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Sulforaphane: A nutraceutical against diabetes-related complications

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ABSTRACT

There is an increasing interest in the use of nutraceuticals and plant-derived bioactive compounds from foods for their potential health benefits. For example, as a major active ingredient found from cruciferous vegetables like broccoli, there has been growing interest in understanding the therapeutic effects of sulforaphane against diverse metabolic complications. The past decade has seen an extensive growth in literature reporting on the potential health benefits of sulforaphane to neutralize pathological consequences of oxidative stress and inflammation, which may be essential in protecting against diabetes-related complications. In fact, preclinical evidence summarized within this review supports an active role of sulforaphane in activating nuclear factor erythroid 2-related factor 2 or effectively modulating AMP-activated protein kinase to protect against diabetic complications, including diabetic cardiomyopathy, diabetic neuropathy, diabetic nephropathy, as well as other metabolic complications involving non-alcoholic fatty liver disease and skeletal muscle insulin resistance. With clinical evidence suggesting that foods rich in sulforaphane like broccoli can improve the metabolic status and lower cardiovascular disease risk by reducing biomarkers of oxidative stress and inflammation in patients with type 2 diabetes. This information remains essential in determining the therapeutic value of sulforaphane or its potential use as a nutraceutical to manage diabetes and its related complications. Finally, this review discusses essential information on the bioavailability profile of sulforaphane, while also covering information on the pathological consequences of oxidative stress and inflammation that drive the development and progression of diabetes.

1. Introduction

Diabetes mellitus is considered one of the greatest catastrophes facing the world health structures today. This condition currently ranks among the top ten leading causes of deaths globally, according to the World Health Organization (WHO) [1]. Diabetes mellitus defines a state of impaired glucose tolerance that is characterized by hyperglycemia and insulin resistance, with the latter being considered by far the most

Abbreviations: AGEs, advanced glycation end-products; AKT, protein kinase B; AMPK, AMP-activated protein kinase; CAD, coronary artery disease; CAT, catalase; CRP, C reactive protein; CVD, cardiovascular disease; DCM, diabetic cardiomyopathy; GSH, glutathione; GSK3β, glycogen synthase kinase-3 beta; HbA1c, glycated hemoglobin; GLP1-RA, glucagon like peptide-1 receptor agonists; HDL, high density lipoprotein; IFN-γ, interferon-gamma; IC, interleukin; IKK, IκB kinase; LDL, low density lipoprotein; MDA, malondialdehyde; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; Nrf2, nuclear factor erythroid 2-related factor 2; PI3K, phosphatidylinositol 3-kinase; RNS, reactive nitrogen species; ROS, reactive oxygen species; SOD, superoxide dismutase; T1D, type 1 diabetes; T2D, type 2 diabetes; TNF-α, tumor necrosis factor-alpha; WHO, World Health Organization; UV, ultraviolet.

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important characteristic feature of type 2 diabetes (T2D). Prolonged exposure to hyperglycemia within a diabetic state may give rise to many devastating outcomes that directly contribute to reduced life expectancy. In fact, within their lifetime, individuals with diabetes are likely to develop complications to the eye, kidneys, neurons, and cardiovascular system, leading to the pathogenesis of retinopathy, nephropathy, neuropathy, and cardiovascular disease (CVD). With most people with diabetes likely to die of CVD when compared to those without this condition. This explains accelerated efforts directed at uncovering new pharmacological agents that can effectively manage diabetes and its related complications (Fig. 1).

Over the years, both insulin and metformin have been effectively used to manage diabetic complications, which has somehow prolonged the lives of people with this condition [2,3]. In addition, lifestyle modification that involve controlling one's diet and regular physical activity have equally contributed to effective management of diabetes and its related complications [4,5]. However, the escalating numbers in people living with this condition, including associated deaths, warrant a need for alternative or complementary therapies to curb diabetes-related complications. Alternatively, medicinal plants have been a good and consistent source for the development of pharmaceutical drugs that are used to combat many diseases. For example, over 40 % of pharmaceutical formulations are based on natural products, while groundbreaking drugs like metformin are known to have originated from traditional medicine [6]. Many medicinal plants have been consumed as part of food since ancient times. These medicinal plants and food sources are rich in active ingredients that are increasingly explored for their therapeutic potential against many diseases.

Sulforaphane, is an active ingredient of cruciferous vegetables like broccoli, cabbage, and cauliflower. Growing literature has investigated a connection between the use of sulforaphane or plant extracts containing this bioactive compound with some health benefits, including the amelioration of complications of diabetes and CVDs [7–12]. In fact, the therapeutic properties of sulforaphane are widely attributed to its capacity to activate the antioxidant responses, which leads to leads enhanced expression of genes that code for cytoprotective and detoxifying proteins. As increasingly envisioned [7–11], enhancing the intracellular antioxidant responses to alleviate detrimental effects of oxidative stress and inflammation appears to be the predominant mechanism by which sulforaphane protect against pathological features of diabetes. However, to our knowledge, no review has provided a landscape analysis of scientific literature informing on how sulforaphane affects a broad spectrum of diabetes-related complications. This includes its benefits, possible side effects, bioavailability profile, and food sources.

Here, prominent online databases like PubMed and Google Scholar were accessed to retrieve information reporting on sulforaphane and its effects on diabetes-related complications. Broad search terms were used to identify relevant studies, including "sulforaphane", "diabetes mellitus", and "diabetic complications". Extracted information was mainly included in vivo preclinical models of diabetes. For clinical relevance, reviewed information was extended to assessing how foods rich in this bioactive compound affects people living with diabetes. A general overview of diabetes, its classification, and prominent pathological features involving oxidative stress and inflammation is added to underscore the potential therapeutic effects of sulforaphane.

2. An overview of diabetes mellitus, its prevalence, and its pathological consequences

Diabetes mellitus is a chronic medical disorder that is characterized by elevated blood glucose levels "a hyperglycemic state" that is

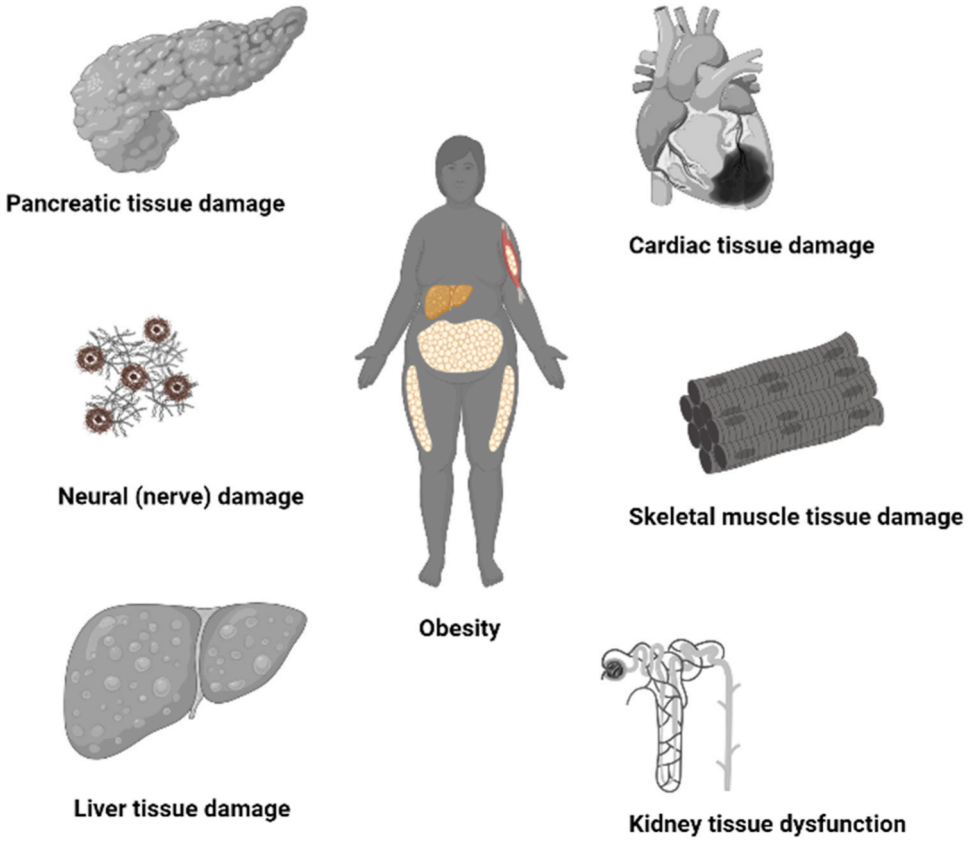

Fig. 1. A general overview of metabolic syndrome and its associated complications. An impaired metabolic state, likely characterized by obesity is associated with the development or pathological consequences that affect the pancreas, liver, skeletal muscle, kidneys, neurons, and the heart tissue, potentially leading to the development of diabetes, non-alcoholic fatty liver disease, diabetic nephropathy, diabetic neuropathy, and skeletal muscle insulin resistance.

