



Protective effect of epicatechin in diabetic-induced peripheral neuropathy: A review

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ABSTRACT

Flavonoids are naturally occurring substances that can be found in plants and various foods and may have health benefits in the treatment of neuropathic pain; however human clinical data are still inadequate. Because of their anti-oxidant characteristics, a plant-derived flavonoid known as epicatechin is widely employed in the treatment of diabetes and its consequences. Furthermore, epicatechin reduces the polyol pathway, the generation of advanced glycation end products, and oxidative stress and neuroinflammation, which are all associated with the advancement of neuropathy induced by diabetes. This review article presents an overview of the different pathology of diabetic neuropathy and the role of epicatechin to ameliorate neuropathic pain, which can be helpful in the management of microvascular complications of diabetes.

INTRODUCTION

Diabetes mellitus is a long-term metabolic disorder characterized by hyperglycemia which might be due to improper secretion of insulin (Okasha *et al.*, 2017). The chronic hyperglycemic condition can impair the eyes, kidneys, brain system, and cardiovascular system, among several other body organs including peripheral nerves (Hashem *et al.*, 2021). The previous report found that diabetic individuals with low anti-oxidant levels, glucose autooxidation, and excess glycosylated proteins promote tissue damage and microvascular complication which might be responsible for peripheral neuropathy (Medakkel and Sheela, 2018; Zhong *et al.*, 2018).

Peripheral neuropathy is the most common secondary complication of diabetic mellitus. It was found that when there is long-lasting hyperglycemia, the damage to the peripheral nerve is increased through different down-regulated cellular

cascade processes. The most important metabolic cascade involved in the pathogenesis of diabetic-induced peripheral neuropathy are increased influx of polyol cascade, enhanced formation of glycation and advanced glycation end-products (AGE) cascade, increased generation of oxidative stress, activation of protein kinase-C (PKC) pathways, induction of pro-inflammatory processes, and formation of cellular and trophic factor (Fig. 1).

Polyol pathway

When the plasma glucose level becomes hyperglycemic, the activation of the aldose reductase (AR) enzyme is more prominent for increased glucose, and the increased flow of polyol cascade is mediated in nervous tissue. Increased influx of polyol resulted in intracellular hyperosmolarity as impermeable sorbitol accumulated in the cytoplasm, resulting in cell expansion and lysis according to previous research based on osmotic theory (Prabhakar and Sai laxmi, 2021). In addition, the polyol cascade increased the utilization of cofactor (reduced nicotinamide adenine dinucleotide phosphate), resulting in decreased formation of reduced glutathione and increasing the level of oxidized glutathione, decreasing the concentration of myo-inositol and nitric oxide (NO). The decreased

