Chapter

Cognitive Impairment in Diabetes Mellitus and Its Management by Transcription Factor Nrf2-Mediated Antioxidant Defense System

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Abstract

Diabetes mellitus has been an epidemic in the twenty-first century and an approximately 50% risk of diabetes predisposed to cognitive decline leading to dementia in humans. There is an urgent need to understand the pathophysiology and identify molecular targets of cognitive impairment in diabetes mellitus that might lead to improved therapy. Mounting evidence indicates that nuclear factor erythroid 2-related factor 2 (Nrf2) and its regulated downstream antioxidant genes are emerging therapeutic targets. In this chapter, we introduce cognitive dysfunction in diabetes mellitus and its hallmarks, particularly its pathological mechanisms related to oxidative stress in the brain, then justify the role of the transcription factor Nrf2-mediated antioxidant defense system in attenuating cognitive decline in diabetes mellitus. Studies on Nrf2 inducers sourced from natural products (i.e., sulforaphane, astaxanthin, resveratrol, quercetin) that have shown potent cognitive improvement in diabetic models are discussed. These studies have demonstrated that Nrf2 inducers drive the antioxidant and anti-inflammatory responses in the hippocampus region and effectively improve the spatial and memory function in diabetic rats/mice. However, evidence from large and well-designed clinical trials is warranted to support Nrf2 inducers as promising therapeutic agents in the management of cognitive impairment in diabetes mellitus.

Keywords: cognitive impairment in diabetes mellitus, Nrf2, natural compounds, oxidative stress, NLRP3 inflammasome, neuroinflammation

1. Introduction

Diabetes mellitus (DM) is a chronic disease characterized by excessively high levels of blood glucose either resulting from insulin resistance or inadequate insulin secretion [1]. High blood glucose levels (hyperglycemia) in DM can cause serious damage

to the heart, blood vessels, eyes, kidneys and nerves, and thus DM complications can significantly impact the quality of life and reduce life expectancy [2]. DM neuropathy is one of the major DM complications affecting 50% of DM sufferers which describes a type of nerve damage throughout the body induced by hyperglycemia [3, 4]. In the central nervous system, both type 1 (T1DM) and type 2 DM (T2DM) can cause nerve damage and result in various degrees of cognitive decline. Mounting epidemiological studies showed that the risk of cognitive decline in middle-aged diabetic patients was 2–3 times higher compared with healthy peers [5, 6]. Moreover, the prevalence of cognitive impairment is predicted to increase dramatically in the future with a longer survival time for diabetic patients [7]. Cognitive decline among children with T1DM is mainly manifested as subtle changes in cognitive development, whereas adults present subtle decrements in cognitive performance compared to age-matched controls [8]. The severity of cognitive impairment may worsen substantially over time [9]. In T2DM adult patients, the cognitive impairment can be divided into three different stages based on the severity [10, 11]: diabetes-associated cognitive decrements, mild cognitive impairment (MCI) and dementia. Diabetes-associated cognitive decrements refer to subtle changes in cognitive function. MCI affects one or more cognitive domains with largely preserved activities of daily life [12]. Dementia is the most severe stage that is defined as acquired objective cognitive impairment affecting multiple cognitive domains and daily activities [13, 14].

Cognitive impairment is a shared abnormality between DM and many neurodegenerative and neuropsychiatric disorders, such as Alzheimer's disease (AD) and schizophrenia [15]. In DM, cognitive impairment can be prevented or slowed down by consistent blood sugar management and a healthy lifestyle. However, there is no effective therapeutic agent to treat the condition at present [16]. The pathological mechanism is not entirely clear. Despite the widespread view that hyperglycemia and insulin resistance are predominant risk factors, convincing evidence demonstrated that oxidative stress plays an important role in contributing to the development of cognitive impairment in DM [17–19]. High-fat diet (HFD) is shown to directly increase oxidative damage and impair cognitive and memory capacity [20]. The dysfunctional metabolism of blood glucose damages the basilar membranes of capillaries leading to a narrowed cavity in the cerebra, thus decreasing blood supply to the brain and resulting in oxygen-free radical injury [21]. Oxidative stress is observed in cognitive impairment by increased levels of reactive oxygen species (ROS) and malondialdehyde (MDA), and decreased phase II antioxidant enzymes activities of glutathione peroxidase (GPx), chloramphenicol acetyltransferase (CAT) and superoxide dismutases (SOD) [22, 23]. The brain is highly susceptible to such oxidative damage partially due to its high oxygen demand, and the fact that high amounts of polyunsaturated fatty acids are easily targeted by free radicals [24]. Consequently, persistent hypoxia and oxygen-free radical injury can lead to neuronal cell injury and apoptosis [25]. Insulin is shown to penetrate the blood–brain barrier (BBB), and protects neurons against excessive free radicals, and the action is related to the nuclear factor erythroid 2-related factor 2 (Nrf2) regulated pathway [25]. Noticeably, insulin shows no protective effect on Nrf2-knockdown PC12 cells after H_2O_2-induced damage, while it significantly alleviated damage in $Nrf2^{+/+}$ cells [25]. Furthermore, insulin was shown to inhibit oxidative stress in neuronal cells as a potential antioxidant agent through the Nrf2-Keap1/antioxidant response element (ARE) signaling pathway [26]. Thus, Nrf2 may play an important role to protect cells against oxidative stress as an oxidative stress-responsive transcription factor. Since the induction of Nrf2 is

shown to ameliorate cognitive impairment in neurological disorders [27], Nrf2 has been considered an emerging therapeutic target for the prevention and treatment of cognitive impairment in DM.

