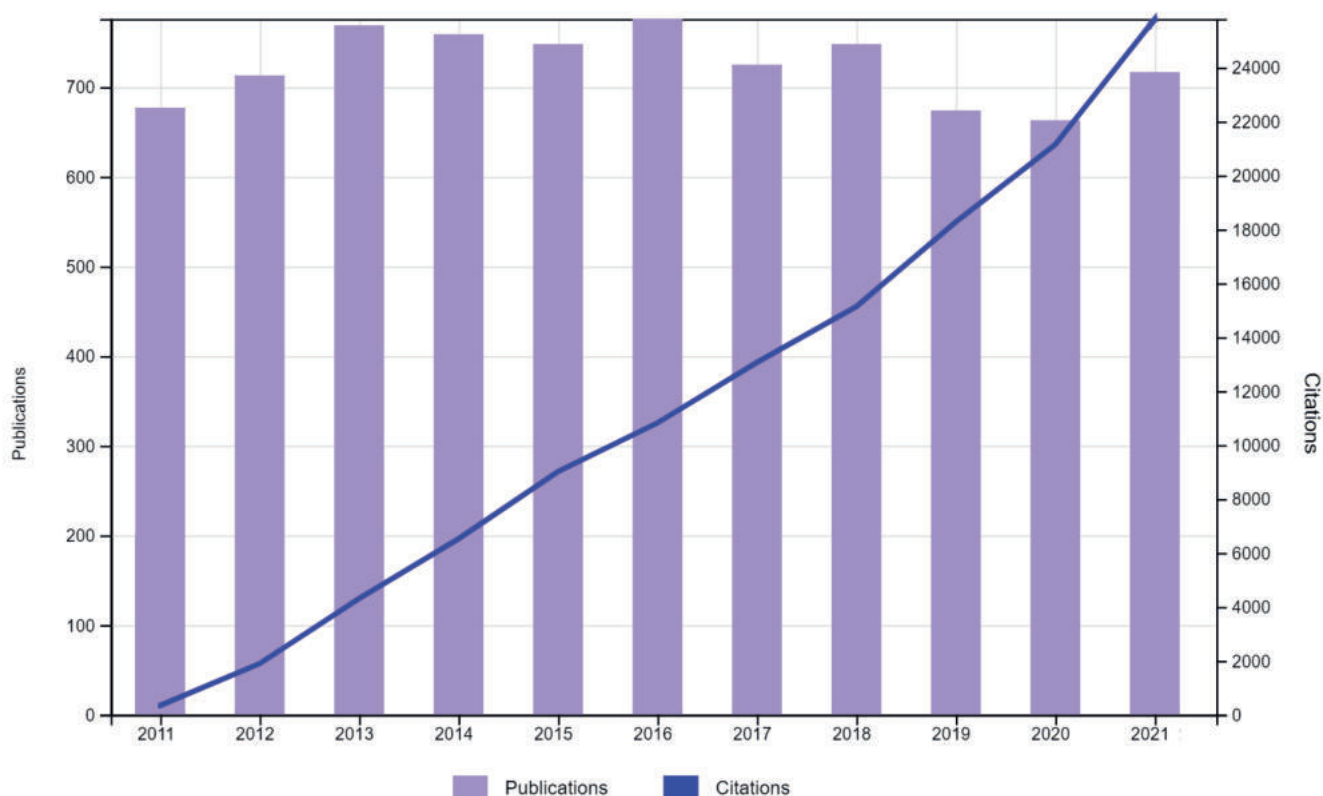


Fig. 17. Trends in research of *Pichia* in the period 2011–2021.

Table 10. Top 10 cited articles related to *Pichia* published in the period 2011–2021.

Rank	Article title	No. of citations	References
1	Not your ordinary yeast: non- <i>Saccharomyces</i> yeasts in wine production uncovered	465	Jolly <i>et al.</i> (2014)
2	The microbial ecology of wine grape berries	360	Barata <i>et al.</i> (2012)
3	Microbial xylanases: engineering, production and industrial applications	268	Juturu & Wu (2012)
4	Oral mycobiome analysis of HIV-infected patients: identification of <i>Pichia</i> as an antagonist of opportunistic fungi	204	Mukherjee <i>et al.</i> (2014)
5	Biotechnological conversions of biodiesel derived waste glycerol by yeast and fungal species	203	Chatzifragkou <i>et al.</i> (2011)
6	Advances in recombinant antibody manufacturing	201	Kunert & Reinhart (2016)
7	Mechanistic insights into selective autophagy pathways: lessons from yeast	195	Farre & Subramani (2016)
8	Production of recombinant proteins by yeast cells	182	Çelik & Çalık (2012)
9	Antimicrobial and probiotic properties of yeasts: from fundamental to novel applications. <i>Frontiers in microbiology</i>	154	Hatoum <i>et al.</i> (2012)
10	A double WAP domain-containing protein Es-DWD1 from <i>Eriocheir sinensis</i> exhibits antimicrobial and proteinase inhibitory activities	153	Li <i>et al.</i> (2013b)

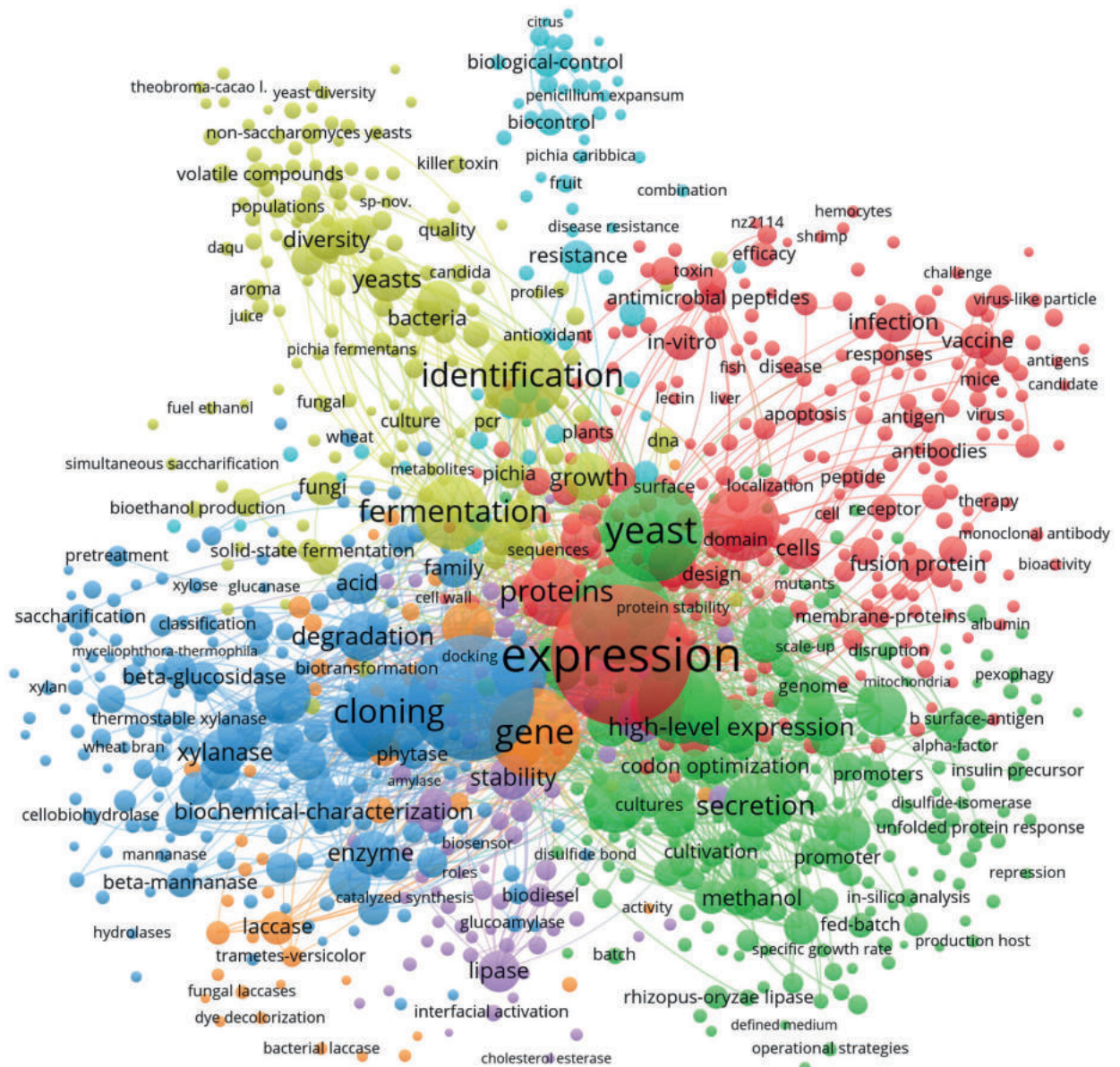


Fig. 18. Network visualisation of keywords of the publications related to *Pichia*. The larger the text and the circle the more often the subject has been cited.

Selected former *Pichia* species

Komagataella pastoris (formerly *Pichia pastoris*) has become a highly successful system for the expression of heterologous genes. A program to convert abundant methanol to a protein source for animal feed that started in the 1960s developed into what is today two important biological tools: a model eukaryote used in cell biology research and a recombinant protein production system (Cregg *et al.* 2000). To date well over 200 heterologous proteins have been expressed in *K. pastoris*. This yeast was developed as a source of single-cell proteins because it can reach high cell densities growing on either glucose or methanol under fermentation conditions. This ability was used to produce large quantities of medically and industrially important proteins (e.g., antibodies, antimicrobial peptides) and enzymes. The species became a model organism for synthetic biology, studies on organelles and the metabolism of eukaryotic cells (Gasser & Mattanovich 2018). Most nodes in the network visualisation of keywords (red, blue, purple, and yellow) refer to research on *Komagataella* (Fig. 18).

Pichia pastoris was reassigned to *Komagataella* following the phylogenetic analysis of ribosomal gene sequences (Yamada *et al.* 1995a, Kurtzman *et al.* 2008, Kurtzman 2009). Discovery of two more species, *K. pseudopastoris* (Dlauchy *et al.* 2003) and *K. phaffii* (Kurtzman 2005), which were practically indistinguishable by reactions on the standard fermentation and assimilation tests commonly used in yeast taxonomy, raised the question of which yeast is being used in studies of gene expression (Kurtzman 2009). Multi-gene sequence analyses demonstrated that commercial *Pichia pastoris* strains commonly used in gene-expression research belong to a different species, namely *K. phaffii* (Kurtzman 2009). With the isolation of new strains and the re-analysis of old *Pi. pastoris* strains, seven species of *Komagataella* are known today (Naumov *et al.* 2018). *Komagataella* species are common in slime fluxes in Canada, the USA and Europe (Péter *et al.* 2017b, Naumov *et al.* 2018).

Wickerhamomyces anomalus (formerly *Pichia anomala*, *Hansenula anomala*) is frequently associated with food and feed products, either as a production organism or as a spoilage yeast (Passoth *et al.* 2006). Physiologically, this species has several extraordinary traits, namely the ability to grow under low pH, high osmotic pressure, and low oxygen tension (Passoth *et al.* 2006). This yeast contributes to the production of wine aroma. *Wickerhamomyces anomalus* was used as a biocontrol agent to inhibit the development of moulds in airtight stored grains and spoilage yeasts in wines. The ability to secrete killer toxins has been demonstrated in many strains and the known toxins differ considerably with respect to their activity spectrum, molecular characteristics, chemical properties, and stability (Passoth *et al.* 2006, Klassen *et al.* 2017). The physiological properties of these yeasts were extensively studied with respect to the regulation of aerobic and anaerobic growth and fermentation on different carbon sources (Passoth *et al.* 2006). *Wickerhamomyces anomalus* produces ethanol under oxygen limitation, while in completely aerobic cultures only a little ethanol is produced (the opposite of the Crabtree effect). This yeast was named among promising species for low-alcohol and non-alcoholic beers (Gibson *et al.* 2017). Most green nodes in the network visualisation of keywords may refer to research on *W. anomalus*.

The placement of *Pichia anomala* in *Wickerhamomyces* following multigene phylogenetic analysis (Kurtzman *et al.* 2008) has raised concern about whether these results argued for the placement of this yeast in a new genus or an earlier described

genus *Hansenula* (Kurtzman 2011b, Daniel *et al.* 2012). The species was described by Hansen in 1891 as *Saccharomyces anomalus* and 45 more taxonomic synonyms exist for this yeast (Kurtzman 2011b). Because of the uncertain origin of old type material (two neotypes of *Hansenula anomala*) or the absence thereof for older names *Saccharomyces anomalus* and *S. sphaericus*, the genus *Hansenula* was considered invalid (Kurtzman 2011b). *Pichia* and *Hansenula* were phenotypically almost indistinguishable and polyphyletic in phylogenetic analyses (Kurtzman 1998, 2011a, b). Because type material of the type species of *Pichia* existed and that of *Hansenula* did not, it was unclear to which phylogenetic clade the name *Hansenula* should be attributed. Therefore, the genus where *Pichia anomala* was placed received a new name *Wickerhamomyces*, and that name was conserved against the name *Hansenula* (Daniel *et al.* 2012).

Scheffersomyces stipitis (formerly *Pichia stipitis*) and some other xylose-fermenting yeasts are particularly interesting for biotechnology because of their ability to convert lignocellulose to ethanol. Members of the genus *Scheffersomyces* formerly known as *Pi. segobiensis*, *Pi. stipitis* and *Candida shehatae* are the best-known species. The genetics of xylose utilisation pathways were extensively studied in *Scheffersomyces stipitis*. Natural habitats of xylose-fermenting yeasts include decaying wood and wood-inhabiting insects (Blackwell 2017, Péter *et al.* 2017b). Less known and distantly related to the genus *Pichia*, the genus *Spathaspora* shares the metabolic trait of xylose fermentation (Martinez-Jimenez *et al.* 2021).

Ogataea polymorpha (formerly *Pichia angusta*, *Hansenula polymorpha*) is an important yeast in industrial biotechnology. *Ogataea* species are methylotrophic yeasts that can grow on methanol as a sole source of energy. The growth on methanol involves the oxidation of methanol into formaldehyde and hydrogen peroxide by the peroxisomal enzyme alcohol oxidase (Saraya *et al.* 2012). The number of peroxisomes depends on the growth substrate. This feature made *O. polymorpha* a good model organism to study peroxisome biology (Saraya *et al.* 2012). Another interesting physiological trait is the ability to assimilate nitrate as the sole source of nitrogen. Molecular mechanisms and transport of nitrate were studied in this yeast. This species is attractive for biotechnology because of its thermotolerant nature (Peter *et al.* 2017, Buzzini *et al.* 2018) and the ability to grow at temperatures reaching (and exceeding for some strains) 50 °C. Together with *Komagataella pastoris* and *K. phaffii*, *Ogataea polymorpha* and *O. methanolica* are the most frequently used yeasts for heterologous protein production. Many species of *Ogataea* were isolated from plant exudates (slime fluxes), decaying plant material (rotting wood and cacti) or in association with insects (Peter *et al.* 2017, Stefanini 2018).

Cyberlindnera jadinii (formerly *Pichia jadinii*, *Candida utilis*, *Torulopsis utilis*, *Torula utilis*) is a well-known fodder yeast and industrial producer of single-cell protein (SCP). Yeast biomass is used as a nutrition and source of proteins and vitamins in animal husbandry and human foods. Industrial utilisation of *Cyberlindnera jadinii* started in Germany during World War I, when common protein sources became scarce (reviewed in Barnett 2004). The yeast efficiently assimilates pentoses (xylose and arabinose), organic acids alcohols, and can grow on hardwood hydrolysates from the pulp industry, agricultural waste, molasses and oils (Buerth *et al.* 2016). *Cyberlindnera jadinii* is rich in glutamic acid and for this reason, it has been used to replace the flavour enhancer monosodium glutamate, MSG (Ritala *et al.* 2017). There is an interest in using this species for the expression of

heterologous genes, but the wide application of the yeast retarded due to polyploidy of *Candida utilis* strains (reviewed in Buerth *et al.* 2016). A common food or feed additive (with FDA GRAS status), *Cyberlindnera jadinii* is well suitable for medical uses as it can transit gastrointestinal tract without losing viability by virtue of acid and temperature tolerance. This edible yeast can be utilised as a probiotic or probably as an antagonist to *Candida albicans* (reviewed in Buerth *et al.* 2016).

The yeast presently known as *Cyberlindnera jadinii* was originally described as *Torula utilis*, though the name *Torula* was already used for some moulds (reviewed in Barnett 2004). The species was reclassified as *Torulopsis utilis* in 1934 and later in 1952 as *Candida utilis* (reviewed in Barnett 2004). Biochemical and physiological studies, and research using properties of DNA, including DNA relatedness, single- and multi-gene phylogenies, suggested that *Candida utilis* is conspecific to *Pichia jadinii* (reviewed in Barnett 2004, Kurtzman *et al.* 2008). The name *Candida utilis* was abandoned in favour of *Pi. jadinii*, which was later reclassified as *Cyberlindnera jadinii*. Astonishingly, the improper and obsolete name “*Torula* yeast” can still be found in the modern literature for *Cyberlindnera jadinii*.

Milleriozyma farinosa (formerly *Pichia farinosa*) is a widely distributed halotolerant yeast (Peter *et al.* 2017, Buzzini *et al.* 2018). Strains have been isolated from such diverse substrates as agricultural products, food (e.g., miso, soy mash), animal dung and petroleum, as well as from clinical samples (Kurtzman 1998). Strains of *M. farinosa* show killer properties.

Meyerozyma guilliermondii (formerly *Pichia guilliermondii*, *Candida guilliermondii*) and closely related *Meyerozyma caribbica* (formerly *Pichia caribbica*) are widespread species isolated from a variety of substrates that include soil, plants, food sources, industrial applications and clinical samples. *Meyerozyma caribbica* is utilised for biocontrol of post-harvest decay in fruits (Cao *et al.* 2013a). This yeast was reported to degrade mould toxin patulin and reduce its concentration in apples (Cao *et al.* 2013a, Zheng *et al.* 2018). *Meyerozyma guilliermondii* can produce the vitamin riboflavin (B2) as well as a sweetener xylitol (Kurtzman 2011c, Averianova *et al.* 2020). This yeast is also present in some traditional fermentations. *Meyerozyma guilliermondii* is considered an opportunistic human pathogen and has been reported to represent on average 2 % of clinical yeast isolates, a prevalence similar to that of *Pichia kudriavzevii* (Stavrou *et al.* 2019). Similar to several prominent human pathogens, *Meyerozyma guilliermondii* possesses genetic machinery to adapt and survive in the human host (Stavrou *et al.* 2019). The two *Meyerozyma* species also show resistance toazole drugs (Stavrou *et al.* 2019).

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9. **Cryptococcus** Vuill., Rev. Gén. Sci. Pures Appl. 12: 741. 1901.

Type species: *Cryptococcus neoformans* (San Felice) Vuill.

Classification: Basidiomycota, Agaricomycotina, Tremellomycetes, Tremellales, Cryptococcaceae.

Background

The first descriptions of *Cryptococcus* date to the 1890s when the German physicians Otto Busse and Abraham Buschke described a yeast infection of a woman's tibia. The obtained culture was described

as *Saccharomyces hominis* (Busse 1894, Buschke 1895). Sanfelice, an Italian researcher, described in 1894 a similar yeast in fermenting peach juice and, subsequently, he observed that the cultured yeast behaved pathogenic when injected in mice (Sanfelice 1894). A few years later, the French mycologist Jean-Paul Vuillemin observed that the *S. hominis* isolates were unable to produce ascospores which led him to move the species to the genus *Cryptococcus* and re-named it *Cryptococcus hominis*. The yeast described by Sanfelice as *Saccharomyces neoformans* was transferred to *Cryptococcus* and the ex-type strain is preserved in the CBS culture collection as CBS 132. Unfortunately, the *Cr. hominis* ex-type strain was not preserved, hence *Cr. neoformans* became the valid species name. Until the late 1970s, *Cryptococcus* yeasts were a relatively rare encounter in medical clinics until the HIV pandemic started. In 1950, three serotypes were recognised based on the serological properties of the polysaccharide capsule and were named serotypes A, B and C (Evans 1950). The fourth serotype named D was described nearly two decades thereafter (Wilson *et al.* 1968). In 1970, an atypical *Cryptococcus* isolate from an infection, in what is now known as the Democratic Republic of Congo was described by Vanbreuseghem & Takashio (1970) as *Cr. neoformans* var. *gattii*. A few years thereafter, Kwon-Chung *et al.* (1982) described the sexual phase of *Cr. neoformans*, and with the dual nomenclature at that time, it was named *Filobasidiella neoformans* with two varieties, var. *neoformans* (for serotype A and D isolates) and var. *gattii* (for serotype B and C isolates). With the adoption of the “One Fungus = One Name” principle, all taxa were later placed in the genus *Cryptococcus*, with *Filobasidiella* becoming a synonym of *Cryptococcus* (Liu *et al.* 2015c, d). Presently, seven species are recognised in the *Cr. neoformans*/*Cr. gattii* complex (Hagen *et al.* 2015), namely *Cr. neoformans*, *Cr. deneoformans*, *Cr. bacillisporus*, *Cr. gattii*, *Cr. deuterogattii*, *Cr. decagattii* and *Cr. tetragattii*. Note that this taxonomy proposal has been fiercely debated (Hagen *et al.* 2017, Kwon-Chung *et al.* 2017). Recently, another lineage of *Cr. gattii* was discovered in Zambia (Farrer *et al.* 2019), but its taxonomic status is not yet settled. *Cryptococcus* species are phylogenetically more closely related to *Tremellomycetes* (Basidiomycota) than to the baker's yeast (Bahn *et al.* 2020).

Research interests

There are 6 909 publications and 95 586 citations from 2011–2021 in the Web of Science (Fig. 19), with the top 10 most cited articles included in Table 11. The research interests of *Cryptococcus* yeasts focus on improving the taxonomy, epidemiology, antifungal therapy, understanding the yeast interaction with the immune system of different host populations, cell wall characteristics, and the role of extracellular vesicles in the cryptococcal pathogenesis (Fig. 20). From the clinical perspective, the top-cited papers mainly include extensive reviews highlighting the human killer fungal pathogens, that include *Cryptococcus* yeasts, covering aspects from the microbiological characteristics to clinical aspects of cryptococcosis; molecular and cellular characteristics to the modulation of the immune response when faced with cryptococcosis; the role of sulphonamides and other carbonic anhydrase inhibitors as promising compounds in the treatment of infections caused by *Cryptococcus* and other microorganisms. Finally, a review of the biology and chemistry of the newest and conventional antifungals, highlighting particularities in the *Cryptococcus* infections is also a highly cited topic.

A recent study on the global incidence of cryptococcosis observed alarmingly high numbers of disease occurrences,

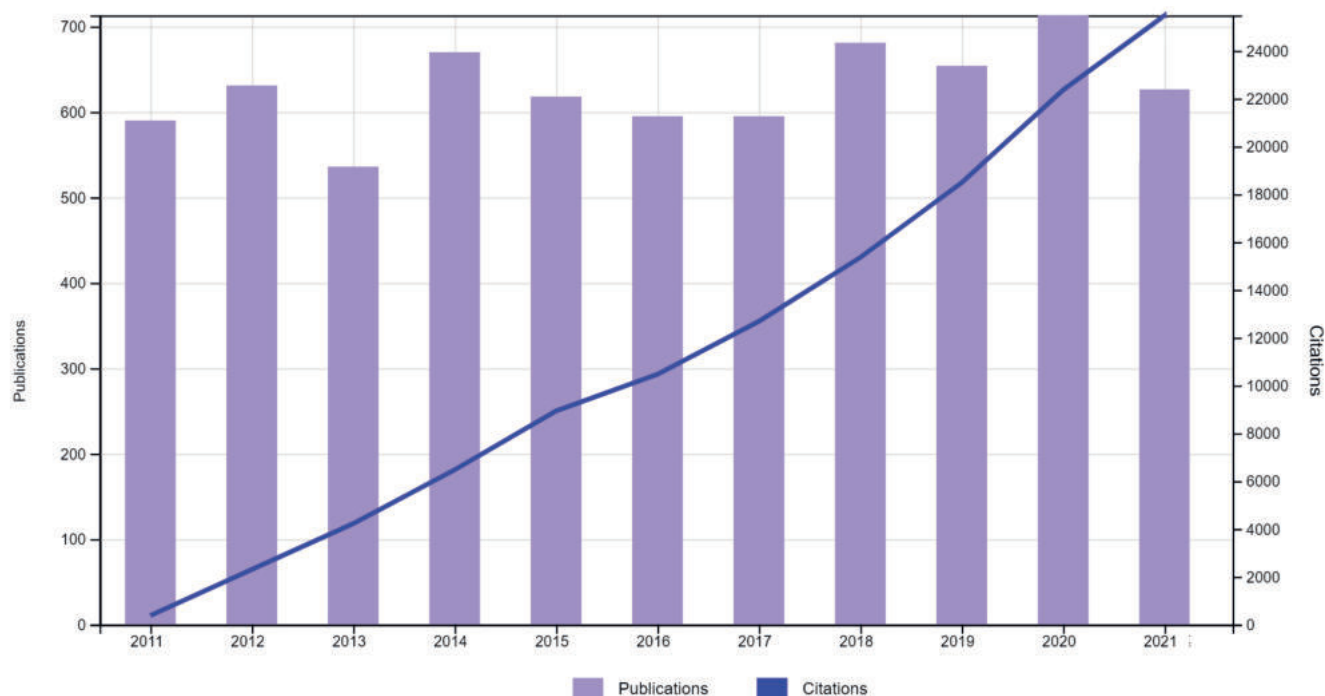


Fig. 19. Trends in research of *Cryptococcus* in the period 2011–2021.

Table 11. Top 10 cited articles related to *Cryptococcus* published in the period 2011–2021.

Rank	Article title	No. of citations	References
1	Hidden killers: human fungal infections	2 175	Brown <i>et al.</i> (2012)
2	Emerging fungal threats to animal, plant and ecosystem health	1 678	Fisher <i>et al.</i> (2012)
3	Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis	863	Rajasingham <i>et al.</i> (2017)
4	Immunity to fungal infections	729	Romani (2011)
5	Through the wall: extracellular vesicles in Gram-positive bacteria, mycobacteria and fungi	520	Brown <i>et al.</i> (2015)
6	Structure-based drug discovery of carbonic anhydrase inhibitors	472	Supuran (2012)
7	The biology and chemistry of antifungal agents: A review	417	Kathiravan <i>et al.</i> (2012)
8	Recognition of seven species in the <i>Cryptococcus gattii</i> / <i>Cryptococcus neoformans</i> species complex	397	Hagen (2015)
9	Membrane vesicle release in bacteria, eukaryotes, and archaea: a conserved yet underappreciated aspect of microbial life	386	Deatherage & Cookon (2012)
10	The fungal cell wall: structure, biosynthesis, and function	365	Gow <i>et al.</i> (2017)

especially among immunocompromised humans in sub-Saharan Africa and parts of Asia and South America (Rajasingham *et al.* 2017). Using the global cryptococcal antigenaemia prevalence as a benchmark, 60 % of people with a CD4 cell count < 100 cells μL^{-1} were found to be positive, with 278 000 (range 195 500–340 600) people positive for cryptococcal antigen globally, and 223 100 (range 150 600–282 400) individuals with cryptococcal meningitis globally in 2014. Importantly, sub-Saharan Africa accounted for 73 % of the estimated cryptococcal meningitis cases in 2014 leading to 162 500 cases (range 113 600–193 900). Annual global deaths from cryptococcal meningitis were estimated at 181 100, with most (135 900) in sub-Saharan Africa. Cryptococcal meningitis was found to be responsible for 15 % of AIDS-related deaths (Rajasingham *et al.* 2017).

Other topics addressed in the top-cited papers include the biological mechanisms used by *Cryptococcus* to impact the

extinction of wild animal hosts, the environmental changes and altered epidemiological dynamics of fungal emerging diseases; the physiological properties of the extracellular vesicles, testing current hypotheses on the mechanisms of vesiculogenesis, and their role in fungal pathogenesis; the reclassification of *Cryptococcus* species from an integrative analysis of molecular, biological and epidemiological data that led to the recognition of *Cr. gattii*/*Cr. neoformans* as a species complex; and the *Cryptococcus* cell wall and capsule, including details of its composition, synthesis, regulation, immune recognition, and therapy.

In the 5th edition of “*The Yeasts, a Taxonomic Study*” (TYTS, Kurtzman *et al.* 2011), 70 species were listed in the genus *Cryptococcus* (Fonseca *et al.* 2011), but it has been known for a long time that the genus in this context was highly polyphyletic (*e.g.*, Fell *et al.* 2000). In 2015, a taxonomic revision of the genus based on a multigene-based phylogeny limited the genus to species of

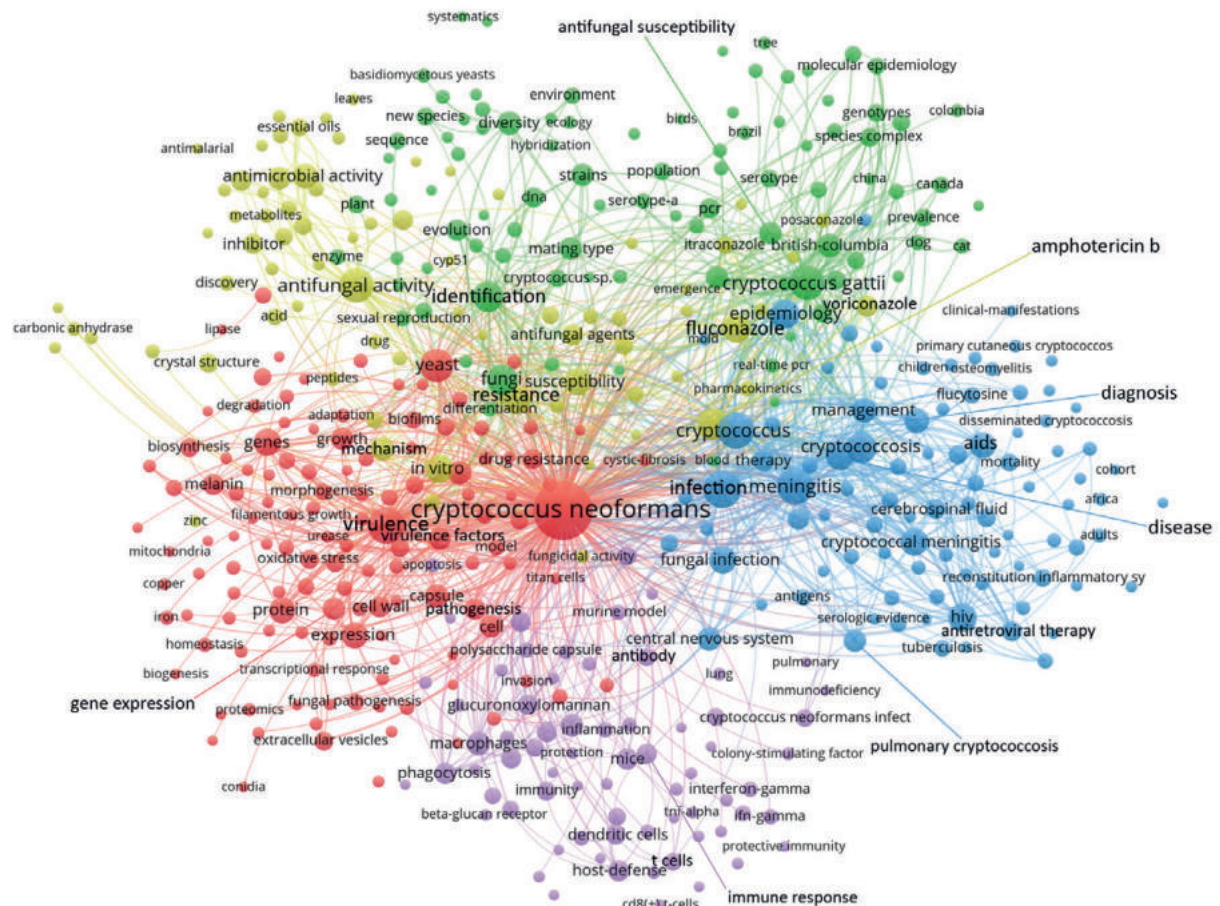


Fig. 20. Network visualisation of keywords of the publications related to *Cryptococcus*. The larger the text and the circle the more often the subject has been cited.

the *Cr. neoformans*/*Cr. gattii* complexes and some phylogenetically related species and, hence, the remainder were transferred to 29 other genera (Liu *et al.* 2015c, d; see also www.theyeasts.org). Species previously classified in the polyphyletic genus *Cryptococcus* are known for several biotechnological applications. Data from TYTS shows that several species formerly classified in *Cryptococcus* produce endoxylanases (e.g., *Naganishia adeliensis*, *N. albidosimilis*, *N. albida*, *Saitozyma podzolica*), pectinases (*N. albida*), amylases (*S. flava*), epoxide hydrolases (*S. podzolica*), and are interesting as oleaginous yeasts that produce for example cacao butter equivalents (*Cutaneotrichosporon oleaginosus* also known as *Apiotrichum curvatum*), tolerate or accumulate heavy metals (*Vanrija humicola*, *S. podzolica*), degrade phenolic compounds (*Solicoccozyma terrea*), produce extracellular polysaccharides (*Papiliotrema flavescens*, *P. laurentii*) or might be used as biocontrol agents (*N. albida*) (Ykema *et al.* 1988, Fonseca *et al.* 2011, Smirnou *et al.* 2015, Bracharz *et al.* 2017a).

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10. *Alternaria* Nees, System der Pilze und Schwämme 72.
1816.

Type species: Alternaria alternata (Fr.) Keissl. (bas. *Torula alternata* Fr., syn. *Alternaria tenuis* Nees)

Classification: Ascomycota, Pezizomycotina, Dothideomycetes, Pleosporales, Pleosporaceae.

Background

Alternaria is a large genus of dematiaceous hyphomycetes with 837 species epithets listed in Index Fungorum (2023), of which 589 species epithets are legitimate (Hongsanan *et al.* 2020a, Wijayawardene *et al.* 2020). Presently, about 366 accepted species are mainly classified into 28 sections, but not all of them have been clarified based on molecular phylogeny (Woudenberg *et al.* 2014a, Lawrence *et al.* 2016, Jayawardena *et al.* 2019, Hongsanan *et al.* 2020a, Wijayawardene *et al.* 2020). *Alternaria* species are widely distributed in the environment and show a diverse ecological lifestyle that includes saprobic, endophytic, and pathogenic to plants and animals. Most species, however, are serious phytopathogens causing several severe diseases (e.g., leaf and stem blight, leaf blotch, leaf spot, stem canker, and stem end rots) on a wide range of crop products often with significant economic losses (Thomma 2003, Polizzotto *et al.* 2012, Kustrzeba-Wójcicka *et al.* 2014, Woudenberg *et al.* 2014a, Ariyawansa *et al.* 2015a, Lawrence *et al.* 2016, Jayawardena *et al.* 2019, Marin-Felix *et al.* 2019a, Nishikawa & Nakashima 2020). Species in sections *Alternantherae*, *Alternaria*, *Brassicicola*, *Crivellia*, *Gypsophila*, *Nimbya*, *Porri*, *Radicina* and *Sonchi* are usually causal agents of pre- and post-harvest diseases and may be both host and non-host specific (Mamgain *et al.* 2013, Woudenberg *et al.* 2014b, 2015, Zhu & Xiao 2015, Lawrence *et al.* 2016, Meena *et al.* 2016, Tralamazza *et al.* 2018).

Phytotoxins are produced during the plant infection process and, although they are not necessary for establishing diseases, they are essential virulence factors and participate in the intensity

of disease symptoms (Thomma 2003, Meena *et al.* 2017). Some *Alternaria* species produce potential phytotoxins that can be used in biotechnological applications as efficient producers of active biological compounds, as biocontrol agents of pests and weeds against serious plant pathogens or as mycoherbicides (Sharma & Sharma 2014, Woudenberg *et al.* 2015, Lawrence *et al.* 2016, Kaur & Kumar 2019, Dalinova *et al.* 2020b).

Mycotoxins have also been described in *Alternaria* species which are a risk to human and animal health worldwide (Barkai-Golan 2008, Lopes *et al.* 2013, Mirhendi *et al.* 2013, Chowdhary *et al.* 2014a, Kustrzeba-Wójcicka *et al.* 2014, Woudenberg *et al.* 2014a, Lawrence *et al.* 2016, Lyskova *et al.* 2017, Cardona *et al.* 2020). *Alternaria* spores are commonly reported as airborne allergens causing mainly respiratory disorders and some species have also been reported to provoke infections, though usually in immunocompromised patients (Pastor & Guarro 2008, De Hoog *et al.* 2020). *Alternaria* species implicated in opportunistic human diseases (alternariosis) have always been identified as *Al. alternata* and *Al. infectoria* as causative agents of phaeohyphomycosis and infection of the cornea, nails, oral, sinus and skin in humans (Lawrence *et al.* 2016).

Alternaria was introduced as a monotypic genus by Nees von Esenbeck in 1816 to accommodate the dematiaceous hyphomycete forming chains of phaeodictyospores, with a beak of tapering apical cells, and was initially typified with *Al. tenuis*. Although years later, *Al. tenuis* was considered conspecific with *Torula alternata* (Fries 1832) and they were both synonymised with *Al. alternata*, which is currently recognised as the type of the genus (Keissler 1912). The genus is characterised mainly by its asexual morph, which shows inconspicuous conidiophores, mono- or polytretic conidiogenous cells, producing commonly large brown or dark dictyoconidia or phragmoconidia, with a terminal conical narrowing or “beak” at the apex, solitary or in chains; although species with meristematic growth are also known (Simmons 2007, Woudenberg *et al.* 2014a, Lawrence *et al.* 2016). Its sexual morph, only known for species of seven *Alternaria* sections, is characterised by small dark brown ascomata containing bitunicate asci and muriform ascospores (Woudenberg *et al.* 2014a, Ariyawansa *et al.* 2015a, Lawrence *et al.* 2016). The sexual morph of *Alternaria* has been linked to the genera *Lewia*, *Allewia* and *Crivellia* (Rossman *et al.* 2015). Phylogenetic results obtained by Woudenberg *et al.* (2014a) demonstrated that these genera formed internal clades within *Alternaria*. Thus, *Lewia*, *Allewia* and *Crivellia* were synonymised under *Alternaria* together with the genera *Brachycladium*, *Chalastospora*, *Chmelia*, *Embellisia*, *Nimbya*, *Sinomyces*, *Teretispora*, *Ulocladium*, *Undifilum* and *Ybotromyces* (Woudenberg *et al.* 2014a, Ariyawansa *et al.* 2015a). Based on taxonomic nomenclature (Article 57.2 of the International Code of Nomenclature for algae, fungi and plants; McNeill *et al.* 2012), Rossman *et al.* (2015) recommended to use *Alternaria* instead of *Lewia*, *Allewia* and *Crivellia* due to *Alternaria* being introduced earlier, widely used and the number of its species.

Taxonomic classification and revisions of *Alternaria* have been discussed by various authors (Elliott 1917, Simmons 1967, 1992, 2007, Joly 1964, Pryor & Gilbertson 2000, Pryor & Bigelow 2003, Hong *et al.* 2005, Lawrence *et al.* 2012, 2013, 2016, Woudenberg *et al.* 2014a, b, 2015). Extensive morphology-based taxonomic investigations on the genus were carried out by Emory G. Simmons (1920–2013), which were summarised in his monograph on *Alternaria* species identification (Simmons 2007). Based on the sporulation patterns and conidial morphology, Simmons (2007) recognised 275 species, which were divided into species-groups, each one typified by a representative species. However,

handicaps to the correct identification of *Alternaria* species are the overlapping of morphological features among taxa and their plasticity, particularly when growing *in vitro*. Several molecular studies have been intended to establish relationships among morphological-based species and found that several species-groups described by Simmons were, in fact, representatives of monophyletic lineages that correlate with the currently established sections within the genus (Hong *et al.* 2005, Lawrence *et al.* 2012, 2013, Woudenberg *et al.* 2014a). Taxonomic traits and species composition of all *Alternaria* sections are summarised in Lawrence *et al.* (2016). However, molecular identification of *Alternaria* species is still a challenge because the conventional gene markers, such as the nrDNA barcodes and other functional genes (*act*, *tub*, *cal*, chitin synthetase, among many others), have failed to discriminate between species particularly belonging to the small-spored *Alternaria* sections, such as sect. *Alternaria* or sect. *Infectoriae* (Woudenberg *et al.* 2015, Lawrence *et al.* 2016, Poursafar *et al.* 2017, Patriarca *et al.* 2019). Consequently, whole-genome sequencing technologies have become essential tools to distinguish most of the described species (Lawrence *et al.* 2013, Woudenberg *et al.* 2015). The genomes of *Alternaria* spp. in sections *Alternaria* and *Brassicicola* are currently publicly available at the National Center for Biotechnology Information (NCBI) (Woudenberg *et al.* 2015).

Ecological and economic significance

Few fungal taxa can match the global impact that *Alternaria* has on natural ecosystems and its effects on human activities and health. *Alternaria* species are common saprobes on a wide range of substrates (e.g., dead plants, paper, and foods) and more than 120 saprobic species have been restricted to the sections *Alternaria*, *Infectoriae*, and *Ulocladioides* (Thomma 2003, Lawrence *et al.* 2016). As saprobic fungi, along with other microorganisms, *Alternaria* species take part in the decomposition and mineralisation of plant residues through cellulolytic activity (Thomma 2003).

Alternaria has also been isolated from various asymptomatic plant tissues as endophytic fungi. Several studies have demonstrated the endophytic capability of *Alternaria* species living inside plant tissue without pathogenesis induction (Ma *et al.* 2010, Chen *et al.* 2011a, Polizzotto *et al.* 2012). However, it is still doubtful whether the fungus is living as an endophyte during the inactive latent period of weak pathogen or the influence of the host's health. Only saprobic species were revealed as endophytes (Ma *et al.* 2010, Lawrence *et al.* 2016). *Alternaria* stands out by the ability to cause diseases not only in plants but also in animals, including humans, and by the production of numerous secondary metabolites with a wide range of effects on different organisms.

Plant diseases

Alternaria species are reported to cause diseases in many economic plants from families such as *Apiaceae*, *Asteraceae*, *Brassicaceae*, *Cyperaceae*, *Fabaceae*, *Poaceae*, *Rosaceae*, *Rutaceae*, *Solanaceae*, *Vitaceae*, among others. They can infect more than 4 000 host plants, and *Al. alternata* can infect close to 100 plant species (Farr & Rossman 2022). Most *Alternaria* species are foliar pathogens, but they also attack flowers, stems, roots, and fruits, causing different kinds of lesions (Thomma 2003, Woudenberg *et al.* 2015, Lawrence *et al.* 2016, Marin-Felix *et al.* 2019a). The most common *Alternaria* diseases are detailed below.

Leaf spot: it is common on the surface of lower and older leaves on a variety of crops, including tomato, cabbage, fava bean, potato, cucumber and other vegetables, but also ornamental plants (Batta 2003, Michereff *et al.* 2012, Agamy *et al.* 2013, Behairy *et al.* 2014, Shoaib *et al.* 2014, Matic *et al.* 2020). Lesions are characterised by small dark circular spots with light brown centres, surrounded by dark concentric rings. Severely infected leaves turn yellow, wilt and fall, and can even show large necrotic areas (Batta 2003). It is a frequent disease in warm (20–32 °C) and moist (dew) weather regions. The main causal agents are *Alternaria alternata*, *Al. arborescens* species complex, *Al. brassicae*, *Al. brassicicola*, *Al. cinerariae*, and *Al. cucumerina* (Batta 2003, Reis & Boiteux 2010, Gannibal 2011, Blagojević *et al.* 2020, He *et al.* 2020a, Matic *et al.* 2020, Zhang *et al.* 2020d).

Leaf blight: the disease affects mature leaves near the crown of the plant and lesions first appear as small brown spots, often with a yellow halo, which progress to form large, irregular, brown spots. Severe infections can produce early defoliation, flower-bud abortion, premature ripening, and seed shrivelling, affecting yield and production (Akhtar *et al.* 1994, 2004). Temperatures between 15 and 25 °C and persistent leaf wetness by rain or dew promote infection (Shrestha *et al.* 2005b). Vegetables and cereals like wheat (Perelló *et al.* 1996), barley (Khudhair *et al.* 2014), tomato (Akhtar *et al.* 2004), onion (Karthikeyan *et al.* 2005) and mustard (Shrestha *et al.* 2005b) are only some of those most frequently affected. Species that are more frequently associated with this kind of lesion are *Alternaria alternata*, *Al. brassicae*, *Al. cucumerina*, *Al. dauci*, *Al. palandui*, *Al. triticina*, and *Al. triticinaculans*, among others (Perelló *et al.* 1996, Akhtar *et al.* 2004, Karthikeyan *et al.* 2005, Shrestha *et al.* 2005b, Khudhair *et al.* 2014).

Early blight: it is one of the most common diseases on tomatoes and potatoes, with *Al. solani*, *Al. tomatophila*, and *Al. alternata* being the main pathogens (Adhikari *et al.* 2017). Apart from the leaves, they can also affect fruits and seedling stems or stems of older plants, reducing crop yield by up to 79 % (Gwary & Nahunnaro 1998, Chaerani & Voorrips 2006, Adhikari *et al.* 2017). The infection is provoked in a wide range of environmental temperatures (8–32 °C), but with high levels of free moisture or near-saturation humidity (Adhikari *et al.* 2017). The most common symptoms include small dark spots that progress to larger spots with target-like concentric rings on leaves, sunken and dry brown areas on stems, and leathery and black spots on fruits. These are visible 2–3 d after infection, and spore production occurs 3–5 d later completing the cycle (Chaerani & Voorrips 2006).

Leaf blotch and fruit spot: *Alternaria alternata* f. sp. *mali* is commonly known as a causal agent of leaf blotch and fruit spot disease on apples worldwide (Hartevelde *et al.* 2013, Woudenberg *et al.* 2015, Gur *et al.* 2017). However, multiple small-spored *Alternaria* species (e.g., *Al. arborescens*, *Al. longipes* and *Al. tenuissima*) have also been implicated in alternaria leaf blotch on apples (Hartevelde *et al.* 2013, 2014a). *Alternaria* leaf blotch is one of the most severe diseases on apples in Asia (e.g., China, India, Israel, Iran, Japan, and South Korea), Australia and USA, causing defoliation of 15–25 %, or up to 80 % crop losses in some countries when conditions are conducive (Horlock 2006, Soleimani & Esmailzadeh 2007, Hartevelde *et al.* 2013, 2014a, Sofi *et al.* 2013, Gur *et al.* 2017). The infection is provoked during winter and spring weather seasons and influenced by high relative humidity, the location of the orchards, mean temperature, cumulative amount of rain and mean rainfall

(Hartevelde *et al.* 2014b). The symptom of alternaria leaf blotch initially appears on leaves as circular to irregular brown spots that become larger in zonate circular or crescent-shaped rings and are lined with a dark brown to purple margin (Hartevelde *et al.* 2013, 2014a, Gur *et al.* 2017). Fruit spot diseases are characterised by small, slightly sunken, light to medium brown spots (Persley & Horlock 2009, Hartevelde *et al.* 2013).

Purple leaf blotch disease, caused by *Alternaria porri* on onions and leeks (*Allium* spp.), is a major foliar fungal disease in all *Allium* growing countries. This disease causes leaf damage and yield losses of up to 2.5–97 % during monsoon season (warm and humid environments) (Suheri & Price 2001, Gothandapani *et al.* 2015, Hahuly *et al.* 2018). The disease symptoms are difficult to distinguish from stemphylium leaf blight and are easily misidentified (Suheri & Price 2001, Hahuly *et al.* 2018). The symptoms appear on the older leaves and flower stalks as initially small whitish necrotic lesions, becoming larger elliptical, sunken purple lesions, subsequently turning brown and darker, with a yellow to pale brown margin (Suheri & Price 2001, Hahuly *et al.* 2018).

Stem canker: *Alternaria arborescens* (syn. *Al. alternata* f. sp. *lycopersici*) has been reported as the causal agent of stem canker on tomatoes worldwide, causing sustainable economic losses (Thomma 2003, Esmailzadeh *et al.* 2008, Woudenberg *et al.* 2015, Shao *et al.* 2020). *Alternaria arborescens* produced a host-specific AAL-mycotoxin and damages leaves and stems of tomatoes by forming necrotic spots on leaves and dark-brown concentric cankers on stems (Grogan *et al.* 1975, Witsenboer *et al.* 1992, Thomma 2003, Somma *et al.* 2011, Shao *et al.* 2020). The infection progresses rapidly in high humidity and temperatures (0.995 a_w at 30 °C) (Vaquera *et al.* 2014, Tomazonia *et al.* 2019).

Human and animal diseases

Alternaria has been associated with a wide range of human and animal syndromes. Although it is commonly known as an agent of allergic processes, it is currently considered an emerging pathogen able to cause infections in immunocompromised patients, although infections in immunocompetent individuals have been also reported (Sood *et al.* 2007, Pastor & Guarro 2008, Dessinioti *et al.* 2013, Hattab *et al.* 2019, De Hoog *et al.* 2020). Since *Alternaria* spores are one of the prevailing constituents in air, they are associated with respiratory disorders such as allergic sinusitis, bronchial asthma, pneumonitis or rhinitis (Pastor & Guarro 2008, Revankar & Sutton 2010, Klimek *et al.* 2015, Levetin *et al.* 2016). Immunosuppressed populations, particularly those who have undergone transplants, cancer treatments or have primary or acquired immunodeficiency, are especially susceptible to cutaneous and subcutaneous infections by *Alternaria* species (Kpodzo *et al.* 2011, González-Vela *et al.* 2014, Ferrándiz-Pulido *et al.* 2018, Iturrieta-González *et al.* 2019), but other types of infections have been also reported, such as ocular mycosis, cerebral and disseminated infections (Konidaris *et al.* 2013, Mirhendi *et al.* 2013, Cardona *et al.* 2020, McGirr *et al.* 2020). There are also documented cases of alternariosis, ranging from cutaneous to systemic infections, in cats, dogs, horses, and other animals (Dedola *et al.* 2010, Seyedmousavi *et al.* 2013, Avsever *et al.* 2017, Dworecka-Kaszak *et al.* 2020, De Hoog *et al.* 2020).

The most reported species are *Alternaria alternata*, *Al. infectoria*, *Al. tenuissima* and *Al. chartarum* (De Hoog *et al.* 2020). However, the real spectrum of pathogenic *Alternaria* species is still obscure because, in as many as 50 % of the cases of alternariosis

reported, the identification of clinical isolates has not been carried out or was based only on morphological features or ITS barcode analysis (Pastor & Guarro 2008, Bajwa *et al.* 2017, Ferrándiz-Pulido *et al.* 2018).

Toxin production

Alternaria is one of the major mycotoxigenic fungi with about 70 described toxins (phytotoxins and mycotoxins) that play an important role in fungal pathogenicity and food safety (Escrivá *et al.* 2017, Pinto & Patriarca 2017).

Phytotoxins: They are formed during the infection and two categories have been recognised: (i) The “host-specific toxins”, which affect a small group of specific plants, and their formation and activity are usually a prerequisite for successful colonisation of the plant host; examples of these toxins are produced by different *Alternaria alternata* pathotypes (Meena *et al.* 2019, Dalinova *et al.* 2020b). (ii) The “non-host specific toxins”, to which a wider range of plants are sensitive, but they cause relatively mild phytotoxic effects and their formation is not necessary for successful colonisation of the host (Thomma 2003, Dalinova *et al.* 2020b). Many phytopathogenic *Alternaria* species produce nonspecific toxins that often target basic cellular processes, so they are regarded as potent mycotoxins, but may also exhibit other types of biological activities (*i.e.*, antimicrobial, insecticidal or cytotoxic activity) that enhance the survival of the fungus in competition with other (micro-)organisms for the substrate (Meena *et al.* 2017, Dalinova *et al.* 2020b).

Mycotoxins: Food contamination by mycotoxins occurs naturally, however, under certain environmental conditions, handling, transport and storage, and even refrigeration conditions mycotoxins may accumulate in vegetable foods and be harmful to humans and animals (Escrivá *et al.* 2017). Although *Alternaria alternata* is regarded as the major mycotoxin producer in the genus, others like

Al. citri, *Al. solani*, *Al. longipes*, *Al. arborescens* and *Al. infectoria*, which are present in seeds, fruits, vegetables, and pet foods, are also relevant mycotoxin producers and all represent a serious threat to health worldwide (Barkai-Golan 2008, Jackson & Al-Taher 2008, Ostry 2008, Streit *et al.* 2013, Puntischer *et al.* 2018). *Alternaria* mycotoxins like alternariol, its methyl ether, as well as altertoxins seem to induce long-term toxicity effects (genotoxicity, carcinogenicity, mutagenicity, *etc.*), in contrast to tenuazonic acid, which is the only *Alternaria* mycotoxin that exhibits pronounced acute toxicity causing haematological disorders to oesophageal cancer (Escrivá *et al.* 2017, Pinto & Patriarca 2017, Dalinova *et al.* 2020b). Despite these harmful effects, *Alternaria* mycotoxin content in feed and food products is not currently regulated by any country. This is due not only to a lack of comprehensive toxicological information from different foodstuffs but also to a lack of research into their toxicity *in vivo* (Lee *et al.* 2015, Dalinova *et al.* 2020b).

Research interests

There are 6 446 publications and 73 134 citations from 2011–2021 in the Web of Science (Fig. 21), with the top 10 most cited articles included in Table 12. The majority of the publications focused on disease management (antifungals and resistances), parasite-host interactions of *Alternaria* species in plants and humans, bioactive compounds production, and taxonomy (Fig. 22).

Disease management

There are various strategies in the management of *Alternaria* diseases in plants, including the use of healthy and treated seed in hot water, 3–4-yr crop rotations, sanitation, weed control, shallow planting, use of balanced nutrients, proper plant density, proper drainage in the field, plant debris management and application of chemical treatments. Of note, however, is that no single method or approach in current use is feasible, viable, stable, or effective in dealing with any host-pathogen system (Saharan *et al.* 2016).