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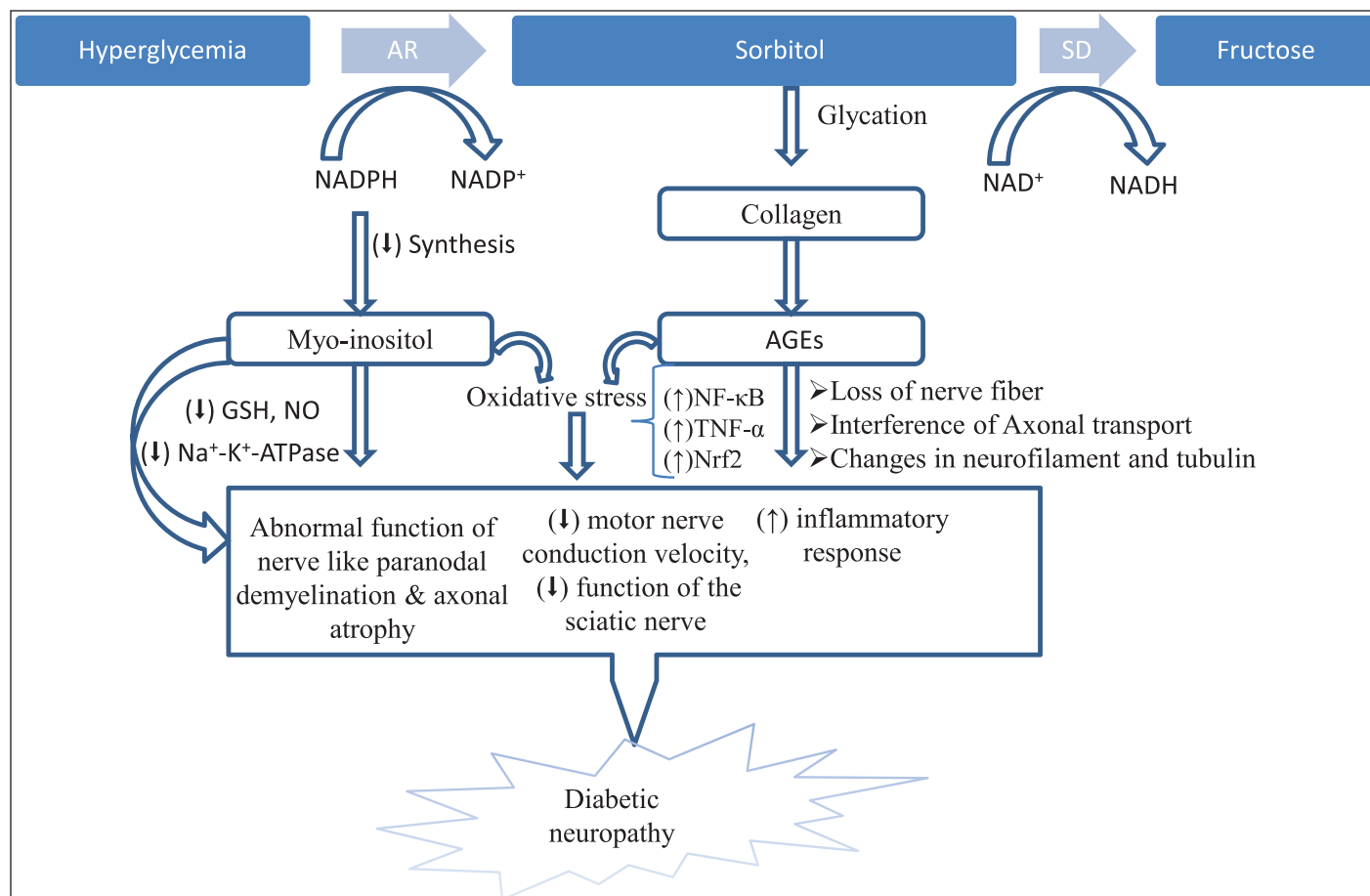


Figure 1. Illustrate the possible mechanism of action involved during diabetic neuropathy.

synthesis of myo-inositol adversely affects the normal function ($\text{Na}^+\text{-K}^+\text{-ATPase}$ activity, nodal remyelination, and conduction velocity) of nerves, suggesting that myo-inositol depletion could be a crucial factor in the genesis of diabetic neuropathy (Pathak *et al.*, 2022). Sima *et al.* (1997) explored the role of myo-inositol in L-fucose-induced diabetic neuropathy in an experimental rat model. After supplementation of the L-fucose diet for 24 weeks to the rats, there were significant decreases in the level of myo-inositol and decreases in the $\text{Na}^+\text{-K}^+\text{-ATPase}$ activity along with significant paranodal demyelination and axonal atrophy. The effect is similar to neuropathy of diabetes. However, the supplementation of a myo-inositol-enriched diet prevents the above-mentioned changes in nerves significantly, suggesting that myo-inositol deficiency could be an important pathological event in diabetic neuropathy (Sima *et al.*, 1997). Further, the reduced level of glutathione and NO could increase the generation of reactive oxygen species (ROS), consequently producing cellular hemolysis and nerve cell damage. Kodani *et al.* (2000) illustrate the mechanism of action of NO in the involvement of diabetic neuropathy using streptozotocin (STZ)-induced male ddY mice. During the study, nociceptive thresholds and cyclic Guanosine monophosphate concentration were assessed after 8 weeks of STZ administration and the result indicates significant increases in nociceptive thresholds in diabetic animals than in the control group. However, injection of L- N^{G} -nitro arginine methyl ester, which is a NO synthase inhibitor, exhibited a significant reduction of nociceptive thresholds in diabetic animals,

concluding that NO has a potential role in the pathogenesis of diabetic neuropathy (Kodani *et al.*, 2000).

Glycation and AGEs pathway

AGEs are heterogeneous molecules produced by reactive dicarbonyls during long-standing hyperglycemia. It is non-enzymatic glycation of plasma proteins via covalent adducts. Accumulation of AGEs in the peripheral nerves causes significant structural and functional modifications such as loss of nerve fiber, and alteration of neurofilament and tubulin. This alteration of nerve fibers leads to interference of axonal transport, which contributes to the genesis of atrophy and degeneration of nerve fibers, which play a vital role in the development of damage of nerve damage (Hotta *et al.*, 2020). In addition, up-regulation of the receptor of AGEs (RAGE) leads to overexpression of endothelial cells of peri- and endoneurial blood vessels, which activates transcription factors of NF- κ B and protein kinase (activator protein-1) to increase the expression of vascular cell adhesion molecule-1 and cytokines such as tumor necrosis factor and interleukin-6, suggesting that activation of RAGE by AGEs could be a crucial mechanism of pathologic processes of endoneurial vascular dysfunction and microangiopathy in the peripheral nerve. Toth *et al.* (2008) experimentally illustrate the relation between RAGE expression and diabetic neuropathy using STZ-induced diabetic mice. The result indicates significant up-regulation of RAGE mRNA and protein in epidermal axon and dorsal root ganglia (DRG)