In this chapter, we aimed to investigate the mechanisms of Nrf2 as an antioxidant master regulator to attenuate the pathological development of cognitive impairment in DM. We also reviewed current evidence on Nrf2 inducers sourced from natural products as promising therapeutic agents to help manage the pathological conditions and symptoms of cognitive impairment in DM.

2. Nrf2 acts as an important therapeutic target for cognitive impairment in DM

2.1 Ameliorate oxidative stress

Oxidative stress is constantly involved in the development and progression of cognitive impairment in DM. The persistent hyperglycemia, excessive lipid, and high-level advanced glycation end products (AGEs) all contribute to the excessive production of ROS [28]. Thus, ROS stress is considered a link between neurodegenerative diseases and T2DM, which induced oxidized DNA, RNA, protein, and lipid products that are used as disease progression marks in patients with both AD and T2DM [1]. The overproduction of ROS also triggers a prolonged state of inflammation through the high generation of white adipose tissue that secretes proinflammatory mediators [29], and subsequent neuronal death that affects the function of organ systems [30, 31]. The chronic oxidative stress and the associated neuroinflammation, in turn, can exacerbate abnormal insulin secretion, insulin action, and immune responses [32].

A number of studies suggested that a high-fat diet induced-adiposity and insulin resistance increased cerebral oxidative stress and downregulated Nrf2 signaling [2, 20, 33–35]. This might be the main reason that triggers the declined cognitive performance in the aged brain [20]. In addition, the diabetes experimental models suggested that enhancing Sirt1/Nrf2 signaling pathway activity prevented oxidative stress-induced neuronal injury, and thus improved cognitive function [2]. Nrf2 is a core transcription factor of antioxidative stress which regulates the cellular redox status. It interacts with ARE and plays a wide range of cytoprotective roles in the prevention of oxidative stress, neurological damage and inflammatory responses [36]. Nrf2 modulates the expression of more than 200 downstream genes encoding Phase II response enzymes during the oxidative challenge, including heme Oxygenase (HO-1), glutathione S-transferase (GST), catalase (CAT), superoxide dismutase (SOD), and NADPH quinone oxidoreductase (NQO1) [37]. The mechanisms of action to suppress oxidative stress by the activation of Nrf2 is mediated through the restored production of many downstream antioxidant genes which directly reduce the intracellular ROS accumulation [38]. The upregulation of Nrf2 target genes in the CNS protects neurons against oxidative insults as shown by a broad array of published studies [24, 39–45].

2.2 Suppress NLR family pyrin domain containing 3 inflammasome-induced neuroinflammation

The nod-like receptor pyrin containing 3 inflammasomes (NLRP3) is a multimeric protein complex containing cytosolic NLRP3, the adaptor protein ASC and caspase-1.

Hyperglycaemia and other repetitive stress stimuli assemble and activate the NLRP3 inflammasome which then triggers the activation of caspase-1 by proteolytic cleavage [46]. The latter converts pro-IL-1β into bioactive IL-1β and consequently initiates inflammatory responses. The sustained inflammatory responses can cause neurotransmitter dysfunction which subsequently leads to a decreased production of brain-derived neurotrophic factor (BDNF), a protein responsible for the learning and memory process [47]. Thereby, it results in neuroinflammation-mediated neuronal damage as well as deterioration of cognitive function [48–50]. The aggravated neurodegeneration caused by the accumulation of IL-1β can be rescued by blocking IL-1β signaling in APP/PS1 mice [50–53], suggesting NLRP3 inflammasome-mediated neuroinflammation is an important therapeutic target. Moreover, inflammatory responses can also induce the overproduction of ROS which then exacerbate the oxidative damage to neurons [54].

Recent studies have shown that Nrf2/ARE signaling is directly implicated in the regulation of inflammation rather than relying on regulating oxidative stress to control inflammatory response [48, 49, 55, 56]. Although not fully understood, Nrf2 regulated AGEs/RAGE pathway is shown to mediate the activation of NLRP3 inflammation by providing a priming signal at a transcriptional level [57, 58] which is essential for the assembly of the NLRP3 inflammasome [59]. Excessive activation of this process exhausts cytosolic NADPH, increases the accumulation of ROS, and disrupts Nrf2/ARE pathway, finally leading to oxidative stress [60]. Besides, several studies revealed that suppressed intracellular ROS accumulation by the activation of Nrf2 resulted in reduced activation of the NLRP3 inflammasome, and subsequently inhibited neuroinflammation [38]. Additionally, Nrf2 activation triggers the restored expressions of HO-1 and NQO1 which then further contribute to the suppression of inflammation-associated cytokine productions and NLRP3 inflammasome formation [61–63].

