Review Article

Neuroprotective Effects of Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors (Gliflozins) on Diabetes-Induced Neurodegeneration and Neurotoxicity: A Graphical Review

Abstract

Diabetes is a chronic endocrine disorder that negatively affects various body systems, including the nervous system. Diabetes can cause or exacerbate various neurological disorders, and diabetes-induced neurodegeneration can involve several mechanisms such as mitochondrial dysfunction, activation of oxidative stress, neuronal inflammation, and cell death. In recent years, the management of diabetes-induced neurodegeneration has relied on several types of drugs, including sodium-glucose cotransporter-2 (SGLT2) inhibitors, also called gliflozins. In addition to exerting powerful effects in reducing blood glucose, gliflozins have strong anti-neuro-inflammatory characteristics that function by inhibiting oxidative stress and cell death in the nervous system in diabetic subjects. This review presents the molecular pathways involved in diabetes-induced neurodegeneration and evaluates the clinical and laboratory studies investigating the neuroprotective effects of gliflozins against diabetes-induced neurodegeneration, with discussion about the contributing roles of diverse molecular pathways, such as mitochondrial dysfunction, oxidative stress, neuro-inflammation, and cell death. Several databases—including Web of Science, Scopus, PubMed, Google Scholar, and various publishers, such as Springer, Wiley, and Elsevier—were searched for keywords regarding the neuroprotective effects of gliflozins against diabetes-triggered neurodegenerative events. Additionally, anti-neuro-inflammatory, anti-oxidative stress, and anti-cell death keywords were applied to evaluate potential neuronal protection mechanisms of gliflozins in diabetes subjects. The search period considered valid peer-reviewed studies published from January 2000 to July 2023. The current body of literature suggests that gliflozins can exert neuroprotective effects against diabetes-induced neurodegenerative events and neuronal dysfunction, and these effects are mediated via activation of mitochondrial function and prevention of cell death processes, oxidative stress, and inflammation in neurons affected by diabetes. Gliflozins can confer neuroprotective properties in diabetes-triggered neurodegeneration, and these effects are mediated by inhibiting oxidative stress, inflammation, and cell death.

Keywords: *Diabetes, gliflozins, neurodegeneration, neurotoxicity*

Mina Gholami, Natalie Coleman-Fuller[1], Mahsa Salehirad, Sepideh Darbeheshti, Majid Motaghinejad

Chronic Respiratory Disease Research Center (CRDRC), National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran, [1]Department of Veterinary and Biomedical Sciences, University of Minnesota, St. Paul, MN, USA

Address for correspondence:
Dr. Majid Motaghinejad, Masih Daneshvari Hospital, Darabad Avenue, Shahid Bahonar Roundabout, Tehran, Iran.
E-mails: Dr.motaghinejad6@gmail.com , M.motaghinejad@sbmu.ac.ir

Access this article online

Website: www.ijpvmjournal.net/www.ijpm.ir

DOI: 10.4103/ijpvm.ijpvm_5_23

Quick Response Code:

Introduction

Diabetes mellitus (DM) is an important metabolic disease characterized by high blood sugar levels and decreased insulin level and function.[1,2] The prevalence of DM has increased in recent years due, in large part, to poor lifestyle choices.[3] DM, also termed type 2 DM (T2DM), is associated with many acute and chronic complications, affecting various organs and tissues, often with irreversible damage.[4-7] Cell death and degenerative disorders are the main damage caused by DM in a variety of systems including the nervous, gastrointestinal, cardiovascular, respiratory, urogenital, kidney, muscle, and skeletal systems. The degeneration and disruption of function in these systems can cause serious disorders in the related organs[1,8-10] [Figure 1]. The nervous system is one of the most important systems affected by diabetes, as diabetes can cause damage and neuronal cell degeneration in both the central nervous system (CNS) and the peripheral nervous system (PNS)[1,8-10] [Figure 1]. In fact, diabetes-induced retinopathy and tracheal neuropathy are known to involve neuronal degeneration.[11,12] Furthermore, diabetes can cause neurobehavioral conditions such as anxiety, depression, cognitive disability, and motor activity dysfunction.[13-15] Molecular studies have

How to cite this article: Gholami M, Coleman-Fuller N, Salehirad M, Darbeheshti S, Motaghinejad M. Neuroprotective Effects of sodium-glucose Cotransporter-2 (SGLT2) Inhibitors (Gliflozins) on Diabetes-Induced Neurodegeneration and Neurotoxicity: A Graphical Review. Int J Prev Med 2024;15:28.

shown that DM-induced neurodegenerative damage is due to destructive neurochemical events involved in mitochondria dysfunction, which leads to oxidative stress, neuronal inflammation, cell death and apoptosis, and finally activation of neurodegeneration[16-18] [Figure 2]. In addition, diabetes induces neurobehavioral and neurochemical changes in brain cells.[13,19] Consistent with these findings, there appears to be a close connection between diabetes and neurodegenerative diseases and disorders such as Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), motor neuron disease (MND), epilepsy, spinocerebellar ataxia, and spinal muscular atrophy.[1,17,18] Many studies suggest that DM-induced neurodegenerative events are caused by elevated inflammation, apoptosis, oxidative stress, and mitochondrial dysfunction in neuronal cells [Figure 2]. Thus, recent years have seen increased use of novel anti-hyperglycemic agents that have cell-protective characteristics and therapeutic potential for preventing or managing molecular and neuronal functional problems caused by diabetes, and increased capability for anti-oxidative stress, anti-inflammatory, and anti-apoptosis.[20,21]

One group of antidiabetic agent with neuroprotective properties is sodium-glucose cotransporter (2SGLT2) inhibitors, also known as gliflozins, which are prescribed for patients with DM.[21,22] Several limited studies indicate that gliflozins have mood-elevating, antidepressant, anxiolytic, and cognitive enhancement properties, particularly in diabetic subjects.[23-26] A broad body of literature shows that gliflozins have anti-oxidative, anti-inflammatory, and anti-apoptotic properties. Based on these features, gliflozins can be effective against DM-induced neurodegenerative events,[26-28] as they positively impact antioxidant enzyme activities and mitochondrial functions and exert potent inhibitory effects on oxidative stress.[29,30] Gliflozins have anti-apoptotic effects and can enhance mitochondrial biogenesis in cells

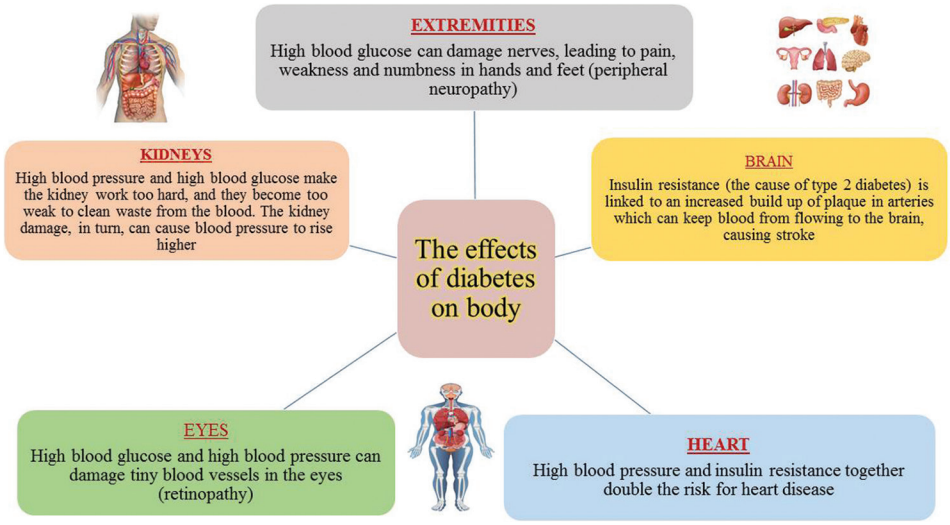

Figure 1: Deleterious effects of diabetes on body organs

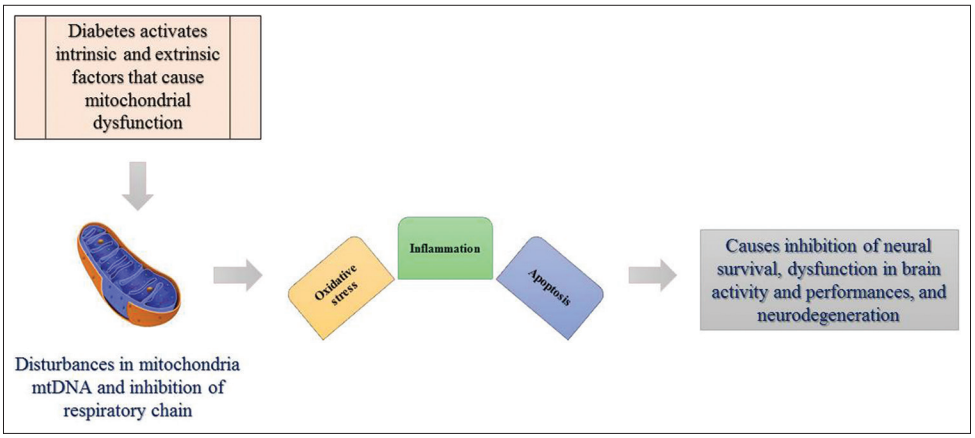

Figure 2: Diabetes-induced brain toxicity is mediated by mitochondrial dysfunction and the effects of oxidative stress, inflammation, and apoptosis, which causes organ damage and dysfunction

of multiple organ systems, particularly in the CNS and PNS in DM subjects.[21,31] Additionally, gliflozins can act effectively against DM-induced neuro-inflammatory events,[32,33] showing potent neuroprotective properties in both DM-induced neurodegenerative events and other types of neurodegenerative diseases or disorders.[23,26,28]

This narrative review first provides an overview of the harmful effects of DM on the molecular pathways leading to neurodegeneration. Next, we present a comprehensive analysis of the neuroprotective activities of gliflozins against DM-induced neurodegeneration and neurotoxicity, with an emphasis on the inhibitory effects on the hallmarks of neurodegeneration, including neuro-apoptosis, neuronal mitochondrial dysfunction, neuronal oxidative stress, and neuro-inflammation.

Methods

A literature review was performed to assess publications investigating the neuroprotective activities of gliflozins against DM-induced neurodegeneration and neurotoxicity. Multiple databases—including Scopus, Web of Science, PubMed, Google Scholar, Cochrane, Elsevier/Science Direct, and Core Collection—were queried for valid peer-reviewed papers published between January 2000 and July 2023 using the major keywords "gliflozins," "diabetes mellitus," "DM and neurodegeneration or neurotoxicity," "Gliflozins plus DM," and "Gliflozins against DM-induced neurodegeneration/neurotoxicity." Additional-related keywords included neuronal mitochondrial dysfunction, neuronal oxidative stress, neuro-inflammation, hallmarks of cell death (apoptosis, necrosis, and autophagy), and gliflozins against DM-induced neurodegeneration.

DM-Induced Neuronal Oxidative Stress

Oxidative stress plays a critical role in DM-induced neurodegeneration, as it is one of the important cascades that contribute to DM-induced neuronal damage and neurotoxicity.[34,35] DM-induced oxidative stress can be a critical predisposing factor for neurodegeneration and can activate neurodegenerative diseases or disorders.[34,36-38] Generally, oxidative stress occurs when two separate events are present: 1) augmented formation or production of oxidant parameters including free radicals, increased radical oxygen species (ROS) and radical nitrogen species (RNS), and elevated lipid and protein peroxidation products and byproducts; and 2) impaired cell defenses and decreased antioxidant enzymes—such as superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GR), and catalase (CAT)—and disturbances in the glutathione cycle.[39] DM can induce these general pathways of oxidative stress, which can lead to neuronal cell injury and cause neurodegeneration.[16,40]

DM can induce lipid peroxidation and elevated levels of reactive aldehyde or lipid peroxidation components, including 4-hydroxy-2-nonenal (HNE) and 4-oxo-2-nonenal (ONE), malondialdehyde (MDA) and isolevuglandin (IsoLG) in neuronal cells.[17,41,42] DM-induced lipid peroxidation is one of the main players in both the PNS and CNS in DM-induced neurodegenerative events such as neuropathy and retinopathy.[16,35,43-45] DM-induced neurodegeneration involves protein oxidation,[43,46] lipid peroxidation, and neuronal protein deformation and peroxidation.[39,47] Protein peroxidation is involved in neuropathy, retinopathy, and other types of neuronal damage in the PNS and CNS of DM subjects.[36,43,44,48-52] At the molecular level, DM can cause peroxidation of essential amino acids such as cysteine, methionine, and tyrosine.[39,47,53] Also, carbonyls and AOPPs' groups—the main components or products of protein oxidation—play strategic roles in DM-induced neurodegeneration in the PNS and CNS.[54,55] DM-induced lipid or protein peroxidation can exacerbate neurodegenerative diseases such as AD, PD, seizures, MS, and ALS.[56-63]

DM-induced oxidative stress causes dysfunction of neuronal cellular defenses and decreases antioxidant enzymes[64,65] such as SOD, GR, GPx, and CAT.[66] Normally, SOD activity plays a critical role in the conversion of O_2^- into hydrogen peroxide[67,68] and it is a critical component in the neuronal cellular defense against cell damage.[69,70] SOD also reduces the mitochondrial release of cytochrome C and NO and can inhibit occurrences of oxidative stress.[68,71] GR, another important antioxidant enzyme, causes the reduction of GSSG to GSH and triggers the formation of the protective form of glutathione; it also activates the conversion of NADPH to NAD^+.[16,35,72,73] DM interferes with all these pathways. In addition to causing disturbances in SOD activity and initiating cellular damage,[74] DM causes decreased GR activity, which leads to dysfunction of glutathione level and reduction of GSH, the protective form of glutathione.[44,75,76] DM-stimulated neurotoxicity and neurodegeneration have been reported to be mediated via the GPx pathway, the same process that occurs with GR.[77-79]

CAT is another antioxidant enzyme involved in the conversion of hydrogen peroxide to water and oxygen.[80] Dysregulation of this enzyme is involved in many kinds of neurodegenerative events and also DM.[81,82] CAT dysfunction causes increased hydrogen peroxide, which plays a critical role in the pathophysiology of DM-induced neurodegenerative events such as neuropathy and retinopathy.[43,83-86] Mitochondrial dysfunction, reduction of ATP production, and alteration of mitochondrial membrane are the main mediators of DM-induced oxidative stress, which cause the formation or production of ROS and RNS.[87-90] In fact, DM-induced formation of free radicals in neuronal tissue is a main contributor to DM-induced neurodegenerative events.[36,69,91] Based on these principles, it appears that diabetes induces oxidative stress and mitochondrial dysfunction, which can induce neurodegeneration and neurotoxicity. Figure 3 summarizes

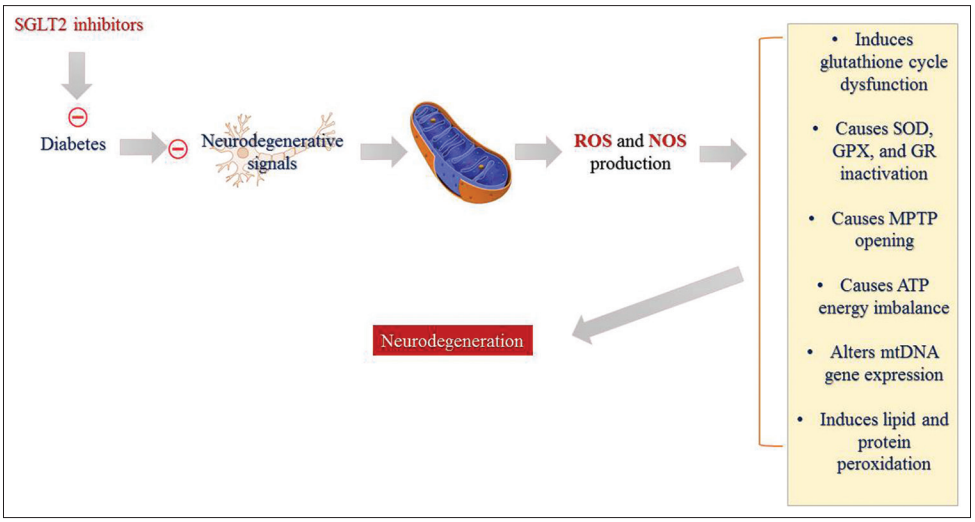

Figure 3: SGLT2 inhibitors (gliflozins) can modulate diabetes-induced neuronal mitochondrial dysfunction, minimize or inhibit diabetes-induced lipid peroxidation, glutathione circulatory impairment, antioxidant enzyme (SOD, GPx, and GR) dysfunction, and inhibit the formation of diabetes-induced ROS and NOS. Metformin attenuates the deleterious effects of diabetes on the mitochondrial respiratory chain and MtDNA output. GPx: Glutathione peroxidase, GR: Glutathione reductase, GSH: Glutathione, GSSG: Glutathione disulfide, MtDNA: mitochondrial DNA, NOS: Nitrogen oxygen species. SGLT2: Sodium-glucose cotransporter-2, SOD: Superoxide dismutase, ROS: Reactive oxygen species

the relationship between disturbances in the oxidant/antioxidant balance and potential diabetes-induced damage in neurons.