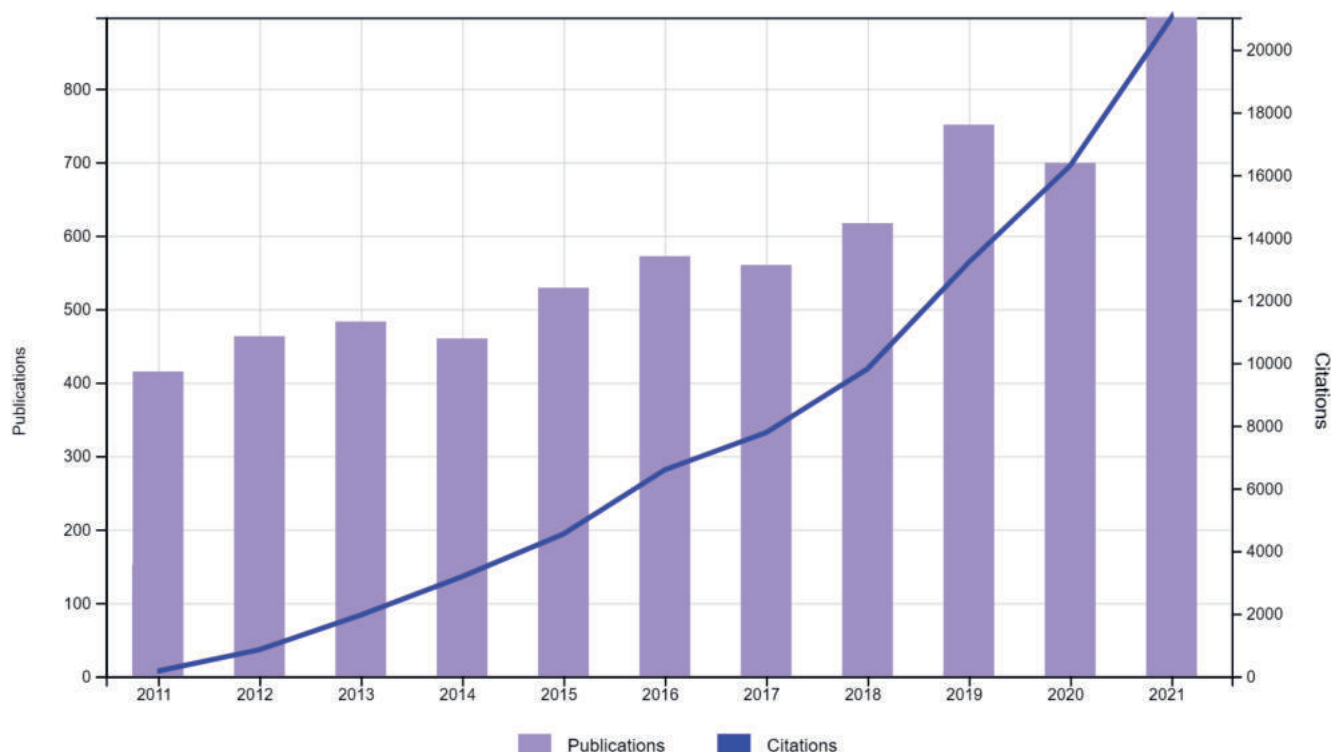


Fig. 21. Trends in research of *Alternaria* in the period 2011–2021.

Table 12. Top 10 cited articles related to *Alternaria* published in the period 2011–2021.

Rank	Article title	No. of citations	References
1	Phytoalexins in defense against pathogens	533	Ahuja <i>et al.</i> (2012)
2	<i>Alternaria</i> redefined	441	Woudenberg <i>et al.</i> (2013)
3	Exosomes secreted by nematode parasites transfer small RNAs to mammalian cells and modulate innate immunity	410	Buck <i>et al.</i> (2014)
4	Next-generation systemic acquired resistance	379	Luna <i>et al.</i> (2011)
5	IL-33-responsive lineage-CD25 ⁺ CD44 ^{hi} lymphoid cells mediate innate type 2 immunity and allergic inflammation in the lungs	372	Bartemes <i>et al.</i> (2012)
6	The danger signal, extracellular ATP, is a sensor for an airborne allergen and triggers IL-33 release and innate Th2-type responses	322	Kouzaki <i>et al.</i> (2011)
7	Fungi and allergic lower respiratory tract diseases	305	Knutsen <i>et al.</i> (2012)
8	Lung type 2 innate lymphoid cells express cysteinyl leukotriene receptor 1, which regulates Th2 cytokine production	275	Doherty <i>et al.</i> (2013)
9	Interferon and IL-27 antagonize the function of group 2 innate lymphoid cells and type 2 innate immune responses.	245	Moro <i>et al.</i> (2015)
10	Reference genes for accurate transcript normalization in citrus genotypes under different experimental conditions	228	Mafra <i>et al.</i> (2012)

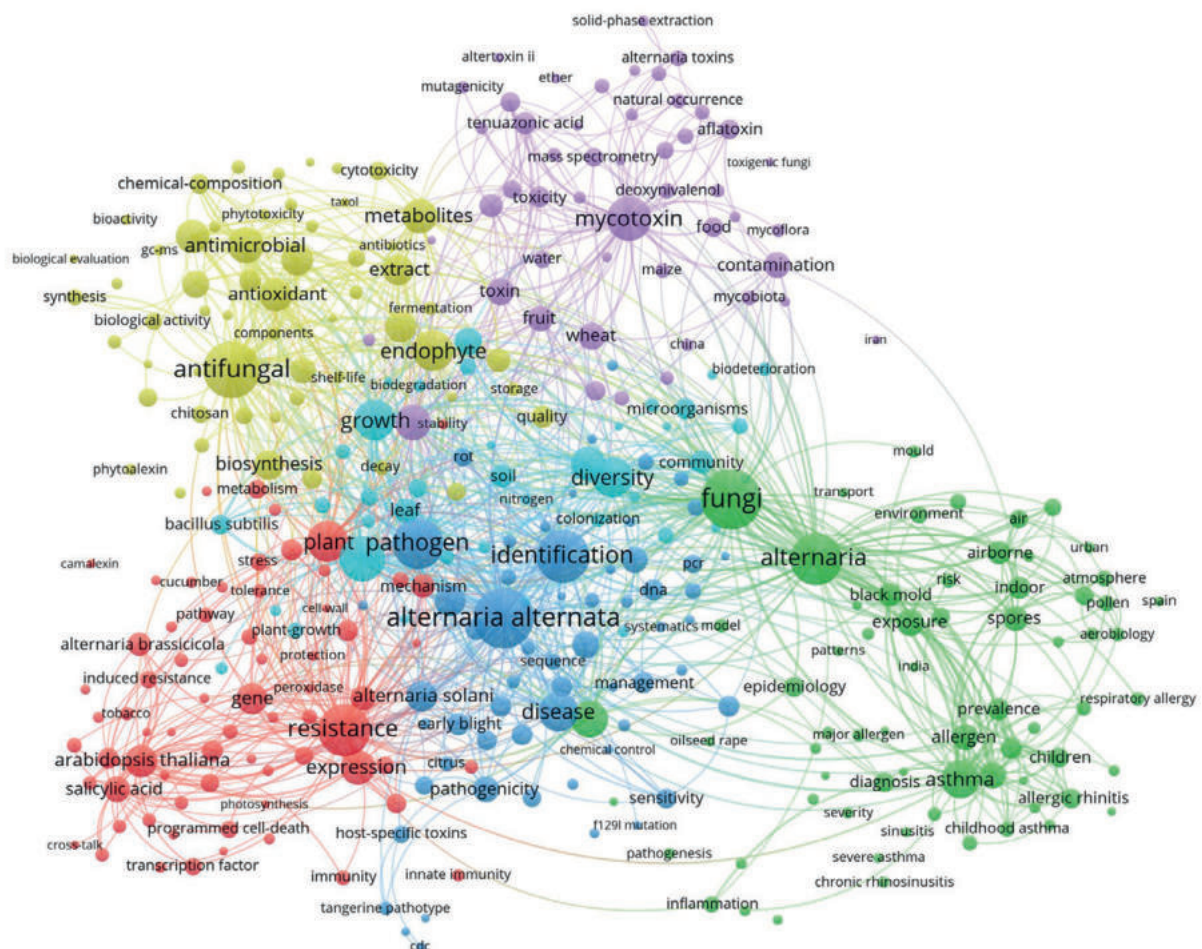


Fig. 22. Network visualisation of keywords of the publications related to *Alternaria*. The larger the text and the circle the more often the subject has been cited.

Common pathogenic fungal strains, including *Alternaria*, are often resistant to fungicides (Iacomi-Vasilescu *et al.* 2004, Fairchild *et al.* 2013, Mallik *et al.* 2014, Yang *et al.* 2019b). Different strategies have been proposed for reducing strain resistance, including mixing fungicides or using chemosensitisers (Brent & Hollomon 2007, Shcherbakova *et al.* 2020). However, with the focus on sustainable agriculture for the replacement of synthetic and toxic substances with environmentally friendly alternatives, research is currently

in the direction of finding effective bioagents as antagonists against *Alternaria*, such as *Chaetomium globosum* or different *Trichoderma* species (Gveroska & Ziberoski 2011, Saharan *et al.* 2016, Ajayabhai *et al.* 2018, Ashwini 2019, Shafique *et al.* 2019); or looking for compounds with potent antifungal activity, such as plant extracts (Latif *et al.* 2006, Meena & Sharma 2012), ionic liquids (Karaman *et al.* 2020) or natural agents in nanoformulations like peppermint oil (Pandey *et al.* 2020) or silver nanoparticles plus

a cyanobacterium (Mahawar *et al.* 2020). However, currently, the easiest, most financially viable, environmentally friendly, and safest way is the use of tolerant or resistant cultivars (Saharan *et al.* 2016), so that research is also focused on the development of *Alternaria* disease-resistant crops (Ceasar & Ignacimuthu 2012, Fatima *et al.* 2019, Meena & Samal 2019, Haque *et al.* 2020).

Because no optimal treatment has been defined for *Alternaria* human infections, multiple therapeutic options have been used, including thermotherapy with a successful outcome (Torres-Rodriguez *et al.* 2005). However, it always depends on the status of the patient concerned and the extent of the disease. Cutaneous and subcutaneous alternarioses commonly require surgical debridement in association with antifungal therapy (Pastor & Guarro 2008, Derber *et al.* 2010). The most used antifungal therapy includes itraconazole, voriconazole, and posaconazole (Chowdhary *et al.* 2014d, Bajwa *et al.* 2017, Ferrándiz-Pulido *et al.* 2018). However, due to hepatic impairment as a side effect reported for voriconazole (Schuermans *et al.* 2017) or significant drug interaction when using itraconazole (Mori *et al.* 2009), currently, posaconazole seems to be the treatment of choice for these infections (Bajwa *et al.* 2017, Schuermans *et al.* 2017). This correlates with the results of *in vitro* antifungal testing in several studies (Badali *et al.* 2009, Alastruey-Izquierdo *et al.* 2011, Gonzalez-Vela *et al.* 2014). Other drugs that show different degrees of effectiveness are amphotericin B, terbinafine or anidulafungin (De Hoog *et al.* 2020), but more *in vitro* and *in vivo* studies are required. Nevertheless, the lack of a standardised methodology for *in vitro* studies or for the correct identification of *Alternaria* species, and the difficulties in getting good sporulation of clinical isolates are handicaps in the advance of these studies.

Parasite-host interaction

The interaction between plants and pathogens induces stress response and, subsequently, the development of an intricate defence system associated with the activation of defence genes, synthesis and secretion of various molecules. In plant infections by *Alternaria*, the production of phytoalexins like camalexin, kauralexins, zealexins, brassinin, and scopoletin (Ahuja *et al.* 2012, Pedras *et al.* 2014, Sun *et al.* 2014, N'Guyen *et al.* 2021), or enzymes like chitinases and β -1,3-glucanases (Fanta *et al.* 2003) have been extensively studied to elucidate their role in the host interaction and pathogenesis of these fungi (Thomma 2003, Meena & Samal 2019). In the same way, the interaction of *Alternaria* with human host cells induces an immune response and research is imperative to understand the fungal biology and details of mechanisms that may protect or drive diseases in humans (Bartemes & Kita 2018). The respiratory system is the most common entry for fungi, and thus several studies have focused on the characterisation of allergic immune responses against *Alternaria* through the study of innate and adaptive response, particularly lymphoid response involved in innate type 2 immunity, production of interleukins, toll-like receptors, among others (Bartemes *et al.* 2012, Kita 2015, Hayes *et al.* 2018). However, only the approaches of integrating genomic, proteomic and metabolomic insights will allow an understanding of the complex biology of host-pathogen interaction and allow the proposal of innovative strategies for mitigating or even eradicating *Alternaria* diseases.

Producers of active biological compounds

More than 300 secondary metabolites produced by *Alternaria* species have been isolated and structurally characterised (Lou *et al.* 2013, Song *et al.* 2019b, Dalinova *et al.* 2020a). In addition to

their toxicogenic effects on plants and animals described previously, these molecules show other biological activities that attract the attention of scientists in various fields (biotechnologists, chemists, pharmacologists, plant pathologists, *etc.*), who investigate a wide range of applications. These molecules are used as prototypes of active chemical pesticides against bacteria (hydroxybostrycin, macrosporin, radiclin, altenusin, porric acid, *etc.*), insects (tenuazoic acid and its synthetic derivatives, altenaene, destruxin B), downy mildews (compounds of diketopiperazine dipeptides), phytopathogenic moulds (helvolic acid, herbarin A, *etc.*), and weeds (cyclic tetrapeptide tentoxin, tenuazonic acid, radicinin, *etc.*). However, they are also the base for development of new drugs as anti-tumour agents (alterporriols, depudecin, destruxin B, *etc.*), anti-leukemic (α pyrone derivatives), anti-bacterial (altenusin, brassicicolin, *etc.*), antiparasitic (depudecin, altenusin) or antiviral (altertoxin V, tetrahydroalternasol C, *etc.*). A promising molecule produced by several *Alternaria* species and of medical interest is altenusin. It has been recently patented in China as a component of medicines for non-alcoholic fatty liver disease, obesity or type 2 diabetes; it is also able to inhibit tau-protein aggregation, a key compound associated with the development of Alzheimer's disease (Lou *et al.* 2013, Zheng *et al.* 2017, Dalinova *et al.* 2020b). Therefore, considering the number of *Alternaria* molecules still needing to be characterised and the large number of species for which secondary metabolite patterns have never been determined, the potential of this genus as a source of interesting compounds is high.

Taxonomy and phylogeny

The taxonomy of *Alternaria* continues to be a subject of debate. Based on several phylogenetic investigations carried out in the last decades, the genus has undergone important taxonomic changes and numerous, morphologically well-defined genera have been found to be congeneric with *Alternaria* (*i.e.*, *Allewia*, *Brachycladium*, *Chalastospora*, *Chmelia*, *Crivellia*, *Embellisia*, *Nimbya*, *Pseudoalternaria*, *Sinomyces*, *Teretispora*, *Ulocladium*, *Undiphilum* and *Ybotromyces*) (Pryor & Gilbertson 2000, Lawrence *et al.* 2012, 2013, Woudenberg *et al.* 2013, Ariyawansa *et al.* 2015a, Rossman *et al.* 2015). Based on the phylogeny of SSU, LSU, ITS, *gapdh*, *rpb2* and *tef1*, Woudenberg *et al.* (2013) emended the generic circumscription of *Alternaria*, and numerous well-supported internal clades were elevated to the taxonomic status of section, some of them correlated with the above-mentioned genera as well as some of Simmons' morphological species-groups. Therefore, in addition to six monophyletic lineages, the genus currently comprises 28 sections, each with a type specimen (Woudenberg *et al.* 2013, Lawrence *et al.* 2016, Al Ghafri *et al.* 2019, Jayawardena *et al.* 2019). However, because the phylogenetic relationships among closely related species could not be resolved by those markers, not even the ITS standard barcode for fungi, multi-gene analyses combining different loci have been used to resolve species boundaries in different sections; *i.e.*, ITS, *Alt a-1*, *endoPG*, *gapdh*, OPA10-2, *rpb2* and *tef1* for sect. *Alternaria* (Woudenberg *et al.* 2015); ITS, *ATPase* and *gapdh* for sect. *Chalastospora* (Marin-Felix *et al.* 2019a); combinations of three to five loci (ITS, *ATPase*, *gapdh* *rpb2* and *tef1*) for sections *Infectoriae* and *Pseudoalternaria*, depending on the authors (Deng *et al.* 2018, Poursafar *et al.* 2018, Iturrieta-González *et al.* 2019, Marin-Felix *et al.* 2019a); ITS, *Alt a-1*, *gapdh*, *rpb2* and *tef1* for sect. *Porri* (Woudenberg *et al.* 2014); ITS, *gapdh* and *rpb2* for sect. *Radicina* (Marin-Felix *et al.* 2019a); and ITS, *Alt a-1* and *gapdh* for sect. *Sonchi* (Lawrence *et al.* 2012, Deng *et al.* 2014). Unfortunately, there is no consensus on the molecular

approach for identifying *Alternaria* species, especially those small-spored species involved in crop diseases, food contamination and human infections. To that end, polyphasic approaches have been carried out in recent investigations, integrating datasets on morphological features, molecular analyses, secondary metabolite profiling or experimental host range determination by inoculation tests (Ozkilinc *et al.* 2018, Patriarca *et al.* 2019, Nishikawa & Nakashima 2020). With this integrative approach, Somma *et al.* (2019) suggested that the sect. *Infectoriae* be defined as a separate genus from *Alternaria*. However, further efforts are needed to provide a more solid taxonomic system that allows correct species identification of these so relevant fungi.

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11. *Phytophthora* de Bary, J. Roy. Agric. Soc. England, ser. 2, 12: 240. 1876.

Type species: *Phytophthora infestans* (Mont.) de Bary

Classification: Oomycota, Peronosporomycetes, Peronosporales, Peronosporaceae.

Background

Phytophthora belongs to phylum Oomycota, related to other heterokonts like brown algae rather than in the fungal kingdom like most filamentous plant pathogens. Index Fungorum (2022) lists 352 species epithets, 223 of which are recognised species with an ex-type isolate and available sequence data (Abad *et al.* 2023b). Most species are plant pathogens with single to numerous hosts ranging from field crops, fruit trees, ornamentals and in natural ecosystems (Erwin & Ribeiro 1996, Hansen *et al.* 2012, Jung *et al.* 2015a, Burgess *et al.* 2021), causing a range of symptoms depending on the species, including root rot, stem and branch cankers, leaf blight and fruit rot (Erwin & Ribeiro 1996).

Sporangia, which can be caducous or persistent, produce zoospores, the infective propagule, that encysts and germinates to penetrate the host (Erwin & Ribeiro 1996). The majority of species are soil pathogens with persistent sporangia, while most *Phytophthora* causing diseases in aerial plant parts have caducous, air-borne sporangia. *Phytophthora* reproduces sexually by forming oospores; heterothallic species require two mating types while homothallic species are self-fertile. Oospores are often thick-walled and are thought to be a vital survival structure for over-wintering and/or surviving drought (González *et al.* 2019, Gyeltshen *et al.* 2021), although there is mounting evidence that many species persist within dead fragments of their hosts (Jung *et al.* 2013). Zoospores are motile and require free water to find and infect a host and are best suited to moist environments, especially those causing aerial diseases. However, some of the most significant impacts are in Mediterranean climates, where the relatively warm moist winter favours infection, and then plants cannot survive the long dry summer with compromised root systems (Dunstan *et al.* 2020, González *et al.* 2020).

De Bary introduced *Phytophthora* in 1876, with the type species, *Phytophthora infestans*, one of the first plant pathogens to be described. It was the causal agent of potato leaf blight and famine in the mid-19th century. Over the following 110 years, 60 more species were described, mainly causing diseases in plants of economic importance (Erwin & Ribeiro 1996). Most of these species have a global distribution associated with agriculture.

Species were described based on the morphology of sporangia, their proliferation, oogonia, antheridia, oospores and the presence of chlamydospores and hyphal swellings or aggregations. Waterhouse (1963) classified species into six groups depending on whether the sporangia were papillate, semi-papillate or non-papillate and whether the antheridial attachment was amphigynous or paragynous. The seminal paper by Cooke *et al.* (2000) on the molecular phylogeny of *Phytophthora* based on ITS sequences divided the genus into 10 phylogenetic clades. These clades have been robust as additional nuclear and mitochondrial genes (Blair *et al.* 2008, Robideau *et al.* 2011, Martin *et al.* 2014, Yang *et al.* 2017b) have been added to the phylogenies and have laid the path for the description of numerous new taxa, many of which were morphologically indistinct but phylogenetically distant (Brasier *et al.* 2003, Burgess *et al.* 2009). While historically, new species recovery and descriptions were from agricultural settings, since 2000 most new species are from natural ecosystems.

Ecological and economic significance

Phytophthora species cause numerous economically significant plant diseases and also serious diseases within natural ecosystems; many species are cosmopolitan, while others are more host-specific. Below we consider the diseases caused by the most cited *Phytophthora* species.

Late blight of potatoes (and tomatoes) is caused by *Phytophthora infestans*, a predominantly aerial *Phytophthora* species infecting leaves and stems, favouring moist, cool environments (Grünwald & Flier 2005). Under ideal conditions, plants die within a few days. Rain washes sporangia into the soil where zoospores infect tubers. *Phytophthora infestans* is a poor saprophyte in the absence of a host and is killed off by frost and hot conditions. However, it can overwinter within infected tubers in a field. Globally, late blight causes around 10 % of crop loss annually and is especially severe in the Indo-Gangetic Plain (Savary *et al.* 2019).

Phytophthora root rot

Several species from the *Phytophthora megasperma* complex have been described, including *Phy. rosacearum* and *Phy. sansomeana* (Hansen *et al.* 2009). Following the description of a related species, *Phy. crassamura* (Scanu *et al.* 2015), many isolates of *Phy. megasperma* recovered from woody plants globally have been reassigned to *Phy. crassamura*. True *Phy. megasperma* is probably limited to *Fabaceae*. *Phytophthora medicaginis* (*Phytophthora* root rot of lucerne) and *Phy. trifolii* (*Phytophthora* root rot of clover) were considered subspecies of *Phy. megasperma* before being formally described (Hansen & Maxwell 1991). Interestingly, *Phy. megasperma* resides in clade 6 of the *Phytophthora* phylogeny, as does *Phy. crassamura* and *Phy. rosacearum*, while *Phy. sansomeana*, *Phy. medicaginis* and *Phy. trifolii* reside in clade 8 (Yang *et al.* 2017b). *Phytophthora* root rot of soybeans caused by *Phytophthora sojae* is one of the most studied *Phytophthora* diseases (Tyler 2007). The symptoms include damping-off of seedlings and then root rot of older seedlings. Management costs and annual crop losses amount to 1–2 billion US dollars. It has a very narrow host range and a global distribution.

Phytophthora stem rot of cowpea caused by *Phytophthora vignae* was first described in Australia and has a narrow distribution limited to Australia and Asia. It causes stem rot, leaf spots and

may ultimately destroy root systems. Natural hosts predominantly include (*Fabaceae*) *Vigna unguiculata* and *V. sinensis*. In Queensland, Australia, it is associated with significant disease and can cause catastrophic loss and complete loss in susceptible commercial crops (Davis *et al.* 1994).

Red stele or red core root rot is the most important disease of garden strawberries (*Fragaria × ananassa*) (Ho & Jong 1988). It is caused by *Phytophthora fragariae* and has been reported in most regions except Africa and South America. The only other natural host of this pathogen is boysenberry (*Rubus ursinus* var. *longanobaccus*). Resistance has been uncovered in strawberries and used to breed resistant varieties (Al-Khayri & Islam 2018). Chemical control is usually used, but there is good evidence that integrated cultural and biological control could reduce the use of fungicides (Norman *et al.* 1996).

White tip is a significant disease of leeks (*Allium porrum*) caused by *Phytophthora porri*, with the most significant impacts during wet and cold periods (Smilde *et al.* 1996). The pathogen has a wide distribution, causing diseases in Africa, Asia, Oceania, Europe and North America (Declercq *et al.* 2010). The pathogen typically causes leaf blight and impacts the bulbs, collar and roots of *Allium* species, although also associated with *Campanula*, *Daucus*, *Dianthus*, *Gladiolus*, *Hyacinthus*, *Lactuca* and *Tulipa* species.

Lima Bean downy mildew is a destructive disease caused by *Phytophthora phaseoli*. At least six races have been identified, leading to severe disease outbreaks in the eastern United States (Evans *et al.* 2007). The impacts are most evident and destructive on pods, but the pathogen also infects shoots, leaves, and petioles. Symptoms include early irregularly shaped and purplish lesions on the leaves. The disease appears most commonly under humid conditions. This species has a wide distribution in the eastern United States and a limited distribution in Central America, Africa, Asia and Europe. Known natural hosts include *Phaseolus lunatus*, *Phaseolus limensis*, and *Phaseolus vulgaris*, although it has caused symptoms on a range of agricultural hosts following artificial inoculations (Erwin & Ribeiro 1996).

Black shank of tobacco, caused by *Phytophthora nicotianae* (syn. *Phy. parasitica*), mainly affects the roots and basal stem area; however, all parts of the plant can become infected (Panabieres *et al.* 2016). Roots become blackened and decayed, and in the final stages of the disease, the stem begins to turn black. The disease is predominantly managed with good hygiene, crop rotations and chemical control. Breeding new varieties of tobacco for resistance to the pathogen has had limited commercial success, although it is an area of ongoing research (Bao *et al.* 2019). *Phytophthora nicotianae* has been extensively researched as an important global pathogen; it has a wide distribution and host range including agriculture, horticulture and ornamental species, where it can affect the roots, stems, trunk, leaves, fruits and pods (Panabieres *et al.* 2016).

Pink rot of potatoes is caused by *Phytophthora erythroseptica*, a species with a global distribution but a very narrow host range. The tubers become infected while in the soil, but symptoms develop during storage. Avoiding the wounding of tubers during harvest and handling and rapid cooling and storage below 10 °C will reduce the impact (Salas *et al.* 2000). Management within the field is more difficult as the pathogen is resistant to common fungicides such

as metalaxyl (Taylor *et al.* 2002). *Phytophthora cryptogea* is often also isolated alone or in association with *Phy. erythroseptica* from symptomatic tubers.

Root and stem rot is a common disease of numerous cultivated flowers, annual crops and ornamentals. Two of the pathogens often recovered in these situations are *Phytophthora cryptogea* and *Phy. drechsleri*; both are cosmopolitan species with numerous hosts (Erwin & Ribeiro 1996). These species are more often recovered from managed landscapes than from natural ecosystems. Several related species have now been described from the *Phy. cryptogea* species complex, including *Phy. pseudocryptogea*, which appears to be more common in natural ecosystems than *Phy. cryptogea* (Safaiefarahani *et al.* 2015). Isolates previously classified as *Phy. drechsleri* based on morphology have now been described as new species, many of which are not closely related to *Phy. drechsleri* (Burgess *et al.* 2009).

Phytophthora blight

Phytophthora capsici is a caducous species causing *Phytophthora* blight in vegetable crops, including capsicum and various other *Solanaceae* and *Cucurbitaceae*. The pathogen affects fruit and stems and causes root rot, stunted growth, and death of older plants (Hausbeck & Lamour 2004). Disease incidence and severity have increased significantly in recent decades, and very little natural resistance has been found in most crops. Disease management depends on cultivation, sanitation, and fungicides (Lamour *et al.* 2012). Many records of *Phy. capsici* in the tropics, especially those associated with woody hosts, are most likely records of a related species, *Phy. tropicalis* (Aragaki & Uchida 2001).

Diseases of fruits and pods

There are several *Phytophthora* diseases of fruits and pods, stem cankers, leaf diseases and root rot of important tropical crops such as cocoa, coconut, durian, rubber and taro (Erwin & Ribeiro 1996, Drenth & Guest 2004). Some species such as *Phy. palmivora* have a global distribution, while others have a more limited distribution; for example, *Phy. meadii* which is limited to Asia and the Pacific. While several species can cause the same symptoms on the same tree species, some of the best-known diseases include black stripe of rubber, bud rot and nut fall of coconut caused by *Phy. heveae*, taro leaf blight caused by *Phy. colocasiae*, bud rot of oil palm caused by *Phy. palmivora*, pod rot of rubber caused by *Phy. meadii* and black pod disease of cocoa caused by *Phy. megakarya* (Erwin & Ribeiro 1996, Drenth & Guest 2004).

Brown rot of citrus fruit caused by *Phytophthora hibernalis* was first described in Western Australia in 1926, although the disease had been known since 1916 (Carne 1926). It is now known to have an almost global distribution on *Citrus* species and other *Rutaceae*, and it is doubtful *Phy. hibernalis* originated in Australia. The most effective control is the use of fungicides in orchards (also to control other *Phytophthora* diseases of *Citrus*) and postharvest treatments (Adaskaveg & Förster 2014). *Phytophthora boehmeriae* also causes brown rot of citrus fruit and a variety of other diseases, including cotton boll blight. *Phytophthora boehmeriae* has a more limited distribution than *Phy. hibernalis*, and has not been reported in most of Europe or North America (Erwin & Ribeiro 1996).

Gummosis of citrus trees is the leading cause of stunted growth and mortality globally. The most common species associated with

this disease is *Phytophthora citrophthora*, one of the first species described (Leonian 1925). This disease has been extensively studied, especially cultural and chemical control (Cacciola & di San Lio 2008). Resistant rootstocks (Matheron *et al.* 1998) and phosphite use (Matheron & Matejka 1988) are common control measures.

Sudden oak death

Phytophthora ramorum causes a significant disease of oak species on the west coast of North America known as sudden oak death. The pathogen spreads through aerial spores under moist conditions and causes significant bleeding cankers on trunks and branches, foliage dieback and death. In North America, there are sporulating hosts such as California bay laurels (*Umbellularia californica*), where the pathogen infects leaves and produces significant inoculum, and dead-end hosts such as tanoak (*Lithocarpus densiflorus*) and coast live oak (*Quercus agrifolia*), where infection often leads to death (Rizzo *et al.* 2002). Ramorum blight is common on numerous woody ornamentals, in particular *Rhododendron* (Grünwald *et al.* 2008). Within Europe, *Phy. ramorum* does not cause disease of oaks; however, it has been reported in commercial nurseries in over 20 countries (Grünwald *et al.* 2008), and it causes a significant decline of Japanese larch (*Larix kaempferi*) plantations (Brasier & Webber 2010) in the UK. *Phytophthora kernoviae* also causes significant disease in *Rhododendron* spp., *Fagus grandifolia* and *Vaccinium* spp. in the UK (Brasier *et al.* 2005). As *Phytophthora kernoviae* has limited impact on native species in New Zealand, it is hypothesised to be the species' origin (Gardner *et al.* 2015).

Port-Orford cedar root disease

Phytophthora lateralis is an invasive soilborne pathogen responsible for Port-Orford cedar root disease (*Chamaecyparis lawsoniana*) in the USA, first noted in Washington State in the 1920s. The disease causes distinct colour changes in the foliage and mass collapse. The pathogen is found throughout the natural range of Port-Orford cedar in the USA, in Europe and from old growth *C. obtusa* in Taiwan (Hansen 2015). The pathogen spreads readily through contaminated water, organic material, infected earth-moving equipment, and nursery stock. The disease is managed within the USA by mapping the pathogen distribution and controlling its spread and replanting with resistant cultivars identified within infected forests and from a breeding program (Hansen *et al.* 2000).

Phytophthora dieback

Phytophthora cinnamomi is one of the world's most devastating plant pathogens; it has a vast host range and a global distribution (Burgess *et al.* 2017). *Phytophthora cinnamomi* is the only oomycete and one of the only three plant pathogens listed as one of the 100 worst invasive alien species (Lowe *et al.* 2000). The pathogen was first described as the causal agent of stripe rust of *Cinnamomum burmannii* in Sumatra in 1922, and while the origin is unknown, most evidence points to a natural distribution in the uplands in south-east Asia (Arentz & Simpson 1986). While *Phy. cinnamomi* is a destructive plant pathogen of tree crops such as avocado and woody ornamentals, perhaps the most significant destruction is seen in Mediterranean climates where it causes *Phytophthora* dieback in susceptible *Proteaceae* communities in the Cape Floristic region of South Africa (Nagel *et al.* 2013) and

the Southwest Botanical Province of Western Australia (Shearer *et al.* 2007). The most effective chemical control within managed landscapes is systemic fungicides (Coffey 1987) while preventing the spread into new areas is the primary control strategy for natural ecosystems (Cahill *et al.* 2008). As *Phy. cinnamomi* is a poor saprophyte, some success in eradication has been achieved using fallow periods (Dunstan *et al.* 2020).

Alder dieback is a serious root and collar rot disease of *Alnus* species throughout large regions of Europe and parts of North America. The disease is caused by *Phytophthora alni* (homoploid triploid hybrid) and the parental organisms *Phy. multiformis* (allotetraploid hybrid) and *Phy. uniformis* (diploid species) (Husson *et al.* 2015). *Phytophthora alni* is found throughout Europe and is associated with root and collar rot of riparian, nursery, and shelterbelt *Alnus glutinosa* and other *Alnus* species, including *A. incana* and *A. cordata*. *Phytophthora uniformis* occurs sporadically throughout parts of Europe in association with *Phy. alni* and is found in North America in Alaska and Oregon, where it is associated with declining *Alnus rubra* (Sims *et al.* 2015). *Phytophthora multiformis* has been found in fewer countries in Europe (Husson *et al.* 2015). The pathogens have significant impacts on riparian and forest ecosystems and are dispersed through water movement and flooding cycles, poor hygiene and infected plant material (Elegbede *et al.* 2010). Alders resistant to the disease have been identified, and screening and breeding have been proposed to help manage the disease (Chandelier *et al.* 2016).

Kauri dieback, caused by *Phytophthora agathidicida*, is a serious soil-borne disease of the keystone ecological species kauri (*Agathis australis*) in the rare podocarp forests of northern New Zealand. The pathogen has a devastating impact causing mass collapse and large bleeding cankers of the collar and trunk (Scott & Williams 2014). The disease has significant ecosystem impacts due to the loss of kauri, including large ancient trees and the subsequent loss of a range of rare understory species dependent upon the unique soil and ecological characteristics created by established kauri. Kauri has significant ecological and cultural roles for New Zealand's indigenous people. Maori groups have led a range of responses to manage kauri dieback, involving traditional knowledge (mātauranga Māori) and contemporary approaches (Lambert *et al.* 2018). The disease is managed using forest hygiene and chemical control, including injections of the systemic chemical control agent phosphite (Bradshaw *et al.* 2020c).

Red needle cast of radiata pine is an important disease of exotic forestry within New Zealand caused by *Phytophthora pluvialis*. The disease can cause needle banding and casting of radiata pine (*Pinus radiata*) and Douglas fir (*Pseudotsuga menziesii*) during seasons with conducive high rainfall environmental conditions, although it causes minimal symptoms during dry years (Dick *et al.* 2014). The pathogen does not infect or colonise woody tissue; however, the cumulative impact of needle casting can significantly impact wood development and commercial forestry (Hood *et al.* 2014, Scott & Williams 2014). Within New Zealand, the pathogen is effectively managed with chemical control using aerial copper application and screening and breeding for resistance (Rolando *et al.* 2017). *Phytophthora pluvialis* is also known to cause casting and productivity impacts in Douglas fir and *Pinus* species in North America (Oregon), although it is unknown to have severe impacts on natural forestry ecosystems in that region (Reeser *et al.* 2013).

Canker and root rot of woody trees

There are several cosmopolitan *Phytophthora* species with a broad host range and almost global distribution; *Phy. cambivora*, *Phy. niederhauseri*, *Phy. syringae*, *Phy. nicotianae*, *Phy. cinnamomi*, *Phy. multivora* and *Phy. plurivora*. These are pathogens of trees and woody perennial shrubs in agriculture, ornamentals and natural ecosystems. *Phytophthora multivora* (Scott *et al.* 2009) and *Phy. plurivora* (Jung & Burgess 2009) are within the *Phy. citricola* species complex only recognised using molecular taxonomy. *Phytophthora citricola* was first recognised as a disease of *Citrus* spp. and many records from other hosts are incorrect. *Phytophthora cambivora* is commonly associated with cankers of chestnuts in Europe (Vettraino *et al.* 2005). *Phytophthora niederhauserii* was only recently described but already has an extensive host and geographic range and is common in orchards (Abad *et al.* 2014).

Research interests

There are 6 909 publications and 69 739 citations from 2011–2021 in the Web of Science (Fig. 23), with the top 10 most cited articles given in Table 13. The majority of the most cited publications focus on taxonomy, genomics, infection processes and molecular plant-microbe interactions and how these could be manipulated to aid disease management, the global movement of *Phytophthora* species and biological invasions, especially into natural ecosystems (Fig. 24). The highly cited papers are from the start of the decade, but similar themes remain essential today. *Phytophthora* species continue to be important pathogens in managed landscapes and natural ecosystems and are, in some cases, becoming tolerant of the fungicides used to control them (Hollomon 2015). The increasing impact of *Phytophthora* pathogens in natural ecosystems has led to increased emphasis on landscape-level management of disease and DNA metabarcoding to establish the diversity and distribution of *Phytophthora* within the landscape (Burgess *et al.* 2019).

Genomics and molecular plant-microbe interactions

Due to their impact on numerous crops, *Phytophthora* is a commonly studied plant pathogen. There are six species, *Phy. infestans*, *Phy. ramorum*, *Phy. sojae*, *Phy. capsici*, *Phy. cinnamomi* and *Phy. nicotianae*, among the top 10 oomycete pathogens in molecular plant pathology (Kamoun *et al.* 2015). Effectors and proteins expressed by plant pathogens aid in the infection process. Pathogenic *Phytophthora* species are known to have an extensive effector repertoire and are the topic of numerous studies. The most highly cited paper among these looked at effectors from *Phy. sojae* and found that different effectors play an important role at different stages of the infection process (Wang *et al.* 2011). If the expression of effectors from early in the infection process is disrupted, transformants lose their virulence. Mycorrhizal fungi have a demonstrated protective effect against colonisation by soilborne pathogens such as *Phytophthora*. It is through that a modulation of plant defences occurs due to mycorrhizal priming of the plant defences (generalised induced resistance) (Jung *et al.* 2012).

Many oomycetes have large genomes, and the genes involved in host interactions are often polymorphic. These genome regions are highly adaptable and plastic, enabling them to adapt to new hosts and new environments (Raffaele & Kamoun 2012). One excellent example of this is *Phy. infestans* which has undergone major population shifts over time due to successive emergence and migration of lineages usually involving the displacement of existing less fit lineages (Cooke *et al.* 2012). The genome of one lineage that emerged and dominated in Great Britain over three years had extensive changes to the effector genes, enabling it to overcome resistance in some common potato varieties (Cooke *et al.* 2012).

Biological invasions and climate change

Numerous *Phytophthora* species associated with food crops have a cosmopolitan distribution, and many species true origin remains unknown. More recently, the most common pathway for introduction, especially for species that invade natural ecosystems,

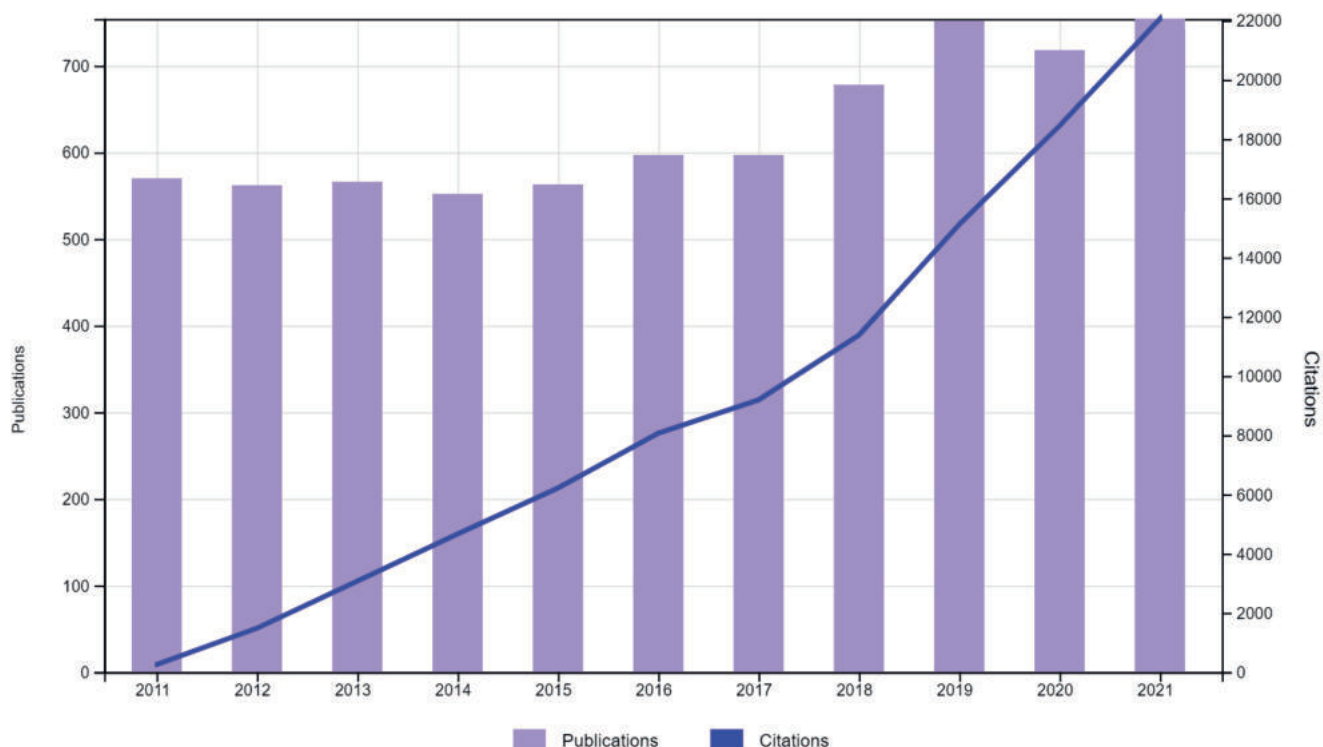


Fig. 23. Trends in research of *Phytophthora* in the period 2011–2021.

Table 13. Top 10 cited articles related to *Phytophthora* published in the period 2011–2021.

Rank	Article title	No. of citations	References
1	Emerging fungal threats to animal, plant and ecosystem health	1 678	Fisher <i>et al.</i> (2012)
2	Mycorrhiza-induced resistance and priming of plant defenses	439	Jung <i>et al.</i> (2012)
3	The top 10 oomycete pathogens in molecular plant pathology	383	Kamoun <i>et al.</i> (2015)
4	DNA barcoding of oomycetes with cytochrome c oxidase subunit I and internal transcribed spacer	375	Robideau <i>et al.</i> (2011)
5	Genome evolution in filamentous plant pathogens: why bigger can be better	361	Raffaele & Kamoun (2012)
6	Climate change and forest diseases	359	Sturrock <i>et al.</i> (2011)
7	Live plant imports: the major pathway for forest insect and pathogen invasions of the US	347	Liebhold <i>et al.</i> (2012)
8	Biogeographical patterns and determinants of invasion by forest pathogens in Europe	323	Santini <i>et al.</i> (2013)
9	Transcriptional programming and functional interactions within the <i>Phytophthora sojae</i> RXLR effector repertoire	265	Wang <i>et al.</i> (2011b)
10	Genome analyses of an aggressive and invasive lineage of the Irish potato famine pathogen	237	Cooke <i>et al.</i> (2012)

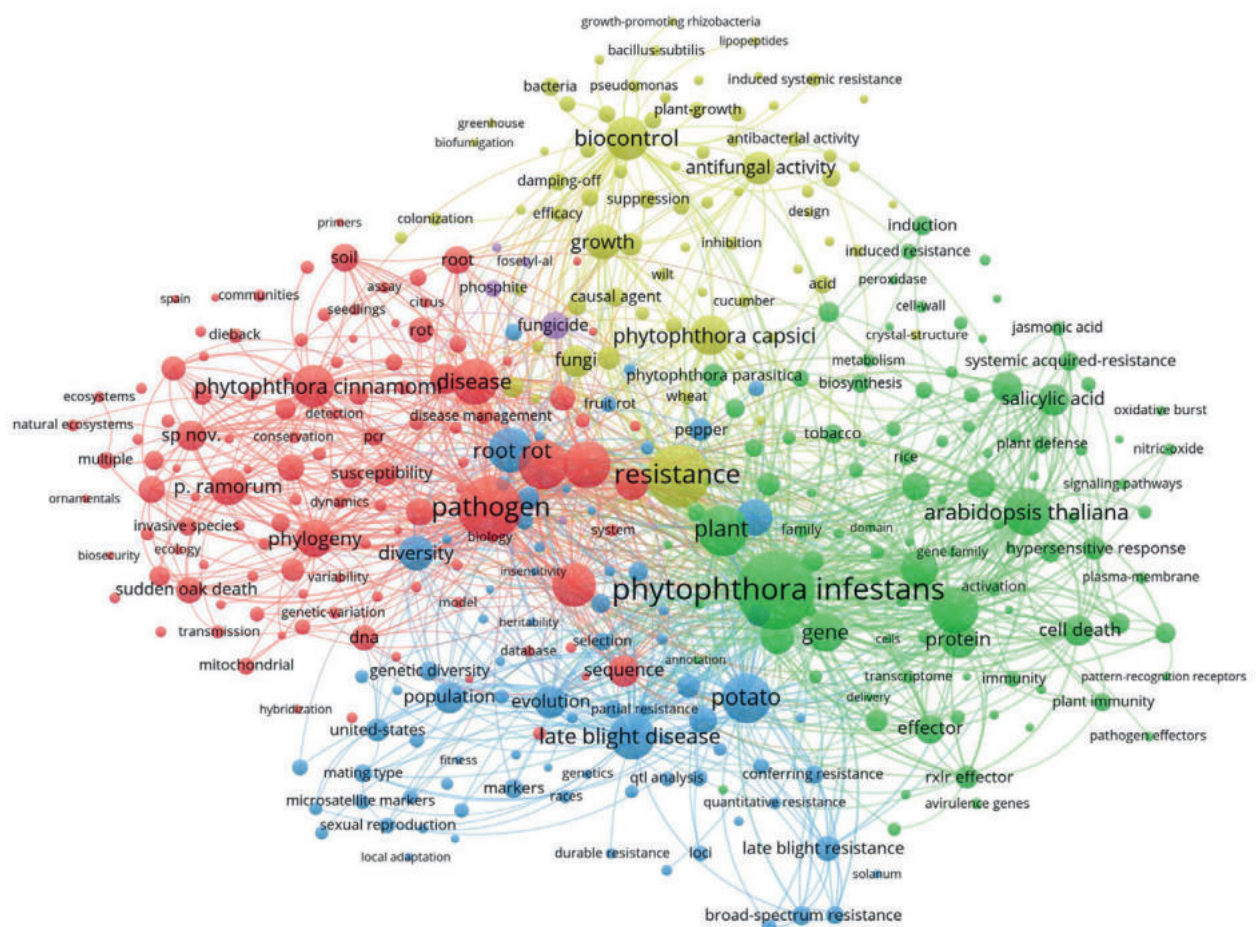


Fig. 24. Network visualisation of keywords of the publications related to *Phytophthora*. The larger the text and the circle the more often the subject has been cited.

has been through the nursery trade and live plant imports (Liebhold *et al.* 2012, Santini *et al.* 2013). While being significant agricultural pathogens, perhaps the greatest impact of introduced *Phytophthora* species has been in the natural environment (Sturrock *et al.* 2011, Fisher *et al.* 2012, Hansen *et al.* 2012). Sudden oak death caused by *Phy. ramorum* in the west coast USA (Rizzo & Garbelotto 2003), and *Phytophthora* dieback caused by *Phy. cinnamomi* in Australia (Cahill *et al.* 2008) have permanently changed the structure and

function of impacted ecosystems. Sturrock *et al.* (2011) predicted that the impact of *Phytophthora* diseases would remain the same, or decrease, in warmer drier climates and increase in warmer wetter climates. These predictions have been supported by a species distribution model developed for *Phy. cinnamomi* using a global dataset of presence and absence records (Burgess *et al.* 2017).

Taxonomy and phylogeny

Until Cooke *et al.* (2000) published the first molecular phylogeny of *Phytophthora*, species descriptions had been based solely on morphological features, resulting in some species complexes that are now known to have been comprised of morphologically similar but phylogenetically unrelated species. There have been several phylogenetic studies including increasingly more *Phytophthora* species; Cooke *et al.* (2000) included 48 species from eight clades, this has increased to 82 species (Blair *et al.* 2008), then 109 species (Martin *et al.* 2014) and most recently 185 species representing 10 clades (Yang *et al.* 2017b). The ITS and CO1 phylogenies of Robideau *et al.* (2011) are particularly cited as this publication included 1 205 isolates from 23 genera of oomycetes (not just *Phytophthora*), and it has thus been very useful for metabarcoding studies using environmental DNA. The most updated phylogeny based on type isolates and a complete revision of the genus has recently been published (Abad *et al.* 2023a).

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12. *Rhizopus* Ehrenb., Nova Acta Phys.-Med. Acad. Caes. Leop. -Carol. 10: 198. 1821.

Type species: *Rhizopus stolonifer* (Ehrenb.) Vuill.

Classification: Mucoromycota, Mucoromycotina, Mucoromycetes, Mucorales, Rhizopodaceae.

Background

Rhizopus constitutes an important genus within *Mucorales* with 11 accepted species (Walther *et al.* 2019, Jayawardena *et al.* 2020) and around 150 epithets listed in Index Fungorum (2022). They are common post-harvest pathogens, human pathogens, and saprobes. They pose a threat to agricultural products by damaging the taste and appearance of crops such as strawberries and sweet potatoes. They are also opportunistic pathogens causing mucormycosis in immunosuppressed humans and the cause of some animal diseases. Furthermore, endosymbiotic bacteria residing in the hyphae of some *Rhizopus* species produce the phytotoxin rhizoxin which can lead to human poisoning (Partida-Martinez *et al.* 2007, Gryganskyi *et al.* 2018). *Rhizopus* species have industrial and medical importance and occur worldwide. They are bio-industrial fermenters for food and are used in metabolite production. They are used to produce fermented products such as tempeh.

The conventional taxonomy of *Rhizopus* was primarily based on morphology and physiological characteristics. Similar to most *Mucorales*, the taxonomy of *Rhizopus* is based on asexual morphological characters and growth parameters. These characteristics included maximum growth temperature, sugar fermentation, and formation of acids. Organic acid patterns were used as a critical criterion for *Rhizopus* because it was shown that the ITS sequences had a clear relationship with acid production and that ITS was simple and effective for classification (Abe *et al.* 2003). Inui *et al.* (1965) concluded that 10 characters were important in the taxonomy of *Rhizopus* which includes the characteristics mentioned above. Other characteristics include the formation of sporangia, chlamydospores, rhizoids, and the shape and colour of the sporangia (Zheng *et al.* 2007). Karyological studies of isolated species from Korean soil showed that chromosome numbers can vary from a minimum of eight (*Rhiz. arrhizus*) to a maximum of 16 (*Rhiz. stolonifer*).

Even with the use of DNA sequence data, the classification of this genus remains contentious. Abe *et al.* (2006) provided the first molecular phylogenetic study of *Rhizopus* and separated the genus into three groupings which is congruent with the study of Schipper (1984); *Rhiz. microsporus*, *Rhiz. stolonifer*, and *Rhiz. arrhizus*. Later studies, based on ribosomal DNA (rDNA) and orotidine-5'-monophosphate decarboxylase gene (*pyrG*) sequences and morphology, either organised the genus into 10 species and seven varieties or into eight species (Liu *et al.* 2007, Zheng *et al.* 2007). In the phylogenetic reconstruction of the genus, several inconsistencies in topology have been noticed depending on which genes are used and the phylogenetic methods utilised. These have been demonstrated in Gryganskyi *et al.* (2018). Phylogenomic analysis based on 192 orthologous protein-coding genes from whole-genome sequencing supports the findings of Liu *et al.* (2007). It suggests that there may be a reduction in the number of accepted species in the future as these species may be phylogenetically nested within *Rhiz. deleamar*, *Rhiz. stolonifer*, *Rhiz. arrhizus*, or *Rhiz. microsporus*.

Ecological and economic significance Postharvest pathogens

Rhizopus species are known pathogens of several crops such as strawberries, tomatoes, and sweet potatoes. They cause diseases such as *Rhizopus* soft rot, head rot, and *Rhizopus* blight. The common causative species are *Rhiz. stolonifer*, *Rhiz. arrhizus*, and *Rhiz. microsporus*. Typically, a wound is necessary for infection to occur. Aerial spores land on these wounds or cracks and then produce enzymes that degrade the host cells (Jayawardena *et al.* 2020). Tomato which is highly consumed and is the second most important horticultural crop in the world (Alfaro-Sifuentes *et al.* 2019) is highly perishable and susceptible to mechanical damage during postharvest handling. It is estimated that 30 % of these fruits are lost due to postharvest disease of which 80 % are caused by *Rhiz. stolonifer* (Alfaro-Sifuentes *et al.* 2019). Soft rot by *Rhizopus* is also a devastating postharvest disease in sweet potatoes resulting in a 2 % loss in the stored roots (Scruggs *et al.* 2016).

***Rhizopus* soft rot** also affects peaches (Bautista-Baños *et al.* 2014). In Egypt and Brazil, postharvest diseases result in quality loss and rejection during sales (Bautista-Baños *et al.* 2014, Baggio *et al.* 2017). Notably, in Egypt, the frequency of isolating *Rhiz. stolonifer* from diseased peaches in markets was 56.5 % (Bautista-Baños *et al.* 2014). The presence of decayed fruits during postharvest handlings such as during transportation and storage can affect the quality and sale price of the fruit even if visible rotten fruits have been discarded and no apparent symptoms are seen. An increase of 1 % in the incidence of rots can reduce retail and wholesale prices by 1.24 % and 0.91 % respectively (Baggio *et al.* 2017).

Research interests

There are 3 353 publications and 51 691 citations from 2011–2021 in the Web of Science (Fig. 25), with the top 10 most cited articles listed in Table 14. Most publications are related to the application of *Rhizopus* to produce secondary metabolites, human pathogenicity (Mucormycosis), and taxonomy (Fig. 26).