2.3 Alleviate endoplasmic reticulum stress

The endoplasmic reticulum (ER) is involved in glucose-modulated secretory protein folding, intracellular Ca2+ storage, synthesis of unsaturated fatty acids, sterols, and phospholipids [64, 65]. High glucose levels in the body disrupt the internal balance of the ER, resulting in the accumulation of unfolded or misfolded proteins, which leads to ER stress (ERS) [66]. Oxidative stress also can induce ER stress responses [67] which are triggered by the accumulation of ROS [68].

Excessive ERS impairs neuronal function through various pathways. In hippocampal cells, high glucose and palmitic acid-induced ERS significantly decrease proBDNF, but were restored when ER stress was reduced [69]. In the neuroinflammatory pathway, ERS can activate the NLRP3 inflammasome and lead to the subsequent secretion of proinflammatory cytokines such as IL-1β [67, 68, 70] which is detrimental to the neuronal function as described above. In addition, ERS can further impair neuronal survival. The double-stranded RNA-dependent protein kinase (PKR)-like ER-resident kinase (PERK) pathway is one of the three ERS-related protective signaling pathways identified so far. PERK pathway can activate caspase-12, which is a specific mediator of ER stress-induced apoptosis, to impair protein synthesis and synaptic functions [70]. Excessive or prolonged ER stress could up-regulate the transcription factor C/EBP Homologous Protein (CHOP), which is a critical mediator of the Bax/Bcl-2 -dependent pathway, thus converting neuronal cells from the pro-survival to

pro-apoptosis phase [71, 72]. Thus, ERS is considered a valuable therapeutic target in neuroprotection such as the cognitive decline in DM [73].

ERS can cause and exacerbate oxidative stress, whereas oxidative stress can worsen ERS. In response to ERS, the onset of the PERK pathway quickly activates Nrf2 as an antioxidant defensive system [66], although the clear link remains to be explored. As an endogenous defense system against oxidative stress, Nrf2 regulates the expression of a subset of detoxifying enzymes including NQO1 and γ-GCS. This suggests an important cytoprotective role of Nrf2 against ERS, and that the Nrf2 pathway represents a useful therapeutic strategy in cognitive decline by attenuating ERS. However, the moderate self-defense response of PERK and Nrf2 maybe not be enough to prevent damage [73]. The other pathway that Nrf2 may exert a beneficial effect in attenuating ERS is that the Nrf2 activation contributes to the maintenance of glutathione levels, which, in turn, functions as a buffer for the accumulation of ROS during the unfolded protein response in ER and thus may attenuate ERS. In addition, the reduced level of ROS may reduce apoptotic induction as a consequent event after ERS [74].

2.4 Repair a leaking BBB

Impairment of BBB induced by hyperglycemia, oxidative damage, and inflammation is a critical neurovascular complication of DM that adversely affects the microvascular environment, health, and function of the central nervous system. Many studies have demonstrated that hyperglycemia-driven neuroinflammation is a risk factor for BBB disruption leading to a high permeability of BBB [75–77]. The BBB leakage leads to many adverse impacts on the central nervous system including decreased waste transport, increased infiltration of immune cells and subsequent glial and neuron dysfunction, over-active immune sensitivity, hormone dysregulation, and cognitive impairment [78]. The excessive production of ROS also induces endothelial oxidative stress and mitochondrial damage which has been recognized as a central pathological mechanism for BBB dysfunction in DM.

A study from Sajja et al. suggested a close link of Nrf2 protein expression to that of the BBB permeability, as evidenced by a significantly down-regulated brain Nrf2 protein expression in the db/db diabetic mice with a strong increase in BBB permeability (to 70 kDa dextran) [79]. The role of Nrf2 induction in the repairment of BBB appeared to be associated with the mitochondrial transporter *ABCB10* which is considered as an essential player in mitochondrial function and redox balance at BBB endothelium. The *ABCB10* knockdown resulted in a strong induction of Nrf2-driven antioxidant responses manifested as increased expression of Nrf2 and its downstream antioxidant genes [79]. In addition, several studies suggested that Nrf2-driven free radical detoxification pathways are essential in protecting against oxidative stress-induced endothelial injuries [80], and thus may in turn contribute to the protection of BBB [81].

2.5 Protect mitochondria function

Mitochondrial dysfunction is implicated in the pathogenesis of most neurodegenerative disorders including cognitive impairment in DM [82]. Mitochondria is the main source of energy in the cell, by providing ATP through oxidative phosphorylation and harboring several metabolic pathways such as fatty acid oxidation (FAO) and

the tricarboxylic acid cycle (TCA) cycle [82]. Accumulated oxidative damage causes an altered oxidative phosphorylation and redox imbalance in mitochondria [83]. The long-lasting effect can lead to the des-regulation of mitochondrial protein homeostasis, and consequent proteotoxic stress in the neurons [84]. Neurons in the central nervous system have a high requirement for energy as attributed to their constant activity and signaling, and thus are especially vulnerable to mitochondrial dysfunction. Decreased ATP production is a common hallmark of neurodegenerative diseases and can be caused by various mechanisms, such as the impaired activity of any of the complexes of the respiratory chain, alterations in glucose uptake, glycolysis, TCA cycle, or uncoupling [85].