DM-Induced Neuro-Inflammation

DM induces multiple neuro-inflammation pathways and cascades that lead to neurodegenerative events and diseases in DM subjects.[37,92,93] DM induces abnormalities in neuronal cells and activates glial cells, triggering many kinds of neuro-inflammatory pathways that lead to neurodegeneration.[94-97]

The cytokine system is a major pathway involved in DM-induced neural inflammation and neurodegeneration.[98,99] Pro-inflammatory and inflammatory cytokines such as tumor necrosis factor (TNF)-α, interferon (IFN)-γ, interleukin (IL)-1, IL-12, IL-18, and granulocyte macrophage-colony stimulating factor (GM-CSF) are the main players of DM-stimulated neurodegeneration.[100,101] Hyperglycemia and metabolic disturbances in DM cause the discoordination of cytokine functions.[99] DM can cause microglial activation and induce the activation of peripheral inflammatory cells to secrete cytokines that cause central and peripheral nerve cell damage.[37,93] Inhibiting microglial cell activation and decreasing cytokine production are potential candidates for modulating neuronal cell degeneration in DM subjects.[99]

Pro-inflammatory cytokines—such as TNF-α, IL-1β, and IL-6—are main players that are upregulated in DM-induced neuro-inflammation and consequent neurodegeneration.[102-108] In contrast, anti-inflammatory cytokines—such as IL-2,[109] IL-4, IL-6, and IL-10[110-112]—are downregulated in DM. Thus, some aspects of DM-induced neuro-inflammation and neurodegeneration are due to decrease in IL-2, IL-4, IL-6, and IL-10 levels and function.[110-112] IFNγ is increased in DM subjects.[112] In addition, chemokines—such as CCL2, CCL20, CXCL5, CXCL7, and CXCL12—play critical roles in DM-stimulated neuro-inflammation.[113,114] In fact, cytokines and chemokines are collaboratively involved in DM-induced neuro-inflammation.[115] Systemic inflammation and some general inflammatory biomarkers such as C-reactive protein (CRP) are also involved in DM-prompted neuronal inflammation.[116-118]

DM-induced neuro-inflammation involves other neuro-inflammatory signaling pathways, including the NF-kb pathway, nitric oxide synthase (NOS)-nitric oxide (NO) pathways, cyclooxygenase (COX)-prostaglandin (PG), Janus kinase/signal transducers and activators of transcription (JAK/STAT) and toll-like receptor (TLR) cascade and GF.[16,115,119,120] COX-PG signaling cascades are activated in DM subjects, leading to neuropathy, retinopathy, and other comorbidities of neurodegenerative disorders.[121] DM can cause induction of COX activation and downstream neuro-inflammation pathways that can lead to nerve damage.[122] DM/hyperglycemia is an activator of cytosolic phospholipase (PLP) (A2) in nerve cells, which causes activation of COX-2 and production of PG, triggering neuronal cell death.[16,115,123,124]

Several studies indicate that DM, via stimulation of iNOS, can cause overproduction of NO synthesis, and can trigger neuronal cell death by activating NOS pathways.[104,121,125,126] Additional studies suggest that DM-induced retinopathy, neuropathy, and other neurodegenerative events are mediated via the NOS pathway.[37,93] The NF-κβ family acts as transcription factors for most pro-inflammatory molecules, enzymes, cytokines, and chemokines.[127] DM induces the stimulation of NF-κB, an inflammatory transcription factor, and overexpression of NF-κB

causes neuro-inflammation, which leads to neuropathy, retinopathy, and similar neurodegenerative conditions.[128] DM, via activation of mtDNA, can cause NF-kβ expression in neuronal cells.[129-131] DM-triggered neuropathy and retinopathy are mediated via JAK/STAT3 signaling cascades in both microglia in the CNS and in other inflammatory cells in the PNS.[132-134] Other indirect data suggest the critical role of the TLR family in DM-mediated inflammation.[135] Although the precise and specific role of TLRs in the inflammatory processes caused by diabetes as well as the damage of neuronal cells has not been fully determined and evaluated, it seems that these receptors and their downstream pathways play a key role in inducing neuro-inflammation in neurodegeneration caused by DM.[136,137]

Based on these principles, it seems that DM induces neuro-inflammation and related pathways, which induces neurodegeneration and neurotoxicity. Figure 4 summarizes the relationship between DM and the induction of neuro-inflammation and neurodegeneration.

DM-Induced Neuro-Apoptosis and Cell Death

Cell death pathways such as mitochondrial disruption, apoptosis, pyroptosis, necrosis, and autophagy are other cascades involved in DM-induced neurodegeneration and neuronal dysfunction.[138-140] DM-induced cell death is responsible for the occurrence of neurodegeneration in both the PNS and CNS.[141-143] DM can cause activation of apoptosis cell death signaling cascades via both intrinsic and extrinsic pathways, which ultimately lead to neurodegenerative events.[144,145] DM induces neuropathy and retinopathy and exacerbates neurological diseases—such as PD, AD, MS, or stroke—via activation of one or more apoptotic cascades.[59-63]

Apoptosis occurs in two separate extrinsic and intrinsic cascades. In extrinsic pathways, death ligands—such as the adaptor proteins, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), and Fas-associated protein with death domain (FADD)—cause caspase-8 and -10 activation, which in turn causes caspase 3 and 7 stimulation, thus leading to apoptosis. In intrinsic pathways, any kind of mitochondrial dysfunction or DNA damage can induce the production of apoptosomes and activation of caspase-9, -3, and -7.[146] DM causes activation or stimulation of death ligand or mitochondrial dysfunction, which contributes to brain cell damage and causes neuronal cell death.[147-149] The grades of neural cell apoptosis depend on the severity of DM, and the severity of apoptosis has a close relation with neurodegeneration.[149,150] DM can cause an increase in the apoptotic index in neuronal cells,[46,150] and DM-induced apoptosis is due to the activation of inflammation, oxidative stress, and cell death.[46,79,151] Many studies show that DM subjects have decreased Bcl-2 levels in both the PNS and CNS, and increased Bax and caspase family protein levels.[70,141,142,146,152-154] Bcl-2 is essential for mitochondrial outer membrane permeabilization (MOMP) function and can regulate mitochondrial functions. Mitochondrial dysfunction in DM subjects can cause activation of apoptosis intrinsic factors and can cause stimulation of Bcl-2 and caspase family proteins, which lead to initiation of the intrinsic pathways of apoptosis.[70,141,142,146,152-154] In animal models of DM—generated using streptozotocin (STZ) and/or alloxan to induce diabetes—apoptosis has been shown to be closely related to pyroptosis,[155,156] an event that also depends on mitochondrial dysfunction and disturbance in DNA function. Pyroptosis relies on plasma membrane pore function and activation of caspase-1 and inflammatory cascades.[155,156] Necrosis is another DM-induced cell death event[157] that occurs without programmed cell death when blood flow in the nervous system is disrupted.[157] Necrosis involves the main cascades of neuro-inflammation and oxidative stress[37,158] and functions in close collaboration with apoptosis in DM-induced neurodegeneration.[142,157] DM induces neuropathy, retinopathy, and other related neurodegeneration in both the PNS and CNS after necrosis in neuronal cells.[91,159,160]

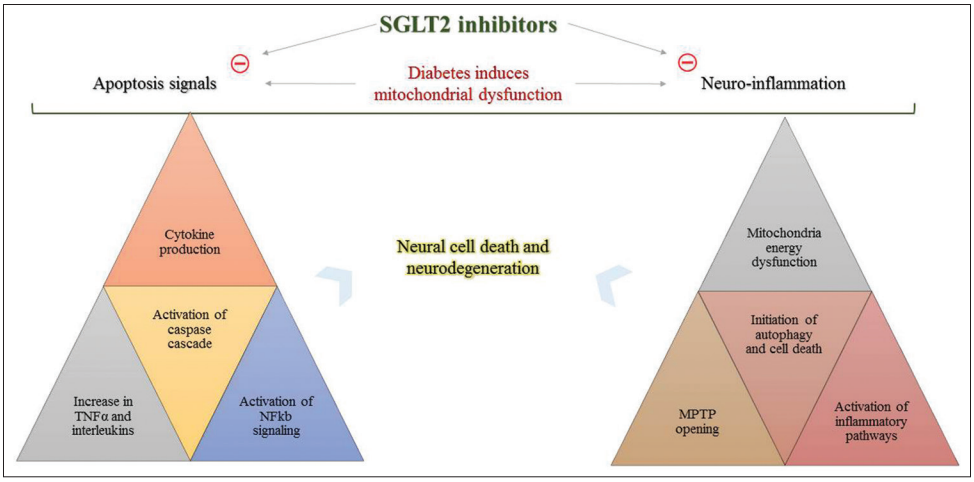

Figure 4: SGLT2 inhibitors (gliflozins) inhibit diabetes-induced apoptosis and inflammation, which attenuates probable neurodegenerative occurrences

Autophagy, another cell death process involved in DM-induced neurodegeneration, is dependent upon lysosome functions.[149] Any kind of DM-induced neuronal cellular damage can initiate autophagy signaling pathways,[149,161] which lead to neuropathy, retinopathy, and other related neurodegenerative complications.[144,145,149,161]

Many studies have shown that DM can exacerbate or cause the onset of neurodegenerative diseases. In AD, diabetes plays a role in the activation of tau proteins[131,162] by activating amyloid beta precursor protein (APP), leading to the activation of alpha- and beta-secretase that causes hyperphosphorylation of Tau protein, which leads to cerebrovascular damage, loss of synapse and activation of microglia associated with AD and dementia.[131,162,163] In PD, by activating oxidative stress and apoptosis, DM causes the formation of misfolded proteins and causes the misfolded dysfunction of α-synuclein which ultimately leads to the destruction of synapses and synaptic vesicles. Additionally, diabetes causes genotoxic stress, and this pathway also causes misfolded dysfunction of α-synuclein, ultimately leading to parkinsonism and movement disorders.[163,164] By a similar mechanism, DM also exacerbates or causes MS, ALS, and epilepsy, in which misfolded proteins trigger the demyelination or synaptic disturbances involved in neurodegenerative diseases.[1,147] Thus, DM-induced mitochondrial dysfunction and cell death plays a critical role in DM-induced neurodegenerative complications.[1,147] Figure 4 summarizes the relationship between DM, cell death, and neurodegeneration.

Therapeutic Approaches for DM-Induced Neurodegenerative Events

An attractive strategy for managing or preventing DM-induced neurodegenerative diseases is the use of therapeutics that inhibit oxidative stress, inflammation, and cell death. The use of novel anti-hyperglycemic agents with neuroprotective characteristics has good potential for the prevention or management of DM-induced molecular and neuronal functional problems, particularly if they show anti-oxidative stress, anti-inflammatory, and anti-apoptosis characteristics.[20,21] SGLT2 inhibitors (gliflozins) are a group of antidiabetic agents that also have neuroprotective properties.[21,22]

SGLT2 Inhibitors (Gliflozins)

SGLT2 inhibitors (gliflozins) are a group of therapeutics used in the management of T2DM; this class of drugs includes phlorizin, dapagliflozin, canagliflozin, and empagliflozin. Gliflozins affect the intestinal mucosa of proximal tubules of nephrons and inhibit reabsorption of sodium and glucose by acting on sodium-glucose channels[165,166] [Figure 5]. This class of medication has other beneficial effects on cardiovascular, hepatocellular, and neuronal systems.[165,166] Research in recent years has confirmed the beneficial effects of these agents on the CNS and PNS and positive changes in neurobehavioral and neurochemical status, particularly in patients with DM[167] [Figure 6].

Effects of Gliflozins on Diabetes-Induced Mood and Cognition Disorders

DM can induce anxiety-like behavior in both human and animal subjects,[168] and diabetes-induced anxiety is closely correlated with neurochemical changes in brain cells.[169,170] Recent pre-clinical and clinical studies show that diabetes induces behaviors linked to anxiety and stress, and this behavioral shift is parallel to neurodegeneration.[170,171] Other related studies report that diabetes causes depressive behavior in both human and animal subjects,[171,172] and that diabetes triggers cognitive impairment and cognitive dysfunction. These forms of DM-induced cognitive dysfunction are linked to neurodegeneration events.[173,174] Modulating diabetes-induced neurobehavioral consequences, on the other hand, poses a significant challenge.[174]

Clinical and experimental trials have shown that gliflozins may act as an antidepressant and mood stabilizer—even at sub-therapeutic doses—in patients with diabetes.[175] Gliflozins may modify anxiety and enhance cognitive function in diabetic subjects and may likely modulate diabetic-induced neurodegeneration, leading to increased cognitive performance in patients.[176] Gliflozins and other related neuroprotective agents are able to alleviate anxiety and stress-like behaviors in diabetic subjects[176,177]; many clinical and pre-clinical studies indicate that gliflozins can modify moods, particularly in patients with metabolic-related disease.[178-180] Thus, gliflozins—possibly by exerting neuroprotective effects of regulating diabetic-induced neurodegeneration—can confer antidepressant, anxiolytic, and cognitive enhancer effects that could alter behavioral disruptions in diabetic subjects [Figure 7].

