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(Article begins on next page)

The efficacy of berries against lipopolysaccharide-induced inflammation: a review

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ABSTRACT

Background: an increasing number of epidemiological studies highlights a remarkable association between a diet rich in fruits and vegetables and a lower incidence of different inflammatory-related pathologies. Berries represent an interesting source of phytochemicals and nutrients, widely investigated for their role in health promotion and disease prevention.

Scope and approach: the aim of this review was to summarize and update the effect of different berry extracts, their fractions and single bioactive compounds against the inflammatory status promoted by the Gram-negative bacteria endotoxin lipopolysaccharide (LPS). The main molecular mechanisms involved have been elucidated, focusing particular attention on the biological response evoked in different *in vitro* and *in vivo* models.

Key Findings and Cocnlusions: the inhibition of inflammatory response mediated by MAPK and NF-kB is the main molecular pathway involved in berries anti-inflammatory role, expecially in grape and blueberry which represent the main investigated fruits, improving antioxidant defence and exerting beneficial effects in the maintenance of healthy conditions in LPS-treated models.

KEYWORDS

Berries, LPS, anti-inflammatory effects, antioxidant role

1. INTRODUCTION

An increasing number of epidemiological studies highlights a remarkable association between a diet rich in fruits and vegetables and a lower incidence of different chronic pathologies, such as obesity, infections, cancer, cardiovascular and neurodegenerative diseases, in which a sustained pro inflammatory state is the major contributing factor to their development, progression and complication (Joseph et al., 2014). Focusing on fruits, it is quite complex to explain their potential health benefits, given their wide variety available for consumption and their complex composition. For these reasons, in recent decades, individual subgroups of fruits have been taken into account, in order to facilitate the observation and promote their specific health benefits. Among these, berries represent the richest fruits in natural compounds, including minerals, vitamins, dietary fibers and polyphenolic phytochemicals. In the last few years, these compounds have attracted considerable attention due to their antioxidant properties, potential in health promotion and disease prevention, thus improving safety and consumer acceptability (Alvarez-Suarez et al., 2014; Forbes-Hernandez et al., 2016; Muceniece et al., 2019). In addition, edible berries may represent a potential important contribution to the intake of fresh fruit for the populations in countries where, as declared by World Health Organization, there is a limited availability of fruits and vegetables, as in northern latitudes (Bazzano, 2005). For this reason, in this review we have summarized the latest 10 years developments on the activities of berries from *in vitro* (Table 1) and *in vivo* (Table 2) studies, on animal and humans, against the inflammatory status and its main related pathologies, with particular attention on lipopolysaccharide (LPS) as inflammatory agent ~~**(Table 1)**~~. The research of the article has been performed using the database PubMed, and typing as keywords “type of berry (i.e. strawberry) and lps”. Only the studies from 2011 to 2020 has been collected and reported in the manuscript.

1.1. OXIDATIVE STRESS AND INFLAMMATION

In physiological conditions, inflammation is the common, protective and temporary response of the innate immune system to pathogens and injury stimuli (Joseph et al., 2014). On the contrary, the interaction of the cellular immune system with endogenous or exogenous antigens results in the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), leading to signalling cascades that can result in hyperactivation of inflammatory responses, inducing tissue damage and oxidative stress phenomena, which represent the main contributing factors to the development, progression and complication of the most known diseases. Quantifiable inflammatory responses are characterized by the production of cytokines, which act as signals between immune cells to coordinate the inflammatory response, and they can play a pro- inflammatory role, such as interleukin (IL)-1β, IL-6 and tumour necrosis factor-α (TNF-α) or anti- inflammatory role, like IL-10 (Joseph et al., 2014). The central orchestrator of the inflammatory response is nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), a redox-sensitive transcription factor, responsible of cytokine and other inflammatory molecules production (Joseph et al., 2014). Other important mediators of inflammation include pattern recognition receptors such as Toll-like receptors (TLR) and kinases, such as mitogen-activated protein kinase (MAPK).

Inflammation can be elicited by different stimuli, such as endotoxins (i.e., LPS from bacteria), changes in ROS levels, viruses, fatty acids, cellular redox status, cytokines, growth factors and carcinogens (Giampieri et al., 2018). The LPS molecule in particular is essential for the viability of most Gram-negative bacteria, exerting a crucial role in the outer-membrane integrity as a permeability barrier, protecting bacteria from toxic molecules, bile salts and lipophilic antibiotics which can be found in several sources, including foods, infections and commensal microbiota (Mayer et al., 1985). In human body, the main source of LPS is the gut. Even if LPS has a strong affinity for chylomicrons and is able to cross easily the gastrointestinal mucosa, under physiological conditions, the intestinal epithelium defends itself from LPS translocation. The absorption of LPS through the intestinal barrier seems to be enhanced by an high-fat diet: dietary fats in fact deeply increase LPS absorption through the modification of the gut microbiota, raising the amount of chylomicrons and increasing the permeability of the gastrointestinal mucosa (Manco et al., 2010). In this context, LPS can be considered an important factor directly involved in the onset of obesity induced by a rich-fat diet and type 2 diabetes, as showed in many studies performed on animal models (Laugerette et al., 2012; Mani et al., 2013) and human subjects (Pendyala et al., 2012, Harte et al., 2012). For all these reasons, the modulation of the inflammatory response by potential food components may represent a strategic tool to avoid immune disorders and maintain health and wellness (Giampieri et al., 2018).

2. BERRIES

Berries are a common worldwide functional fruit and represent a relevant source of micronutrients and nonessential phytochemicals, especially polyphenols (Prasain, et al., 2020; Agudelo et al., 2019; Afrin et al., 2016; Mazzoni et al., 2016). In recent decades, berry phenolics have attracted considerable attention and have been subjected to extensive research due to their antioxidant properties, their ability to detoxify reactive oxygen and nitrogen species, blocking their production, and to repair oxidative DNA damage. Interesting results were also obtained in in counteracting neurodegenerative diseases: dietary intakes of berries were demonstrated to improve memory, protecting the brain against cognitive loss (Morris et al., 2015). All these effects play a synergistic and cumulative role in human health promotion and disease prevention, thus improving safety and consumer acceptability (Afrin et al., 2016; Mazzoni et al., 2016). For these reasons, the improvement of the nutritional quality of berries has become an innovative quality target of breeding and biotechnological strategies, with the aim to control or increase the content of potential health-related compounds in fruits (Mazzoni et al., 2016).

2.1. BIOACTIVE COMPOUNDS AND ANTIOXIDANT CAPACITY OF BERRIES

A diet rich in antioxidant compounds derived from fruits and vegetables, such as the Mediterranean one, can strongly influence the susceptibility to oxidative stress, counteracting the reduction of antioxidant protection that occurs during pathological conditions. Berries, an important fruit in the Mediterranean diet, are among the richest fruits in nutritive compounds, which possess strong antioxidant and anti-inflammatory effects that may reduce sensitivity to oxidative stress (Battino et al., 2019). These fruits are particularly rich in phenolic acids, benzoic acid and derivatives of cinnamic acid, stilbenes, lignans, flavonoids (including anthocyanins), flavonols and flavanols, condensed tannins and hydrolyzable tannins, vitamins, folate, alkaloids, carotenoids, xanthones and polysaccharide (Afrin et al., 2016). The distribution and the type of these different compounds are affected by different factors, including genetic and environmental factors, chemical structures, degree of oxidation and substitution patterns of hydroxylation, abilities to exist as stereoisomers, glycosylation by sugar moieties and other substituents and conjugation to form polymeric molecules (Seeram, 2006). The comprehension of the link between the antioxidant capacity of individual components and the bioactivities of different berries may address the biotechnological improvement of new berry varieties.

2.2. BIOAVAILABILITY AND METABOLITES OF BERRIES

Taking into account the bioavailability of berries bioactive compounds, it is interesting to underline that phenolic compounds of berry are able to survive to digestion in the upper digestive tract and reach different parts of the proximal and distal colon in substantial dose (Wiczkowski et al., 2010). The bioavailability of anthocyanins is very poor and only trace levels can be identified in plasma and urine after absorption and excretion (Felgines et al., 2003). Dietary ellagitannins are hydrolyzed to yield ellagic acid, which is consequently metabolized by colon bacteria to various urolithins, in the distal part of the small intestine and in the colon (Del Rio et al., 2013). Finally, dietary antioxidants, like vitamin C and E and few carotenoids are absorbed in the upper segments of the intestine (Scalbert & Williamson, 2000).

3. BIOLOGICAL ACTIVITIES OF BERRIES AGAINST LPS-INDUCED STRESS: *IN VITRO* AND *IN VIVO* STUDIES

An increase number of evidences has been focused on determining the possible mechanisms for counteracting the LPS-mediated inflammatory response. Different *in vitro* and *in vivo* models have assessed the efficacy of the whole berry extracts, fractionated berry extracts, single bioactive compounds or purified/commercial berries on different LPS-inflammatory models (**Table 1**).

3.1. ELDERBERRY

Elderberry (*Sambucus* spp.) is a widespread species of the Caprifoliaceae family, which are widely grown in Europe, Asia, North Africa and North America. Elderberry cultivars contain high concentrations of anthocyanins and flavonoids, which exhibit antioxidant, cardioprotective, anticarcinogenic, anti-inflammatory, immunomodulating activity, anti-diabetic, antibacterial, antiallergic and antiviral properties (Walker et al., 2013; Simonyi et al., 2015).

The phenolic compounds and ethanolic extracts from elderberry pomace showed high antioxidant and anti-inflammatory responses in human gingival fibroblasts (HGF-1) and human U-937 monocytes, where the pro-inflammatory cytokines, IL-6, IL-8, the matrix metalloproteinases-2 (MMP-2) and MMP-9 were inhibited by methanolic extracts treatment (Walker et al., 2013). In macrophges obtained from BALB/c mice intraperitoneally injected with 20 mg LPS, methanolic elderberry extract reduced NO production (Carneiro et al., 2019), while the ethanol crude extracts from elderberry and the isolated anthocyanins and procyanidins fractions showed strong complement fixating activity and strong inhibitory activity on NO production in LPS-activated RAW cells and murine dendritic D2SC/I cells (Ho et al., 2017).

3.2. WOLFBERRY OR GOJI BERRY

The fruit of *Lycium barbarum* L. (Solanaceae), usually known as wolfberry or Goji berry, is an important herbal medicine as well as tonic, used widely in East Asia, with increasingly popularity in Europe and North America. *Lycium barbarum* polysaccharides (LBP) is one of the major ingredients responsible for different biological activities (Teng et al., 2013; Huang et al., 2019).

LBP showed neuroprotective effects against LPS-induced inflammatory injury in mouse microglial cells, by reducing the levels of caspase 3, TNF-α and heat shock protein (HSP) 60 through the inhibition of NF-kB pathway (Teng et al., 2013). Similarly, neuroprotective effects have been demonstrated in a rat model of sepsis, where LBP attenuated inflammation injury in the kidney via the possible regulation of Keap1-Nrf2/ARE signalling (Huang et al., 2019; Wu et al., 2020). The protective effects and potential molecular mechanisms of LBP against LPS-induced acute respiratory distress syndrome were also detected in mice and in human pulmonary microvascular endothelial cells, through a reduction in lung inflammation and pulmonary edema *in vivo*, significantly reversing the LPS-induced decrease in cell viability, increase in apoptosis and oxidative stress *in vitro* (Chen et al., 2018).

The inhibitory effects of *L. ruthenicum* polysaccharide were investigated on pro-inflammatory mediators in LPS stimulated RAW264.7 macrophages (Peng et al., 2014). The extract significantly inhibited the production of NO, TNF-α and IL-6 and reduced the expression of inducible nitric oxide synthase (iNOS), through the inhibition of TLR-4/NF-κB signaling pathways (Peng et al., 2014). Similar results were obtained with Lycium fruit water extract, in which the anti-inflammatory mechanisms were accomplished by the inhibition of ERK1/2, p38 and JNK MAPKs phosphorylation as well as the suppression of nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (IκBα) degradation and NF-κB upon LPS stimulation (Oh et al., 2012).

3.3. ACAIBERRY

Açai (*Euterpe oleracea* Mart.), one of the most economically significant palm species in the Brazilian Amazon, has widely attracted the attention of the researchers for its nutritional and phytochemical composition. Anthocyanin-rich açai pulp fractions have been examined for their protective effect on LPS-induced oxidative stress and inflammation in BV-2 mouse microglial cells, highlighting a downregulation of the expression of iNOS, cyclooxygenase (COX) 2, p38-MAPK, TNF-α and NF-κB in a concentration-dependent manner (Pouolose et al., 2012). Likewise, Açai polyphenols prevented LPS-induced generation of ROS, mRNA and of pro-inflammatory genes expression in human vascular endothelial cells (HUVEC) and in colon myofibroblasts CCD-18Co cells (Noratto et al., 2011; Dias et al., 2015). Similar results were found in an immortalized rat astrocyte cell line, where Açai extracts down-regulated LPS-induced NF-kB signalling and up-regulated the Nrf2/ARE activities (Ajit, et al., 2016).