Nrf2 can lead to mitochondrial bioenergetic improvement, although the mechanisms of action are not fully explored [82]. There are several mechanisms of action that underpin the role of Nrf2 in protecting mitochondrial function. Nrf2 prevents the oxidative thiol modifications that can modulate the function of proteins implicated in metabolic pathways [86–88]. The accumulative mitochondrial ROS can reversibly modify thiol groups presented in several enzymes implicated in carbohydrate and lipid metabolism. The activation of Nrf2 that scavenge or inhibit the overproduction of mitochondrial ROS may prevent the redox modifications of the sensitive thiol groups [89–91]. Consequently, such antioxidant modification enables the restoration of normal glycolytic metabolism and reduces neuronal apoptosis [92].

2.6 Modulation of glucose metabolism

Diabetic patients (both type 1 and type 2) have a higher risk of AD and vascular dementia, mainly caused by abnormal glucose metabolism induced by hyperglycemia and consequent cerebrovascular lesions in the frontal lobe [93]. The elevated glucose concentration leads to enhanced oxidative phosphorylation and increased levels of glutamate, an excitatory neurotransmitter, whose enhanced levels provoke cognitive dysfunction by causing neuronal damage.

Although the majority of evidence stands for the antioxidant properties of Nrf2 activation, Nrf2 is also involved in glucose metabolism [94, 95]. Nrf2 can directly activate the transcription of enzymes containing ARE-sequences in the gene promoters, which have been described in the promoters of the genes encoding the peroxisome proliferator-activated receptor ɣ (PPAR- ɣ) [96]. PPAR-ɣ is known to regulate adipocyte differentiation and lipid metabolism, as well as the network regulation of glucose homeostasis [97]. It also exhibited a versatile role in early brain development and post-injury brain repair [98]. The activation of PPAR- ɣ is shown to repair damaged tissue through angiogenesis, alleviate neurological deficits, and exhibit neuroprotective activity [96]. Indeed, studies have revealed the connection of Nrf2 and PPAR-ɣ *via* a positive feedback loop that simultaneously strengthens each other's expression [94, 95]. For example, PPAR-ɣ expression was found to be significantly lower in Nrf2 knockout mice [99]. It is also identified that one of the many Nrf2 downstream targets, *TALDO1*, contains an ARE sequence which is a key enzyme in the nonoxidative pentose phosphate pathway, providing ribose-5-phosphatase and NADPH for nucleic acid and lipid biosynthesis [92].

Taken together, the recently recognized abilities of Nrf2 to ameliorate oxidative and ERS, repair BBB, protect mitochondrial function and regulate glucose metabolism make the Nrf2 activation an attractive and comprehensive therapeutic target for

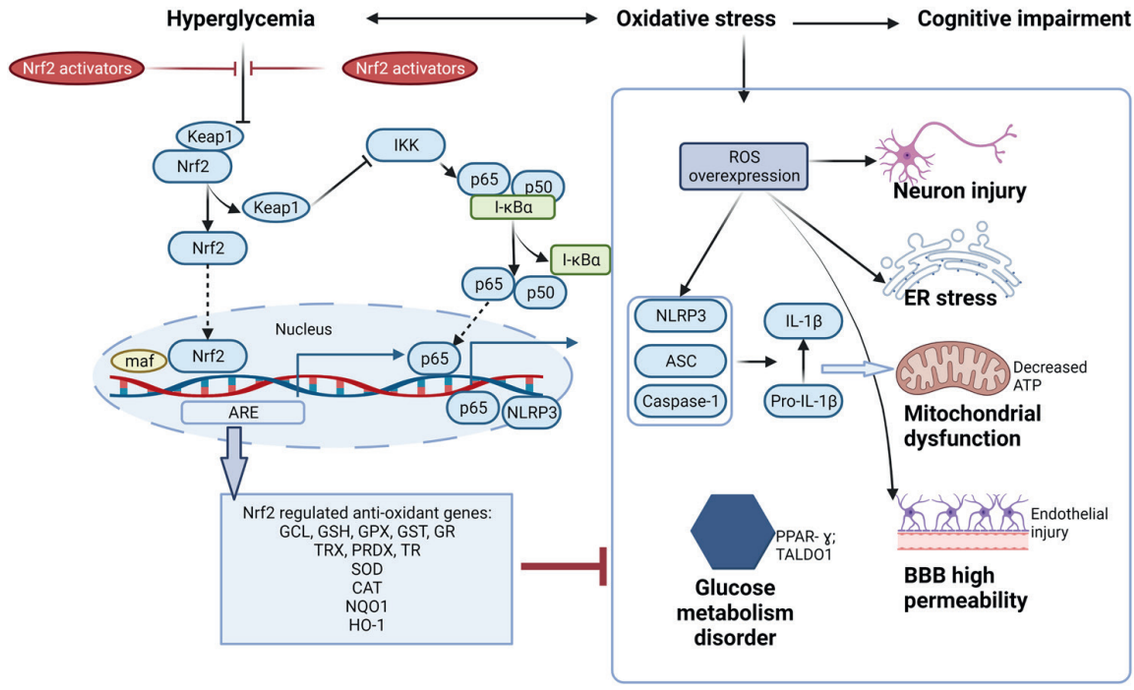

Figure 1.
A summarized diagram of Nrf2-associated pathways in the pathological mechanisms of DCI.

the management of cognitive impairment in DM. A summarized diagram of Nrf2-associated pathways in the pathological mechanisms is shown in **Figure 1**.