Neuroprotection Effects of Gliflozins Against Hallmarks of Diabetes-Induced Neurodegeneration

Effects of gliflozins on diabetes-induced oxidative stress

Potential risk factors for cognitive decline in patients with diabetes include hypoglycemia, micro- and macrovascular disease, inflammation, and psychosocial factors. While some studies suggest that improved glycemic control is associated with better cognitive function, other studies have shown conflicting results. Thus, the potential benefit of antidiabetic agents in preventing cognitive deficits is unknown.[181]

Several studies have investigated the effect of gliflozin on diabetes-induced oxidative stress. Oelze and colleagues showed improvement with empagliflozin on endothelial dysfunction in type 1 (T1) DM rats,[182] indicating a potential therapeutic effect. Lin *et al*.[183] investigated the effect of empagliflozin on cerebral oxidative stress and brain-derived

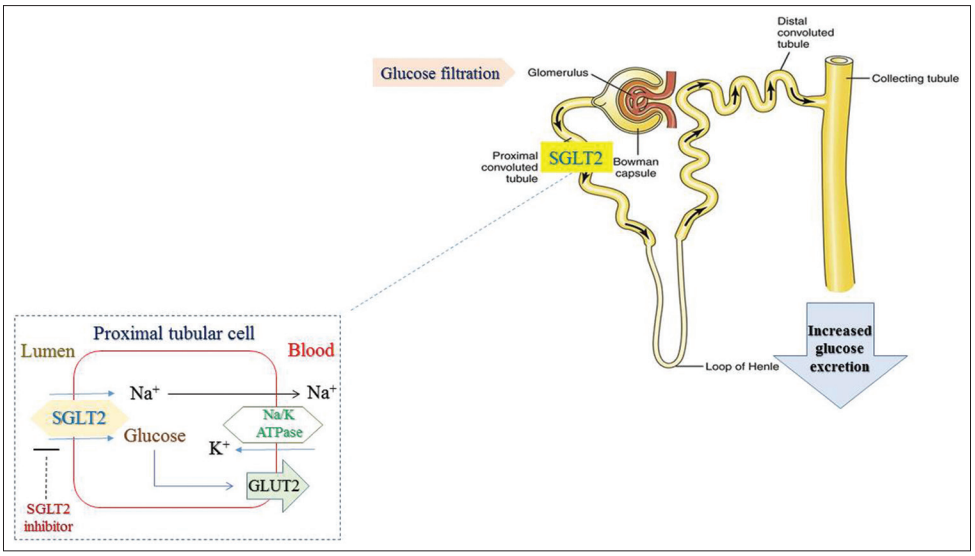

Figure 5: Pharmacological mechanism of SGLT2 inhibitors (gliflozins)

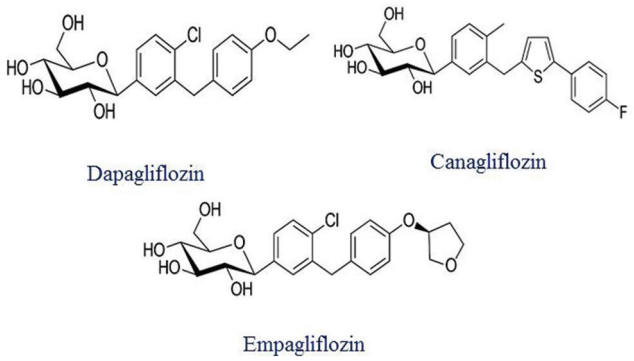

Figure 6: Structures of SGLT2 inhibitors (gliflozins)

nuclear factor (BDNF) in a mouse model of obesity and T2DM. The mice were divided into two subgroups, with one receiving a standard diet and the other receiving a standard diet containing 0.03% empagliflozin for 16 days. Empagliflozin significantly reduced brain oxidative stress in the animals through the reduction of cerebral superoxide, 8-OHdG, and cerebral NADPH oxidase subunits, including gp91 and p67. Empagliflozin also increased cerebral BDNF levels, indicating that it may have a positive effect on cognitive function in diabetic mice. Amin *et al*.[184] found that empagliflozin treatment reduced cerebral oxidative stress, inflammation, and markers of apoptosis in rat brain tissue. Using ischemic stroke-injured hyperglycemic Wistar rats as a study model, treatment with empagliflozin (10 mg/kg) attenuated the alterations in levels of MDA, CAT, and GSH. Empagliflozin treatment significantly increased the levels of cerebral GSH and CAT in the ischemic group by 0.36- and 2.3-fold. Empagliflozin also reduced the elevated levels of MDA in brain tissues of the ischemic group.

A wide range of studies have demonstrated that a high-fat diet (HFD) not only affects insulin function but also impacts cognitive abilities in the brain. The detrimental effects of obesity on the brain are manifested through various mechanisms, including brain mitochondrial dysfunction, increased oxidative stress, and impaired insulin function in brain tissue.[184] In 2017, a group of scientists subjected Wistar rats to HFD for 16 weeks and evaluated the effects of two blood glucose-lowering drugs—empagliflozin and vildagliptin—in three separate groups. HFD rats experienced brain mitochondrial dysfunction, which was manifested through increased production of ROS and mitochondrial membrane depolarization. In addition to mitochondrial changes, the concentration of MDA increased in rat brains, indicating an increased level of brain oxidative stress. Treating the rats with empagliflozin, vildagliptin, and a combination of the two drugs significantly decreased brain mitochondrial ROS production and depolarization. The drugs also led to a decreased level of MDA.[185]

The precise molecular mechanism underlying the development of PD remains uncertain; however, there is a clear association between mitochondrial dysfunction, oxidative stress, and the loss of dopaminergic neurons in PD.[186] The neuroprotective effects of dapagliflozin on PD were investigated using rotenone (1.5 mg/kg)-treated Wistar rats as a PD animal model. Rotenone increased lipid peroxidation and the expression of nuclear Nrf2, DJ-1, and HO-1 compared to control rats. However, treatment with dapagliflozin (1 mg/kg) markedly affected neuronal oxidative stress, lowering lipid peroxides and restoring the disturbed DJ-1/Nrf2 pathway[187] [Figure 3]. Table 1 provides a summary of the experimental studies on the effects of gliflozins on diabetes-induced oxidative stress.

Gliflozins and diabetes-induced inflammation

SGLT2 inhibitors have garnered significant interest due to their positive effects shown in DM, heart failure, and kidney disease. Various mechanisms may explain

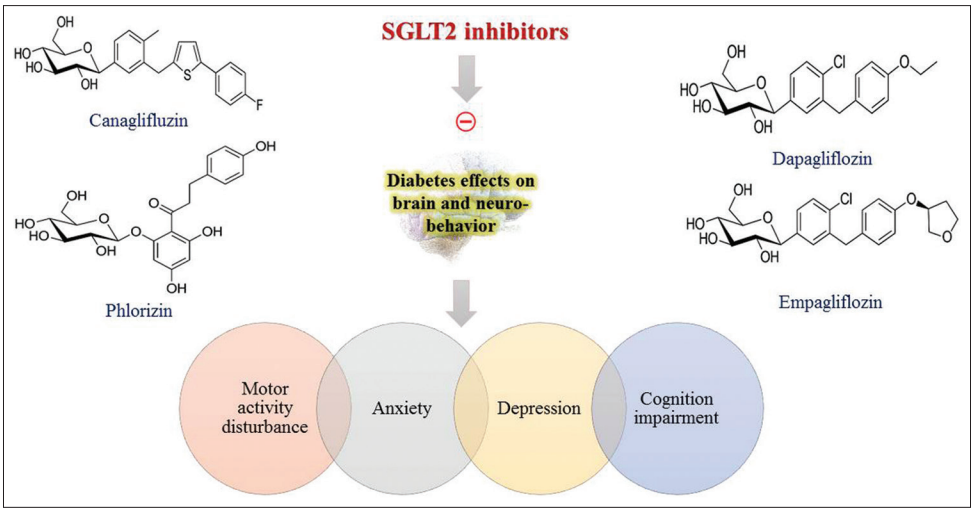

Figure 7: Protective effect of SGLT2 inhibitors (gliflozins) against diabetes-induced neuro-behavioral changes such as anxiety, depression, cognition impairment, and motor activity disturbances

Table 1: Experimental studies investigating the effects of gliflozins on oxidative stress in DM-induced neurodegenerative events

Animal model/cell line/clinical study	Dose, period of treatment, and evaluation of oxidative stress	Major outcomes/effects of treatment with gliflozin	References
STZ-induced rat, T1DM model	Empagliflozin (10 and 30 mg/kg/d) via drinking water for 7 weeks. Oxidative stress parameters assessed.	Reduction of oxidative stress in aortic vessels, development of endothelial dysfunction, improved metabolic parameters.	[183]
db/db mice (obesity model)	db/db mice were used as a model of obesity and T2DM. Two subgroups of animals: - Standard diet group - Standard diet with 0.03% Empagliflozin	Empagliflozin reduced cerebral superoxide, 8-OHdG, gp91 and p67, and increased BDNF levels, which showed a positive effect on cognitive performance in diabetic mice.	[184]
Male Wistar rats	Hyperglycemic rats were subjected to cerebral I/R injury, divided in groups: - Rats with cerebral I/R injury (control group) - I/R injured rats treated with empagliflozin (10 mg/kg) - I/R injured rats treated with gliclazide (2mg/kg).	Empagliflozin treatment increased levels of cerebral GSH and catalase in the ischemic group, and reduced the elevated levels of MDA in brain tissues of the ischemic group.	[185]
HFD-induced obese rats	Vildagliptin (3 mg/kg/day), Dapagliflozin (1 mg/kg/day) or combined drugs for four weeks. Investigated metabolic parameters and brain function.	A combination of the drugs had greater efficacy in improving brain insulin sensitivity and reducing brain oxidative stress than the single drug therapy.	[186]
Rat model of rotenone-Induced Parkinson's Disease (PD)	Dapagliflozin (1 (mg/kg)/day), by gavage for 3 weeks Investigated expression of target signals.	Dapagliflozin markedly alleviated neuronal oxidative stress via lowering lipid peroxides with consequent restoration of the disturbed DJ-1/Nrf2 pathway.	[188]

these diverse effects, including those related to reducing inflammation, correlated with the development of different neurodegenerative conditions and disorders.[188,189]

Long-term inflammation in the brain can result in difficulties with memory that relies on the hippocampus.[190] Several studies have investigated the effect of SGLT2 inhibitors on inflammatory markers such as IL-6, CRP, TNF-α, and MCP-1.[191] Microglia, which are essential regulators of inflammation in the brain, play a significant role in neurodegenerative disorders; decreasing microglia-induced inflammation could potentially decelerate the progression of these diseases. In a 2022 study,[27] primary rat microglia were induced to a pro-inflammatory state by lipopolysaccharide (LPS) stimulation and then investigated as to whether empagliflozin affected the expression of various pro-inflammatory mediators, including NO, NOS2, IL-6, TNF, IL-1B, and the anti-inflammatory mediator—IL-10, as well as the ERK1/2 cascade and NF-κB translocation. The results showed that empagliflozin reduced the expression of both pro-inflammatory and

anti-inflammatory mediators in LPS-activated primary microglia. Naznin *et al*.[192] investigated the effects of canagliflozin on inflammation caused by obesity in mice and demonstrated that canagliflozin reduced body weight, liver weight, and fat accumulation in HFD obese mice. Canagliflozin caused a reduction in the accumulation of mRNA levels of the inflammatory biomarkers Iba1 and IL-6 and decreased the number of macrophages/microglia within the nodose ganglion and hypothalamus. In the skeletal muscle of HFD-fed obese mice, canagliflozin decreased inflammatory cytokine levels, macrophage accumulation, and the mRNA level of the specific atrophic factor atrogin-1. Steven *et al*.[193] investigated the effects of empagliflozin on primary diabetic complications in male Zucker diabetic fatty (ZDF) rats. Administrating empagliflozin (10 and 30 mg/kg/d) via drinking water for 6 weeks restored glycemic control, improved endothelial function, reduced oxidative stress, and prevented inflammation and glucotoxicity. Thus, empagliflozin appeared to ameliorate glucotoxicity via the excretion of glucose and to modify the hepatic metabolome of ZDF rats towards a protective profile.

Empagliflozin (500 nM) has been found to inhibit the expression of several inflammatory response genes in human proximal tubular cells when exposed to IL-1β.[194] This anti-inflammatory effect of empagliflozin is observed

Table 2: Experimental and clinical studies investigating the effects of gliflozins on inflammation in DM-induced neurodegenerative events

Animal model/cell line/clinical study	Dose, period of treatment, and evaluation of inflammation	Major outcomes/effects of treatment with gliflozin	References
Rat primary microglial cells	0.5M, 1M, 5M or 50M empagliflozin in the presence or absence of 5 ng/mL LPS for 24h. Assessed expression of pro-inflammatory mediators and the anti-inflammatory mediator IL10. Investigated changes in the activation of the ERK1/2 cascade by NFkB translocation.	Reduced the expression of pro- and anti-inflammatory mediators in LPS-activated primary microglia	[27]
High-fat diet (HFD)-fed male C57BL/6J mice	HFD-fed male C57BL/6J mice were treated with canagliflozin for 8 weeks.	-Attenuated increases in the mRNA levels of the Iba1 and IL-6 and the number of macrophages/microglia in the nodose ganglion and hypothalamus. -decrease in inflammatory cytokine levels, macrophage accumulation, and the mRNA level of the specific atrophic factor atrogin-1 in the skeletal muscle.	[193]
Zucker diabetic fatty (ZDF) rats	Empagliflozin (10 and 30 mg/kg/d) via drinking water for 6 weeks.	Prevented inflammation and glucotoxicity (AGE/RAGE signaling) epigenetically. Decreased glucotoxicity and oxidative stress, prevented the development of endothelial dysfunction and exhibited anti-inflammatory effects	[194]
Rat model of rotenone-Induced PD	Dapagliflozin (1 (mg/kg)/day), by gavage for 3 weeks Investigated the expression of target signals.	Elicited significant anti-inflammatory activities via curbing neuronal GSK-3β, NF-κB activation and its downstream signal, TNF-α.	[188]
Human proximal tubular cells (HPTCs)	Empagliflozin (500 nM), in both HK-2 and RPTEC/TERT1 cells.	-Inhibited the expression of inflammatory response genes in HPTCs, including MCP-1/CCL2, ET-1, IL-1β, IL-6, TNF-α, and ICAM- -Decreased the expression of several other inflammatory response genes in IL-1β-induced normoglycemic HPTCs	[195]
HFD-induced obese rats	Vildagliptin (3 mg/kg/day), dapagliflozin (1 mg/kg/day) or combined drugs for four weeks. Investigated metabolic parameters and brain function.	-Attenuated brain apoptosis and brain inflammation -Greater efficacy of dapagliflozin in improving peripheral insulin sensitivity and a similar efficacy in reducing oxidative stress, attenuating brain mitochondrial dysfunction, brain apoptosis, and brain inflammation, and preventing cognitive decline. -Greater anti-oxidative effects and improving brain insulin sensitivity to a greater degree in the combined drugs therapy	[186]
Rat model of depression	Dapagliflozin (1 mg/kg/day; p.o.) with and without BQ-788 (1 mg/kg/day; i.p.), for 5-week chronic unpredictable stress protocol.	-NLRP3 inflammasome may be a promising therapeutic target for depression. -Dapagliflozin can significantly suppress its activation to halt both neuro-inflammation and BBB disturbance, mediated through the NLRP3/IL/TNF-α/miR-501-3p/ZO-1 axis	[196]

under normoglycemic conditions. It also improves renal ischemia-reperfusion (IR) injury by reducing inflammation and enhancing mitochondrial fusion through the AMPK-OPA1 pathway.