Production of lactic acid through fermentation

Lactic acid, known as 2-hydroxypropanoic acid, is an organic acid that can be used as a preservative, acidulant, or as inhibitor

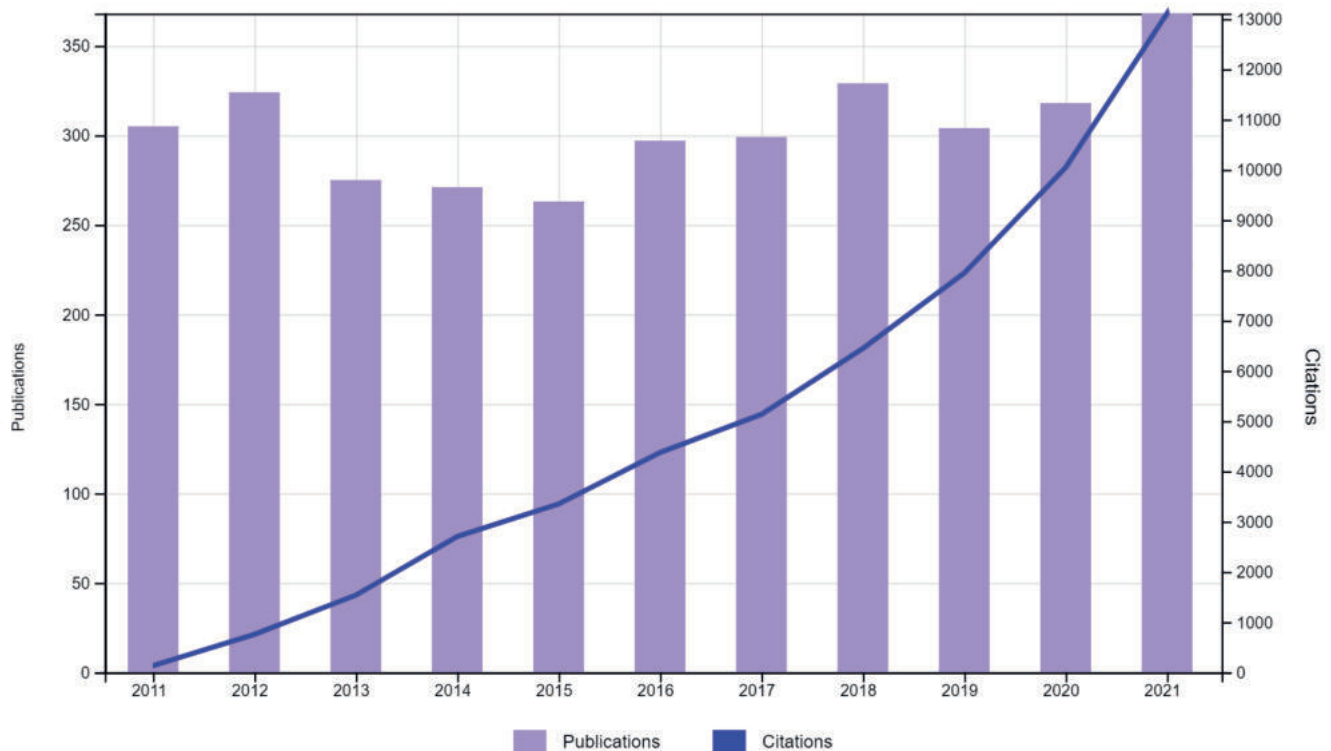


Fig. 25. Trends in research of *Rhizopus* in the period 2011–2021.

Table 14. Top 10 cited articles related to *Rhizopus* published in the period 2011–2021.

Rank	Article title	No. of citations	References
1	Zygomycosis in Europe: analysis of 230 cases accrued by the registry of the European Confederation of Medical Mycology (ECMM) Working Group on zygomycosis between 2005 and 2007	380	Skiada <i>et al.</i> (2011)
2	Biological activities of α -pinene and β -pinene enantiomers	321	Da Silva Rivas <i>et al.</i> (2012)
3	Pathogenesis of mucormycosis	283	Ibrahim <i>et al.</i> (2012)
4	A global analysis of mucormycosis in France: The RetroZygo Study (2005–2007)	271	Lanternier <i>et al.</i> (2012)
5	Synthesis, characterization and catalytic activity of gold nanoparticles biosynthesized with <i>Rhizopus oryzae</i> protein extract	240	Das <i>et al.</i> (2012)
6	One stop shop: backbones trees for important phytopathogenic genera: I (2014)	235	Hyde <i>et al.</i> (2014)
7	Antibacterial effects of biosynthesized silver nanoparticles on surface ultrastructure and nanomechanical properties of gram-negative bacteria viz. <i>Escherichia coli</i> and <i>Pseudomonas aeruginosa</i>	223	Ramalingam <i>et al.</i> (2016)
8	Global epidemiology of mucormycosis	217	Prakash & Chakrabarti (2019)
9	The epidemiology and clinical manifestations of mucormycosis: a systematic review and meta-analysis of case reports	213	Jeong <i>et al.</i> (2019)
10	Daqu - A Traditional Chinese Liquor Fermentation Starter	173	Zheng <i>et al.</i> (2011b)

of bacterial spoilage in foods (Ajala *et al.* 2020, 2021). This acid can be produced using fermentation processes or chemical methods. Fermentative methods enable the use of renewable carbohydrates, which are cleaner and more ecological. However, the choice of substrate is key as it determines the efficiency and cost of production. *Rhizopus* species can be used for both surface and submerged fermentation to produce lactic acid. This species is also widely used as the cells have better resistance to a high concentration of lactic acid than commonly used bacterial producers (Ajala *et al.* 2021). However, homofermentative lactic acid bacteria are significantly more efficient than fungi in converting sugars to

lactic acid because of the production of other by-products such as ethanol and fumaric acid by the *Rhiz. oryzae*-based process (Abedi & Hashemi 2020).

Mucormycosis

Mucormycosis (also known as zygomycosis) is a rare and lethal form of fungal infection (Rodríguez-Lobato *et al.* 2017). The disease is primarily caused by *Rhizopus* species, with 70 % of mucormycosis associated with this genus (Andrianaki *et al.* 2018). Over the past few decades, mucormycosis has become the third most common fungal infection in patients having haematological malignancies

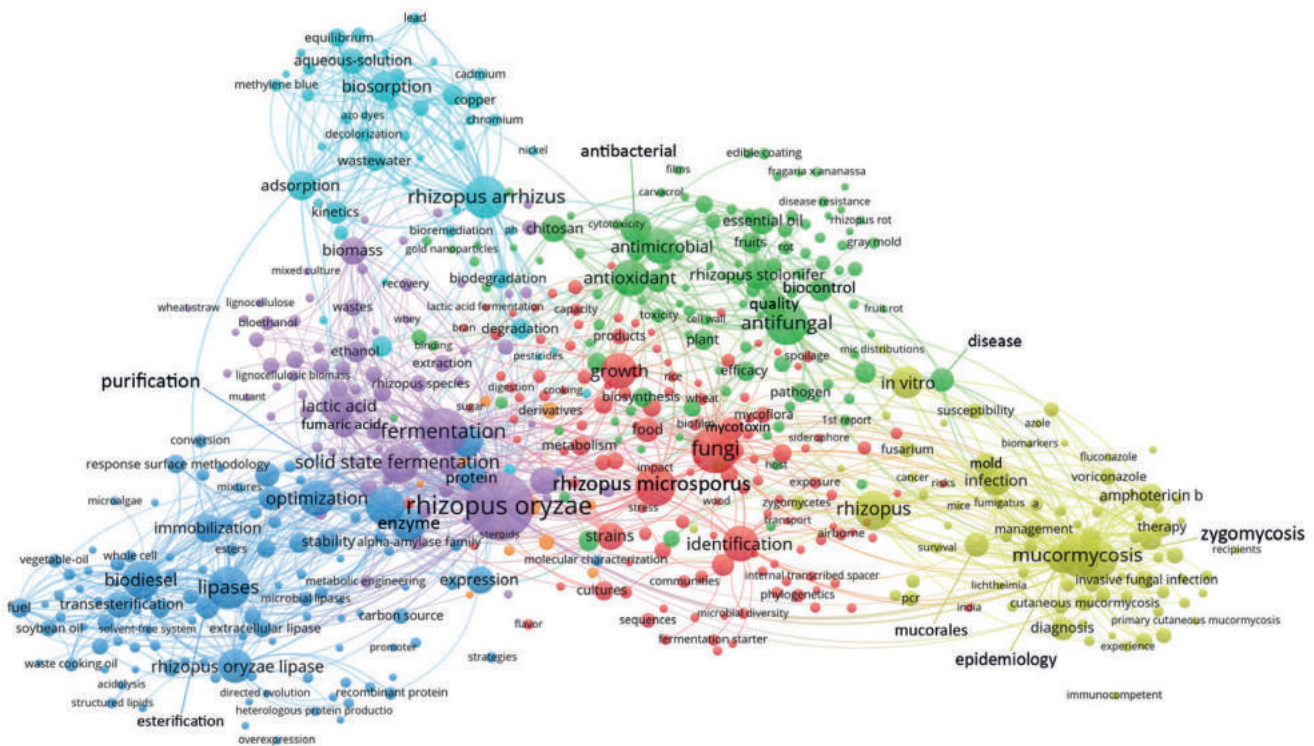


Fig. 26. Network visualisation of keywords of the publications related to *Rhizopus*. The larger the text and the circle the more often the subject has been cited.

or those having organ transplantation. The predominant species involved in this life-threatening disease are *Rhiz. delema* and *Rhiz. arrhizus* (syn. *Rhiz. oryzae*). Other species are found in the genera *Mucor*, *Lichtheimia*, *Rhizomucor*, *Apophysomyces*, and *Cunninghamella* (Baldin & Ibrahim 2017). The main risk factors that make an individual prone to mucormycosis are neutropenia due to cancer treatment and diabetes mellitus especially those presenting with ketoacidosis, hematopoietic and organ transplantation (Baldin & Ibrahim 2017). The mortality rate of cutaneous mucormycosis is 31 % if a deep extension is present but primary cutaneous mucormycosis mortality is lower, especially in immunocompromised patients (Rodríguez-Lobato *et al.* 2017).

Disease management

Due to the devastating effect of *Rhizopus* species on postharvest crops, studies in controlling and managing the disease are crucial. Fungistatic mechanisms against *Rhizopus* rot such as antibiotics, antifungal activity, direct parasitism in pathogens, and induction of resistance of the host and competition by microbial antagonists have been suggested. Among these, the induction of disease resistance by other microbial agents of the host has been regarded as pivotal (Zhang *et al.* 2020). After treatment, resistance can be obtained through the production of antifungal substances, providing systemic and long-lasting resistance against the pathogenic organism. Chemical treatment methods are also used where the fruits are immersed in ethanol solutions and are effective in controlling decay by fungi. Other studies have tested several methods such as UV or β -aminobutyric acid (Özer Uyar & Uyar 2018).

Author: V.G. Hurdeal

13. *Phanerochaete* P. Karst., Bidr. Känn. Finl. Nat. Folk 48: 426. 1889.

Type species: *Phanerochaete alnea* (Fr.) P. Karst.

Classification: Basidiomycota, Agaricomycotina, Agaricomycetes, Polyporales, Phanerochaetaceae.

Background

Phanerochaete was introduced by Karsten (1889) with *Pha. alnea* as the type. This genus is a saprobic homobasidiomycete on woody debris and logs (De Koker *et al.* 2003). Most species of *Phanerochaete* are associated with white-rot of wood and are widely distributed on fallen branches and logs, branches attached to trees, twigs, and even wood buried in the soil (Eriksson *et al.* 1978, Burdsall 1985). It is a large genus of the family *Phanerochaetaceae*, with 204 records in Index Fungorum (2022). Intraspecific names in *Phanerochaete* and additional new species are anticipated (De Koker *et al.* 2000).

Phanerochaete is a member of the corticioid fungi, and it is characterised by resupinate, membranaceous basidiomata with or without rhizomorphs, a monomitic hyphal system with primarily simple-septate generative hyphae, clavate basidia with four sterigmata, and smooth, thin-walled, inamyloid basidiospores (Eriksson *et al.* 1978, Burdsall 1985, Bernicchia & Gorjón 2010). The simplicity of the morphological characters of *Phanerochaete* and the existence of species with sporocarps that fulfil only some of these morphological criteria renders the limits of the genus uncertain (Floudas & Hibbett 2015). Other authors have also discussed and approached the taxonomy of *Phanerochaete* in different ways (Parmasto 1968, Eriksson *et al.* 1978, Jülich & Stalpers 1980, Xu *et al.* 2020, Chen *et al.* 2021a, Wang *et al.* 2021).

Molecular studies involving *Phanerochaete* based on ribosomal DNA (rDNA) sequences, revealed the phylogenetic distribution of resupinate forms across the major clades of mushroom-forming fungi, in which *Pha. chrysosporium* nested into the phlebioid clade

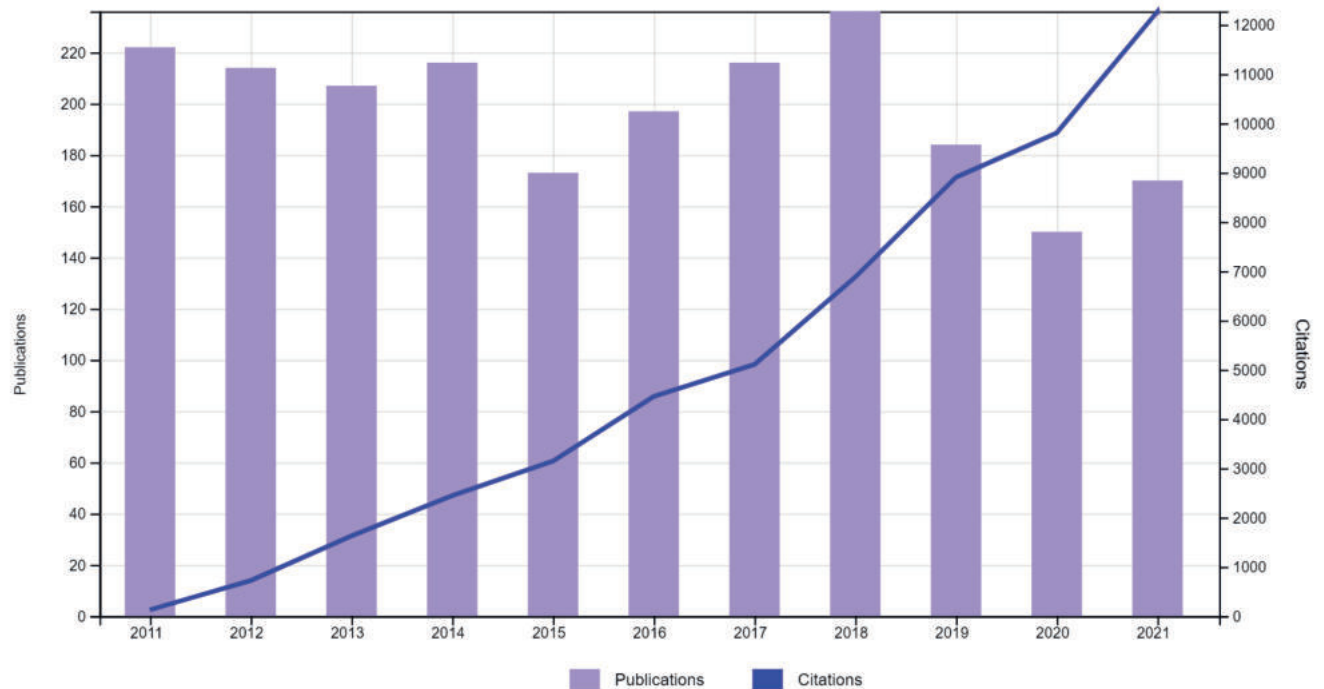


Fig. 27. Trends in research of *Phanerochaete* in the period 2011–2021.

Table 15. Top 10 cited articles related to *Phanerochaete* published in the period 2011–2021.

Rank	Article title	No. of citations	References
1	Expansion of the enzymatic repertoire of the CAZy database to integrate auxiliary redox enzymes	681	Levasseur <i>et al.</i> (2013)
2	High-performance green flexible electronics based on biodegradable cellulose nanofibril paper	499	Jung <i>et al.</i> (2015b)
3	Untapped potential: exploiting fungi in bioremediation of hazardous chemicals	491	Harms <i>et al.</i> (2011)
4	Microbial decolouration of azo dyes: A review	480	Solis <i>et al.</i> (2012)
5	Extensive sampling of basidiomycete genomes demonstrates inadequacy of the white-rot/brown-rot paradigm for wood decay fungi	422	Riley <i>et al.</i> (2013)
6	Bioactive phenolic compounds: Production and extraction by solid-state fermentation. A review	367	Martins <i>et al.</i> (2011)
7	Lignocellulosic agriculture wastes as biomass feedstocks for second-generation bioethanol production: concepts and recent developments	316	Saini <i>et al.</i> (2015)
8	Fungal pretreatment of lignocellulosic biomass	257	Wan & Li (2012)
9	Lignin-degrading enzymes	230	Pollegioni <i>et al.</i> (2015)
10	Microbial decolorization and degradation of synthetic dyes: a review	206	Khan <i>et al.</i> (2013b)

in *Polyporales* (Binder *et al.* 2005). A DNA-phylogeny-based and morphology-based study to reconcile the polypores and genus concepts in the family *Phanerochaetaceae* (Miettinen *et al.* 2016), found the macromorphology of sporocarps and hymenophore construction did not reflect monophyletic groups, and *Ceriporia inflata* was combined into *Phanerochaete*. Amplifying nrLSU, nrITS, and *rpb1* genes across the *Polyporales* revealed that eleven genera clustered into the family *Phanerochaetaceae*, and two families *Hapalopilaceae* and *Bjerkanderaceae* were placed as synonyms of *Phanerochaetaceae* (Justo *et al.* 2017). Recently, morphological studies and phylogenetic analyses found many new taxa of *Phanerochaete* s. str. and determined the taxonomic status of the new taxa within *Phanerochaete* (Wu *et al.* 2018c, Xu *et al.* 2020).

Ecological and economic significance

Phanerochaete is a genus that causes white rot on both softwood and hardwood and has attracted the attention of researchers for a long

time (Floudas & Hibbett 2015). *Phanerochaete* are white-rot fungi that produce extracellular enzymes capable of completely degrading lignocellulose, the main component of wood and other plant cell walls (MacDonald *et al.* 2012) and the genus plays an important role in carbon cycling (Burdsall 1985). *Phanerochaete* species also have potential applications in the production of renewable chemicals and liquid fuel from wood, which is among the largest biomass resources that could be used to produce such chemicals (Lin & Tanaka 2006). The oxidative enzymes involved in wood degradation by *Phanerochaete* have also been shown to degrade a variety of persistent environmental pollutants, including chlorinated aromatic compounds, munitions, pesticides, and dyes (Cameron *et al.* 2000).

Ecology and distribution

Phanerochaete has been studied outside Europe (Burdsall 1985) in North America and Asia (Wu 1990). *Phanerochaete* is widely distributed from boreal to tropical forests (Burdsall 1985).

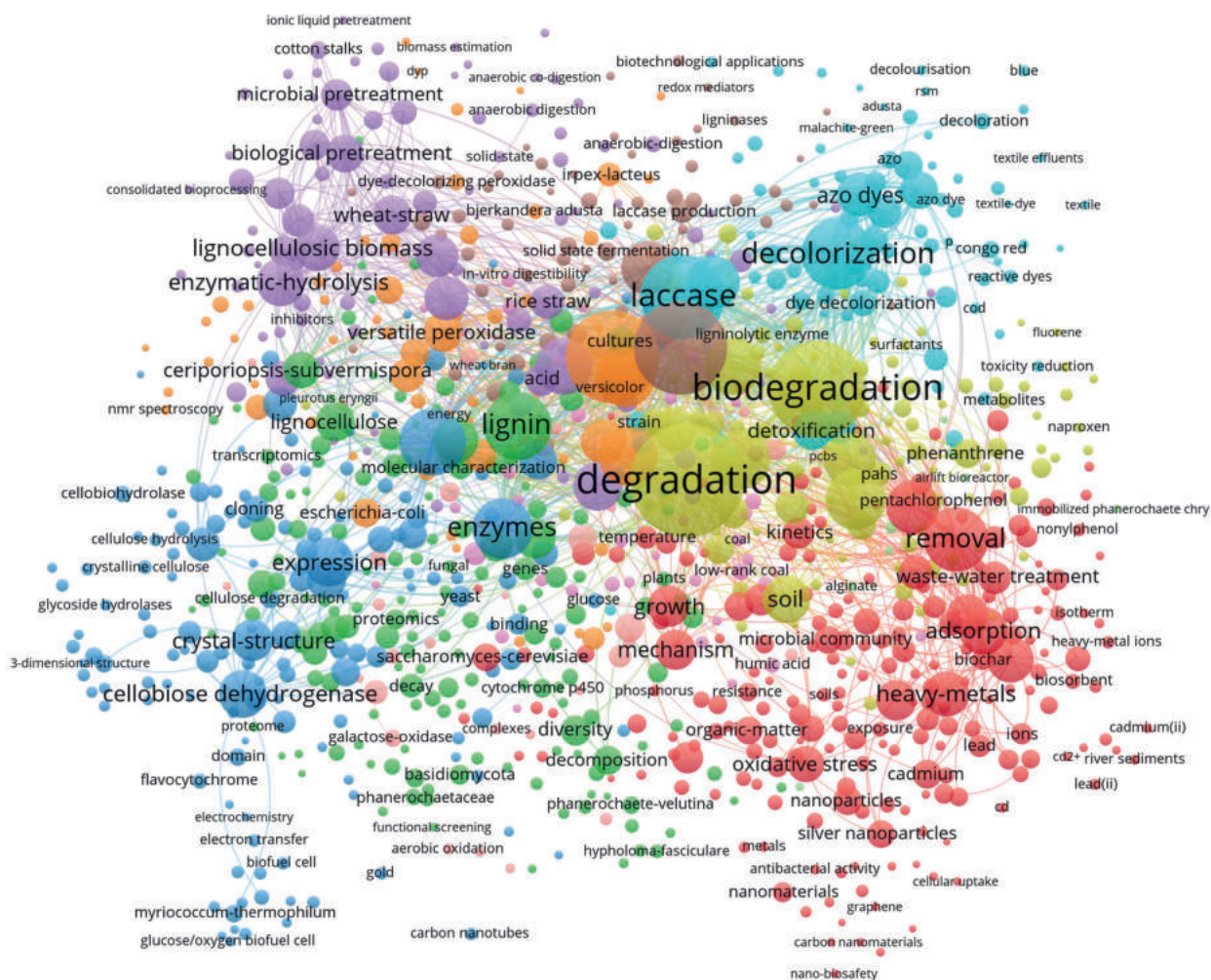


Fig. 28. Network visualisation of keywords of the publications related to *Phanerochaete*. The larger the text and the circle the more often the subject has been cited.

Phanerochaete species have been reported from America, Asia and Europe, New Zealand, and most of them are spreading in a limited region of Asia from the tropical southeast (Wu 1995, Dai 2011, Liu & He 2016, Xu *et al.* 2020, Chen *et al.* 2021a, Wang *et al.* 2021).

Important species and applications of *Phanerochaete*

Phanerochaete chrysosporium is the most intensively studied white-rot basidiomycete and is a model wood-decay organism due to its frequent discovery in wood chip storage piles in Europe and North America (MacDonald *et al.* 2012). *Phanerochaete chrysosporium* grows rapidly, has an optimum growth temperature of around 40 °C and produces numerous conidia (Burdson & Eslyn 1974). Adding tourmaline to *Phanerochaete chrysosporium* can accelerate the effect to enhance the bioremediation process of contaminated soil with polycyclic aromatic hydrocarbons (PAHs) and organochlorine pesticides (OCPs) (Wang *et al.* 2014a). *Phanerochaete chrysosporium* may have potential use in industrial applications such as biopulping (Akhtar *et al.* 1998). Class II peroxidases and glyoxal oxidase, which are among the most important enzymes during lignin degradation, have been discovered in cultures of *Pha. chrysosporium* (Tien & Kirk 1983, Tien & Kirk 1984, Kersten & Kirk 1987). The use of white-rot fungi such as *Pha. chrysosporium* in decolourising textile wastewater has been widely reported (Lankinen *et al.* 1991, Cammarota & Sant

Anna 1992, Bilgic *et al.* 1997, Young & Yu 1997, Tatarko & Bumpus 1998, Gomaa *et al.* 2008, Faraco *et al.* 2009, Sharma *et al.* 2009, Janusz *et al.* 2017).

Research interests

There are 2 185 publications and 50 545 citations from 2011–2021 in the Web of Science (Fig. 27), with the top 10 most cited articles listed in Table 15. Most of the publications focused on the use of lignin enzymes, and application in environmental pollution prevention and control, as well as taxonomy and diversity (Fig. 28).

Lignin enzymes

Lignin accounts for a large percentage of the energy that plants capture from the sun. It has been estimated that 25 % of the carbon fixed by photosynthesis is eventually transformed into lignin. This abundant polymer is a valuable potential resource and is the second most abundant renewable carbon source on earth. Lignin plays an important role in carbon recycling (Tien 1987). Lignin peroxidases were first discovered in *Pha. chrysosporium* (Tien & Kirk 1983, Paszczynski *et al.* 1986, Kirk & Farrell 1987, Janusz *et al.* 2017) The most obvious applications for ligninase are in the pulp and paper industry. The biological (or enzymatic) treatment of pulp can offer numerous advantages. Ligninase is potentially more selective in the removal of lignin than chemical processes. Studies with model

compounds, and to a limited extent with pulps, indicate that the ligninase is highly selective for aromatic substrates. Carbohydrates have not been degraded by the ligninase (Tien 1987).

Environmental pollution prevention and control

The versatile lignin-degrading white-rot fungus, *Pha. chrysosporium*, is a strong degrader in nature and mineralises partially or completely a wide variety of recalcitrant organic pollutants such as chlorophenols, nitrotoluenes and polycyclic aromatic hydrocarbons (Barr & Aust 1994). Xenobiotics which are degraded by *Pha. chrysosporium* also include various azo, heterocyclic and polymeric dyes (Paszczynski *et al.* 1992, Spadaro *et al.* 1992, Ollikka *et al.* 1993). The quantities of contaminated sites with multi-elements have sharply increased (Cao *et al.* 2013b), due to anthropogenic activities such as rapid industrialisation and urbanisation (Sun *et al.* 2011b, Lee *et al.* 2012, Xu *et al.* 2013a). Heavy metals/metalloids and organic pollutants are carcinogenic and mutagenic (Xu *et al.* 2012c, Zeng *et al.* 2013a) and they may arouse amplification effects through the food chain in organisms, threatening human health and natural ecosystems (Zeng *et al.* 2013b, Dai *et al.* 2021).

Taxonomy and phylogeny

Recent molecular studies demonstrate that *Phanerochaete s. lat.* is polyphyletic and distributed across several lineages in the phlebioid clade of the *Polyporales* and also the *Hymenochaetales* (De Koker *et al.* 2003, Greslebin *et al.* 2004, Wu *et al.* 2010, Floudas & Hibbett 2015, Miettinen *et al.* 2016, Justo *et al.* 2017, Chen *et al.* 2018a). Revisiting the taxonomy of *Phanerochaete* based on a four gene dataset and extensive ITS sampling indicated that *Phanerochaete s. lat.* was polyphyletic and distributed across nine lineages in the phlebioid clade, in which six lineages could be assigned to described genera (Floudas & Hibbett 2015). Recent phylogenetic studies have also revealed morphologically cryptic taxa in *Phanerochaete s. str.* (e.g., Volobuev *et al.* 2015, Spirin *et al.* 2017, Phookamsak *et al.* 2019, Xu *et al.* 2020, Chen *et al.* 2021a, Wang *et al.* 2021).

Authors: C.L. Zhao, K.Y. Luo, D.Q. Wang and J.J. Li

14. *Colletotrichum* Corda, in Sturm, Deutschl. Fl., 3 Abt. (Pilze Deutschl.) 3(12): 41. 1831.

Type species: Colletotrichum lineola Corda

Classification: Ascomycota, Pezizomycotina, Sordariomycetes, Glomerellales, Glomerellaceae.

Background

Colletotrichum is one of the most common and most important genera of plant pathogenic fungi with currently 1 040 epithets listed in Index Fungorum (2024) and more than 300 accepted species; with both numbers constantly increasing (Jayawardena *et al.* 2021, Liu *et al.* 2022, Talhinhas & Baroncelli 2023).

Colletotrichum species cause diseases on fruits, leaves, stems and other aerial plant parts, commonly referred to as anthracnose (Udayanga *et al.* 2013). Other diseases caused by *Colletotrichum* species are for example leaf spot diseases, ripe rots and seedling blights (Yang *et al.* 2011, Cannon *et al.* 2012, Lima *et al.* 2013, Yan *et al.* 2015, Jayawardena *et al.* 2016). The symptoms caused are often dark sunken lesions or lesions with a dark margin (Than *et al.* 2008b). Germination and infection of *Colletotrichum* conidia require high relative humidity (≥ 95 –98 %); pre-harvest disease is

most serious in a warm environment (20–30 °C) (Khan & Hsiang 2003, Boddy 2016, Ansari *et al.* 2018, Hyde *et al.* 2020a). Species of *Colletotrichum* can be seed-borne and may survive in soil as saprobes on dead plants or as endophytes in non-host species (Freeman *et al.* 2002, Cannon *et al.* 2012, Ranathunge *et al.* 2016). A list of *Colletotrichum* species and host families and up-to-date trees are provided by Talhinhas & Baroncelli (2023).

The asexual morph of *Colletotrichum* species produces aseptate, hyaline, straight or curved conidia endogenously from hyaline conidiogenous cells, often intermingled with straight dark setae, in an acervulus that is formed under the epidermis or cuticle of the host plant that breaks due to increased tension and subsequently the acervulus is exposed to the environment (Sutton 1992, Khan & Hsiang 2003, Wharton & Diéguez-Uribeondo 2004, Than *et al.* 2008b, Huang *et al.* 2013a). Aseptate, hyaline ascospores formed in cylindrical to clavate asci in perithecia represent the sexual morph that was previously referred to as *Glomerella* and has only been observed in some of the species (Cannon *et al.* 2012, Damm *et al.* 2019). Conidia and ascospores may spread upon contact with water (dew, rain splash, irrigation) and via wind to new locations, new hosts or new plants or plant parts of the same host species (Ntahimpera *et al.* 1997). The plants are infected via appressoria that develop on the plant surface from the germinating spores and build up turgor pressure that enables infective hyphae to penetrate the cuticle or epidermis of the host (Chethana *et al.* 2021a). Further development depends on the production of host-induced virulence factors by the fungus (Kleemann *et al.* 2012, O'Connell *et al.* 2012).

Species of *Colletotrichum* are known to have different lifestyles and infection mechanisms, ranging from intracellular hemibiotrophy to subcuticular intramural necrotrophy (Perfect *et al.* 1999). Best studied is the hemibiotrophic lifestyle that is known from most of the species in the *Col. destructivum*, *Col. graminicola* and *Col. orbiculare* species complexes (Münch *et al.* 2008, O'Connell *et al.* 2012, Damm *et al.* 2013, 2014). These species have an initial biotrophic stage, in which host response is suppressed and the plants remain symptomless, and eventually switch to a necrotrophic stage, in which a significant number of plant cells are killed resulting in the development of symptoms (O'Connell *et al.* 2012).

Colletotrichum was introduced by Corda (1831), who observed rows of acervuli with curved conidia on dead stems of *Apiaceae* plants near Prague (today Czech Republic). Subsequently, hundreds of species were described from various host plants assuming *Colletotrichum* species to be strictly host-specific, until Von Arx (1957) reduced the number of species to 11 based on morphology. Von Arx (1957) regarded about 600 species that form straight cylindrical conidia as synonyms of *Col. gloeosporioides*. Since its description by Simmonds (1965), forms with straight conidia and acute ends were regarded as *Col. acutatum* and those with round ends as *Col. gloeosporioides*; both species being the most frequently reported and regarded as anthracnose pathogens of numerous host plants.

However, with the introduction of phylogenetic species recognition, species were circumscribed based on multi-locus sequence data in combination with informative morphological characters as well as data on physiology, pathogenicity, cultural characteristics and secondary metabolites as far as available, referred to as a polyphasic approach (Cai *et al.* 2009). As a result, host-specificity of individual species of the genus was revealed to be species-dependent and morphology to be unreliable (Damm *et al.* 2012a, Weir *et al.* 2012). Upon their epitypification, *Col. acutatum* and *Col. gloeosporioides* in a broad sense were identified as species complexes with more than 20 closely related species

each and in a narrow sense revealed to be pathogens of a restricted host spectrum (Cannon *et al.* 2008, Phoulivong *et al.* 2010, Damm *et al.* 2012, Weir *et al.* 2012). Today, *Colletotrichum* species with more or less curved conidia are classified in the dematium, destructivum, graminicola/caudatum, spaethianum and truncatum species complexes (Crouch *et al.* 2009, Crouch 2014, Damm *et al.* 2009, 2014), and species with more or less straight conidia in the acutatum, agaves, boninense, dracaenophilum, gigasporum, gloeosporioides, magnum, orbiculare and orchidearum species complexes (Damm *et al.* 2012a, b, 2013, 2019, Weir *et al.* 2012, Liu *et al.* 2014, Bhunjun *et al.* 2021b). Further species complexes have recently been proposed (Liu *et al.* 2022, Talhinhos & Baroncelli 2023). Species that had previously been regarded as synonyms of *Col. gloeosporioides* or strains that were previously identified as this species were allocated to many of these complexes (e.g., Damm *et al.* 2012a, 2014, 2019, Liu *et al.* 2014, 2016). Additionally, there are more than ten species that do not belong to any species complex and are referred to as singletons (Hyde *et al.* 2014, Jayawardena *et al.* 2021).

Ecological and economic significance

Colletotrichum is an important genus in both ecological and economic aspects. *Colletotrichum* species are widespread, especially in the tropics and subtropics, cause diseases of many different plant families and can infect every crop on earth, especially fruits, vegetables and ornamentals (Dean *et al.* 2012, Bhunjun *et al.* 2019, Jayawardena *et al.* 2020, Armand *et al.* 2023, Peng *et al.* 2023, Talhinhos & Baroncelli 2023, Zhang *et al.* 2023b, c); some of the most important diseases are discussed below.

Anthracnose of fruits and fruit rots

Colletotrichum species are of high economic importance for the fruit industry by causing diseases on fruits (e.g., apple, citrus, grape and strawberry) like anthracnose and fruit rot that can cause yield losses of up to 100 % (Huang *et al.* 2013a, Leonberger *et al.* 2019, Dowling *et al.* 2020). Postharvest diseases of fruits are usually caused by several *Colletotrichum* species mainly belonging to the acutatum and gloeosporioides species complexes; most of these species are not host specific (Damm *et al.* 2012a, Weir *et al.* 2012, Jayawardena *et al.* 2021). For example, bitter rot of apples in the Southeastern USA is caused by 12 different *Colletotrichum* species; at least 22 species mostly belonging to the above-mentioned complexes are known from apples worldwide (Damm *et al.* 2012a, b, Weir *et al.* 2012, Bragança *et al.* 2016, Munir *et al.* 2016, Grammen *et al.* 2019, Moreira *et al.* 2019b). There are three important citrus diseases caused by *Colletotrichum*: post-bloom fruit drop (PFD), Key lime anthracnose (KLA) and postharvest anthracnose; the first two were almost exclusively reported from the Americas and are caused by *Col. abscissum*, *Col. gloeosporioides* and *Col. limetticola*, respectively (Damm *et al.* 2012a, Timmer & Peres 2015, Silva *et al.* 2017). *Colletotrichum abscissum* (often still referred to as *Col. acutatum*) is the main PFD pathogen and produces reddish-orange lesions with salmon-pink spore masses on citrus petals, which subsequently results in drop of fruitlets, while the calyces and floral buttons remain attached to the twigs, however, it does not cause postharvest anthracnose (Timmer & Peres 2015). *Colletotrichum gloeosporioides* is the most aggressive *Colletotrichum* species on citrus fruits in Europe and can be found on symptomatic leaves, fruits, petals and twigs of citrus species (Guarnaccia *et al.* 2017). At least 16 species belonging to

the acutatum, boninense, dracaenophilum, gloeosporioides and truncatum species complexes have been reported associated with symptomatic citrus (Damm *et al.* 2012a, b, 2019, 2020, Crous *et al.* 2015, Liu *et al.* 2016a, Guarnaccia *et al.* 2017). Grape ripe rot is also caused by 16 *Colletotrichum* species in the acutatum, boninense and truncatum species complexes (Jayawardena *et al.* 2018b, Echeverrigaray *et al.* 2020), while over 20 *Colletotrichum* species in various species complexes are known from strawberry (Farr & Rossman 2022).

Anthracnose of chili pepper

Chili (*Capsicum annum*) is the fourth most important cultivated crop in the world (Saxena *et al.* 2016) and one of the most important ingredients and spices of tropical and subtropical cuisines. Anthracnose is one of the major constraints in chili production throughout Asia, as well as in Australia and Brazil, causing 10–80 % yield loss and reducing the marketability of the fruit (Than *et al.* 2008a, De Silva *et al.* 2019a). About 30 species are known from chili, belonging to the acutatum, boninense, gloeosporioides, spaethianum, truncatum, orchidearum and magnum species complexes (Diao *et al.* 2017, Mongkolporn & Taylor 2018, Damm *et al.* 2019, De Silva *et al.* 2017, 2019). *Colletotrichum truncatum* (syn. *Col. capsici*) was the most frequently isolated species from infected chili fruit in a survey in Asia (Indonesia, Malaysia, Sri Lanka, Thailand, Taiwan), followed by *Col. scovillei* and *Col. siamense* (De Silva *et al.* 2017). In a study from Korea, only *Col. scovillei* was found, which is absent in Australia (De Silva *et al.* 2017, Oo *et al.* 2017). Pathogenicity tests on chili fruit showed that *Col. scovillei* and *Col. javanense* are highly aggressive (De Silva *et al.* 2019a).

Anthracnose of legumes

Legumes like common beans (*Phaseolus vulgaris*), soybeans (*Glycine max*) and lentils (*Lens culinaris*) are important sources of protein for human and animal nutrition. Anthracnose diseases can devastate up to 50 % of grain production (Bouffleur *et al.* 2021). Typical symptoms, for example of soybean anthracnose, are damping-off, dark spots on cotyledons, stems, petioles and pods and necrotic veins on leaves resulting in premature defoliation and grain germination, and pod rot (Bouffleur *et al.* 2021). *Colletotrichum truncatum* is the main anthracnose pathogen of many legumes (Damm *et al.* 2009), while *Col. lindemuthianum* (orbiculare complex), although reported from 28 plant genera (Farr & Rossman 2022), within the legumes is restricted to *Phaseolus vulgaris* and *Phaseolus coccineus* (Damm *et al.* 2013, Liu *et al.* 2013a). Additional species are associated with beans, e.g., *Col. spaethianum* with common beans and *Col. chlorophyti* and *Col. incanum* with soybeans, while *Col. musicola*, *Col. plurivorum* and *Col. sojae* were reported from both hosts (Damm *et al.* 2019, Yang *et al.* 2012c, 2014, Bouffleur *et al.* 2020). Based on sequence data, Bouffleur *et al.* (2021) revealed 13 species belonging to at least nine species complexes to be associated with soybeans with different global distribution and different roles in disease incidence, as some had been predominantly isolated from either symptomatic or asymptomatic tissue. In contrast, the main pathogen of lentil anthracnose is *Col. lentis* which belongs to the destructivum complex; the only other species from lentils identified using sequence data is *Col. nigrum* (Liu *et al.* 2013a).

Several *Colletotrichum* species are also known as endophytes of plants (Cannon *et al.* 2012, Damm *et al.* 2012b, Liu *et al.* 2015a, Jayawardena *et al.* 2020, 2021, Bhunjun *et al.* 2024). Many of them

can switch their lifestyle from endophytic to pathogenic based on the physiological condition and genotype of the host plant and environmental factors (Photita *et al.* 2004, Promputtha *et al.* 2007, Hardoim *et al.* 2015, Da Silva *et al.* 2020b). Apart from being plant pathogens or endophytes, *Colletotrichum* species can also be pathogens of animals *e.g.*, insects and humans. Several species, including *Col. dematium*, *Col. fructicola*, *Col. gloeosporioides*, *Col. tropicale* and *Col. truncatum* were reported to cause keratitis in humans (Buchta *et al.* 2019, Hung *et al.* 2020). *Colletotrichum gloeosporioides* (s. lat.) was reported to cause a deep tissue mycosis in a person in Australia (Figtree *et al.* 2013), a severe corneal infection (Rodriguez 2014) and a cutaneous infection (Lin *et al.* 2015).

Research interests

Colletotrichum was listed as one of the top 10 fungal pathogens in molecular plant pathology based on their scientific and economic importance (Dean *et al.* 2012), which is also reflected in the high number of publications and high citation rate. The Web of Science lists 4 767 publications and 46 970 citations from 2011–2021 (Fig. 29). The 10 most cited articles are listed in Table 16. Most of the publications focused on certain species or species complexes, their identification and pathogenicity to specific plant hosts, molecular studies of the plant-pathogen interactions and diseases and their control (Fig. 30).

Taxonomy, phylogeny and identification

An accurate circumscription of the causal agent of a disease is the key to unambiguously identify it, understanding plant-pathogen interactions, host range and distribution and thus providing the basis for effective disease control and prevention. After many decades of uncertainty in *Colletotrichum* systematics, an international initiative started in 2009 with the epitypification of the type species *Col. lineola* and several other important species

with curved conidia, multi-locus phylogenetic studies especially of species from *Amaryllidaceae* and *Poaceae*, a critical revision of the current application of species names and recommendations for studying and identifying *Colletotrichum* species (Cai *et al.* 2009, Crouch *et al.* 2009, Damm *et al.* 2009, Hyde *et al.* 2009, Yang *et al.* 2009). In the following years, a robust framework of more than 15 species complexes was established and many new species were revealed (Cannon *et al.* 2012, Crouch 2014, Damm *et al.* 2012a, 2012b, 2013, 2014, 2019, Weir *et al.* 2012, Liu *et al.* 2014, Bhunjun *et al.* 2021b, Liu *et al.* 2022); the data on the new species are regularly fed in a multi-locus online identification tool (qbank.eppo.int/fungi/). This facilitated the accurate identification of known and the allocation of previously unknown pathogens and endophytes and resulted in numerous surveys on specific hosts, disease studies and first reports that often include new species discoveries and pathogenicity tests (*e.g.*, Tao *et al.* 2013, Vieira *et al.* 2014, Sun *et al.* 2019, Damm *et al.* 2020, Alizadeh *et al.* 2022, Yang *et al.* 2023a). This process is progressing and a transition to genome-based systematics is foreseeable (O'Connell *et al.* 2012, Li *et al.* 2021b, Liu *et al.* 2022).

Colletotrichum species as model organisms to study plant-pathogen interactions

Colletotrichum species have been successfully used as model organisms to study plant-pathogen interactions because they can easily be manipulated in the laboratory and of the hemibiotrophic lifestyle of many species (Perfect *et al.* 1999, O'Connell *et al.* 2012, Baroncelli *et al.* 2017).

Initially, studies were based on morphological observations of hemibiotrophic growth of *Colletotrichum* species inside plants (O'Connell *et al.* 2012). The genetic basis of pathogenicity was investigated by manipulating individual genes, *e.g.*, of *Col. magnum* (Freeman & Rodriguez 1993, Rodriguez & Redman 2008). Now whole or partial genomes and transcriptomes are sequenced encircling the molecular origins of pathogenicity, host susceptibility,

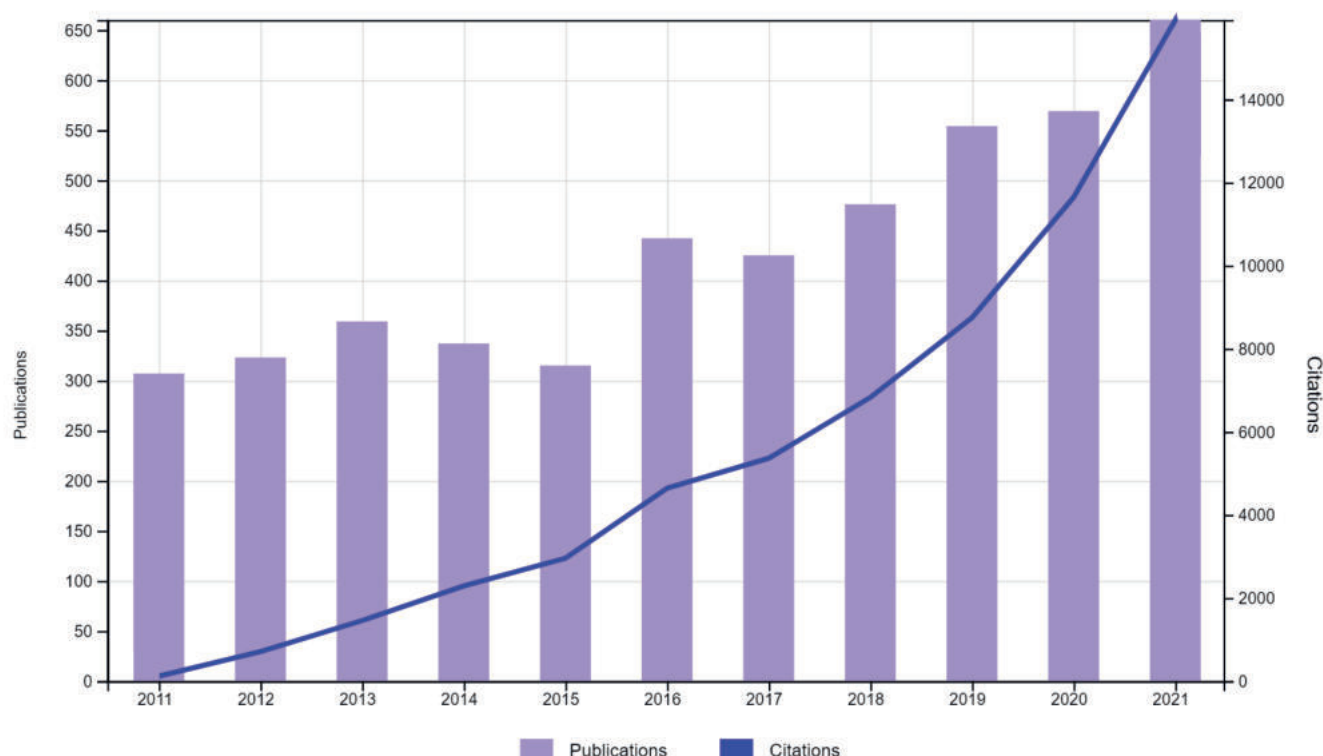


Fig. 29. Trends in research of *Colletotrichum* in the period 2011–2021.

Rank	Article title	No. of citations	References
1	The top 10 fungal pathogens in molecular plant pathology	1 769	Dean <i>et al.</i> (2012)
2	The <i>Colletotrichum gloeosporioides</i> species complex	717	Weir <i>et al.</i> (2012)
3	Lifestyle transitions in plant pathogenic <i>Colletotrichum</i> fungi deciphered by genome and transcriptome analyses	536	O'Connell <i>et al.</i> (2012)
4	<i>Colletotrichum</i> – current status and future directions	500	Cannon <i>et al.</i> (2012)
5	The <i>Colletotrichum acutatum</i> species complex	479	Damm <i>et al.</i> (2012a)
6	Root endophyte <i>Colletotrichum tofieldiae</i> confers plant fitness benefits that are phosphate status dependent	273	Hiruma <i>et al.</i> (2016)
7	One stop shop: backbones trees for important phytopathogenic genera: I (2014)	235	Hyde <i>et al.</i> (2014)
8	The <i>Colletotrichum boninense</i> species complex	231	Damm <i>et al.</i> (2012b)
9	Sequential delivery of host-induced virulence effectors by appressoria and intracellular hyphae of the phytopathogen <i>Colletotrichum higginsianum</i>	213	Kleemann <i>et al.</i> (2012)
10	Comparative genomic and transcriptomic analyses reveal the hemibiotrophic stage shift of <i>Colletotrichum</i> fungi	209	Gan <i>et al.</i> (2013)

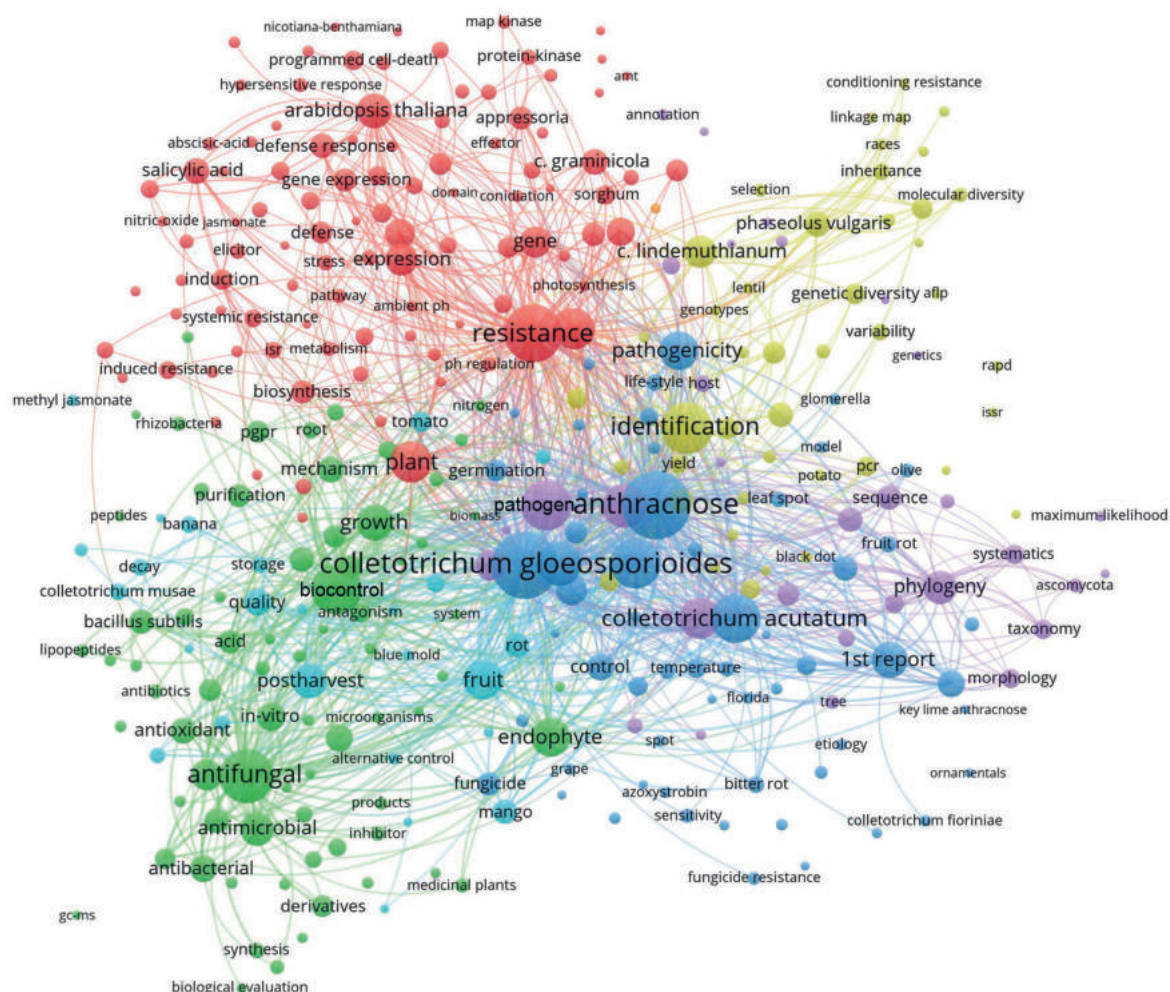


Fig. 30. Network visualisation of keywords of the publications related to *Colletotrichum*. The larger the text and the circle the more often the subject has been cited.

individual responses, drawbacks and benefits on both sides increasingly tighter. Comparative genomics and transcriptomics demonstrate for example the shift from biotrophic to necrotrophic lifestyle of hemibiotrophic species like *Col. graminicola*, *Col. higginsianum* and *Col. orbiculare* on gene level (Kleemann *et al.* 2012, O'Connell *et al.* 2012, Gan *et al.* 2013) and the thin line between pathogenic and beneficial interactions of closely related

Colletotrichum species to *Arabidopsis thaliana* under phosphate deprivation (Hacquard *et al.* 2016, Hiruma *et al.* 2016).

The results of these studies also include the genome sequences of an increasing number of species, especially of those belonging to the *acutatum*, *destructivum*, *graminicola* and *orbiculare* complexes (O'Connell *et al.* 2012, Baroncelli *et al.* 2014a, b, Viswanathan *et al.* 2016, Gan *et al.* 2019a, b) that can be used to link different

research and applied fields like evolutionary plant pathology, epidemiology and resistance breeding (www.colletotrichum.org/genomics/). Studies of plant-pathogen interactions, for example, focusing on genes involved in pathogenicity or fungicide resistance are the basis for disease management.

Disease management

Colletotrichum species cause anthracnose and other diseases of numerous hosts, including important crops and cause high yield losses and quality reductions of economic importance. Diseases caused by *Colletotrichum* species are currently controlled by fungicides like azoxystrobin, mancozeb, cabendazim, thiophanate methyl and triazoles (Dias *et al.* 2016, Nataraj *et al.* 2020, Damm *et al.* 2020, Poti *et al.* 2020). However, fungicide efficiency gradually decreases due to the development of resistance of the pathogens, which is based on variations in specific genes (Chen *et al.* 2013c, Poti *et al.* 2020). Biocontrol and resistance breeding offer more ecological and sustainable solutions.