3. Nrf2 activators from natural products that prevent or treat cognitive impairment in DM

Natural products have served as a rich source of novel drug discovery and development. This section focuses on the promising Nrf2 inducers sourced from natural products that have shown beneficial effects in the prevention or treatment of cognitive impairment in DM. A literature search was conducted in scientific databases (PubMed, MEDLINE and EMBASE) and Google Scholar for English-published studies between January 2000 and September 2022. Clinical and pre-clinical studies of natural products (i.e., herbal extracts, vegetables, plants, chemicals, nutraceuticals, and supplements sourced from plant or plant extract) that showed effects in attenuating cognitive impairment in DM and the mechanism of action was associated with the Nrf2 activation were included. Studies investigating pharmaceutical drugs, analog drugs, and synthesized compounds were excluded.

Nineteen preclinical studies demonstrated that various natural compounds attenuated cognitive impairment in DM at least partially through the induction of Nrf2 (see **Table 1**). The effects on cognitive impairment by the natural products were mostly demonstrated in the diabetic animal models, either on high-fat diet (HDF) or streptozotocin (STZ) injection-induced diabetic rats [111, 113, 114], db/db mice (model phase 1 to 3 of diabetes type II and obesity) [100, 115], or diabetic Goto-Kakizaki rats (non-obese type 2 diabetic model) [110]. One cellular study was included which utilized chronic high glucose-exposed SHSY5Y neurons [116]. The studies on natural Nrf2 activators with strong preclinical evidence and associated molecular mechanisms are discussed in detail below.

Natural compounds	Source	Administration	Key results	Mechanism related to Nrf2 activation
Sulforaphane [100, 101]	Vegetables	1 mg/kg, i.p. for 28 days	Mitigated cognitive impairment of db/db mice; decreased Aβ oligomers and plaques, phosphor-tau and Thr231 in hippocampus	↑Nrf2 → ↑HO-1 and NQO1 → ↓ROS level
		25 mg/kg, orally once daily for consecutive 14 days	Prevented the memory impairment, decreased the apoptosis of hippocampal neurons in STZ-injected SD rats	↓ Caspase-3 and myeloid cell leukemia 1 (MCL-1); ↑ p-Akt, p-GSK3β, NGF and BDNF
Troxerutin [102, 103]	*Sophora japonica*	60 mg/kg, 1 mL/kg, i.p., 12 weeks	Improved learning and memory levels in STZ-induced diabetic rats	↑Nrf2 → ↑SOD and ↓MDA
		150 mg/kg/day intraperitoneally for 6 weeks	Improved cognitive impairment in STZ-induced diabetic rats	↑ Nrf2 translocation → ↑ HO-1 and NQO1 → NOX subunits → ↓MDA and ↑SOD
Strawberry leaf extract [104]	Strawberry tree	200 mg/kg for 4 weeks	Alleviated cognitive impairment in STZ-induced diabetic rats	↑Nrf2 -HO-1 signaling → ↓ROS, ↓MDA, ↑SOD and CAT; ↓IL-6 and TNF-α; ↓caspase-3 and caspase-9 in hippocampus
Betulin [105]	Birch tree bark	20 or 40 mg/kg for 4 weeks	Improved glucose intolerance and modify basal learning performance in STZ-induced diabetic rats	↑Nrf2 -HO-1 signaling and ↓NF-κB → ↑SOD and ↓MDA; ↓inflammatory cytokines in serum and hippocampus
S-allyl cysteine [106]	Aged garlic extract	150 mg/kg/day for 7 weeks (p.o.)	Lowered serum glucose, improved spatial recognition memory, discrimination ratio in novel object recognition task, and restored step-through latency (STL) in passive avoidance paradigm in STZ-induced diabetic rats	↑Nrf2-HO-1 signaling and ↓TLR4-NF-κB signaling → ↓ acetylcholinesterase activity, MDA; ↑SOD and GSH
Caffeic acid phenethyl ester [107]	Propolis	200 and 400 mg/kg p.o. for 14 days	Rescued the diabetic brain atrophy and diminish CA1 and CA3 cells of hippocampus and cerebral cortex in STZ-induced diabetic mice; decrease Aβ and p-tau (S396)	↑Nrf2-related anti-oxidation mechanisms → antioxidation, anti-inflammation and autophagy induction
AB-38b [108]	Fructus *Schisandrae chinensis*	0, 10, 20 and 40 mg/kg by gavage for 8 weeks	Increased the preference index to novel object and the number of neurons in hippocampal CA1 area of diabetic mice	↑Nrf2 expression and phosphorylation → ɣ-GCS