3.4. EMBLIC

Emblic fruit (*Phyllanthus emblica* L.), known as amla, represents a potential functional food due to its numerous pharmacological applications, with hydrolyzable tannins and flavonoids that represent the major bioactive compounds. It is commonly used in the Indian traditional Ayurvedic and unani medicine literature (Rao et al., 2013). The effects of amla fruit extract have been investigated in LPS-treated RAW macrophages, amla fruit extract powder decreased ROS production and reduced NF-kB, iNOS and COX-2 expressions (Sato et al., 2018; Wang et al., 2019). Similarly, the *in vivo* anti-inflammatory effects of this berry were tested in a LPS-induced endotoxaemia rat model, in which oral administration of the amla extract remarkably decreased the serum levels of pro-inflammatory TNF-α and IL-6 cytokines (Rao et al., 2013).

3.5. LINGONBERRY

Lingonberries (*Vaccinium vitis-idaea* L.), native to Scandinavia, Alaska and Canada, possess a complex polyphenolic profile consisting principally of a mixture of flavan-3-ols and proanthocyanidins with remarkably antioxidant, antimicrobial, antiadhesive, and anti-inflammatory effects (Kylli et al., 2011; Afrin et al., 2016). Lingonberries crude extract and its proanthocyanidins-rich phenolic fraction showed protective effects against LPS-induced inflammation in RAW 264.7 (Grace et al., 2014, Esposito et al., 2019) and J774 macrophages (Kylli et al., 2011), through the reduction of NO production and COX-2, iNOS and pro-inflammatory cytokine expressions (Grace et al., 2014, Esposito et al., 2019). Similar results were also obtained in LPS-induced astrocytic damage, where lingonberry extract exerted a glioprotective effect through an anti-oxidative mechanism in both reversal and prevention models, attenuating ROS, nitrite levels and acetylcholinesterase activity and increasing cellular viability, thiol content and SOD activity, corroborating the historic use of this berry as medicinally important foods mainly in Alaska Native communities (Pacheco et al., 2018).

3.6. CHOKEBERRY

Chokeberries (*Aronia melanocarpa* L.) have attracted substantial attention thank to their high polyphenolic content, including procyanidins, anthocyanins and phenolic acids. Appel et al. (2015) investigated the role of polyphenol-rich chokeberry juice concentrate in LPS-treated human primary monocytes isolated from peripheral blood and RAW264.7 macrophages. The obtained results indicated that chokeberry extract significantly inhibited the release of TNF-α, IL-6 and IL-8 in human monocytes and the activation of the NF-κB pathway in macrophages. Similar results were recently obtained in LPS-treated BV2 cells and in mice received a single intraperitoneal injection of LPS, where black chokeberry ethanolic extract significantly reduced tissue damage in the hippocampus by downregulating iNOS, COX-2 and TNF-α levels, highlighting its protective and anti-inflammatory role against LPS-induced stress (Lee et al., 2018).

3.7. SEABUCKTHORN

Seabuckthorn (*Hippophae rhamnoides* L.) is a high-altitude medicinal plant used for a long history in Tibetan folk medicine (Du et al., 2017) with a large number of nutrients, phytochemicals, and bioactive substances like vitamin C. Only one study investigated the anti-inflammatory role of this berry in stress condition, highlighting significant protection against LPS-induced acute lung injury in mice treated with seabuckthorn berries paste, through maintaining redox homeostasis, with a mechanism involving Nrf2 nuclear translocation and activation (Du et al., 2017).

3.8. GRAPE

Grapes (*Vitis vinifera L.*) represent one of the most popular and consumed berries in the world. They are particularly rich in phytochemicals, mainly phenolic acids, stilbenes (resveratrol), anthocyanins, and proanthocyanidins with remarkable antioxidant and anti-inflammatory properties (Zunino et al., 2014; Afrin et al., 2016). The efficacy of grape, and its different fraction/extract, against LPS-induced stress has been widely investigated in different *in vitro* and *in vivo* models. Grape seeds procyanidins extract (GSPE) efficiently counteracted the LPS-induced inflammatory stress in RAW macrophages reducing (i) pro-inflammatory cytokines expression, (ii) NO production and (iii) NF-κB and MAPK signalling pathway activation (Bak et al., 2013; Perez et al., 2015).

In macrophages and microglia cells, GSPE showed protective effect against LPS-promoted stress, reducing the LPS-induced TLR-4 activation (Kim et al., 2018). Similar results were obtained in LPS-treated rat hepatic stellate cell line and human ovarian cancer cells, in which GSPE reduced the activation of protein kinase B (AKT)/NF-kB and MAPK/ERK pathways, induced by LPS (Zhao et al., 2013; Jiang et al., 2017). Finally, in rats treated with various doses of GSPE the LPS-induced inflammation was efficiently reduced by inhibiting iNOS expression and inflammatory cytokines production, also preventing endotoxin-induced-intestinal inflammation (Pallares et al., 2013; Gil-Cardoso et al., 2019).

Additionally, interesting results were found with grape skin (GSE), grapefruit (GE), grape pomace (GPCE) and grape powder (GPE) extracts. GSE, GE and GPCE efficiently counteracted the inflammation in LPS-treated microglia cells, decreasing inflammatory cytokine levels (Pistol et al., 2018); in addition GSE exerted protective effect also in human primary monocytes, reducing LPS-stimulated tissue factor synthesis and fibrin formation in blood cells (Milella et al., 2012). In Sprague-Dawley rats, red and white GE efficiently counteracted the LPS-induced inflammation through the inhibition of liver NF-κB, iNOS and COX-2 expression (Nishiumi et al., 2012), attenuating the increase in serum secretory phospholipase A2 activity and the decrease in haematocrit level (Tsao et al., 2012).

~~GPE attenuated LPS-mediated inflammation in macrophages reducing (i) induction of inflammatory cytokines, (ii) activation of MAPKs, NF-kB and activator protein 1 (AP-1) pathway and (iii) decreasing the capacity of LPS-stimulated cells to inflame adipocytes and cause insulin resistance (Overman et al., 2010). Similar results were obtained in~~ In a mouse model of inflammation, ~~where~~ GPE suppressed the steady-state low levels of LPS-mediated inflammatory signalling, modulating NF-κB activity and cytokines production (Miller et al., 2018). On the contrary, in LPS-activated peripheral blood mononuclear cells from obese male and female volunteers, GPE increased the level of IL-1β and IL-6, suggesting that the grape consumption increased the sensitivity of the monocyte population to bacterial challenges. The increased sensitivity may represent an important tool by which fruit consumption could be beneficial to obese individuals which are particularly exposed to infection risks (Zunino et al., 2014).

Polyphenol fraction from grape and red wine also possessed interesting effect against LPS-induced inflammation. As showed by Rodriguez-Morgado et al. (2015) and Nicod et al. (2014) these fractions exhibited anti-inflammatory activities in microglia cells and human intestinal cells, significantly reducing the level of inflammatory cytokines in both cellular models.

Additionally, different studies investigated the role of single compound extracted from grape against LPS-induced inflammatory conditions. Among these, resveratrol, a natural polyphenol present in grape, red wines and contained in various food components, exhibits pleiotropic effects, being recognised as one of the most promising natural molecules in the prevention and treatment of chronic inflammatory disease (Panaro et al., 2012). In human chondrocytes resveratrol exerted its anti-inflammatory effects through the inhibition of different inflammatory mediators, such as prostaglandin E2 (PGE2), MMP and COX-2 (Wang et al., 2011). In a cortical network created with neurons and astrocytes, resveratrol treatment counteracted LPS-induced inflammation, reducing cytokine and iNOS production, thus suggesting a therapeutic potential for this compound in neurodegenerative diseases accompanied by microglial activation (Gullo et al., 2017). Similar results were obtained in LPS-treated Caco2 and human colon adenocarcinoma cell lines: in this case resveratrol significantly attenuated several components of the intestinal cells' response to pro-inflammatory stimuli (NO production and iNOS and TLR-4 expressions), underlying its potential therapeutic effect in the treatment of inflammatory bowel diseases (Panaro et al., 2012).

Finally, ~~resveratrol prevented LPS induced uveitis (EIU)-associated cellular and molecular inflammatory responses, by inhibiting oxidative damage and redox-sensitive NF-kB activation in male mice (Kubota et al., 2009). Also~~ in rabbit treated with LPS, resveratrol injection efficiently counteracted the development of inflammatory arthritis, through the reduction of PGE2, MMP-3, and MMP-13 expressions (Wang et al., 2011).

3.9. POMEGRANATE

Pomegranate (*Punica granatum L.*) is commercially cultivated in the Mediterranean region, the drier regions of Southeast Asia and the United States. It is a polyphenol-rich fruit with potential anti-inflammatory and antioxidant properties with antitumor, antibacterial, antifungal and antiulcer potentials (~~Kumar-Roiné et al., 2009;~~ Mastrogiovanni et al., 2019). Pomegranate exerted also beneficial role in a wide range of conditions where inflammation is believed to play an essential role. ~~For example, pomegranate peel fruit extracts reduced NO production and NF-κB and TNF-α expression in LPS-treated RAW macrophages (Kumar-Roiné et al., 2009).~~ Polyphenols present in the fruit, in the peel or in the husk extract of pomegranate, showed ~~also~~ anti-inflammatory properties in RAW macrophages and in colon CCD-18Co myofibroblastic cells, in Caco-2 cells and also in *ex vivo* porcine colonic tissue explants, by modulating inflammatory pathways and reducing the pro-inflammatory gene transcription and protein levels (Du et al., 2019), indicating their potential use in the treatment of inflammatory colitis disease and in the prevention of intestinal chronic inflammation (Kim et al., 2017a; Hollebeeck et al., 2012; Mastrogiovanni et al., 2019; Zhao et al., 2019). Polyphenol rich pomegranate extract efficiently counteracted also the LPS-induced pancreatitis in mice, through the reduction of TLR4, total NF-κB, IL-6 and TNFα and apoptosis, with the concomitant upregulation of Nrf2 mediated pathways (Gupta et al., 2019). Interesting anti-inflammatory results were also detected with punicalagin, an ellagitannin isolated from pomegranate polyphenols, abundant in the fruit husk and juice in significant quantities (Xu et al., 2014; Olajide et al., 2014). In LPS-treated RAW macrophages punicalagin treatment decreased NO and pro-inflammatory cytokine productions, via the suppression of TLR4-mediated MAPKs and NF-κB activation (BenSaad et al., 2017; Xu et al., 2014; Du et al., 2019), and with a mechanism that involved the downregulation of the FoxO3a/autophagy signaling pathway (Cao et al., 2019). Similar results were obtained in cultured astrocytes and microglial cells, suggesting its potential as a nutritional preventive strategy in neurodegenerative and neuroinflammatory disorders (Kim et al., 2017b; Olajide et al., 2014). *In vivo* models confirmed the results obtained *in vitro*: in LPS-treated mice punicalagin protected against different pathophysiological conditions, such as acute lung injury, memory impairment and oxidative stress perturbation in the process of spermatogenesis, suppressing NF-κB activation, preventing pro-inflammatory cytokine production and improving antioxidant defences (Peng et al., 2015; Kim et al., 2017b; Rao et al., 2016). Punicalagin also counteracted inflammation in kidney of LPS-treated rats, reducing oxidative/nitrative stress and apoptosis, attenuating the histopathological injury and ameliorating the endotoxemic acute damage (Frouad et al., 2016).

3.10. BILBERRY

Bilberry fruit (Vaccinium myrtillus L.) is a low-growing ericaceous dwarf sharb which belongs to the Ericaceae family and has been used in folk medicine for centuries. It has been found in Europe and north America and it is extensively studied as a source of anthocyanins and phenolic compounds, which possess protective effects on various pathophysiological conditions (~~Yao et al., 2010;~~ Afrin et al., 2016). Despite this, to date there are few studies which investigated the role of this berry in LPS-mediated inflammatory conditions. ~~In murine macrophages and in human monocytic cell line, bilberry treatments efficiently decreased the expression level of different inflammatory markers and the NF kB activation, evoked by LPS treatment (Chen et al., 2008a; Karlsen et al., 2010). Similar results were found in mice models, where~~ Reecently it has been showed that bilberry extracts counteracted the LPS-induced liver and eye injuries in mice models, through the reduction of NO production~~,~~ and the suppression of inflammatory markers ~~(Luo et al., 2014) and the promotion of antioxidant defences (Yao et al., 2010)~~.