In the rotenone-induced PD model, rats show marked neuronal inflammation, as evidenced by the activation of NF-κB signaling/upregulation of its downstream effector TNF-α. Using this model, dapagliflozin showed potential neuroprotective effects against PD-associated neurodegenerative aberrations/motor dysfunction,[187] attenuation of PD motor dysfunction and improvement in motor coordination, diminished histopathologic alterations and α-synuclein expression, augmented tyrosine hydroxylase and dopamine levels, and suppression of neuro-inflammation by restraining the activation of the NF-κB pathway and TNF-α levels.

In depressive animal models, the NLRP3 inflammasome pathway is activated along with peripheral and central inflammatory responses. Dapagliflozin was found to play an antidepressant role by regulating the NLRP3/ET-1/ETBR/BDNF axis.[195] In a study conducted on HFD-induced obese rats,[185] treatment with both a SGLT2 inhibitor and a DPP-4 inhibitor showed the development of brain function by attenuating mitochondrial dysfunction, insulin resistance, inflammation, and apoptosis. Single therapy resulted in equally improved brain mitochondrial function, insulin signaling, and apoptosis and prevented cognitive decline. However, only dapagliflozin made a positive

Table 3: Experimental and clinical studies investigating the effects of gliflozins on modulating cell death in DM-induced neurodegenerative events

Animal model/cell line/clinical study	Dose, period of treatment, and evaluation of Cell death	Major outcomes/effects of treatment with gliflozin	References
HFD-induced obese rat	The HFD-fed rats divided into four subgroups (at week 13): 1-vehicle group 2- vildagliptin (3 mg/kg/day) group 3- dapagliflozin (1 mg/kg/day) group 4- Combination of both drugs	-Decreased expression of apoptosis-related factors, including Bax and Bcl2 in rats treated with dapagliflozin, vildagliptin, or both drugs. -Decreased brain inflammation.	[186]
Male Wistar rats	1 and 10 mg/kg of empagliflozin, 1 and 24 h after reperfusion.	-Downregulated the expression of caspase-3, upregulated HIF-1α and its downstream mediator VEGF in the ischemic brain. -Confirmed the anti-apoptotic effect of empagliflozin through increasing the expression of HIF-1a and VEGF.	[200]
Hyperglycemic rats	Hyperglycemic rats were subjected to cerebral I/R injury and divided to: - Rats with cerebral I/R injury (control group). - I/R injured rats treated with empagliflozin (10 mg/kg). - I/R injured rats treated with gliclazide (2mg/kg).	-Decreased caspase-3 and the number of apoptotic cells in I/R injured rats by empagliflozin and gliclazide treatments. -The reduction of apoptotic cells by empagliflozin and gliclazide was 85% and 90.7%, respectively.	[185]
Huntington Disease (HD) rat model	40 wistar rats divided in to 4 groups: - Normal control group - Dapagliflozin group (1 mg/kg) - 3-NP group (30 mg/kg) - Dapagliflozin plus 3 -NP group	-Elevated levels of apoptotic markers due to HD stimulation, attenuated by dapagliflozin treatment. -dapagliflozin induced autophagy by enhancing beclin-1 and LC3 expression and reducing DRAM expression.	[203]
Rat model of rotenone-Induced PD.	Rotenone-induced PD rats were treated with Dapagliflozin (1(mg/kg)/day).	Treatment with dapagliflozin decreased Bax and caspase-3. Dapagliflozin also restored the PI3K/AKT/GSK-3β pathway, proving its role in anti-apoptotic mechanisms.	[188]
Ovariectomized/D-galactose Alzheimer's rat model	Dapagliflozin (1 mg/kg/day; p.o.).	-Elevation of energy sensors; AMP/ATP ratio and LKB1/AMPK protein expressions along with autophagic markers; SIRT1, Beclin1, and LC3B expressions. - Dapagliflozin implied its anti-AD effect, via boosting hippocampal LKB1/AMPK/SIRT1/mTOR signaling in OVX/D-Gal rat model	[204]

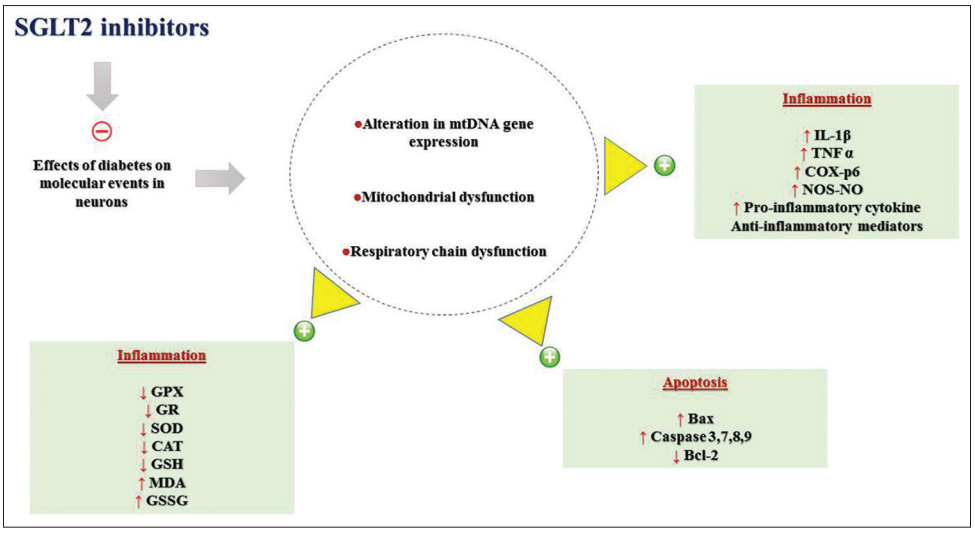

Figure 8: SGLT2 inhibitors (gliflozins) exert neuroprotective effects via inhibition of apoptosis, inflammation, and oxidative stress, leading to attenuation of diabetes-induced neurodegenerative occurrences. Bax: Bcl-2-associated X protein, Bcl-2: B-cell lymphoma 2, CAT: Catalase, COX: Cyclooxygenase, GPx: Glutathione peroxidase, GR: Glutathione reductase, GSH: Glutathione, GSSG: Glutathione disulfide, MDA: Malondialdehyde, NO: Nitric oxide, NOS: Nitric oxide synthase, TNF: Tumor necrosis factor

impact on hippocampal synaptic plasticity [Figure 4]. Table 2 summarizes the experimental studies of the effects of gliflozins on diabetes-induced inflammation.

Effects of gliflozins on diabetes-induced apoptosis and cell death

SGLT2 inhibitors are among the most prominent oral anti-hyperglycemic agents. SGLT2s are primarily expressed in segments 1 and 2 of the proximal convoluted kidney tubules and play an important role in the reabsorption of urinary glucose, which is dependent on a sodium concentration gradient. However, SGLT2s are not exclusively expressed by renal cells, as they are present in the mammalian CNS including the hippocampus, cerebellum, and blood-brain barrier (BBB) endothelial cells. This particular distribution may be responsible for the intriguing evidence suggesting their neuroprotective properties.[196,197]

The global incidence of AD is on the rise, and finding new effective treatment options is critically important. The main pathological mechanism of AD is the extra- and intracellular accumulation of plaques containing beta-amyloid and neurofibrillary tangles (NFTs). Several studies have investigated the effectiveness of SGLT2 inhibitors in controlling the AD process. In empagliflozin-treated APP/PS1xd/db mice (AD-T2D model), Hierro-Bujalance *et al*. showed a reduction in senile plaque density and overall soluble and insoluble amyloid β (Aβ) levels in the cortex and hippocampus. Empagliflozin treatment caused a significant increase in neural cognition and amelioration of AD-related symptoms.[198]

The effect of SGLT2 inhibitors has also been investigated in models of non-neuron-related diseases using male Wistar rats subjected to global cerebral I/R injury by occluding the bilateral common carotid arteries for 30 minutes, followed by one-hour reperfusion. Empagliflozin treatment, at doses of 1 and 10 mg/kg for 1 and 24 hours after reperfusion, significantly reduced the size of the infarct and improved neurobehavioral functions in a dose-dependent manner in the I/R-injured rats. In the I/R rats, cerebral ischemia caused neuronal death along with the activation of apoptotic mechanisms and an increased level of the pro-apoptotic factor, caspase-3. Importantly, empagliflozin administration in two different doses significantly downregulated the expression of caspase-3 in brain tissues and inhibited apoptotic cell death. Additionally, empagliflozin treatment upregulated the protein expressions of HIF-1α and its downstream mediator vascular endothelial growth factor (VEGF) in the ischemic brain. These findings suggest that empagliflozin exerts an anti-apoptotic effect via augmenting HIF-1a and VEGF expressions in ischemic brain tissues.[199]

Long-term HFD consumption not only causes obesity but also leads to various negative effects on the body, including impaired insulin sensitivity, increased brain oxidative stress, and cognitive decline.[200] Vildagliptin, a dipeptidyl peptidase-4 inhibitor, has shown beneficial effects on insulin sensitivity and neuroprotection in individuals with obesity and insulin resistance. Additionally, recent studies have shown the neuroprotective properties of dapagliflozin in diabetic patients. However, there is a lack of research investigating the comparative effects of both drugs and their combination on metabolic dysfunction and impaired brain function.

The effects of dapagliflozin and vildagliptin on diabetic neural complications were investigated in a study containing 40 HFD male Wistar rats divided into two groups: one group receiving a normal diet (ND) and the other receiving HFD for 16 weeks. At week 13, the rats were further divided into four subgroups receiving: vehicle (V),

Table 4: Clinical trials investigating the effect of SGLT-2 inhibitors as neuroprotective agents

Subjects	Dose, period of treatment	Recruitment Status and results	References Or code of study in www. clinicaltrials.gov
Adults with preclinical Alzheimer's disease (AD) and amnestic mild cognitive impairment (aMCI) or early AD.	Randomized, double-blind trial comparing the effects of 4 weeks of intranasal insulin (40 International Units four times daily), empagliflozin (10 mg daily) and combined intranasal insulin and empagliflozin compared with placebo on cerebrospinal fluid biomarkers and cognition.	Recruiting	NCT05081219
Aging-associated cognitive impairment as well as for AD and related dementias	Empagliflozin (25 mg) for 14 days on systemic and brain metabolism in 21 non-diabetics aged 55 years old or older.	Completed. -Empagliflozin potentially promotes neuronal survival through activation of the canonical pathway of insulin signaling and may act as a neuroprotectant through upregulation of IGF-1R (based on studying NEVs). -Empagliflozin decreases potentially harmful excitatory neurotransmission in the brain by decreasing glutamate and glutamine (based on brain MRS).	NCT03852901 [216]
Patients with type 2 diabetes	14 days treatment with 25 mg empagliflozin compared to placebo treatment.	Completed. Two weeks of empagliflozin treatment did not change DNA or RNA oxidation. However, a posthoc analysis revealed that longer-term dapagliflozin treatment decreased DNA oxidation.	NCT02890745 [217]
Patients with type 2 diabetes after kidney transplantation	Compared the difference in oxidative modifications before and after 90 days treatment with 25 mg empagliflozin plus insulin compared to insulin treatment.	Recruiting	NCT04918407
Glycemic variability (GV) on drug-naïve T2DM patients.	Patients with new onset T2DM treated with dapagliflozin + metformin during a 12-week period.	Completed Improved glycemic variability measured by MAGE (-19.63%) and achieved longer periods within target range for glycemic control in comparison with patients treated only with metformin. Plasmatic insulin levels, and weight reduction were also significantly reduced with dapagliflozin; nominal reductions in HbA1c and SBP were observed. All these findings support early use of dapagliflozin in patients with newly onset T2DM.	NCT04090580 [218]
AD patients	12 weeks of 10 mg dapagliflozin once daily.	Completed Results were not published.	NCT03801642

vildagliptin (3 mg/kg/day), dapagliflozin (1 mg/kg/day), or a combination of both drugs for a period of four weeks. To investigate brain apoptosis, pro-apoptotic markers (Bax) and anti-apoptotic markers (Bcl-2) were determined. The results showed that the HFD-V rats had increased Bax protein expression, decreased Bcl-2 protein expression, and increased Bax/Bcl-2 ratio, when compared with ND rats receiving vehicle (ND-V). However, rats treated with dapagliflozin, vildagliptin, or both drugs showed decreased expression of Bax and Bcl-2, as well as decreased brain inflammation compared to HFD rats. These findings suggest that dapagliflozin, vildagliptin, and their combination have anti-apoptotic and anti-inflammatory effects in the brains of HFD-induced obese rats.[185]

Ischemic stroke is recognized globally as a major contributor to adult disability and death. Elevated blood glucose level exacerbates ischemic damage and is indicative of unfavorable clinical outcomes in patients with stroke. Glycemic control strategies have shown beneficial effects on modulating oxidative stress, inflammation, and programmed cell death.[201] The neuroprotective effects of empagliflozin were investigated in hyperglycemic Wistar

rats with global ischemic stroke divided into four groups: sham-operated rats, rats with cerebral I/R injury, rats treated with empagliflozin (10 mg/kg at 1 and 24 h after the reperfusion), and rats treated with gliclazide (2 mg/kg at 1 and 24 h after the reperfusion). The findings showed significantly increased caspase-3 immunoreactivity in the brain tissues of rats with cerebral I/R injury compared to the sham group. However, both empagliflozin and gliclazide treatments significantly reduced caspase-3 immunoreactivity and the number of apoptotic cells in the I/R injured group. Empagliflozin reduced apoptotic cells by 85%, while gliclazide reduced them by 90.7%.[184]

HD is a rare neurodegenerative disorder that affects glucose metabolism and leads to behavioral disturbances, including memory and locomotion problems. Several studies have reported a high prevalence of glucose intolerance and DM in patients with HD. In an HD animal model, generated using 3-nitropropionic acid (3-NP)-treated Wistar rats, 3-NP-treated rats showed a significant increase in the levels of cytochrome c (cyt-c), P53, calpain, lactate, NF-κB, TIGAR, HK-II, and PEA15, indicating the activation of apoptosis, glycolysis, and toxicity processes. Treating the rats with 1mg/kg of dapagliflozin for 28 days followed by a single dose of (30 mg/kg), 3-NP rats at day 29 showed reductions in the above markers. The administration of 3-NP inhibits autophagy, as shown by decreased expression of beclin-1 and LC3. Surprisingly, damage-regulated autophagy modulator (DRAM), an autophagy indicator, is increased after acute intoxication with 3-NP. DRAM plays a critical role in the P53-mediated apoptotic response, which may explain its increased expression after 3-NP intoxication. However, pretreatment with dapagliflozin reverses the inflammatory indicators, induces autophagy by enhancing Beclin-1 and LC3 expression, and reduces DRAM expression.[202]

SGLT2 inhibitors are promising antioxidant and anti-apoptotic agents that demonstrate a wide range of therapeutic effects in murine models. However, their effects on PD were a mystery until a recent 2021 study in which subcutaneous rotenone-treated (1.5 mg/kg) Wistar rats were used as PD study models. The rats were treated with dapagliflozin (1 (mg/kg)/day, by gavage for 3 weeks) and alterations in motor dysfunction, dopamine levels, neuronal oxidative stress, ROS-dependent neuronal apoptosis, and neuro-inflammation were thoroughly surveyed. Rotenone increased the protein expression of the pro-apoptotic Bax (2.52-fold) and cleaved caspase-3 (2.32-fold), which are involved in programmed cell death. Dapagliflozin reversed apoptotic aberrations by downregulating the expression of Bax and the cleaved form of caspase-3. Additionally, dapagliflozin increased the expression of glial cell line-derived neurotrophic factor (GDNF) and restored the PI3K/AKT/GSK-3β pathway, which was suppressed by rotenone. The restoration of GDNF and the PI3K/AKT/GSK-3β pathway by dapagliflozin suggests its underlying anti-apoptotic mechanisms.[187]

Gliflozins affect core pathological features of neurodegeneration.[197] In addition to inhibiting SGLT2, gliflozins have an affinity for inhibiting the SGLT1 receptor. This effect is responsible for mediating neuroprotective effects and mediating anti-inflammatory and anti-atherosclerotic effects, and causing decreases in pro-inflammatory cytokines, M2 macrophage polarization, JAK2/STAT1, and prohibition of NLRP3 inflammasome, as well as carotid intima-media thickness (cIMT) regression. Gliflozins also improve endothelial function, prevent remodeling, and exert a protective effect on the neurovascular unit, BBB, pericytes, astrocytes, microglia, and oligodendrocytes. Another unique feature of these compounds is that they inhibit the production of misfolded proteins and inappropriate molecules. By this mechanism, they can inhibit the initiation or exacerbation of processes involved in neurodegenerative diseases, including AD, PD, seizures MS, and ALS. These agents also cause inhibition of AChE, improvement in cognitive performance and can restore circadian rhythm via mTOR activation. Some gliflozins, such as empagliflozin, can cause increased brain BDNF, which modulates neurotransmission, plasticity of neurons, growth, and survival.[197] Ibrahim *et al*.[203] suggested the involvement of LKB1/AMPK/SIRT1-induced autophagy and mitochondrial biogenesis in dapagliflozin neuroprotection against OVX/D-Gal-induced AD-like pathology [Figure 4]. Table 3 summarizes the experimental studies investigating the effects of gliflozins on DM-induced cell death.