Natural compounds	Source	Administration	Key results	Mechanism related to Nrf2 activation
Fish oil supplementation [109]	Fish oil	1.5 g/kg/d (34% EPA, 24% DHA) for 10 weeks	Improved spatial learning and memory in STZ-induced diabetic rats	Nrf2 and HO-1 in cortex and hippocampus → ↓oxidative stress → ↓ IL-1β, IL-6, and TNF-α, ↑ IL-4 and IL-10
Soy isoflavones [110]	Soy	20 mg/kg once a day for 4 weeks	Alleviated the cognitive dysfunction of the diabetic Goto-Kakizaki rats	↑ Nrf2, HO-1 and NQO1 → oxidative reactions
Resveratrol [111, 112]	Grapes, berries, etc.	30 mg/kg every other day for 4 months by intragastric administration	Prevented the learning and memory decline and hippocampal neuron destruction and synaptic ultrastructural damage in HFD and STZ- induced T2DM mice	↑ Nrf2 → ↑ HO-1 and NQO1 proteins; ↑ SOD and CAT → ↓ TNF-α and IL-1β
		20 mg/kg, intraperitoneally once daily for 4 weeks	Significantly elevated total oxidant species (1.22-fold) and Malonedialdehyde (MDA) (1.38-fold) contents in diabetic rat brain cortex tissues in STZ (55 mg/kg)-injected Wistar rats	↓oxidative conditions
Thymol (2-isopropyl-5-methylphenol) [113]	Thyme	20, 40 mg/kg for 12 weeks	Reversed the gain of body weight and peripheral insulin resistance induced by HFD; improved the cognitive impairments; decreased HFD-induced Aβ deposition and tau hyperphosphorylation	↑ Nrf2-HO-1 signaling → ↓ oxidative stress and inflammation
Astaxanthin [114]	Algae, yeast, salmon, trout, krill, shrimp, and crayfish	25 mg/kg 3 times/week for 6 weeks by intraperitoneally	Ameliorated the impairment in the neurons of HFD and STZ-induced diabetic rats	↑Nrf2-HO-1 and ↓NF-κB signalings → ↑ SOD and ↓ MDA; ↓IL-1β and IL-6
Notoginsenoside R1 [115]	*Panax notoginseng*	10, 30 mg/kg once daily administrated intragastrically for 10 weeks	Ameliorated cognitive dysfunction, depression-like behaviors, insulin resistance, hyperinsulinemia, dyslipidemia, and inflammation in db/db mice	↑Akt → ↑ Nrf2 and ↓ NLRP3
Albiflorin [7]	*Paeonia lactiflora*	100, 200 mg/kg by gastric gavage for 10 weeks	Improved spatial and learning ability; decrease in Aβ plaque density in the hippocampus of rats;	Regulate Nrf2/HO-1/HMGB1/NF-κB → ↓ oxidative stress and inflammation

Natural compounds	Source	Administration	Key results	Mechanism related to Nrf2 activation
Quercetin [116, 117]	Fruits and vegetables	5, 10, 20 μmol/L for 72 h	Increased cell viability, and enhanced Glo-1 functions in SHSY5Y neurons	↑Nrf2 and p-Nrf2 levels → ↑ ɣ-GCS protein and mRNA
		50 mg/kg i.p. for 18 days	Significantly mitigated the STZ-induced increase in cholinergic dysfunction in STZ (3 mg/kg)-induced brain mitochondrial toxicity in Alzheimer's disease -like rats	↑α7nAChR/Nrf2/HO-1-mediated neuroprotection

Table 1.
Summarized studies for natural products that attenuate cognitive impairment in DM and associated symptoms via the mechanism of Nrf2 activation.

3.1 Sulforaphane

Sulforaphane is a hydrolysis product of glucoraphanin, a group of sulfur-containing glycosides, found in many raw vegetables such as broccoli, cauliflower, bok choy, and watercress [118–121]. Upon consumption, glucoraphanin is hydrolyzed to sulforaphane which has been demonstrated to penetrate BBB [122] and exhibit a neuroprotective effect *via* a number of mechanisms [123]. In particular, strong evidence has indicated that sulforaphane is a potent Nrf2 activator. The molecular mechanisms are linked with increased Nrf2 transcription by reducing methylation of the first 15 CpGs of Nrf2 promoters [124], modulation of Kelch-like ECH-associated protein 1 (Keap1) [125–127], prevention of ubiquitination of Nrf2 [128], and enhanced Nrf2 translocation [128]. The activation of Nrf2 by sulforaphane was reported to mediate a long-lasting effect of the upregulation of cytoprotective enzymes (4-hour exposure of sulforaphane led to 24 hrs NQO1 and HO-1 mRNA elevation and over 48 hrs increase of corresponding proteins) [129].