consistent with impaired insulin action. Impairments in insulin secretion within the human body is considered one of the fundamental features of diabetes. Current estimates show that at least 8.5 % of adults aged 18 years and older have diabetes [13]. In 2019, diabetes was directly responsible for about 1.5 million deaths, of which 48 % of all deaths due to diabetes occurred prior to the age of 70 years [14]. Even worse, this global number of adults with this condition are estimated to reach 783 million by 2045 [13]. There are two main types of diabetes mellitus. First is type 1 diabetes (T1D), which cannot be prevented and represents the predominant form that occurs at childhood or in juveniles. The second is T2D, which accounts for over 90 % of diabetes cases worldwide, and this form of the disease can be prevented or delayed depending on a specific intervention applied [14].

The rising numbers of people with obesity and the metabolic syndrome [15] are largely fueled by unwanted lifestyle modifications that are coupled by reduced physical activity and excess nutrient availability as a result of overnutrition [16]. This consequence can lead to the progression of T2D, with excess nutrient availability implicated in many undesirable effects that favor the development of insulin resistance. Indeed, conditions of obesity and T2D are consistent with elevated levels of non-esterified fatty acids and adipogenic factors that interfere with insulin signaling by blocking the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/ mammalian target of rapamycin (mTOR) pathway. This is one of the predominant mechanisms that is increasingly targeted to reverse insulin resistance and improve glucose metabolism [17,18]. Well beyond the adverse effects of insulin resistance [19], exacerbated levels of lipid products such as ceramides and diacylglycerols are directly implicated in the progression of pathological effects of T2D [20,21]. These pathological effects can cause damage to different cellular systems by augmenting the lipogenic transcription factor sterol regulatory element binding protein 1c (SREBP1c), stimulating fatty acid synthase, mobilization of lipid droplet proteins to enhance retention of triacylglycerol, and stimulating transcription of lipogenic enzymes [22]. This may also be accompanied by impairments in energy regulation, through alterations of AMP-activated protein kinase (AMPK), an essential energy sensor that regulates cellular metabolism [23]. This has been prominently reported in experimental models of diabetes [18,24,25]. Interestingly, some antidiabetic drugs like metformin are known to activate AMPK to improve intracellular glucose uptake to enhance insulin sensitivity and ameliorate diabetes-associated complications [26,27]. Anyway, the past few years have seen a great interest therapeutic agents such as glucagon like peptide-1 receptor agonists (GLP1-RA) in improving the metabolic status by alleviating the detrimental effects of inflammation and impaired immune response within pathological conditions of diabetes [28,29]. With reviewed evidence indicating that new antidiabetic drugs, particularly GLP1-RA and tirzepatide, are the most effective in promoting weight loss, beyond their role in ameliorating oxidative stress and inflammation in patients with T2D [30,31]. Indeed, beyond obesity or excess nutrient availability, there are many diverse pathological consequences by which hyperglycemia can instigate toxic effects on cells, tissues, and organ systems. Evidence [32–34] has indicated that hyperglycemia can cause destruction to vital metabolic processes and drive the progression of diabetes, though an upsurge in the polyol pathway, activation of protein kinase, and enhancement in hexosamine biosynthetic pathway, to promote the formation of advanced glycation end-products (AGEs) and ultimately alteration of essential gene expression [35–37]. In fact, the generation of oxidative stress and the destructive consequences of inflammation highlight the fundamental processes linked with the development and acceleration of diabetes and its complications.

3. Oxidative stress and inflammation as major therapeutic targets in diabetes mellitus

Oxidative stress describes an imbalance between the toxic effects of free radical species, mainly via overproduction of reactive oxygen species (ROS), and the suppressed ameliorative capability of intracellular antioxidants. This is a well-studied phenomenon, predominantly for its contribution to the development and progression of many disease conditions including diabetes mellitus [38,39]. The essential role of ROS in cellular signaling or essential physiological processes is acknowledged [40], however uncontrolled production of these molecules can cause damage to tissues by accelerating cellular apoptosis. Within a diabetic state, both hyperglycemia and lipid toxicity, can drive the destructive effects of oxidative stress, leading to cellular damage [34]. This process is implicated in many conditions of diabetes, including retinopathy, nephropathy, neuropathy, and CVDs [41,42]. Because of their significant contribution to the global number of deaths occurring each year [14,43], coronary artery disease (CAD) and diabetic cardiomyopathy (DCM) remain the leading forms of CVDs. While abnormalities within the endothelium driven by nitric oxide dysregulation that are mainly associated with atherosclerosis uniquely influence the development of CAD [44,45], toxic ROS can directly cause damage to the cardiac tissue, giving rise to DCM [46]. By now, many sources of ROS have been described in literature, including the obscured activity of nicotinamide adenine dinucleotide phosphate oxidase (NADPH) oxidase [34,47], as well as those associated with high oxygen consumption like peroxisomes, endoplasmic reticulum, and mitochondria [48]. In fact, ferroptosis, an intracellular iron-dependent form of cell death that is different from apoptosis, necrosis, and autophagy, is also facilitated by oxidative stress, and can have a profound effect during the development and progression of many destructive effects of diabetes [49].

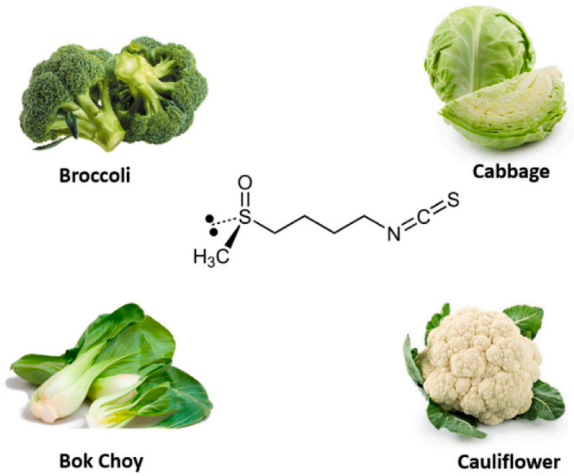

Fig. 2. A chemical structure of sulforaphane and natural sources rich in this bioactive compound, including broccoli, cabbages, boy choy, and cauliflower.

Inflammation is another pathological feature that shares a close relationship with oxidative stress and may have devastating outcomes during the development and progression of diabetes-associated complications. Briefly, inflammation infers to the body's response to a toxic stimulus and is necessary to initiate the healing process. However, pathological conditions like diabetes, mainly because of persistent hyperglycemic state, are associated with impaired inflammatory process, as a result drive undesired cellular response. For example, inflamed pancreatic tissue, especially inadequacies in insulin secretion, have long been associated with impaired immunological processes, this includes the recruitment and dysregulations in T-cell biology [50,51]. Importantly, abnormal T cell activation can drive chronic inflammatory, and even increase the risk of CVD in T2D [52,53]. Consistently, raised Th1/Th2 cytokines such as interferon-gamma (IFN-γ)/interleukin (IL)−5 and IL-2/IL-5 ratios are considered strong contributors to the worsening of diabetic conditions like retinopathy and CVD, in both preclinical models and subjects with T2D [54]. Many studies agree that elevation of pro-inflammatory markers like tumor necrosis factor-alpha (TNF-α), highly sensitive-C reactive protein (CRP), IL-6, IL-1β can

Table 1
An overview of preclinical evidence reporting on the therapeutic effects of sulforaphane against diabetes-related cardiovascular complications.