SGLT2 Inhibitors as Neuroprotective Agents in Clinical Trials

Several studies have reported the positive effects of SGLT2 inhibitors on cardiovascular and renal outcomes. The putative beneficial mechanisms of SGLT2 inhibitors involve factors such as reduced levels of pro-inflammatory cytokines, a metabolic shift towards using free fatty acids and ketone bodies, reduced oxidative stress, decreased glomerular hyperfiltration, inhibition of advanced glycation end-product signaling, and increased hepatic glycogen depletion leading to proper catabolic periods. These are the very factors considered crucial in the onset of neurodegenerative disorders, like PD. SGLT2 inhibitors seemed to be effective in these conditions. Recent clinical trials are summarized in Table 4.

Discussion

This review presents the current understanding about the neuroprotective effects of SGLT2 inhibitors in DM-induced neurobehavioral and neurochemical changes, and the related molecular antioxidant, anti-inflammatory, and anti-apoptosis effects of SGLT2 inhibitors in DM-induced neurodegenerative events.

DM negatively affects neuronal function, which may serve as one of the key causes of neurodegenerative events.[89,204]

Several pathways, such as protein aggregation, apoptosis, oxidative stress, neuro-inflammation, and autophagia, have been shown to induce neuronal and neural cell malfunction during diabetes.[16,125] Oxidative stress is a major mechanism involved in DM-induced neurodegeneration,[18,36,43,44,48-52] which can induce neuropathy and retinopathy and exacerbate other neurodegenerative events or diseases. Diabetes can dampen SOD, GPx, and GR activity and increase the level of MDA, a marker of lipid peroxidation, in neuronal cells in the CNS and PNS.[118,205,206] Diabetes can cause mitochondrial dysfunction and alteration of respiratory chain antioxidant enzymes in brain cells reducing cell defenses in neuronal cells.[118,206,207]

SGLT2 inhibitors can reduce oxidative stress, thereby conferring neuroprotective effects against DM-induced neurodegeneration found in neuropathy, retinopathy, and other neurodegenerative disorders.[26,182,193] Gliflozins can activate SOD, GPx, and GR activity while diminishing the level of lipid peroxidation and protein oxidation in neuronal cells in DM subjects.[26,182,185,193]

The inflammatory cascades—including cytokine and chemokine activation, NOS-NO pathways, COX-PG cascades, NF-kβ and TLRs pathways, and other inflammatory components—are involved in DM-induced neuronal degeneration that leads to neuropathy, retinopathy, and similar disorders.[118,208] Gliflozins show strong neuroprotective effects and can inhibit DM-induced neurotoxicity and neurodegeneration through inhibiting inflammatory signaling cascades[192,209] and modulating inflammatory processes.[196]

DM activates intrinsic and extrinsic mechanisms of apoptosis in brain cells,[210,211] and causes accelerated neuronal cell death, by apoptosis, autophagy, and necrosis,[212] which can lead to neurodegeneration.[212,213] Studies indicate that gliflozins are antidiabetic protective drugs that prevent DM-induced apoptosis in neuronal cells.[70,185] Whereas DM decreases overall anti-apoptosis and increases neuronal levels of biomarkers for apoptosis—including Bax, Caspase-3 and 7—gliflozins can regulate these harmful forms of diabetes-induced effects in the PNS and CNS.[185,196] Gliflozins provide a substantial defense against DM-induced neuronal damage,[196,199] showing neuroprotective activity against DM by inhibiting apoptosis, necrosis, and autophagy.[212-216] Taken together, the current literature supports the conclusion that SGLT2 inhibitors confer neuroprotection against DM-induced neurobehavioral and neurochemical events due to their capacity for exerting antioxidant, anti-inflammatory, and anti-apoptosis effects.

Conclusion

The harmful effects of DM can lead to neurodegeneration and neurotoxicity. Diabetes can activate lipid peroxidation, cause dysfunction of glutathione levels and antioxidant enzymes, and induce mitochondrial dysfunction in neuronal cells, which can initiate neuro-inflammation. In addition, DM-induced neuronal cell degeneration is mediated by the development of autophagy, necrosis, and apoptosis in intrinsic and extrinsic pathways. This literature review presents the current understanding of the effects of gliflozins as powerful neuroprotective agents in diabetic subjects by restoring mitochondrial function and causing decreased DM-induced lipid peroxidation, antioxidant, and glutathione dysfunction. Gliflozins can also prevent neuro-inflammation and neuronal cell death in diabetic subjects by inhibiting DM-induced inflammatory pathways or DM-induced apoptosis, autophagy, and necrosis-mediated cell death [Figure 8]. Collectively, the findings suggest that gliflozin therapies can decrease DM-induced neurodegenerative hallmarks and can function as neuroprotective agents against neurodegeneration and neurotoxicity induced by DM.

Further studies are needed to investigate the molecular changes associated with the neuroprotective effects of gliflozins and to investigate whether lower doses of gliflozins would be effective for preventing neurodegeneration in patients with or without diabetes. Considering the ability of these compounds to reduce destructive and neurodegenerative processes, gliflozins may be promising candidates as neuroprotective agents in multiple neurodegenerative diseases other than DM.

Availability of data and material

Not applicable.

Code availability

Not applicable.

Abbreviations

AChE: Acetylcholinesterase, **AD:** Alzheimer's disease**, AKT:** Protein kinase B, **ALS:** Amyotrophic lateral sclerosis, **AMPK:** AMP-activated protein kinase, **AOPP:** Advanced oxidation protein product, **APP:** Amyloid beta precursor protein, **ATP:** Adenosine triphosphate**, Bax:** Bcl-2-associated X protein, **Bcl-2:** B-cell lymphoma 2, **BDNF:** Brain-derived neurotrophic factor, **CAT:** catalase**, CCL2:** chemokine (C-C motif) ligand 2, **CCL20:** Chemokine (C-C motif) ligand 20, **cIMT:** carotid intima-media thickness, **CNS:** Central nervous system, **COX:** Cyclooxygenase, **CRP:** C-reactive protein, **CXCL5:** C-X-C motif chemokine 5, **CXCL7:** C-X-C motif chemokine 7, **CXCL12:** C-X-C motif chemokine 12, **DM:** Diabetes mellitus**, DPP-4:** Dipeptidyl peptidase 4, **DRAM:** damage-regulated autophagy modulator, **ERK:** Extracellular signal-regulated kinase, **ET-1:** Endothelin 1**, ETBR:** Ethidium bromide**, FADD:** Fas-associated protein with death domain, **GDNF:** Glial cell line-derived neurotrophic factor, **GF:** Growth factor, **GM-CSF:** Granulocyte

macrophage-colony stimulating factor**, GPx:** Glutathione peroxidase, **GR:** Glutathione reductase, **GSH:** Glutathione, **GSK-3β:** Glycogen synthase kinase 3β, **GSSG:** Glutathione disulfide, **HD:** Huntington's disease**, HFD:** High-fat diet, **HFV:** High-fat diet group receiving vehicle, **HIF-1α:** Hypoxia-inducible factor 1-alpha, **HK-II:** Mitochondrial hexokinase II, **HNE:** 4-Hydroxynonenal**, HO-1:** Heme oxygenase-1, **I/R injury:** Ischemia/reperfusion injury, **Iba1:** Ionized calcium-binding adaptor molecule 1, **IFN-γ:** Interferon gamma**, IL:** Interleukin, **iNOS:** Inducible nitric oxide synthase, **IsoLG:** Isolevuglandin, **JAK/STAT:** Janus kinase/signal transducers and activators of transcription, **LC3:** Microtubule-associated proteins 1A/1B light chain 3B, **LPS:** Lipopolysaccharide, **MCP-1:** Monocyte chemoattractant protein-1, **MDA:** Malondialdehyde, **MND:** Motor neuron disease**, MOMP:** Mitochondrial outer membrane permeabilization, **MPTP:** Mitochondrial permeability transition pore; **MS:** Multiple sclerosis, **mtDNA:** Mitochondrial DNA, **NAD+:** Nicotinamide adenine dinucleotide, **NADPH:** Nicotinamide adenine dinucleotide phosphate Hydrogen**, NF-kb:** Nuclear factor kappa B, **NFT:** Neurofibrillary tangle, **NDV:** Normal diet group receiving vehicle, **NLRP3:** NLR family pyrin domain containing 3, **NO:** Nitric oxide, **NOS:** Nitric oxide synthase, **3-NP: 3**-Nitropropionic acid, **Nrf2:** Nuclear factor erythroid 2-related factor 2, **8-OHdG:** 8-hydroxy-2-deoxyguanosine, **ONE:** 4-oxo-2-nonenal, **OPA1:** optic atrophy-1, **PD:** Parkinson's disease, **PEA15:** phosphoprotein enriched in astrocytes, **PG:** Prostaglandin, **PI3K:** Phosphoinositide 3-kinase, **PLP (A2):** phospholipase A2, **PNS:** Peripheral nervous system, **RNS:** Reactive nitrogen species**, ROS:** Reactive oxygen species**, SGLT2:** Sodium-glucose cotransporter-2, **SGLT2i**: Sodium-glucose cotransporter-2 inhibitor, **SOD:** Superoxide dismutase**, STZ:** Streptozotocin, **T1DM:** Type 1 diabetes mellitus, **T2DM:** Type 2 diabetes mellitus**, Tau:** Tubulin-associated unit, **TLR:** Toll-like receptor, **TNF-α:** Tumor necrosis factor alpha, **TRAIL:** Tumor necrosis factor-related apoptosis-inducing ligand, **VEGF**: Vascular endothelial growth factor, **ZDF**: Zucker diabetic fatty.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Received: 03 Jan 23 **Accepted:** 20 Feb 24
Published: 06 Aug 24

References

1. Umegaki H. Neurodegeneration in diabetes mellitus. Neurodegener Dis 2012:258-65.
2. Lieth E, Gardner TW, Barber AJ, Antonetti DA. Retinal neurodegeneration: Early pathology in diabetes. Clin Exp Ophthalmol 2000;28:3-8.
3. Moran C, Beare R, Phan TG, Bruce DG, Callisaya ML, Srikanth V. Type 2 diabetes mellitus and biomarkers of neurodegeneration. Neurology 2015;85:1123-30.
4. Pessina AC. Target organs of individuals with diabetes caught between arterial stiffness and damage to the microcirculation. J Hypertension 2007;25:S13-8.
5. Mohamed J, Nafizah AN, Zariyantey A, Budin S. Mechanisms of diabetes-induced liver damage: The role of oxidative stress and inflammation. Sultan Qaboos Univ Med J 2016;16:e132-41.
6. Levey AS, Astor BC, Stevens LA, Coresh J. Chronic kidney disease, diabetes, and hypertension: What's in a name? Kidney Int 2010;78:19-22.
7. Bree AJ, Puente EC, Daphna-Iken D, Fisher SJ. Diabetes increases brain damage caused by severe hypoglycemia. Am J Physiol Endocrinol Metab 2009;297:E194-201.
8. Kennedy JM, Zochodne DW. Impaired peripheral nerve regeneration in diabetes mellitus. J Peripher Nerv Syst 2005;10:144-57.
9. Obrosova IG. Diabetes and the peripheral nerve. Biochim Biophys Acta 2009;1792:931-40.
10. Adler A. Obesity and target organ damage: Diabetes. Int J Obes 2002;26:S11-4.
11. Lynch SK, Abràmoff MD. Diabetic retinopathy is a neurodegenerative disorder. Vis Res 2017;139:101-7.
12. Tesfaye S. Neuropathy in diabetes. Medicine 2010;38:649-55.
13. Omidi G, Karimi SA, Rezvani-Kamran A, Monsef A, Shahidi S, Komaki A. Effect of coenzyme Q10 supplementation on diabetes induced memory deficits in rats. Metab Brain Dis 2019;34:833-40.
14. Zhou X, Gan T, Fang G, Wang S, Mao Y, Ying C. Zeaxanthin improved diabetes-induced anxiety and depression through inhibiting inflammation in hippocampus. Metab Brain Dis 2018;33:705-11.
15. Aswar U, Chepurwar S, Shintre S, Aswar M. Telmisartan attenuates diabetes induced depression in rats. Pharmacol Rep 2017;69:358-64.
16. Muriach M, Flores-Bellver M, Romero FJ, Barcia JM. Diabetes and the brain: Oxidative stress, inflammation, and autophagy. Oxid Med Cell Longev 2014;2014:102158. doi: 10.1155/2014/102158.
17. Kahya MC, Nazıroğlu M, Övey İS. Modulation of diabetes-induced oxidative stress, apoptosis, and Ca^{2+}entry through TRPM2 and TRPV1 channels in dorsal root ganglion and hippocampus of diabetic rats by melatonin and selenium. Mol Neurobiol 2017;54:2345-60.
18. Chung SS, Ho EC, Lam KS, Chung SK. Contribution of polyol pathway to diabetes-induced oxidative stress. J Am Soc Nephrol 2003;14(Suppl 3):S233-6.
19. Jangra A, Datusalia AK, Khandwe S, Sharma SS. Amelioration of diabetes-induced neurobehavioral and neurochemical changes by melatonin and nicotinamide: Implication of oxidative stress–PARP pathway. Pharmacol Biochem Behav 2013;114:43-51.
20. Cinteza M. Gliflozins–a new border stone. Maedica 2019;14:3-4.
21. Lee KA, Jin HY, Lee NY, Kim YJ, Park TS. Effect of empagliflozin, a selective sodium-glucose cotransporter 2 inhibitor, on kidney and peripheral nerves in streptozotocin-induced diabetic rats. Diabetes Metab J 2018;42:338.
22. Jakubiak GK. Antidiabetic Drugs from Group of Gliflozins and their Role in Pharmacotherapy of Diabetes. Medycyna Rodzinna; 2016;3,146-51.
23. Millar P, Pathak N, Parthsarathy V, Bjourson AJ, O'Kane M, Pathak V, *et al*. Metabolic and neuroprotective effects of dapagliflozin and liraglutide in diabetic mice. J Endocrinol

2017;234:255-67.