Two *in vivo* studies have investigated the effect of IP/oral injection of sulforaphane on mitigating cognitive impairment in diabetic models [100, 101]. In particular, the study by Pu et al. suggested that the IP injection of sulforaphane (1 mg/kg for 28 days) improved the spatial learning and memory function of db/db mice examined by the Morris water maze tests. Sulforaphane was shown to decrease the levels of Aβ oligomers, Aβ 1–42 plaques, phosphor-tau at Ser396 and Thr231 in the hippocampus. The molecular mechanisms were related to Nrf2-mediated upregulation of HO-1 and NQO1 protein expression, and reduced ROS/RNS levels [100]. In line with the research finding, a study by Wang et al. revealed that the oral administration of sulforaphane (25 mg/kg) for consecutive 14 days prevented memory impairment in STZ-induced diabetic rats [101]. It was revealed that sulforaphane markedly reduced apoptotic neurons levels and it was associated with decreased phospho-protein kinase B (Akt), phosphor-glycogen synthase kinase 3β (GSK3β), nerve growth factor (NGF) and BDNF expressions. However, the link between the reduced neuronal apoptotic level and the Nrf2 activation remains to be explored. Broadly speaking, many studies have agreed the strong neuroprotective effect of sulforaphane by activating Nrf2 antioxidant signaling cascade, and such activity can be used in many neurodegenerative diseases including AD, traumatic brain injury, and ischemic stroke [130]. Future studies are suggested to explore the safety profile and pharmacokinetic characteristics

of sulforaphane to further demonstrate its therapeutic value in improving cognitive function in humans.

3.2 Astaxanthin

Astaxanthin is a red pigment belonging to a group of carotenoids that causes the pink-red color in salmon. Astaxanthin has various biological and pharmacological activities such as antioxidant, anti-inflammatory, and antidiabetes [131]. Many studies demonstrated that astaxanthin exhibited potential neuroprotective effects, of which the mechanism was associated with Nrf2 activation [131–134]. Astaxanthin administration was shown to accelerate nuclear translocation of Nrf2 *via* inducing PI3K/Akt signaling, resulting in a decrease in ROS levels, and inhibiting apoptosis in neuronal cells [135].

Orally or parenterally administered astaxanthin has been shown to improve insulin resistance and insulin secretion, attenuate hyperglycemia, and exert protective effects against many DM complications including retinopathy, nephropathy, and neuropathy [136]. Specifically, for cognitive impairment in DM, astaxanthin administration improves cognitive function [137] and diminish oxidative stress, nitric oxide synthase, and inflammation in DM rat [137]. Furthermore, Feng et al. suggested that IP injection of astaxanthin (25 mg/kg) ameliorated the impairment in the neurons of HFD and STZ-induced diabetic rats, and the action was associated with upregulated the Nrf2-HO-1 signaling pathway which drove the increased expressions of SOD and declined MDA. The intermediate metabolites from the Nrf2-HO-1 axis contribute to the suppressed inflammatory response by inhibiting the activation of NF-κB leading to decreased levels of IL-1β and IL-6 [114].

3.3 Resveratrol

Resveratrol (3,4′,5-trihydroxy-stilbene, RES) is a very popular nutraceutical that is a naturally occurring compound found in grapes, cereals, vegetables, dry legumes and plant-derived beverages, including tea, coffee, and wine. A large number of studies supported its beneficial use in anti-diabetes, anti-inflammatory, and antioxidative conditions [138–142]. In diabetes, resveratrol is shown to exhibit an insulin-sensitizing effect, enhance glucose uptake and metabolism, preserve islet β-cells and release insulin from β-cells [138]. Among all the associated molecular mechanisms of resveratrol in treating diabetic complications, one of the key pathways was the upregulation of Nrf2 nuclear translocation which then induced the increased expressions of GSH, SOD, NQD1, and HO-1, reduced ROS production, and declined oxidative stress [138]. Two studies specifically investigated the protective effect of resveratrol on cognitive function in diabetic rats *via* regulating oxidative biomarkers and antioxidant enzymes in the brain [111, 112]. A study from Sadi et al. suggested that resveratrol significantly elevated total oxidant species in diabetic rat brain cortex tissues in STZ-injected Wistar rats [112]. Moreover, Wang et al. showed that resveratrol prevented the learning and memory decline in STZ-induced T2DM mice [111], and such action was linked with upregulated Nrf2 and its mediated HO-1 and NQO1 proteins, SOD and CAT enzymes, as well as reduced IL-1β and TNF-α. A randomized, double-blind, placebo-controlled clinical trial demonstrated that a total of 48 patients with T2D received 800 mg/day of resveratrol for 2 months markedly increased Nrf2 and SOD expressions in peripheral blood mononuclear cells. Resveratrol was well tolerated without causing any serious adverse events [143]. Thus, it is encouraging

that resveratrol may exhibit beneficial clinical outcomes in T2D patients with cognitive decline as a stronger Nrf2 activator.