3.11. STRAWBERRY

Strawberries (Fragaria X ananassa Duch.; family: Rosaceae) represent a remarkable source of phytochemicals (ellagic acid, anthocyanins, quercetin, and catechin), vitamins (ascorbic acid and folic acid), mineral and fibers (Afrin et al., 2016). They are produced in the Americas and, in particular, in the United States, confirming this country as the first manufacturer in the world, followed by Spain, Japan, Italy, Korea and Poland. Recent studies highlighted the potential role of strawberries on health promotion and disease prevention with particular attention to the effects against the most common diseases related to oxidative stress driven pathologies, such as cancer, cardiovascular diseases, type II diabetes, obesity and neurodegenerative diseases and inflammation (Giampieri et al., 2018; Amatori et al., 2016; Forbes-Hernandez et al., 2017). In particular strawberry extract showed protective effect against LPS-induced stress in murine macrophages (Gasparrini et al., 2017a; Liu et al., 2013; Van de Velde et al., 2019) and human dermal fibroblast cells (Gasparrini et al., 2017b; Gasparrini et al., 2018), through the reduction of ROS and NO, the inhibition of pro-inflammatiry cytokines production, the decrease of damage to lipid, protein and DNA with a concomitant improvement of antioxidant defences and mitochondria functionality, by a mechanism 5' AMP-activated protein kinase (AMPK)/NF-kB mediated. Interesting data were also collected with strawberry polysaccharides and hydrosylates: in LPS-treated macrophages, strawberry maintained health under inflammatory stress, by the inhibition of cytokines secretion (Liu et al., 2012a; Dia et al., 2014). Similar results were obtained in male Sprague-Dawley rats, where white strawberry aqueous extract reduced serum level of transaminase, alanine transaminase, aspartate transaminase, and inflammatory cytokines, also improving GSH/glutathione disulfide liver ratio, favouring the normalization of oxidative and inflammatory responses after a liver injury induced by LPS (Molinett et al., 2015). Moreover, serum from strawberry-supplemented older adults significantly attenuated NO production and iNOS, COX-2, TNF-α expressions in LPS-treated HAPI cells, suggesting that berry metabolites, present in the circulating blood following ingestion, may mediate the anti-inflammatory effects of dietary berry fruit (Rutledge et al., 2019). Finally, in *ex vivo* peripheral blood mononuclear cells, the production of TNF-α was increased in obese volunteers consuming strawberries, suggesting that its consumption may increase the immune response of monocytes in obese people which are at high risk for developing infections (Zunino et al., 2013).

3.12. KIWI

Kiwi fruit has been ranked as the second highest antioxidant fruit among commonly consumed fruits, following plums (An et al., 2016). It is native to northern China and is one of the most popular fruits in New Zealand, USA and many European countries. It is widely reported as a functional food and a nutraceutical source with some additional health-promoting properties, such as anti-allergic, anti-diabetic and anti-inflammatory effects (An et al., 2016; Deng et al., 2016). In this context kiwi extracts and its fruit seed polyphenols showed interesting activities against LPS-induced inflammation in RAW macrophages, as highlighted by the reduction of ROS, NO and pro-inflammatory cytokines (An et al., 2016; Deng et al., 2016).

3.13. BLUEBERRY

Bluberries (*Vaccinium corymbosum L.*, family: Aricaceae) are rich in polyphenols, such as anthocyanins, flavonols, tannins and phenolic acids, which are the main responsible of their biological activities (Afrin et al., 2016). USA represents, with Canada and Poland, the largest blueberry-producing countries, and thank to its rapidly production growing, its nutritional values and benefits for human health are attracting much more interest from the international scientific communities (Afrin et al., 2016). In the detail, in the last 10 years numerous studies investigated the role of blueberry extract and its fractions against inflammatory condition mediated by LPS endotoxin. In microglia and macrophages, blueberry extract counteracted the LPS-mediated inflammatory response reducing ROS and NO production and pro-inflammatory cytokine expression, comprising a potential therapeutic tool against comorbidities associated with obesity development (~~Zhu et al., 2008;~~ Reyes-Farias et al., 2015; Xie et al., 2011). Positive effects were observed in human umbilical vein endothelial cells, where blueberry treatment increased LPS-compromised cell viability and phosphoinositide-specific phospholipase C enzyme expression (Lo Vasco et al., 2017). Interesting results were also obtained in the hippocampal and renal regions of rats subjected to LPS treatment: in these models blueberries supplementation improved renal glomerular filtration rate, blood flow vascular resistance and ROS and superoxide production (Nair et al., 2014), showing beneficial properties against neurodegenerative process and kidney injuries. Moreover, in LPS-stimulated splenocytes isolated from C57BL/6 mice fed with a high-fat diet with blueberry, berry supplementation reduced cytokines production, suggesting that dietary blueberry can buttress T-cell and systemic immune function against high fat diet-obesity-associated insults (Lewis et al., 2018). Taking into account the different fractions isolated from whole blueberry fruits, polyphenols and in particular anthocyanins represent the most widely investigated class of compounds. In RAW macrophages, blueberry polyphenol enriched-fractions efficiently counteracted the LPS-induced stress mainly reducing NO and inflammatory cytokines, production and lowering ROS and iNOS levels through the modulation of the NF-kB pathway (Xie et al., 2011; Carey et al., 2013; Grace et al., 2014; Cheng et al., 2014; Cheng et al., 2016; Su et al., 2017; Esposito et al., 2019). Similarly in LPS-treated HAPI cells, serum from blueberry-supplemented older adults significantly attenuated NO production and iNOS, COX-2, TNF-α expressions, suggesting that berry metabolites, present in the circulating blood following ingestion, may exert the anti-inflammatory effects of dietary berry fruit (Rutledge et al., 2019). The same results were found with blueberry anthocyanins extracts, which exerted positive effects in murine macrophages (Johnson et al., 2013; Lee et al., 2014a; Garcia-Diaz et al., 2015; Xu et al., 2016) and in bone marrow-derived macrophages prepared from bone marrows isolated from Nrf2 wild-type and Nrf2 knockout mice (Lee et al., 2014a), underlying how their anti-inflammatory effects could be due to the inhibition of nuclear translocation of NF-κB independently from the Nrf2-mediated pathways (Lee et al., 2014a).

3.14. MANGOSTEEN

The mangosteen (*Garcinia mangostana L*., family: Clusiaceae) is recognized as a medicinal plant thanks to its notable pharmacological effects. It is a tropical evergreen tree, commonly cultivated in Thailand, Malaysia, and Indonesia. Mangosteen fruit is a rich source of phenolic compounds such as condensed tannins, anthocyanin and xanthones. Traditionally, mangosteen is famous for its anti-inflammatory properties and it is mainly used for skin infections and wounds treatments (Afrin et al., 2016). Most of the studies focused their attention on the effect of the principal xanthones isolated from mangosteen, in particular α, β and γ mangostin. α-mangostin represents the main constituent of the fruit hull (Franceschelli et al., 2016). It showed protective effect against LPS-induced inflammation in different cellular models: in rat intestinal epithelial cells (Zou et al., 2019), murine macrophages (Chen et al., 2008b; Gutierrez-Orozco et al., 2013; Mohan et al., 2018), monocyte-derived (Gutierrez-Orozco et al., 2013), human macrophages (Bumrungpert et al., 2010) and in bone marrow-derived dendritic cells (Herrera-Aco et al., 2019), α-mangostin exerted positive effects through the reduction of pro-inflammatory genes (iNOS, COX-2) and cytokines (IL-6, TNF-α) and their mainstream pathways such as NF-kB and MAPK. Similar effects were obtained in human adipocyte, where α-mangostin attenuated LPS-mediated inflammation and insulin resistance, possibly by inhibiting the activation of MAPK, NF-kB and AP-1 (Bumrungpert et al., 2009). Finally, the same results were detected in human myeloid leukemic cell line, monocyte-like leukemia cells and colorectal adenocarcinoma cells, in which α-mangostin efficiently counteracted the inflammatory insult, suggesting its possible use in the development of alternative pharmacological strategies aimed at reducing the inflammatory process (Franceschelli et al., 2016; Liu et al., 2012b; Gutierrez-Orozco et al., 2013). Recently, Nava Catorce et al. (Nava Catorce et al., 2016) and Lotter et al., (Lotter et al.,2020) showed that α-mangostin reduced brain levels of pro-inflammatory IL-6,TNF-α, COX-2 and 18 kDa translocator protein in an animal model of peripheral LPS-induced neuro-inflammation, proposing this natural xanthone as an adjuvant treatment in preclinical models of Alzheimer's disease, Parkinson disease, schizophrenia, multiple sclerosis and other disease with known shared pathology. Interesting results were also obtained with γ-mangostin, another xanthone isolated from mangosteen fruit. Finally, in LPS-treated macrophages (Chen et al., 2008b; Bumrungpert et al., 2010) and adipocytes (Bumrungpert et al., 2009), γ-mangostin exhibited anti-inflammatory effects lowering the production of NO, inflammatory cytokines, PGE-2 and COX-2 and down-regulating NF-kB and MAPK signaling pathways.

3.15 RASPBERRY

Raspberry (*Rubus sp.*, family: Rosaceae) has recently received much attention from both scientists and consumers for its health benefits, mainly due to the high amount of ellagic acid that it contains (Afrin et al., 2016). Various kinds of raspberries can be cultivated all around the world: in fact, it is possible to distinguish Asian, European, Australian and American raspberry, characterized also by different colorations, such as black, red and yellow ones (Wu et al., 2019). Taking into account the anti-inflammatory effect of this berry, interesting results have been obtained with different extracts of Rubus Coreanus raspberry: in LPS-treated RAW macrophages these extracts showed strong anti-inflammatory effects through the suppression of NF-κB and MAPK activation (Lee et al., 2014b; Seo et al., 2019), the inhibition of inflammatory mediators such as NO, PGE2 and inflammatory cytokines productions (Seo et al., 2019) and the augment of phase II antioxidant gene expression (Kim et al., 2013a).

In the last years, different studies demonstrated the efficacy of diverse raspberry fractions against LPS stress. Polyphenols, cyanidin and triterpenoid-rich fraction obtained from black raspberry (Kim et al., 2013b; Jo et al., 2015; Shin et al., 2014), red raspberries anthocyanin-rich fractions (Li et al., 2014) and different nortriterpenes isolated from raspberry roots (Chen et al., 2015) efficiently counteracted the inflammation promoted in RAW macrophages, by downregulating pro-inflammatory cytokines production, NO level and suppressing the inflammatory-related pathways. Interesting results were also obtained by Garcia et al. (Garcia et al., 2017), which showed for the first time that raspberry metabolites present in the gastrointestinal bio-accessible fraction significantly inhibited microglial pro-inflammatory activation by LPS, through the inhibition of ionized calcium binding adaptor molecule 1 (Iba1) expression, TNF-α release and NO production, revealing that raspberry polyphenols may represent a dietary tool to the retardation or amelioration of neurodegenerative-related dysfunctions (Garcia et al., 2017).

3.16. BLACKBERRY

Blackberries (Rubus fruticosus L.) belong to the family of Rosaceae and are widely known for their high antioxidant capacity due to their content in ellagic acid, tannins, ellagitannins, quercetin, gallic acid, anthocyanins, and cyanidin (Afrin et al., 2016). Mexico represents the main producer of blackberries, even if in Europe and United States numerous cultivars have been selected for commercial cultivation. In addition to its antioxidant role, in the last decade different studies have investigated the effect of this berry against LPS-mediated inflammation. In J774 (Azofeifa et al., 2013; Choe et al., 2020), bone marrow-derived (Lee et al., 2014a) and RAW LPS-treated macrophages (~~Cuevas-Rodriguez et al., 2010;~~ Johnson et al., 2013; Lee et al., 2014a; Garcia-Diaz et al., 2015; Van de Velde et al., 2019b) blackberry extract and its anthocyanin- and proanthocyanidins-enriched fractions exerted their anti-inflammatory effects reducing ROS and NO level and pro-inflammaory cytokines production, at least in part, by inhibiting nuclear translocation of NF-κB and MAPK activation.

3.17. CRANBERRY

The cranberry (Vaccinium macrocarpon Aiton, family: Ericaceae), a traditional folk remedy commonly produced in Canada and in the north-eastern and north-central area of United States, attracted great attention over the past decade due to its phytochemical content, composed by flavonol glycosides, anthocyanins, proanthocyanidins, and organic and phenolic acids (Afrin et al., 2016). Cranberry extracts and juice exerted anti-inflammatory effects in ~~human peripheral blood mononuclear leukocytes (Huang et al., 2009),~~ monocyte cells (Hannon et al., 2016) and murine macrophages (~~Van et al., 2009;~~ Grace et al., 2014) targeting specific pathways involved in LPS-induced inflammation and reducing pro-inflammatory cytokines productions.

Interesting data were also obtained with cranberry non-extractable polyphenols fraction, which decreased the expression of iNOS, increasing the expression of HO-1 (Han et al., 2019) and with phenolic and volatile extracts, that reduced NO production when applied before or after LPS stimulation in RAW macrophages (Moore et al., 2019). Similar results were also found with polyphenol fraction isolated from cranberry (Kylli et al., 2011; Grace et al., 2014), in particular with the proanthocyanidins which counteracted the LPS-induced inflammation in murine macrophages (~~Madrigal-Carballo et al., 2009;~~ Carballo et al., 2017), reducing iNOS and COX-2 expression through the inhibition of NF-kB activation. In detail, A-type cranberry proanthocyanidins showed promising results as potential adjunctive therapies for treating inflammatory conditions, as highlighted by ~~(i) the inhibition of the LPS-stimulated MMP-mediated tissue destruction in monocyte-derived macrophages (La et al., 2009), (ii)~~ the decrease of LPS-induced secretion of the pro-inflammatory mediators IL-1β, TNF-α, IL-6 and IL-8 in monoblastic leukemia-derived macrophages (Feldman et al., 2012) and ~~(iii)~~ the reduction of the secretion of several cytokines in an LPS-stimulated 3D co-culture model of oral gingival epithelial cells and fibroblasts (Lombardo Bedran et al., 2015). Finally, cranberry powder enriched-diet showed beneficial effects in animal models, providing appropriate antioxidants to counteract the diminished antioxidant status and modifying serum lipids and the early inflammatory response, in rats and obese mice subjected to LPS injection (Kim et al., 2011; Kim et al., 2013c; Kim et al., 2014).