There are many approaches of biological control of *Colletotrichum* species by other filamentous fungi like *Trichoderma viride* and *Epicoccum dendrobii*, by yeasts such as *Saccharomyces cerevisiae* and *Cryptococcus laurentii*, by bacteria like *Bacillus subtilis* or by essential oils of plants like thyme, sage and peppermint (Ghosh & Chakraborty 2012, Bautista-Rosales *et al.* 2014, Ryu *et al.* 2014, Lopes *et al.* 2015, Morkeliūnė *et al.* 2021, Bian *et al.* 2021). Patel *et al.* (2019) screened bacterial strains for their antifungal activity against *Col. falcatum*, the causal agent of red rot of sugar cane. Most strategies against postharvest diseases focus on *Col. acutatum*, *Col. gloeosporioides* and *Col. truncatum*; promising results with yeast strains were achieved here, however, are not yet commercialised (Shi *et al.* 2021).

Pathogenicity tests are initially important to characterise a fungus as either a pathogen or an endophyte; they play a key role in resistance breeding programs against anthracnose, both to determine the aggressiveness of the *Colletotrichum* strains and to screen the host genotypes for anthracnose resistance (Mongkolporn & Taylor 2018). For example, to develop chili genotypes resistant to the three most important anthracnose pathogens, plant breeders transfer resistance genes from *Capsicum chinense* and *Ca. baccatum* into *Ca. annuum* (Mongkolporn & Taylor 2018). Genotypes of soybeans resistant to *Col. truncatum* have been reported in different countries. However, no studies involving other *Colletotrichum* species have been performed so far (Bouffleur *et al.* 2021), and there is currently no breeding program for anthracnose-resistant soybean cultivars (Yang & Hartman 2015). Apart from the problem of multiple species being involved, more than one gene may also be involved in resistance, for example, soybeans against anthracnose caused by *Col. truncatum* (Nataraj *et al.* 2020).

However, several *Colletotrichum* species have been tested as potential biocontrol agents themselves, mostly as bioherbicides against weeds, such as species in the orbiculare complex (Damm *et al.* 2013). *Colletotrichum gloeosporioides* (s. lat.) was successfully used to control an obligate parasitic plant *Arceuthobium tsugense* (Askew *et al.* 2011), and the herbicidal activity of metabolites (colletochlorins) of *Col. higginsianum* against leaves of *Sonchus arvensis* and tomato was demonstrated (Masi *et al.* 2017).

Authors: U. Damm and R.S. Jayawardena

15. *Trametes* Fr., Fl. Scan.: 339. 1836.

Type species: *Trametes suaveolens* (L.) Fr.

Classification: Basidiomycota, Agaricomycotina, Agaricomycetes, Polyporales, Polyporaceae.

Background

The genus *Trametes* was established by Elias Magnus Fries treating *Tra. suaveolens* as the type (Fries 1836). Members of the genus are cosmopolitan in distribution and can be easily found in boreal, temperate, and tropical forest ecosystems (Gilbertson & Ryvarden 1987, Ryvarden 1991, Carlson *et al.* 2014, Olou *et al.* 2020). Historically, many genera like *Cerrena*, *Coriopsis*, *Daedalea*, *Microporus*, *Fomitopsis*, and *Trametopsis* were once placed within the genus *Trametes* by Corner (1989) based on characters like trimitic hyphal systems (Ko & Jung 1999, Tomšovský *et al.* 2006, Tomšovský 2008, Justo & Hibbett 2011). Ryvarden (1991) redefined the *Trametes* group and included most of the genera synonymised by Corner (1989) based on features like the trimitic hyphal system and white-rot type of wood decay.

With the advancement of molecular phylogenetic studies, Ko & Jung (1999) and Tomšovský *et al.* (2006) performed a detailed study and placed most species of *Trametes* in the core polyporoid clade suggesting that the genus is either paraphyletic or polyphyletic. Conflicts over the generic limit of *Trametes*, due to a lack of distinct morphological features, resulted in the genus consisting of a large number of nomenclatural combinations. There are 250 well-recognised species of *Trametes*, according to Index Fungorum. Currently, the genus is circumscribed by the combination of features like a pileate basidiocarp with poroid hymenophore; smooth, thin-walled, IKI-basidiospores, presence of trimitic hyphal system, and symptoms like a white-rot type of decay on hardwood and conifer wood (Gilbertson & Ryvarden 1987, Gomes-Silva *et al.* 2010, Justo & Hibbett 2011).

Traditionally, the genus has long been used in Chinese medicine (Knežević 2015, Soković *et al.* 2018). Several species of the genus are enriched with antioxidant, anti-inflammatory, antimicrobial, and anticancer properties (Yamaç & Bilgili 2006, Kamiyama *et al.* 2013, Knežević *et al.* 2015, Milovanovic *et al.* 2015, Zhao *et al.* 2015g). Maniak *et al.* (2020) discovered a new class of low-molecular-weight hydrazide-hydrazones as laccase inhibitors in *Tra. versicolor*. *Trametes versicolor* is also used to produce higher amounts of divanillin, a bio-based aromatic building block for synthesising semi-aromatic polymers, and this is again polymerised with 2,7-diaminocarbazole and benzene-1,4-diamine to formulate divanillin-based poly-azomethines which show excellent thermal and mechanical properties (Garbay *et al.* 2020).

Ecological and economic significance

Trametes species are a common wood decay fungus due to their lignin degradation ability and can be found on several species of hardwood trees (Roy 1982, Levin & Castro 1998, Hapuarachchi *et al.* 2021). They are commonly known as a predator of natural forest ecosystems (Bari *et al.* 2016). Besides their usefulness as a wood decomposer in natural ecosystems, *Trametes* species are also used in the biodegradation of agricultural waste and bioremediation (Wang *et al.* 2012e, Carlson *et al.* 2014, Wu *et al.* 2016b).

Trametes species are well known to cause white rot decay of wood and details of this decay are given below:

White rot decay of woods

Trametes species have a broad range of host plant species (Eaton & Hale 1993, Schmidt 2006). In the USA and the northern part of Iran, over 90 % of wood decay is due to *Trametes* species causing white rot disease (Gilbertson 1980, Bari *et al.* 2015). These fungi produce filamentous hyphae that are 20–30 times smaller than the invaded wood cell walls (Goodell *et al.* 2008). The filamentous hyphae initially infect the wood ray cells, and then gradually pass from one cell to another cell through the pits. In the growing stages when microclimatic conditions are favourable, the hyphae extend lengthwise through the lumen of the wood cells and secrete enzymatic and non-enzymatic metabolites for the degradation of wood cell wall for the acquisition of nutrients (Goodell *et al.* 2008). The enzymes responsible for decomposing lignin substances include lignin peroxidase, laccase, and manganese peroxidases, which cause oxidation and mineralisation (Hatakka 1994, Hatakka *et al.* 2002, Karim *et al.* 2017). As a result, a bleached-like appearance develops where fibres and parenchyma cells completely degrade the remaining vessels (Levin & Castro 1998). The wood becomes soft and stringy where the softened wood fibres can be easily separated allowing the wood to be peeled apart (Goodell *et al.* 2008). Besides the simultaneous degradation of lignin, the degradation of cell wall polysaccharides continues, leaving cells perforated with holes and erosion troughs (Eriksson *et al.* 1990). However, in the case of selective removal of lignin present in the middle lamellae and secondary wall there remains in higher quantities (Blanchette 1994).

Apart from wood decay, some *Trametes* species have also been used as biocontrol agents, such as *Tra. versicolor* used to control *Fusarium oxysporum* f. sp. *lycopersici*, *Fusarium moniliforme*, *Alternaria solani*, *Rhizoctonia solani*, *Cercospora capsici*, *Botrytis cinerea*, and *Verticillium dahliae* (Ruiz-Dueñas & Martínez 1996, Deketelaere *et al.* 2017, Mendieta *et al.* 2019).

Research interests

There are 2 834 publications and 46 427 citations from 2011–2021 in the Web of Science (Fig. 31), with the top 10 most cited articles shown in Table 17. Most publications focused on fungal laccase (production, purification, characterisation, dye synthesis), bioremediation of hazardous chemicals, nutraceutical activities, as well as taxonomy (Fig. 32).

Laccase enzyme from *Trametes* species

Trametes species are good producers of the enzyme laccase. Studies have focused on the production of laccase from *Tra. gallica* (Dong *et al.* 2005), *Tra. hirsuta* (Rodríguez Couto *et al.* 2004, Rosales *et al.* 2005, Koroleva *et al.* 2002), *Tra. modesta* (Nyanhongo *et al.* 2002), *Tra. pubescens* (Galhaup *et al.* 2002), *Tra. trogii* (Trupkin *et al.* 2003), and *Tra. versicolor* (Fähræus & Reinhammar 1967, Mikiashvili *et al.* 2005, Rodríguez Couto *et al.* 2003). Laccase is a promising biocatalyst with a wide range of applications, including chemical synthesis, bioremediation, delignification, biosensing, pulp bleaching, textile finishing, and wine preservation, *etc.* (Dwivedi *et al.* 2011, Fernández-Fernández *et al.* 2013). Laccases can polymerise natural phenols and aid in the development of novel cosmetic dyes, hair colouring materials, toothpaste, deodorants, mouthwashes, and other commodities (Dwivedi *et al.* 2011). These features make laccase a fascinating enzyme to investigate in terms of structure, function, and application (Dwivedi *et al.* 2011). Laccases mediate the oxidation process of various environmental contaminants including non-phenolic and phenolic compounds (Dwivedi *et al.* 2011). As storage and operational stabilities are routinely improved, immobilisation of laccase through adsorption, encapsulation, entrapment, self-immobilisation, and covalent binding offers various advantages for its applications over free enzymes in terms of reusability (Fernández-Fernández *et al.* 2013).

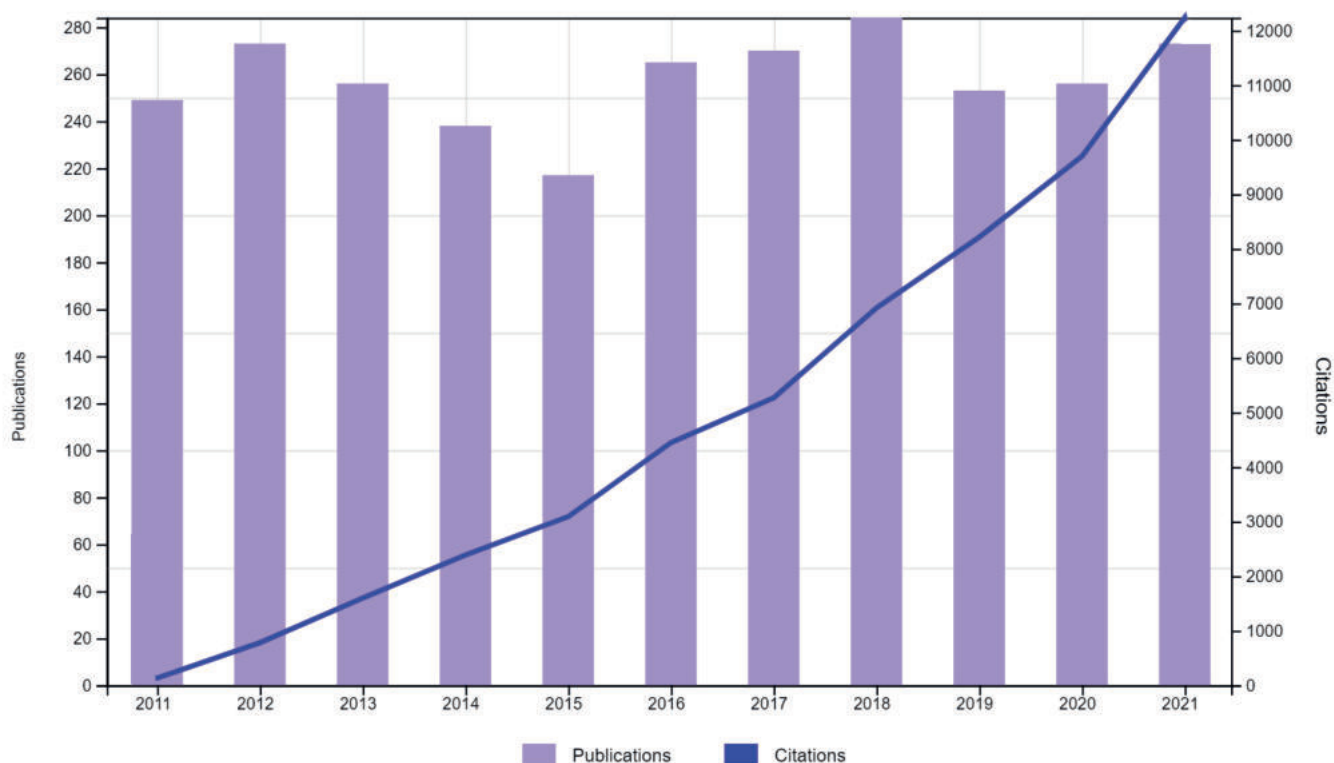


Fig. 31. Trends in research of *Trametes* in the period 2011–2021.

Table 17. Top 10 cited articles related to *Trametes* published in the period 2011–2021.

Rank	Article title	No. of citations	References
1	Untapped potential: exploiting fungi in bioremediation of hazardous chemicals	491	Harms <i>et al.</i> (2011)
2	Enzyme immobilization by adsorption: a review	477	Jesionowski <i>et al.</i> (2014)
3	Recent developments and applications of immobilized laccase	401	Fernandez-Fernandez <i>et al.</i> (2013)
4	The role of culinary-medicinal mushrooms on human welfare with a pyramid model for human health	341	Chang & Wasser (2012)
5	From the conventional biological wastewater treatment to hybrid processes, the evaluation of organic micropollutant removal: A review	338	Grandclement <i>et al.</i> (2017)
6	Enzymes as green catalysts for precision macromolecular synthesis	300	Shoda <i>et al.</i> (2016)
7	Structure-function relationship among bacterial, fungal and plant laccases	286	Dwivedi <i>et al.</i> (2011)
8	Biotechnological strategies to overcome inhibitors in lignocellulose hydrolysates for ethanol production: review	267	Parawira & Tekere (2011)
9	Potential applications of laccase-mediated coupling and grafting reactions: A review	238	Kudanga <i>et al.</i> (2011)
10	Lignin-degrading enzymes	230	Pollegioni <i>et al.</i> (2015)

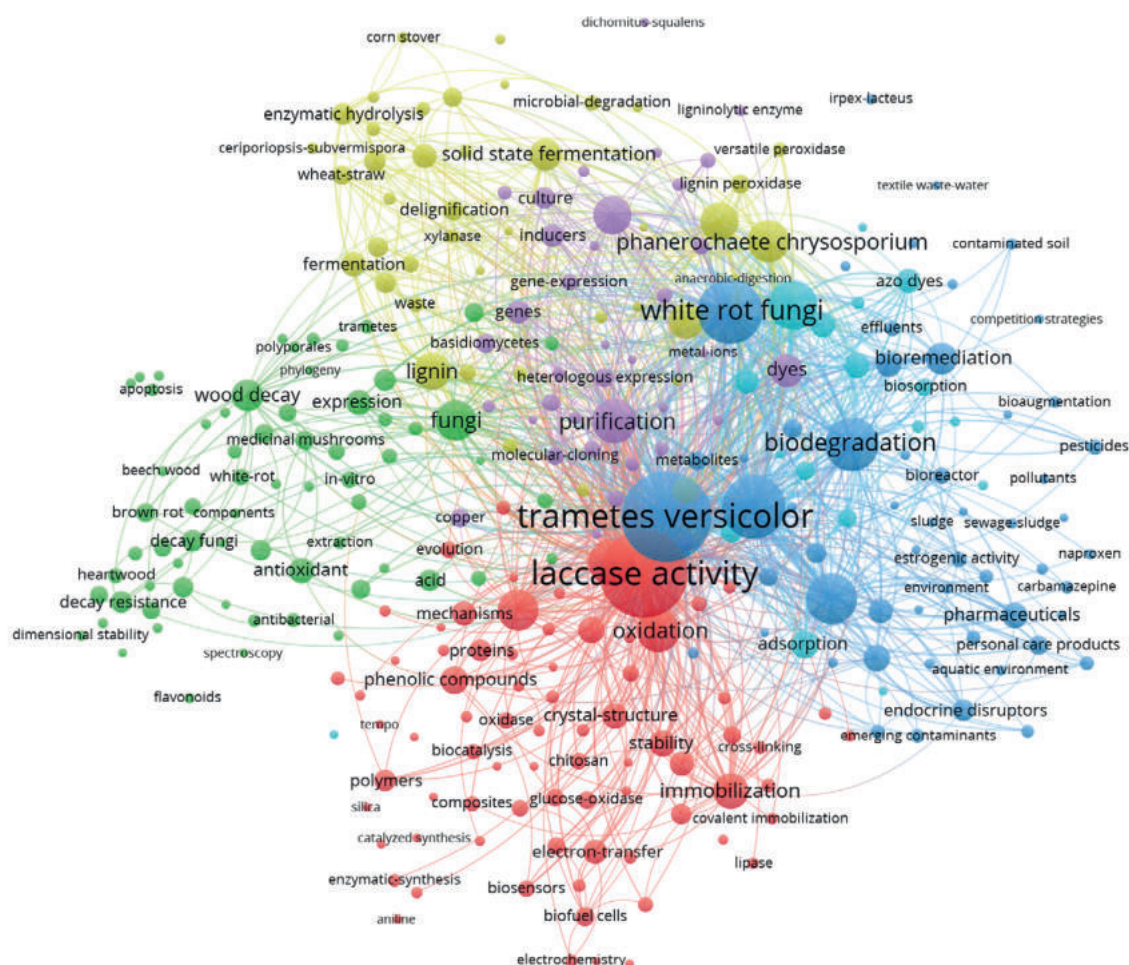


Fig. 32. Network visualisation of keywords of the publications related to *Trametes*. The larger the text and the circle the more often the subject has been cited.

Nutraceutical activities

Trametes versicolor has been widely studied and the acetone extract of the mushroom has been found to contain considerably higher antioxidant activity compared to other extracts like methanol, chloroform, and n-hexane (Kamiyama *et al.* 2013). The major compounds responsible for showing potent antioxidant activities

of the mushroom include furfural, furfuryl alcohol, γ -butyrolactone, 2-methoxy-4-vinylphenol, benzaldehyde, and 2,6-dimethoxy-4-vinylphenol (Kamiyama *et al.* 2013, Soković *et al.* 2018). Methanolic extract of *Tra. ochracea* mushrooms contains higher antioxidants compared to the hexane extracts and the mushrooms are enriched with significant amounts of various compounds like

phenols, alkaloids, flavonoids, steroids, saponins, tannins, resins, carbohydrates, and proteins (Melappa *et al.* 2015). Experiments performed by Knežević *et al.* (2015) revealed that the antioxidant activities of *Tra. gibbosa* and *Tra. hirsuta* were lower compared to that of *Tra. versicolor*. Cheng & Leung (2008) demonstrated that *Tra. versicolor* proteo-glucans exhibit immunostimulatory properties by promoting the synthesis of interferons, interleukin-6, macrophages, immunoglobulin-G, and T-lymphocytes. The laccase enzyme produced from *Tra. versicolor* showed promising antimicrobial properties against Gram-positive bacteria when encapsulated in a chitosan-nanobiochar matrix suggesting encapsulation as an effective method of keeping the enzyme stable and active for a variety of biological applications (Naghdi *et al.* 2019).

Bioremediation of hazardous chemicals

Trametes spp. are widely used for bioremediation purposes due to their poor specificity of catabolic enzymes, and the formation of long stretches of mycelial mats (Harms *et al.* 2011). These fungi potentially degrade organic molecules in the environment and considerably reduce the harmful effects related to various hazardous substances like metals, radionuclides, and metalloids through chemical alteration or by affecting chemical bioavailability. *Trametes* spp. mineralises various chloro-aromatics, and TNT (Harms *et al.* 2011). *Trametes versicolor* degrades different classes of chemicals (phenols, parabens, and phthalate) in a mixture of endocrine disrupting chemicals (EDCs) in a cost-effective process that enables its application in a water treatment process (Pezzella *et al.* 2017). García-Vara *et al.* (2021) showed that *Tra. versicolor* eliminates bentazone, a widely used herbicide in rice and cereal crops, an average of 48 % from water through the use of laccase and cytochrome P450 enzymatic systems. This fungus is potent for bioremediating diuron [3-(3,4-dichlorophenyl)-1,1-dimethylurea], present in polluted aquatic environments, converting it to two other non-toxic metabolites like 1-(3,4-dichlorophenyl)-urea and 1-(3,4-dichlorophenyl)-3-methylurea under low- and high-nitrogen conditions (Mori *et al.* 2018). Significant breakdown of BPA and decolourisation of commercial colours can also be achieved through the use of *Tra. versicolor* (Manna & Amutha 2017). Species of *Trametes* absorb and accumulate cadmium and are applied in the removal process of heavy metals (Manna & Amutha 2017). In semi-arid and Mediterranean habitats, *Tra. versicolor* decomposes atrazine mixed in low moisture and organic-matter rich calcareous clay soils up to 98 % and is a promising option for atrazine bioremediation (Bastos & Magan 2009). According to Morato (2013), *Tra. versicolor* degrades and reduces overall toxicity of a wide range of xenobiotic and recalcitrant contaminants like antibiotics (ofloxacin), antiepileptics (carbamazepine), analgesics and anti-inflammatory (ketoprofen and diclofenac), lipid regulators (clofibrilic acid), and an X-ray contrast agent (iopramide) in urban and hospital wastewater through their unspecific enzyme system.

Taxonomy and phylogeny

Phylogenetic reconstruction of the family *Polyporaceae* by the mtSSU rDNA region came into focus with the studies of Hibbett & Donoghue (1995), and Ko & Jung (1999), where the *Trametes*-clade resided within the “core *Polyporaceae* group”. Later, Ko (2000) with the help of sequence data from two marker regions (ITS and mtSSU rDNA) divided the “core *Polyporaceae* group” into two subgroups, where subgroup “B” included the genus *Trametes* together with *Coriopsis polyzona*, and other members of the genera *Pycnoporus*, and *Lenzites* that was further supported by the study of Rajchenberg (2011) incorporating several morphological

and cytological features. Based on the data from two gene sequence regions (*rpb2* and ITS rDNA), Welti *et al.* (2012) demarcated the *Trametes*-clade into three lineages viz. a lineage with members of the genus *Trametes* along with its type species, *Tra. suaveolens*, and *Lenzites*, and *Coriopsis*; another lineage including some species of *Trametes* (*Tra. lactinea*, *Tra. cingulata*, *Tra. menziesii*, and *Tra. ljubarskyi*), together with the genus *Pycnoporus*; and a single lineage with *Artolenzites elegans*. Justo & Hibbett (2011) re-delimited the concept of the genus based on the data from ribosomal markers and protein-coding gene regions where the “trametoid clade” consisted of most of the *Trametes* species together with *Coriopsis polyzona*, and species of genera *Pycnoporus*, and *Lenzites*. However, according to the studies of Justo & Hibbett (2011), designating the trametoid clade after the name *Trametes* suggested the necessity of incorporating more molecular sequence data together with a few novel nomenclatural combinations.

Authors: N. Roy and A.K. Dutta

16. *Rhizoctonia* DC., Fl. franç., Edn 3 (Paris) 5–6: 110. 1815.

Type species: Rhizoctonia solani Kühn

Classification: Basidiomycota, Agaricomycotina, Agaricomycetes, Cantharellales, Ceratobasidiaceae.

Background

Rhizoctonia was first described by De Candolle in 1815 with *R. crocorum* as the original type species. Due to the confusion around what defined members of this genus, a re-definition of the genus concept was later provided by Ogoshi (1987) to include characteristics such as the absence of asexual spores (conidia) and rhizomorphs, hyphal branching from distal septa of vegetative hyphae, constriction at hyphal branching, and sclerotia with no cellular differentiation into rind or medulla. Three main groups are widely recognised as pathogens of crop plants worldwide: *R. solani* (*Thanatephorus*), *R. zeae* (*Waitea*), and *Ceratorhiza* (*Ceratobasidium*). While these groups share important attributes that define the genus *Rhizoctonia*, they can be differentiated based on vegetative characteristics. Members of *Ceratorhiza* have binucleate cell compartments, while *R. solani* and *R. zeae* are multinucleate. The salmon-coloured mature hyphae of *R. zeae* are distinguished from *R. solani* hyphae which are brown in culture.

Rhizoctonia solani is the most studied species of the three genera by virtue of its importance to agricultural production. It was first described on potato plants by Julius Kühn in 1858 and has since been associated with diseases of other economically important crops. The unique characteristics of *R. solani* make laboratory identification straightforward. Isolates are hyaline when young and become brown with age; the mycelia are made up of septate hyphae that branch at 90° angles with constrictions at the point of branching; hyphae consist of dolipore septa that permit cell-to-cell movement of cytoplasmic organelles, mitochondria, and nuclei; and asexual forms do not produce conidia, clamp connections, rhizomorphs, or pigmentations other than brown. All members of this species have the same sexual morph (*Thanatephorus cucumeris*) (Homma *et al.* 1983, Ogoshi 1984, Neate & Warcup 1985, Carling *et al.* 1994), and differentiation based on the sexual morph has yet to be reported.

Earlier attempts to resolve the diversity existent within this species utilised hyphal anastomosis to group isolates into anastomosis groups (AG) (Parmeter *et al.* 1969) and the different AGs of *R. solani* are considered non-interbreeding populations (Anderson *et al.* 1972). Hyphae of isolates belonging to the same AG, when paired on a suitable growth medium, recognise and fuse and may undergo cytoplasmic and nuclei exchange. Fourteen AGs (AGs 1–13 and AG-B1) have been identified to date (Ogoshi 1987, Carling 1996, 1999), and additional characteristics have been used to further delineate subgroups within certain AGs. Aside from genetic diversity, host crop diversity within AGs and AG subgroups makes *R. solani* a remarkable pathogen (Table 18). For the binucleate *Rhizoctonia* spp., *Ceratobasidium*, 18 AGs have been identified (Sneh *et al.* 1991, Sharon *et al.* 2008), and for *Waitea*, two anastomosis groups, WAG-O (*W. circinata* var. *oryzae*, asexual morph *R. oryzae*) and WAG-Z (*W. circinata* var. *zeae*, asexual morph *R. zeae*), are currently defined (Oniki *et al.* 1985).

Ecological and economic significance

Diseases caused by *R. solani* have gathered more attention than those caused by other species of *Rhizoctonia*. Host range includes, but is not limited to, members of *Poaceae*, *Fabaceae*, *Solanaceae*, *Asteraceae*, and *Brassicaceae*, causing symptoms such as root rot, foot rot, seed rot, crown rot, stem rot, sheath blight, web blight, brown patch, *etc.* Below is a summary of some of the most important diseases of crop plants caused by *Rhizoctonia* spp.

Sheath blight of rice, (*Oryza sativa*) caused by *R. solani* AG1-1A, is an economically important disease of rice worldwide. Although first reported in Japan in 1910, the disease has become prominent

in high-fertility rice-production systems around the globe (Eizenga *et al.* 2002). It is one of the most devastating diseases of rice in Eastern Asia and one of the leading causes of yield loss in rice-producing states in the USA. Under favourable environmental conditions (high humidity and warm temperatures), yield losses, particularly on susceptible varieties, can be as high as 50 % (Lee & Rush 1983, Savary *et al.* 2000). There are no rice varieties with complete resistance to the pathogen, and resistance is quantitatively inherited (Hashiba 1984, Linscombe *et al.* 1992, Eizenga *et al.* 2002), which has most likely hampered the development of rice varieties for use on a commercial scale. As a result, sheath blight management has relied mostly on an integrated approach involving a combination of cultural practices, such as field sanitation, nutrient management, crop rotation to non-hosts, and fungicides.

Crown and root rot of sugar beet (*Beta vulgaris*) is one of the most important diseases of sugar beet in the USA (Schneider & Whitney 1986) and has gained importance in sugar beet-producing areas in Europe (Buhre *et al.* 2009). In the USA, the disease is caused by two AGs of *R. solani*, AG-2-2 IIIB and AG-2-2 IV, although the former is generally more aggressive on sugar beet (Bolton *et al.* 2010, Windels & Brantner 2007). In Germany and other parts of Europe, AG-2-2 IIIB is the main subgroup causing crown and root rot in sugar beet (Büttner *et al.* 2002). Yield losses as high as 50 % can occur (Herr 1996), and in Europe at least 36 000 ha of fields planted to sugar beet are affected on an annual basis (Garcia *et al.* 2001). In Europe, there are no fungicides registered for the control of the disease. Thus, control is mostly achieved through strategies that combine host resistance with agronomic practices like crop rotation (Herr 1996, Buhre 2009). In the USA chemical control is widely used and is the most effective method (Jacobsen

Table 18. Anastomosis groups of *Rhizoctonia solani* and their host crops.

Anastomosis group (subgroups)	Host crop	References
AG-1 (1A, 1B, 1C, 1D, 1E, 1F)	Rice, corn, soybean, bean, turfgrass, cabbage, lettuce, coffee, sorghum	Mukou <i>et al.</i> (1975), Martin & Lucas (1984), Jones & Belmar (1989), Yang <i>et al.</i> (1990), Herr (1992), Priyatmojo <i>et al.</i> (2001), Grosch <i>et al.</i> (2004)
AG-2- (1, t, Nt), AG-2- (2IIIB, 2IV, 2LP, 3, 4)	Soybean, sugar beet, rice, turfgrass, corn, canola, wheat, tulip, tomato	Sumner & Bell (1982), Windels & Nabben (1989), Liu & Sinclair (1991), Muyolo <i>et al.</i> (1993a), Watanabe & Matsuda (1966), Engelkes & Windels (1996), Nelson <i>et al.</i> (1996), Schneider <i>et al.</i> (1997), Dorrance <i>et al.</i> (2003), Paulitz <i>et al.</i> (2006), Misawa & Kuninaga (2010)
AG-3 (TB, PT, TM)	Potato, tobacco, soybean, tomato	Meyer <i>et al.</i> (1990), Nelson <i>et al.</i> (1996), Windels <i>et al.</i> (1997), Woodhall <i>et al.</i> (2007), Misawa & Kuninaga (2010)
AG-4 (HGI, HGII, HGIII)	Soybean, tomato, dry bean, peanut, cotton, potato, melon, broccoli, spinach	Windels & Nabben (1989), Muyolo <i>et al.</i> (1993b), Balali <i>et al.</i> (1996), Brennenman (1996), Rothrock (1996), Fenille <i>et al.</i> (2002), Kuramae <i>et al.</i> (2003)
AG-5	Potato, turfgrass, bean, soybean, sugar beet	Martin & Lucas (1984), Balali <i>et al.</i> (1995), Nelson <i>et al.</i> (1996), Windels <i>et al.</i> (1997)
AG-6 (HG-I, GV)	Non-pathogenic (mycorrhizal with orchids)	Carling <i>et al.</i> (1999), Pope & Carter (2001)
AG-7	Soybean, potato, cotton, watermelon	Baird <i>et al.</i> (1996), Carling <i>et al.</i> (1998), Abd-Elsalam <i>et al.</i> (2010)
AG-8-ZG (1, 2, 4, 5)	Small grains (wheat, barley)	Neate & Warcup (1985), Roberts & Sivasithamparam (1986)
AG-9 (TP, TX)	Potato, lettuce, carrot	Carling <i>et al.</i> (1987)
AG-10	Non-pathogenic	MacNish <i>et al.</i> (1995)
AG-11	Wheat, lupin, soybean, cotton, potato, radish	Carling <i>et al.</i> (1994), Sweetingham (1989), Kumar <i>et al.</i> (1999)
AG-12	Cauliflower, radish, mycorrhizal with orchids	Carling <i>et al.</i> (1999), Pope & Carter (2001)
AG-13	Cotton	Carling <i>et al.</i> (2002)
AG-B1 (Bridging Isolate)	Non-pathogenic	None reported to date

et al. 2001, Khan & Bradley 2010) for controlling the disease, although agronomic practices, such as rotation to non-hosts and host resistance, are also encouraged.

Rhizoctonia root rot and bare patch, caused by *R. solani* AG-8 and *R. oryzae*, is a major disease of direct-seeded cereals in Australia (MacNish & Neate 1996) and the Pacific Northwest region of USA (Weller *et al.* 1986, Paulitz *et al.* 2002) and is considered the most important disease limiting the adoption of no-till technology (Schroeder & Paulitz 2006) in these regions. There is no single method for controlling *Rhizoctonia* root rot and bare patch, however, various combinations of available management methods can achieve the desired results. Tillage to disrupt pathogen networks (Pumphrey *et al.* 1987), elimination of green bridges (Roget *et al.* 1987, Smiley *et al.* 1992), and the application of nitrogen at seeding (MacNish 1985) are management practices that have proven effective.

Rhizoctonia root and hypocotyl rot is an important seedling disease of soybean (*Glycine max*) in continental America, particularly in the north-central region, where most of the USA soybean is grown (American Soybean Association 2021). *Rhizoctonia* seedling disease of soybean together with diseases caused by other seedling pathogens (*Pythium*, *Fusarium*, *Phomopsis*) are the second most important group of diseases limiting soybean yields in the USA and Ontario, Canada from 2015 to 2019 (Bradley *et al.* 2021). Several AGs have been associated with this disease, however, isolates of AG-2-2 IIIB, AG-4 and AG-5 (Liu & Sinclair 1991, Muyolo *et al.* 1993a, Nelson *et al.* 1996, Zhao *et al.* 2005, Ajayi-Oyetunde & Bradley 2017) are considered most aggressive on soybean seedlings. Resistant soybean cultivars are not commercially available (Bradley *et al.* 2001), and crop rotation alone may be insufficient to mitigate the risk of infection due to the host range (Nelson *et al.* 1996, Ajayi-Oyetunde & Bradley 2017) and longevity of infection propagules in soil. Thus, seed treatment fungicides are the method of choice for managing the disease (Dorrance *et al.* 2003).

Sharp eyespot of wheat caused by *R. cerealis* (sexual morph: *Ceratobasidium cereale*) is a stem-base disease of wheat (*Triticum aestivum*) in temperate regions of the world. The disease has attracted significant attention only in the past few decades owing to its wide geographical distribution across Europe, North America, Asia, and Africa, widespread use of wheat cultivars susceptible to the pathogen, global climate change, and its ability to infect a wide range of host crops (Cromey *et al.* 2005, Hamada *et al.* 2011). *Rhizoctonia cerealis* also causes disease on other members of the grass family (barley, oats, rye, turf grasses) (Tomaso-Peterson & Trevathan 2007, Lemańczyk & Kwaśna 2013), as well as on other crops, including sugar beet, cotton, potato, and some legumes (Kataria & Hoffmann 1988). While the impacts of the disease on yield can vary (Bateman *et al.* 2000), economic losses of over 150 million US dollars have been reported in wheat production fields in China (Chen *et al.* 2008). Cultural methods such as delayed sowing, mulching, and straw management can reduce sharp eyespot severity in wheat fields (Colbach *et al.* 1997, Diao *et al.* 1998, Miao *et al.* 1998, Bateman & Jenkyn 2001, Cromey *et al.* 2006). Although resistance to sharp eyespot is quantitative (Cai *et al.* 2006b), and germplasm with complete resistance has not been identified, transgenic wheat lines with enhanced resistance to the pathogen have been developed (Chen *et al.* 2008, Li *et al.* 2011f). Despite this, there are no commercially available resistant wheat cultivars, and management has relied mostly on the application of fungicides.

Research interests

There are 3 938 publications and 46 317 citations from 2011–2021 in the Web of Science (Fig. 33), with the top 10 most cited articles shown in Table 19. The major research themes cover fungal identification and disease management strategies such as biological control, host resistance through traditional breeding and biotech approaches, and other control methods (Fig. 34).

Due to the intractable nature of *Rhizoctonia* diseases, extensive research work on the biological control of *Rhizoctonia* diseases has been carried out for the most economically important

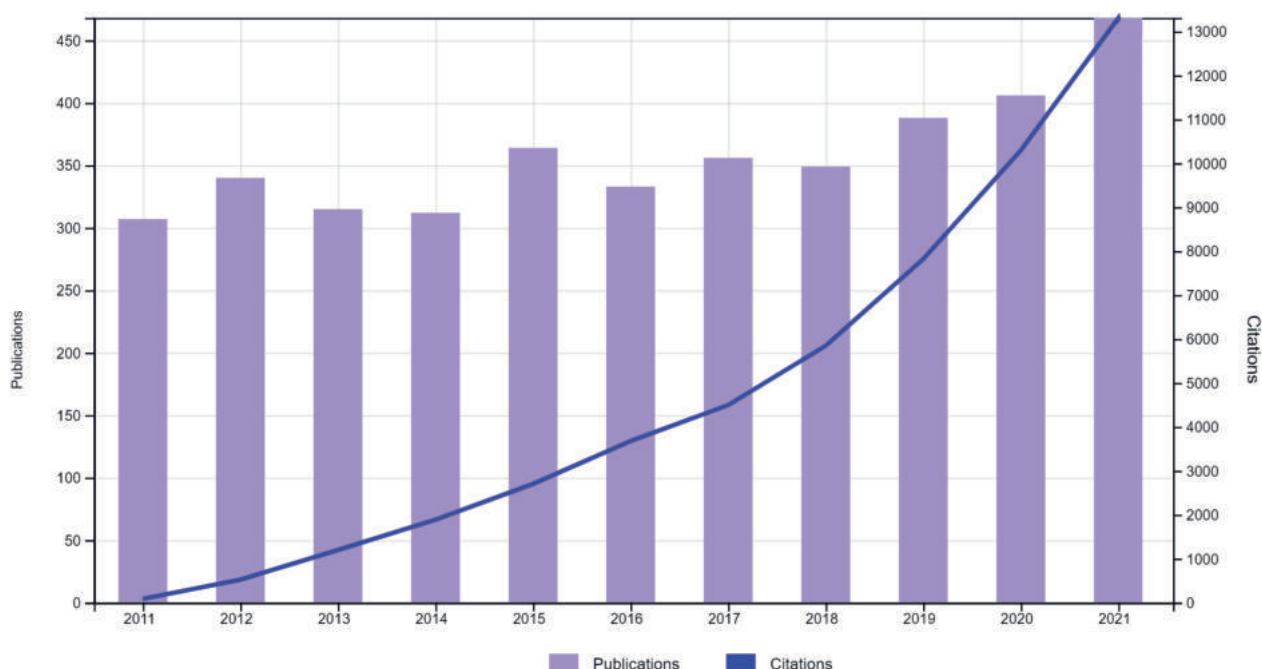


Fig. 33. Trends in research of *Rhizoctonia* in the period 2011–2021.

Table 19. Top 10 cited articles related to *Rhizoctonia* published in the period 2011–2021.

Rank	Article title	No. of citations	References
1	Optimization for rapid synthesis of silver nanoparticles and its effect on phytopathogenic fungi	202	Krishnaraj <i>et al.</i> (2012)
2	Pathogen-induced activation of disease-suppressive functions in the endophytic root microbiome	195	Carrión <i>et al.</i> (2019)
3	Effects of <i>Bacillus amyloliquefaciens</i> FZB42 on lettuce growth and health under pathogen pressure and its impact on the rhizosphere bacterial community	172	Chowdhury <i>et al.</i> (2013)
4	The evolution and pathogenic mechanisms of the rice sheath blight pathogen	166	Zheng <i>et al.</i> (2013)
5	Mitochondrial complex II has a key role in mitochondrial-derived reactive oxygen species influence on plant stress gene regulation and defense	157	Gleason <i>et al.</i> (2011)
6	Comparative transcriptomics reveals different strategies of <i>Trichoderma</i> mycoparasitism	146	Atanasova <i>et al.</i> (2013)
7	Constitutive expression of rice <i>WRKY30</i> gene increases the endogenous jasmonic acid accumulation, <i>PR</i> gene expression and resistance to fungal pathogens in rice	142	Peng <i>et al.</i> (2012)
8	Role of bacterial communities in the natural suppression of <i>Rhizoctonia solani</i> bare patch disease of wheat (<i>Triticum aestivum</i> L.)	126	Yin <i>et al.</i> (2013)
9	Compost amendments enhance peat suppressiveness to <i>Pythium ultimum</i> , <i>Rhizoctonia solani</i> and <i>Sclerotinia minor</i>	118	Pane <i>et al.</i> (2011)
10	Biocontrol of <i>Rhizoctonia solani</i> damping-off and promotion of tomato plant growth by endophytic actinomycetes isolated from native plants of Algerian Sahara	110	Goudjal <i>et al.</i> (2014)

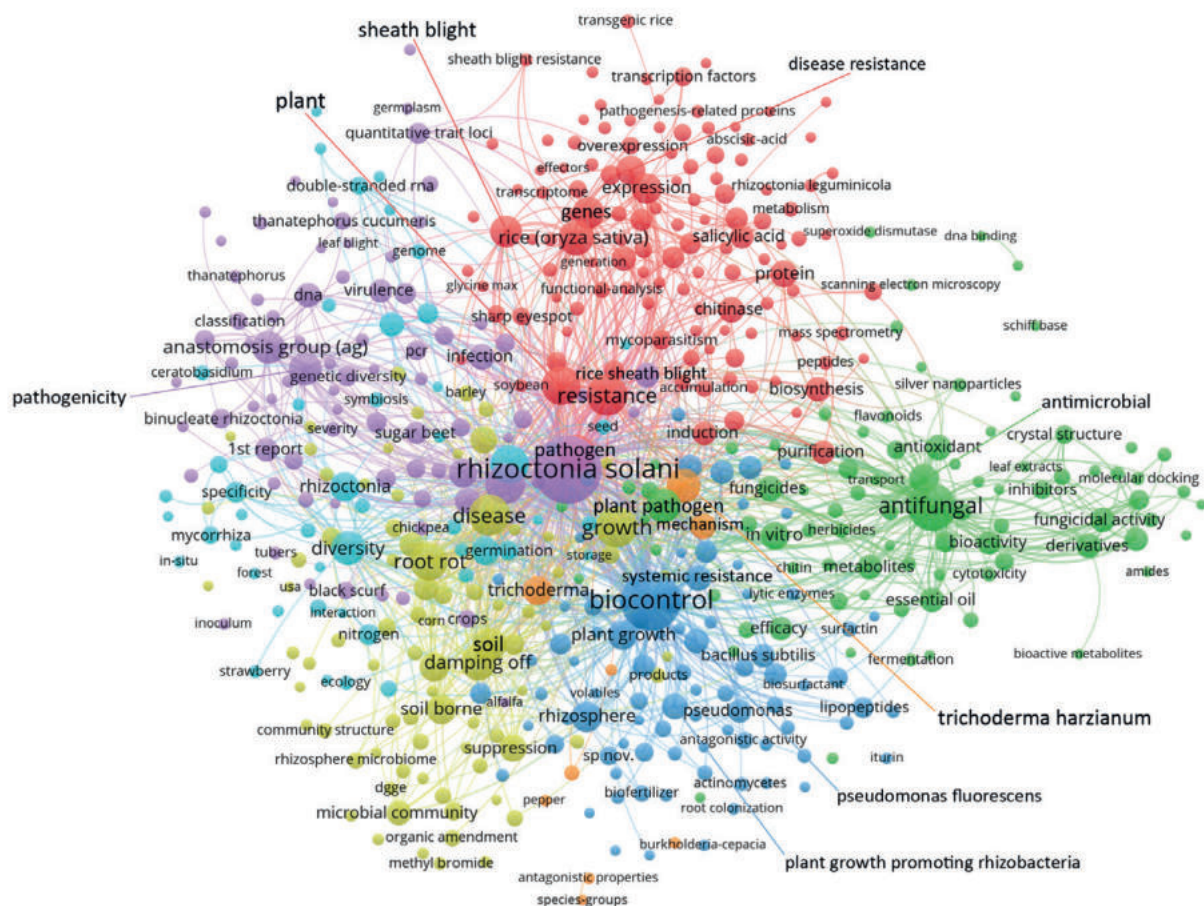


Fig. 34. Network visualisation of keywords of the publications related to *Rhizoctonia*. The larger the text and the circle the more often the subject has been cited.

hosts. Plant-growth promoting rhizobacteria such as *Pseudomonas* and *Bacillus* (Brewer & Larkin 2005, Chen *et al.* 2010, Kumar *et al.* 2012a, Haque & Khan 2021), Actinomycetes such as *Streptomyces* (Kulik 1996), as well as certain fungi including arbuscular mycorrhizae (Larkin 2008), *Trichoderma* (Boogert 1996, Grosch *et al.* 2006), *Gliocladium*, and hypovirulent strains of *Rhizoctonia* (Pascual *et al.* 2000, Sneh *et al.* 2004) have demonstrated varying

levels of control of different *Rhizoctonia* species in both controlled environment and field conditions. In rice, control of *R. solani* by *Pseudomonas fluorescens* has been linked to the production of various antimicrobial metabolites, including chitinases, HCN, IAA, etc. (Radjacommaré *et al.* 2004, Weller 2007), while various *Bacillus* spp. are known to produce pathogenicity-related proteins (He *et al.* 2002). In potatoes, *Trichoderma* species have shown

acceptable levels of control of *Rhizoctonia* diseases in commercial applications (Brewer & Larkin 2005, Wilson *et al.* 2008). In wheat, the role of disease-suppressive soils has been investigated, and several bacteria have been associated with the suppression of root rot and bare patches (Barnett *et al.* 2006, Mendes *et al.* 2011, Yin *et al.* 2013). Despite the promise of *Rhizoctonia* disease control, biocontrol agents alone have not provided the level of control needed to mitigate high losses caused by *Rhizoctonia* species in field settings.

Host resistance is not available for the majority of *Rhizoctonia* diseases, and if available, resistance is quantitatively inherited, making traditional breeding methods tedious and lengthy. As a result, approaches to crop improvement for disease resistance other than traditional breeding methodologies have been investigated in a few crops. In rice, RNA interference (Tiwari *et al.* 2017), gene editing technologies such as CRISPR/Cas9 (Gao *et al.* 2018), and transcriptional regulation of gene expression (Singh *et al.* 2015b, Peng *et al.* 2016) have shown promise for the targeted control of sheath blight. Similarly, transgenic wheat lines with enhanced resistance to *R. cerealis* have also been developed but are yet to be deployed for sharp eyespot control.

Other aspects of *Rhizoctonia* biology that warrant further investigation include an in-depth understanding of its interaction with various hosts. Specifically, functional genomics approaches, such as transcriptomics, proteomics, and metabolomics, may be exploited to identify pathogenic determinants of infection and reveal the biochemical pathways underlying quantitative resistance in different host plants, which may ultimately lead to the identification of novel resistance mechanisms in different hosts.

Authors: O. Ajayi-Oyetunde and C.A. Bradley

17. ***Pleurotus*** (Fr.) P. Kumm., Führ. Pilzk. (Zerbst): 24. 1871.

Type species: *Pleurotus ostreatus* (Jacq. ex Fr.) P. Kumm.

Classification: Basidiomycota, Agaricomycotina, Agaricomycetes, Agaricales, Pleurotaceae.

Background

Pleurotus is a gill mushroom belonging to the family *Pleurotaceae*. *Pleurotus* was described by Paul Kummer in 1871, but over the years has been moved to many genera such as *Favolaschia*, *Hohenbuehelia*, *Lentinus*, *Marasmiellus*, *Omphalotus*, *Panellus*, *Pleurocybella*, and *Resupinatus* (Singer 1986). There are 771 taxon names listed in Index Fungorum (2022), with 25 species recognised by He *et al.* (2019b). Macroscopic and microscopic morpho-characters and molecular data, including colour of the basidiomata, spore print, and type of hyphal system, all play an important role in the taxonomic classification of the genus (Guzmán 2000). Identification of *Pleurotus* is difficult as it is based mostly on morphological characteristics of the basidiomata. *Pleurotus* is an edible mushroom, with *Ple. ostreatus* (oyster mushroom) as the most famous species and cultivated worldwide (Cohen *et al.* 2002, Chang & Miles 2004). There are “species complexes” of commercial strains such as *Pleurotus djamor* (Zervakis *et al.* 2019), *Ple. eryngii* (Zervakis *et al.* 2001), *Ple. ostreatus* (Eger *et al.* 1979), and *Ple. pulmonarius* (Bao *et al.* 2005). The main morphological characteristics of *Pleurotus* are defined by pleurotoid basidiomata, decurrent lamellulae, smooth and elongated to cylindrical basidiospores, dimitic hyphal system with skeletal hyphae and

generative hyphae, and presence of clamp connections (Largent 1986, Seelan 2015).

Ecological and economic significance

Mushrooms play important roles in forest ecosystems. Wild strains and commercial strains of *Pleurotus* species can provide diverse ecological, environmental and economic services for local communities around the world. The ecosystem services provided by mushrooms also include provisioning services since many mushroom species are collected as food and for cultural services. Mushroom picking can also be a recreational and physical activity (Olah *et al.* 2020). Gathering *Pleurotus* sporocarps can also provide income for rural economies (Sánchez 2010). *Pleurotus* species can be found in both tropical and temperate areas (Chang & Miles 2004, Laessle & Petersen 2019), and species are widespread in hardwood forests around the world (Gunde-Cimerman 1999). Most species of *Pleurotus* cause white rot, growing on both decayed and dead hardwoods (Cohen *et al.* 2002, Tsujiyama & Ueno 2013). The mycelia of some *Pleurotus* species can produce adhesive knobs in asexual stages that can attack and consume nematodes (Thorn *et al.* 2000). *Pleurotus* is cultivated worldwide because they can grow with lignocellulosic waste materials that are easy to find. Thus, it is not expensive to cultivate *Pleurotus* for food.

Research interests

There are 4 025 publications and 45 475 citations from 2011–2021 in the Web of Science (Fig. 35), with the top 10 most cited articles shown in Table 20. Most publications focused on biotechnological applications, and cultivation of *Pleurotus* (Fig. 36). *Pleurotus* sporocarps contain several bioactive compounds, have high nutritional value, potential medicinal value, and are important functional foods or nutraceuticals. However, the biochemical mechanisms of healing of disease remain largely unknown (Gregori *et al.* 2007), and future research should focus on ways forward in the therapeutic activities and cultivation of *Pleurotus* species.

Biotechnological applications of *Pleurotus* species

Pleurotus species are saprobes and can play an important role in managing organic wastes whose disposal has become a problem (Li *et al.* 2020e). *Pleurotus* species have important medical and bioactive properties, producing primary and secondary metabolites (Renuga Devi & Krishnakumari 2015, Mapook *et al.* 2022). Bioactivities include hepatoprotective (Zhang *et al.* 2016a), antioxidant (Jayakumar *et al.* 2011, Zhang *et al.* 2016), antimicrobial (Schillaci *et al.* 2013), antiviral, anticancer, anti-inflammatory, anti-ageing, anti-tumour, antimutagenic, antilipidemic, hepatoprotective, antihyperglycemic, hypotensive, and immunostimulant properties with nutraceutical and pharmaceutical applications (Gunde-Cimerman 1999, Khan & Tania 2012, Patel *et al.* 2012, Wahab *et al.* 2014). *Pleurotus ostreatus* can produce extracellular laccase isoenzymes (Palmieri *et al.* 2000). Pre-treatment with *Ple. ostreatus* for enzymatic hydrolysis of rice straw found increased degrees of enzymatic solubilisation of holocellulose and cellulose fractions as the content of Klason lignin decreased (Taniguchi *et al.* 2000). The β -glucans contained in *Ple. ostreatus* have been clinically identified to possess immunostimulating properties (Patel *et al.* 2012). Kavanagh *et al.* (1951) reported that pleuromutilin was isolated in crystalline form from *Ple. multilus* and *Ple. passeckerianus*, which can be inhibitory for *Staphylococcus aureus*. *Pleurotus djamor* was able to inhibit gram-negative bacteria such as *Vibrio cholera*,

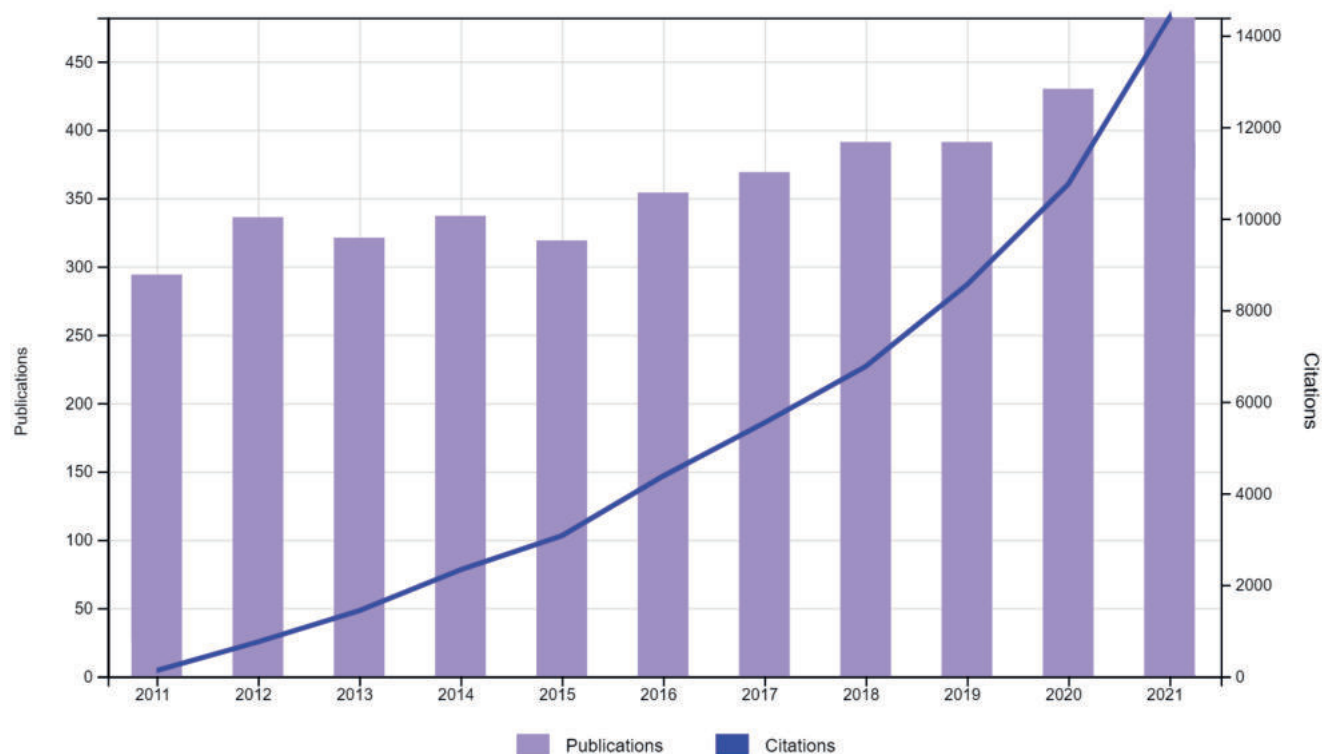


Fig. 35. Trends in research of *Pleurotus* in the period 2011–2021.