Author, year	Experimental model	Dose and intervention period	Main findings
[115] Miao et al., 2012	Streptozotocin (STZ)-induced type 1 diabetic (T1D) FVB mice	Received sulforaphane (injected subcutaneously) at 0.5 mg/kg 5 days a week for 3 months	Protected against diabetes-induced aortic damage by suppressing markers of oxidative stress and inflammation in the aorta. This was followed by enhanced expression of nuclear factor erythroid 2–related factor 2 (Nrf2) and its downstream antioxidants
[116] Bai et al., 2013	STZ-induced T1D FVB mice	Received sulforaphane (injected subcutaneously) at 0.5 mg/kg 5 days a week for 3 and 6 months	Protected against diabetic cardiomyopathy (DCM) by reducing high blood pressure and cardiac dysfunction. Also ameliorated hypertrophy and fibrosis and alleviated markers of oxidative stress (3-nitrotyrosine and 4-hydroxynonenal-4-HNE) and inflammation (tumor necrotic factor(TNF)-α and plasminogen activator inhibitor 1 expression), through activation of Nrf2
[117] Wang et al., 2014	High fat diet (HFD) + STZ- induced type 2 diabetic (T2D) C57BL/6 J mice	Received sulforaphane (injected subcutaneously) at 0.5 mg/kg 5 days a week for 3 months	Protected against diabetes-induced aortic damage by reducing wall thickness and structural derangement, along with decreasing markers of fibrosis (connective tissue growth factor and transforming growth factor), inflammation (tumor necrosis factor-α and vascular cell adhesion molecule 1), oxidative/ nitrative stress like 3-nitrotyrosine and 4-HNE (4-hydroxynonenal), and apoptosis. This was followed by enhanced Nrf2 expression
[101] Xu et al., 2016	Transgenetic preclinical model of T2D (*db/db*) (mice)	Received sulforaphane (orally) at 0.5 and 1 mg/kg for 3 months	Protected against DCM by improving cardiac function and ameliorating pathological changes (hypertrophy, fibrosis, inflammation, and oxidative damage), through activation of Nrf2 and its downstream gene expression
[118] Gu et al., 2017	HFD + STZ-induced T2D Nrf2 knockout (KO) mice, metallothionein-KO, and wild type (WT) mice	Received sulforaphane (injected subcutaneously) at 0.5 mg/kg 5 days a week for 4 months	Protected against DCM by alleviating cardiac dysfunction, including markers of oxidative damage, inflammation, fibrosis, and hypertrophy, with enhancement of Nrf2 and metallothionein expressions in the WT mice. Such effects were not seen in Nrf2-KO mice but protected against cardiac damage in metallothionein-KO mice
[119] Pereira et al., 2017	Transgenetic (T2D) Goto-Kakizaki rats, an animal model T2D	Received sulforaphane (intraperitoneal) at 1 mg/ Kg, or in combination with pyridoxamine (in drinking water) at 100 mg/Kg/day, for 8 weeks	Ameliorated endothelial dysfunction in aorta and mesenteric arteries by reducing vascular oxidative damage, advanced glycation end products (AGEs) and glycated hemoglobin (HbA1c) levels. Its combination with pyridoxamine was more effective in decreasing systemic free fatty acids levels, normalizing endothelial function, nitric oxide bioavailability and glycation
[120] Xin et al., 2018	Transgenic (FVB) mice, including Nrf2-KO and their WT C57BL/6 J control mice	Received sulforaphane (injected subcutaneously) at 0.5 mg/kg 5 days a week for 3 months	Protected against DCM by preventing angiotensin II-induced cardiac oxidative stress, inflammation, remodeling, and dysfunction. This was related to the activation of Nrf2 and protein kinase B (Akt)
[121] Wang et al., 2019	Transgenic (T1D) OVE26 and FVB mice	Received sulforaphane (orally) at 0.5 mg/kg, and/ or zinc sulphate (5 mg/kg) for 5 days a week for 18 weeks	Combination treatment was more effective in preventing DCM by improving cardiac dysfunction, ameliorating pathological alterations, and remodelling, while lessening cardiac hypertrophy, fibrosis, as well as markers of inflammation and oxidative damage
[98] Sun et al., 2020	HFD + STZ- induced (T2D) C57BL/6 J mice with AMP-activated protein kinase (AMPK) isoform 2 and WT mice	Received sulforaphane (injected subcutaneously) at 0.5 mg/kg 5 days a week for 3 months	Protected against DCM by alleviating cardiac remodeling, including complications of inflammation and oxidative damage WT mice. In AMPKα2-KO mice, restoring cardiac function was associated with AMPK-mediated lipid lowering effects, as well as activation of Nrf2 through AMPK, protein kinase B (AKT), and glycogen synthase kinase-3 beta (GSK3β) pathways
[100] Wang et al., 2022	HFD + STZ- induced (T2D) FVB mice	Received sulforaphane (injected subcutaneously) at 0.5 mg/kg 5 days a week for 3 months	Protected against DCM by ameliorating cardiac ferroptosis. This protective effect on ferroptosis was dependent on activation of Nrf2 and modulation of AMPK, resulting in alleviation of diastolic dysfunction

directly contribute to tissue damage, ageing, and worsening conditions such as obesity and T2D [55,56]. As a result, beyond oxidative stress, exacerbated pro-inflammatory response, has become an essential pathological component to target to alleviate tissue damage improve metabolic function [57–60].

4. Available treatment for diabetes mellitus and antioxidants as alternative or complementary therapy

Available and effective interventions for diabetes to lower blood glucose levels mainly involve diet and physical activity [5,14]. This includes common antidiabetic agents like insulin and metformin that have been used for many years to manage glucose control to reduce the risk factors that damage blood vessels. Indeed, for many years, insulin replacement has been the only therapy for most people living with T1D. Well beyond immunotherapies targeting T cells which mainly protect against pancreatic beta-cell damage [61], improved comprehension of insulin and glucose physiology has necessitated the development of better insulins that will enhance the quality of life for those already diagnosed with this irreversible condition [62]. Ultimately, sodium-glucose transport protein 2 inhibitors may be the most potent adjuvant therapy to insulin in T1D, if used prudently and with appropriate guidance to reduce the risk of diabetic ketoacidosis [63,64]. Importantly, this class of drugs can indirectly target the IL-1β pathway and thus alleviate low-grade inflammation, a clinically relevant feature in diabetic patients with high CVD risk [64]. Moreover, people with T2D can be treated with oral medication but may also need insulin, beyond the use of metformin, which is the common medical prescribed to lower blood glucose and other relevant complications [14]. Besides its recognized pleiotropic effects [65], the use of metformin has been

associated with weight loss, enhanced insulin sensitivity, alleviation of inflammation, and improvement in adipokine levels in diabetic conditions [66,67]. Unfortunately, the rising trends of diabetes [13] warrants further investigation into alternative or complementary therapies to reduce the disease burden.

The use of nutraceuticals, as complementary medicine, to counteract diverse metabolic conditions has risen over the years [68,69]. Nutraceuticals can be described as substances that have physiological advantages or offer protection against chronic diseases [70]. These substances are considered to have abundant antioxidant that are necessary to promote health and prevent life threatening diseases such as diabetes [70]. Many studies have reported on the potential therapeutic effects of antioxidants against diabetic complications. For example, our group has increasingly explored the beneficial effects of dietary supplements rich in antioxidants like selenium, curcumin, coenzyme Q_{10}, omega-3 fatty acids, and vitamin C against metabolic diseases, including complication linked with diabetes [71–74]. No doubt that the focal point of current research has been to determine how foods rich in antioxidants can prolong the lives of people with diabetes by ameliorating pathological features of this condition like oxidative stress and inflammation. Besides the fact that these molecules can directly block and neutralize the damaging effects of ROS [75], their capacity to intracellular antioxidants to alleviate tissue damage by activating nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway has attract considerable interest [76,77]. Notably, increased expression of genes and enzymes that transcribe cytoprotective defense antioxidants like glutathione peroxidase, superoxide dismutase, heme oxigenase-1 (HO-1), thioredoxin 1, and NADPH quinone oxidoreductase 1 (NQO-1) has been directly attributed to the activation or enhanced expression of Nrf2 [76,78,79]. Beyond the amelioration of oxidative stress [80], upregulation of Nrf2/Kelch-like ECH-associated protein 1 (Keap1) signal pathway and its downstream genes, may block inflammation by interfering with nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway and NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) inflammasome [81,82]. Both NF-κB pathway and NLRP3 inflammasome are well described mechanisms of inflammation that are activated in response to sustained hyperglycemia and may have a profound effect in causing tissue damage, leading to the progression of diabetes-associated complications [83,84]. While herbal medicine and some nutraceuticals have been increasingly evaluated for its capacity to protect against oxidative stress and inflammation by activating Nrf2 to preserve cellular function [78,82].