24. Lee YH, Kim SH, Kang JM, Heo JH, Kim D-J, Park SH, *et al*. Empagliflozin attenuates diabetic tubulopathy by improving mitochondrial fragmentation and autophagy. Am J Physiol Renal Physiol 2019;317:F767-80.
25. Keles R, Hazar-Yavuz AN, Yildiz S, Cam ME, Sener G. Dapagliflozin attenuates anxiolytic-like behavior of rats in open field test. Eur J Pharmacol 2019;29:201-2.
26. Khan T, Khan S, Akhtar M, Ali J, Najmi AK. Empagliflozin nanoparticles attenuates type 2 diabetes induced cognitive impairment via oxidative stress and inflammatory pathway in high fructose diet induced hyperglycemic mice. Neurochemistry Int 2021;150:105158. doi: 10.1016/j.neuint. 2021.105158.
27. Heimke M, Lenz F, Rickert U, Lucius R, Cossais F. Anti-inflammatory properties of the SGLT2 inhibitor empagliflozin in activated primary microglia. Cells 2022;11:3107. doi: 10.3390/cells11193107.
28. Motawi TK, Al-Kady RH, Abdelraouf SM, Senousy MA. Empagliflozin alleviates endoplasmic reticulum stress and augments autophagy in rotenone-induced Parkinson's disease in rats: Targeting the GRP78/PERK/eIF2α/CHOP pathway and miR-211-5p. Chem Biol Interact 2022;362:110002. doi: 10.1016/j.cbi. 2022.110002.
29. De A, Chattopadhyay P, Singh M. In-vitro antioxidant activity and free radical scavenging potential of phlorizin derived sodium glucose cotransporter 2 inhibitor. J Drug Deliv Ther 2019;257-64.
30. Ala M, Khoshdel MRF, Dehpour AR. Empagliflozin enhances autophagy, mitochondrial biogenesis, and antioxidant defense and ameliorates renal ischemia/reperfusion in nondiabetic rats. Oxid Med Cell Longev 2022;2022:1197061. doi: 10.1155/2022/1197061.
31. Secker PF, Beneke S, Schlichenmaier N, Delp J, Gutbier S, Leist M, *et al*. Canagliflozin mediated dual inhibition of mitochondrial glutamate dehydrogenase and complex I: An off-target adverse effect. Cell Death Dis 2018;9:1-13. doi: 10.1038/s41419-018-0273-y.
32. Bendotti G, Montefusco L, Pastore I, Lazzaroni E, Lunati M, Fiorina P. The anti-inflammatory and immunological properties of SGLT-2 inhibitors. J Endocrinol Invest 2023;46:2445-52.
33. Lee N, Heo YJ, Choi S-E, Jeon JY, Han SJ, Kim DJ, *et al*. Anti-inflammatory effects of empagliflozin and gemigliptin on LPS-stimulated macrophage via the IKK/NF-κB, MKK7/JNK, and JAK2/STAT1 signalling pathways. J Immunol Res 2021;2021:9944880. doi: 10.1155/2021/9944880.
34. Sasaki M, Ozawa Y, Kurihara T, Kubota S, Yuki K, Noda K, *et al*. Neurodegenerative influence of oxidative stress in the retina of a murine model of diabetes. Diabetologia 2010;53:971-9.
35. Silva KC, Rosales MA, Biswas SK, Lopes de Faria JB, Lopes de Faria JM. Diabetic retinal neurodegeneration is associated with mitochondrial oxidative stress and is improved by an angiotensin receptor blocker in a model combining hypertension and diabetes. Diabetes 2009;58:1382-90.
36. Pop-Busui R, Sima A, Stevens M. Diabetic neuropathy and oxidative stress. Diabetes Metab Res Rev 2006;22:257-73.
37. Sandireddy R, Yerra VG, Areti A, Komirishetty P, Kumar A. Neuroinflammation and oxidative stress in diabetic neuropathy: Futuristic strategies based on these targets. Int J Endocrinol 2014;2014:674987. doi: 10.1155/2014/674987.
38. Du Y, Veenstra A, Palczewski K, Kern TS. Photoreceptor cells are major contributors to diabetes-induced oxidative stress and local inflammation in the retina. Proc Natl Acad Sci 2013;110:16586-91.
39. Yang H, Jin X, Lam CWK, Yan S-K. Oxidative stress and diabetes mellitus. Clin Chem Lab Med 2011;49:1773-82.
40. Gandhi S, Abramov AY. Mechanism of oxidative stress in neurodegeneration. Oxid Med Cell Longev 2012;2012:428010. doi: 10.1155/2012/428010.
41. Cohen G, Riahi Y, Sunda V, Deplano S, Chatgilialoglu C, Ferreri C, *et al*. Signaling properties of 4-hydroxyalkenals formed by lipid peroxidation in diabetes. Free Radic Biol Med 2013;65:978-87.
42. Kumawat M, Singh N, Singh S. Status of antioxidant enzymes and lipid peroxidation in type 2 diabetes mellitus with neuropathy. Ann Neurosci 2010;12:49-52.
43. Vincent AM, Russell JW, Low P, Feldman EL. Oxidative stress in the pathogenesis of diabetic neuropathy. Endocr Rev 2004;25:612-28.
44. Kowluru RA, Chan P-S. Oxidative stress and diabetic retinopathy. Exp Diabetes Res 2007;2007:43603. doi: 10.1155/2007/43603.
45. Calderon G, Juarez O, Hernandez G, Punzo S, De la Cruz Z. Oxidative stress and diabetic retinopathy: Development and treatment. Eye 2017;31:1122-30.
46. Barber AJ. A new view of diabetic retinopathy: A neurodegenerative disease of the eye. Prog Neuropsychopharmacol Biol Psychiatry 2003;27:283-90.
47. Asmat U, Abad K, Ismail K. Diabetes mellitus and oxidative stress—A concise review. Saudi Pharm J 2016;24:547-53.
48. Hosseini A, Abdollahi M. Diabetic neuropathy and oxidative stress: Therapeutic perspectives. Oxid Med Cell Longev 2013;2013:168039. doi: 10.1155/2013/168039.
49. Kasznicki J, Kosmalski M, Sliwinska A, Mrowicka M, Stanczyk M, Majsterek I, *et al*. Evaluation of oxidative stress markers in pathogenesis of diabetic neuropathy. Mol Biol Rep 2012;39:8669-78.
50. Pan H-Z, Zhang H, Chang D, Li H, Sui H. The change of oxidative stress products in diabetes mellitus and diabetic retinopathy. Br J Ophthalmol 2008;92:548-51.
51. Abcouwer SF, Gardner TW. Diabetic retinopathy: Loss of neuroretinal adaptation to the diabetic metabolic environment. Ann N Y Acad Sci 2014;1311:174-90.
52. Behl T, Kaur I, Kotwani A. Implication of oxidative stress in progression of diabetic retinopathy. Surv Ophthalmol 2016;61:187-96.
53. West IC. Radicals and oxidative stress in diabetes. Diabet Med 2000;17:171-80.
54. Turk Z. Glycotoxines, carbonyl stress and relevance to diabetes and its complications. Physiological Res 2010;59:147-56.
55. Naudi A, Jove M, Ayala V, Cassanye A, Serrano J, Gonzalo H, *et al*. Cellular dysfunction in diabetes as maladaptive response to mitochondrial oxidative stress. Exp Diabetes Res 2012;2012:696215. doi: 10.1155/2012/696215.
56. Mule NK, Singh JN. Diabetes mellitus to neurodegenerative disorders: Is oxidative stress fueling the flame? CNS Neurol Disord Drug Targets 2018;17:644-53.
57. Rosales-Corral S, Tan D-X, Manchester L, Reiter RJ. Diabetes and alzheimer disease, two overlapping pathologies with the same background: Oxidative stress. Oxid Med Cell Longev 2015;2015:985845. doi: 10.1155/2015/985845.
58. Niedowicz DM, Daleke DL. The role of oxidative stress in diabetic complications. Cell Biochem Biophys 2005;43:289-330.
59. Hassan A, Kandel RS, Mishra R, Gautam J, Alaref A, Jahan N. Diabetes mellitus and Parkinson's disease: Shared pathophysiological links and possible therapeutic implications. Cureus 2020;12:e9853. doi: 10.7759/cureus. 9853.
60. Domínguez R, Pagano M, Marschoff E, González S, Repetto M,

Serra J. Alzheimer disease and cognitive impairment associated with diabetes mellitus type 2: Associations and a hypothesis. Neurología (English Edition) 2014;29:567-72.

61. Magyari M, Sorensen PS. Comorbidity in multiple sclerosis. Front Neurol 2020;11:851.
62. Chen R, Ovbiagele B, Feng W. Diabetes and stroke: Epidemiology, pathophysiology, pharmaceuticals and outcomes. Am J Med Sci 2016;351:380-6.
63. Luscher TF, Creager MA, Beckman JA, Cosentino F. Diabetes and vascular disease: Pathophysiology, clinical consequences, and medical therapy: Part II. Circulation 2003;108:1655-61.
64. Song Y, Ding W, Bei Y, Xiao Y, Tong H-D, Wang L-B, *et al*. Insulin is a potential antioxidant for diabetes-associated cognitive decline via regulating Nrf2 dependent antioxidant enzymes. Biomed Pharmacother 2018;104:474-84.
65. Ceretta LB, Réus GZ, Abelaira HM, Ribeiro KF, Zappellini G, Felisbino FF, *et al*. Increased oxidative stress and imbalance in antioxidant enzymes in the brains of alloxan-induced diabetic rats. Exp Diabetes Res 2012;2012:302682. doi: 10.1155/2012/302682.
66. Kowluru RA, Kennedy A. Therapeutic potential of anti-oxidants and diabetic retinopathy. Expert Opin Investig Drugs 2001;10:1665-76.
67. Zhong Q, Kowluru RA. Epigenetic changes in mitochondrial superoxide dismutase in the retina and the development of diabetic retinopathy. Diabetes 2011;60:1304-13.
68. Younus H. Therapeutic potentials of superoxide dismutase. Int J Health Sci 2018;12:88.
69. Yorek MA. The role of oxidative stress in diabetic vascular and neural disease. Free Radic Res 2003;37:471-80.
70. Schmeichel AM, Schmelzer JD, Low PA. Oxidative injury and apoptosis of dorsal root ganglion neurons in chronic experimental diabetic neuropathy. Diabetes 2003;52:165-71.
71. Iranzo O. Manganese complexes displaying superoxide dismutase activity: A balance between different factors. Bioorganic Chem 2011;39:73-87.
72. Shanmugam KR, Mallikarjuna K, Kesireddy N, Reddy KS. Neuroprotective effect of ginger on anti-oxidant enzymes in streptozotocin-induced diabetic rats. Food Chem Toxicol 2011;49:893-7.
73. Alipour M, Salehi I, Soufi FG. Effect of exercise on diabetes-induced oxidative stress in the rat hippocampus. Iran Red Crescent Med J 2012;14:222-8.
74. Madsen-Bouterse SA, Zhong Q, Mohammad G, Ho Y-S, Kowluru RA. Oxidative damage of mitochondrial DNA in diabetes and its protection by manganese superoxide dismutase. Free Radic Res 2010;44:313-21.
75. Sytze van Dam P. Oxidative stress and diabetic neuropathy: Pathophysiological mechanisms and treatment perspectives. Diabetes Metab Res Rev 2002;18:176-84.
76. Obrosova IG. Update on the pathogenesis of diabetic neuropathy. Curr Diab Rep 2003;3:439-45.
77. Fernyhough P. Mitochondrial dysfunction in diabetic neuropathy: A series of unfortunate metabolic events. Curr Diab Rep 2015;15:1-10.
78. Shamsul Ola M, S Alhomida A. Neurodegeneration in diabetic retina and its potential drug targets. Curr Neuropharmacol 2014;12:380-6.
79. Simó R, Hernández C. Neurodegeneration in the diabetic eye: New insights and therapeutic perspectives. Trends Endocrinol Metab 2014;25:23-33.
80. Clausen A, Doctrow S, Baudry M. Prevention of cognitive deficits and brain oxidative stress with superoxide dismutase/catalase mimetics in aged mice. Neurobiol Aging 2010;31:425-33.
81. Infante-Garcia C, Garcia-Alloza M. Review of the effect of natural compounds and extracts on neurodegeneration in animal models of diabetes mellitus. Int J Mol Sci 2019;20:2533. doi: 10.3390/ijms20102533.
82. Sofic E, Salkovic-Petrisic M, Tahirovic I, Sapcanin A, Mandel S, Youdim M, *et al*. Brain catalase in the streptozotocin-rat model of sporadic Alzheimer's disease treated with the iron chelator–monoamine oxidase inhibitor, M30. J Neural Transm 2015;122:559-64.
83. Giordano CR, Roberts R, Krentz KA, Bissig D, Talreja D, Kumar A, *et al*. Catalase therapy corrects oxidative stress-induced pathophysiology in incipient diabetic retinopathy. Invest Ophthalmol Vis Sci 2015;56:3095-102.
84. Kwong-Han K, Zunaina E, Hanizasurana H, Che-Badariah AA, Che-Maraina CH. Comparison of catalase, glutathione peroxidase and malondialdehyde levels in tears among diabetic patients with and without diabetic retinopathy. J Diabetes Metab Disord 2022;21:681-8.
85. Djordjević GM, Djurić SS, Djordjević VB, Apostolski S, Zivkovic M. The role of oxidative stress in pathogenesis of diabetic neuropathy: Erythrocyte superoxide dismutase, catalase and glutathione peroxidase level in relation to peripheral nerve conduction in diabetic neuropathy patients. Role of the Adipocyte in Development of Type. Vol. 2. 2011. p. 153-72.
86. Tiwari BK, Pandey KB, Abidi A, Rizvi SI. Markers of oxidative stress during diabetes mellitus. J Biomark 2013;2013. doi: 10.1155/2013/378790.
87. Figueroa-Romero C, Sadidi M, Feldman EL. Mechanisms of disease: The oxidative stress theory of diabetic neuropathy. Rev Endocr Metab Disord 2008;9:301-14.
88. Sims-Robinson C, Kim B, Rosko A, Feldman EL. How does diabetes accelerate Alzheimer disease pathology? Nat Rev Neurol 2010;6:551-9.
89. Chowdhury SKR, Smith DR, Fernyhough P. The role of aberrant mitochondrial bioenergetics in diabetic neuropathy. Neurobiol Dis 2013;51:56-65.
90. Srinivasan S, Stevens M, Wiley JW. Diabetic peripheral neuropathy: Evidence for apoptosis and associated mitochondrial dysfunction. Diabetes 2000;49:1932-8.
91. Piotrowski P, Wierzbicka K, Smialek M. Neuronal death in the rat hippocampus in experimental diabetes and cerebral ischaemia treated with antioxidants. Folia Neuropathol 2001;39:147-54.
92. Kempuraj D, Thangavel R, Natteru P, Selvakumar G, Saeed D, Zahoor H, *et al*. Neuroinflammation induces neurodegeneration. J Neurol Neurosurg Spine 2016;1:7267. doi: 10.3390/ijms23137267.
93. Srodulski S, Sharma S, Bachstetter AB, Brelsfoard JM, Pascual C, Xie XS, *et al*. Neuroinflammation and neurologic deficits in diabetes linked to brain accumulation of amylin. Mol Neurodegener 2014;9:1-12. doi: 10.1186/1750-1326-9-30.
94. Fletcher EL, Phipps JA, Ward MM, Puthussery T, Wilkinson-Berka JL. Neuronal and glial cell abnormality as predictors of progression of diabetic retinopathy. Curr Pharm Design 2007;13:2699-712.
95. Nagayach A, Patro N, Patro I. Experimentally induced diabetes causes glial activation, glutamate toxicity and cellular damage leading to changes in motor function. Front Cell Neurosci 2014;8:355. doi: 10.3389/fncel. 2014.00355.
96. Zeng H-Y, Green WR, Tso MO. Microglial activation in human diabetic retinopathy. Arch Ophthalmol 2008;126:227-32.
97. Zhang T-T, Xue R, Fan S-Y, Fan Q-Y, An L, Li J, *et al*. Ammoxetine attenuates diabetic neuropathic pain through inhibiting microglial activation and neuroinflammation in the

spinal cord. J Neuroinflammation 2018;15:1-13. doi: 10.1186/s12974-018-1216-3.