Escherichia coli and *Pseudomonas* sp. (Suresh *et al.* 2017). *Pleurotus eryngii* var. *eryngii*, *Ple. eryngii* var. *ferulae*, *Ple. eryngii* var. *elaeoselini*, and *Ple. nebrodensis* inhibited activity of bacterial strains of medical relevance such as *Staphylococcus aureus*, *S. epidermidis*, *Pseudomonas aeruginosa*, and *Escherichia coli* (Schillaci *et al.* 2013). *Pleurotus* species contain a high content of proteins, carbohydrates, fibre, minerals, vitamins, and low-fat content (Cohen *et al.* 2002, Bonatti *et al.* 2004). *Pleurotus* species have been used in traditional medicine for approximately 35 disorders or diseases (Guzmán 2000). *Pleurotus* species are also becoming increasingly attractive as sources for the development of new drugs and functional foods development.

Cultivation of *Pleurotus* species

Mushrooms have been consumed by humankind for millennia, and have high value. Cultivation of mushrooms is important economically (Girmay *et al.* 2016). *Pleurotus* species are the largest group of cultivated mushrooms in the world, ranking second in the world mushroom market, and the most popular consumed. *Pleurotus* species can be cultivated on a number of low-cost agro-industrial and forestry wastes, and they thrive on hardwood by-products such as sawdust (Girmay *et al.* 2016, Thongklang & Luangharn 2016), paper wastes (Girmay *et al.* 2016), pulp sludge, several agricultural wastes such as cocoa shell waste (Martínez-Carrera 1998), corn (Dias *et al.* 2003, Naraian *et al.* 2009), cotton waste (Chang *et al.* 1981), cotton seed (Girmay *et al.* 2016), diverse plant leaves, grass (Girmay *et al.* 2016), cereal straw (Mehta *et al.* 1990),

Table 20. Top 10 cited articles related to *Pleurotus* published in the period 2011–2021.

Rank	Article title	No. of citations	References
1	Lignocellulosic agriculture wastes as biomass feedstocks for second-generation bioethanol production: concepts and recent developments	316	Saini <i>et al.</i> (2015)
2	Structure–function relationship among bacterial, fungal and plant laccases	286	Dwivedi <i>et al.</i> (2011)
3	Fungal pretreatment of lignocellulosic biomass	257	Wan & Li (2012)
4	Antioxidant properties of phenolic compounds occurring in edible mushrooms	250	Palacios <i>et al.</i> (2011)
5	Macro and trace mineral constituents and radionuclides in mushrooms: health benefits and risks	238	Falandysz <i>et al.</i> (2013)
6	Recent developments in mushrooms as anti-cancer therapeutics: a review	216	Patel & Goyal (2012)
7	Induction and transcriptional regulation of laccases in fungi	200	Piscitelli <i>et al.</i> (2011)
8	Fungal laccase, manganese peroxidase and lignin peroxidase: Gene expression and regulation	191	Janusz <i>et al.</i> (2013)
9	The amazing potential of fungi: 50 ways we can exploit fungi industrially	186	Hyde <i>et al.</i> (2019b)
10	Antioxidant properties and phenolic profile of the most widely appreciated cultivated mushrooms: A comparative study between <i>in vivo</i> and <i>in vitro</i> samples	182	Reis <i>et al.</i> (2012)

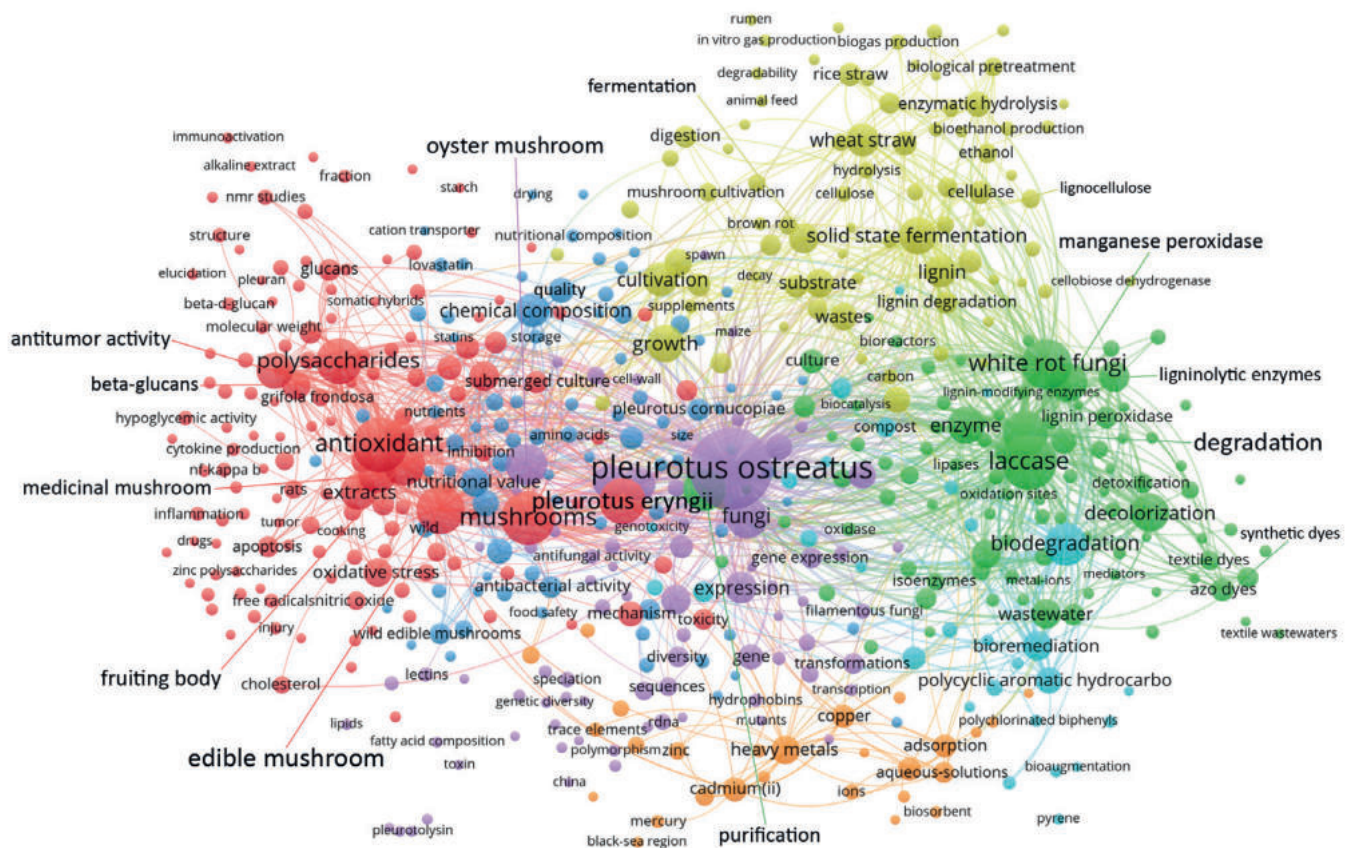


Fig. 36. Network visualisation of keywords of the publications related to *Pleurotus*. The larger the text and the circle the more often the subject has been cited.

sugarcane bagasse (Ragunathan *et al.* 1996), wheat straw (Zhang *et al.* 2002), coffee residues such as coffee grounds (Fan *et al.* 2000), and hulls, stalks, and leaves of banana (Mondal *et al.* 1970). The production and consumption of *Pleurotus* have increased significantly in recent years (Chang 1999), with prices varying between 3.91 and 7.84 US dollars per kg depending on product presentation (Vargas *et al.* 2020). The article "Cultivation of *Ple. ostreatus* and other edible mushrooms" (Sánchez 2010) is ranked among the top 10 cited published articles. Oyster mushrooms are cultivated in a shorter growth time when compared with other edible mushrooms (Sánchez 2010). *Pleurotus ostreatus* is the most cultivated mushroom for food purposes and to obtain income (Cohen *et al.* 2002). Other commercial species reported include *Ple. citrinopileatus* (yellow oyster mushroom or golden oyster mushroom), *Ple. cystidiosus* (abalone mushroom or maple oyster mushroom), *Ple. cornucopiae*, *Ple. djamor* (pink oyster mushroom), *Ple. florida* (white oyster mushroom), *Ple. flabellatus* (red oyster mushroom), *Ple. giganteus* (giant oyster mushroom), *Ple. ostreatus* (tree oyster), *Ple. pulmonarius* (Indian oyster or Italian oyster), *Ple. sapidus* (black oyster mushroom), and *Ple. tuber-regium* (king tuber mushroom) (Samsudin & Abdullah 2019).

Author: M. Phonemany

18. ***Ganoderma*** P. Karst., Revue Mycol., Toulouse 3(9): 17.
1881.

Type species: Ganoderma lucidum (Curtis) P. Karst.

Classification: Basidiomycota, Agaricomycotina, Agaricomycetes, Polyporales, Ganodermataceae.

Background

Ganoderma was established by Karsten (1881) with *G. lucidum* as the type species. Justo *et al.* (2017) treated *Ganodermataceae* as a synonym of *Polyporaceae*, while Cui *et al.* (2019) stated that *Ganoderma* was not included in *Polyporaceae* because their double-walled basidiospores are quite different from *Polyporaceae*. Sun *et al.* (2022) treated *Ganodermataceae* as an independent family based on its remarkable morphological features. The genus *Ganoderma* has been divided into three subgenera known as *Ganoderma* (which includes two sections *Ganoderma* and *Phaenema*), *Elfvigia*, and *Trachyderma*. *Ganoderma* species delimitation is unique to lacate and non-lacate basidiocarps, truncated double-walled basidiospores, and an apical germinal pore (Moncalvo & Ryvarden 1997, Ryvarden 2004). Kirk *et al.* (2008) mentioned that globally there are 80 species of *Ganoderma*, while Index Fungorum (2022) lists 489 taxa (currently 495) and MycoBank records about 500 taxa (currently 539) (Crous *et al.* 2004). The taxonomy of *Ganoderma* is unclear, and it can be a confusing genus to study due to the highly variable morphological features of the species (Ryvarden 2000, Chen *et al.* 2012b, Papp *et al.* 2017, Hapuarachchi *et al.* 2019, Tchotet-Tchoumi *et al.* 2019). A high level of phenotypic plasticity of the basidiomes at the macroscopic level has led to considerable confusion in the taxonomy of *Ganoderma* (Pilotti *et al.* 2005). Its basidiome features are also influenced by the interaction of both intrinsic and extrinsic factors (Moore *et al.* 2008). *Ganoderma* has high genetic diversity and substantial morphological variation, even within species. *Ganoderma* morphology may alter due to the influence of climate, nutrition, vegetation, and geography (Wu & Dai 2005).

Ganoderma is a cosmopolitan genus and some of the species are pathogenic and grow as facultative parasites that can live as

saprobies on decaying logs and stumps or associated with roots of living and dead trees (Moncalvo & Ryvarden 1997, Pilotti *et al.* 2005, Singh *et al.* 2007). Diseases caused by *Ganoderma* species result in lower yields in economically important trees (Wong *et al.* 2012). Most *Ganoderma* species are regarded as plant pathogens of trees, such as *G. australe* which is associated with *Castanopsis* spp. (Luangham *et al.* 2017), *G. boninense* which is pathogenic to oil palm (Pilotti 2005), *G. leucocontextum* causes diseases in *Cyclobalanopsis glauca* trees (Li *et al.* 2015b), and *G. tropicum*, which grows in a solitary manner on living *Dipterocarpus* species (Luangham *et al.* 2019).

Ganoderma species have been widely utilised as traditional medicines for millennia in Asia (Chang & Wasser 2012, Li *et al.* 2015b, Zhou *et al.* 2015a, Hapuarachchi *et al.* 2018). *Ganoderma* species are economically important as they have potential nutritional and therapeutic values. Its highly prized medicinal value is widely researched (De Silva *et al.* 2012b, Hapuarachchi *et al.* 2018).

Ecological and economic significance

Ganoderma species are distributed in sub-tropical to tropical and temperate regions but are particularly diverse in tropical regions (Cao & Yuan 2013). They are important wood-decaying fungi. Most species are regarded as pathogens that possess a wide host range (Wong *et al.* 2012) with more than 44 species from 34 genera of host plants (Venkatarayan 1936). *Ganoderma* can cause severe diseases in economically important trees and perennial crops, especially in tropical countries (Pilotti 2005). *Ganoderma* species are white rot fungi and have ecological importance in the breakdown of woody plants. These fungi decay lignin, hemicellulose and cellulose resulting in a severe loss of woody plant strength (Čilerdžić *et al.* 2017). *Ganoderma* possess lignocellulose decomposing enzymes useful for bioenergy production and bioremediation (Kües *et al.* 2015). There is a high degree of morphological variation, even within species, perhaps

due to ecological factors (Pilotti *et al.* 2004).

Ganoderma has been used in traditional medicines for hundreds of years in Asian countries and is increasingly being used in pharmaceutical industries worldwide. However, these fungi are not edible, since their basidiomes are always corky, tough, and bitter in taste (Hapuarachchi *et al.* 2019). Over the past two decades, the *Ganoderma* industry has developed greatly and today offers thousands of products to the markets. *Ganoderma* products are available in many forms such as dried sporocarps, dietary supplements, spore capsules, and cosmetic products (Taofiq *et al.* 2016a, b). Currently, *G. lucidum* is estimated to be worth more than 2.5 billion US dollars in Asian countries such as China, Korea and Japan (Lai *et al.* 2004). *Ganoderma tsugae* is regarded as a healthy food as it enhances the immune system and improves metabolic functions (Lai *et al.* 2004, Singh *et al.* 2013). *Ganoderma lucidum* is a high-priced product which is used as ornamental in Bonsai products to decorate gardens, ornaments and many other art products. However, there are problems with the industry which prevent it from establishing an effective market (Hapuarachchi *et al.* 2018).

Research interests

There are 3 699 publications and 44 643 citations from 2011–2021 in the Web of Science (Fig. 37), with the top 10 most cited articles listed in Table 21. Most of the publications focused on valuable medicinal mushrooms and natural bioactive compounds (polysaccharides, triterpenoids, sterols, and secondary metabolites) for potential use in clinical perspectives applications (anticancer, antioxidant, anti-tumour, immunomodulating) (Fig. 38).

The genus *Ganoderma* is economically important, as its members are regarded as valuable medicinal mushrooms (Dai *et al.* 2009, Chang & Wasser 2012). *Ganoderma* consumption has consistently been shown to have beneficial effects on human health and can be used to remedy a wide range of human diseases (Zong *et al.* 2012, Richter *et al.* 2015, Wang *et al.* 2015e).

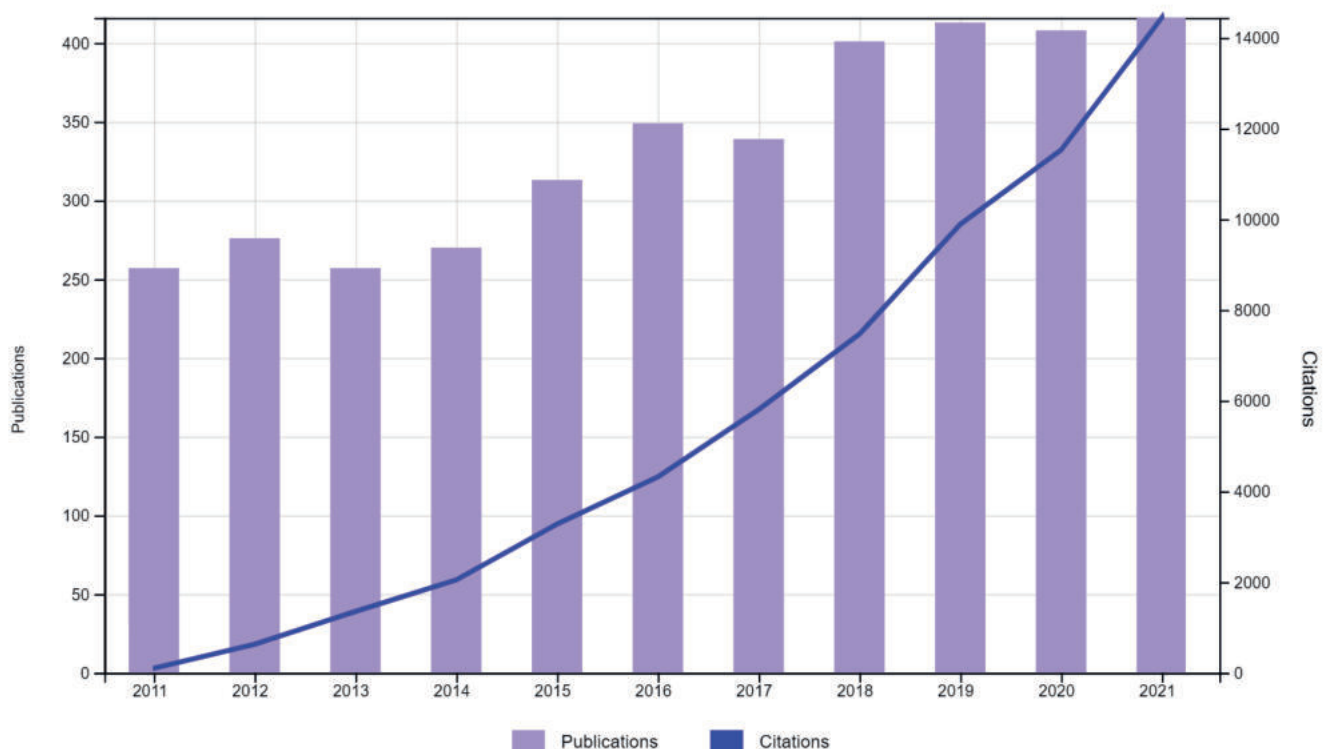
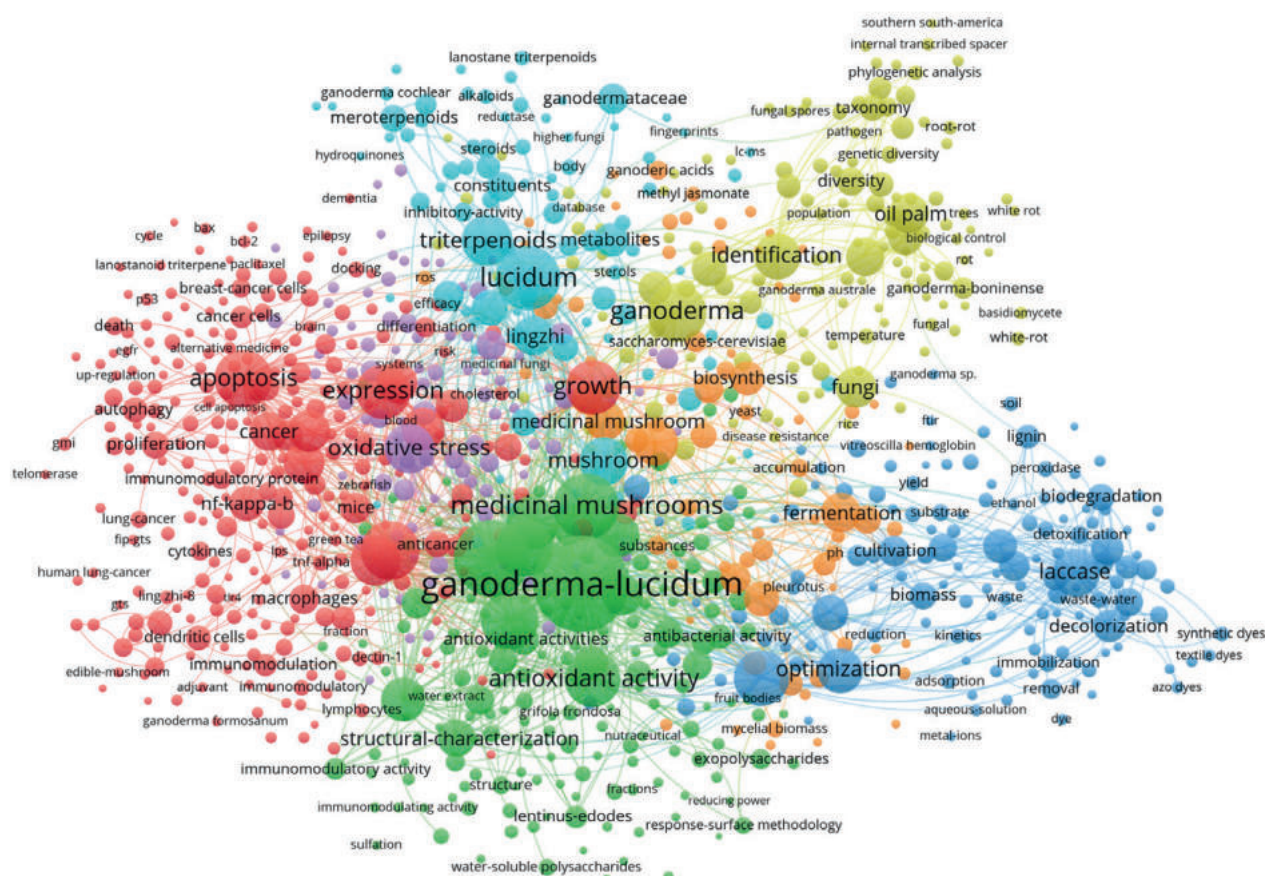


Fig. 37. Trends in research of *Ganoderma* in the period 2011–2021.

Table 21. Top 10 cited articles related to *Ganoderma* published in the period 2011–2021.

Rank	Article title	No. of citations	References
1	<i>Ganoderma lucidum</i> reduces obesity in mice by modulating the composition of the gut microbiota	702	Chang <i>et al.</i> (2015)
2	Immune evasion in cancer: Mechanistic basis and therapeutic strategies	637	Vinay <i>et al.</i> (2015)
3	Reviews on mechanisms of <i>in vitro</i> antioxidant activity of polysaccharides	399	Wang <i>et al.</i> (2015)
4	Anticancer polysaccharides from natural resources: A review of recent research	387	Zong <i>et al.</i> (2012)
5	The role of culinary-medicinal mushrooms on human welfare with a pyramid	341	Chang & Wasser (2012)
6	Genome sequence of the model medicinal mushroom <i>Ganoderma lucidum</i>	304	Chen <i>et al.</i> (2012b)
7	Tissue invasion and metastasis: molecular, biological and clinical perspectives	281	Jiang <i>et al.</i> (2015)
8	Antioxidative and immunomodulating activities of polysaccharide extracts of the medicinal mushrooms <i>Agaricus bisporus</i> , <i>Agaricus brasiliensis</i> , <i>Ganoderma lucidum</i> and <i>Phellinus linteus</i>	279	Kozarski (2011)
9	Current findings, future trends, and unsolved problems in studies of medicinal mushrooms	267	Wasser (2011)
10	Macro and trace mineral constituents and radionuclides in mushrooms: health benefits and risks	238	Falandysz & Borovička (2013)

**Fig. 38.** Network visualisation of keywords of the publications related to *Ganoderma*. The larger the text and the circle the more often the subject has been cited.

More than 400 bioactive compounds have been found in various *Ganoderma* species such as fatty acids, polysaccharides, protein, steroids, triterpenoids, and secondary metabolites (*i.e.*, ganoderic acids, ganodermanondiol, ganodermanontriol, and ganodermediol) (Shim *et al.* 2004, Qiao *et al.* 2005, Teng *et al.* 2011, Richter *et al.* 2015). Those valuable natural compounds are used to treat and remedy many pathological diseases such as hypertension, hypercholesterolemia, bronchitis, asthma, diabetes,

and cancer (Chang & Wasser 2012, De Silva *et al.* 2012a, Richter *et al.* 2015, Abate *et al.* 2020). Additionally, there are reports of several metabolic activities of *G. lucidum* performed in both *in vitro* and *in vivo* studies. The major consideration is given to therapeutic strategies (Chang *et al.* 2015, Vinay *et al.* 2015), the benefits that have been claimed for the use of mushrooms in treating cancer, and the prospects of using medicinal mushrooms (Wasser 2011).

Bioactive metabolites isolated from *Ganoderma* mushrooms have also shown potential success in cancer treatment as biological immunotherapeutic agents that stimulate the immune system against cancer cells (Kozarski 2011). Hence, pharmacologically active constituents of *G. lucidum* contribute to positive immune responses. Improved application methods and further clinical research on *G. lucidum* on human subjects are needed.

Author: T. Luangharn

19. *Neurospora* Shear & B.O. Dodge, J. Agric. Res., Washington 34: 1025. 1927.

Type species: *Neurospora sitophila* Shear & B.O. Dodge

Classification: Ascomycota, Pezizomycotina, Sordariomycetes, Sordariales, Sordariaceae.

Background

The genus *Neurospora* was first found in bakeries in France in 1843 where it formed an asexual morph on bread, and later the discovery of sexual sporocarps by mycologists Cornelius L. Shear and Bernard O. Dodge placed this fungus in a new genus *Neurospora* (Shear & Dodge 1927). Members of this genus were first usually found in burned/unburned vegetation in terrestrial habitats or soil in tropical and subtropical regions but were later identified across the globe (Perkins *et al.* 1976, Perkins & Raju 1986, Perkins & Turner 1988, Turner *et al.* 2001, García *et al.* 2004). The sexual morph of this genus is characterised by dark brown ascospores with ornamented surfaces and the asexual morph is chrysonilia-like with both macroconidia and microconidia (Shear & Dodge 1927, Arx 1981a, b, Jacobson *et al.* 2004). There are three mating strategies in *Neurospora* viz.: homothallism, pseudohomothallism and heterothallism (Shear &

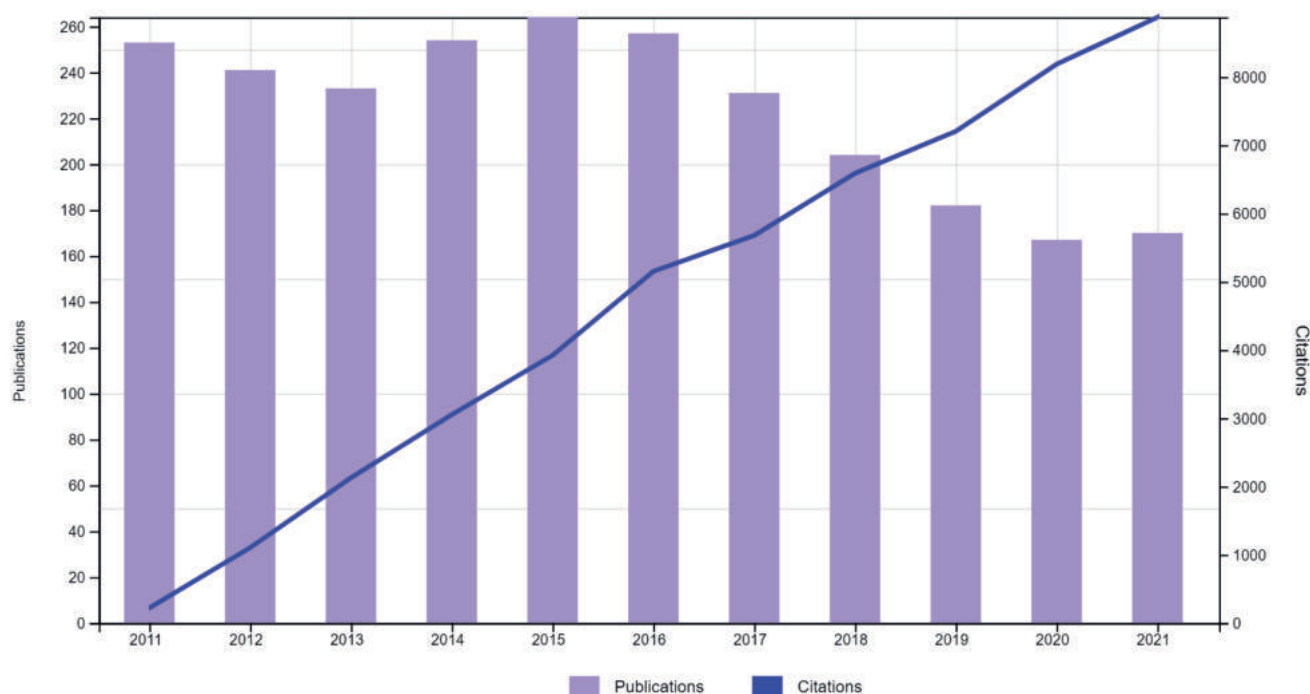


Fig. 39. Trends in research of *Neurospora* in the period 2011–2021.

Table 22. Top 10 cited articles related to *Neurospora* published in the period 2011–2021.

Rank	Article title	No. of citations	References
1	Cellobiose dehydrogenase and a copper-dependent polysaccharide monooxygenase potentiate cellulose degradation by <i>Neurospora crassa</i>	419	Phillips <i>et al.</i> (2011)
2	Oxidative cleavage of cellulose by fungal copper-dependent polysaccharide monooxygenases	314	Beeson <i>et al.</i> (2012)
3	Fungal cell wall organization and biosynthesis	276	Free (2013)
4	Codon usage influences the local rate of translation elongation to regulate co-translational protein folding	273	Yu <i>et al.</i> (2015a)
5	DNA methylation and demethylation in mammals	266	Chen & Riggs (2011)
6	Non-optimal codon usage affects expression, structure and function of clock protein FRQ	250	Zhou <i>et al.</i> (2013)
7	Discovery of LPMO activity on hemicelluloses shows the importance of oxidative processes in plant cell wall degradation	249	Agger <i>et al.</i> (2014)
8	Quorum sensing in fungi - a review	215	Albuquerque & Casadevall (2012)
9	Extracellular electron transfer systems fuel cellulose oxidative degradation	215	Kracher <i>et al.</i> (2016)
10	A C4-oxidizing lytic polysaccharide monooxygenase cleaving both cellulose and cello-oligosaccharides	210	Isaksen <i>et al.</i> (2012)

Dodge 1927, Tai 1935, Mahoney *et al.* 1969, Krug & Khan 1991). The traditional identification of *Neurospora* species is based on distinguishing ascospore wall ornamentation (García *et al.* 2004, Cai *et al.* 2006a). García *et al.* (2004) and Cai *et al.* (2006a) found that only using ascospore wall structure to distinguish *Neurospora* species results in species being polyphyletic in the *Sordariales* phylogenetic analysis. The mating strategy and ornamentation of the epispore are the most important characteristics to define the phylogenetic relationship in *Neurospora* (Whitehouse 1949, Taylor & Natvig 1989, Grognet & Silar 2015, García *et al.* 2004, Cai *et al.* 2006a).

The asexual growth and reproduction, the asexual-sexual transition, and sexual development and reproduction are well-studied developmental phases of the life cycles of *Neurospora* (Lehr *et al.* 2014, Dunlap *et al.* 2007). In addition, *Neurospora crassa* is known as a model eukaryotic multicellular organism which is used in research for the one-gene-one-enzyme, genetics, developmental biology, and molecular biology (Beadle & Tatum 1941, Cogoni & Macino 1999, Loros & Dunlap, 2001, Davis & Perkin 2002, Honda *et al.* 2020). Systematic sampling of natural populations of *Neurospora* was started in 1968 and the results were presented by Perkins *et al.* (1976). A comprehensive review of the genus *Neurospora* was presented with useful information on experimental laboratory studies, field-collection and analysing data together with ecology, geographical distribution, species status, genetic variation, and polymorphism was provided by Perkins and Turner (1988). Studies on biological and phylogenetic species of *Neurospora* (Dettman *et al.* 2001, 2003, 2006) helped to understand the clock variation within different ecotypes of *Neurospora*.

Among filamentous fungi, *Neurospora* species have been widely used as a model for clock variation studies (Koritala & Lee 2017). Several *Neurospora* species were listed as natural variant studies in Koritala & Lee (2017). *Neurospora* species are well-characterised, especially *Neurospora crassa* (Colot *et al.* 2006, McCluskey *et al.* 2010, Koritala & Lee 2017). *Neurospora* species have multiple advantages and have been widely used as model species to understand the biological aspects of natural variations, viz. biochemistry, ecology, evolution, genetics, and circadian biology (Koritala & Lee 2017, Perkins *et al.* 1976, Turner *et al.* 2001).

There are 2 456 publications and 44 091 citations from 2011–2021 in the Web of Science (Fig. 39), with the top 10 most cited articles listed in Table 22. Most publications focused on a model for clock variation studies of *Neurospora* (Fig. 40).

Neurosporin A and the salicylaldehyde sordarial are toxins produced by *Neurospora* species which have a defense mechanism (Zhao *et al.* 2017c, 2019c).

Taxonomy and phylogeny

Huang *et al.* (2021c) referred to sequence data by Cai *et al.* (2006a), Wang *et al.* (2019d, e) and Vu *et al.* (2019) to build a phylogenetic tree and used combined sequence data from the markers LSU, ITS and *tub*. Based on a multi-gene analysis of *Neurospora*, Huang *et al.* (2021c) divided *Sordaria* into four clades within *Sordariaceae*. They mentioned that the positions of *Neurospora* and *Sordaria* species are usually unstable in single-gene or even multi-gene analyses. Thus, the morphology of *Neurospora* and *Sordaria* can be used to distinguish them.

Author: S. Tibpromma

20. *Cladosporium* Link, Mag. Ges. Naturf. Freunde Berlin 7: 37. 1816.

Type species: *Cladosporium herbarum* (Pers.) Link

Classification: Ascomycota, Pezizomycotina, Dothideomycetes, Cladosporiales, Cladosporiaceae.

Background

Cladosporium is one of the largest genera of hyphomycetes with more than 750 species epithets listed in MycoBank, including about 250 recognised species. Species of *Cladosporium* are among the most common fungi worldwide, being isolated from almost any environmental source and geographic location (Bensch *et al.* 2012). Most species primarily occur in soil, food, paint, textiles and other organic matter (Ma *et al.* 2017, Iturrieta-González *et al.* 2021) or colonise as secondary invaders leaf lesions caused by plant pathogenic fungi (Ellis 1971, 1976, Bensch *et al.* 2012, 2015). Several species are important pathogens of plants (Schubert 2005, Bensch *et al.* 2012, Rosado *et al.* 2019) or occur as hyperparasites on other fungi (Heuchert *et al.* 2005). Some are also able to affect animals and humans (De Hoog *et al.* 2000, Sandoval-Denis *et al.* 2015, 2016, Yew *et al.* 2016, Batra *et al.* 2019, Velázquez-Jiménez *et al.* 2019). *Cladosporium* species are considered among the most widespread fungi in buildings and indoor environments as well as in outdoor and indoor air (Fradkin *et al.* 1987, Flannigan 2001, Horner *et al.* 2004, Bensch *et al.* 2018). With their relatively small conidia, usually formed in branched chains, they are well adapted to be spread easily in large numbers over long distances. Because many *Cladosporium* species are cosmopolitan agents of decay, deterioration, or may cause allergies or even diseases of plants, animals and human beings, and are often of high environmental impact, the genus is of special interest to researchers in a wide variety of disciplines (Bensch *et al.* 2012).

Cladosporium, a monophyletic genus residing in the *Cladosporiaceae* (*Cladosporiales*, *Dothideomycetes*; Abdollahzadeh *et al.* 2020), is well circumscribed by having a unique coronate structure of its conidiogenous loci and conidial hila, consisting of a central convex dome surrounded by a raised periclinal rim (David 1997, Braun *et al.* 2003, Bensch *et al.* 2012). *Cladosporium* was established by Link in 1816, who included four species of which *Cl. herbarum* was proposed as lectotype species by Clements & Shear (1931), a decision followed by De Vries (1952) and Hughes (1958). It developed to be one of the most heterogeneous genera of hyphomycetes as all kinds of unrelated dematiaceous hyphomycetes characterised by

having amero- to phragmosporous conidia formed in acropetal chains have been assigned to *Cladosporium s. lat.* Various authors discussed the heterogeneity of *Cladosporium s. lat.* and proposed new, more natural circumscriptions of this genus (e.g., Von Arx 1981, 1983, Morgan-Jones & Jacobsen 1988, McKemy & Morgan-Jones 1990, Morgan-Jones & McKemy 1990, Braun 1995, Partridge & Morgan-Jones 2002, 2003). David (1997) revised *Cladosporium* species previously referred to as *Heterosporium* and demonstrated that the genus *Cladosporium* is well-characterised and easily recognisable by its unique structure of the conidiogenous loci and conidial hila. A few years later, the first attempts were made to revise and monograph *Cladosporium s. lat.* (Crous *et al.* 2001a). Braun *et al.* (2003) published results of the first molecular examination of *Cladosporium s. lat.*, clearly confirming the strong heterogeneity of this genus. In the last two decades, various genera with cladosporium-like morphs could be separated from *Cladosporium s. str.* (De Hoog *et al.* 1995, Seifert *et al.* 2004, Heuchert *et al.* 2005, Crous *et al.* 2006a, 2007, 2017, Braun *et al.* 2008, Bezerra *et al.* 2017), based on re-assessments of morphological features and molecular data. Efforts to clarify the phylogeny and taxonomic structure of *Cladosporium* species and allied fungi have resulted in a modern redefinition of the genus (Crous *et al.* 2007, Schubert *et al.* 2007, Zalar *et al.* 2007, Bensch *et al.* 2010, 2012, 2018). Due to continuous isolations from a wide range of substrates, collected on various continents, the number of *Cladosporium* species has steadily increased (Crous *et al.* 2014a, Bensch *et al.* 2015, Braun *et al.* 2015, Razafinarivo *et al.* 2016, Marin-Felix *et al.* 2017, Sandoval-Denis *et al.* 2016, Ma *et al.* 2017, Crous *et al.* 2018, Tibpromma *et al.* 2018a, Rosario *et al.* 2019, Iturrieta-González *et al.* 2021, Costa *et al.* 2022, Moharram *et al.* 2022, Chethana *et al.* 2023, Lee *et al.* 2023, Yang *et al.* 2023b). Sexual morphs, previously assigned to the genus *Davidiella*, are known for only a few species.

Within *Cladosporium*, three major species complexes are recognised: *Cl. herbarum*, *Cl. sphaerospermum* and *Cl. cladosporioides* species complexes. Morphological features used for the circumscription of these complexes have been summarised in Bensch *et al.* (2012, 2015) and Marin-Felix *et al.* (2017a). Most *Cladosporium* species can be referred to one of the three species complexes based on their morphology. However, within a given species complex, the differentiation of particular species of *Cladosporium* is often difficult based on morphological characters alone since many species have overlapping characteristics. Therefore, polyphasic approaches including multilocal phylogenetic analyses are necessary for species delimitations and proper identifications. Previous studies have already revealed the existence of numerous cryptic species in the three species complexes (Schubert *et al.* 2007, Zalar *et al.* 2007, Bensch *et al.* 2010, 2018, Sandoval-Denis *et al.* 2016), but many more are to be expected.

Ecological and economic significance

Cladosporium cladosporioides

This species represents a species complex of morphologically almost indistinguishable, but phylogenetically distinct species (Bensch *et al.* 2010, 2018). Given their high morphological similarity, the use of a molecular approach for the correct identification of all these species is highly recommended. *Cladosporium cladosporioides s. lat.* is a common air- and soil-borne saprotroph and is frequently encountered as a contaminant. It has been isolated from food

sources such as cereal grain, coffee and peas, as fruit contaminants causing spoilage in low-temperature storage and from indoor environment sources such as water-damaged wood, wallpaper and plaster (Samson *et al.* 2019). It is one of the most predominant fungi in outdoor air (Fradkin *et al.* 1987), its spores being important in seasonal allergic diseases. *Cladosporium cladosporioides* rarely causes invasive disease in animals and humans, but is an important agent of plant disease, attacking both the leaves and fruits of many plants (Nam *et al.* 2015). It is found as a common endophytic fungus as well as a secondary invader on necrotic parts of many different host plants, including lesions caused by pathogenic fungi (Bensch *et al.* 2012). Some leaf-spotting races have been reported, but such host-specific pathogenicity is largely untested (Meneses *et al.* 2018, Robles-Yerena *et al.* 2019). Furthermore, this species is relevant as a potential biocontrol agent for plant diseases (Wang *et al.* 2013, Köhl *et al.* 2015, Torres *et al.* 2017). *Cladosporium anthropophilum*, a member of the *Cl. cladosporioides* species complex, represents a clinically relevant fungus, being the second most prevalent species identified in a set of clinical isolates from the USA after *Cl. halotolerans* (Sandoval-Denis *et al.* 2015, 2016).

Cladosporium herbarum

Cladosporium herbarum has been isolated from food sources, such as weathered cereal grain, mouldy fruit and vegetables, living and decaying plant material, cheese, butter and margarine and from indoor environment sources such as water-damaged wood, wallpaper and plaster (Samson *et al.* 2019). It is the most studied species in allergy research (Breitenbach 2008, Poll *et al.* 2009), but in recent studies (Segers *et al.* 2015, Bensch *et al.* 2018) none of the studied strains turned out to be *Cl. herbarum*. The closely allied and morphologically similar species *Cl. allicinum* proved to be one of the most common *Cladosporium* species in indoor environments instead (Segers *et al.* 2015, Bensch *et al.* 2018, Andersen *et al.* 2021).

Cladosporium sphaerospermum

Similar to the other two species, *Cladosporium sphaerospermum* represents a species complex of morphologically similar and closely allied species. *Cladosporium halotolerans* proved to be the most common *Cladosporium* species in indoor environments and is very often isolated from house dust. It is commonly found both indoors and outside and is frequently encountered as a contaminant. It has been isolated from hypersaline water, from indoor environment sources such as water-damaged bathroom and basement walls, gypsum wallboard, inner roofing in attics and from human sputum and skin (Bensch *et al.* 2018, Samson *et al.* 2019). *Cladosporium sphaerospermum* and related taxa develop under low nutrient conditions and easily cope with humidity changes, both very characteristic for indoor situations. Sandoval-Denis *et al.* (2015) reported *Cl. halotolerans* as the most frequent *Cladosporium* species recovered from clinical samples in the USA.

Research interests

There are 2 641 publications and 38 580 citations from 2011–2021 in the Web of Science (Fig. 41). The top 10 most cited articles are listed in Table 23. Most of the publications focused on the identification, diversity and phylogeny of *Cladosporium* species, their occurrence as airborne, endophytic and allergy-inducing microorganisms and their role in biodegradation, biodeterioration and indoor environments, their potential as biocontrol and antifungal agents and their produced metabolites (Fig. 42). *Cladosporium fulvum*, the causal agent of tomato leaf mould, which is frequently used as a model organism to study plant-pathogen interactions, does not belong in the genus *Cladosporium* but is *Fulvia fulva* (Videira *et al.* 2017), which belongs in the *Mycosphaerellaceae*, *Mycosphaerellales*.

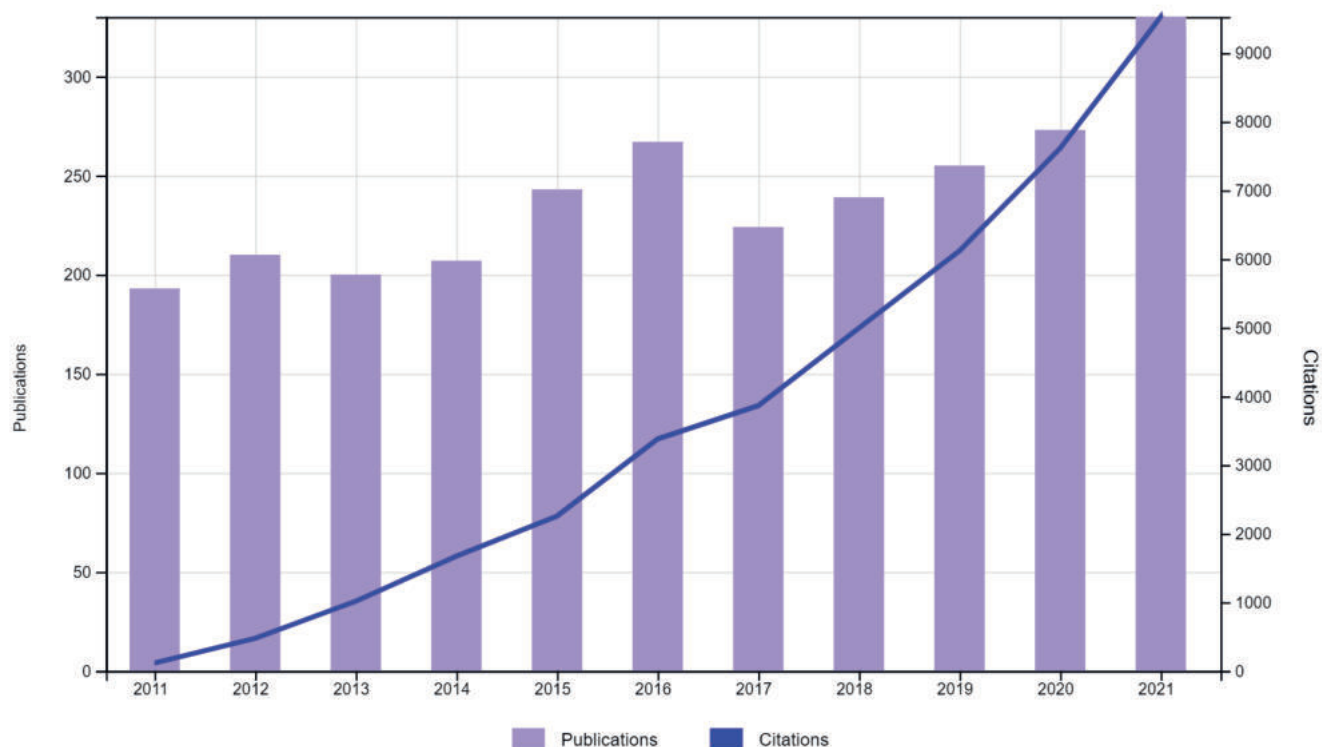


Fig. 41. Trends in research of *Cladosporium* in the period 2011–2021.

Table 23. Top 10 cited articles related to *Cladosporium* published in the period 2011–2021.

Rank	Article title	No. of citations	References
1	Fungal effectors and plant susceptibility	505	Lo Presti <i>et al.</i> (2015)
2	The genus <i>Cladosporium</i>	352	Bensch <i>et al.</i> (2012)
3	Fungi and allergic lower respiratory tract diseases	305	Knutsen <i>et al.</i> (2012)
4	Associations between fungal species and water-damaged building materials	213	Andersen <i>et al.</i> (2011)
5	Analysis of two <i>in planta</i> expressed LysM effector homologs from the fungus <i>Mycosphaerella graminicola</i> reveals novel functional properties and varying contributions to virulence on wheat	196	Marshall <i>et al.</i> (2011)
6	Receptor-like kinase SOBIR1/EVR interacts with receptor-like proteins in plant immunity against fungal infection	175	Liebrand <i>et al.</i> (2013)
7	Dual disease resistance mediated by the immune receptor Cf-2 in tomato requires a common virulence target of a fungus and a nematode	171	Lozano-Torres <i>et al.</i> (2012)
8	Two for all: receptor-associated kinases SOBIR1 and BAK1	163	Liebrand <i>et al.</i> (2014)
9	The genomes of the fungal plant pathogens <i>Cladosporium fulvum</i> and <i>Dothistroma septosporum</i> reveal adaptation to different hosts and lifestyles but also signatures of common ancestry	153	De Wit <i>et al.</i> (2012)
10	Fungal effector Ecp6 outcompetes host immune receptor for chitin binding through intrachain LysM dimerization	152	Sanchez-Vallet <i>et al.</i> (2013)

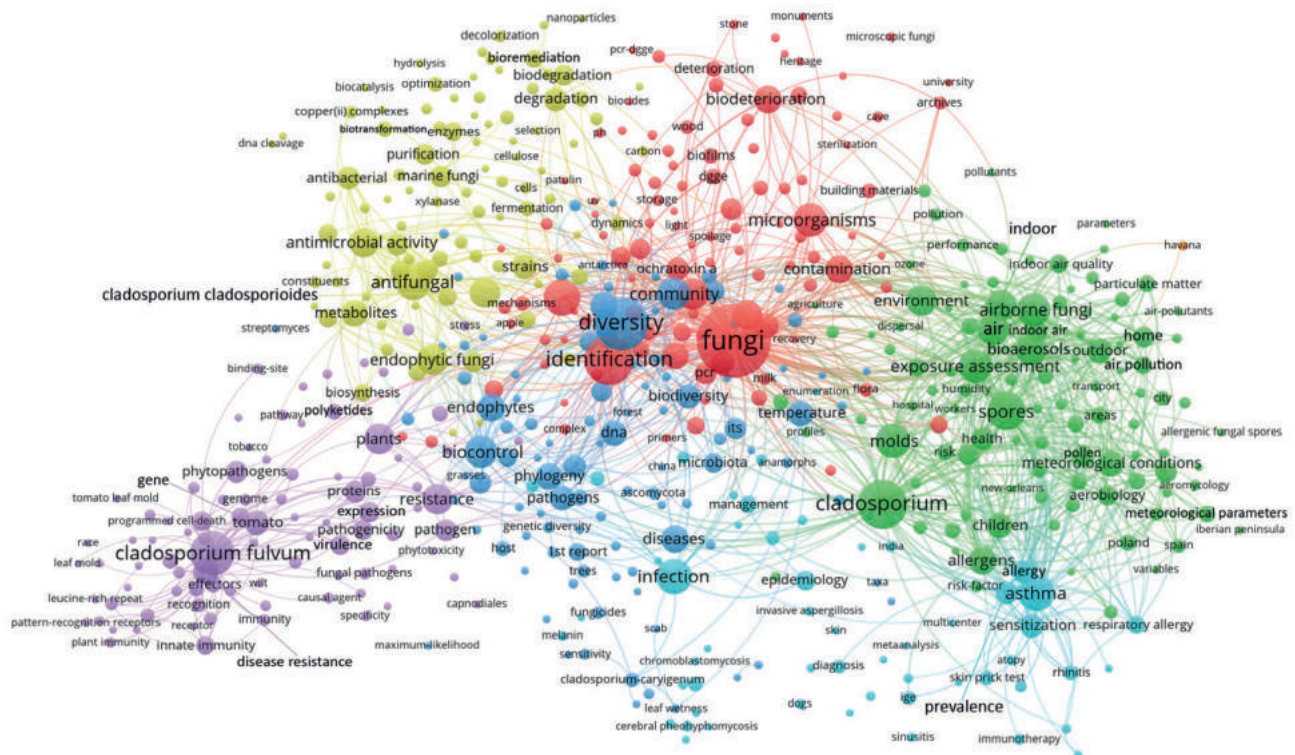


Fig. 42. Network visualisation of keywords of the publications related to *Cladosporium*. The larger the text and the circle the more often the subject has been cited.

Disease management

There are only a few economically important diseases caused by *Cladosporium* species. *Cladosporium* leaf spot of spinach, caused by *Cl. variable*, occurs to some extent almost every year but is rarely severe. Hot water as well as chlorine seed treatment effectively eliminates *Cladosporium* from spinach seed (Du Toit *et al.* 2005). QoI fungicides have also been shown to control this disease. *Cladosporium cucumerinum*, the causal organism of crown blight and scab or gummosis disease, is widespread among members of the *Cucurbitaceae*. Several fungicides can reduce the severity of this scab if applied on a schedule after the first bloom. Fairy ring

leaf spot affecting carnations, caused by *Cl. echinulatum*, can be most effectively treated with sodium bicarbonate and *Trichoderma virens* (Sandoval *et al.* 2009).

Toxins

Several mycotoxins are known to be produced by *Cladosporium* species, viz., cladosporin, isocladosporin, emodin, cladosporid, cladosporol as well as several others, which represent antifungal, anti-bacterial or insecticidal compounds that have plant growth regulators or plant inhibiting activities while others are inhibitors of protein kinase C (Alwatban *et al.* 2016, Wang *et al.* 2013, 2015).

Cladosporinone was found as a new viriditoxin derivative and was studied for its cytotoxicity against the murine lymphoma cell line L5187Y (Liu *et al.* 2016f). Salvatore *et al.* (2021) provided a survey of bioactive natural compounds from *Cladosporium* species, including toxins.

Taxonomy and phylogeny

The most phylogenetically informative markers proved to be *actA* and *tef1*, while ITS sequences are usually identical for species of the same complex (Bensch *et al.* 2010, 2012, 2018, Sandoval-Denis *et al.* 2016). Although ITS is a suitable locus to identify an isolate as belonging to the genus *Cladosporium* and to some extent to a species complex, additional loci are required to reach a conclusive species (or even species complex) identification. The use of a molecular approach is strongly recommended for correct identifications of the species in this complex fungal group. A sufficient number of isolates should be included in the phylogenetic analysis to ensure that the genetic diversity of a species is covered. As starting material, a reliable backbone tree should be used. It is not advisable to blindly go on the names in GenBank as many of the names of older sequences are outdated.

Authors: U. Braun and K. Bensch

21. *Yarrowia* Van der Walt & Arx, Antonie van Leeuwenhoek 46: 519. 1981.

Type species: *Yarrowia lipolytica* (Wick. *et al.*) Van der Walt & Arx

Classification: Ascomycota, Saccharomycotina, Dipodascomycetes, Dipodascales, incertae sedis.

Background

Yarrowia species are widespread and have been isolated from various sources such as food, soil, insects, salt and fresh water as well as humans (Kurtzman *et al.* 2011, Groenewald *et al.* 2014). The first observation of the sexual morph of *Yarrowia lipolytica*, the type species, was made by Wickerham *et al.* (1970a, b) and described as *Endomycopsis lipolytica*. Yarrow (1972) transferred *E. lipolytica* to the genus *Saccharomycopsis*. *Saccharomycopsis lipolytica* appeared distinct from the other members of the genus because of the shape of its ascospores and the presence of coenzyme Q-9. Based on this, the genus *Yarrowia* was proposed by Van der Walt & Von Arx (1980) to accommodate *Y. lipolytica*. This species remained the only member of the genus for more than 30 years until Groenewald & Smith (2013) illustrated the presence of the sexual life cycle of *Candida deformans* and proposed a new combination *Yarrowia deformans*. Most of the sexually reproducing *Yarrowia* species were found to be mainly heterothallic (Knutzen *et al.* 2007, Groenewald & Smith 2013) as asci are formed following the conjugation of complementary mating types. However, a few *Y. lipolytica* isolates were found to be self-sporulating.