3.18. BLACKCURRANT

Blackcurrant fruit (*Ribes nigrum L.*; family: Grossulariceae) is commonly rich in phytonutrients, vitamin C and antioxidants (Afrin et al., 2016). It is native to central Europe and has been used in traditional oriental medicine for more than 1,000 years. Up to date, few investigations have taken into account the anti-inflammatory role of blackcurrant against LPS-induced stress. In LPS-treated macrophages (Desjardins et al., 2012; Menghini et al., 2014; Lee et al., 2014a) ~~and monocytic cell lines (Lyall et al., 2009)~~ blackcurrant extract and its anthocyanin fraction exerted anti-inflammatory effects counteracting efficiently pro-inflammatory cytokines production in a dose-dependent manner, partially by the inhibition of NF-kB activation. ~~Similar data were obtained in mice fed with blackcurrant powder, which modulated also *in vivo* the NF-κB signalling, following LPS induced stress (Balstad et al., 2010). Finally, interesting results were also highlighted in subjects fed with a blackcurrant enriched diet: in this case berry consumption reduced TNF-α and IL-6 levels in peripheral blood of subjects post-exercise, ameliorated the LPS-stimulated inflammatory response in THP-1 cells, alleviating the general oxidative stress condition (Lyall et al., 2009).~~

3.19. BARBERRY

Barberry fruit is distributed in different part of the world, in Japan and parts of China as *Berberis amurensis*, in Argentina and Chile as *Berberis microphylla*, in Korea as *Berberis koreana* but the most common variety is represented by *Berberis vulgaris*, the European barberry (Reyes-Farias et al., 2015). In 2015 Reyes-Farias et al. (Reyes-Farias et al., 2015) showed that barberry polyphenol-extract reduced NO secretion, iNOS and TNF-α expressions, concomitantly increasing IL-10 level, in LPS-induced RAW macrophages. Similarly, in murine peritoneal macrophages barberry extract strongly suppressed production of NO, ROS, iNOS, inflammatory cytokines as well as chemokines, also investigating the molecular mechanisms involved, against LPS-stimuli (Sharma et al., 2020).

3.20. JAMUN BERRY

Eugenia jambolana Lam. is a fruit tree mainly distributed in the tropical and subtropical regions of the world. The fruit of *E. jambolana* is a popular edible berry commonly known as Jamun and widely consumed in India and other parts of the world (Liu et al., 2018). In 2018, Liu et al. (Liu et al., 2018) showed the protective effects of different phenolic isolated from Jamun seeds in LPS-induced RAW264.7 cell against advanced glycation endproducts activities, mainly through the reduction of ROS production, demonstrating that phenolics might play an important role in the hypoglycemia effects attributed to this edible plant.

3.21. OTHER BERRY

To the best of our knowledge there are no published studies which investigated the effect of cloudberry, silverberry, white current, artic brumble and rosehip on LPS-stressed *in vitro* and *in vivo* models.

4. CONCLUSIONS

Berry fruits possess a remarkable amount of nutritive and bioactive compounds, with flavonoids and anthocyanins the most representative ones. Numerous *in vitro* and *in vivo* studies have highlighted the efficacy of berry extracts and its single fractions or constituents against the inflammatory status evoked by the endotoxin LPS. Grape, in particular resveratrol, and blueberry represent the main investigated berry in this sense, even if the mechanisms involved in the prevention and/or treatment of stress condition are common in all the tested fruit. The inhibition of MAPK and NF-kB activation, with the consequently reduction of pro-inflammatory cytokines and NO production, represent the main pathway involved in their anti-inflammatory role, improving antioxidant defence and providing beneficial effects for the maintenance of healthy conditions in LPS-treated models.

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7. FIGURE CAPTIONS

FIGURE 1. Antioxidant and anti-inflammatory effect of berries after LPS-induced stress. Berries attenuated the LPS-induced stress through the downregulation of different factors produced after the stress stimulus and the upregulation of antioxidant enzymes. LPS: lipopolysaccharide; TRL4: toll-like receptor 4; NADPH: nicotinamide adenine dinucleotide phosphate hydrogen; ROS: reactive oxygen species; MyD88: myeloid differentiation primary response 88; IκBα: nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; MAPK: mitogen-activated protein kinase; SOD: superoxide dismutase; Erk1/2: extracellularly-regulated kinase-1 and -2; AP-1: activator protein 1; Nrf2: nuclear factor erythroid 2–related factor 2; ARE: antioxidant response element; iNOS: inducible nitric oxide synthase; NO: nitric oxide; COX2: cyclooxygenase 2; IL-1: interleukin 1; IL-6: interleukin 6; TNF-α: tumor necrosis factor alpha

TABLE 1. Effects of different berries on LPS-stimulated inflammatory models: *in vitro* studies~~.~~

Berry	Extracts/Fraction/Component	Dosage of LPS induced	Dosage of berry and testing system	Biological response	Reference
Elderberry	Ethanolic extract and the isolated anthocyanins and procyanidins fractions	500 ng/mL for 1h	0.1, 1, 10 and 100 µg/mL (extract) or 0.1, 1, 10, and 100 µM (pure compounds) *In vitro*: RAW 264.7 macrophages and murine dendritic D2SC/I cells	-↓ ROS and NO	(Ho et al., 2017)
	Methanolic extracts	0.1–10 µg/mL for 12-24 h	10 µg/mL for 12-24 h *In vitro*:HGF-1 and human U-937 monocytes.	-↓ IL-6 and IL-8, MMP-2 and MMP-9	(Walker et al., 2013)
	~~Methanolic extract~~	~~0.5 µg/mL for 24 h~~	~~100, 50, 25 and 12.5 µg/mL for 24 h *Ex vivo:* macrophages obtained from BALB/c mice intraperitoneally injected with 20 mg LPS~~	~~-↓ NO~~	~~(Carneiro et al., 2019)~~
Wolfberry or Goji berry	LBP	200 ng/mL for 1 h	0, 200, 400, 600 or 800 µg/mL for 24 h *In vitro*: BV-2 mouse microglial cells	-↓ NF-κB -↓ caspase 3, TNF-α and HSP60.	(Teng et al., 2013)
	~~LBP~~	~~5 mg/kg BW i.p. injection~~	~~200, 400, 800 mg/kg BW for 12 h *In vivo*: Sprague-Dawley male rats~~	~~-↓ IL-1β, IL-6, IL-8, TNF-α, NF-κB, ROS and Keap1 in kidneys -↑ Nrf2, HO-1, NQO1 in kidneys~~	~~(Huang et al., 2019)~~
	~~LBP~~	~~5 mg/kg BW i.p. injection~~	~~200, 400, 800 mg/kg BW for 6, 12, 24, 48 h *In vivo*: Sprague-Dawley male rats~~	~~-↓ IL-1β, IL-6, IL-8, TNF-α, NF-κB and ROS levels in serum -↓ NF-κB and Keap1 in kidneys -↑ Nrf2, HO-1, NQO1 in kidneys~~	~~(Wu et al., 2020)~~
	~~LBP~~	~~5 mg/kg BW i.p. injection~~	~~200 mg/kg BW for 24 h *In vivo*: C57BL/6 mice~~	~~-↓ IL-6, TNF-α, lung injury and pulmonary edema~~	~~(Chen et al., 2018)~~
	LBP	100 ng/mL for 24 h	200 µg/mL for 24 h *In vitro*: human pulmonary microvascular endothelial cells	-↓ apoptosis, ROS, NF-κB	(Chen et al., 2018)
	Lycium ruthenicum polysaccharide	1 µg/mL for 24 h	10-80 µg/mL for 24 h *In vitro:* RAW 264.7 macrophage cells	-↓ NO, TNF-α, IL-6, iNOS -↓ TLR-4/ NF-κB	(Peng et al., 2014)
	Lycium fruit water extract	200 ng/mL for 48 h	10, 100, 500 and 1000 µg/mL for 48 h *In vitro:* RAW 264.7 macrophage cells	-↓ NO, TNF-α, IL-6, iNOS and COX-2. -↓p-Erk1/2, p-p38-MAPK, p-JNK. -↓ IκBα, NF-κB	(Oh et al.,2012)
Acaiberry	Freeze-dried açai pulp was fractionated using methanol, ethanol and acetone	100 ng/mL overnight	50 µg−10 mg/mL for 24 h *In vitro*: BV-2 microglial cells	-↓ iNOS, COX-2, p38-MAPK, TNF-α and NF-κB.	(Poulose et al., 2012)
	Açai polyphenolics extracts	1 µg/L for 3 h	5–20 mg gallic acid equivalent/L for 24 and 48 h *In vitro*: HUVEC	-↓ROS -↓ NF-kB -↓VCAM-1, ICAM-1, and E-selectin -↑ microRNA-126	(Noratto et al., 2011)
	Açai polyphenolics extracts	2 µg/mL for 4 h	1–10 mg gallic acid equivalent/L for 24 and 48 h *In vitro*: Colon myofibroblast CCD-18Co cells	-↓ROS -↓TNF-α, COX-2, TLR-4, TNF receptor-associated factor -6, NF-κB, VCAM-1 and ICAM-1	(Dias et al., 2015)
	Açai extract	100 ng/mL for 6 h	6.25-50 µg/mL for 6 h *In vitro*: rat astrocyte	-↓ NF-kB -↑ Nrf2 and HO-1	(Ajit, et al., 2016)

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Emblic	Amla fruit extract	1 µg/mL for 4 h	3-100 mg/mL for 4 h *In vitro*: human umbilical vein endothelial cells HUVEC and human monocytic cells THP-1 cells.	-↓ E-selectin and tissue factor expression	(Rao et al., 2013)
	Amla fruit powder extracts	5 µg/mL for 6 h.	0.13–2 mg/mL for 1 h *In vitro*: RAW 264.7 macrophages	-↓ ROS, NF-kB, iNOS, COX-2	(Wang et al., 2019)
	Dried seedless Amla fruits	1 µg/mL for 12 h	10 µg/mL of fruit composition for 3 h *In vitro*: RAW 264.7 macrophages	-↓ ROS, TNF-α, iNOS, COX-2	(Sato et al., 2018)
	~~Amla fruit extract~~	~~2 mg/kg BW~~	~~50 mg/kg BW for 4-24 h *In vivo:* male Wistar rats~~	~~-↓ TNF-α and IL-6 in serum~~	~~(Rao et al., 2013)~~
Lingonberry	Lingonberry crude extract and polyphenol-rich fraction	1 µg/mL for 4 h	50, 100 and 150 µg/mL for 5 h *In vitro*: RAW 264.7 macrophages	-↓ IL-1β, IL-6, COX-2, iNOS	(Grace et al., 2014)
	Lingonberry polyphenol-rich fraction (LE), anthocyanin-rich fraction (ANC), proanthocyanidin-rich fraction (PNC)	50 µg/mL for 24 h	50 mg for 24 h (LE) 24-80 mg for 24 h (ANC) 163 mg for 24 h (PNC) *In vitro*: RAW 264.7 macrophages	-↓ ROS, NO, COX-2, iNOS	(Esposito et al., 2019)
	Lingonberry phenolic extract	10 ng/mL for 24 h	30 and 100 µg/mL for 24 h *In vitro*: J774 macrophages	-↓ NO, TNF-α, IL-1β, IL-6	(Kylli et al., 2011)
	~~Lingonberry extract~~	~~1 µg/mL for 24-48 h (prevention) 1 µg/mL for 3 h (reversal)~~	~~10-100 µg/mL for 3 h (prevention) 24-48 h (reversal) *Ex vivo*: Primary astrocytic cultures from Wistar rats~~	~~-↓ ROS, NO and acetylcholinesterase activity -↑ viability, thiol content and SOD~~	~~(Pacheco et al., 2018)~~
Chokeberry	Black chokeberry ethanolic extract	500 ng/mL for 48 h	30 µg/mL-1mg/mL *In vitro*: BV2 cells	-↓ NO, iNOS, COX-2, IL-1β , TNF-α	(Lee et al., 2018)
	~~Black chokeberry ethanolic extract~~	~~250 µg/kg~~	~~50 mg/kg/day for 7 days *In vivo*: male ICR mice received a single intraperitoneal injection of LPS~~	~~-↓ iNOS, COX-2, TNF-α~~	~~(Lee et al., 2018)~~
	Polyphenol-rich chokeberry juice concentrate	10 ng/mL for 24 h.	0.01-0.5% for 30 min *In vitro*: human primary monocytes isolated from peripheral blood	-↓ TNF-α IL-6, IL-8	(Appel et al., 2015)
	Polyphenol-rich chokeberry juice concentrate	1 µg/mL for 6 h	0.01-0.5% for 30 min *In vitro*: RAW 264.7 macrophages	-↓ NF-κB	(Appel et al., 2015)
~~**Seabuckthorn**~~	~~Seabuckthorn berries paste~~	~~10 mg/kg BW.~~	~~200, 400 and 800 mg/kg BW for 7 days *In vivo*: male SPF KM mice~~	~~-↓ body weight loss, lung tissue, microstructure lesions, transvascular leakage increase, malondialdehyde augmentation -↑ SOD, GPx, Nrf2~~	~~(Du et al., 2017)~~
Grape	GSPE	1 µg/mL for 24 h	35 µg/mL for 24 h *In vitro*: RAW 264.7 macrophages	-↓ ROS, NO, iNOS, PGE2, COX-2, TNF-α, IL-1β, p-p65, p-pIkBα, p-AKT, p-p38 p-JNK, p-ERK	(Bak et al., 2013)
	GSPE	0.4 µg/mL for 24 h	12.5-50 µg/mL for 24 h. *In vitro*: RAW264.7 macrophages	-↓ NO production;	(Perez et al., 2015)
	GSPE	1 µg/mL for 8 h	25 µg/mL for 16 h *In vitro*: RAW264.7 macrophages and	-↓ TLR-4 activation.	(Kim et al., 2016)