3.4 Quercetin

Quercetin is one of the most abundant polyphenolic flavonoids, which is present in fruits and vegetables and displays a strong health-promoting effect [144]. In addition, quercetin plays an indirect role in neutralizing oxidative stress by activating the Nrf2-ARE antioxidant pathway and inducing the expression of antioxidant enzymes like CAT and SOD. In lipopolysaccharides (LPS)-induced murine BV-2 microglial cells, quercetin produced a greater stimulating effect on Nrf2-induced increase expression of heme-oxygenase-1 (HO-1) protein than cyanidin against endotoxic stress *via* the participation of mitogen-activated protein kinase (MAPKs) [145, 146]. In particular, quercetin was found to increase cell viability and enhance glyoxalase-I (Glo-1) functions in SHSY5Y cells which were related to activated Nrf2 and phosphor-Nrf2 levels [116]. Furthermore, IP injection of quercetin (50 mg/kg) for 18 days significantly mitigated the STZ-induced increase in cholinergic dysfunction in STZ (3 mg/kg)-induced brain mitochondrial toxicity in AD-like rats, which the mechanism was associated with α7nAChR/Nrf2/HO-1-mediated neuroprotection [117]. However, a clinical trial is warranted to further investigate the effect of quercetin in humans.

4. Conclusion and future perspectives

A number of natural compounds, such as sulforaphane, astaxanthin, resveratrol, and quercetin [115] were found to significantly improve the spatial and memory function in diabetic animals models (rats/mice) with the effective daily dosage ranging from 1 mg/kg to 30 mg/kg. Most of the treatments were given after the induction of DM. In addition, most treatments from natural products were long-term treatment duration (14 days to 4 months) with a daily administration to see an obvious effect. The summarized information is listed in **Table 1**. However, clinical trials are largely lacking to further demonstrate their safety and efficacy in humans.

Nrf2 inducers sourced from natural products upregulated Nrf2 activity, Nrf2 translocation (nuclear Nrf2 protein expression) and/or phosphorated Nrf2 expression. This leads to the activation of Nrf2-regulated downstream antioxidant genes including HO-1, NQO1, SOD and CAT [102–104, 106, 111, 114]. The reduced levels of ROS and MDA in the hippocampus were often reported as the consequent events. Interestingly, many studies also mentioned the inhibited NF-κB signaling in addition to the Nrf2-mediated antioxidant response [7, 106, 114]. The upregulated expression of HO-1 protein in response to the Nrf2 upregulation suppresses the NF-κB activation which governs the transcriptions and productions of proinflammatory cytokines. Thus, Nrf2/HO-1 pathway not only drives the antioxidant response but also plays a critical role in regulating the proinflammatory reactions. The suppressed proinflammatory response in the animals is evidenced by the reduced production of IL-6 and TNF-α and increased levels of IL-4 and IL-10 [109, 114]. However, the inner relationship among Nrf2-mediated antioxidants and anti-inflammatory by the Nrf2 activators is not fully explored.

It is worth mentioning that the Nrf2 activation in cognitive impairment was shown to be mediated by the induction of protein kinase B (Akt) as an upstream mediator.

A study from Zhai et al. suggested that notoginsenoside R1 (NR1) activated the Nrf2 pathway as well as inhibited NLRP3 inflammasome which both contributed to ameliorated cognitive function. However, the neuroprotective effect after the Nrf2 activation and NLRP3 inflammasome inhibition was abolished by the co-treatment of Akt inhibitor and NR1 [115]. It has been well-studied that the activation of Akt regulates cell survival and apoptosis as well as glucose transport [147, 148]. NR1 was capable to improve glucose tolerance and insulin sensitivity in db/db mice and reducing neuron apoptosis in the hippocampal CA1 region, and the mechanisms may be associated with the activation of the Akt and Nrf2 signaling cascade [115]. These two studies highlight the possible molecular action of Nrf2 inducers mediated by the Akt pathway in protecting neuronal survival in the hippocampal region. Further studies are warranted to elucidate the link between Akt and Nrf2 pathways.

Taken together, this book chapter introduces cognitive impairment in DM as the major complication in both type 1 and type 2 DM, and explained the associated pathological mechanisms, particularly the detrimental role of oxidative stress that impairs cognitive and memory capacity. Nrf2, the core intracellular transcription factor of antioxidative stress, has been considered an emerging therapeutic target against cognitive impairment in DM. The induction of Nrf2 signaling drives the antioxidant defense system to ameliorate oxidative and ER stress, repair the BBB, protect mitochondrial function, and regulate glucose metabolism, which eventually protects neurons against oxidative stresses and hyperglycemia and helps to restore cognitive function. A number of studies, predominantly based on diabetic animal models, have demonstrated that Nrf2 inducers sourced from natural products such as vegetables, soy, garlic, and strawberry leaf improved cognitive and memory function. The associated mechanisms of action were shown as Nrf2-mediated antioxidant and anti-inflammatory responses. Although the results are supportive, conclusive evidence for each proposed therapeutic candidate is weak due to the low quantity of studies. The safety human trials to further demonstrate their safety and efficacy are warranted. However, the findings of this chapter may shed light on the development of natural Nrf2 activators as promising pharmacological agents to prevent or slow the progress of cognitive impairment in DM.

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Conflict of interest

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