In the past years, *Yarrowia* was expanded from comprising only one species to 14 species. Several studies included numerous phylogenetically closely related asexual *Candida* species as new combinations, and novel species were described (Kurtzman *et al.* 2011, Groenewald & Smith 2013, Nagy *et al.* 2014, Crous *et al.* 2017a). The currently described *Yarrowia* species are *Y. deformans*, *Y. lipolytica*, *Y. parophonii* and *Y. porcina* having a sexual morph and the asexual reproducing species *Y. alimentaria*, *Y. bubula*, *Y. brassicae*, *Y. divulgata*, *Y. galli*, *Y. hollandica*, *Y. keelungensis*,

Y. osloensis, *Y. phangngaensis* and *Y. yakushimensis*. *Candida hispaniensis*, although not yet proposed as a new combination within *Yarrowia*, clusters with the rest of the *Yarrowia* species in most phylogenetic studies. Most species of *Yarrowia* can assimilate only a few carbon compounds and are almost indistinguishable physiologically from one another (Kurtzman *et al.* 2011, Groenewald & Smith 2013, Nagy *et al.* 2014, Crous *et al.* 2017a).

The currently most used and best method to describe novelties and distinguish among species of this genus is by sequence analysis of the D1/D2 domains of LSU nrRNA gene and the ITS regions (Kurtzman & Robnett 1994, 1995, 1998, Fitzpatrick *et al.* 2006, James *et al.* 2006, Kurtzman *et al.* 2011, Groenewald & Smith 2013, Nagy *et al.* 2014, Crous *et al.* 2017b, Liu *et al.* 2018b). *Yarrowia* is phylogenetically distantly related to most members of the *Saccharomycotina* yeast genera and present at the base of the *Saccharomycetales*. However, multigene and phylogenomic analyses that included a greater number of genera showed genera belonging to the families *Lipomycetaceae*, *Dipodascaceae* and *Phaffomycetaceae* to be basal to *Yarrowia* (Kurtzman *et al.* 2011, Kurtzman & Robnett 2013, Shen *et al.* 2018).

Yarrowia species are commonly found in food products such as meat (beef, pork, poultry) and dairy (cheeses, milk, yoghurt, butter, cream, and margarine), but they have also been isolated from fish, maize, traditional food, soil, insects (beetles), salt and fresh water, human tissue as well as petroleum storage tanks (Kurtzman *et al.* 2011, Groenewald *et al.* 2014). *Yarrowia* has been described as an oleaginous genus indicating that strains can grow on a variety of hydrophobic substrates and those that contain high proportions of lipids (fat and/or protein). It is known that the type species *Y. lipolytica* can accumulate lipids intracellularly to 40 % of its cell dry weight (Beopoulos *et al.* 2011).

Economical and medical significance

It is clear from literature that *Yarrowia* species are widespread and play an essential role in the food industry (beneficial or undesirable), they have importance in medical fields and have industrial utility (Kurtzman *et al.* 2011, Groenewald *et al.* 2014). These characteristics together with the knowledge that *Y. lipolytica* is a “safe-to-use” organism, indicate that this genus has great ecological and economic significance (reviewed in Groenewald *et al.* 2014).

Food and food safety

Yarrowia lipolytica is a species commonly associated with food products (reviewed in Groenewald *et al.* 2014). It is a regular component of food and beverage microbiota, either with desirable and beneficial effects (Wyder *et al.* 1999, Encinas *et al.* 2000, Boekhout & Robert 2003, Ferreira & Viljoen 2003, Patrignani *et al.* 2007) or occasionally it contributes to spoilage (Deak & Beuchat 1987, 1996, Ismail *et al.* 2000, Boekhout & Robert 2003). However, for food safety concerns it is important to know that *Y. lipolytica* is regarded to be a “safe-to-use” organism.

Yarrowia species are often associated with (fermented) dairy products. These include a diversity of cheeses, milk from ewe, water buffalo and cow as well as yoghurt, butter, cream, margarine and traditional products such as kefir, *nunu* and *amas* (reviewed in Groenewald *et al.* 2014). *Yarrowia lipolytica* contributes to the organoleptic characteristics of cheese and is one of the top three most prevalent yeast species in cheese such as mould-ripened, smear-ripened, blue-veined and fresh cheeses. It is frequently

used as a cheese starter as it reduces ripening times, extends the shelf life and inhibits the growth of undesirable bacteria and green mould. However, there is sometimes a thin line between the desirable and beneficial effects and its occasional contribution to spoilage as it can produce off-flavours, affects the cheese texture negatively, increases the formation of biogenic amines and causes surface browning that affects appearance.

Yarrowia species also occur on red meat (e.g., Vienna, traditional sausages of southern Italy, Spanish and German fermented sausages, salami, ham, salted bacon, beef, biltong) and occasionally also in poultry and fish products (reviewed in Groenewald *et al.* 2014). *Yarrowia alimentaria* was found to co-exist with *Y. lipolytica* in processed meat products (Nielsen *et al.* 2008). *Yarrowia lipolytica* was also reported from fermented products such as wine, must, cider, tempeh and sourdough, also in products at refrigeration temperatures such as soft drinks, juices, fruit concentrates, mayonnaise, salad dressings and salads, as well as in chilled and frozen, processed food. Whether *Yarrowia* species have a desirable or undesirable effect on the flavor and/or texture of these products is not fully known. However, *Y. galli* was found to be a spoilage organism in non-processed chicken and processed chicken meat due to its lipolytic and proteolytic activities (Kurtzman *et al.* 2011).

Although *Y. lipolytica* is commonly associated with food products it can be hypothesised that some of the earlier identifications of this species in food may refer to closely related *Yarrowia* species, and previously known *Candida* species, that are physiologically not distinguishable from *Y. lipolytica*.

Industrial significance

The great variety of potential commercial applications of *Y. lipolytica* for a more biobased economy is extensively reviewed by Coelho *et al.* (2010), Groenewald *et al.* (2014) and Abeln & Chuck (2021) and it has several physiological properties of industrial significance. It has already been deployed in multiple industrial applications. These applications include (i) as a high-quality protein source for livestock feeding (Bamberg 2000) and production of cell protein (SCP), (ii) as a biotechnological production host for various organic acids and/or hydrophobic substances, and (iii) as a heterologous production host for pharmaceutical and industrial proteins and enzymes, for the mass production of biofuels as well as for bioremediation purposes (reviewed in Groenewald *et al.* 2014, Abeln & Chuck 2021). The affinity of *Y. lipolytica* towards hydrophobic substrates accelerated its industrial relevance to SCP and citric acid and its genetic accessibility makes *Y. lipolytica* an industrially-relevant versatile microbe that can produce a variety of valuable metabolites not limited to SCP and citric acid, but also carotenoids, erythritol,

lipids, lipases, mannitol, *etc.* (Ledesma-Amaro & Nicaud 2016). Due to the advanced development of genetic tools and the early genetic accessibility of *Y. lipolytica*, this yeast was already used as a genetically modified organism to produce fatty alcohols (Wang *et al.* 2016g) and unusual fatty acids such as long-chain polyunsaturated fatty acids (Ledesma-Amaro & Nicaud 2016).

The listed current applications are just a selection but there is a great variety of potential commercial usage for this species. *Yarrowia lipolytica* probably has some close relatives with great potential that should be investigated further in order to be used towards more a bio-based economy.

Medical importance

Infections by *Yarrowia* species are very rare with only a few cultures originating from human sources. This is clear from the limited number of cases and publications indicating species of *Yarrowia* cause infections and public culture collections maintaining *Yarrowia* strains isolated from humans. It is also clear that it is mostly immunocompromised patients that have been infected. The low pathogenicity of *Y. lipolytica* was also illustrated by Walsh *et al.* (1989). Some *Yarrowia* species tested by Desnos-Ollivier *et al.* (2012) showed high Minimum Inhibitory Concentrations (MICs) to some antifungals (Table 24). Among the four ascomycetes isolates resistant to all antifungal drugs tested, were *Y. lipolytica* and *C. hispaniensis*. Unlike *Y. lipolytica*, *C. hispaniensis* is not known to be a potential human pathogen but it can also grow at 37 °C (Desnos-Ollivier *et al.* 2012). Although *Y. deformans* was recovered twice from clinical materials, its inability to grow at 37 °C makes it unlikely to be an agent of systemic infection (Kurtzman *et al.* 2011). Jacques & Casaregola (2008) pointed out that the common occurrence of *Y. lipolytica* and probably related species on a variety of food products provide a ready source of inoculum to those people who may be susceptible to infection. Resistance to various antifungals may occur in *Yarrowia* species or close relatives but opportunistic infections by *Y. lipolytica* can be treated well or disappear even without treatment (Hazen 1995, Walsh *et al.* 2004, Belet *et al.* 2006, Groenewald *et al.* 2014); this might be the case for other opportunistic pathogenic *Yarrowia* species.

Research interests

There are 2 558 publications and 37 460 citations from 2011–2021 in the Web of Science (Fig. 43), with the top 10 most cited articles shown in Table 25. Most of the publications focused on biotechnological applications, generic engineering and future processes (Fig. 44).

Table 24. Species tested by Desnos-Ollivier *et al.* (2012) and their corresponding MIC values to different antifungals.

	<i>C. hispaniensis</i>	<i>Y. deformans</i>	<i>Y. galli</i>	<i>Y. phangngaensis</i>	<i>Y. lipolytica</i>
Fluconazole	High MIC	High MIC	High MIC	Low MIC	High MIC
Itraconazole	High MIC	Low MIC	Low MIC	Low MIC	High MIC
Posaconazole	High MIC	High MIC	Low MIC	Low MIC	High MIC
Voriconazole	High MIC	High MIC	High MIC	High MIC	High MIC
Caspofungin	High MIC	Low MIC	Low MIC	Low MIC	High MIC
Amphotericin B	High MIC	High MIC	High MIC	High MIC	High MIC
5FC	High MIC	High MIC	High MIC	Low MIC	High MIC
Terbinafine	High MIC	Low MIC	Low MIC	High MIC	High MIC

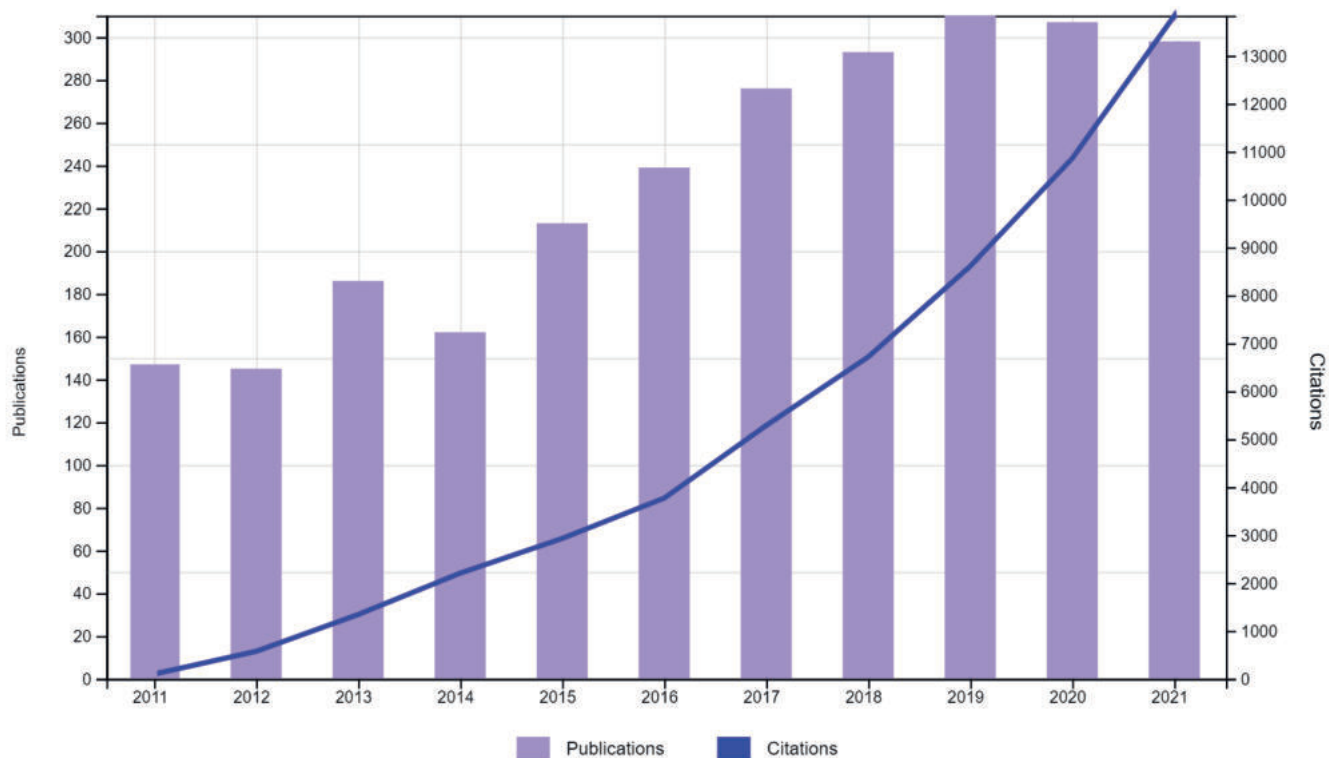


Fig. 43. Trends in research of *Yarrowia* in the period 2011–2021.

Table 25. Top 10 cited articles related to *Yarrowia* published in the period 2011–2021.

Rank	Article title	No. of citations	References
1	Value-added uses for crude glycerol - a byproduct of biodiesel production	659	Yang <i>et al.</i> (2012b)
2	Lipids of oleaginous yeasts. Part I: Biochemistry of single cell oil production	410	Papanikolaou (2011)
3	Engineering the push and pull of lipid biosynthesis in oleaginous yeast <i>Yarrowia lipolytica</i> for biofuel production	406	Tai & Stephanopoulos (2013)
4	Harnessing <i>Yarrowia lipolytica</i> lipogenesis to create a platform for lipid and biofuel production	361	Blazeck <i>et al.</i> (2014)
5	Oily yeasts as oleaginous cell factories	353	Ageitos <i>et al.</i> (2011)
6	Production of omega-3 eicosapentaenoic acid by metabolic engineering of <i>Yarrowia lipolytica</i>	314	Xue <i>et al.</i> (2013)
7	Oil production by oleaginous yeasts using the hydrolysate from pretreatment of wheat straw with dilute sulfuric acid	313	Yu <i>et al.</i> (2011a)
8	Macromolecular organization of ATP synthase and complex I in whole mitochondria	310	Davies <i>et al.</i> (2011)
9	Lipids of oleaginous yeasts. Part II: Technology and potential applications	273	Papanikolaou & Aggelis (2011)
10	Microbial xylanases: Engineering, production and industrial applications	268	Juturu <i>et al.</i> (2012)

(Bio-)industry

As *Y. lipolytica* is regarded to be a “safe-to-use” organism, the study of its use in the food and food-related industries, for *Yarrowia*-derived products or as a production host for biotechnological applications is warranted. Follow-up studies to explore the effectiveness of this species to be used as a probiotic (Liu & Tsao 2009) and its cell-free extract as a prebiotic (Kumura *et al.* 2009) was proposed and reviewed in Groenewald *et al.* (2014). Due to its immense capability to accumulate high concentrations of lipids intracellularly, *Y. lipolytica* featured in the first-ever commercial oleaginous yeast process (Abeln & Chuck 2021). As this species has numerous physiological properties of industrial significance, interest in exploring and developing *Y. lipolytica* for further usage in the (bio-)

industry is growing (reviewed in Coelho *et al.* 2010, Groenewald *et al.* 2014, Abeln & Chuck 2021), opening the door for more properties to be discovered and known properties to be explored. Advancing yeast lipid technology as a sustainable source of oil in the place of palm and soybean oil, as a novel route to advanced biofuels (Beopoulos *et al.* 2009, Blazeck *et al.* 2014, Abeln & Chuck 2021), and to produce biofuels sustainably in the form of large biodiesel, will be an important research interest in coming years. It is clear that *Y. lipolytica* and probably some of its close relatives will play an important role in bio-processes, and especially due to its oleaginous ability multiple industrial applications to exploit this species should be considered.

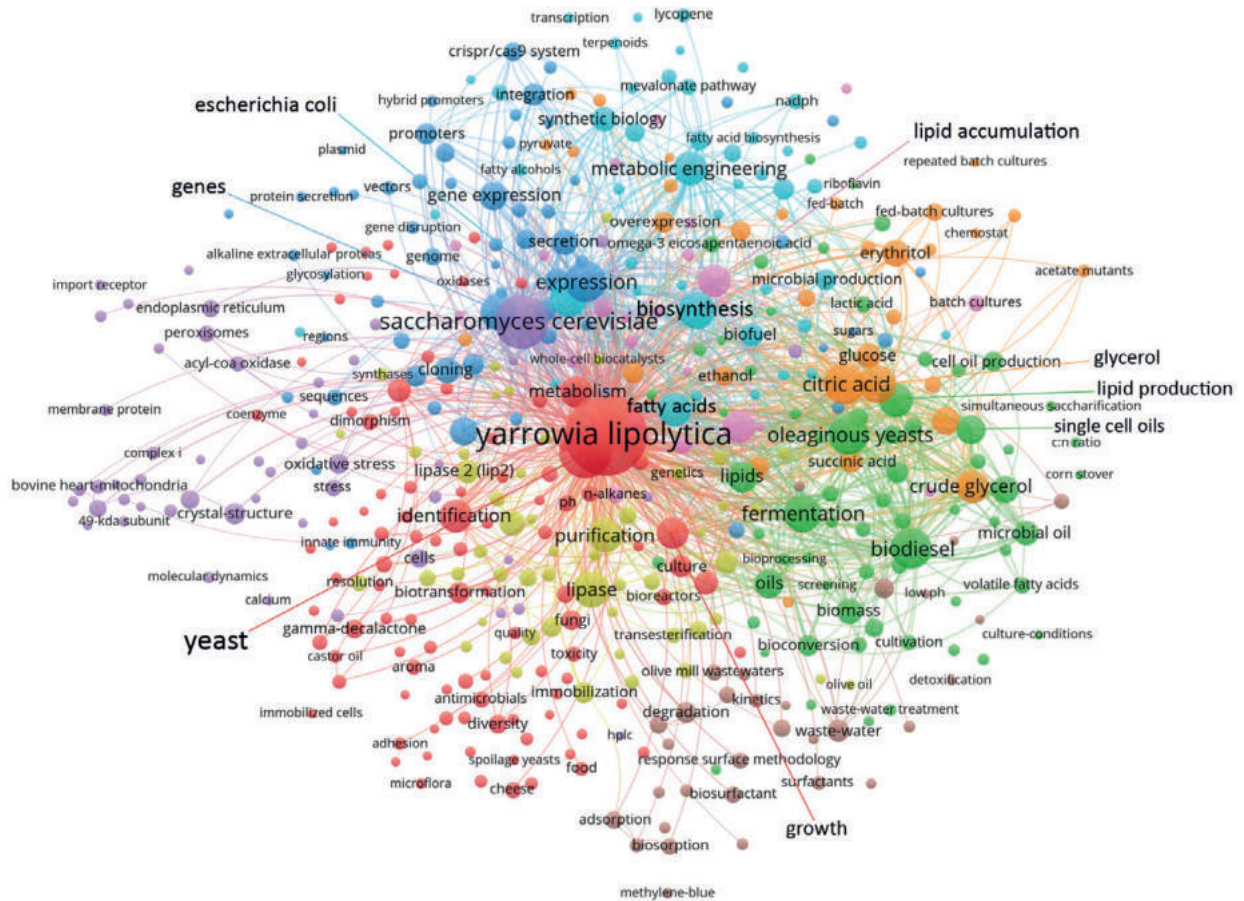


Fig. 44. Network visualisation of keywords of the publications related to *Yarrowia*. The larger the text and the circle the more often the subject has been cited.

Generic engineering and future processes

Yarrowia lipolytica was an early selection for whole genome sequencing. Kerscher *et al.* (2001) reported the sequence for the complete mitochondrial genome, which was then followed by the sequence of the complete nuclear genome (Dujon *et al.* 2004). It is also the most frequently genetically modified yeast (over 50 % of modified yeasts) due to the advanced development of genetic tools that can be applied to this species and due to its genetic accessibility. Approximately 70 % of the genetically engineered oleaginous yeasts cultured are of *Y. lipolytica* (Abeln & Chuck 2021). Recent work has also demonstrated successful adaptive evolution strategies, increasing single cell oil (SCO) production at the expense of citric acid biosynthesis, a process that is still being improved (Juturu & Chuan 2012). Bigey *et al.* (2003) investigated the ability of *Y. deformans* to excrete powerful lipolytic enzymes that are active in a mostly aqueous environment and characterised several genes that code for these enzymes.

Oleaginous yeast processes, with *Y. lipolytica* as one of the main species involved, have been intensively investigated and brought to scale in times of crisis and uncertainty (Abeln & Chuck 2021). With the many problems mankind is facing due to climate change, depletion of fossil resources and ecological damage affecting global food supply chains, *Yarrowia* species could play a vital role in multiple areas due to their extensive lipid production. It is essential that microbial processes are developed, scaled and ready to produce lipids on the industrial scale in the short to medium term and *Yarrowia* species, especially *Y. lipolytica*, can play a crucial role in achieving a sustainable future in these areas.

22. *Agaricus* L., Sp. pl. 2: 1171. 1753.

Type species: Agaricus campestris L.

Classification: Basidiomycota, Agaricomycotina, Agaricomycetes, Agaricales, Agaricaceae.

Background

Agaricus is the type genus of *Agaricaceae*. It has a worldwide distribution extending to all continents except Antarctica (Zhao *et al.* 2011, Hyde *et al.* 2017b). Species of *Agaricus* are characterised by sporocarps with an annulate stipe and free lamellae that produce dark brown spore prints. They are saprobic and can be found in natural environments such as forests, grasslands and/or urban areas such as gardens, roadsides and pastures (Parra 2008). There are an estimated 600 species of *Agaricus* (He *et al.* 2022a). Many *Agaricus* species are edible, for example, *Ag. arvensis*, *Ag. augustus* and *Ag. campestris* (Li *et al.* 2021a). *Agaricus* species have long been collected in the wild and are preferred as food worldwide. Some of them are successfully cultivated. The best-known species is *Ag. bisporus*, also called button mushrooms, which has been widely cultivated for at least 300 years (Kerrigan 2016, Bhushan & Kulshreshtha 2018). Many species are of medicinal value as they can produce antimicrobial, antioxidant and anti-allergenic biocompounds (Kerrigan 2005, Stojković *et al.* 2014).

Most monographs of *Agaricus* deal with species from temperate areas, such as those from Europe (Möller 1950, Pilát 1951, Konrad & Maublanc 1952, Kühner & Romagnesi 1953, Wasser 1980,

Table 26. Nutritional value of *Ag. bisporus* (white button mushrooms) per 100 g.

Nutritional components	Amount/per 100 g	Nutritional components	Amount/per 100 g
Protein	2.89 g	Riboflavin	0.444 mg
Calcium, Ca	5 mg	Niacin	3.88 mg
Iron, Fe	0.23 mg	Vitamin B-6	0.077 mg
Magnesium, Mg	10.2 mg	Biotin	9 µg
Phosphorus, P	93 mg	Folate	35 µg
Potassium, K	373 mg	Vitamin D (D2 + D3)	0.02 µg
Sodium, Na	6 mg	Ergosta-7-enol	1.63 mg
Zinc, Zn	0.51 mg	Ergosta-5,7-dienol	5.84 mg
Copper, Cu	0.389 mg	Ergosta-7,22-dienol	1.54 mg
Manganese, Mn	0.054 mg	Ergosterol	56 mg
Selenium, Se	20 µg	Ergothionine	4 mg
Thiamin	0.065 mg	Energy	31 kcal

Cappelli 1984, Parra 2008) and North America (Kerrigan 1986, Singer 1986), although those from tropical areas have been treated by Heinemann (1956, 1978, 1980). With the advent of the molecular era, *Agaricus* has undergone systemic studies with evidence from single and/or multiple sequences (Mitchell & Bresinsky 1999, Challen *et al.* 2003, Geml *et al.* 2004, Kerrigan *et al.* 2005, 2008, Zhao *et al.* 2011, 2016b, Chen *et al.* 2017a, He *et al.* 2017a, Ortiz-Santana *et al.* 2021). The current taxonomic system for *Agaricus* is based on combined phylogenetic analyses, phenotypic characteristics and divergence times. The latest *Agaricus* taxonomic system recognises six subgenera and 26 sections (Zhao *et al.* 2011, 2016, Chen *et al.* 2017a, He *et al.* 2017a, Ortiz-Santana *et al.* 2021). The phylogenetically informative characteristics including the structure of the annulus (superior vs inferior; simple vs double or two-layered), odour, discolouration of context when cut or rubbed and Schaffer reaction (aniline × nitrogen acid) are the major criteria for the infrageneric classification of *Agaricus*. *Agaricus* is the first genus in ranking fungi with divergence times and using divergence times as an additional criterion to be accepted in fungal systematics studies (Hongsanan *et al.* 2017, Hyde *et al.* 2017a, Liu *et al.* 2017a, Zhao *et al.* 2017b, Tedersoo *et al.* 2018, Ji *et al.* 2022).

Economic significance

Agaricus is a diverse genus with high economic potential. *Agaricus bisporus* and *Ag. subrufescens* are the most widely cultivated species for both edible and medicinal value. Several recently described species are also edible and can be cultivated. For example, *Ag. flocculosipes* and *Ag. sinodeliciosus* are two edible species originally found in Thailand and China (Zhao *et al.* 2012a, Wang *et al.* 2015i). Not all *Agaricus* species are edible and some are poisonous, for example, species of section *Xanthodermatei*. They can cause serious gastrointestinal irritation which requires treatment (Gill & Strauch 1984, Hender *et al.* 2000, Boxshall *et al.* 2021).

Agaricus bisporus

The global edible mushroom market is estimated to be worth 42 000 million US dollars per year and is expected to exhibit a compound annual growth rate (CAGR) of 9.5 % from 2021 to 2028. *Agaricus bisporus* accounts for 61.8 % of the world's total edible mushroom production and was worth 28 500 million US dollars in 2020 (Willis 2018, Grand view research 2022). Due to its high

protein, low calories and nutrition-rich features (Table 26, accessed from U.S. Department of Agriculture, FoodData Central, on 21st February 2022), there is an increased demand for this product.

Agaricus subrufescens

Agaricus subrufescens, also called almond mushrooms, was wrongly named *Ag. blazei* for a long time (Kerrigan 2005). It is widely cultivated for its medicinal value. The bioactive compounds isolated from the basidiomes or mycelia proved to be antimicrobial, antioxidant and anti-allergenic (Wisitrassameewong *et al.* 2012, Stojković *et al.* 2014). The reported beneficial properties are listed in Table 27.

Agaricus flocculosipes

Agaricus flocculosipes was originally found in Thailand and Mayotte Island and later found in China (Zhao *et al.* 2012a, Gui *et al.* 2015). This taxon is potentially cultivatable as it is presumably heterothallic and is a member of section *Arvenses*, indicating its edibility (Zhao *et al.* 2012a). Thongklang *et al.* (2014) successfully cultivated this species in Thailand and it has good potential as a new mushroom in the market.

Agaricus sinodeliciosus

Agaricus sinodeliciosus was originally found in northwestern China (Wang *et al.* 2015i). It is widely collected and consumed by the local people in the Xinjiang and Qinghai provinces, even before it was formally named. Studies have focused on its cultivation including the offspring analysis and habitat microbial communities (Zhou *et al.*

Table 27. Medicinal properties reported for *Agaricus subrufescens*.

Medicinal properties	References
Tumour growth reduction	Pinto <i>et al.</i> (2009), Jumes <i>et al.</i> (2010)
Immunomodulatory activities	Niu <i>et al.</i> (2009), Ramberg <i>et al.</i> (2010)
Immunostimulatory effects	Endo <i>et al.</i> (2010), Førlund <i>et al.</i> (2010, 2011)
Antimicrobial activities	Bernardshaw <i>et al.</i> (2005, 2006)
Antiviral activities	Bruggemann <i>et al.</i> (2006), Faccin <i>et al.</i> (2007)
Anti-allergy effects	Ellertsen & Hetland (2009)
Antioxidant activities	Lavitschka <i>et al.</i> (2007)

al. 2017a, Ling *et al.* 2019). Some isolates are domesticated and suitable for bagged and industrialised facility cultivation (Xu *et al.* 2021).

Agaricus xanthodermus

Species of section *Xanthodermatei* are poisonous and can cause gastrointestinal irritation. *Agaricus xanthodermus* is from this section and is frequently consumed (Kerrigan 2016). Phenols are thought to be the main toxic agents in the basidiomes. A study from Australia indicated that the concentration of the phenols varies between basidiomatal structures, different developmental

stages, and different nutritional substrates (Boxshall *et al.* 2021). Awareness should always be given when collecting *Agaricus* in the wild for food.

Research interests

There are 2 668 publications and 34 079 citations from 2011–2021 in the Web of Science (Fig. 45). The top 10 most cited articles are listed in Table 28. Most publications mostly focused on medicinal properties and systematics (Fig. 46).

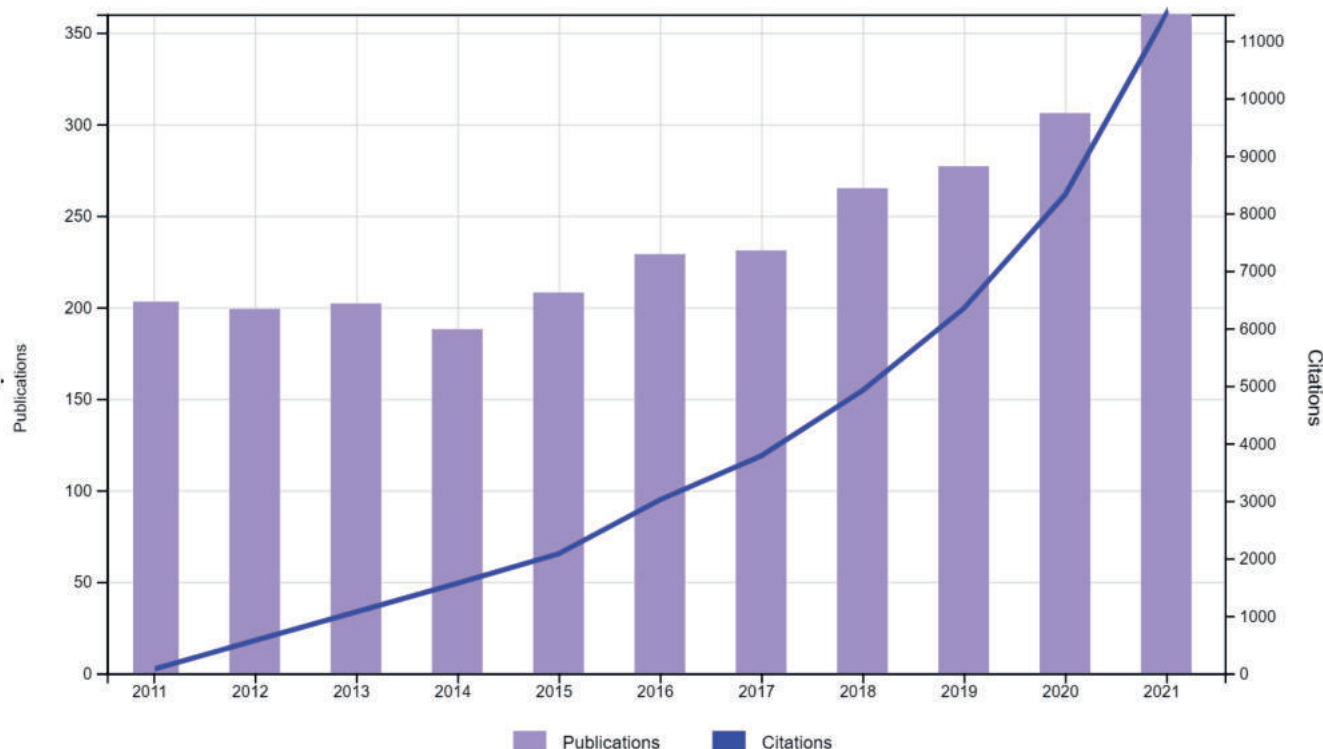


Fig. 45. Trends in research of *Agaricus* in the period 2011–2021.

Table 28. Top 10 cited articles related to *Agaricus* published in the period 2011–2021.

Rank	Article title	No. of citations	References
1	Crystal structure of <i>Agaricus bisporus</i> mushroom tyrosinase: Identity of the tetramer subunits and interaction with tropolone	485	Ismaya <i>et al.</i> (2011)
2	<i>In vitro</i> and <i>in vivo</i> antioxidant activity of ethanolic extract of white button mushroom (<i>Agaricus bisporus</i>)	327	Liu <i>et al.</i> (2013b)
3	A review of chemical composition and nutritional value of wild-growing and cultivated mushrooms	322	Kalac (2013)
4	A comprehensive review on tyrosinase inhibitors	317	Zolghadri <i>et al.</i> (2019)
5	Tissue invasion and metastasis: Molecular, biological and clinical perspectives	281	Jiang <i>et al.</i> (2015)
6	Antioxidative and immunomodulating activities of polysaccharide extracts of the medicinal mushrooms <i>Agaricus bisporus</i> , <i>Agaricus brasiliensis</i> , <i>Ganoderma lucidum</i> and <i>Phellinus linteus</i>	279	Kozarski <i>et al.</i> (2011)
7	Chemical composition and nutritional value of the most widely appreciated cultivated mushrooms: An inter-species comparative study	267	Reis <i>et al.</i> (2012a)
8	Current findings, future trends, and unsolved problems in studies of medicinal mushrooms	267	Wasser (2011)
9	Antioxidant properties of phenolic compounds occurring in edible mushrooms	250	Palacios <i>et al.</i> (2011)
10	Genome sequence of the button mushroom <i>Agaricus bisporus</i> reveals mechanisms governing adaptation to a humic-rich ecological niche	234	Morin <i>et al.</i> (2012)

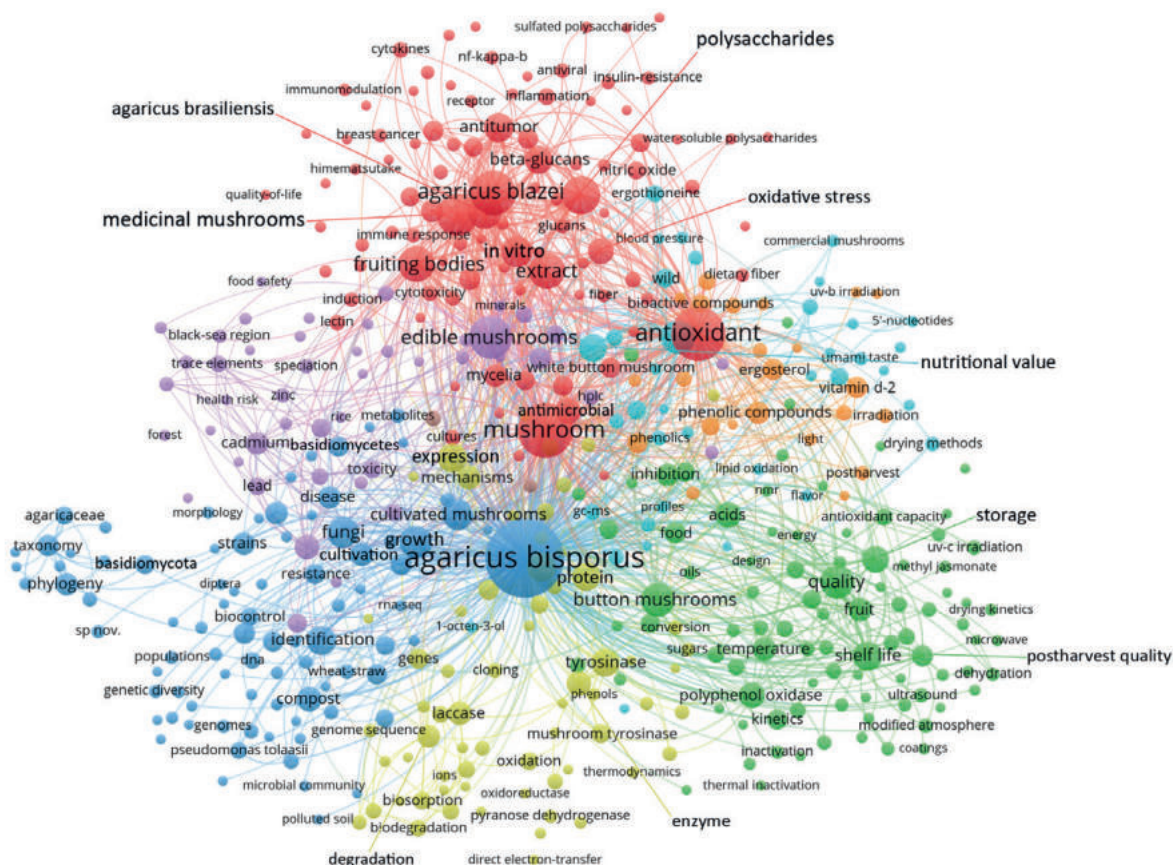


Fig. 46. Network visualisation of keywords of the publications related to *Agaricus*. The larger the text and the circle the more often the subject has been cited.

Medicinal properties

Many bioactive compounds have been isolated from *Agaricus* species and these attract researchers to explore their medicinal values (Wasser 2011). Polysaccharides isolated from *Ag. bisporus* and *Ag. subrufescens* are antioxidative and immunomodulating-active (Kozarski *et al.* 2011). Tyrosinase isolated from *Ag. bisporus* is important in browning reactions in the food industry and medicinal use as an anticancer agent (Ismaya *et al.* 2011, 2017).

Authors: M.Q. He and R.L. Zhao

23. *Kluyveromyces* Van der Walt, Antonie van Leeuwenhoek
22: 271. 1956.

Type species: Kluyveromyces marxianus (E.C. Hansen) Van der Walt

Classification: Ascomycota, Saccharomycotina, Saccharomycetes, Saccharomycetales, Saccharomycetaceae.

Background

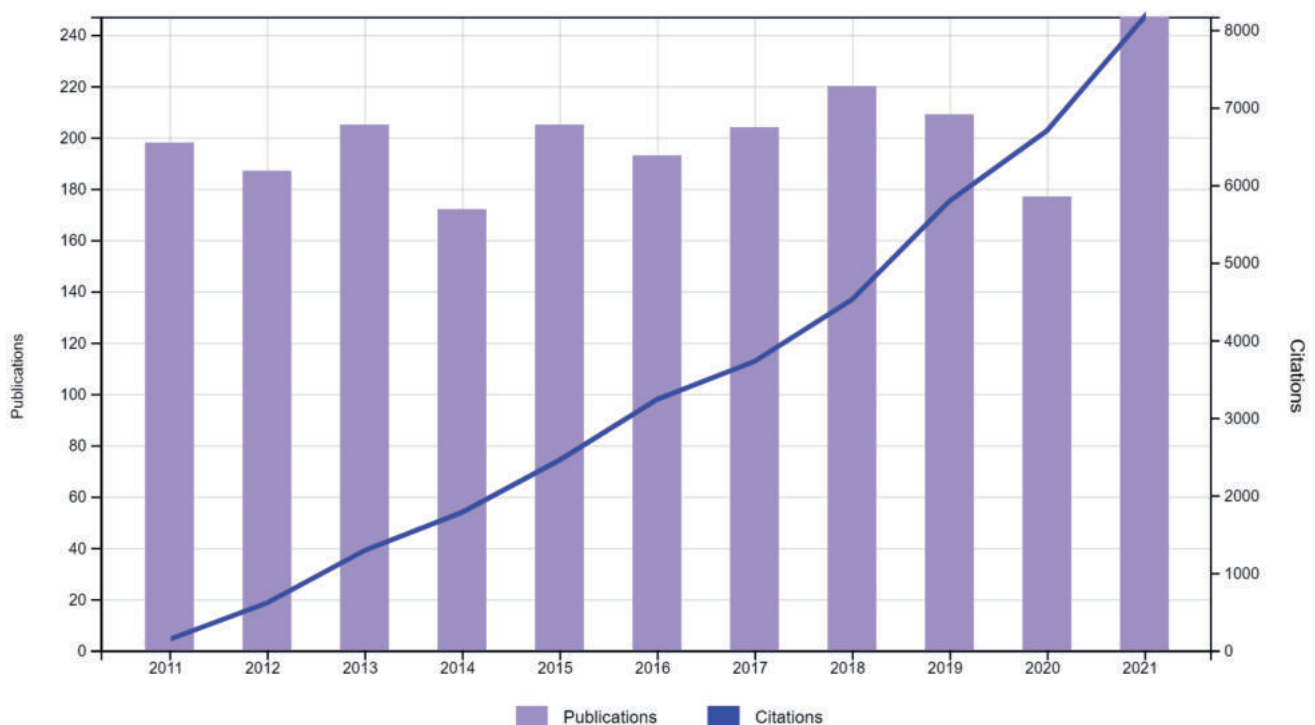
Our current understanding of the genus *Kluyveromyces* bears only a passing resemblance with its original conception. Van der Walt (1956) created *Kluyveromyces* to accommodate a fermentative species with the unique property of forming asci containing up to 100 spores, in contrast to most other ascomycetous yeast species, which form up to four (rarely eight) ascospores. The genus was soon emended (Van der Walt 1965) to include several other species, some formerly assigned to *Saccharomyces*, on the basis of deliquescence of the ascus in combination with a vigorous

fermentative ability and the formation of smooth ascospores. That definition persisted through the fourth edition of “*The Yeasts, a Taxonomic Study*” (TYTS, Lachance 1998), although the phylogenetic heterogeneity of the genus had already become abundantly clear. The possibility of defining the genus on a unique set of growth characteristics vanished with the discovery of a non-fermentative species (Nagahama *et al.* 1999), and DNA sequence data were making it clear that most *Kluyveromyces* species could not be considered congeneric with the originally proposed type species, *K. polysporus* (Zhan 1994, James *et al.* 1997, Kurtzman & Robnett 1998). To avoid a nomenclatural catastrophe, Kurtzman *et al.* (2001) proposed the conservation of *Kluyveromyces*, but with *K. marxianus* as the new type species. Two-thirds of the species were reassigned to other genera in the family *Saccharomycetaceae* (Kurtzman 2003); this included the original type species, which was renamed *Vanderwaltozyma polyspora*.

Although one nightmare was averted, the changes have had a considerable impact on our ability to retrieve relevant literature, as exemplified by the fact that four of the references listed in Table 29 deal mostly with species that are no longer included in *Kluyveromyces*, as obsolete names continue to be applied. Noteworthy is the transfer of *K. thermotolerans* (syn. *Saccharomyces veronae*) to the genus *Lachancea*, the continued use of names such as *Candida kefyri*, *C. pseudotropicalis*, *K. fragilis*, or even *Saccharomyces fragilis*, all of which are defunct synonyms of *K. marxianus*, or the use of *K. marxianus* to designate other species, including *K. lactis* and *K. dobzhanskii*. Such nomenclatural ambiguities may result in misleading assumptions about the expected properties of strains used in comparative studies (e.g., Alves *et al.* 2019). Details of these nomenclatural changes have been reviewed by Lachance (2007).

Table 29. Top 10 cited articles related to *Kluyveromyces* published in the period 2011–2021.

Rank	Article title	No. of citations	References
1	Production of liquid biofuels from renewable resources	1 257	Nigam & Singh (2011)
2	Selected non-saccharomyces wine yeasts in controlled multistarter fermentations with <i>Saccharomyces cerevisiae</i>	366	Comitini <i>et al.</i> (2011)
3	Extraction of genomic DNA from yeasts for PCR-based applications	247	Löoke <i>et al.</i> (2011)
4	Past and future of non-saccharomyces yeasts: from spoilage microorganisms to biotechnological tools for improving wine aroma complexity	243	Padilla <i>et al.</i> (2016b)
5	<i>Lachancea thermotolerans</i> and <i>Saccharomyces cerevisiae</i> in simultaneous and sequential co-fermentation: a strategy to enhance acidity and improve the overall quality of wine	233	Gobbi <i>et al.</i> (2013)
6	Structure of yeast Argonaute with guide RNA	212	Nakanishi <i>et al.</i> (2012)
7	Biotechnological potential of inulin for bioprocesses	192	Chi <i>et al.</i> (2011)
8	Production of recombinant proteins by yeast cells	182	Çelik & Çalık (2012)
9	Efficient multiplexed integration of synergistic alleles and metabolic pathways in yeasts via CRISPR-Cas	175	Horwitz <i>et al.</i> (2015)
10	Inulin-type fructans: a review on different aspects of biochemical and pharmaceutical technology	159	Apolinario <i>et al.</i> (2014)

**Fig. 47.** Trends in research of *Kluyveromyces* in the period 2011–2021.

2011). The genus as it now stands consists of eight species (Freitas *et al.* 2020). All form evanescent asci which release up to four spheroidal, ovoid, or reniform ascospores that tend to agglutinate. The mitotic state is normally haploid and undergoes isogamous or mother-bud diploidisation prior to ascus formation. Most species form the iron-containing pigment pulcherrimin and assimilate lactose oxidatively, both of which are infrequent properties among ascomycetous yeasts. Three species, namely *K. aestuarii*, *K. nonfermentans*, and *K. siamensis*, form a distinct clade and are confined to marine sources. The most recently described, *K. starmeri*, is known only from Brazilian cacti. The remaining species are isolated with regularity in wild *Drosophila* species and their plant habitats. *Kluyveromyces lactis* and *K. marxianus* are also frequently isolated from cheese and other

dairy products, due to their unique ability to ferment lactose. The taxonomy of *K. lactis* has received some attention in the past due to the polymorphic nature of the species. Lactose-negative biotypes are assigned to the variety *drosophilorum*; some of the biotypes were originally described as separate species and do show a small amount of divergence at the level of ITS sequences (Lachance 2011b).

Ecological and economic significance

As indicated in Fig. 48, two species, *K. lactis* and *K. marxianus*, attract much of the attention. The former serves as a rival model organism to *Saccharomyces cerevisiae* (Fukuhara 2006, Morrissey 2010). Of prime interest is their shared ability to assimilate and

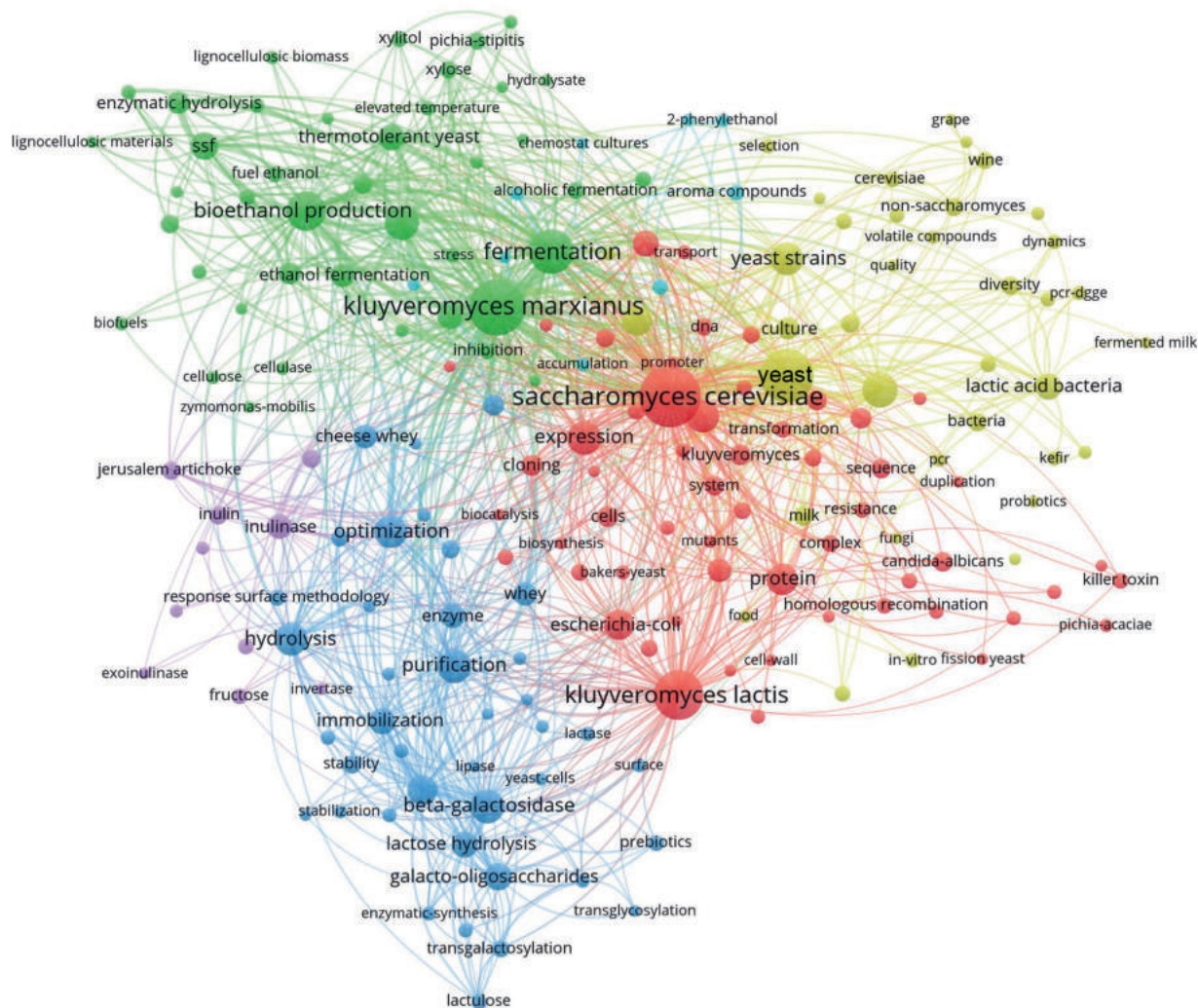


Fig. 48. Network visualisation of keywords of the publications related to *Kluyveromyces*. The larger the text and the circle the more often the subject has been cited.

ferment lactose combined with a GRAS (generally regarded as safe) status. As already noted, the former *Kluyveromyces* (now *Lachancea*) *thermotolerans* has also become a focal point.

Lactose utilisation and fermentation are confined to only about 1 % of ascomycetous yeasts (Lyutova *et al.* 2021). Although β -galactosidase is present in several *Kluyveromyces* species, only *K. lactis* var. *lactis* and *K. marxianus* possess the respiration-independent permeases required for uptake of lactose under low oxygen conditions, which allows them to metabolise the sugar by ethanol-yielding fermentation. The ability to ferment lactose has been used extensively to provide value added to whey, the major by-product of cheese making. Worldwide generation of whey approaches 200 million tonnes annually, equivalent to 10 million tonnes of lactose (Guimarães *et al.* 2010). A large proportion of recycled whey is dried into a protein powder for use primarily as animal feed, leaving behind a dilute lactose solution that has the potential to be converted to about 3.5 % of the bioethanol produced worldwide. Some industrial plants successfully execute the fermentation of whey permeate using *K. marxianus*. The process can be adapted to benefit small cheesemakers, allowing them to alleviate the environmental impact of whey disposal and even profit financially by generating potable alcohol products. Whey gin and vodka involving *K. marxianus* are available in several countries (Hughes *et al.* 2018). *Kluyveromyces* species are also the main

source of commercial β -galactosidase (Zolnere & Ciprovica 2017).

Of much interest is the evolution of lactose genes among *Kluyveromyces* species. Naumov *et al.* (2006) demonstrated that the *LAC4LC12* gene cluster is absent in the known biotypes of *K. lactis* var. *drosophilorum*, indicating that the variety *lactis* acquired the genes by introgression. Based on gene phylogenies, they identified *K. marxianus* as the most likely source. Varela *et al.* (2019) provided strong support for this by using chromosome-size sequences to demonstrate the transfer of a 15-kb region from *K. marxianus* to *K. lactis*. The region contained *LAC4* and *LAC12* as well as a flocculin gene that subsequently pseudogenised in *K. lactis*. They dated the acquisition of lactose genes by *K. lactis* to a time that coincides with the beginnings of dairy agriculture.

Kluyveromyces lactis as a model organism was chosen in the 1960s for its interesting sugar metabolism and the availability of heterothallic mating types, which would favour the design of genetic analyses (Fukuhara 2006). Interest in the species was further stimulated by the discovery of plasmids and killer systems that can be used in the expression and secretion of heterologous proteins. The species soon followed *S. cerevisiae* in having its genome sequenced. As a result of these attributes, *K. lactis* has figured prominently among yeasts used to produce recombinant proteins (Çelik & Çalık 2012). Its early use to produce bovine chymosin, the major component of rennet used in cheesemaking,

established the species as a battle horse. Inserted genes can be put under the control of the inducible and repressible *LAC4* promoter, well understood after seven decades of β -galactosidase production. The yeast is even part of an easy-to-use commercial kit for heterologous gene expression. Among the approximately 100 successfully expressed proteins figure interleukin-1 β , a granulocyte colony-stimulating factor, a hepatitis B surface antigen, human serum albumin, and several enzymes such as D-amino acid oxidase, glucoamylase, lipase, xylanase, and esterase. Spohner *et al.* (2016) provided a detailed overview of the proteins along with the various genetic techniques that made this possible. Horwitz *et al.* (2015) demonstrated the feasibility of using the CRISPR-Cas system to insert a complete novel metabolic pathway in yeast. The production of muconic acid was first acquired by the single-step integration of six large DNA fragments at three different locations in *S. cerevisiae*. The successful transformation of *K. lactis*, reported as the first use of the CRISPR-Cas system in the species served to show that its application is not limited to *S. cerevisiae*.