98. Krady JK, Basu A, Allen CM, Xu Y, LaNoue KF, Gardner TW, *et al*. Minocycline reduces proinflammatory cytokine expression, microglial activation, and caspase-3 activation in a rodent model of diabetic retinopathy. Diabetes 2005;54:1559-65.
99. Skundric DS, Lisak RP. Role of neuropoietic cytokines in development and progression of diabetic polyneuropathy: From glucose metabolism to neurodegeneration. Exp Diabesity Res 2003;4:303-12.
100. Cheung CMG, Vania M, Ang M, Chee SP, Li J. Comparison of aqueous humor cytokine and chemokine levels in diabetic patients with and without retinopathy. Mol Vis 2012;18:830-7.
101. Chatzigeorgiou A, Harokopos V, Mylona-Karagianni C, Tsouvalas E, Aidinis V, Kamper E. The pattern of inflammatory/anti-inflammatory cytokines and chemokines in type 1 diabetic patients over time. Ann Med 2010;42:426-38.
102. King GL. The role of inflammatory cytokines in diabetes and its complications. J Periodontol 2008;79:1527-34.
103. Saleh A, Smith DR, Balakrishnan S, Dunn L, Martens C, Tweed CW, *et al*. Tumor necrosis factor-α elevates neurite outgrowth through an NF-κB-dependent pathway in cultured adult sensory neurons: Diminished expression in diabetes may contribute to sensory neuropathy. Brain Res 2011;1423:87-95.
104. Purwata TE. High TNF-alpha plasma levels and macrophages iNOS and TNF-alpha expression as risk factors for painful diabetic neuropathy. J Pain Res 2011;4:169-75.
105. Mendiola AS, Cardona AE. The IL-1β phenomena in neuroinflammatory diseases. J Neural Transm 2018;125:781-95.
106. Andriambeloson E, Baillet C, Vitte PA, Garotta G, Dreano M, Callizot N. Interleukin-6 attenuates the development of experimental diabetes-related neuropathy. Neuropathology 2006;26:32-42.
107. Herder C, Carstensen M, Ouwens D. Anti-inflammatory cytokines and risk of type 2 diabetes. Diabetes Obes Metab 2013;15:39-50.
108. Zhang W, Liu H, Rojas M, Caldwell RW, Caldwell RB. Anti-inflammatory therapy for diabetic retinopathy. Immunotherapy 2011;3:609-28.
109. Carbonetto P, Stephens M. Integrated enrichment analysis of variants and pathways in genome-wide association studies indicates central role for IL-2 signaling genes in type 1 diabetes, and cytokine signaling genes in Crohn's disease. PLoS Genet 2013;9:e1003770. doi: 10.1371/journal.pgen.1003770.
110. Creusot RJ, Chang P, Healey DG, Tcherepanova IY, Nicolette CA, Fathman CG. A short pulse of IL-4 delivered by DCs electroporated with modified mRNA can both prevent and treat autoimmune diabetes in NOD mice. Mol Ther 2010;18:2112-20.
111. Akbari M, Hassan-Zadeh V. IL-6 signalling pathways and the development of type 2 diabetes. Inflammopharmacology 2018;26:685-98.
112. Rodrigues KF, Pietrani NT, Bosco AA, Campos FMF, Sandrim VC, Gomes KB. IL-6, TNF-α, and IL-10 levels/polymorphisms and their association with type 2 diabetes mellitus and obesity in Brazilian individuals. Arch Endocrinol Metab 2017;61:438-46.
113. Hanifi-Moghaddam P, Kappler S, Seissler J, Müller-Scholze S, Martin S, Roep B, *et al*. Altered chemokine levels in individuals at risk of type 1 diabetes mellitus. Diabetic Med 2006;23:156-63.
114. Herder C, Haastert B, Müller-Scholze S, Koenig W, Thorand B, Holle R, *et al*. Association of systemic chemokine concentrations with impaired glucose tolerance and type 2 diabetes: Results from the cooperative health research in the Region of Augsburg Survey S4 (KORA S4). Diabetes 2005;54(Suppl 2):S11-7.
115. Lontchi-Yimagou E, Sobngwi E, Matsha TE, Kengne AP. Diabetes mellitus and inflammation. Curr Diabs Rep 2013;13:435-44.
116. Laaksonen D, Niskanen L, Nyyssönen K, Punnonen K, Tuomainen T-P, Valkonen V-P, *et al*. C-reactive protein and the development of the metabolic syndrome and diabetes in middle-aged men. Diabetologia 2004;47:1403-10.
117. Chase HP, Cooper S, Osberg I, Stene LC, Barriga K, Norris J, *et al*. Elevated C-reactive protein levels in the development of type 1 diabetes. Diabetes 2004;53:2569-73.
118. Pugazhenthi S, Qin L, Reddy PH. Common neurodegenerative pathways in obesity, diabetes, and Alzheimer's disease. Biochim Biophys Acta Mol Basis Dis 2017;1863:1037-45.
119. De Felice FG, Ferreira ST. Inflammation, defective insulin signaling, and mitochondrial dysfunction as common molecular denominators connecting type 2 diabetes to Alzheimer disease. Diabetes 2014;63:2262-72.
120. Rübsam A, Parikh S, Fort PE. Role of inflammation in diabetic retinopathy. Int J Mol Sci 2018;19:942. doi: 10.3390/ijms19040942.
121. Yu Y, Chen H, Su SB. Neuroinflammatory responses in diabetic retinopathy. J Neuroinflammation 2015;12:1-15. doi: 10.1186/s12974-015-0368-7.
122. Debnath M, Agrawal S. Diabetic neuropathy: Oxidative stress and neuroinflammation. Med Res 2016;3:237-41.
123. Madonna R, Giovannelli G, Confalone P, Renna FV, Geng Y-J, De Caterina R. High glucose-induced hyperosmolarity contributes to COX-2 expression and angiogenesis: Implications for diabetic retinopathy. Cardiovasc Diabetol 2016;18:15. doi: 10.1186/s12933-016-0342-4.
124. Wong WT, Tian XY, Huang Y. Endothelial dysfunction in diabetes and hypertension: Cross talk in RAS, BMP4, and ROS-dependent COX-2–derived prostanoids. J Cardiovasc Pharmacol 2013;61:204-14.
125. Mastrocola R, Restivo F, Vercellinatto I, Danni O, Brignardello E, Aragno M, *et al*. Oxidative and nitrosative stress in brain mitochondria of diabetic rats. J Endocrinol 2005;187:37-44.
126. Costagliola C, Romano V, De Tollis M, Aceto F, Romano MR, Pedicino C, *et al*. TNF-alpha levels in tears: A novel biomarker to assess the degree of diabetic retinopathy. Mediators Inflamm 2013;2013:629529. doi: 10.1155/2013/629529.
127. Serasanambati M, Chilakapati SR. Function of nuclear factor kappa B (NF-kB) in human diseases-A review. South Indian J Biol Sci. 2016;2:368-87.
128. Ghanaatfar F, Ghanaatfar A, Isapour P, Farokhi N, Bozorgniahosseini S, Javadi M, et al. Is lithium neuroprotective? An updated mechanistic illustrated review. Fundamental & clinical pharmacology. 2023;37:4-30.
129. Patel S, Santani D. Role of NF-κB in the pathogenesis of diabetes and its associated complications. Pharmacol Rep 2009;61:595-603.
130. Li J, Tang Y, Cai D. IKKβ/NF-κB disrupts adult hypothalamic neural stem cells to mediate a neurodegenerative mechanism of dietary obesity and pre-diabetes. Nat Cell Biol 2012;14:999-1012.
131. Granic I, Dolga AM, Nijholt IM, van Dijk G, Eisel UL. Inflammation and NF-κB in Alzheimer's disease and diabetes. J Alzheimer's Dis 2009;16:809-21.
132. Yun JH, Lee DH, Jeong HS, Kim HS, Ye SK, Cho CH. STAT3

activation in microglia exacerbates hippocampal neuronal apoptosis in diabetic brains. J Cell Physiol 2021;236:7058-70.

133. Chowdhury SR, Saleh A, Akude E, Smith DR, Morrow D, Tessler L, *et al*. Ciliary neurotrophic factor reverses aberrant mitochondrial bioenergetics through the JAK/STAT pathway in cultured sensory neurons derived from streptozotocin-induced diabetic rodents. Cell Mol Neurobiol 2014;34:643-9.
134. Cho C-H, Roh K-H, Lim N-Y, Park SJ, Park S, Kim HW. Role of the JAK/STAT pathway in a streptozotocin-induced diabetic retinopathy mouse model. Graefes Arch Clin Exp Ophthalmol 2022;260:3553-63.
135. Abdul Y, Abdelsaid M, Li W, Webb RC, Sullivan JC, Dong G, *et al*. Inhibition of toll-like receptor-4 (TLR-4) improves neurobehavioral outcomes after acute ischemic stroke in diabetic rats: Possible role of vascular endothelial TLR-4. Mol Neurobiol 2019;56:1607-17.
136. Dasu MR, Ramirez S, Isseroff RR. Toll-like receptors and diabetes: A therapeutic perspective. Clin Sci 2012;122:203-14.
137. Wong FS, Wen L. Toll-like receptors and diabetes. Ann N Y Acad Sci 2008;1150:123-32.
138. Vincent AM, Brownlee M, Russell JW. Oxidative stress and programmed cell death in diabetic neuropathy. Ann N Y Acad Sci 2002;959:368-83.
139. Muranyi M, Fujioka M, He Q, Han A, Yong G, Csiszar K, *et al*. Diabetes activates cell death pathway after transient focal cerebral ischemia. Diabetes 2003;52:481-6.
140. Martin PM, Roon P, Van Ells TK, Ganapathy V, Smith SB. Death of retinal neurons in streptozotocin-induced diabetic mice. Invest Ophthalmol Vis Sci 2004;45:3330-6.
141. Li Z-G, Zhang W, Grunberger G, Sima AA. Hippocampal neuronal apoptosis in type 1 diabetes. Brain Res 2002;946:221-31.
142. Barber AJ, Gardner TW, Abcouwer SF. The significance of vascular and neural apoptosis to the pathology of diabetic retinopathy. Invest Ophthalmol Vis Sci 2011;52:1156-63.
143. Sadeghi A, Hami J, Razavi S, Esfandiary E, Hejazi Z. The effect of diabetes mellitus on apoptosis in hippocampus: Cellular and molecular aspects. Int J Prev Med 2016;7:57. doi: 10.4103/2008-7802.178531.
144. Kong F-J, Ma L-L, Guo J-J, Xu L-H, Li Y, Qu S. Endoplasmic reticulum stress/autophagy pathway is involved in diabetes-induced neuronal apoptosis and cognitive decline in mice. Clin Sci 2018;132:111-25.
145. Liu Y-P, Shao S-J, Guo H-D. Schwann cells apoptosis is induced by high glucose in diabetic peripheral neuropathy. Life Sci 2020;248:117459. doi: 10.1016/j.lfs. 2020.117459.
146. Hengartner MO. The biochemistry of apoptosis. Nature 2000;407:770-6.
147. Cheng H, Gang X, Liu Y, Wang G, Zhao X, Wang G. Mitochondrial dysfunction plays a key role in the development of neurodegenerative diseases in diabetes. Am J Physiol Endocrinol Metab 2020;318:E750-E64.
148. Nazarnezhad S, Rahmati M, Shayannia A, Abbasi Z, Salehi M, Khaksari M. Nesfatin-1 protects PC12 cells against high glucose-induced cytotoxicity via inhibiting oxidative stress, autophagy and apoptosis. Neurotoxicology 2019;74:196-202.
149. Bhattacharya D, Mukhopadhyay M, Bhattacharyya M, Karmakar P. Is autophagy associated with diabetes mellitus and its complications? A review. EXCLI J 2018;17:709-20.
150. Wang X, Zhang B, Xia R, Jia Q. Inflammation, apoptosis and autophagy as critical players in vascular dementia. Eur Rev Med Pharmacol Sci 2020;24:9601-14.
151. Schubert M, Gautam D, Surjo D, Ueki K, Baudler S, Schubert D, *et al*. Role for neuronal insulin resistance in neurodegenerative diseases. Proc Natl Acad Sci 2004;101:3100-5.
152. Liu J, Liu L, Han YS, Yi J, Guo C, Zhao HQ, *et al*. The molecular mechanism underlying mitophagy-mediated hippocampal neuron apoptosis in diabetes-related depression. J Cell Mol Med 2021;25:7342-53.
153. Zhang X, Xu L, He D, Ling S. Endoplasmic reticulum stress-mediated hippocampal neuron apoptosis involved in diabetic cognitive impairment. Biomed Res Int 2013;2013:924327. doi: 10.1155/2013/924327.
154. Lavrik IN. Systems biology of apoptosis signaling networks. Curr Opin Biotechnol 2010;21:551-5.
155. Yu P, Zhang X, Liu N, Tang L, Peng C, Chen X. Pyroptosis: Mechanisms and diseases. Signal Transduct Target Ther 2021;6:1-21. doi: 10.1038/s41392-021-00507-5.
156. Bergsbaken T, Fink SL, Cookson BT. Pyroptosis: Host cell death and inflammation. Nat Rev Microbiol 2009;7:99-109.
157. Zhang X, Wang N, Barile GR, Bao S, Gillies M. Diabetic retinopathy: Neuron protection as a therapeutic target. Int J Biochem Cell Biol 2013;45:1525-9.
158. Chen X, Famurewa AC, Tang J, Olatunde OO, Olatunji OJ. Hyperoside attenuates neuroinflammation, cognitive impairment and oxidative stress via suppressing TNF-α/NF-κB/caspase-3 signaling in type 2 diabetes rats. Nutr Neurosci 2022;25:1774-84.
159. Park S-H, Park J-W, Park S-J, Kim K-Y, Chung J-W, Chun M-H, *et al*. Apoptotic death of photoreceptors in the streptozotocin-induced diabetic rat retina. Diabetologia 2003;46:1260-8.
160. Shamsaei N, Abdi H, Shamsi M. The Effect of a continuous training on necrosis and apoptosis changes in the hippocampus of diabetic rats. J Ilam Univ Med Sci 2017;25:1. doi: ⁅10.29252/sjimu. 25.1.1.
161. Yang J-S, Lu C-C, Kuo S-C, Hsu Y-M, Tsai S-C, Chen S-Y, *et al*. Autophagy and its link to type II diabetes mellitus. Biomedicine 2017;7:8. doi: 10.1051/bmdcn/2017070201.
162. Kimura N. Diabetes mellitus induces Alzheimer's disease pathology: Histopathological evidence from animal models. Int J Mol Sci 2016;17:503.
163. Martins IJ. Nutritional and genotoxic stress contributes to diabetes and neurodegenerative diseases such as Parkinson's and Alzheimer's diseases. Front Endocrinol (Lausanne) 2018;9:196. doi: 10.3389/fendo.2018.00196.
164. Pagano G, Polychronis S, Wilson H, Giordano B, Ferrara N, Niccolini F, *et al*. Diabetes mellitus and Parkinson disease. Neurology 2018;90:e1654-62.
165. Ogawa W, Sakaguchi K. Euglycemic diabetic ketoacidosis induced by SGLT2 inhibitors: Possible mechanism and contributing factors. J Diabetes Investig 2016;7:135-8.
166. Sha W, Wen S, Chen L, Xu B, Lei T, Zhou L. The role of SGLT2 inhibitor on the treatment of diabetic retinopathy. J Diabetes Res 2020;2020:8867875. doi: 10.1155/2020/8867875.
167. Karami F, Jamaati H, Coleman-Fuller N, Zeini MS, Hayes AW, Gholami M, *et al*. Is metformin neuroprotective against diabetes mellitus-induced neurodegeneration? An updated graphical review of molecular basis. Pharmacol Rep 2023;75:511-43.
168. Hsia DS, Grove O, Cefalu WT. An update on SGLT2 inhibitors for the treatment of diabetes mellitus. Curr Opin Endocrinol Diabetes Obes 2017;24:73.
169. Dong D, Lou P, Wang J, Zhang P, Sun J, Chang G, *et al*. Interaction of sleep quality and anxiety on quality of life in individuals with type 2 diabetes mellitus. Health Qual Life Outcomes. 2020;18:1-7.