5. The discovery of sulforaphane as a bioactive isothiocyanate

5.1. A general overview of sulforaphane

Cruciferae or Brassicaceae are an outstanding source of bioactive compounds such as polyphenols, essential minerals, ascorbic acid, and isothiocyanates [85]. This family consist of edible green plants species such as *Brassica oleracea var. italica* (broccoli), *Brassica oleracea var. capitata* (cabbage), *Brassica oleracea var. botrytis* (cauliflower), and *Brassica oleracea var. sabellica* (kale) that contain important compounds like glucoraphanin. This compound is mainly found in the aerial portions of the plant such as flower buds and seeds [86]. Fig. 2 displays a chemical structure of sulforaphane and natural sources rich in this bioactive compound, including broccoli, cabbages, boy choy, and cauliflower. Naturally, glucoraphanin, 4-(methylsulfinyl)butyl glucoslinolate, is chemically stable and biologically inert, however, upon consumption (biting or chewing), glucoraphanin reacts with the enzyme

Table 2
An overview of preclinical evidence reporting on the therapeutic effects of sulforaphane against diabetic neuropathy or associated complications.

Author, year	Experimental model	Dose and intervention period	Main findings
[124] Negi et al., 2011	Streptozotocin (STZ)-induced type 1 diabetic (T1D) Sprague-Dawley rats	Received sulforaphane at 0.5 and 1 mg/kg intraperitoneally for 6 weeks	Protected against diabetic neuropathy by improving motor nerve conduction velocity, nerve blood flow and pain behavior, while reducing malondialdehyde (MDA) levels. This was accompanied by activation of nuclear erythroid 2-related factor 2 (Nrf2) and downstream targets hemeoxygenase-1 (HO-1) and NAD(P)H: quinone oxidoreductase 1 (NQO-1) in neuro2a cells and sciatic nerves. Also, reduced the expression of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and IκB kinase (IKK) phosphorylation as well as that of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) and tumor necrosis factor-α (TNF-α) and interleukine-6 (IL-6) levels
[125] Souza et al., 2013	High fat diet (HFD)-induced type 2 diabetic (T2D) Wistar rats	Received sulforaphane (orally) at 1 mg/kg for 4 months	Protected against diabetes associated changes on the cerebral cortex and hypothalamus by improving glucose tolerance and liver triacylglycerols. This was followed by reducing the expression of glucose transporter (GLUT)3 in the cortex and hypothalamus
[126] Wang et al., 2016	STZ-induced T1D Sprague-Dawley rats	Received sulforaphane (orally) at 25 mg/kg for 14 days	Protected against neuronal apoptosis and memory impairment by correcting the abnormal expression of caspase-3 and myeloid cell leukemia 1 (MCL-1), while also improving neurotropic factors protein kinase B (Akt), glycogen synthase kinase-3 beta (GSK3β)
[127] Moustafa et al., 2018	Nicotinamide and STZ-induced T1D Wistar rats	Received sulforaphane (orally) at 1 mg/kg for 15 days	Protected against diabetic peripheral neuropathy by ameliorating oxidative stress, inflammation, and extracellular matrix remodeling. This was specific to reducing sciatic nerve MDA, nitric oxide, interleukin-6, and matrix metalloproteinase-2 and − 9 contents. While also decreasing sciatic nerve DNA fragmentation and expression of cyclooxygenase-2 and nuclear factor kappa-B p65. Meanwhile, it increased sciatic nerve superoxide dismutase and interleukin-10 contents
[128] Pu et al., 2018	Transgenic T2D (*db/db*) mice	Received sulforaphane (intraperitoneally) at 1 mg/kg for 28 days	Protected against cognitive impairments and Alzheimer's disease-like lesions by reducing levels of amyloid-β oligomers as well as activation of Nrf2 and the downstream antioxidants like HO-1 and NQO-1, which was accompanied by reduced the levels of reactive oxygen/nitrogen species (ROS/RNS) in mouse brains
[129] Sharma et al., 2021	STZ-induced T1D Wistar rats	Received sulforaphane (orally) at 25 mg/kg alone or in combination with, a glycoprotein ulinastatin at10 000 U/kg for 26 days	Protected against vascular dementia related complications by improving endothelial dysfunction and improving animal behavior. These were accompanied by amelioration of other abnormalities like brains' oxidative stress, inflammation, acetylcholinesterase (AChE)-activity, and cerebral cortex histopathological changes

Table 3
An overview of preclinical evidence reporting on the therapeutic effects of sulforaphane against diabetic nephropathy and its associated complications.

Author, year	Experimental model	Dose and intervention period	Main findings
[135] Zheng et al., 2011	Streptozotocin (STZ)-induced type 1 diabetic (T1D) C57BL/6 mice	Received sulforaphane (intraperitoneally) at 12.5 mg/k 3 times a week for 16 weeks	Protected against diabetic nephropathy by improving renal performance and limiting pathological alterations in the glomerulus. This was followed by the amelioration of oxidative damage and reduced expression of transforming growth factor beta 1, extracellular matrix proteins. This was in part through activation of nuclear factor erythroid 2–related factor 2 (Nrf2) in glomerulus
[136] Cui et al., 2012	STZ-induced T1D FVB mice	Received sulforaphane (injected subcutaneously) at 0.5 mg/kg 5 days a week for 3 months	Protected against diabetic nephropathy by reducing renal inflammation, oxidative disruption, and alleviating tissue fibrosis, in part by enhancing Nrf2 expression
[137] Shang et al., 2015	STZ-induced T1D Sprague Dawley rats	Received sulforaphane at 5 mg/kg for 12 weeks	Protected against diabetic nephropathy by blocking urine albumin excretion, matrix expansion, transforming growth factor-β1 expression, fibronectin, and type IV collagen deposition in the diabetic kidney. This was modulated in part though the glycogen synthase kinase-3 beta (GSK3β)/Nrf2 signaling pathway
[134] Wu et al., 2015	High fat diet (HFD)-induced T2D C57BL/6 J mice, including Nrf2 knockout (KO) mice	Received sulforaphane at 0.5 mg/kg for 4 months	Protected against diabetic nephropathy by reducing the levels of albuminuria, renal fibrosis, and inflammation. However, metallothionein expression was elevated, while renal protection was completely lost in Nrf2-KO diabetic mice
[138] Li et al., 2019	STZ-induced T1D Sprague Dawley rats	Received sulforaphane at 0.5 and 1 mg/kg daily for 12 weeks	Protected against diabetic retinopathy by suppressing inflammation markers like TNFα, IL-6, and IL-1β, as well as inhibiting oxidative stress via enhancing levels of glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT) improvement. Also, Nrf2 expression along with hemeoxygenase-1 (HO-1) and NQO-1. Not only that, but there was also a reduction in the expression of NOD-like receptor (NLR) proteins (NLRP3)
[139] Li et al., 2020	High fat diet (HFD) + STZ- induced T2D AMP-activated protein kinase (AMPK)α2-KO and WT FVB mice	Received sulforaphane (injected subcutaneously) at 0.5 mg/kg 5 days a week for 3 months	Protected against renal dysfunction by alleviating hypertrophy, oxidative disruption, inflammation, as well as fibrosis in WT mice, but not but not in AMPKα2-KO T2D mice. This positive effect in WT mice was associated amendments in renal lipotoxicity and in association with AMPK-mediated activation, as well as antioxidant activity linked with Nrf2 activation
[140] Lin et al., 2020	STZ-induced T1D Wistar rats	Received sulforaphane (orally) at 12.5 mg/kg for 10 days	Protected against bladder dysfunction by promoting Nrf2/HO-1 axis, as well as reducing bladder levels of reactive oxygen species, mitochondrial Bax translocation, cytochrome c release, and caspase 3/PARP/apoptosis, leading to improved voiding function
[141] Kong et al., 2021	STZ-induced T1D FVB mice	Received sulforaphane (injected subcutaneously) at 0.5 mg/kg 5 days a week for 4 months	Protected against renal dysfunction by reducing renal fibrosis, and through epigenetic up-regulation of bone morphologic protein 7 (BMP-7)
[142] Khaleel et al., 2019	STZ-induced T1D Wistar rats	Received sulforaphane (intraperitoneally) at 3 mg/kg for 20 h	Protected against diabetic nephropathy by restoring altered nephrotoxicity parameters, histological features, and oxidative stress. This followed by enhanced expression of Nrf2 and downstream target genes like HO-1, as well as inflammation and apoptotic markers IL-6 and caspase3