***Kluyveromyces marxianus* is a rare thermotolerant yeast**

Less than a third of described yeast species share the ability to grow at 37 °C or above, and only a handful have maximum growth temperatures exceeding 40 °C. *Kluyveromyces marxianus* stands out by its ability to grow at temperatures up to 52 °C and it can produce ethanol at 50 °C (Banat *et al.* 1992). Matsumoto *et al.* (2018) attributed this unique property to a higher resistance to heat shock and a greater ability to deal with the elevated levels of reactive oxygen species triggered by high temperatures. A higher cellular concentration of trehalose compared to *S. cerevisiae* is also thought to play a role. In a broad review of the production of biofuels, Nigam & Singh (2011) singled out *K. marxianus* by virtue of its thermotolerance. Biofuel research is the target of intense research activity in view of humanity's desperate need to wean itself off fossil fuels.

***Kluyveromyces marxianus* assimilates inulin** due to a powerful *exo*- β -fructosidase capable also of invertase activity, as demonstrated in the former variety *bulgaricus* (Kushi *et al.* 2000). The potential significance of this property should be seen in the light of the biotechnology of β -fructans used by a wide variety of plants for energy storage (Chi *et al.* 2011). A simplistic taxonomy of β -fructans divides them into inulin, with β (2-1) bonds, and levan, with β (2-6) bonds (Apolinario *et al.* 2014). Inulin may constitute over 50 % of tuber biomass and is more readily converted to fermentable sugars than cellulose, starch, or xylan. Intact inulin may be used as a food ingredient for its properties as a low-calorie sweetener, a source of dietary fibre, or a prebiotic. Of major interest in biotechnology are methods for the extraction, purification, and transformation of inulin. *Kluyveromyces marxianus* may come in next as a source of enzyme for the production of fructose to be used directly or as an intermediate in the biosynthesis of other metabolites, including bioethanol. The yeast itself is also used in the direct transformation of inulin into biomass or ethanol.

***Lachancea thermotolerans* is gaining popularity in winemaking**

Kluyveromyces species are among those that may appear as secondary components of spontaneous fermentations and are

known to influence wine aroma (Padilla *et al.* 2016b). Of these *K. lactis* has been reported as a minor producer of volatile activity, but much of the interest is focused on a former member of the genus, *L. thermotolerans*. Comitini *et al.* (2011) found *L. thermotolerans* in mixed culture with *S. cerevisiae* to be unique in the ability to generate lactic acid, a low amount of volatile acidity, and a high yield of glycerol and 2-phenylethanol. Larger scale studies (Gobbi *et al.* 2013) indicated that such mixed cultures result in a more complex profile, with notably spicier and more acidic notes. This is due in part to enzyme activity. Of five such enzymes, two were detected in *L. thermotolerans*, namely β -glucosidase and carbon-sulfur lyase (Padilla *et al.* 2016b). The former enzyme catalyses the release of a vast array of terpenols and other floral flavour compounds, whereas the latter enzyme cleaves fruity thiols from non-volatile molecules. The species is notable for its ability to release 4-mercapto-4-methylpentan-2-one and 3-mercaptohexan-1-ol in grape must, imparting wines with special floral notes. The release of lactic acid has also been put to use by Benito *et al.* (2015) as a substitute for the spontaneous and temperamental malolactic fermentation process. *Schizosaccharomyces pombe* consumes the malic acid and *L. thermotolerans* generates lactic acid. One should also mention the use of the species in the fermentation of sour beer (Domizio *et al.* 2016), a product of growing interest in the world of artisanal brewing.

Research interests

There are 2 217 publications and 33 194 citations from 2011–2021 in the Web of Science (Fig. 47), with the top 10 most cited articles shown in Table 29. The results presented in Table 29 exemplify the perils of performance metrics combined with the caprices of taxonomic nomenclature. As a result, some of the papers listed deal only peripherally with *Kluyveromyces* species. Of these, the report by Nakanishi *et al.* (2012) is concerned with the Argonaute protein of *Vanderwaltozyma polyspora* (formerly *K. polysporus*, original type species of the genus). The protein is a component of the RNA interference phenomenon. The species had been chosen in a previous study (Drinnenberg *et al.* 2009) due to its intermediate phylogenetic position with respect to *S. cerevisiae*, which does not engage in RNA interference. It is noteworthy that of the eleven species considered in that study, six were designated by names that were obsolete at the time of publication.

The report by Lööke *et al.* (2011) explores a method for the extraction of DNA to be used for PCR amplification from yeasts. The study used the model species *K. lactis*, *Ogataea* (*Hansenula*) *polymorpha*, *Schizosaccharomyces pombe*, *Candida albicans*, *Komagataella* (*Pichia*) *pastoris*, and *S. cerevisiae*. Cells are heated in the presence of lithium acetate and sodium dodecyl sulfate, and DNA is precipitated with ethanol, redissolved in buffer, and debris is removed by centrifugation, resulting in a solution that is suitable for PCR amplification. Conspicuously absent is a simpler control where intact yeast cells are added directly to the reaction mixture (Lachance *et al.* 1999).

Author: M.A. Lachance

24. ***Mucor*** Fresen., Beitr. Mykol. 1: 7. 1850.

Type species: *Mucor mucedo* Fresen.

Classification: *Mucoromycota*, *Mucoromycotina*, *Mucoromycetes*, *Mucorales*, *Mucoraceae*.

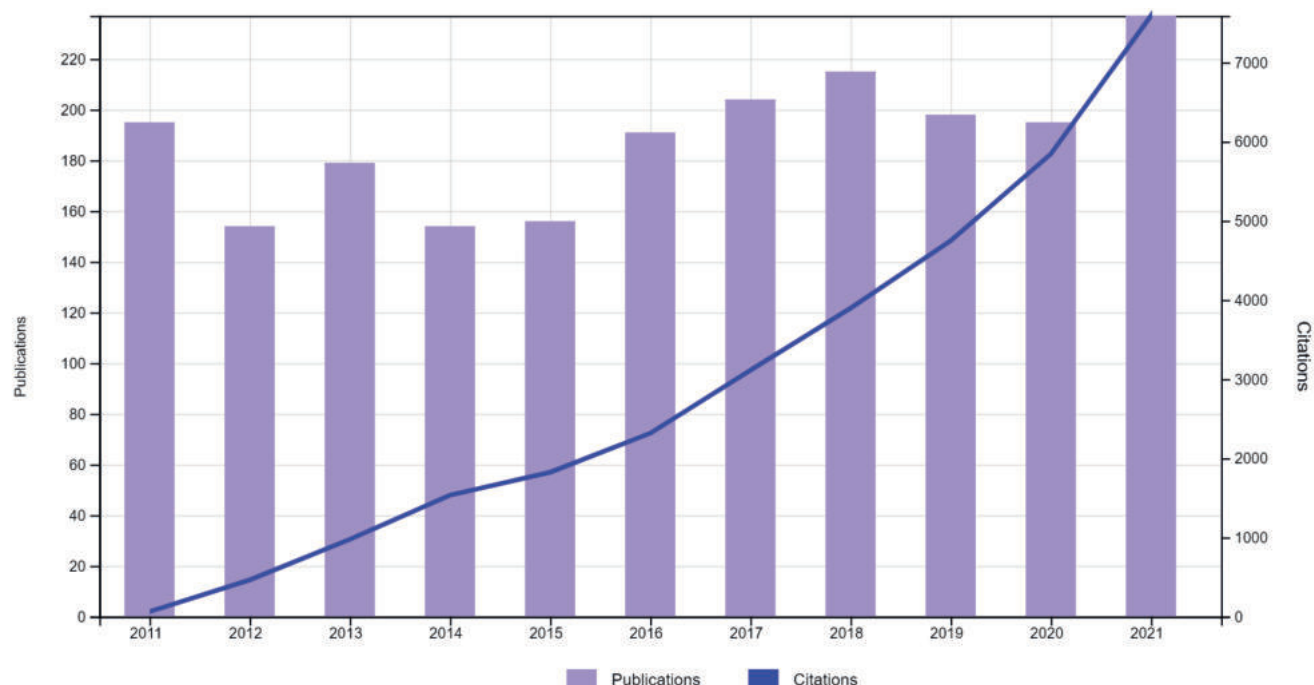


Fig. 49. Trends in research of *Mucor* in the period 2011–2021.

Table 30. Top 10 cited articles related to *Mucor* published in the period 2011–2021.

Rank	Article title	No. of citations	References
1	One stop shop: backbone trees for important phytopathogenic genera: I (2014)	235	Hyde <i>et al.</i> (2014)
2	Global epidemiology of mucormycosis	217	Prakash & Chakrabarti (2019)
3	Associations between fungal species and water-damaged building materials	213	Andersen <i>et al.</i> (2011)
4	DNA barcoding in <i>Mucorales</i> : an inventory of biodiversity	176	Walther <i>et al.</i> (2013)
5	Complex microbiota of a Chinese “Fen” liquor fermentation starter (Fen-Daqu), revealed by culture-dependent and culture-independent methods	146	Zheng <i>et al.</i> (2012)
6	Quantitative polymerase chain reaction detection of circulating DNA in serum for early diagnosis of mucormycosis in immunocompromised patients	141	Millon <i>et al.</i> (2013)
7	Obesity changes the human gut mycobiome	140	Rodriguez <i>et al.</i> (2015)
8	Chondroitin sulfate, hyaluronic acid and chitin/chitosan production using marine waste sources: characteristics, applications and eco-friendly processes: a review	137	Antonio Vazquez <i>et al.</i> (2013)
9	Survival outcomes in acute invasive fungal sinusitis: a systematic review and quantitative synthesis of published evidence	134	Turner <i>et al.</i> (2013)
10	Bioethanol production from sweet sorghum bagasse by <i>Mucor hiemalis</i>	115	Goshadrou <i>et al.</i> (2011)

Background

Mucor is the largest genus within the order *Mucorales* (phylum *Mucoromycota*). The genus is one of the most studied groups of *Mucorales* and early diverging lineages of fungi (Jayawardena *et al.* 2020). More than 300 species have been described (Lima *et al.* 2020), but recent studies (e.g., Wijayawardene *et al.* 2018b) accept around 60 *Mucor* species while others suggest 50–76 valid taxa (Walther *et al.* 2020). The genus has 734 epithets in Index Fungorum (2022) which includes infra-specific taxa, invalid names, and synonyms. *Mucor* species are mostly saprobes, ubiquitous, and collected from a wide range of substrates such as soil and herbivore dung (Lima *et al.* 2020). The genus consists of coprophilous and non-coprophilous species which are involved in the decomposition of organic matter, and carbon and nitrogen cycles. They are also known to be opportunistic pathogens, causing cutaneous and subcutaneous mucormycosis (Lima *et al.* 2020).

Mucor species are valued for being fast-growing and have many biotechnological benefits. Most mucoralean species are mesophilic while some are psychrophiles. They are used in bioremediation, the production of biofuels, pharmaceuticals, and industrial enzymes. Some species have also been used for fermenting food, especially in Asian and African foods such as tempeh (Chai *et al.* 2019). This genus is one of the main causes of mucormycosis with 12 species known to be involved in human infections. The infections range from cutaneous, and rhino cerebral, or have gastrointestinal manifestations. In plants, *Mucor* species can cause rot and soft rot. *Mucor fragilis*, *Mu. piriformis*, *Mu. racemosus*, and *Mu. irregularis* are known to cause postharvest diseases mentioned above. Infection is usually possible if the crop or fruit has wounds or cracks on the surface (Jayawardena *et al.* 2020).

Mucor species are characterised by the formation of non-apophysate sporangia with pigmented and ornamented zygosporangia walls, simple or branched sporangiophores, and

Mucormycosis

Mucor irregularis is a common causative agent of mucormycosis globally (Prakash & Chakrabarti 2019). It is the main cause of cutaneous mucormycosis in Australia, China, India, Japan, and the USA. To date, more than 20 cases of cutaneous mucormycosis caused by *Mu. irregularis* have been reported in China. However, the causative agent of mucormycosis may vary depending on the geographical area (Liang *et al.* 2018a, Skiada *et al.* 2020). Studies reviewing the global incidence of the disease state that mucormycosis caused by *Rhizopus*, *Mucor*, and *Lichtheimia* species account for 75 % of all cases (Skiada *et al.* 2020). Unlike other mucormycosis cases, this species mostly involves immunocompetent individuals. Main factors such as injuries and surgeries increase susceptibility to infections. The disease is characterised by progressive swelling, necrosis of the tissues, ulceration, and in severe cases leads to disfigurement (Liang *et al.* 2018a, Wang *et al.* 2019).

Author: V.G. Hurdeal

25. *Verticillium* Nees, Syst. Pilze (Würzburg): 56. 1816.

Type species: *Verticillium dahliae* Kleb.

Classification: Ascomycota, Pezizomycotina, Sordariomycetes, Trichosphaeriales, Trichosphaeriaceae.

Background

Verticillium is a large and heterogeneous hyphomycetous genus that was introduced by Nees von Esenbeck (1816) to accommodate the monotypic species *V. tenerum*. The type species is now accommodated in *Acrostalagmus* (Zare *et al.* 2004). In order to preserve the important plant pathogenic name *Verticillium*, *V. dahliae* was proposed as a neotype for this genus (Gams *et al.* 2005). There are 274 records in Index Fungorum (2022) and 292 records in MycoBank (Crous *et al.* 2004). However, this genus has changed dramatically, especially after molecular evidence became widely used for fungal taxonomy (Zare *et al.* 2000, 2001, 2004, 2007, Gams & Zare 2001, Sung *et al.* 2001, Zare & Gams 2001a, b, Fahleson *et al.* 2004, Gams 2017). Gams (1971) introduced the sect. *Prostrata* and provided a key to some *Verticillium* species. Gams & Van Zaayen (1982) accepted four sections, viz. sect. *Verticillium*, sect. *Nigrescentia*, sect. *Prostrata*, sect. *Albo-erecta*, and a residual group. A key to these sections and detailed descriptions for some fungicolous *Verticillium* species were provided by Gams & Van Zaayen (1982). However, the sections singled out by Gams (1971) and Gams & Van Zaayen (1982) are still heterogeneous. Gams & Zare (2001) introduced the genera *Haptocillium* and *Lecanicillium*, while *V. balanoides* and *V. lecanii* were transferred to *Haptocillium* and *Lecanicillium*, respectively. In addition, *V. chlamydosporium* was synonymised under *Pochonia chlamydosporia* by Gams & Zare (2001). Zare & Gams (2001a) transferred several *Verticillium* species to *Lecanicillium*, and several were placed under the new genus *Simplicillium*. *Verticillium nigrescens* and *V. theobromae* were transferred to *Gibellulopsis* and *Musicillium*, respectively (Zare *et al.* 2007). Inderbitzin *et al.* (2011) provided conclusive phylogenetic analyses for this genus based on ITS, partial sequences of the protein coding genes *act*, *tef1*, *gapdh* and tryptophan synthase (*ts*). Ten species were accepted, viz. *V. albo-atrum*, *V. alfalfa*, *V. dahlia*, *V. isaacii*, *V. klebahnii*, *V. longisporum*, *V. nonalfalfae*, *V. nubilum*, *V. tricornis*, *V. zaregamsianum*. These 10 species represent *Verticillium* s. str. An annotated checklist of

epithets published in *Verticillium* and *Acrostalagmus*, some similar genera, and sexual morphs associated with verticillium-like asexual morphs was provided by Gams (2017).

Verticillium is characterised by having verticillate, septate, hyaline to brown conidiophores, monophialidic, hyaline conidiogenous cells, aseptate, or rarely 1-septate, hyaline, ellipsoidal or cylindrical with rounded ends, slimy conidia. Some species can produce chlamydospores, brown moniloid hyphae or microsclerotia (Zare *et al.* 2004, Seifert *et al.* 2011, Giraldo & Crous, 2019, Hyde *et al.* 2020d). It is similar to *Chlorocillium*, *Gibellulopsis*, *Haptocillium*, *Lecanicillium*, *Leptobacillium*, *Musicillium*, *Ovicillium*, *Pochonia*, *Rotiferophthora*, *Simplicillium*, *Sphaerostilbella* (Gams & Zare 2001, Zare & Gams 2001a, b, 2016, Zare *et al.* 2001, 2007, Seifert *et al.* 2011, Giraldo & Crous 2019, Wei *et al.* 2019). A key to verticillium- and gliocladium-like genera bearing one or several whorls of awl-shaped or flask-shaped phialides was provided by Seifert *et al.* (2011).

Ecological and economic significance

Verticillium species are important plant pathogens and causal agents of wilt in many host plants. *Verticillium albo-atrum* and *V. dahliae* are the two species that cause the most economic damage, including wilt on a wide range of plant hosts, including high-value crops such as cotton, lettuce, mango, olive, potato and strawberry (Pegg & Brady 2002, Jimenez-Diaz *et al.* 2017, Jayawardena *et al.* 2019), resulting in high yield losses.

There are seven plant-pathogenic species historically associated with the genus *Verticillium*, viz. *V. albo-atrum*, *V. dahliae*, *V. fungicola* (now known as *Lecanicillium fungicola*), *V. nigrescens* (now known as *Gibellulopsis nigrescens*), *V. nubilum*, *V. theobromae* (now known as *Musicillium theobromae*) and *V. tricornis* (Pegg & Brady 2002, Barbara & Clewes 2003, Klosterman *et al.* 2009).

Verticillium species infect many important crops, e.g., banana, bean, beet, cherry, coffee, cotton, cucumber, eggplant, gold kiwifruit, lettuce, mango, muskmelon, olive tree, peach, pepper, potato, pumpkin, tomato, watermelon (Rudolph 1931, Himelick, 1969, Bhat & Subbarao 1999, Pegg & Brady, 2002, Klosterman *et al.* 2009, Jayawardena *et al.* 2019). Because of their soil habitat, their ability to produce resting structures and their capacity to infect a wide range of hosts, *Verticillium* wilt is a challenge for agricultural production (Barbara & Clewes, 2003, Klosterman *et al.* 2009).

Research interests

There are 2 545 publications and 30 674 citations from 2011–2021 in the Web of Science (Fig. 51), with the top 10 most cited articles listed in Table 31. Most of the publications focused on disease management, and research on pathogenic *Verticillium* species and *Verticillium* wilt (*V. albo-atrum* and *V. dahliae*), as well as taxonomic and phylogenetic studies (Fig. 52).

Verticillium wilt

Verticillium wilt is a common plant disease caused by *Verticillium* spp., especially *V. albo-atrum* and *V. dahliae*, and it is the most extensively researched area related to *Verticillium* species. Because *Verticillium* species infect such a large number of crops and ornamental plants, *Verticillium* wilt has caused economic losses of billions of dollars (Lazarovits & Subbarao 2009). Many studies have reported and introduced this widespread disease (Van Zaayen & Gams 1982, Bhat & Subbarao 1999, Barbara & Clewes 2003, Klosterman *et al.* 2009, Hyde *et al.* 2014, Jayawardena *et al.* 2019).

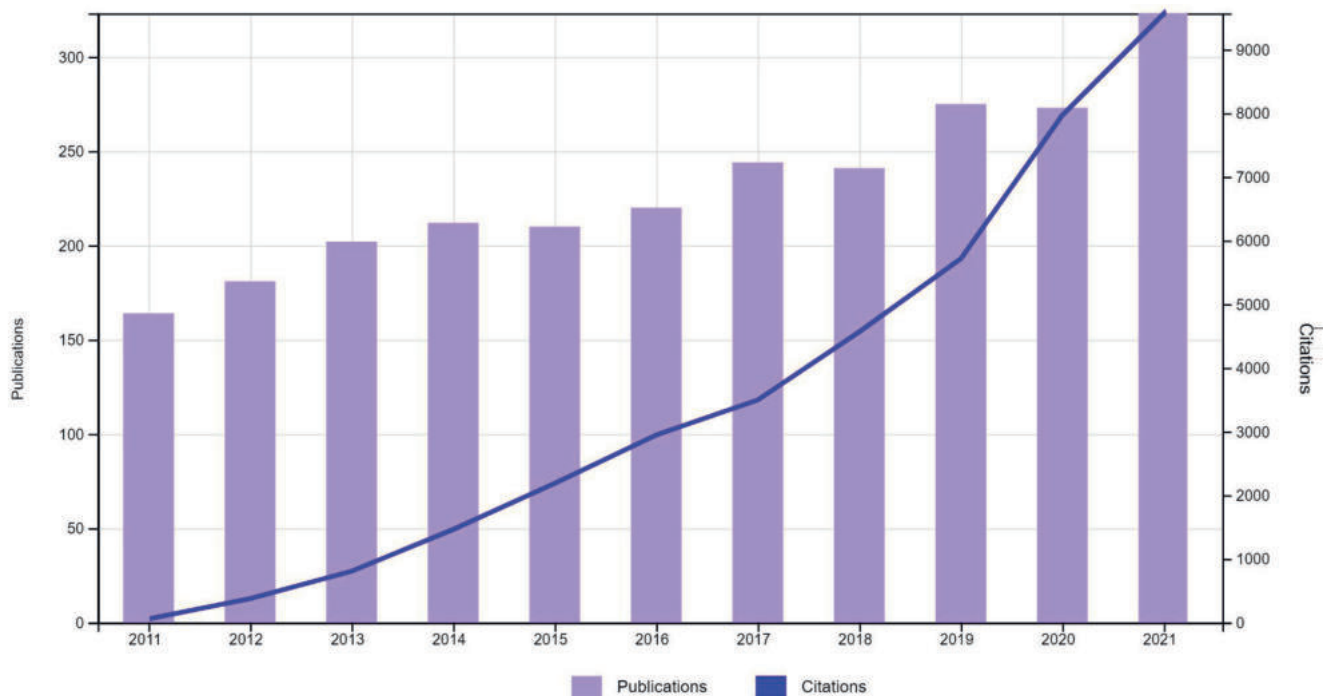


Fig. 51. Trends in research of *Verticillium* in the period 2011–2021.

Table 31. Top 10 cited articles related to *Verticillium* published in the period 2011–2021.

Rank	Article	No. of citations	References
1	Genome sequence of the cultivated cotton <i>Gossypium arboreum</i>	580	Li <i>et al.</i> (2014b)
2	Machine learning for high-throughput stress phenotyping in plants	360	Singh <i>et al.</i> (2016a)
3	Tomato immune receptor Ve1 recognizes effector of multiple fungal pathogens uncovered by genome and RNA sequencing	329	De Jonge <i>et al.</i> (2012)
4	Towards a natural classification and backbone tree for <i>Sordariomycetes</i>	326	Maharachchikumbura <i>et al.</i> (2015)
5	Comparative genomics yields insights into niche adaptation of plant vascular wilt pathogens	314	Klosterman <i>et al.</i> (2011)
6	Bidirectional cross-kingdom RNAi and fungal uptake of external RNAs confer plant protection	277	Wang <i>et al.</i> (2016d)
7	Lignin metabolism has a central role in the resistance of cotton to the wilt fungus <i>Verticillium dahliae</i> as revealed by RNA-Seq-dependent transcriptional analysis and histochemistry	272	Xu <i>et al.</i> (2011b)
8	MYB72-dependent coumarin exudation shapes root microbiome assembly to promote plant health	269	Stringlis <i>et al.</i> (2018)
9	One stop shop: backbones trees for important phytopathogenic genera: I (2014)	235	Hyde <i>et al.</i> (2014)
10	Families of <i>Sordariomycetes</i>	159	Maharachchikumbura <i>et al.</i> (2016)

Disease management

Reducing the populations of microsclerotia in soil, which are resting structures produced by *Verticillium* spp., is an effective approach to reduce losses due to *Verticillium* wilt (Lazarovits & Subbarao 2009). Soil fumigation with methyl bromide plus chloropicrin was used in some areas and in some conditions it is useful (Klosterman *et al.* 2009). However, soil fumigation can bring environmental pollution problems. Because of the wide host range of *Verticillium* species, crop rotation is not a good option for the management of *Verticillium* wilt (Klosterman *et al.* 2009). In some conditions, high nitrogen organic amendments and products containing volatile fatty acids (VFAs) can significantly reduce disease severity (Lazarovits & Subbarao 2009). Studies on the management of *Verticillium* wilt are ongoing, and an effective method that can be adapted to different environmental conditions and host plants is particularly needed.

Taxonomy and phylogeny

Because phylogenetic analyses are widely used in *Verticillium*, great changes have taken place in this genus (Zare *et al.* 2000, 2001, 2004, 2007, Gams & Zare 2001, Sung *et al.* 2001, Zare & Gams 2001a, b, Fahleson *et al.* 2004, Gams 2017). There are many *Verticillium* species recorded in Index Fungorum (2022) and MycoBank, however, most of them have been synonymised or transferred to other genera (Gams & Van Zaayen 1982, Zare & Gams 2001a, b, Zare *et al.* 2001, 2004, 2007, Seifert *et al.* 2011). The most conclusive study for this genus was carried out by Inderbitzin *et al.* (2011) and ten species were accepted in *Verticillium* s. str. However, it is necessary to recollect and epitypify the described taxa and amplify all the necessary genes for this genus.

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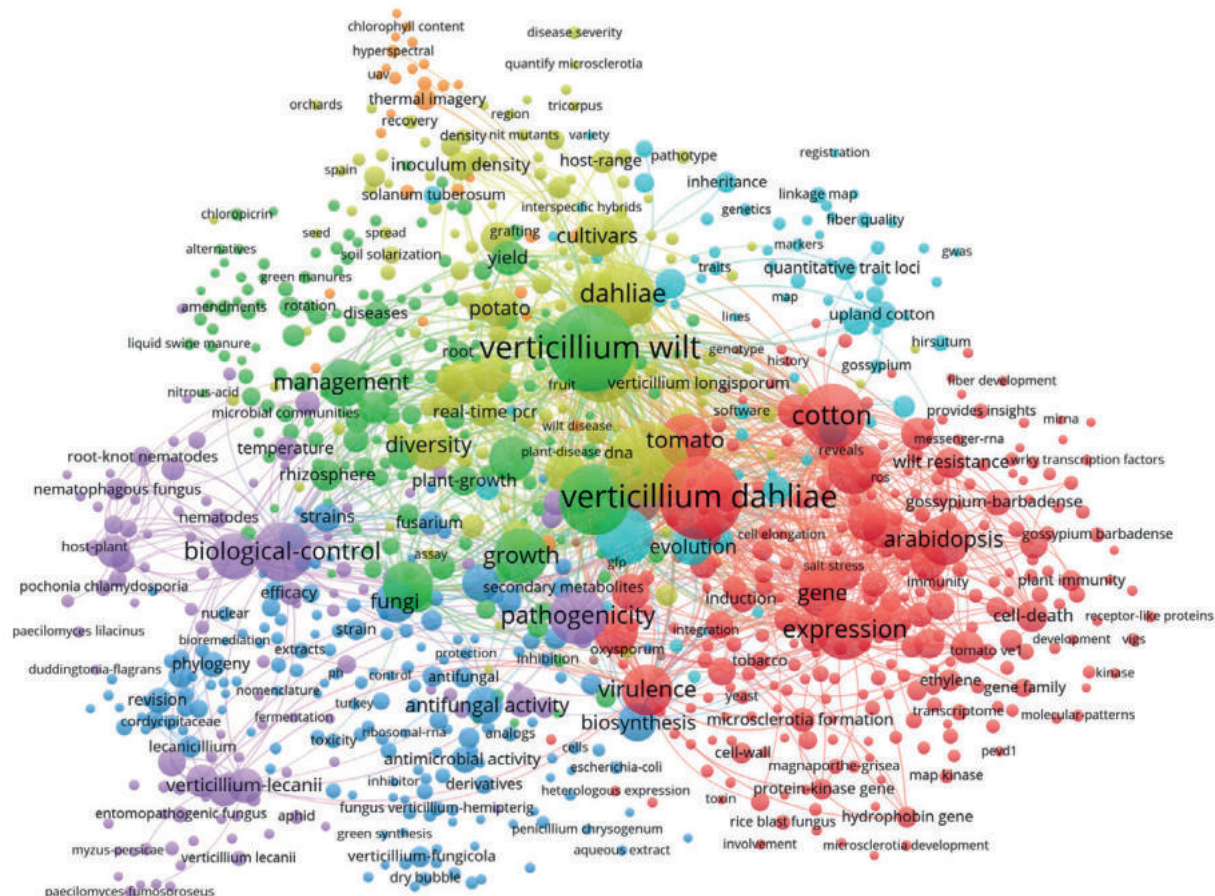


Fig. 52. Network visualisation of keywords of the publications related to *Verticillium*. The larger the text and the circle the more often the subject has been cited.

26. ***Sclerotinia*** Fuckel, Jb. Nassau. Ver. Naturk. 23–24: 330.
1870.

Type species: Sclerotinia libertiana Fuckel (syn. *Scl. sclerotiorum*)

Classification: Ascomycota, Pezizomycotina, Leotiomyces, Helotiales, Sclerotiniaceae.

Background

Sclerotinia is a genus of plant pathogenic hyphomycetes with more than 200 epithets listed in Index Fungorum (2022). *Sclerotinia* was introduced by Fuckel (1870), based on the type species *Sc. libertiana* found on *Sclerotium compactum* in Germany. Despite the importance of *Sclerotinia* as a devastating plant pathogen, there are few studies on taxonomic classification available besides early monographic works on the *Sclerotiniaceae* (Whetzel 1945, Dumont & Korf 1971, Carbone & Kohn 1993, Holst-Jensen *et al.* 1997) and on the genus *Sclerotinia* (Kohn 1979a, b, Kohn *et al.* 1988). The complexity of *Sclerotinia* taxonomic classifications is illustrated by the recent reclassification of *Clarireedia* *homoeocarpa* (*Sc. homoeocarpa*), associated with dollar spot of turf grass (Salgado-Salazar *et al.* 2018). Although there are 122 currently accepted *Sclerotinia* names, it has been universally accepted that *Sclerotinia* s. str. contains three valid species only: *Sc. minor*, *Sc. sclerotiorum*, and *Sc. trifoliorum* (Kohn 1979a, b, Kohn *et al.* 1988, Bolton *et al.* 2006) and the vast majority of *Sclerotinia* diseases are caused by these three species. *Sclerotinia asari* and *Sc. nivalis* were later found as members of *Sclerotinia* based on DNA analyses (Wu & Wang 1983, Saito 1997, Clarkson *et al.* 2017). However, recent research is

exploring *ScL. subartica*, a morphologically indistinguishable species related to *ScL. sclerotiorum*. *Sclerotinia subartica* requires unique climatic conditions for germination and disease initiation than that of *ScL. sclerotiorum* (Clarkson *et al.* 2017). Additionally, *ScL. subartica* has been distinguished from three accepted *Sclerotinia* spp. through adapted qPCR primers (Leyronas *et al.* 2018). The genetic variability of *Sclerotinia* populations is 'typically' considered clonal (Lehner *et al.* 2015, Steyn 2015), although, reports vary depending on the specific host plant, the origin of the isolate, climatic zones, and continuous availability of host crops (Lehner *et al.* 2017). This is illustrated by contrasting studies that have reported high variability and populations which are genetically and phenotypically distinct from one another (Attanayake *et al.* 2013, Aldrich-Wolfe *et al.* 2015). Due to the lack of contemporary studies on the taxonomy and classification of species in *Sclerotinia*, our understanding of species diversity and genetic relationships in this group remains obscure.

Plant pathogens in the genus *Sclerotinia* are among the few considered to be necrotrophs, deriving nutrients from killed host cells (Amselem *et al.* 2011). The active modulation of the host redox status and the subversion of the host (programmed) cell death pathways by *Sclerotinia* spp. appear to be crucial for disease development (Kim *et al.* 2008a, Amselem *et al.* 2011). A wide array of substances that facilitate a necrotrophic lifestyle are secreted, including cell-wall-degrading enzymes and oxalic acid (OA) (Kim *et al.* 2008a, b). Oxalic acid is known to play a key role in pathogenesis and fungal development, as its absence renders non-pathogenic isolates incapable of infecting host plants and unable to produce sclerotia (Kim *et al.* 2008a). Furthermore, the absence of OA plays a role in the processes leading to the development of melanised hyphal masses associated with pathogen survival *i.e.* sclerotia. The formation of

sclerotial stromata is commonly associated with *Sclerotinia* and members of *Sclerotiniaceae* (Willett 1997, Bolton *et al.* 2006).

The most common pathogenic species, *Scl. minor*, *Scl. sclerotiorum*, and *Scl. trifoliorum* are distributed worldwide and occur on more than 440 different hosts, including numerous cultivated grains, oil- and protein seed, horticultural and vegetable crops (Bardin & Huang 2001, Heffer & Johnson 2007, Peltier *et al.* 2012, Farr & Rossman 2022, Khan *et al.* 2022). Wild plant hosts, such as broad-leaved weeds and wildflowers, are also known hosts of *Sclerotinia* spp. (Boland & Hall 1994, Heffer & Johnson 2007). Common disease names are derived from the symptoms and signs observed on the respective host crop (Purdy 1979); for example, cottony rot (carrot), blight (groundnut), drop (lettuce), head rot (sunflower), stem rot (canola and soybean) and white mould (multiple crops) (Purdy 1979, McDonald & Boland 2004, Heffer & Johnson 2007, Peltier *et al.* 2012, Khan *et al.* 2022). Due to the extensive host range, there are no unique symptoms that belong to all the plants affected by *Sclerotinia* diseases. However, initial symptoms, depending on the host, include a bleached appearance of infected tissues or a watery soft rot, a general characteristic associated with necrotrophic fungi (Amselem *et al.* 2011, Kabbage *et al.* 2015). Subsequently, white cottony mycelial mats form, a characteristic sign of infection, and in severe scenarios, the complete necrosis and shredding of plant organs may be evident (Purdy 1979, Bolton *et al.* 2006). As the disease progresses, the cottony hyphae of the pathogen aggregate into clumps of mycelium that eventually mature into hard black melanised sclerotia (Willett & Bullock 1992). Sclerotia can be found on the outer surface of the diseased tissue, inside of soft host tissues or cavities such as floral receptacles, fruits, and the pith of stems.

Pathogenic species within *Sclerotinia* spend a significant portion of their life cycle in and on soil in the form of sclerotia. The survival efficiency of sclerotia is attributed to the melanised rind, playing an important role in protection from adverse conditions and microbial degradation, as well as in some cases a function in virulence (Bell & Wheeler 1986, Henson *et al.* 1999, Butler *et al.* 2009). Sclerotia can survive for prolonged periods, ranging from one to 10 years before viability starts to decline (Ben-Yephet *et al.* 1993, Barding & Huang 2001, Amselem *et al.* 2011). The size, shape, and weight of sclerotia are dependent on multiple factors, however, the host crop is one of the primary driving variables (Bolton *et al.* 2006, Taylor *et al.* 2018). The disease cycle is initiated through carpogenic or myceliogenic germination depending on conducive environmental conditions. Carpogenic germination produces apothecia, containing inoperculate asci with ellipsoid ascospores, which are forcibly ejected into the air. The production of both large and small ascospores within one ascus and differences between ascospore length/width was used for the early morphological identification of *Scl. trifoliorum* from *Scl. sclerotiorum* and *Scl. minor* (Kohn 1979, Ekins *et al.* 2005). Airborne ascospores are chiefly responsible for infecting above-ground tissues, resulting in stem blights, stalk rot, head rot, pod rot, white mould, and blossom blights (Barding & Huang 2001, Bolton *et al.* 2006). In contrast, myceliogenic germination produces mycelia directly from sclerotia, able to infect crown and root tissues, causing crown and root rots (Barding & Huang 2001). Stipes (associated with carpogenic germination) have been observed on sclerotia which germinated myceliogenically, suggesting that sclerotia are capable of simultaneous dual-germination pathway events (Hao *et al.* 2003). *Sclerotinia* includes species that do not produce macroconidial asexual morphs, however, microconidia can be produced on hyphae or the apothecial hymenium. These microconidia might function as spermatia in some *Sclerotinia* species; however, they do not germinate

and their role in the biology of these fungi is mostly unknown (Kohn 1979, Willett 1997). Infected seed and sclerotia-infested seed bags are associated with the long-distance dissemination of *Sclerotinia* spp. (Hoes & Huang 1976, Mueller *et al.* 1999). Dispersal of the pathogen among regions and on-farm can be due to farm equipment, animal or human activities, runoff irrigation water and plant residues (Schwartz & Steadman 1978, Adam & Ayers 1979, Barding & Huang 2001). Localised in-field dissemination is associated with windblown ascospores and colonised plant material encountering healthy plant material (Ben-Yephet & Bitton 1985).

Ecological and economic significance

Sclerotinia species cause many significant diseases on economically important plants; three of the most well-known are detailed below.

Sclerotinia stem rot of soybean (*Glycine max*) caused by *Scl. sclerotiorum* is considered the second most important cause of yield loss in soybean-producing areas (Savary *et al.* 2019). When environmental conditions are conducive, *Sclerotinia* stem rot can reduce seed number and weight, seed quality and price discounts for foreign material (sclerotia) delivered at the grain elevator. Infected seeds are an important source of inoculum and can have reduced germination, and in some cases, oil and protein concentrations can be reduced (Peltier *et al.* 2012). The long-term survival of sclerotia in the soil is one of the biggest challenges for disease management (Peltier *et al.* 2012, Willbur *et al.* 2019). Selecting soybean cultivars with resistance to *Sclerotinia* stem rot is an important part of a disease management plan, although only partial resistance is available (Kim & Diers 2000, Chen & Wang 2005, McCaghey *et al.* 2019). Stem rot is also associated with other leguminous crops, such as dry beans (*Phaseolus vulgaris*) and peanuts (*Arachis hypogaea*) (Purdy 1970, McCreary *et al.* 2016).

Sclerotinia stem rot of Brassica oilseeds caused by *Scl. sclerotiorum* is a damaging disease of oilseed brassicas (*B. juncea*, *B. napus* and others). *Brassica* crops are important commodities in Europe, North America, and Indo-Pacific region (India, Australia, and China), with oilseed rape, *B. napus*, accounting for 13 % of total world edible oil production (Taylor *et al.* 2017). The oil-rich seeds of oilseed rape are also processed as biodiesel and high-quality animal feed (Derbyshire & Denton-Giles 2016). Management of *Sclerotinia* diseases is still difficult as sown rapeseed cultivars do not have high levels of resistance, and fungicide-resistant strains are increasingly reported. *Sclerotinia sclerotiorum* does not exhibit a gene-for-gene response during interactions with the host unlike other *B. napus* pathogens such as *Leptosphaeria maculans* (syn. *Plenodomus lingam*) or *Plasmodiophora brassicae*, and therefore despite advances made in the understanding of the *B. napus*–*Scl. sclerotiorum* interaction, few control strategies using genetic tools have proven successful (Wytyneck *et al.* 2022).

Sclerotinia stalk/stem and head rot of sunflower (*Helianthus annuus*) caused by *Sclerotinia sclerotiorum* is one of the most destructive diseases of sunflowers. *Sclerotinia sclerotiorum* causes the most damage to sunflowers in cool and humid production regions resulting in more than 50 % seed yield loss. This disease has been reported in all important sunflower-producing regions of the world (Talukder *et al.* 2014). Unlike other hosts, sunflowers are vulnerable to infection by *Scl. sclerotiorum* both via floral and root infection, subsequently, causing head

and stalk/stem rot. Myceliogenic germination of sclerotia leads to infection of nearby sunflower roots result in basal stalk rot and wilt. Head rot occurs when sclerotia germinate carpogenically releasing airborne ascospores and infecting senescing florets. Cultivated sunflowers generally lack complete resistance to *Scl. sclerotiorum*, although differences in susceptibility exist yielding variation of host responses under various environmental conditions. However, in over 51 species of *Helianthus*, a diverse pool of potential sources of *Sclerotinia* resistance exists. Evaluation of wild germplasm has indicated that several wild perennial species possess high levels of resistance to *Sclerotinia* head rot and stalk rot (Seiler *et al.* 2017).

Research interests

There are 2 705 publications and 27 698 citations from 2011–2021 in the Web of Science (Fig. 53), with the top 10 most cited articles listed in Table 32. Most publications focused on *Sclerotinia sclerotiorum* plant-pathogen interaction (host defense process, host resistance, pathogen virulence), disease management (disease suppression by cultural practices), fungal viruses (*Sclerotinia* ssDNA virus) and research on the host and pathogen genomes to understand host defences and defences and pathogen virulence. Shared research interests between *Botrytis*, *Monilinia* and *Sclerotinia* are often cited as they have shared taxonomic features belonging to the *Sclerotiniaceae* and may co-occur in field (Fourie *et al.* 2002).

Plant pathogen interaction

As necrotrophs, *Sclerotinia* spp. produce a wide array of degradative lytic enzymes (e.g., endo- and exo-pectinase, cellulase, hemicellulase, protease) as well as oxalic acid, believed to facilitate colonisation and host cell wall degradation. Oxalic acid contributes to numerous physiological processes (e.g., reduction in pH, acidity-induced activation of enzymes, the elevation of Ca²⁺, guard cell

regulation, vascular plugging with oxalate crystals) that augment fungal colonisation of host plants (Williams *et al.* 2011). Studies with OA-deficient mutants strongly suggest that OA is an essential pathogenicity determinant and a key factor governing the broad pathogenic success of *Sclerotinia*. Oxalic acid also aids *Sclerotinia* pathogenicity indirectly by acting as a signalling molecule, via manipulation of the host reactive oxygen system (ROS) (Williams *et al.* 2011, Heller & Witt-Geiges 2013). Understanding of host-*Sclerotinia* interactions can contribute to the efforts of breeding for resistance.

Disease management

Diseases caused by *Sclerotinia* spp. require an integrated pest management program that includes a combination of cultural practices, cultivar selection with host resistance and crop rotation, chemical control, and biological control (Bardin & Huang 2001, Peltier *et al.* 2012). For economically important crops, targeted disease forecasting programs based on epidemiological data for fields have been developed, however, these programs are targeted for specific growing regions (Derbyshire & Denton-Giles 2016). Breeding programs are also exploring sources of partial resistance in wild relatives of cultivated plants, which can help reduce losses associated with *Sclerotinia* diseases (Taylor *et al.* 2017).

Biological control

Research groups in China, the USA, and New Zealand found that *Scl. sclerotiorum* hosts various mycoviruses, including double-stranded RNA (dsRNA) viruses, positive-sense single-stranded RNA (+ssRNA) viruses, DNA viruses and negative-sense single-stranded RNA (–ssRNA) viruses (Xie & Jiang 2014). *Sclerotinia sclerotiorum* hypovirulence-associated DNA virus 1 (SsHADV-1) was the first DNA mycovirus to be found to confer hypovirulence to the fungi infected (Yu *et al.* 2010). The investigation of different *Scl. sclerotiorum*-mycovirus interaction systems might supply new insights regarding virus-host interactions as well as control

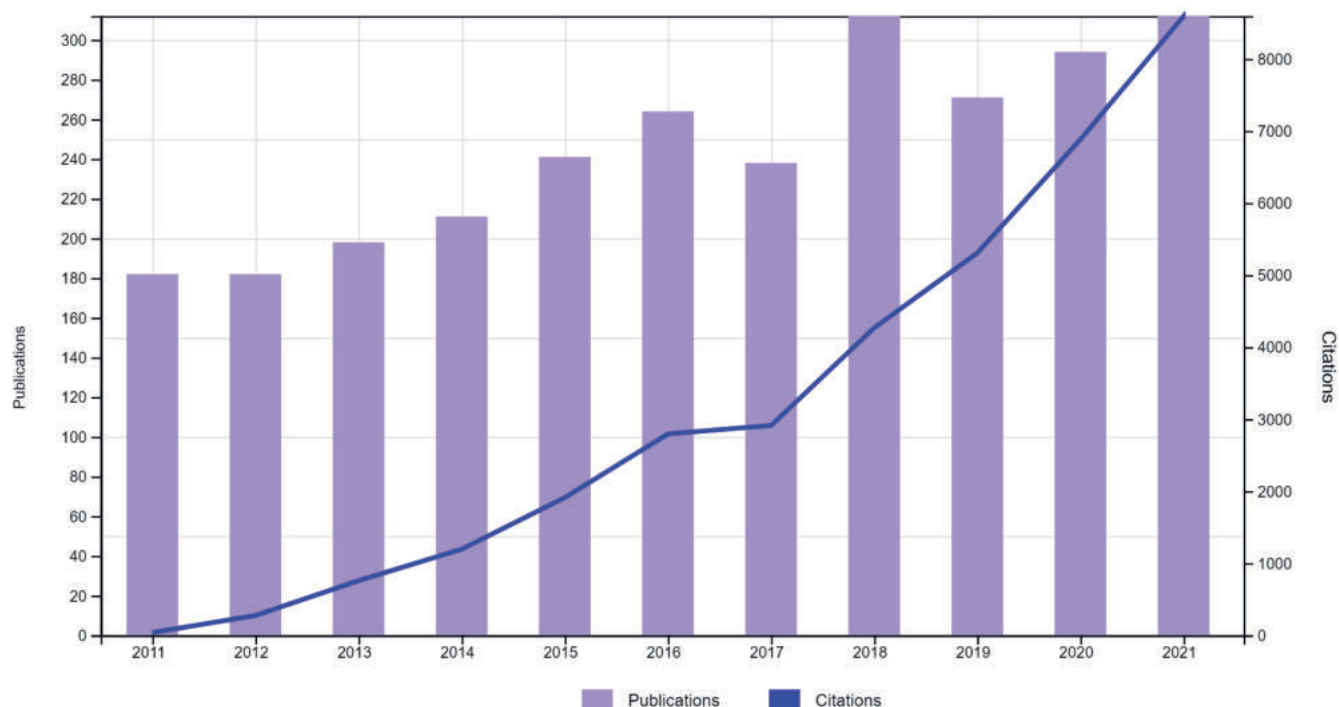


Fig. 53. Trends in research of *Sclerotinia* in the period 2011–2021.

Table 32. Top 10 cited articles related to *Sclerotinia* published in the period 2011–2021.

Rank	Article title	No. of citations	References
1	Evolution of jasmonate and salicylate signal crosstalk	678	Thaler <i>et al.</i> (2012)
2	Genomic analysis of the necrotrophic fungal pathogens <i>Sclerotinia sclerotiorum</i> and <i>Botrytis cinerea</i>	603	Amselem <i>et al.</i> (2011)
3	Have biopesticides come of age?	348	Glare <i>et al.</i> 2011
4	50-plus years of fungal viruses	323	Ghabrial <i>et al.</i> (2015)
5	Plant immunity to necrotrophs	311	Mengiste (2012)
6	Tipping the balance: <i>Sclerotinia sclerotiorum</i> secreted oxalic acid suppresses host defenses by manipulating the host redox environment	277	Williams <i>et al.</i> (2011)
7	Crops that feed the World 2. Soybean-worldwide production, use, and constraints caused by pathogens and pests	238	Hartman <i>et al.</i> (2011)
8	A review of current knowledge of resistance aspect for the next-generation succinate dehydrogenase inhibitor fungicides	235	Sierotzki & Scalliet (2013)
9	New insights into mycoviruses and exploration for the biological control of crop fungal diseases	213	Xie & Jiang (2014)
10	<i>Bacillus</i> strains isolated from rhizosphere showed plant growth promoting and antagonistic activity against phytopathogens	208	Kumar <i>et al.</i> (2012)

strategies for *Sclerotinia* diseases (Xie & Jiang 2014). Additionally, (–)ssRNA viruses are also known to be dangerous human viruses, however, the discovery of these viruses in fungi can provide a safe model system to study function and to screen antiviral compounds against them (Xie & Jiang 2014).

Authors: C. Salgado-Salazar and L. Rothmann

27. *Rhodotorula* F.C. Harrison, Proc. & Trans. Roy. Soc. Canada, ser. 3 21(5): 349. 1927.

Type species: *Rhodotorula glutinis* (Fresen.) F.C. Harrison

Classification: Basidiomycota, Pucciniomycotina, Microbotryomycetes, Sporidiobolales, Sporidiobolaceae.

Background

The genus *Rhodotorula* was introduced by Harrison (1928), with *Rho. glutinis* (bas. *Cryptococcus glutinis*) as the type species. The genus has about 190 records registered in Index Fungorum (2022); however, several species have been transferred to other genera and a new generic concept was introduced by Wang *et al.* (2015b). In the most recent outline of fungi, *Rhodotorula* is placed in the family Sporidiobolaceae with about 15 accepted species (Wijayawardene *et al.* 2022). The recently introduced species, *Rho. sampaiiana* (from subsurface waters, Argentina) and *Rho. frigidialcoholis* (from permafrost, Antarctica), were described by Tiwari *et al.* (2021) and Touchette *et al.* (2022), respectively.

Morphologically, *Rhodotorula* species are mainly characterised by having subglobose, ovoid, ellipsoid or elongate cells, occasionally producing pseudohyphae or true hyphae. Species produce red or yellow pigments and asexual reproduction is by multilateral or polar budding (Sampaio *et al.* 2011). Fermentative ability is absent but the capacity to assimilate several carbon sources has been reported. However, *Rhodotorula* species are positive for diazonium blue B (DBB) reaction and production of urease (Sampaio *et al.* 2011). The genus description was emended to include the sexual morph *Rhodospidium*, based on multi-gene phylogenetic analyses (Wang *et al.* 2015c), which revealed that some species

of *Rhodotorula* were also described as having sexual reproduction by producing transversely septate basidia and ovoid basidiospores germinating by budding.

In the Global Biodiversity Information Facility (GBIF) (<https://www.gbif.org/species/2518125/metrics>), there are 5 433 occurrences registered in the database, with the most registrations (1 404) from Australia, and the years 2011 to 2016 having the highest numbers of registration (e.g., 379–508). *Rhodotorula* species have been mostly reported as environmental yeasts (i.e., saprobes and psychrophiles), being frequently isolated from plant material, soil, and water (Sampaio *et al.* 2011, Li *et al.* 2020b, Tiwari *et al.* 2021, Touchette *et al.* 2022). For instance, most of the species accepted by Wang *et al.* (2015b) were first isolated from plant materials and water obtained in the USA, Chile, Japan, and New Zealand, among other countries. However, some studies have reported some *Rhodotorula* species as opportunist pathogens, mainly among immunocompromised individuals (Sampaio *et al.* 2011, Ioannou *et al.* 2019), causing nosocomial and opportunist infections (Sampaio *et al.* 2011, Ioannou *et al.* 2019), with bloodstream, central nervous system, and ocular infections as the most commonly observed manifestations (Ioannou *et al.* 2019).

Importance in public health (pathogenesis)

Rhodotorula species have not been included as important etiological agents of mycosis (Sampaio *et al.* 2011). However, there are several case reports of *Rhodotorula* species causing disease, mainly in immunocompromised patients (Miceli *et al.* 2011, Wirth & Goldani 2012, Ioannou *et al.* 2019). Ioannou *et al.* (2019) reviewed cases of infections caused by *Rhodotorula* species in all five continents, with Asian, European and North American countries having the highest number of cases. Ioannou *et al.* (2019) showed that *Rhodotorula* infections usually manifest as fungemia, central nervous system (CNS) and ocular infections, as well as peritoneal dialysis-associated peritonitis. *Rhodotorula mucilaginosa*, *Rho. glutinis*, *Rho. minuta*, and *Rho. marina* were the most reported species in these infections. However, *Rho. minuta* and *Rho. marina* are not accepted as species of *Rhodotorula* (Wang *et al.* 2015c), being treated in *Cystobasidium* (Yurkov *et al.* 2015) and *Symmetrospora* (Wang *et al.* 2015c), respectively.

Different factors were observed in the *Rhodotorula* lifestyle acting as an opportunistic etiologic agent of infections. For example, Ioannou *et al.* (2019) outlined that fungemia is more frequent in male patients (with a mean age of 33.5 years) that had previous malignancy (mainly hematologic malignancies), or presented an immune depression condition (by AIDS or due to chemotherapy and organ transplant), or autoimmune diseases. Most of these infections were associated with the use of central venous catheter (CVC) and parenteral nutrition (Ioannou *et al.* 2019). These authors also observed a tendency in which AIDS patients have more common CNS infections, and the patients with ocular infections were preceded by trauma or surgery (Ioannou *et al.* 2019). The mortality rate of patients affected by *Rhodotorula* infection is around 10–15 % (Toun & Costa 2008, Miceli *et al.* 2011, Ioannou *et al.* 2019), but in some cases, such as for the CNS infections, overall mortality can reach 41 % (Ioannou *et al.* 2019); however, these rates should be treated independently and the characteristics of each patient need to be evaluated (Ioannou *et al.* 2019).

Research interests

There are 1 810 publications and 26 581 citations from 2011–2021 in the Web of Science (Fig. 54), with the top 10 most cited articles listed in Table 33. Most of the publications focused on applied microbiology (e.g., biotechnology, food science, energy fuel), and some papers report the medical importance of *Rhodotorula* species.

Taxonomy and phylogeny

Since the introduction of *Rhodotorula* (Harrison 1928), and over subsequent years, species in this genus were mainly characterised based on morphology and physiology/biochemistry, including red-pigmented yeasts with no formation of ascospores (Sampaio *et al.* 2011). Later, Lodder (1934) included all yeasts producing carotenoid pigments in *Rhodotorula*. Following this treatment, little change was included in the generic concept of *Rhodotorula* (Lodder & Kreger-van Rij 1952, Lodder 1970). Another important

fact was the increase in the number of *Rhodotorula* species, growing from seven (Lodder & Kreger-van Rij 1952) to 47 accepted species (Sampaio *et al.* 2011). One of the most important steps in *Rhodotorula* classification and taxonomy was the establishment of the genus as a basidiomycetous yeast and the sexual related species classified in *Rhodospodium* (Lodder 1970). Sampaio *et al.* (2011) highlighted that *Rhodotorula* is polyphyletic with species classified into two subphyla (*Pucciniomycotina* and *Ustilaginomycotina*) and four classes (*Microbotryomycetes*, *Cystobasidiomycetes*, *Ustilaginomycetes* and *Exobasidiomycetes*). These authors recommended including species related to the type species, *Rho. glutinis*, from the order *Sporidiobolales* for a modern classification for this genus.

Wang *et al.* (2015b) conducted a large study of the classification of yeasts and related taxa and based on multi-locus phylogeny and morphological, physiological and biochemical information known over years, introduced a new generic concept to *Rhodotorula* and several species were transferred to other genera. The generic description of *Rhodotorula* was emended to include the sexual morph features of species previously treated in *Rhodospodium* and 15 species were accepted in the genus. *Rhodotorula* was initially considered a polyphyletic genus, as highlighted by Sampaio *et al.* (2011), but its polyphyly was resolved by Wang *et al.* (2015b) based on DNA markers and the genus was placed in *Sporidiobolaceae* (*Sporidiobolales*); the same treatment was followed by Wijayawardene *et al.* (2022).