			fibroblast-like synoviocytes		
	GSPE	1 µg/mL for 30 min or 24 h	0-40 µg/mL for 90 min or 24 h. *In vitro*: rat hepatic stellate cell line HSC-T6	-↓ AKT, ERK and JNK phosphorylation -↓ NF-kB translocation from cytosol to nuclear	(Jiang et al., 2017)
	GSPE	1 µg/mL for 30 min	0-40 µM for 6 h or 24 h *In vitro*: human ovarian cancer cells A2780 and its multidrug resistant subline A2780/T	-↓AKT/NF-kB pathway -↓MAPK/ERK pathway	(Zhao et al., 2013)
	~~GSPE~~	~~7 mg/kg BW~~	~~50, 75, 100 and 200 mg/kg/day BW for 15 days~~ ~~*In vivo*: Wistar female rats~~	~~-↓ NO level in the plasma, red blood cells, spleen, and liver;~~ ~~-↓ TNF-α and IL-10 in plasma;~~ ~~-↓ hepatic level of IL-6, iNOS, glutathione disulfide/total glutathione~~	~~(Pallares et al., 2013)~~
	~~GSPE~~	~~0.3 mg/kg BW for 5 days~~	~~75and 375 mg/kg BW for 15 days~~ ~~*In vivo*: male Wistar rats~~	~~-↓ TNF-α in plasma~~ ~~-↓ MPO, COX-2, ROS in the small and large intestinal sections~~	~~(Gil-Cardoso et al., 2019)~~
	GPCE	5 µg/mL for 4 h	50 µg/mL for 4 h *In vitro*: BV2 microglia cells	-↓ NF-κB cytokines, chemokines	(Pistol et al., 2018)
	GSE	1 µg/mL for 150-180 min.	0-24 µg/mL *In vitro*: human peripheral blood mononuclear cells	-↓LPS-stimulated tissue factor synthesis -↓ tissue factor-dependent fibrin formation	(Milella et al., 2012)
	~~Red and white GE~~	~~10 µg/kg BW~~	~~100-500 mg/kg BW for 24 h~~ ~~*In vivo*: Sprague–Dawley rats~~	~~-↓ NF-κB, iNOS, COX-2 in liver~~	~~(Nishiumi et al., 2012)~~
	~~GE~~	~~3-15 mg/kg BW~~	~~0, 100, or 300 mg/kg/day BW for 3 weeks~~ ~~*In vivo*: Sprague–Dawley rats~~	~~-↓ phospholipases A2 activity in serum;~~ ~~-↑ hematocrit in serum~~	~~(Tsao et al., 2012)~~
	~~GPE~~	~~100 ng/ml for 30 min-3 h~~	~~10, 30 and 100 mg/mL for 1 h~~ ~~*In vitro*: human macrophages~~	~~-↓ TNF-α, IL-6 and IL-1β; interferon gamma-induced protein 10; COX-2;~~ ~~-↓ MAPKs, NF-kB and AP-1;~~ ~~-↓ inflame adipocytes, cause insulin resistance~~	~~(Overman et al., 2010)~~
	~~GPE~~	~~0.5 mg/kg BW one i.p. injection or 0.25 mg/kg BW for 1 week~~	~~4% of diet for 4 weeks~~ ~~*In vivo*: mice~~	~~-↓ NF-κB in whole body and abdominal/peritoneal regions of interest~~ ~~-↓ TNF-α, IL-6 serum~~	~~(Miller et al., 2018)~~
	~~GPE~~	~~10 µg/L for 24, 48 and 72 h~~	~~46 g two times a day, for 3 weeks~~ ~~*Ex vivo*: monocyte populations in the peripheral blood mononuclear cells obtained from blood samples of healthy obese male and female volunteer~~	~~-↑ IL-1β, IL-6~~	~~(Zunino et al., 2014)~~
	Grape polyphenol enzymatic extract	0.01 µg/mL for 1, 4 and 6 h	0, 1, 5 and 10 µg/mL for 1, 4 and 6 h *In vitro*: N13 microglia cells	-↓ iNOS, TNF-α, IL-1β, ionized calcium-binding adapter molecule 1 and TLR-4	(Rodriguez-Morgado et al., 2015)
	Polyphenolic extracts from red	10 µg/mL for 2 h	50 µM for 4 h	-↓ IL-6	(Nicod et al.,

ha formattato: Tipo di carattere: Corsivo

	wine		*In vitro*: Caco-2 cell		2014)
	Resveratrol	1 µg/mL for 18 h	10 µM for 18 h *In vitro*: human chondrocytes	-↓ PGE2, MMP-3, MMP-13, COX-2	(Wang et al., 2011)
	~~Resveratrol~~	~~3 µg/mL for 6-12 h~~	~~200 nM for 6-12 h *Ex vivo*: cortical networks of neurons, astrocytes and microglia~~	~~-↓ TNF-α~~	~~(Gullo et al., 2017)~~
	Resveratrol	1 µg/mL for 48 h	30, 40 and 50 mM for 1 h *In vitro*: Caco-2 and human colon adenocarcinoma cell	-↓ NO, iNOS, TLR-4; -↓ IkBα degradation	(Panaro et al., 2012)
	~~Resveratrol~~	~~9 mg/kg BW~~	~~5, 50, 100, or 200 mg/kg BW at day, for 5 days *In vivo*: C57BL/6 mice~~	~~-↓ leukocyte adhesion to retinal vessels of EIU mice; -↓ MCP-1 and ICAM-1 in the retina -↓ retinal 8-Oxo-2'-deoxyguanosine, NF-kB translocation~~	~~(Kubota et al., 2009)~~
	~~Resveratrol~~	~~10 ng in 100 µL PBS~~	~~10 mg/ kg BW, once every 2 days, for 6 days *In vivo*: New Zealand white rabbits~~	~~-↓ inflammatory arthritis, PGE2, MMP-3, MMP-13~~	~~(Wang et al., 2011)~~
Pomegranate	~~Pomegranate fruit extract~~	~~10 µg/mL for 24 h~~	~~0.0025, 0.025, 0.25 and 2.5 g/l for 24 h *In vitro*: RAW 264.7 macrophages~~	~~-↓ NO production~~	~~(Kumar-Roiné et al., 2009)~~
	Pomegranate peel polyphenolics extract	1 µg/mL for 20 min or 24 h	0-100 µg/mL for 1 h *In vitro*: RAW 264.7 macrophages	-↓ ROS, TLR-4, MAPKs, NF-κB -↓ NO, PGE2, IL-1β, IL-6, TNF-α	(Du et al., 2019)
	Pomegranate polyphenolics extract	1 µg/mL for 4-24 h	5-10 mg/L for 4-24 h *In vitro*: Human colon CCD-18Co myofibroblastic cells	-↓ ribosomal protein S6 kinase beta-1, hypoxia-inducible factor 1-alpha -↑ miR-145	(Kim et al., 2017b)
	Pomegranate fruit husk polyphenolic extract	1 mg/L for 24 h	0.02-0.5 mg/mL for 1 h *In vitro:* Caco-2 cells	-↓ IL-6, IL-8, MCP-1	(Hollebeeck et al., 2012)
	~~Pomegranate peel extract~~	~~10 mg/L for 3 h~~	~~0-25 µg/mL for 3 h *Ex vivo*: porcine colonic tissue explants~~	~~-↓ CXCL8, IL-1A, IL-6~~	~~(Mastrogiovanni et al., 2019)~~
	Pomegranate peel polyphenolics extract	100 µg/mL 24 h	0-100 µg/mL for 24 h *In vitro:* Caco-2 cells	-↑ tight junction protein expression level	(Zhao et al., 2019)
	~~Polyphenol rich pomegranate extract~~	~~100 µg/kg BW i.p. injection, twice weekly, for 4 weeks~~	~~0.2 ml of 0.2% POMx via oral gavage (daily) for 4 weeks *In vivo.* male swiss albino mice~~	~~-↓ ROS, TLR-4, NF-κB, IL-6, TNF-α, BAX -↑ Nrf2, Bcl-2, heme-oxygenase-1~~	~~(Gupta et al., 2019)~~
	Punicalagin	1 µg/mL for 24 h	50, 100, 150, 200 µg/mL for 2 h *In vitro*: RAW 264.7 macrophages	-↓ NO, PGE2, IL-6	(BenSaad et al., 2017)
	Punicalagin	1 µg/mL for 24 h	25, 50, or 100 µM for 1 h *In vitro*: RAW 264.7 macrophages	-↓ TLR-4, MAPKs, NF-κB -↓ NO, PGE2, IL-1β, IL-6, TNF-α	(Xu et al., 2014)
	Punicalagin	1 µg/mL for 20 min or 24 h	0-50 µg/mL for 1 h *In vitro*: RAW 264.7 macrophages	-↓ ROS, TLR-4, MAPKs, NF-κB -↓ NO, PGE2, IL-1β, IL-6, TNF-α	(Du et al., 2019)
	Punicalagin	1 µg/mL for 30 min or 24 h	0-50 µM for 1 h *In vitro*: RAW 264.7 macrophages	-↓ NO, IL-6, TNF-α, MAPKs, NF-κB, FoxO3a	(Cao et al., 2019)
	Punicalagin	1 µg/mL for 24 h	10, 20, 50 µM for 24 h *In vitro*: Primary astrocyte and microglial BV-2 cell	-↓ NF-kB, iNOS, COX-2, ROS, NO, TNF-α, IL-1β -↓ amyloid beta$_{1\text{-}42}$ generation	(Kim et al., 2017)

				-↓ amyloid precursor protein, beta-secretase 1	
	Punicalagin	10 ng/mL for 24 h	5–40 μM for 24 h *In vitro*: Rat primary mixed glial cell cultures	-↓ NF-κB, IL-6, TNF-α, PGE2	(Olajide et al., 2014).
	Punicalagin	20 mg/kg BW for 7 h	12.5, 25, 50 mg/kg BW for 1 h *In vivo*: Male BALB/c mice	-↓ NF-kB, TLR-4, TNF-α, IL-6, IL-1β, myeloperoxidase in lung	(Peng et al., 2015)
	Punicalagin	250 μg/kg 7 times a day, for 1 week	1.5 mg/kg BW at day for 4 weeks *In vivo*: Male imprinting control region mice	-↓ memory impairment -↓ NF-kB in brain -↓ amyloid beta$_{1-42}$ generation in brain -↓ amyloid precursor protein, beta-secretase 1 in brain	(Kim et al., 2017)
	Punicalagin	600 μg/kg BW at day, for 7 days	9 mg/kg BW at day, for 7 days *In vivo*: Male ICR mice	-↑ Nrf2, GSH, SOD, catalase in testes -↑ fertility indices	(Rao et al., 2016)
	Punicalagin	5 mg/kg BW	50 mg/kg BW, for 2 h *In vivo*: Rats	-↓ serum creatinine and neutrophil gelatinase-associated lipocalin -↓ IL-18, TNF-α, IL-6, MDA, NO, Bax/Bcl2 ratio, iNOS, caspase 3, caspase 8 and caspase 9 in kidneys -↓ histopathological injury and molecule-1 expression in kidneys.	(Fouad et al., 2016)
Bilberry	Bilberry extracts	40 ng/mL for 6 h.	75 μg/mL for 30 min *In vitro*: RAW 264.7 macrophages	-↓ TNF-α, IL-1β, IL-6, COX-2, prostaglandin-endoperoxide synthase, tenascin C, CCL22, interferon gamma inducible protein 11 and 47	(Chen et al., 2008a)
	Bilberry polyphenols	1 μg/mL for 6 h	1-50 μg/mL for 30 min *In vitro*: human monocytic cell line	-↓ NF-κB	(Karlsen et al., 2010)
	Bilberry extract	1 mg/kg BW on the 2nd and 7th day of bilberry treatment	50, 100, 20 mg/kg at day for 7 days *In vivo*: Mice	-↓ plasma alanine transaminase, aspartate transaminase; -↓ liver NOS, TNF-α, IL-1β, IL-6, NF-κB, MDA, NO	(Luo et al., 2014)
	Bilberry extract	100 mg for 24 h	50, 100, 200 mg/kg BW at day for 5 days *In vivo*: Male BALB/C mice	-↓ eye NO, MDA -↑ eye ORAC, GSH, SOD, vitamin c, GPx	(Yao et al., 2010)
Strawberry	Strawberry extract	1 μg/mL for 24 h	100 μg/mL for 24 h *In vitro*: RAW 264.7 macrophages	-↓ NF-kB, pIkBα, iNOS, TNF-α, IL-1β, IL-6, IL-10; -↓ ROS, NO; -↓protein carbonyl, thiobarbituric acid-reactive substances, 8-oxoguanine glycosylase level; -↑ Nrf2, GPx, glutathione reductase, glutathione trasferase, SOD, catalase, heme oxygenase-1, GSH; -↑ p-AMPK, sirtuin-1, peroxisome proliferator-activated receptor c coactivator	(Gasparrini et al., 2017)