myrosinase, a ß-thioglucosidase. Notably, this enzyme hydrolysis glucoraphanin to liberate glucose and form an unstable aglucone that spontaneously rearranges to a range of reactive products, such as isothiocyanate sulforaphane [85,86]. Sulforaphane, 1-isothiocyanato-4-(-methylsulfinyl)butane), is a sulfur-rich compound, known of its role as an antioxidant and potent stimulator of endogenous detoxifying enzymes [87]. Sulforaphane has become the most attractive product of glucoraphanin due to its remarkable health-promoting properties. Going back, sulforaphane, was firstly synthesized around 1940's, during the period to which it also merged that this molecule was contained in hoary cress (*Cardaria draba*), broccoli, and cabbage [88]. Since then, various groups have synthesized this compound [89]. According to the literature, sulforaphane has generated great interest in the past decade, with an exponentially growing number of scientific articles reaching a total of 2799 on PubMed, since 1948 [90], which is in part due to its envisaged health promoting properties. Such accumulating evidence is related to the effects of sulforaphane ameliorating complications linked with cancer [91,92], hypertension [93], diabetes [7], and obesity [94,95]. The mechanism underlying the health-promoting effect of sulforaphane relates to its activation of Nrf2/Keap1 signaling pathway [7–11]. This action generally leads to enhanced intracellular antioxidant response and has been reported in human subjects consuming cruciferous vegetables [96–101]. Thus, there has been a general interest in understanding the therapeutic effects of sulforaphane against diseases, including diabetes mellitus.

5.2. Metabolism and bioavailability of sulforaphane

No doubt there has been a need to exploit the health-promoting effects of sulforaphane in humans. Briefly, in humans, sulforaphane can be administered directly in its active form or as glucoraphanin which undergoes the hydrolysis during digestion by the action of vegetable and gut microflora myrosinase [8,85,102]. Humans or mammalian do not produce the enzyme, myrosinase; however, the conversion of glucoraphanin to sulforaphane still occurs. Apparently, this crucial can be carried out by the bacterial microflora of the gastrointestinal tract [8,85,102]. The content of these bacterial microflora can be affected by several factors such mechanical cleansing or antibiotic treatment which can reduce the glucosinolate conversion in healthy human subjects [103]. This indicates that the gastrointestinal microflora represents a critical factor in determining the extent of glucosinolate hydrolysis. After intake, sulforaphane follows the mercapturic acid pathway until its conversion in dithiocarbamates before final excretion [85]. After absorption, glucoraphanin and sulforaphane may be reduced to their methylthiobutyl analogue, commonly known as glucoerucin and erucin respectively, either through enzymic activity by the gut microbiota or non-enzymically through changes in the redox environment [8104]. Compared to glucoraphanin, sulforaphane is rapidly absorbed and eliminated with small inter-individual variations and typical urinary excretion of at least 70 % of the dose, whereas the conversion of glucoraphanin is slow and with high inter-individual variations. However,

Table 4
An overview of preclinical evidence reporting on the therapeutic effects of sulforaphane against retinopathy and diverse diabetes-related complications like nonalcoholic fatty liver disease (NAFLD) and insulin resistance.

Author, year	Experimental model	Dose and intervention period	Main findings
[155] Souza et al., 2012	Streptozotocin (STZ)-induced type diabetic (T1D) Wistar rats	Received sulforaphane (orally) at 0.1, 0.25, or 0.5 mg/kg for 10 days	Protected against metabolic complications by effectively controlling fasting glycemia, enhancing insulin sensitivity, and lowering hepatic glycogen concentrations. These were also related to reduction in serum triacylglycerols, urea, and creatinine
[158] Jiang et al., 2014	STZ-induced T1D FVB mice	Received sulforaphane (injected subcutaneously) at 0.5 mg/kg 5 days a week for 3 months	Protected against diabetes-induced testicular apoptosis by suppressing endoplasmic reticulum stress and mitochondrial cell death pathways. While also enhancing nuclear factor erythroid 2–related factor 2 (Nrf2) expression, as well as ameliorating testicular oxidative damage, inflammation and fibrosis, and germ cell proliferation
[157] Wang et al., 2014	High fat diet (HFD) + STZ- induced type 2 diabetic (T2D) C57BL/6 J male	Received sulforaphane (injected subcutaneously) at 0.5 mg/kg 5 days a week for 4 months	Protected against testicular apoptotic cell death by enhancing B-cell lymphoma 2 (Bcl2) expression and blunting cleavage of caspase-3 and caspase-8 without overtly affecting endoplasmic reticulum stress. This was concomitant to the amelioration of oxidative damage and inflammation, in part by activating Nrf2
[159] Souza et al., 2016	STZ-induced T1D Wistar rats	Received sulforaphane at (intraperitoneally) at 0.5 mg/kg) for 21 days	Ameliorated some features of clinical diabetic complications, especially lipid profiles and insulin responsiveness, but did not affect antioxidant response, including superoxide dismutase, and catalase in in the pancreas, liver, and kidney
[148] Lv et al., 2020	STZ-induced T1D BALB/c mice	Received sulforaphane (intraperitoneally) at 0.5, 1, and 2 mg/kg daily for 2 weeks	Protected against diabetes-induced retinal photoreceptor cell degeneration by blocking inhibition of endoplasmic reticulum stress, inflammation, and thioredoxin-interacting protein (Txnip) expression and activation of the AMPK pathway
[11] Tian et al., 2020	HFD + STZ- induced T2D mice	Received sulforaphane (orally) at2 and 10 mg/kg for 12 weeks	Protected against NAFLD and pancreatic damage by improving glucose/insulin metabolism and lipid profiles, including reduction in triglycerides and low-density lipoprotein-cholesterol (LDL-c). Antioxidant capacities in the liver and pancreas were also increased
[153] Wang et al., 2020	Transgenic T2D (*db/db*) mice	Received sulforaphane (intraperitoneally) at 0.5 mg/kg for 1 month	Protected against skeletal muscle dysfunction by enhancing the grip strength, including the lean and gastrocnemius mass, while restoring skeletal muscle fiber organization. This was followed by activation of Nrf2/hemeoxygenase-1 (HO-1) signal pathway, and reducing the expression of inflammatory and apoptotic associated proteins
[156] Ma et al., 2022	HFD-induced T2D C57BL/6 mice	Received sulforaphane at 10 mg/ kg for 12 weeks	Protected against NAFLD by limiting the accumulation of excess liver lipids and reducing inflammation and enhancing antioxidant levels
[154] Zhang et al., 2022	HFD-induced T2D ICR mice	Received sulforaphane (injected subcutaneously) at 0.5 mg/kg 5 days a week for 8 months	Ameliorated insulin resistance and improved metabolic parameters, including reducing body weight, and alleviating hyperglycemia and hyperlipidemia, as well as enhancing liver function. This was followed by increased expression of antioxidant genes downstream of Nrf2 and reduced accumulation of lipid peroxides malonaldehyde (MDA) and 4-hydroxynonenal (4-HNE)