170. Shinkov A, Borissova A-M, Kovatcheva R, Vlahov J, Dakovska L, Atanassova I, *et al*. Increased prevalence of depression and anxiety among subjects with metabolic syndrome and known type 2 diabetes mellitus–A population-based study. Postgrad Med 2018;130:251-7.
171. Muscatello M, Troili GM, Pandolfo G, Mento C, Gallo G, Lanza G, *et al*. Depression, anxiety and anger in patients with type 1 diabetes mellitus. Recenti Prog Med 2017;108:77-82.
172. Amiri S, Behnezhad S. Diabetes and anxiety symptoms: A systematic review and meta-analysis. Int J Psychiatry Med 2019:0091217419837407. doi: 10.1177/0091217419837407.
173. Tang Y, Yu C, Wu J, Chen H, Zeng Y, Wang X, *et al*. Lychee seed extract protects against neuronal injury and improves cognitive function in rats with type II diabetes mellitus with cognitive impairment. Int J Mol Med 2018;41:251-63.
174. Li W, Huang E, Gao S. Type 1 diabetes mellitus and cognitive impairments: A systematic review. J Alzheimer's Dis 2017;57:29-36.
175. Clar C, Gill JA, Waugh N. Systematic review of SGLT2 receptor inhibitors in dual or triple therapy in type 2 diabetes. BMJ Open 2012;2:e001007. doi: 10.1136/bmjopen-2012-001007.
176. Herat LY, Matthews VB, Rakoczy PE, Carnagarin R, Schlaich M. Focusing on sodium glucose cotransporter-2 and the sympathetic nervous system: Potential impact in diabetic retinopathy. Int J Endocrinol. 2018;2018:9254126. doi: 10.1155/2018/9254126.
177. Hemmingsen B, Krogh J, Metzendorf MI, Richter B. Sodium-glucose cotransporter (SGLT) 2 inhibitors for prevention or delay of type 2 diabetes mellitus and its associated complications in people at risk for the development of type 2 diabetes mellitus. Cochrane Database Syst Rev 2016;4:CD012106. doi: 10.1002/14651858.CD012106.pub2.
178. Ferrannini E, Solini A. SGLT2 inhibition in diabetes mellitus: Rationale and clinical prospects. Nat Rev Endocrinol 2012;8:495-502.
179. Chao EC, Henry RR. SGLT2 inhibition — A novel strategy for diabetes treatment. Nat Rev Drug Discov 2010;9:551-9.
180. Filippas-Ntekouan S, Filippatos TD, Elisaf MS. SGLT2 inhibitors: Are they safe? Postgrad Med 2018;130:72-82.
181. Feinkohl I, Price JF, Strachan MW, Frier BM. The impact of diabetes on cognitive decline: Potential vascular, metabolic, and psychosocial risk factors. Alzheimers Res Ther 2015;7:1-22.
182. Oelze M, Kröller-Schön S, Welschof P, Jansen T, Hausding M, Mikhed Y, *et al*. The sodium-glucose co-transporter 2 inhibitor empagliflozin improves diabetes-induced vascular dysfunction in the streptozotocin diabetes rat model by interfering with oxidative stress and glucotoxicity. PloS One 2014;9:e112394. doi: 10.1371/journal.pone.0112394.
183. Lin B, Koibuchi N, Hasegawa Y, Sueta D, Toyama K, Uekawa K, *et al*. Glycemic control with empagliflozin, a novel selective SGLT2 inhibitor, ameliorates cardiovascular injury and cognitive dysfunction in obese and type 2 diabetic mice. Cardiovasc Diabetol 2014;13:1-15. doi: 10.1186/s12933-014-0148-1.
184. Amin EF, Rifaai RA, Abdel-latif RG. Empagliflozin attenuates transient cerebral ischemia/reperfusion injury in hyperglycemic rats via repressing oxidative–inflammatory–apoptotic pathway. Fundam Clin Pharmacol 2020;34:548-58.
185. Sa-Nguanmoo P, Tanajak P, Kerdphoo S, Jaiwongkam T, Pratchayasakul W, Chattipakorn N, *et al*. SGLT2-inhibitor and DPP-4 inhibitor improve brain function via attenuating mitochondrial dysfunction, insulin resistance, inflammation, and apoptosis in HFD-induced obese rats. Toxicol Appl Pharmacol 2017;333:43-50.
186. Chen C, Turnbull DM, Reeve AK. Mitochondrial dysfunction in Parkinson's disease—cause or consequence? Biology 2019;8:38.
187. Arab HH, Safar MM, Shahin NN. Targeting ROS-dependent AKT/GSK-3β/NF-κB and DJ-1/Nrf2 pathways by dapagliflozin attenuates neuronal injury and motor dysfunction in rotenone-induced Parkinson's disease rat model. ACS Chem Neurosci 2021;12:689-703.
188. El Mouhayyar C, Riachy R, Khalil AB, Eid A, Azar S. SGLT2 inhibitors, GLP-1 agonists, and DPP-4 inhibitors in diabetes and microvascular complications: A review. Int J Endocrinol 2020;2020:1762164. doi: 10.1155/2020/1762164.
189. Lin K-J, Wang T-J, Chen S-D, Lin K-L, Liou C-W, Lan M-Y, *et al*. Two birds one stone: The neuroprotective effect of antidiabetic agents on Parkinson disease—focus on sodium-glucose cotransporter 2 (SGLT2) inhibitors. Antioxidants 2021;10:1935. doi: 10.3390/antiox10121935.
190. Rizzo MR, Di Meo I, Polito R, Auriemma MC, Gambardella A, di Mauro G, *et al*. Cognitive impairment and type 2 diabetes mellitus: Focus of SGLT2 inhibitors treatment. Pharmacol Res 2022;176:106062. doi: 10.1016/j.phrs.2022.106062.
191. Theofilis P, Sagris M, Oikonomou E, Antonopoulos AS, Siasos G, Tsioufis K, *et al*. The impact of SGLT2 inhibitors on inflammation: A systematic review and meta-analysis of studies in rodents. Int Immunopharmacol 2022;111:109080. doi: 10.1016/j.intimp.2022.109080.
192. Naznin F, Sakoda H, Okada T, Tsubouchi H, Waise TZ, Arakawa K, *et al*. Canagliflozin, a sodium glucose cotransporter 2 inhibitor, attenuates obesity-induced inflammation in the nodose ganglion, hypothalamus, and skeletal muscle of mice. Eur J Pharmacol 2017;794:37-44.
193. Steven S, Oelze M, Hanf A, Kröller-Schön S, Kashani F, Roohani S, *et al*. The SGLT2 inhibitor empagliflozin improves the primary diabetic complications in ZDF rats. Redox Biol 2017;13:370-85.
194. Pirklbauer M, Sallaberger S, Staudinger P, Corazza U, Leierer J, Mayer G, *et al*. Empagliflozin inhibits IL-1β-mediated inflammatory response in human proximal tubular cells. Int J Mol Sci 2021;22:5089. doi: 10.3390/ijms22105089.
195. Muhammad RN, Ahmed LA, Abdul Salam RM, Ahmed KA, Attia AS. Crosstalk among NLRP3 inflammasome, ET BR signaling, and miRNAs in stress-induced depression-like behavior: A modulatory role for SGLT2 inhibitors. Neurotherapeutics 2021;18:2664-2681.
196. Wiciński M, Wódkiewicz E, Górski K, Walczak M, Malinowski B. Perspective of SGLT2 inhibition in treatment of conditions connected to neuronal loss: Focus on Alzheimer's disease and ischemia-related brain injury. Pharmaceuticals 2020;13:379. doi: 10.3390/ph 13110379.
197. Pawlos A, Broncel M, Woźniak E, Gorzelak-Pabiś P. Neuroprotective effect of SGLT2 inhibitors. Molecules 2021;26:7213. doi: 10.3390/molecules26237213.
198. Hierro-Bujalance C, Infante-Garcia C, Del Marco A, Herrera M, Carranza-Naval MJ, Suarez J, *et al*. Empagliflozin reduces vascular damage and cognitive impairment in a mixed murine model of Alzheimer's disease and type 2 diabetes. Alzheimers Res Ther 2020;12:1-13.
199. Abdel-Latif RG, Rifaai RA, Amin EF. Empagliflozin alleviates neuronal apoptosis induced by cerebral ischemia/reperfusion injury through HIF-1α/VEGF signaling pathway. Arch Pharm Res 2020;43:514-25.
200. Freeman LR, Haley-Zitlin V, Rosenberger DS, Granholm A-C. Damaging effects of a high-fat diet to the brain and

cognition: A review of proposed mechanisms. Nutr Neurosci 2014;17:241-51.

201. Palaiodimou L, Lioutas V-A, Lambadiari V, Paraskevas GP, Voumvourakis K, Tsivgoulis G. Glycemia management in acute ischemic stroke: Current concepts and novel therapeutic targets. Postgrad Med 2019;131:423-37.
202. El-Sahar AE, Rastanawi AA, El-Yamany MF, Saad MA. Dapagliflozin improves behavioral dysfunction of Huntington's disease in rats via inhibiting apoptosis-related glycolysis. Life Sci 2020;257:118076.
203. Ibrahim WW, Kamel AS, Wahid A, Abdelkader NF. Dapagliflozin as an autophagic enhancer via LKB1/AMPK/SIRT1 pathway in ovariectomized/d-galactose Alzheimer's rat model. Inflammopharmacology 2022;30:2505-20.
204. Madhusudhanan J, Suresh G, Devanathan V. Neurodegeneration in type 2 diabetes: Alzheimer's as a case study. Brain Behav 2020;10:e01577. doi: 10.1002/brb3.1577.
205. Panahi Y, Khalili N, Sahebi E, Namazi S, Karimian MS, Majeed M, *et al*. Antioxidant effects of curcuminoids in patients with type 2 diabetes mellitus: A randomized controlled trial. Inflammopharmacology 2017;25:25-31.
206. Hamed SA. Brain injury with diabetes mellitus: Evidence, mechanisms and treatment implications. Expert Rev Clin Pharmacol 2017;10:409-28.
207. Dobi A, Rosanaly S, Devin A, Baret P, Meilhac O, Harry GJ, *et al*. Advanced glycation end-products disrupt brain microvascular endothelial cell barrier: The role of mitochondria and oxidative stress. Microvasc Res 2021;133:104098. doi: 10.1016/j.mvr. 2020.104098.
208. Venkat P, Chopp M, Chen J. Blood–brain barrier disruption, vascular impairment, and ischemia/reperfusion damage in diabetic stroke. J Am Heart Assoc 2017;6:e005819. doi: 10.1161/JAHA.117.005819.
209. Hasan R, Lasker S, Hasan A, Zerin F, Zamila M, Parvez F, *et al*. Canagliflozin ameliorates renal oxidative stress and inflammation by stimulating AMPK–Akt–eNOS pathway in the isoprenaline-induced oxidative stress model. Sci Rep 2020;10:14659. doi: 10.1038/s41598-020-71599-2.
210. Zhong Y, Zhu Y, He T, Li W, Li Q, Miao Y. Brain-derived neurotrophic factor inhibits hyperglycemia-induced apoptosis and downregulation of synaptic plasticity-related proteins in hippocampal neurons via the PI3K/Akt pathway. Int J Mol Med 2019;43:294-304.
211. Moreira PI, Santos MS, Seiça R, Oliveira CR. Brain mitochondrial dysfunction as a link between Alzheimer's disease and diabetes. J Neurol Sci 2007;257:206-14.
212. Shibusawa R, Yamada E, Okada S, Nakajima Y, Bastie CC, Maeshima A, *et al*. Dapagliflozin rescues endoplasmic reticulum stress-mediated cell death. Sci Rep 2019;9:9887.
213. Faridvand Y, Kazemzadeh H, Vahedian V, Mirzajanzadeh P, Nejabati HR, Safaie N, *et al*. Dapagliflozin attenuates high glucose-induced endothelial cell apoptosis and inflammation through AMPK/SIRT1 activation. Clin Exp Pharmacol Physiol 2022;49:643-51.
214. Avgerinos KI, Mullins RJ, Vreones M, Mustapic M, Chen Q, Melvin D, *et al*. Empagliflozin induced ketosis, upregulated IGF-1/insulin receptors and the canonical insulin signaling pathway in neurons, and decreased the excitatory neurotransmitter glutamate in the brain of non-diabetics. Cells 2022;11:3372. doi: 10.3390/cells11213372.
215. Larsen EL, Andersen A, Kjær LK, Eickhoff MK, Frimodt-Møller M, Persson F, *et al*. Effects of two-and twelve-weeks sodium-glucose cotransporter 2 inhibition on DNA and RNA oxidation: Two randomized, placebo-controlled trials. Free Radic Res 2023;57:140-51.
216. Guerrero-Castillo AP, Sigfrido Benitez-Renteria A, Cuevas-Ramos D, López-Carrasco G, Silva A, Brito GX, *et al*. 885-P: Impact on glycaemic variability in newly onset T2DM patients initiating dapagliflozin plus metformin vs. metformin alone, a randomized open label clinical study—The MAGNNIFY trial. Diabetes 2023;72(Suppl 1). doi: 10.2337/db23-885-P.