ha formattato: Tipo di carattere: Corsivo

				1 alpha; -↑ mitochondria functionality	
	Strawberry phenolic-rich extract	5 µg/mL for 48 h	0, 250, 500, 1000 µg/mL for 48 h *In vitro*: Mouse primary peritoneal macrophages	-↓ TNF-α, IL-1β, IL-2, IL-4, IL-6, IL-12, IL-10, interferon-γ;	(Liu et al., 2013)
	Strawberry crude extract, anthocyanin-enriched fractions, proanthocyanidin-enriched fractions	1 µg/mL for 24	50 µg/mL for 24 h *In vitro*: RAW 264.7 mcrophages	-↓ ROS, NO, iNOS, COX-2, IL-1β, IL-6	(Van de Velde et al., 2019b)
	Strawberry extract	10 µg/mL for 24 h	50, 100, 1000 µg/mL for 24 h *In vitro*: Human Dermal Fibroblast	-↑ cell viability; -↓ ROS, NO; -↑ GSH; -↓protein carbonyl, thiobarbituric acid-reactive substances, 8-oxoguanine glycosylase	(Gasparrini et al., 2017b)
	Strawberry extract	10 µg/mL for 24 h	50 µg/mL for 24 h *In vitro*: Human Dermal Fibroblast	-↑ GPx, GR, GST, SOD, catalase; -↓ ROS, apoptosis, NF-kB, iNOS, TNF-α, IL-1β, IL-6, hemeoxygenase-1 -↑ p-AMPK, sirtuin-1, peroxisome proliferator-activated receptor c coactivator 1 alpha; -↑ mitochondria functionality	(Gasparrini et al., 2018)
	Strawberry polysaccharides	5 µg/mL for 48 h	0, 250, 500, 1000 µg/mL for 48 h *In vitro*: Mouse primary peritoneal macrophages	-↓ TNF-α, IL-1β, IL-6, IL-12, IL-10; -↓ Bcl-2, Bak	(Liu et al., 2012)
	Strawberry-banana soymilk hydrosylates	1 µg/mL for 24 h	400 lg hydrolysates/ml for 48 h *In vitro*: RAW 264.7 macrophages	-↓ NO, TNF-α, IL-1β, iNOS, COX-2	(Dia et al., 2014)
	Chilean white strawberry aqueous extract	5 mg/kg BW for 3 h	4 g/kg BW at day for 10 days *In vivo*: Male Sprague-Dawley rats	-↓ serum transaminase, alanine transaminase, aspartate transaminase; -↓ serum TNF-α, IL-1β, IL-6, IL-10; -↑ liver GSH/glutathione disulfide ratio	(Molinett et al., 2015)
	Strawberry serum metabolites	100 ng/mL for 16 h	10% serum for 8 h from individual subjects fed with 24 g/day pf blueberry for 90 days. *In vitro*: HAPI rat microglial cells	-↓ NO, iNOS, COX-2, TNF-α	(Rutledge et al., 2019)
	Freeze-dried strawberry powder	10 µg/L for 24, 48, 72 h	Four servings of frozen strawberries per day for 3 weeks *Ex vivo*: peripheral blood mononuclear cells	-↑ TNF-α	(Zunino et al., 2015)
Kiwi	Kiwi extracts	100 ng/mL for 24 h	0, 50, 100, and 500 µg/mL for 24 h *In vitro*: RAW 264.7 macrophages	-↓ IL-6, TNF-α, NO	(An et al., 2016)
	Kiwi fruit seed polyphenols	1 µg/mL for 1 h	0, 20, 40, 60 µg/mL for 12 h *In vitro*: RAW 264.7 macrophages	-↓ IL-1β, TNF-α	(Deng et al., 2016)
Blueberry	Blueberry extract	50 ng/mL for 2 h	50 µg/mL for 1 h *In vitro*: Primary mouse microglia	-↓ TNF-α, IL-6, amyloid beta aggregation	(Zhu et al., 2008)

	Blueberry extract	5 µg/mL for 24 h	100 µM for 24 h *In vitro*: RAW 264.7 macrophages	-↓ NO, iNOS, IL-10, TNF-α	(Reyes-Farias et al., 2015)
	~~Blueberry extract~~	~~100 ng/mL for 16 h~~	~~1% of diet for 5 weeks *Ex vivo*: thioglycollate-elicited peritoneal macrophages from apoE$^{-/-}$ mice~~	~~-↓ TNF-α, IL-6~~	~~(Xie et al., 2011)~~
	Blueberry extract	100 ng/mL for 3, 6, 24 h	50 µM for 3, 6, 24 h *In vitro*: human umbilical vein endothelial cells	-↑ cell viability, phosphoinositide-specific phospholipase C enzyme expression	(Lo Vasco et al., 2017)
	~~Blueberry powder~~	~~10 mg/kg BW, for 6 h~~	~~2 % of diet, for 2 days, once at days *In vivo*: Sprague-Dawley rats~~	~~-↑ glomerular filtration rate, renal blood flow in kidney; -↓ renal vascular resistance, ROS, superoxide, TLR4, TNF-α, kidney injury molecule-1~~	~~(Nair et al., 2014)~~
	~~Freeze-dried whole blueberry powder~~	~~1 µg/mL for 24 - 48 h~~	~~4 % of diet/day, for 8-12 weeks *Ex vivo*: splenocytes isolated from C57BL/6 mice~~	~~-↓ IL-1β, IL-6, TNF-α~~	~~(Lewis et al., 2018)~~
	Blueberry extract or its components (pterostilbene, resveratrol, delphinidin-3-O-glucoside, or malvidin-3-O-glucoside)	100 ng/mL overnight	Blueberry extract (0, 0.25, 0.50, 1.0, 2.0 mg/mL) or del-3-gluc, mal-3-gluc, pterostilbene, or resveratrol (0, 1, 10, 20, and 30 µM), for 1 h *In vitro*: BV-2 murine microglial cells	-↓ NO, iNOS, COX-2, TNF-α	(Carey et al., 2013)
	Blueberry crude extracts and polyphenol-rich fractions	1 µg/mL for 4 h	50, 100, 150 µg/mL for 1 h *In vitro*: RAW 264.7 macrophages	-↓ iNOS, IL-1β, COX-2, IL-6	(Grace et al., 2014)
	Extractable polyphenols and non-extractable polyphenols from blueberries	1 µg/mL for 24 h	10, 100, 200, 400 µg/mL for 48 h or 100 µg/mL for 6-72 h *In vitro*: RAW 264.7 macrophages	-↓ iNOS, NO, COX-2, NF-kB	(Cheng et al., 2015)
	Blueberry polyphenol enriched extracts, obtained from serum of rats fed with blueberry-enriched diet	100 ng/mL for 16 h	10% of diet for 6 weeks *In vitro*: RAW 264.7 macrophages	-↓ TNF-α, IL-6, NF-kB (p-NFκBp65; p-IκBα), MAPK (p-p38 p-JNK p-Erk1/2)	(Xie et al., 2011)
	Blueberry polyphenol-enriched fractions	100 ng/mL for 18 h	Different amount of phenolic acid (from 5.4 to 21.8 mg) / 100 g fresh blueberry equivalent *In vitro*: RAW 264.7 macrophages	-↓ TNF-α, IL-6; -↓ miR-21, miR-125b, miR-146a	(Su et al., 2017)
	Blueberry polyphenols	1 µg/mL for 24 h	10, 100, 200, 400 µg/mL for 48 h or 100 µg/mL for 6-72 h *In vitro*: RAW 264.7 macrophages	-↓ IL-1β, IL-6, IL-12p35	(Cheng et al., 2014)
	Blueberry polyphenol-rich fraction (BE), anthocyanin-rih fraction (ANC), proanthocyanidin-rich fraction (PNC)	50 µg/mL for 24 h	50 mg for 24 h (LE) 50-120 mg for 24 h (ANC) 128 mg for 24 h (PNC) *In vitro*: RAW 264.7 macrophages	-↓ ROS, NO, COX-2, iNOS	(Esposito et al., 2019)
	Blueberry serum metabolites	100 ng/mL for 16 h	10% serum for 8 h from individual subjects fed with 24 g/day pf blueberry for 90 days. *In vitro*: HAPI rat	-↓ NO, iNOS, COX-2, TNF-α	(Rutledge et al., 2019)

			microglial cells		
	Blueberry anthocyanin extracts	1 µg/mL for 24 h	400, 800, 1200, 1600 µg/mL for 24 h *In vitro*: RAW 264.7 macrophages	-↑ cell viability; -↓ NO, PGE2, IL-6, IL-1β, interferon-γ, COX-2, TNF-α, MCP-1, NF-kB	(Xu et al., 2016)
	Anthocyanin fraction	100 ng/mL for 3-24 h	0-20 µg/mL for 12 h *In vitro*: RAW 264.7 macrophages	-↓ TNF-α, NF-kB, IL-1β	(Lee et al., 2014a)
	Anthocyanin-enriched fractions from blueberry beverages	1 µg/mL for 24 h	100 µM C3G for 24 h *In vitro*: RAW 264.7 macrophages	-↓ NO, TNF-α, NF-kB	(Garcia-Diaz et al., 2015)
	Anthocyanins and proanthocyanidins from fermented blueberry beverages	1 µg/mL for 24 h	25, 50, or 100 µM C3G (for anthocyanins) or with epicatechin (for proanthocyanidins) equivalents for 24 h *In vitro*: RAW 264.7 macrophages	-↓ NO, iNOS, COX-2, NF-kB	(Johnson et al., 2013)
	Anthocyanin fraction	100 ng/mL for 3 h	20 µg/mL for 12 h *In vitro*: Bone marrow-derived macrophages prepared from bone marrows isolated from Nrf2 wild-type and Nrf2 knockout mice	-↓ ROS, IL-1β	(Lee et al., 2014a)
Mangosteen	α-mangostin, γ-mangostin	500 ng/mL for 18 h	3-25 µM for 18 h *In vitro*: RAW 264.7 macrophages	-↓ NO, iNOS, COX-2, PGE_2	(Chen et al., 2008b)
	α-mangostin	10 µg/ml for 24 h	2.5-10 µM for 1 h *In vitro*: IEC-6, rat intestinal epithelial cells	-↓ apoptosis, NO, PGE2, IL-6, TNF-α, IL-1β, TLR4, NF-kB	(Zou et al., 2019)
	α-mangostin	5 ng/mL for 16 h	10 µM for 2 h *In vitro*: RAW 264.7 macrophages	-↓ NO	(Gutierrez-Orozco et al., 2013)
	α-mangostin	10 ng/mL, 1-10 µg/mL for 30 min, 4-20 h	0-14 µg/mL for 30 min, 4-20 h *In vitro*: RAW 264.7 macrophages	-↓ NO, iNOS, NF-kB, TNF-α, IL-6, PGE_2	(Mohan et al., 2018)
	α-mangostin	100 ng/mL for 10 h	4.5 µM for 4 h *In vitro*: monocyte-derived macrophages	-↓ TNF-α	(Gutierrez-Orozco et al., 2013)
	α-mangostin, γ-mangostin	100 µg/mL for 30 min or 3 h	3, 10, or 30 µmol/L for 2 h *In vitro*: human macrophages	-↓ IL-6, TNF-α, interferon gamma-induced protein 10, p-MEK, p-JNK, p-ERK, p-p38, NF-kB	(Bumrungpert et al., 2010)
	α-mangostin, γ-mangostin	10 µg/L for 3 or 8 h	3 µmol/L for 24 h *In vitro*: human adipocytes	-↓ IL-1β, IL-6, IL-8, TNF-α, MCP-1, TLR-2; -↓ p-JNK, p-ERK, p-p38, NF-Kb, p-c-Jun, IkBα, NF-kB; -↑ glucose uptake, peroxisome proliferator-activated receptor gamma, AP-1	(Bumrungpert et al., 2009)
	α-mangostin	100 ng/mL for 4-24 h	0-10 µg/mL for 4-24 h *Ex vivo*: Murine bone marrow-derived dendritic cells generated from the bone marrow cells of the tibia and femur of 7 to 8 week old male BALB/c mice fed with α-mangostin	-↓ INF-γ, IL-12, TNF-α, IL-6 -↑ IL-10	(Herrera-Aco et al., 2019)
	α-mangostin	10 µg/mL for 24 h	1, 5, 10, 50, and 100 µM for 24 h *In vitro*: U937cells and monocytes from peripheral blood mononuclear cells	-↓ NO, iNOS, NF-kB, sirtuin-1, COX-2, PGE_2	(Franceschelli et al., 2016)