the fact remain sulforaphane is still considered unstable compared to glucoraphanin [8]. For that reason, direct administration of sulforaphane on humans has been limited. Currently, there are studies that are looking at possible ways to stabilize sulforaphane, some researchers have prompted the development of stabilized preparations, such as an α-cyclodextrin-encapsulated form of sulforaphane [105,106] and a stabilized version of pure plant-derived sulforaphane, known as prostaphane [105]. Alternatively, glucoraphanin-rich preparations containing active myrosinase have also been used [107]. Some researchers have shown that another way to administer sulforaphane to humans is through broccoli sprout extracts or minimally processed broccoli, given the instability of sulforaphane most clinical studies about the effect of sulforaphane have used broccoli extracts and focused on validating the efficacy of sulforaphane-rich food, not on sulforaphane as a drug [85]. Notably, (R)-sulforaphane is the naturally occurring isomer, found in broccoli, this is a sulforaphane in which the sulfinyl group has R configuration. This form is mainly known of its protective properties such as antioxidative, anti-inflammatory, anti-atherosclerotic, cardioprotective, anticoagulant, antibiotic, and chemo preventive activities in diverse disease settings [7,92,108,109]. Researchers suggests that the *R*-isomer may be more bioactive than the *S*-isomer, hence the synthetically derived *R,S*-sulforaphane which is now commonly used, especially in animal studies and in vitro studies [110,111]. In other animal models, *R,S*-sulforaphane has been shown to inhibits TNF-α-induced adhesion of monocytes in epithelial cells [112], while some suggests that this compound may prolong the activation of Nrf2 and expression of catalase, thus protecting against ultraviolet (UV)-induced oxidative damage in ex vivo models [113]. Even though chemical synthesis of sulforaphane looks promising, it appears this process is likely costly and time-consuming and requires several highly toxic substances, while some products from these reactions require further purification [114]. Therefore, because of these limitations, sulforaphane consumed from vegetables is more favorable for humans, especially when consumed daily for potential health benefits [86].

6. Potential therapeutic effects of sulforaphane against diabetes-associated complications

6.1. Characteristic features of included studies

Briefly, a systematic search revealed 34 preclinical studies reporting on the potential therapeutic effects of sulforaphane against diabetes-associated complications. These studies are subsequently discussed based on the type of diabetic complication being targeted by sulforaphane, including ten studies on its potential efficacy against CVD-related complications, seven studies focusing on diabetic neuropathy, eight studies on diabetic nephropathy, and the last nine studies were on its effects against diverse pathologies of diabetes, including nonalcoholic fatty liver disease (NAFLD), skeletal muscle dysfunction, insulin resistance, and retinopathy. Diverse preclinical systems, mainly involving rats and mice with both T1D and T2D, were used as representative models for diabetes-related complications. Since clinical studies directly reporting on the therapeutic effects of sulforaphane are lacking, included literature was mainly from broccoli, which is rich in

Table 5
Clinical evidence reporting on the potential benefits of broccoli against diabetes-associated complications.

Authors, year	Study design	Study population	Intervention	Main findings
Taniguchi et al., 2008 [160]	Randomized cross-over design	Healthy Japanese subjects (n = 11), with an average age between 23 and 33 years	Received 200 g of white rice containing broccoli, with comparable amounts of carbohydrate, fat, protein, and fiber over 180 min	Effective at reducing acute glycemia and insulinemia
Bahadoran et al., 2011 [161, 162]	Randomized double-blind clinical trial	Patients with type 2 diabetes (n = 56), with an average age between 18 and 60 years	Received broccoli sprouts powder at 5 or 10 g/day for 4 weeks	Significantly reduced lipid peroxidation by decreasing malonaldehyde (MDA), increasing antioxidant capacity, and oxidized low density lipoprotein cholesterol. While also reducing serum insulin concentration and homeostatic model assessment for insulin resistance (HOMA-IR)
Bahadoran et al., 2012 [163]	Randomized double-blind clinical trial	Patients with type 2 diabetes (n = 56), with an average age between 18 and 60 years	Received broccoli sprouts powder at 5 or 10 g/day for 4 weeks	Improved lipid profiles, especially reducing oxidized low-density lipoprotein ratio, to lower the risk factors for cardiovascular disease
Saeidi et al., 2021 [164]	Randomized control trial	Patients with T2D (n = 11), with an average age between 40 and 60 years	Received broccoli supplements at 10 g of broccoli supplement per day for 12 weeks	Reversed insulin resistance and dectin-1 in participants with T2D
Thorup et al., 2021 [165]	Randomized control trial	Patients with T2D (n = 92), with an average age between 30 and 70 years	Received *Brassica* and root vegetables at 500 g daily for 12 weeks	Enhanced insulin sensitivity, reduced body fat mass and blood pressure, while also improving glycemic control
Imai et al., 2023 [166]	Randomized controlled cross-over study	Healthy subjects (n = 18), with an average age of 21 years	Received a meal containing tomato, broccoli, fried fish, and boiled white rice for up to 60 min	Improved postprandial blood glucose and insulin concentrations

this bioactive compound, against diabetes-related complications. Importantly, the below sections discuss both preclinical and clinical evidence on the impact of sulforaphane or broccoli against diverse diabetes-related complications. Critical points which are part of the discussion include effective doses of the bioactive compound, intervention period, and the type of experimental model of diabetes used.

6.2. Potential therapeutic effects of sulforaphane against diabetes-associated cardiovascular complications

Diabetes, through its major characteristic features like hyperglycemia, is known to contribute to the development and progression of cardiovascular-related complications. Indeed, an impaired oxidative and inflammatory status is central to the development of these diabetes-related cardiovascular complications [34]. As a result, various preclinical models depicting diabetes-related cardiovascular complications have been developed to assess the efficacy of various pharmaceutical drugs, including naturally derived bioactive compounds against such abnormalities. Table 1 shows various animal models of diabetes that are currently used to investigate the cardioprotective effects of sulforaphane. For example, subcutaneous injection of sulforaphane (at 0.5 mg/kg 5 days a week for 3 months) could protect against diabetes-induced aortic damage by suppressing markers of oxidative stress and inflammation T1D FVB mice [115]. These results were consistent with enhanced expression of Nrf2, which is the major antioxidant response factor responsible for the therapeutic benefits of sulforaphane against diabetes induced cardiovascular damage. The inbred FVB/N mouse strain is distinguished by vigorous reproductive performance [122], while displaying severity to the development of diabetes and insulin resistance after injecting with low-dose streptozotocin [123]. In fact, more studies included within the study support the use of subcutaneous injection of sulforaphane (at 0.5 mg/kg 5 days a week for 3–4 months) to alleviate diabetes-associated cardiovascular complications in mice [98, 100,115–117,120,121].

The intervention was shown to be even more effective in preventing DCM by improving cardiac dysfunction, through neutralizing oxidative stress and reducing markers of inflammation to reverse cardiac hypertrophy/ fibrosis. These studies indicated that enhanced expression of Nrf2 or its activation within the diabetic heart was crucial for alleviation markers of oxidative stress and inflammation, including 3-nitrotyrosine and 4-hydroxynonenal, TNF-α, and vascular cell adhesion molecule 1 in T1D and T2D mice [98,100,101,115–118,120,121]. Potential therapeutic mechanisms of sulforaphane also implicates effective modulation of energy metabolism through the activation of AMPK. For example, sulforaphane could restore cardiac function while effectively modulating lipid metabolism and alleviating cardiac remodeling through the regulation in mice with T2D [98].

Other studies showed that sulforaphane could also be effective at protecting against diabetes-associated cardiovascular complications when administered intraperitoneally or orally in rodents (Table 1). For example, 8-week intraperitoneal administration of sulforaphane (at 1 mg/Kg) as a monotherapy, or in combination with pyridoxamine (in drinking water) could improve endothelial function by reducing vascular oxidative damage, and this was related to the reduction of AGEs and glycated hemoglobin (HbA1c) levels in transgenetic (T2D) Goto-Kakizaki rats [119]. Whereas 18-week oral administration of sulforaphane (at 0.5 mg/kg) in combination with zinc sulphate (5 mg/kg) was more effective in preventing DCM by improving cardiac dysfunction, by reducing cardiac remodeling, including markers of inflammation and oxidative damage in transgenic (T1D) OVE26 and FVB mice [121]. Further indicating that preclinical evidence strongly suggests enhanced its potential as a potential remedy to protect against diabetes-induced cardiovascular complications.