Environment and biotechnology

Rhodotorula species are frequently isolated from the environment (e.g., living as saprobes and mainly obtained from plants, soils, and water) (Sampaio *et al.* 2011, Li *et al.* 2020) and also reported from spoiled foods and beverages (Barata *et al.* 2012, Wirth & Goldani 2012, Garnier *et al.* 2017). Species in this genus are among the most important fungi to be used in biotechnological processes (Kot *et al.* 2016) being known as “biotechnological machine” used in industries for the production of pigments, lipids, and enzymes capable of degrading rejected low-cost materials (Ageitos *et*

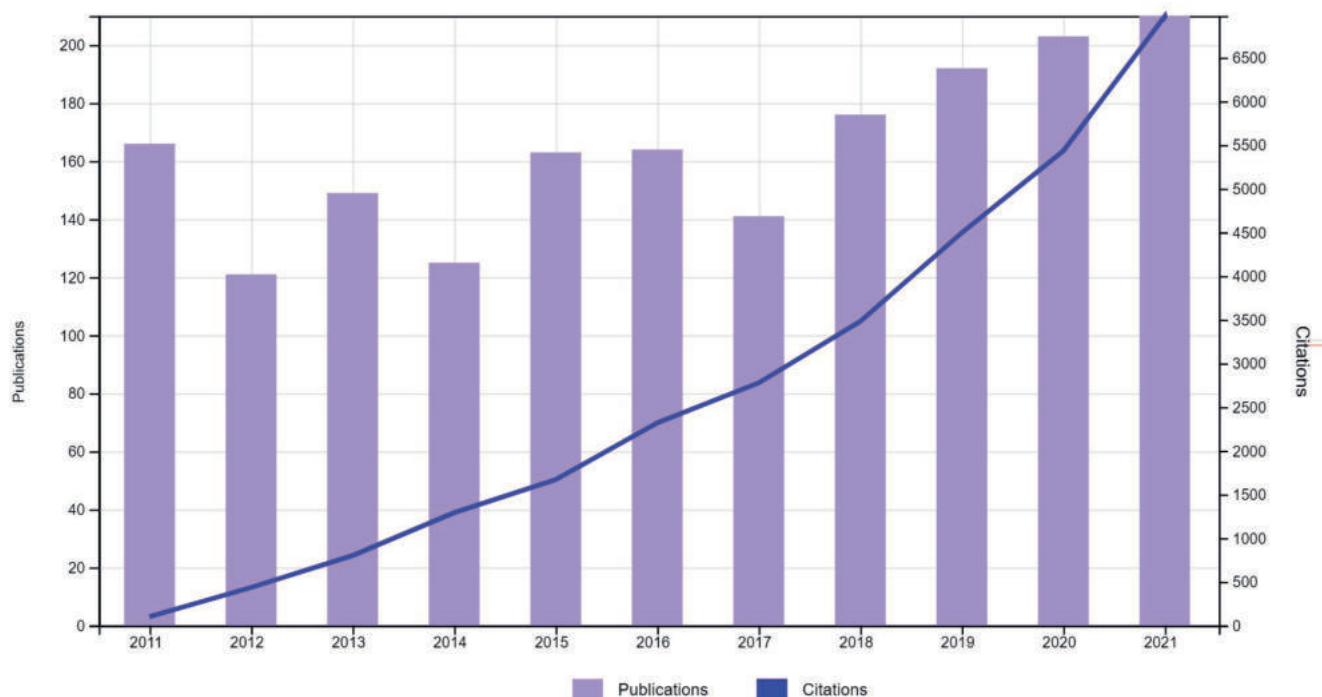


Fig. 54. Trends in research of *Rhodotorula* in the period 2011–2021.

Table 33. Top 10 cited articles related to *Rhodotorula* published in the period 2011–2021.

Rank	Article title	No. of citations	References
1	Emerging opportunistic yeast infections	530	Miceli <i>et al.</i> (2011)
2	Neonatal gut microbiota associates with childhood multisensitized atopy and T cell differentiation	477	Fujimura <i>et al.</i> (2016)
3	The microbial ecology of wine grape berries	360	Barata <i>et al.</i> (2012)
4	Oily yeasts as oleaginous cell factories	353	Ageitos <i>et al.</i> (2011)
5	Oil production by oleaginous yeasts using the hydrolysate from pretreatment of wheat straw with dilute sulfuric acid	313	Yu <i>et al.</i> (2011a)
6	ESCMID and ECMM joint clinical guidelines for the diagnosis and management of rare invasive yeast infections	305	Arendrup <i>et al.</i> (2014)
7	Characterization of the fungal microbiota (mycobiome) in healthy and dandruff-afflicted human scalps	250	Park <i>et al.</i> (2012b)
8	Potential use of oleaginous red yeast <i>Rhodotorula glutinis</i> for the bioconversion of crude glycerol from biodiesel plant to lipids and carotenoids	220	Saenge <i>et al.</i> (2011)
9	Terminal olefin (1-alkene) biosynthesis by a novel P450 fatty acid decarboxylase from <i>Jeotgalicoccus</i> species	219	Rude <i>et al.</i> (2011)
10	Biotechnological conversions of biodiesel derived waste glycerol by yeast and fungal species	203	Chatzifragkou <i>et al.</i> (2011)

al. 2011, Chatzifragkou *et al.* 2011, Saenge *et al.* 2011, Yu *et al.* 2011a, Kot *et al.* 2016). Over the years, some researchers have focused on the potential of *Rhodotorula* species/isolates to be used in the production of oils (Ageitos *et al.* 2011, Chatzifragkou *et al.* 2011, Saenge *et al.* 2011, Yu *et al.* 2011a, Mussagy *et al.* 2021), carotenoids and enzymes (Kot *et al.* 2016, Mussagy *et al.* 2021).

Carotenoids produced by *Rhodotorula* species are important in the food industry as pigments and diet supplements (Saenge *et al.* 2011, Kot *et al.* 2016). Because of the health benefits of carotenoids, they have also been used in cosmetic and pharmaceutical industries (Kot *et al.* 2016, Mussagy *et al.* 2021), with promising global markets (see the reports of “The Global Market for Carotenoids” in 2018 and “Yeasts, Yeast Extracts, Autolysates and Related Products: The Global Market” in 2017).

Diagnosis in human health

Similar to other yeasts already known as etiologic agents of mycosis, *e.g.*, *Candida* and *Cryptococcus* species, *Rhodotorula* is a genus that needs attention during the treatment of hospitalised patients (Toun & Costa 2008, Miceli *et al.* 2011, Ioannou *et al.* 2019). Over the years, *Rhodotorula* isolates have been frequently reported as etiologic agents of human infections, mainly in immunocompromised patients (Toun & Costa 2008, Miceli *et al.* 2011, Arendrup *et al.* 2013, Ioannou *et al.* 2019). Diagnostic methods broadly used for other mycoses, *e.g.*, candidiasis and cryptococcosis, could also be used for the isolation and identification of *Rhodotorula* species. The molecular markers usually studied for analyses of DNA sequences are ITS and D1/D2 domain of the LSU rDNA regions (Arendrup *et al.* 2013). In addition, protein analysis by MALDI-TOF has been applied for yeast identification (Fraser *et al.* 2016). In 2013, a panel of experts proposed a clinical guideline for the diagnosis and management of rare invasive yeast infections, including important highlights for *Rhodotorula* species (Arendrup *et al.* 2013).

Virulence factors

Virulence factors of *Rhodotorula* species is an understudied topic. Some studies suggest that virulence is related to the capacity of *Rhodotorula* isolates to form biofilm on medical devices (*e.g.*,

catheter fragments) (Arendrup *et al.* 2013, Thomson *et al.* 2017, Maciel *et al.* 2019, Jarros *et al.* 2020, 2021). These studies showed that these isolates also have the potential to form biofilm and should be studied similarly to other medically important yeasts. For example, species of *Candida* are widely studied because of their medical importance, and their virulence factors are also well understood (Rocha *et al.* 2021). Other surveys showed that similar to *Cryptococcus* cells, *Rhodotorula* capsules may act as a resistance mechanism against phagocytosis (Yockey *et al.* 2019). The emergence of *Rhodotorula* species as opportunistic pathogens needs more attention.

Management of the disease

Rhodotorula species have been associated with healthcare workers and found in hospital environments (Khodavaisy *et al.* 2011, Sham *et al.* 2021). Due to their capacity to adhere to surfaces, medical equipment (*e.g.*, flexible endoscopes) could also be a source of contamination (Arendrup *et al.* 2013, Ioannou *et al.* 2019). Good biosafety practices in the hospital environment could also minimise external contamination of patients. For the treatment of hospitalised patients due to *Rhodotorula* infection, amphotericin B is the most common antifungal drug used, followed by fluconazole, 5-fluorocytosine, itraconazole, voriconazole, and ketoconazole (Ioannou *et al.* 2019); however, there are reports of resistance of *Rhodotorula* species to azoles and echinocandins (Arendrup *et al.* 2013, Yockey *et al.* 2019). Combined use of drugs is necessary in some cases (Ioannou *et al.* 2019). Ioannou *et al.* (2019) reported a high clinical cure rate for patients with *Rhodotorula* infection.

Author: J.D.P. Bezerra

28. *Beauveria* Vuill., Bull. Soc. Bot. France 59: 40. 1912.

Type: *Beauveria bassiana* (Bals.-Criv.) Vuill.

Classification: Ascomycota, Pezizomycotina, Sordariomycetes, Hypocreales, Cordycipitaceae.

Background

The discovery of *Beauveria bassiana* dates back to the causal agent of white muscardine disease on silkworms that was found by an Italian entomologist, Agostino Bassi di Lodi (Bassi 1835, 1836). *Beauveria bassiana* was initially described as *Botrytis bassiana* by Giuseppe Gabriel Balsamo-Crivelli, in honour of Bassi's discovery (Rehner 2005). Later, Vuillemin (1912) formally erected the genus *Beauveria* and designated *Beauveria bassiana* as the type species, in honour of Beauveria who had studied the fungus in 1911. *Beauveria brongniartii* was the second species described in this genus by the end of the 19th century (MacLeod 1954). Since then, many *Beauveria* species have been introduced from soil and arthropod hosts (Zimmermann 2007).

Beauveria originally was known as an anamorphic genus which was placed in *Moniliacea* (*Moniliales*, *Hyphomycetes*, *Deuteromycotina*) (Imoulan *et al.* 2017). Nowadays, multi-loci phylogenies have necessitated the transfer of *Beauveria* to *Cordycipitaceae* (*Hypocreales*) (Sung *et al.* 2007, Maharachchikumbura *et al.* 2016a, b) and the sexual-asexual connection between *Beauveria* and *Cordyceps* has been established based on molecular analyses (Liu *et al.* 2002, 2001, Rehner *et al.* 2005, Shrestha *et al.* 2014). The sexual morph of *Beauveria* is characterised by brightly-pigmented, stipitate, fleshy stromata and semi-immersed, ovoid perithecia which are produced on the upper part of stromata and cylindrical asci with thickened apex and hyaline, filiform, multiseptate ascospores which disarticulate into cylindrical, one-celled secondary spores when mature (Khonsanit *et al.* 2020). The key diagnostic character of asexual *Beauveria* species is the basally inflated conidiogenous cells with a zig-zag rachis from which the conidia are produced (De Hoog 1972). Cultural and morphological characteristics present a low resolution on interspecific delimitation within *Beauveria*, due to the extensive overlap in conidial shape and dimensions (Imoulan *et al.* 2017). For a long time, many strains were consigned to *Beauveria bassiana* and *Be. brongniartii*, based on the shape of conidia, which included many cryptic species, leading to taxonomic confusion in *Beauveria* (Zimmermann 2007, Imoulan *et al.* 2017). Recently, some cryptic species of *Beauveria* were restudied employing both maximum likelihood and neighbor-net phylogenetic analyses based on combined markers (*tef-rpb1-rpb2-ITS-Bloc*) (Khonsanit *et al.* 2020). To date, 40 morphological species are accepted in *Beauveria*, including 25 species with sequence data (Hyde *et al.* 2020d).

Ecological and economic significance

Beauveria includes some of the most well-known species used in biological control against insect pests (Lacey *et al.* 2015, García-Estrada *et al.* 2016). *Beauveria* species can persist in soil as dormant propagules; in plants as endophytes or associated with the rhizosphere (Ownley *et al.* 2008, Vega *et al.* 2009, Greenfield *et al.* 2016, Vega 2018); they are also plant disease antagonists (Dara 2019). Thanks to the great diversity in ecological niches and wide arthropod host range, this genus has huge potential in pest management with significant ecological and economic impacts. *Beauveria bassiana* is the most widely used species and can infect insects belonging to over 521 genera (Imoulan *et al.* 2017). From its discovery 200 years ago as the cause of devastating disease in economically important silkworm, *Be. bassiana* became a popular entomopathogenic fungus used as an agent against various agricultural pests (Lacey *et al.* 2015, García-Estrada

et al. 2016, Baron *et al.* 2019, 2020) with many mycopesticide products developed from *Beauveria* and available in niche markets (Zimmermann 2007). *Beauveria*, especially *Be. bassiana* and *Be. brongniartii*, were shown also to be effective against invasive insects causing damage to trees in natural habitats such as Eucalyptus weevil, Asian long-horned beetle, emerald ash borer and oak lace bug (Dara 2019). *Beauveria* species have been used also against insect vectors of protozoan and bacterial diseases to humans and animals such as *Triatoma infestans* (kissing bug) carrying Chaga's disease that has infected over 20 million people in South America (Forlani *et al.* 2015); ticks carrying *Borrelia burgdorferi*, a bacterium causing Lyme disease (Kirkland *et al.* 2004). *Beauveria bassiana* has been used also against mosquito vectors of important human diseases such as malaria (Kikankie *et al.* 2010, Ragavendran *et al.* 2017) and Zika virus (Deng *et al.* 2019).

Research interests

There are 3 620 publications and 26 077 citations from 2011–2021 in the Web of Science (Fig. 55), with the top 10 most cited articles shown in Table 34. The publications cover the evolution and mechanisms of virulence, production of secondary metabolites and virulence-associated molecules, the interest for biocontrol and appropriate formulation for practical use, and also diversity and taxonomy.

Phylogeny and taxonomy

Beauveria includes many cryptic species with ambiguous morphological characters. The size and shape of conidia can be used to some extent to discriminate species but multigene phylogenies have been the basis for circumscribing new species during the last decade (Rehner & Buckley 2005, Rehner *et al.* 2011, Imoulan *et al.* 2017, Khonsanit *et al.* 2020). The species status of certain taxa might be doubtful as they were proposed based on a few samples with incomplete species sampling (Chen *et al.* 2018d). Future studies should include comprehensive data for the genus, and propose detailed morphometric analyses on conidia size and shape to propose new species.

Virulence and host specificity

Beauveria is well known for *Be. bassiana*, largely studied for its virulence and pathogenicity against arthropods (Xiao *et al.* 2012). The variation of virulence and host specificity are generally elusive with contrasting results. For example, some studies found a strong to intermediate association between hosts and genetic groups (Maurer *et al.* 1997, Chen *et al.* 2015f) while other studies (Wang *et al.* 2005, Meyling *et al.* 2009, Mei *et al.* 2020) found that genetic structure cannot be explained by host association but rather by geographic origins. The level of virulence can be highly variable between strains toward specific insect groups (Boston *et al.* 2020) without apparent association to population genetic structure. Variation in virulence seems to be due to the mutation and positive selection of some categories of genes, particularly toxin-producing genes (Zhang *et al.* 2020). Highly virulent strains seem to arise by gaining specific genes such as polyketide synthases (PKSs) and bacterial toxins (Xiao *et al.* 2012, Valero-Jiménez *et al.* 2016).

Toxins and secondary metabolite

Beauveria produces a diverse array of biologically active secondary metabolites that include non-peptide pigments and polyketides, non-ribosomally synthesised peptide antibiotics and other secreted metabolites implicated in insect pathogenesis and

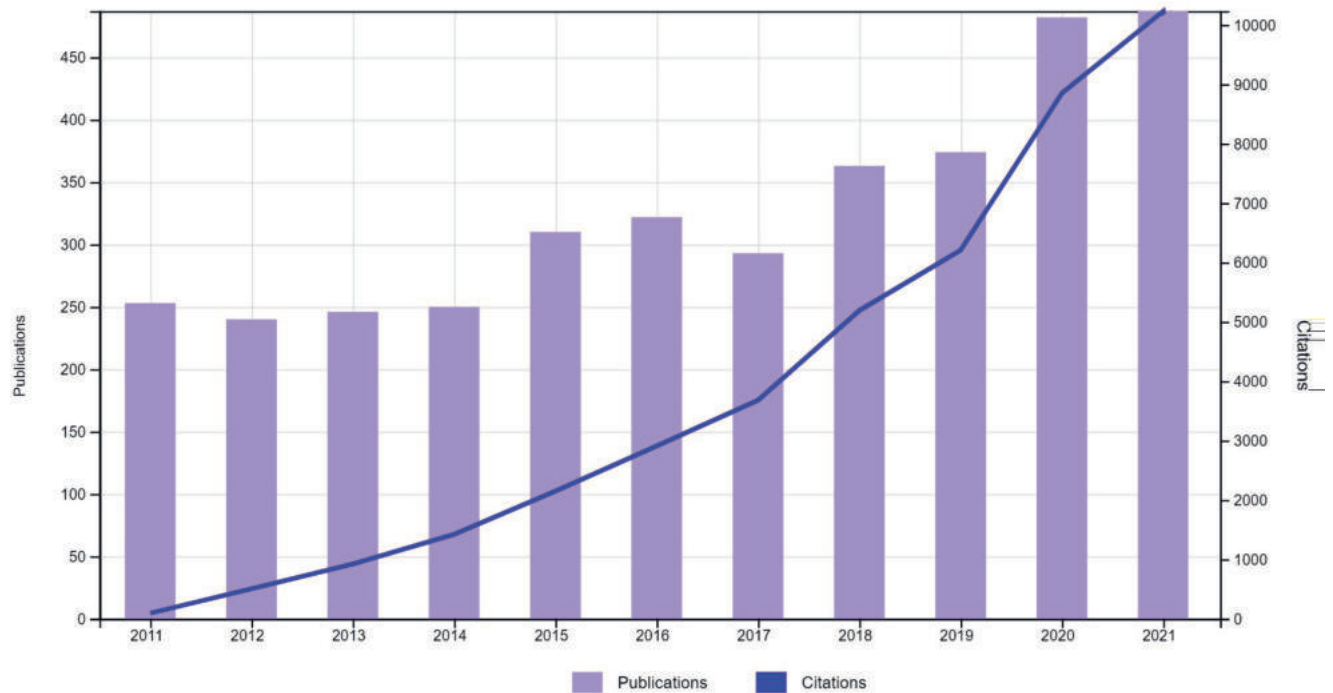


Fig. 55. Trends in research of *Beauveria* in the period 2011–2021.

Table 34. Top 10 cited articles related to *Beauveria* published in the period 2011–2021.

Rank	Article title	No. of citations	References
1	Insect pathogens as biological control agents: back to the future	623	Lacey <i>et al.</i> (2015)
2	Genomic perspectives on the evolution of fungal entomopathogenicity in <i>Beauveria bassiana</i>	370	Xiao <i>et al.</i> (2012)
3	Phylogeny and systematics of the anamorphic, entomopathogenic genus <i>Beauveria</i>	232	Rehner <i>et al.</i> (2011)
4	Insect pathogenic fungi: genomics, molecular interactions, and genetic improvements	168	Wang & Wang (2017)
5	Two hydrophobins are involved in fungal spore coat rodlet layer assembly and each play distinct roles in surface interactions, development and pathogenesis in the entomopathogenic fungus, <i>Beauveria bassiana</i>	161	Zhang <i>et al.</i> (2011)
6	Fungal secondary metabolites as modulators of interactions with insects and other arthropods	155	Rohlf & Churchill (2011)
7	Additive contributions of two manganese-cored superoxide dismutases (MnSODs) to antioxidation, UV tolerance and virulence of <i>Beauveria bassiana</i>	137	Xie <i>et al.</i> (2012)
8	More than a colour change: insect melanism, disease resistance and fecundity	118	Dubovskiy <i>et al.</i> (2013)
9	Evolutionary interaction networks of insect pathogenic fungi	109	Boomsma <i>et al.</i> (2014)
10	A phylogenetically based nomenclature for <i>Cordycipitaceae</i> (<i>Hypocreales</i>)	89	Kepler <i>et al.</i> (2017)

virulence that have potential use in industrial, pharmaceutical and agricultural aspects (Rehner *et al.* 2012). These metabolites exhibit insecticidal, antiviral, antibacterial, antifungal, anticancer, anti-tumour, antiatherosclerotic, cytotoxic, herbicidal activities, *etc.* (Strasser *et al.* 2000 a, b, Gurulingappa *et al.* 2011, Sahab 2012, Lozano-Tovar *et al.* 2017, Cheong *et al.* 2020, Du *et al.* 2020). Some important mycotoxins derived from *Beauveria* species have been elucidated with chemical structure, synthesis mechanism, physicochemical properties and bioactive activity (Logrieco *et al.* 2002, Zobel *et al.* 2016, Amobonye *et al.* 2020). Beauvericin and pyridovericin have significant cytotoxicity to a variety of cancer cell lines, showing high potential in cancer therapeutics (Strasser *et al.* 2000b, Wu *et al.* 2018b, Amobonye *et al.* 2020). Oosporein, bassianin and tenellin have ability to inhibit insect immunity, allowing

the fungus to overcome and kill its hosts (Basyouni *et al.* 1968, Jeffs & Khachatourians 1997, Zibae *et al.* 2011, Fan *et al.* 2013, Feng *et al.* 2015a, Mc Namara *et al.* 2019). The compound S-(-)-10,11-dihydroxyfarnesic acid methyl ester (I) can inhibit melanin synthesis and does not irritate the skin or eyes of humans, for which it can be developed as cosmetic biomaterials (Son & Lee 2013). Additionally, batryticated silkworms infected by *Be. bassiana* have traditionally been used as folk medicine to treat stroke, urticaria, diabetes, *etc.* (Patočka 2016). Much research has been conducted to investigate the pharmacological activities, main compositions and clinical uses of batryticated silkworms (Hu *et al.* 2017).

Authors: D.P. Wei, J. Luangsa-ard and N. Kobmoo

29. *Puccinia* Pers., Syn. Meth. Fung. 1: 225. 1801.

Type species: *Puccinia graminis* Pers.

Classification: Basidiomycota, Pucciniomycotina, Pucciniomycetes, Puccinales, Pucciniaceae.

Background

Puccinia graminis on cultivated Triticum was designated as the type species of *Puccinia* by Cunningham (1931) and subsequently lectotypified by Jørstad (1958). Over the last century, *Puccinia* has typified taxonomic ranks up to the Pucciniomycotina.

Puccinia (Pucciniaceae) has almost 6 000 named species, which accounts for almost half of the known species of rust fungi (He *et al.* 2022a). *Puccinia* species are obligate plant pathogens on hosts in many plant families, especially Asteraceae, Cyperaceae, Fabaceae, Lamiaceae, Liliaceae s. lat., Malvaceae and Poaceae (Fig. 56). Some species of *Puccinia* cause rust diseases on agriculturally important hosts in the Poaceae and Asteraceae (Aime & McTaggart 2021) while others have been utilised as beneficial biological control agents for invasive weeds, e.g., *Puccinia chondrillina*, *Pu. myrsiphyllii* and *Pu. xanthii*.

Most species of *Puccinia* form conspicuous, powdery, yellow to red pustules (uredinia) on leaves and stems. The rusty colour of uredinia reveals the etymology of both the name that applies to

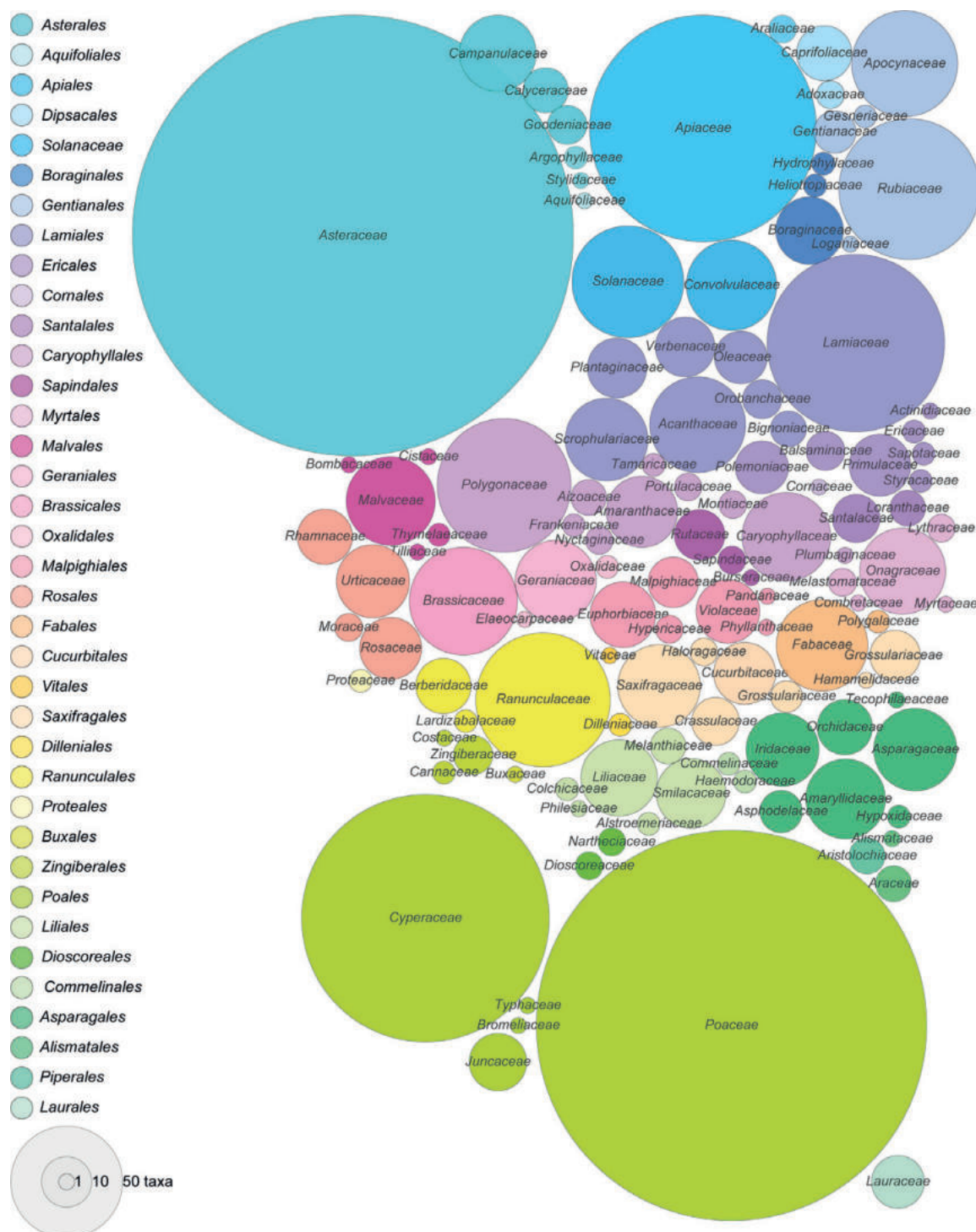


Fig. 56. Bubble plot of 3 214 species of *Puccinia* based on the telial host family. Bubbles are coloured by host at order rank, and size is proportional to the biodiversity of described rust fungi.

disease symptoms as well as the collective name for the *Pucciniales* (the order of rust fungi). Life cycles of *Puccinia* are variable, with species that produce between 1–5 different spore types, and species that complete their life cycle on one (autoecious) or two (heteroecious) host plants. The five spore stages of *Puccinia* are (i) spermatogonia that exude hundreds of haploid spermatia, which fertilise other compatible spermatogonia; (ii) aecia, which are formed adjacent to spermatogonia after dikaryotisation (or fertilisation) and produce dikaryotic aeciospores that disperse new genotypes; (iii) uredinia, which are also dikaryotic and produce urediniospores, the primary means of inoculum that spread one genotype; (iv) telia, which produce teliospores that are 2-celled, with each cell dikaryotic and able to germinate and undergo karyogamy and meiosis; and (v) basidia, which are four-celled and produce haploid basidiospores.

Puccinia and related genera are the crown radiation of rust fungi, sharing a most recent common ancestor between 15–65 million years ago (McTaggart *et al.* 2016b, Aime *et al.* 2018, Aime & McTaggart 2021). There are four main clades in the *Pucciniaceae*, each having species primarily on (i) *Asteraceae*, *Cyperaceae* and *Fabaceae*; (ii) *Amaranthaceae* and *Poaceae*; (iii) ferns, *Apocynaceae*, *Araceae* and *Loranthaceae*; and (iv) *Poaceae* (Van der Merwe *et al.* 2008, Dixon *et al.* 2010, Marin-Felix *et al.* 2017a). *Puccinia* is paraphyletic with respect to many other genera in the *Pucciniaceae*, such as *Baeodromus*, *Ceratocoma*, *Cumminsella*, *Desmella*, *Didymopsora*, *Dipyxis*, *Hapalophragmium*, *Macruropyxis*, *Uromyces* and *Stereostroma* (Aime & McTaggart 2021). Many rust fungi, particularly species of *Aecidium* and *Uredo*, which have been described only from aecial and uredinal stages, respectively, will need recombination in *Puccinia* or other monophyletic genera, pending their taxonomic resolution.

Species of *Puccinia* on cultivated grasses have become model organisms to study the genomes of rust fungi (Aime *et al.* 2017). The genomes of *Pu. graminis* (Duplessis *et al.* 2011), *Pu. coronata* (Miller *et al.* 2018), *Pu. striiformis* (Schwessinger *et al.* 2018) and *Pu. sorghi* (Rochi *et al.* 2018) have been assembled to near-chromosome resolution. Fully phased nuclei of *Pu. graminis* f. sp. *tritici* have been used to support somatic hybridization of rust fungi (Li *et al.* 2019b, Wu *et al.* 2019c), and a phased genome of *Pu. triticina* has been used to support tetrapolar mating in *Puccinia* (Wu *et al.* 2020a).

Ecological and economic significance

There are 5 845 species names in *Puccinia* listed on MycoBank, of which 140 have been described in the last 10 years (accessed 12 April 2022). The reduction in the discovery of new rust species may reflect that only rare and cryptic species remain to be discovered. Six examples have been chosen to illustrate the ecological and/or economic significance of *Puccinia*.

Leaf rust of peanut/groundnut (*Arachis hypogaea*) caused by *Puccinia arachidis* can significantly reduce pod and fodder yield, as well as oil quality. The rust co-evolved with its host in South America and the last 200 years has spread around the world to wherever *A. hypogaea* are cultivated. Spermatogonia and aecia have not been reported for *Pu. arachidis*, which is considered brachycyclic and autoecious. *Puccinia arachidis* spreads in the field by repeated cycles of urediniospores that are dispersed by wind and rain.

Crown rust of oats (*Avena sativa*) caused by *Puccinia coronata* and **leaf rust of wheat** (*Triticum aestivum*) caused by *Puccinia*

graminis are two species that demonstrate the diagnostic difficulties and taxonomic confusion that surround the cereal rusts. *Puccinia coronata* has been reported from about 290 species of grass (Nazareno *et al.* 2018, Liu & Hambleton 2013). *Puccinia graminis* has been reported on hosts in 77 grass genera (Cummins 1971). The emergence of the Ug99 race of *Pu. graminis* on wheat has been a threat to wheat production worldwide for more than a decade, with the potential to cause crop losses on widely used varieties that are not resistant (Singh *et al.* 2015a).

Puccinia coronata and *Pu. graminis* share some similar characteristics in that each (i) causes economic diseases on some cultivated grasses; (ii) is macrocyclic and heteroecious; and (iii) has been divided into numerous *formae speciales* based on host identity. Taxonomic resolution of species of *Puccinia* on grasses remains mostly unresolved, by molecular methods alone or in combination with morphology, host range, host taxonomy, and geographic origin. One exception is the excellent work of Liu & Hambleton (2013), who used a polyphasic approach to resolving taxonomic issues in *Puccinia coronata* s. lat. The inevitable molecular phylogenetic solutions have been complicated by agriculture and the global movement of populations. Complex species or species complex well applies.

Orange rust of sugarcane (*Saccharum* spp. and cultivated hybrids) caused by *Puccinia kuehnii* is endemic in the southeast Asian and Oceania regions. *Puccinia kuehnii* is hemicyclic, producing only teliospores and urediniospores on *Saccharum* and some closely related grass genera (*Erianthus*, *Sclerostachya*, *Narenga*) (Ryan & Egan 1989). In 2000, *Pu. kuehnii* was responsible for the largest single-season loss (200 million AUS dollars) caused by a disease in the history of the Australian sugarcane industry (Magarey *et al.* 2001).

Rust on Asteraceae (*Asteroideae*) caused by *Puccinia lagenophorae* is an example of an endemic Australian rust that has spread worldwide infecting about 150 species (Scholler *et al.* 2011, McTaggart *et al.* 2014). *Puccinia lagenophorae* has spread to Europe (Mayor 1962), North America (Scholler *et al.* 2001) and South America (Delhey *et al.* 1988). *Puccinia lagenophorae* is an autoecious species that forms aecia and telia.

Rust of Noogoora burr (*Xanthium pungens*) caused by *Puccinia xanthii* was considered a biological control agent for this introduced weed in Australia prior to its detection in 1975 (Alcorn 1976). *Puccinia xanthii* is native to North America where it is widespread and commonly infects Noogoora burr, *Ambrosia trifida* (giant ragweed), and other plants in the tribe *Heliantheae* of the *Asteraceae* (Morin *et al.* 1993). *Puccinia xanthii* is microcyclic and autoecious.

Research interests

Puccinia species were collectively listed in the top 10 plant pathogens based on socio/economic importance in a survey of plant pathologists conducted by *Molecular Plant Pathology* (Dean *et al.* 2012). There are 3 123 publications and 25 970 citations from 2011–2021 in the Web of Science (Fig. 57), with the top 10 most cited articles shown in Table 35.

Research into *Puccinia* is dominated by studies on the wheat infecting *Puccinia* spp. This research covers the threats that cereal rusts pose to global food production (Huerta-Espino *et al.* 2011, Singh *et al.* 2011, Wellings *et al.* 2011, Savoury *et al.* 2019) as well

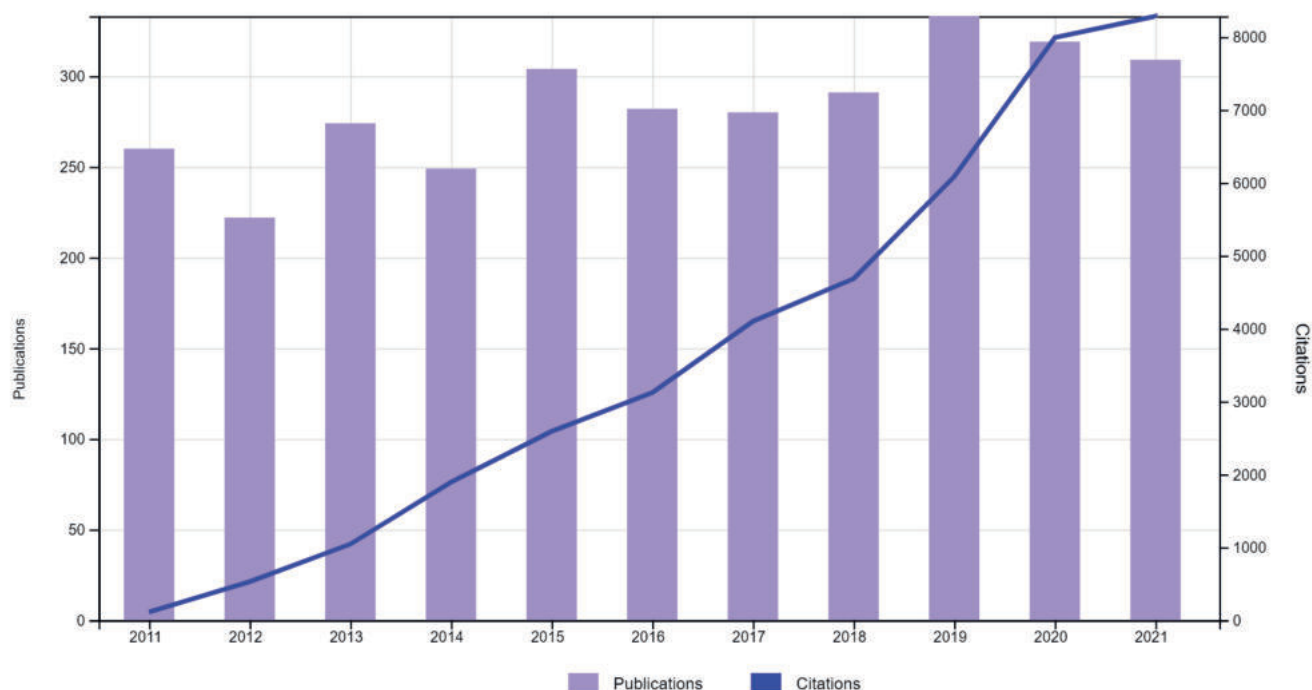


Fig. 57. Trends in research of *Puccinia* in the period 2011–2021.

Table 35. Top 10 cited articles related to *Puccinia* published in the period 2011–2021.

Rank	Article	No. of citations	References
1	The top 10 fungal pathogens in molecular plant pathology	1 769	Dean <i>et al.</i> (2012)
2	The global burden of pathogens and pests on major food crops	524	Savary <i>et al.</i> (2019)
3	Obligate biotrophy features unraveled by the genomic analysis of rust fungi	415	Duplessis <i>et al.</i> (2011)
4	The emergence of Ug99 races of the stem rust fungus is a threat to world wheat production	390	Singh <i>et al.</i> (2011)
5	Evaluation of the antibacterial potential of liquid and vapor phase phenolic essential oil compounds against oral microorganisms	346	Wang <i>et al.</i> (2016e)
6	Global status of stripe rust: a review of historical and current threats	314	Wellings <i>et al.</i> (2011)
7	The two-speed genomes of filamentous pathogens: waltz with plants	240	Dong <i>et al.</i> (2015)
8	One stop shop: backbones trees for important phytopathogenic genera: I (2014)	235	Hyde <i>et al.</i> (2014)
9	The gene Sr33, an ortholog of barley Mla genes, encodes resistance to wheat stem rust race Ug99	226	Periyannan <i>et al.</i> (2013)
10	Global status of wheat leaf rust caused by <i>Puccinia triticina</i>	217	Huerta-Espino <i>et al.</i> (2011)

as insights into how these threats may be mitigated (Periyannan *et al.* 2013, Watson *et al.* 2018, Dinh *et al.* 2020).

Authors: R.G. Shivas and A.R. McTaggart

30. *Cordyceps* Fr., *Observ. Mycol. (Havniae)* 2: 316 (cancellans). 1818.

Type species: Cordyceps militaris Fr.

Classification: Ascomycota, Pezizomycotina, Sordariomycetes, Hypocreales, Cordycipitaceae.

Background

Cordyceps is a hypocrealean entomogenous genus, parasitising several orders of arthropods from larva to adult stages (Sung *et al.* 2007, Shrestha *et al.* 2016, Araújo & Hughes 2016) and

comprises 280 recognised species (Index Fungorum 2022). It is named after the Latin “*cord*” meaning club and “*ceps*” meaning head, as it describes the club-shaped stroma emerging from the insect larva as depicted in *Cor. militaris*. In the past, taxonomic classifications were mainly based on morphological characters on the host and were extensively studied by Kobayasi (1941, 1982) and Mains (1958). Less than two decades ago *Cordyceps s. lat.* belonged to the family *Clavicipitaceae s. lat.* characterised by the presence of cylindrical asci, thickened ascus apices, and filiform ascospores that often disarticulate into secondary ascospores (Mains 1958, Kobayasi 1941, 1982, Rossman *et al.* 1999, Sung *et al.* 2007).

This genus is the most diverse group of *Clavicipitaceae s. lat.* due to the large number of species and wide host range. Understanding the evolutionary relationships and host-switching over the past decades have come through molecular studies and these have provided stable phylogenies. The analyses of multi-gene sequences to reconstruct the phylogeny of *Cordyceps*, including

the morphologies of its sexual and asexual morph, led Sung *et al.* (2007) to split *Cordyceps s. lat.* into three families, *Clavicipitaceae*, *Cordycipitaceae*, and *Ophiocordycipitaceae*.

Cordyceps militaris, the type species, is nested in the *Cordycipitaceae*; it is a cosmopolitan species reported from North and South America, Europe and Asia (Mains 1958, Shrestha *et al.* 2005a). Most species in *Cordyceps* have been reported from several countries in Asia such as China, Japan, Korea, Nepal, Taiwan and Thailand, while others have been reported from Europe, South America (Columbia), and North America (Kobayasi & Shimizu 1978, 1982).

Cordyceps species are parasitic on spiders (*Araneae*) and insects belonging to orders *Coleoptera*, *Diptera*, *Hemiptera*, *Hymenoptera*, *Lepidoptera* and *Orthoptera*, in which infections occur at various stages of the arthropod life cycle from larvae to adults (Torres *et al.* 2005, Liang *et al.* 2008, Cabanillas *et al.* 2013, Yan & Bau 2015, Tasanathai *et al.* 2016, Chiriví *et al.* 2017, Mongkolsamrit *et al.* 2018, 2020b, Crous *et al.* 2019b, Zha *et al.* 2019). *Cordyceps* species are characterised by fleshy, pallid to bright yellow, orange or red stromata with crowded or loosely embedded perithecia. Three kinds of ascospore morphologies are known: (1) bola-shaped, whole ascospores characterised by a thin filamentous middle part and fusiform ends, like a skipping rope, (2) filiform, multiseptate, whole ascospores, and (3) filamentous, multiseptate ascospores disarticulating into part-ascospores (Tasanathai *et al.* 2016, Mongkolsamrit *et al.* 2018, 2020b, Crous *et al.* 2019b, Zha *et al.* 2019). The asexual morph associated with *Cordyceps* includes species in *Isaria*, *Lecanicillium*, and *Evlachovaea*.

Ecological and economic significance

Bioactive compounds and medicinal value

The past decades have witnessed an increasing interest in seeking bioactive compounds from *Cordyceps* species. *Cordyceps militaris* is a renowned traditional Chinese medicine and edible fungus, receiving considerable attention due to its plentiful bioactive compounds (Chiu *et al.* 2016). Experimental evidence has shown that *Cor. cicadae* (*Isaria cicadae*), *Cor. takaomontana*, *Cor. pruinosa* and *Cor. kyushuensis* possess similar biological activity and chemical composition as found in *Cor. militaris* and *Ophiocordyceps sinensis* (Lee *et al.* 2009, Ling *et al.* 2009, Kim *et al.* 2010, Deng *et al.* 2020, Nxumalo *et al.* 2020). The aforementioned *Cordyceps* species have been successfully cultivated *in vitro* and advanced progress has been made in their pharmacological research (Xiao *et al.* 2004, Gui & Zhu 2008, Hama *et al.* 2019, Li *et al.* 2019d, Zhao *et al.* 2019b).

Many pharmacological experiments have been conducted based on aqueous, ethanolic and methanolic extracts from sporocarps, cultured mycelia and fermentation broth (Zhou *et al.* 2009). These crude extracts exert broad biological activities, such as anti-ageing, anti-bacterial, antifungal, antihypertensive, anti-inflammatory, anti-lupus, antimalarial, anti-metastatic, antioxidant, antiproliferative, antithrombotic, anti-tumour, antiviral, hepatic-protective, hypoglycaemic, hypolipidaemic, immunomodulatory, insecticidal, neuroprotective, renal-protective, *etc.* (Ng & Wang 2005, Zhang *et al.* 2006, Lee *et al.* 2015, Kim *et al.* 2017, Jin *et al.* 2018, Hu *et al.* 2019, Ke & Lee 2019, Liu *et al.* 2019c). To understand the pharmacological mechanism of these raw extracts, an array of effective components has been purified and their structure and biological activities elucidated (Zhou *et al.* 2009, Zhao *et al.* 2014a). These components include adenosine, amino acids, carotenoids, cordycepic acid, cordycepin, cyclic dipeptides,

ergosterol, fatty acids and their derivatives, lectins, nucleosides, nucleotides, phenolic compounds, polyamines, polysaccharides, proteins, proteoglycans, saccharides, steroids, sterols, sugar derivatives, terpenoids, vitamins and metal elements, volatile components, *etc.* (Cheng *et al.* 2011, Zheng *et al.* 2012, Dong *et al.* 2013, Cohen *et al.* 2014, Zhao *et al.* 2014a, Nallathamby *et al.* 2015, Yin *et al.* 2018b, Zhu *et al.* 2016, Wang *et al.* 2017a, Lu *et al.* 2019, Singpoonga *et al.* 2020, Zhang *et al.* 2020a).

Biological control

Cordyceps farinosa (syn. *Isaria farinosa*) and *Cor. fumosorosea* (syn. *I. fumosorosea*) are entomopathogenic fungi that have shown great potential in the control of a wide range of insect pests (Zimmermann 2008). *Cordyceps fumosorosea* under laboratory conditions was able to control the solanum whitefly *Aleurothrixus trachoides*, a polyphagous pest known to attack more than 70 crops worldwide. It is also effective against ambrosia beetles, *Anisandrus dispar* and *Xylosandrus germanus* (*Coleoptera: Curculionidae: Scolytinae*), which are significant pests of hazelnuts. There are important reports that nymphs and adults of *Bemisia tabaci* are also highly sensitive to *Cor. fumosorosea* (Avery *et al.* 2010, Mascarin *et al.* 2014, Murillo-Alonso *et al.* 2015, Tian *et al.* 2015). Due to its safety to non-target organisms and humans, despite its broad insecticidal activity and host range, *Cor. fumosorosea* has been commercialised for the management of various insect pests, causing a significant reduction in insect pest population (Ali *et al.* 2010a, b, 2017, Huang *et al.* 2010).

Research interests

There are 2 073 publications and 23 831 citations from 2011–2021 in the Web of Science (Fig. 58), with the top 10 most cited articles shown in Table 36. The publications are mostly about the bioactive compounds produced by *Cor. militaris* for pharmacological and therapeutic implications, as well as the potential use in biological control, diversity, and taxonomy.

Pharmacological and therapeutic implications

Cordycepin (3'-deoxyadenosine) is a crucial bioactive compound commonly found in *Cordyceps* species (Zheng *et al.* 2011a, Cohen *et al.* 2014). Clinical trials have shown that cordycepin exhibits therapeutic potential against many types of cancers (Khan & Tania 2020). With these properties, cordycepin is considered an important supplement or substitute medicine drug for cancer treatment (Jin *et al.* 2018). The market price of cordycepin has reached more than 500 000 US dollars per kilogram (Yang *et al.* 2020). To satisfy market needs, the metabolic pathways and synthesis mechanism of some important compounds, such as carotenoid and cordycepin, including their antioxidant and anti-ageing activities have been elucidated (Liu *et al.* 2020b, Wang *et al.* 2020e, Zhu *et al.* 2020c), which could facilitate the mass production of target compounds. Additionally, the optimisation of culture conditions and the extraction process has enabled the harvest of more sporocarps and the production of more target bioactive compounds (Chou *et al.* 2020). *Cordyceps* species typically have fleshy sporocarps, for which different drying approaches have been exploited to prolong their shelf life and retain their commercial value (Wu *et al.* 2019e).

Toxins and other secondary metabolites

Although there has been a lot of research on the application of various bioactive metabolites isolated from *Cordyceps* spp.

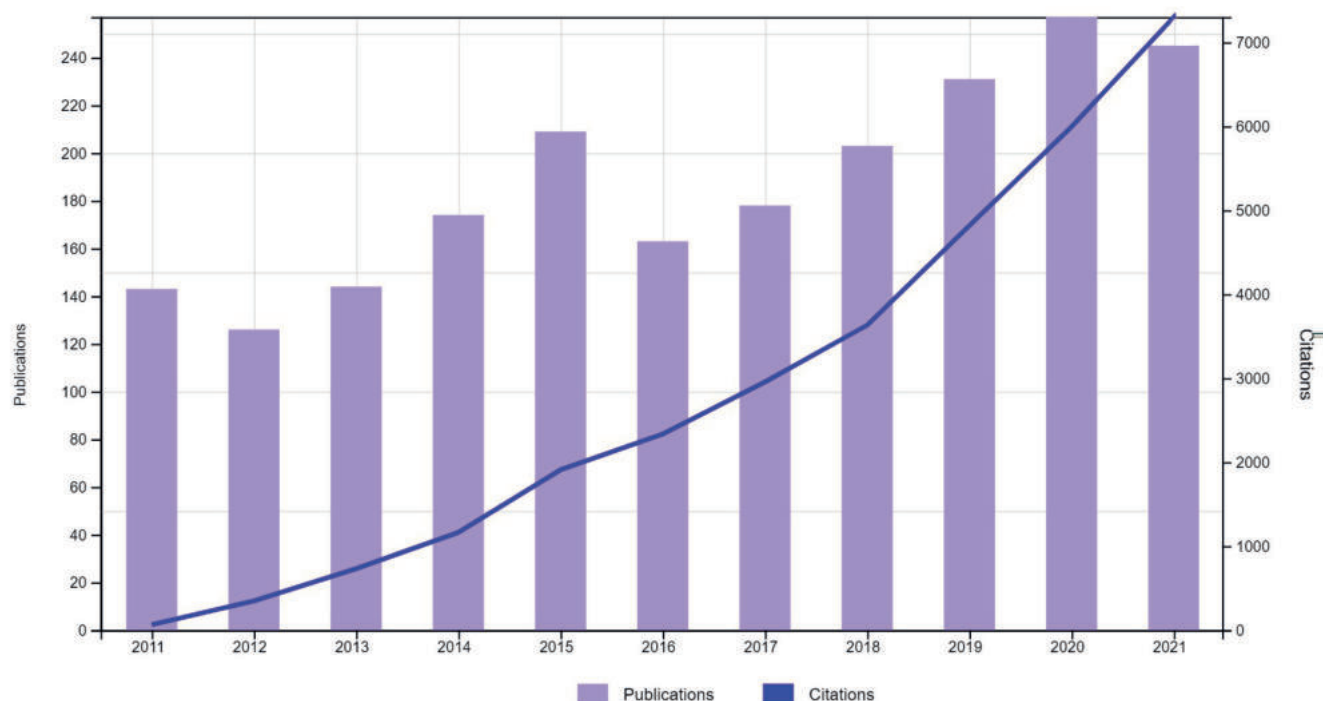


Fig. 58. Trends in research of *Cordyceps* in the period 2011–2021.

Table 36. Top 10 cited articles related to *Cordyceps* published in the period 2011–2021.

Rank	Article title	No. of citations	References
1	Tissue invasion and metastasis: molecular, biological and clinical perspectives	281	Jiang <i>et al.</i> (2015)
2	Genome sequence of the insect pathogenic fungus <i>Cordyceps militaris</i> , a valued traditional chinese medicine	275	Zheng <i>et al.</i> (2011a)
3	Recent developments in mushrooms as anti-cancer therapeutics: a review	216	Patel & Goyal (2012)
4	A review on the effects of current chemotherapy drugs and natural agents in treating non-small cell lung cancer	191	Huang <i>et al.</i> (2017)
5	Cordycepin: a bioactive metabolite with therapeutic potential	167	Tuli <i>et al.</i> (2013)
6	A phylogenetically-based nomenclature for <i>Cordycipitaceae</i> (<i>Hypocreales</i>)	139	Kepler <i>et al.</i> (2017)
7	Toll-like receptor 4-related immunostimulatory polysaccharides: primary structure, activity relationships, and possible interaction models	111	Zhang <i>et al.</i> (2016f)
8	Advances in fundamental and applied studies in China of fungal biocontrol agents for use against arthropod pests	106	Wang & Feng (2014)
9	Enhancement of the antioxidant capacity of chickpeas by solid state fermentation with <i>Cordyceps militaris</i> SN-18	101	Xiao <i>et al.</i> (2014b)
10	Induction of apoptosis by cordycepin via reactive oxygen species generation in human leukemia cells	83	Jeong <i>et al.</i> (2011)

to develop biocontrol agents or to use in traditional Chinese medicine, safety and health issues in the consumption and use of these fungi have long been a concern. Thus, research on their secondary metabolites (SMs) is considered beneficial to improving the safety of these fungal products. In the case of *Cor. cicadae* (syn. *Isaria cicadae*), its SMs mainly include nucleosides, amino acids, beauvericins, myriocin, and oosporein while trichothecene derivatives, isariotins, cyclopenta benzopyrans and PKs are found in *Cor. tenuipes* (syn. *Isaria tenuipes*, *Paecilomyces tenuipes*). Among them, beauvericins, myriocin, oosporein and many trichothecene derivatives are toxic compounds. Most of these SMs for pharmaceutical or beneficial uses are dependent on the dose and can show cytotoxicities, neurological toxicities and or toxicological effects in humans and animals (Zhang *et al.* 2019c, Chen *et al.* 2020a).

Taxonomy and phylogeny

Cordyceps is a genus with diverse sexual and asexual morphologies. The sexual morphs of *Cordyceps* vary in the structure of the stromata, possessing brightly coloured, fleshy stromata as in the type species, *Cor. militaris* or having pallid stromata as in the case of many spider pathogens. There is no evident morphological difference between species found in *Cordyceps*, *Blackwellomyces*, *Flavocillium* and *Samsoniella* in *Cordycipitaceae* (Mongkolsamrit *et al.* 2018, 2020b, Wang *et al.* 2020f). The sexual morphs are known as *isaria*-, *evlachovaea*-, or *lecanicillium*-like. Species used in traditional Chinese medicine, e.g., *Cordyceps cicadae*, known as “chanhua” or cicada flower, or producing a compound that could be used in medicine, e.g., *Isaria sinclairii* (syn. *Cordyceps sinclairii*) producing myriocin have turbulent taxonomic histories and proper identification of these species are imperative for further applications.

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