ha formattato: Tipo di carattere: Corsivo

	α-mangostin	0.1 ng/mL for 4 h	6, 12 nM for 4 h *In vitro*: human myeloid leukemic cell line U937	-↓ TNF-α, IL-4, p-ERK, p-JNK, p-p38, p-EIK1, p-MAPK kinase 3/MAPK kinase 6, p- signal transducers and activators of transcription-1, p-c-Fos, p-c-Jun	(Liu et al., 2012c).
	α-mangostin	0.1 ng/mL for 4 h	10 μM for 4 h *In vitro*: THP-1 monocyte-like leukemia	-↓ IL-8	(Gutierrez-Orozco et al., 2013)
	α-mangostin	100 ng/mL for 16 h	10 μM for 1 h *In vitro*: HT-29 colorectal adenocarcinoma cells	-↓ IL-8	(Gutierrez-Orozco et al., 2013)
	~~α-mangostin~~	~~2 mg/kg BW, 3 daily injections at 24 h intervals~~	~~40 mg/kg BW, at day for 14 days~~ ~~*In vivo*: female C57BL/6J mice~~	~~-↓ brain IL-6, COX-2, translocator protein, ionized calcium-binding adapter molecule 1~~	~~(Nava Catorce et al., 2016).~~
	~~α-mangostin and ground dried pericarp Garcinia mangostana Linn~~	~~100 μg/kg BW administered subcutaneously~~	~~20 mg/kg or 50 mg/kg BW for 15 days~~ ~~*In vivo*: Sprague-Dawley rats~~	~~-↓ TNF-α, IL-6, depressive behavuiours~~	~~(Lotter et al., 2019)~~
Raspberry	Different raspberry extracts	1 μg/mL for 20 min, 4 h or 18 h	400 μg/mL for 24 h *In vitro*: RAW 264.7 macrophages	-↓ NO, iNOS, PGE2, COX-2, IL-1β, IL-6, TNF-α -↓ NF-kB, p-p38, p-JNK, p-ERK	(Lee et al., 2014b)
	Different raspberry extracts	1 μg/mL for 18 h	25-400 μg/mL for 1 h *In vitro*: RAW 264.7 macrophages	-↓ NO, iNOS, COX-2, IL-1β, IL-6, TNF-α,p-IkB-α	(Sao et al., 2019)
	Unripe raspberry fruit aqueous extract	100 ng/mL for 30 min or 14 h	250-500 μg/mL for 4 h *In vitro*: RAW 264.7 macrophages	-↓ NO and ROS production -↓ NF-kB IL-1β, TNF-α, iNOS -↑ phase II antioxidant gene expression (heme oxygenase-1, glutamate cysteine ligase, and peroxiredoxin-1)	(Kim et al., 2013b)
	Polyphenols from unripe fruit of black raspberry	0.1 μg/mL for 24 h	0-100 μg/mL for 24 h *In vitro*: RAW 264.7 macrophages	-↓ NO, PGE2, IL-1β, IL-6, IL-10, TNF-α, iNOS, COX-2	(Kim et al., 2013a)
	Triterpenoid-rich fraction from black raspberry	1 μg/mL for 24 h	25, 50, 100 μg/mL for 1 h *In vitro*: RAW 264.7 macrophages	-↓ NO, PGE2, IL-1β, IL-6, TNF-α, iNOS, COX-2 -↓ NF-kB, pIkBα, p-p38, p-JNK, p-ERK	(Shin et al., 2014)
	Different black raspberry fractions	100 ng/mL for 15 h	100, 300, 500 μg/mL for 15 h *In vitro*: RAW 264.7 macrophages	-↓ IL-6, IL-1β, TNF-α, iNOS, COX-2 -↓ p-STAT3, p-p38, p-JNK, p-ERK	(Jo et al., 2015)
	Red raspberries anthocyanin-rich fractions	1.5 μg/mL for 1-24 h	0-200 μg/mL for 12-24 h *In vitro*: RAW 264.7 macrophages	-↓ NO, iNOS, COX-2, IL-1β , IL-6; -↓ NF-kB, AP-1, IkBα, p65, JNK.	(Li et al., 2014)
	Different nortriterpenes isolated from raspberry roots	1 μg/mL for 24 h	4 and 20 μM for 24 h *In vitro*: RAW 264.7 macrophages	-↓ TNF-α, IL-6, IL-1β production	(Chen et al., 2015)
	Gastrointestinal bioaccessible fraction of raspberry	300 ng/mL for 2, 4, 6, 24 h	1.25 μg of gallic acid equivalents/mL for 2, 4, 6, 24 h *In vitro*: N9 microglial cells	-↓ cell death, -↓ Iba1 and TNF-α expression and NO production	(Garcia et al., 2017)
Blackberry	Blackberry extract	10 ng/mL for 10 or 24 h	12.5-25-50-100 μg/mL for 4 or 24 h *In vitro*: J774A.1 murine macrophage	-↓ NO production, iNOS and IL-6 levels	(Azofeifa et al., 2013)
	Seed flour extract	10 ng/mL for 4 h	0.4 mg flour eq/ml for 48 h *In vitro*: J774 mouse macrophages	-↓ IL-1β	(Choe et al., 2020)

ha formattato: Tipo di carattere: Corsivo

	Anthocyanin fraction	100 ng/mL for 3 h	20 µg/mL for 12 h *In vitro*: Bone marrow-derived macrophages prepared from bone marrows isolated from Nrf2 wild-type and Nrf2 knockout mice	-↓ ROS, IL-1β	(Lee et al., 2014a)
	Anthocyanin fraction	100 ng/mL for 3-24 h	0-20 µg/mL for 12 h *In vitro*: RAW 264.7 macrophages	-↓ TNF-α, NF-kB, IL-1β	(Lee et al., 2014a)
	~~Total polyphenolic, anthocyanin and proanthocyanidin rich fractions~~	~~1 µg/mL for 24 h~~	~~0.5, 5 and 50 µM equivalents of cyanidin-3-Oglucoside or catechin for 24 h~~ ~~*In vitro*: RAW 264.7 macrophages~~	~~-↓ NO, iNOS, COX-2 and PGE2 level~~	~~(Cuevas-Rodriguez et al., 2010)~~
	Anthocyanin-enriched fractions from blackberry beverages	1 µg/mL for 24 h	100 µM C3G for 24 h *In vitro*: RAW 264.7 macrophages	-↓ NO, TNF-α, NF-kB	(Garcia-Diaz et al., 2015)
	Anthocyanins (ANC) and proanthocyanidins (PNC) from fermented blackberry beverages	1 µg/mL for 24 h	25, 50, or 100 µM C3G (for ANC) or with epicatechin (for PAC) equivalents for 24 h *In vitro*: RAW 264.7 macrophages	-↓ NO, iNOS, COX-2, NF-kB	(Johnson et al., 2013)
	Blackberry crude extract, anthocyanin-enriched fractions, proanthocyanidin-enriched fractions	1 µg/mL for 24	50 µg/mL for 24 h *In vitro*: RAW 264.7 macrophages	-↓ ROS, NO, iNOS, COX-2, IL-1β, IL-6	(Van de Velde et al., 2019b)
Cranberry	~~Cranberry extract~~	~~25 ng/mL for 6-16 h~~	~~0-100 µg/mL for 6-16 h~~ ~~*In vitro*: human peripheral blood mononuclear leukocytes~~	~~-↓ TNF-α, IL-6, IL-1β, COX-2~~	~~(Huang et al., 2009)~~
	Cranberry extract or cranberry juice powder	10 ng/mL for 6 h	0-100 µg/mL for 16 h *In vitro*: THP-1human monocyte cells	-↓ TNF-α, interferon-induced protein with tetratricopeptide repeats 1 and 3, macrophage scavenger receptor 1 and colony-stimulating factor 2 expression	(Hannon et al., 2016)
	~~Different fraction (80% ethanol; water-soluble polysaccharide; polyphenolic and ETOAc/H_2O)~~	~~1 µg/mL overnight~~	~~50-100-500 µg/mL for 5 h~~ ~~*In vitro*: RAW 264.7 macrophages~~	~~-↓ IL-1β, IL-6, TNF-α~~	~~(Van et al., 2009)~~
	Cranberry crude extract and polyphenol-rich fraction	1 µg/mL for 4 h	50, 100 and 150 µg/mL for 5 h *In vitro*: RAW 264.7 macrophages	-↓ IL-1β, IL-6, COX-2, iNOS	(Grace et al., 2014)
	Non-extractable polyphenols fraction	1 µg/mL for 24 h	2-12 µg gallic acid eq/mL for 24 h *In vitro*: RAW 264.7 macrophages	-↓ iNOS, p50/PARP -↑ HO-1, Nrf2	(Han et al., 2019)
	Phenolic and volatile extracts	100 ng/mL for 24 h	0.45-1.8 µg/g volatile fraction for 1 h 636-159 µg/g phenolic fraction for 1 h *In vitro*: RAW 264.7 macrophages	-↓ NO	(Moore et al., 2019)
	Phenolic extracts	10 ng/mL for 24 h	30 or 100 µg/mL for 24 h *In vitro*: J774 macrophages and human THP-1 promonocytes	-↓ NO, iNOS, COX-2, IL-6, IL-1β, TNF-α	(Kylli et al., 2011)
	~~Cranberry proanthocyanidins~~	~~100 ng/mL for 4 h~~	~~0.5–2.0% v/v for 2 h~~	~~-↓ iNOS, COX-2~~	~~(Madrigal-Carballo et al., 2009~~
	Proanthocyanidins fraction	100 ng/mL for 4 h	different ratio (0.5:1.0 to 2.0:1.0) *In vitro*: RAW 264.7	-↓ COX-2, iNOS expressions	(Carballo et al., 2017)

			macrophages		
	A-type cranberry proanthocyanidins	1 µg/mL for 1-24 h	25-50-100 µg/mL for 1-2 h *In vitro*: monocyte-derived macrophages	-↓ NF-kB -↓ MMP-1, MMP-3, MMP-7, MMP-8, MMP-9, MMP-13	(La et al., 2009)
	A-type cranberry proanthocyanidins	1 µg/mL for 24 h	25-50 µg/mL for 2 h *In vitro*: monoblastic leukemia-derived macrophages	-↓ IL-1β, TNF-α, IL-6, IL-8	(Feldman et al., 2012)
	A-type cranberry proanthocyanidins	1 µg/mL for 24 h	25-50 µg/mL for 2 h *In vitro*: a 3D co-culture model of gingival epithelial cells and fibroblasts	-↓ granulocyte colony-stimulating factor, CXC-chemokine ligand 1, IL-6, IL-8, interferon-γ inducible protein-10, monocyte chemoattractant protein-1 expressions	(Lombardo Bedran et al., 2015)
	Cranberry powder	0.5 mg/kg BW for 12 h	5 or 10 % of atherogenic diet for 6 weeks *In vivo*: Sprague-Dawley rats	-↑ plasma antioxidant status and total phenolics and flavonoid content -↑ SOD activity in erythrocytes -↓ serum thiobarbituric acid-reactive substances content	(Kim et al., 2014)
	Cranberry powder	0.5 mg/kg BW for 18 h	5-10 % of the diet for 6 weeks *In vivo*: Sprague-Dawley rats	-↑ serum HDL level -↓ serum total cholesterol, CRP, IL-1β, IL-6 levels	(Kim et al., 2011)
	Cranberry powder	0.5 mg/kg BW for 18 h	5-10 % of the diet for 6 weeks *In vivo*: obese diabetic homogeneous C57BL/KsJ-db/db mice	-↑ serum HDL level, antioxidant capacity -↓ serum total cholesterol, atherogenic index, glucose, insulin, GPx, carbonyl content levels	(Kim et al., 2013c)
Blackcurrant	Blackcurrant extract or cyanidin-3-O-ge lucoside	1 µg/mL for 24 h	0, 5 and 25 µg/mL for 2 h *In vitro*: monoblastic-leukemia derived macrophage-like cells	-↓ IL-6	(Desjardins et al., 2012)
	Blackcurrant-enriched formulation	1 µg/mL for 24 h	10-50-150 µg/mL for 24 h *In vitro*: U937 macrophages	-↓ PGE2, ROS, IL-6, IL-8, TNF-α	(Menghini et al., 2014)
	Anthocyanin fraction	100 ng/mL for 3 h	20 µg/mL for 12 h *In vitro*: Bone marrow-derived macrophages prepared from bone marrows isolated from Nrf2 wild-type and Nrf2 knockout mice	-↓ ROS, IL-1β	(Lee et al., 2014a)
	Anthocyanin fraction	100 ng/mL for 3-24 h	0-20 µg/mL for 12 h *In vitro*: RAW 264.7 macrophages	-↓ TNF-α, NF-kB, IL-1β	(Lee et al., 2014a)
	Anthocyanin-rich extract	500 ng/mL for 1-24 h	5-50 ng/mL for 30 min *In vitro*: monocytic THP-1 cells	-↓ TNF-α, IL-6, p-NF-kB -↑ IkBα	(Lyall et al., 2009)
	Diluted plasma isolated from blood collected preexercise and immediately postexercise from subject fed with blackcurrant-enriched diet	50 ng/mL for 3, 6, or 24 h	25 % in cell media for 30 min *In vitro*: monocytic THP-1 cells	-↓ TNF-α, IL-6	(Lyall et al., 2009)
	Freeze-dried whole fruit extract	500 ng/mL for 24 h	48 g (4 capsules, 2 before and 2 after exercise) *Ex vivo*: peripheral blood collected prior to and immediately postexercise	-↓ TNF-α, IL-6	(Lyall et al., 2009)