6.3. Potential therapeutic effects of sulforaphane against diabetic neuropathy and associated complications

Diabetic neuropathy describes damage to nerves, giving rise to peripheral neuropathy, autonomic neuropathy, and proximal neuropathy [130]. This condition remains difficult to treat, and is linked with diminished quality of life, lack of sleep, depression, and anxiety. Both oxidative stress and inflammation, because of prolonged exposure to hyperglycemia and other complications of diabetes, are central the development of neuropathy. This explains increased interest in targeting the alleviation of oxidative stress and inflammation to protect against nerve damage in experimental of diabetes, and even in human subjects with this condition [131–133].

Table 2 gives an overview of preclinical evidence reporting on the therapeutic effects of sulforaphane against diabetic neuropathy or its associated complications. Here, it is evident that 6-week intraperitoneal administration of sulforaphane (at 0.5 and 1 mg/kg) could protect against diabetic neuropathy by improving motor nerve conduction velocity, nerve blood flow and pain behavior, while neutralizing oxidative stress by reducing malondialdehyde (MDA) levels in streptozotocin

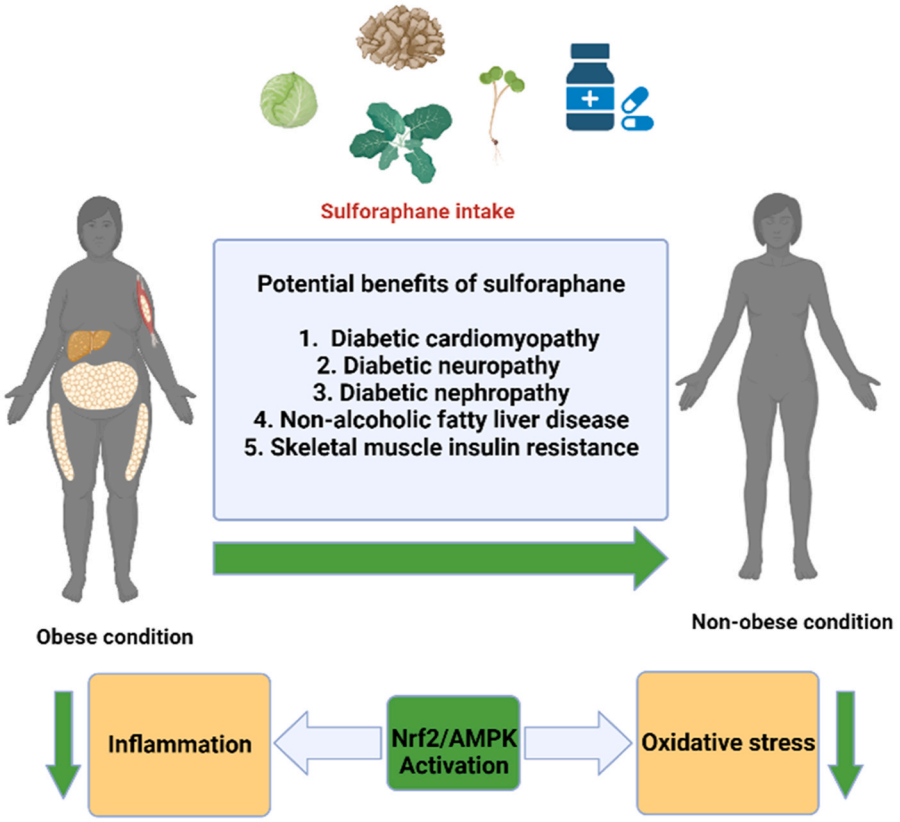

Fig. 3. A summary of preclinical evidence supporting an active role of sulforaphane (and food sources rich in this bioactive compound) in activating nuclear factor erythroid 2-related factor 2 (Nrf2) or AMP-activated protein kinase (AMPK) to protect against diabetic complications, including diabetic cardiomyopathy, diabetic neuropathy, diabetic nephropathy, and other metabolic complications involving non-alcoholic fatty liver disease and skeletal muscle insulin resistance. Alleviation of oxidative stress and inflammation is the predominant mechanism by which sulforaphane protects against diabetes associated complications. With clinical evidence suggesting that foods rich in sulforaphane like broccoli can improve the metabolic status and lower cardiovascular disease risk by reducing biomarkers of oxidative stress and inflammation in patients with type 2 diabetes.

(STZ) induced T1D Sprague-Dawley rats [124]. Such effects were related with activation of Nrf2, including its downstream target enzymes, including HO-1 and NQO-1. Also, the reduced expression of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and IκB kinase (IKK) phosphorylation as well as that of inducible nitric oxide synthase (NOS) and cyclooxygenase-2, TNF-α, and IL-6 levels in these diabetic conditions [124]. These positive effects were confirmed in T2D *db/db* mice, receiving sulforaphane (intraperitoneally) at 1 mg/kg for 28 day, showing enhanced cognitive function and alleviation of Alzheimer's disease-like lesions by reducing the levels of amyloid-β oligomers as well as activation of Nrf2 and the downstream antioxidants like HO-1 and NAD(P)H: quinone oxidoreductase 1 (NQO-1), which was accompanied by lower levels of reactive oxygen/nitrogen species (ROS/RNS) in mouse brains of these animals. The significant role of Nrf2 activation in protecting against diabetic neuropathy-related complications was confirmed in mice, showing reduced protective effects against levels of albuminuria, renal fibrosis, and inflammation in animals lacking Nrf2 [134].

Other studies showed that the therapeutic effects of sulforaphane extend beyond the activation of Nrf2 (Table 1). For example, 4-month oral administration of sulforaphane (at 1 mg/kg) in rodents could protect against diabetes-associated changes on the cerebral cortex and hypothalamus by improving glucose tolerance and liver triacylglycerols in HFD-induced T2D rats [125]. And this was followed by reducing the expression of glucose transporter (GLUT)3 in the cortex and hypothalamus [125]. Likewise, 2-week oral administration with sulforaphane (at 25 mg/kg) could protect against neuronal apoptosis and memory impairment by correcting the abnormal expression of caspase-3 and myeloid cell leukemia 1 (MCL-1), while also improving neurotropic factors protein kinase B (Akt), glycogen synthase kinase-3 beta (GSK3β) in STZ-induced T1D Sprague-Dawley rats [126]. These effects were also confirmed when sulforaphane was administered at similar doses in other diabetic rats, showing enhanced protection against vascular dementia related complications by improving endothelial dysfunction and improving animal behavior in STZ-induced T1D rodents [126,127,129].

6.4. Potential therapeutic effects of sulforaphane against diabetic nephropathy and its associated complications

Diabetic nephropathy also remains one of the devastating complications of diabetes, and its diagnosis is traditionally based on microalbuminuria [143]. Poor glycemic control, together with other complications of diabetes, including dyslipidemia, AGEs, as well as genetic factors are all implicated in the development of diabetic nephropathy [144]. Lately, it has become apparent that both oxidative stress and inflammation are the common denominators that are implicated in the development and progression of micro- and macrovascular complications of diabetes [145,146]. This is mainly through enhanced levels of ROS, AGEs, and defects in polyol pathway, uncoupled NOS, and alterations in mitochondrial respiratory chain, occurring consistently with raised pro-inflammatory factors within preclinical models of diabetes [145,146]. A recent report even indicates that targeting the IL-8-C-X-C chemokine receptor (CXCR)1/2 axis may be a feasible therapeutic strategy to protect against inflammation to potentially reduce the burden of diabetic kidney disease [147].

Table 3 gives an overview of preclinical evidence reporting on the therapeutic effects of sulforaphane against diabetic nephropathy and its associated complications. Here, it was apparent that 16-week intraperitoneal administration of sulforaphane (at 12.5 mg/kg) could protect against diabetic nephropathy by improving renal performance and limiting pathological alterations in the glomerulus in STZ-induced T1D Wistar rats [140]. This was followed by the amelioration of oxidative damage and reduced expression of transforming growth factor beta 1, extracellular matrix proteins in STZ-induced T1D mice [135]. This was in part through activation of nuclear factor erythroid 2–related factor 2 (Nrf2) in glomerulus in diabetic mice [135]. In fact, it was clear that administration of sulforaphane (at doses between 0.5 and 12.5 mg/kg), as early as 20 h up to 3 months, could activate Nrf2, including its

downstream antioxidant genes to protect against diabetic nephropathy in mice with T1D [136,138,140,142]. These findings indicated that activation of Nrf2 in response to sulforaphane administration was also associated with the suppression of inflammation markers, including TNFα, IL-6, and IL-1β, the NOD-like receptor (NLR) proteins (NLRP3).

Evidence covered in Table 3 indicate that, in addition to Nrf2, other molecular mechanisms may explain the potential therapeutic effects of sulforaphane against diabetic nephropathy in preclinical models. For example, 12-weeks administration of sulforaphane (at 5 mg/kg) could protect against diabetic nephropathy by blocking urine albumin excretion, matrix expansion, transforming growth factor-β1 expression, fibronectin, and type IV collagen deposition in the diabetic kidney in rats with T1D [137]. Sulforaphane can potentially interact with AMPK to alleviate renal dysfunction, which is associated with attenuation of oxidative disruption and inflammation transgenic diabetic mice. This positive effect in WT mice was associated amendments in renal lipotoxicity and in association with AMPK-mediated activation, as well as antioxidant activity linked with Nrf2 activation [139]. With recent literature indicating that administration of sulforaphane (injected subcutaneously at 0.5 mg/kg 5 days a week for 4 months) could protect against renal dysfunction by reducing renal fibrosis, and through epigenetic up-regulation of bone morphologic protein 7 (BMP-7) [141]. From summarized literature it has become apparent that administration that sulforaphane remains effective in attenuating toxic effects of oxidative stress and inflammation to protect against the development of nephropathy in preclinical modes of T1D.

6.5. Potential therapeutic effects of sulforaphane against retinopathy and other complications involved in the development of diabetes

Diabetes is associated with other diverse metabolic complications, that go beyond the implications of pathological features of CVD, neuropathy, or nephropathy. Some of these diabetes-related complications include retinopathy, NAFLD, and insulin resistance. Impaired substrate metabolism through enhanced availability of free fatty acids, together with increased oxidative stress and inflammation are the predominant factors that drive diabetes-induced tissue damage. Available information already highlights the potential benefits of sulforaphane in protecting against diabetes-induced retinopathy by blocking NLRP3 inflammasome formation [138], reducing mitochondrial stress [148], and enhancements of intracellular antioxidants through Nrf2-dependent and independent mechanisms in preclinical models [149,150]. Existing data have also indicated the potential therapeutic effects of sulforaphane against diverse pathological consequences of NAFLD [151,152] and insulin resistance [153,154], within various preclinical models of diabetes.

Table 4 gives an overview of preclinical evidence reporting on the therapeutic effects of sulforaphane against diverse diabetes-related complications, including retinopathy, NAFLD and insulin resistance. The administration of sulforaphane (at doses mounting to 0.5 mg/kg) could attenuate metabolic complications by improving glucose control, enhancing insulin sensitivity, and reducing hepatic glycogen concentrations in rats with T1D [155]. Interestingly, more evidence did report on the therapeutic effects of sulforaphane against complications related ton NAFLD. With others showing that diabetic rodents receiving sulforaphane (at 2 and 10 mg/kg for 12 weeks) could protect against NAFLD and pancreatic damage by improving glucose/insulin metabolism and lipid profiles, including reduction in triglycerides and LDL-c in experimental models of T2D [11,156]. Interestingly, these studies further showed that activation of Nrf2 and its downstream antioxidant genes [157,158], the efficacy of sulforaphane was associated with the amelioration of skeletal muscle dysfunction, which was accompanied by restoration of skeletal muscle fiber organization in T2D (*db/db*) mice [153]. Like with other diabetes related complications, activation of AMPK seems to an mechanisms by which sulforaphane protects diabetes-related complications, including reducing body weight, and alleviating hyperglycemia and hyperlipidemia, blocking the accumulation of lipid peroxides malonaldehyde (MDA) and 4-HNE [148,154].

7. Clinical relevance of sulforaphane-enriched food assumption against diabetes-related complications

There is an increasing need to understand the clinical relevance of plants or potential nutraceuticals in protecting against a variety of metabolic diseases. Unfortunately, not many studies have directly evaluated the clinical benefits, except for apparent preclinical evidence on the potential benefits of these bioactive compounds [167–169]. However, as one of the food products that contains about 10–100 times higher levels of sulforaphane than most mature plants [170,171], there has been ongoing efforts to evaluate the potential benefits of broccoli sprouts against some metabolic complications [172]. Interestingly, different cooking methods have also been tested for their capacity to enhance the bioavailability of bioactive compounds in broccoli, which may be necessary to promote the health benefits of broccoli in the diet [171,173]. Table 5 gives an overview of clinical evidence reporting on the potential benefits of broccoli against diabetes-associated complications. For example, it was demonstrated that consumption of white rice containing broccoli, with comparable amounts of carbohydrate, fat, protein, and fiber was effective at reducing acute glycemia and insulinemia over 180-minute period in healthy Japanese subjects [160]. Similarly, healthy individuals receiving a meal containing tomato, broccoli, fried fish, and boiled white rice for up to 60 min displayed improved postprandial blood glucose and insulin concentrations [166]. In human participants with accomplished T2D, it was also shown that consumption of broccoli sprouts powder (at 5 or 10 g/day) for 4–12 weeks could enhance antioxidant capacity, while significantly reducing lipid peroxidation by decreasing malonaldehyde (MDA), and oxidized low density lipoprotein cholesterol [161–165]. These effects were consistent with improvements in basic metabolic profiles and cardiovascular status, including reducing body mass index, lowering blood pressure, and alleviating homeostatic model assessment for insulin resistance (HOMA-IR).

8. Summary and future perspectives

It is currently acknowledged that a greater understanding of the mechanisms through which herbal supplements neutralize the damaging effects of oxidative stress and inflammation may provide a rational approach to protect against diabetes and its related complications [174,175]. Traditionally, herbal supplements, including their phenolic constituents like sulforaphane have attracted considerable interest because of their health-promoting properties [176,177]. Sulforaphane is an isothiocyanate that is mainly found in cruciferous vegetables. Reviewed evidence already indicates that activation of Nrf2, including its associated cytoprotective genes, is the predominant mechanism by which sulforaphane enhances cellular defense mechanisms including improving redox status in experimental models of diabetes [9]. In fact, another prominent feature of Nrf2 activation by sulforaphane is inhibition of inflammation [178]. Preclinical evidence covered within the current study indicates that subcutaneous or intraperitoneal (and even oral) administration of sulforaphane could protect against aortic damage or prevent the development of DCM in diabetic animals (Table 1). These therapeutic effects were consistent with the neutralization of oxidative stress and reduction of inflammation throughout a broad spectrum of experimental models of diabetes, including diabetic neuropathy, diabetic nephropathy, and NAFLD (Tables 2–4). The predominant therapeutic mechanism appeared to be activation of Nrf2, including its downstream antioxidant response genes, leading to reduced markers of oxidative stress and inflammation (Tables 1–4; Fig. 3). Notably, beyond activation on Nrf2, the modulation of AMPK, which plays a major role in energy regulation and insulin signaling [179], may be another essential mechanism by which

sulforaphane potentially combats diabetes-related complications. Even though clinical data directly reporting on the beneficial effects of sulforaphane is very limited, broccoli, which is rich in this isothiocyanate shows enhanced potential to improve the metabolic status and lower CVD-risk by enhancing the antioxidant status of patients with T2D. Although very limited (also encompassing a small sample size), this information is of high quality since is mostly based on randomized controlled trials. Further indicating that more and well-designed clinical trials are required to investigate the therapeutic effects of sulforaphane against diabetic complications, which is necessary to potential use as a nutraceutical in people with diabetes.

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CRediT authorship contribution statement

Sinenhlanhla X.H. Mthembu, Sithandiwe E. Mazibuko-Mbeje, and **Phiwayinkosi V. Dludla**; Conceptualization and original draft. All other authors, including **Marakiya T. Moetlediwa, Ndivhuwo Muvhulawa, Sonia Silvestri, Patrick Orlando, Bongani B. Nkambule, Christo J.F. Muller, Duduzile Ndwandwe, Albertus K. Basson, Luca Tiano** reviewed and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Not applicable.

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