	~~Blackcurrant powder~~	~~2.5 mg/kg BW for 6 h~~	~~180 g/kg of diet for 7 days~~ ~~*In vivo*: C56/BL6 transgenic mice~~	~~-↓ NF-kB activation in different organs~~	~~(Balstad et al., 2010)~~
Barberry	Barberry polyphenol-extract	5 µg/mL for 24 h	100 µM for 24 h *In vitro*: RAW 264.7 macrophages	-↓ NO, iNOS, IL-10, TNF-α	(Reyes-Farias et al., 2015)
	Barberry extract	1.5 µg/mL for 16 h	50, 100, 200 µg/mL for 12 h *In vitro* murine peritoneal macrophages	-↓ NO, iNOS, TNF-α, IL-6, IL-1β, IFN-γ, RANTES, MCP-1, NF-Kb, p-c-Jun,p-ERK, p-JNK -↑ Nrf2, heme oxygenase-1, IL-10	(Sharma et al., 2018)
Jamun berry	Jamun phenolics extract	1 µg/mL for 12 h	20 µM for 24 h *In vitro*: RAW 264.7 macrophages	-↓ ROS	(Liu et al., 2018)

TABLE 2. Effects of different berries on LPS-stimulated inflammatory models: *in vivo* studies

Berry	**Extracts/Fraction/Component**	**Dosage of LPS induced**	**Dosage of berry and testing system**	**Biological response**	**Reference**
Elderberry	Methanolic extract	0.5 µg/mL for 24 h	100, 50, 25 and 12.5 µg/mL for 24 h *Ex vivo:* macrophages obtained from BALB/c mice intraperitoneally injected with 20 mg LPS	-↓ NO	(Carneiro et al., 2019)
Wolfberry or Goji berry	LBP	5 mg/kg BW i.p. injection	200, 400, 800 mg/kg BW for 12 h *In vivo*: Sprague-Dawley male rats	-↓ IL-1β, IL-6, IL-8, TNF-α, NF-κB, ROS and Keap1 in kidneys -↑ Nrf2, HO-1, NQO1 in kidneys	(Huang et al., 2019)
	LBP	5 mg/kg BW i.p. injection	200, 400, 800 mg/kg BW for 6, 12, 24, 48 h *In vivo*: Sprague-Dawley male rats	-↓ IL-1β, IL-6, IL-8, TNF-α, NF-κB and ROS levels in serum -↓ NF-κB and Keap1 in kidneys -↑ Nrf2, HO-1, NQO1 in kidneys	(Wu et al., 2020)
	LBP	5 mg/kg BW i.p. injection	200 mg/kg BW for 24 h *In vivo*: C57BL/6 mice	-↓ IL-6, TNF-α, lung injury and pulmonary edema	(Chen et al., 2018)
Emblic	Amla fruit extract	2 mg/kg BW	50 mg/kg BW for 4-24 h *In vivo:* male Wistar rats	-↓ TNF-α and IL-6 in serum	(Rao et al., 2013)
Lingonberry	Lingonberry extract	1 µg/mL for 24-48 h (prevention) 1 µg/mL for 3 h (reversal)	10-100 µg/mL for 3 h (prevention) 24-48 h (reversal) *Ex vivo*: Primary astrocytic cultures from Wistar rats	-↓ ROS, NO and acetylcholinesterase activity -↑ viability, thiol content and SOD	(Pacheco et al., 2018)
Chokeberry	Black chokeberry ethanolic extract	250 µg/kg	50 mg/kg/day for 7 days *In vivo*: male ICR mice received a single intraperitoneal injection of LPS	-↓ iNOS, COX-2, TNF-α	(Lee et al., 2018)
Seabuckthorn	Seabuckthorn berries paste	10 mg/kg BW.	200, 400 and 800 mg/kg BW for 7 days *In vivo*: male SPF KM mice	-↓ body weight loss, lung tissue, microstructure lesions, transvascular leakage increase, malondialdehyde augmentation -↑ SOD, GPx, Nrf2	(Du et al., 2017)
Grape	GSPE	7 mg/kg BW	50, 75, 100 and 200	-↓ NO level in the	(Pallares et al.,

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Tabella formattata

			mg/kg/day BW for 15 days *In vivo*: Wistar female rats	plasma, red blood cells, spleen, and liver; -↓ TNF-α and IL-10 in plasma; -↓ hepatic level of IL-6, iNOS, glutathione disulfide/total glutathione	2013)
	GSPE	0.3 mg/kg BW for 5 days	75and 375 mg/kg BW for 15 days *In vivo*: male Wistar rats	-↓ TNF-α in plasma -↓ MPO, COX-2, ROS in the small and large intestinal sections	(Gil-Cardoso et al., 2019)
	Red and white GE	10 μg/kg BW	100-500 mg/kg BW for 24 h *In vivo*: Sprague−Dawley rats	-↓ NF-κB, iNOS, COX-2 in liver	(Nishiumi et al., 2012)
	GE	3-15 mg/kg BW	0, 100, or 300 mg/kg/day BW for 3 weeks *In vivo*: Sprague−Dawley rats	-↓ phospholipases A2 activity in serum; - ↑ hematocrit in serum	(Tsao et al., 2012)
	GPE	0.5 mg/kg BW one i.p. injection or 0.25 mg/kg BW for 1 week	4% of diet for 4 weeks *In vivo*: mice	-↓ NF-κB in whole body and abdominal/peritoneal regions of interest -↓ TNF-α, IL-6 serum	(Miller et al., 2018)
	GPE	10 μg/L for 24, 48 and 72 h	46 g two times a day, for 3 weeks *Ex vivo*: monocyte populations in the peripheral blood mononuclear cells obtained from blood samples of healthy obese male and female volunteer	-↑ IL-1β, IL-6	(Zunino et al., 2014)
	Resveratrol	3 μg/mL for 6-12 h	200 nM for 6-12 h *Ex vivo*: cortical networks of neurons, astrocytes and microglia	-↓ TNF-α	(Gullo et al., 2017)
	Resveratrol	10 ng in 100 μL PBS	10 mg/ kg BW, once every 2 days, for 6 days *In vivo*: New Zealand white rabbits	-↓ inflammatory arthritis, PGE2, MMP-3, MMP-13	(Wang et al., 2011)
Pomegranate	Polyphenol rich pomegranate extract	100 μg/kg BW i.p. injection, twice weekly, for 4 weeks	0.2 ml of 0.2% POMx via oral gavage (daily) for 4 weeks *In vivo*. male swiss albino mice	-↓ ROS, TLR-4, NF-κB, IL-6, TNF-α, BAX -↑ Nrf2, Bcl-2, heme-oxygenase-1	(Gupta et al., 2019)
	Punicalagin	20 mg/kg BW for 7 h	12.5, 25, 50 mg/kg BW for 1 h *In vivo*: Male BALB/c mice	-↓ NF-kB, TLR-4, TNF-α, IL-6, IL-1β, myeloperoxidase in lung	(Peng et al., 2015)
	Punicalagin	250 μg/kg 7 times a day, for 1 week	1.5 mg/kg BW at day for 4 weeks *In vivo*: Male imprinting control region mice	-↓ memory impairment -↓ NF-kB in brain -↓ amyloid beta$_{1-42}$ generation in brain -↓ amyloid precursor protein, beta-secretase 1 in brain	(Kim et al., 2017)
	Punicalagin	600 μg/kg BW at day, for 7 days	9 mg/kg BW at day, for 7 days *In vivo*: Male ICR mice	-↑ Nrf2, GSH, SOD, catalase in testes -↑ fertility indices	(Rao et al., 2016)
	Punicalagin	5 mg/kg BW	50 mg/kg BW, for 2 h *In vivo*: Rats	-↓ serum creatinine and neutrophil gelatinase-associated lipocalin -↓ IL-18, TNF-α, IL-6, MDA, NO, Bax/Bcl2 ratio, iNOS,	(Fouad et al., 2016)

ha formattato: Tipo di carattere: Corsivo

				caspase 3, caspase 8 and caspase 9 in kidneys -↓ histopathological injury and molecule-1 expression in kidneys.	
Bilberry	Bilberry extract	1 mg/kg BW on the 2nd and 7th day of bilberry treatment	50, 100, 20 mg/kg at day for 7 days *In vivo*: Mice	-↓ plasma alanine transaminase, aspartate transaminase; -↓ liver NOS, TNF-α, IL-1β, IL-6, NF-κB, MDA, NO	(Luo et al., 2014)
Strawberry	Chilean white strawberry aqueous extract	5 mg/kg BW for 3 h	4 g/kg BW at day for 10 days *In vivo*: Male Sprague-Dawley rats	-↓ serum transaminase, alanine transaminase, aspartate transaminase; -↓ serum TNF-α, IL-1β, IL-6, IL-10; -↑ liver GSH/glutathione disulfide ratio	(Molinett et al., 2015)
	Freeze-dried strawberry powder	10 µg/L for 24, 48, 72 h	Four servings of frozen strawberries per day for 3 weeks *Ex vivo*: peripheral blood mononuclear cells	-↑ TNF-α	(Zunino et al., 2015)
Blueberry	Blueberry extract	100 ng/mL for 16 h	1% of diet for 5 weeks *Ex vivo*: thioglycollate-elicited peritoneal macrophages from apoE-/- mice	-↓ TNF-α, IL-6	(Xie et al., 2011)
	Blueberry powder	10 mg/kg BW, for 6 h	2 % of diet, for 2 days, once at days *In vivo*: Sprague-Dawley rats	-↑ glomerular filtration rate, renal blood flow in kidney; -↓ renal vascular resistance, ROS, superoxide, TLR4, TNF-α, kidney injury molecule-1	(Nair et al., 2014)
	Freeze-dried whole blueberry powder	1 µg/mL for 24 - 48 h	4 % of diet/day, for 8-12 weeks *Ex vivo*: splenocytes isolated from C57BL/6 mice	-↓ IL-1β, IL-6, TNF-α	(Lewis et al., 2018)
Mangosteen	α-mangostin	100 ng/mL for 4-24 h	0-10 µg/mL for 4-24 h *Ex vivo*: Murine bone marrow-derived dendritic cells generated from the bone marrow cells of the tibia and femur of 7 to 8 week old male BALB/c mice fed with α-mangostin	-↓ INF-γ, IL-12, TNF-α, IL-6 -↑ IL-10	(Herrera-Aco et al., 2019)
	α-mangostin	2 mg/kg BW, 3 daily injections at 24 h-intervals	40 mg/kg BW, at day for 14 days *In vivo*: female C57BL/6J mice	-↓ brain IL-6, COX-2, translocator protein, ionized calcium-binding adapter molecule 1	(Nava Catorce et al., 2016).
	α-mangostin and ground dried pericarp Garcinia mangostana Linn	100 µg/kg BW administered subcutaneously	20 mg/kg or 50 mg/kg BW for 15 days *In vivo*: Sprague–Dawley rats	-↓ TNF-α, IL-6, depressive behavuiours	(Lotter et al., 2019)
Cranberry	Cranberry powder	0.5 mg/kg BW for 12 h	5 or 10 % of atherogenic diet for 6 weeks *In vivo*: Sprague-Dawley rats	-↑ plasma antioxidant status and total phenolics and flavonoid content -↑ SOD activity in erythrocytes -↓ serum thiobarbituric acid-reactive substances content	(Kim et al., 2014)

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	Cranberry powder	0.5 mg/kg BW for 18 h	5-10 % of the diet for 6 weeks *In vivo*: Sprague-Dawley rats	-↑ serum HDL level -↓ serum total cholesterol, CRP, IL-1β, IL-6 levels	(Kim et al., 2011)
	Cranberry powder	0.5 mg/kg BW for 18 h	5-10 % of the diet for 6 weeks *In vivo*: obese diabetic homogeneous C57BL/KsJ-db/db mice	-↑ serum HDL level, antioxidant capacity -↓ serum total cholesterol, atherogenic index, glucose, insulin, GPx, carbonyl content levels	(Kim et al., 2013c)
Barberry	Barberry polyphenol-extract	5 µg/mL for 24 h	100 µM for 24 h *In vitro*: RAW 264.7 macrophages	-↓ NO, iNOS, IL-10, TNF-α	(Reyes-Farias et al., 2015)
	Barberry extract	1.5 µg/mL for 16 h	50, 100, 200 µg/mL for 12 h *In vitro* murine peritoneal macrophages	-↓ NO, iNOS, TNF-α, IL-6, IL-1β, IFN-γ, RANTES, MCP-1, NF-Kb, p-c-Jun,p-ERK, p-JNK -↑ Nrf2, heme oxygenase-1, IL-10	(Sharma et al., 2018)