after 5 months of diabetic mice. The electrophysiological and quantitative morphometric test indicates structural abnormalities of the peripheral nerve. The study report also confirmed the activation of NF- κ B and PKC in Schwann cells and peripheral nerves via RAGE expression. However, mice lacking RAGE have minimal activation of the peripheral nerve signal pathway (Toth *et al.*, 2008). It is anticipated that the formation and accumulation of AGEs in the peripheral nerve involves the development of diabetic neuropathy, directly by affecting structural and functional proteins and indirectly by activating RAGE.

Oxidative stress

Hyperglycemia is an important factor in the mechanism of polyol pathway and AGEs generation. This cascade mechanism is involved in hyperglycemia-induced mitochondrial dysfunction which promotes oxidative stress and free radicals, in turn, stimulates nerve cellular injury and contributes to diabetic neuropathy. Oxidative stress in the peripheral nervous system can directly produce impairment in the synthesis of DNA or protein and modify intracellular signaling cascades such as redox-sensitive transcription factors and activation of protein kinase known as a mitogen-activated protein kinase (MAPK) in Schwann cells that contribute to the induction of inflammatory cytokines. The damaged protein in the nerve cell prevents metabolic functions like cell signaling and eventually leads to cell death. In addition, oxidative stress produced during hyperglycemia is also involved in the induction of endothelial abnormalities which leads to the development of micro- and macrovascular dysfunction. Furthermore, it was found that oxidative stress produced during persistent hyperglycemia modulates the expression of nuclear factor erythroid 2-related factor 2 (Nrf2) and NF- κ B transcription factor. In healthy cells, the previous factor responsible for the maintenance of anti-oxidant defense and later involved with the production of the pro-inflammatory cytokine-maintained homeostasis condition in the cell. However, during increased oxidative stress, this cell homeostasis condition is perturbed, resulting in less generation of endogenous anti-oxidant defense, and consequently resulting in dysfunction of nerve microvascular structure and diabetic neuropathy (Kumar and Mittal, 2017; Yerra *et al.*, 2013). Hence, targeting Nrf2 and NF- κ B expression could be a beneficial approach in the management of diabetic neuropathy. Wang *et al.* (2020) illustrate the role of oxidative stress in diabetic peripheral neuropathy and also its alleviation with an anti-oxidant agent diphenyl diselenide using both *in vitro* and *in vivo* methods. During *in vitro* study, rat Schwann cells 96 were incubated with a higher concentration of glucose at 100 mM for about 24 hours, and then the test drug diphenyl diselenide was added with a concentration range of 1–50 μ M to the cell lines for the evaluation of cytotoxicity and oxidative stress. The result indicates significant suppression of ROS and malondialdehyde (MDA) concentration in Schwann cells as well as overexpression of Nrf2 signaling and down-regulation of Keap1 expression in the sciatic nerve. Furthermore, the *in vivo* diabetic neuropathy was developed after the injection of STZ into rats. After administration of diphenyl diselenide (15 mg/kg) for 12 weeks, there was a significant improvement in motor nerve conduction velocity, mechanical hyperalgesia, the function of the sciatic nerve, and prevention of oxidative stress in the sciatic nerve. The result suggests that the anti-oxidant agent ameliorates the pathogenesis

of diabetic-induced neuropathy induced by oxidative stress and could be considered a promising strategy for the management of neuropathy (Wang *et al.*, 2020).

Protein kinase-C pathways

The involvement PKC in the pathophysiology of peripheral diabetic neuropathy has been well investigated (Mizukami *et al.*, 2011). The condition of chronic hyperglycemia promotes the synthesis of 1,2-diacylglycerol which contributes to the activation of different isoforms of PKC such as PKC- α , - β 1/2, and PKC- δ . These isoforms have been involved in the pathogenesis of neurovascular disorders by affecting blood flow and conduction velocity of the small vessel leading to diabetic neuropathy complications. Kim *et al.* (1991) illustrate the association of PKC in nerve tissue function in STZ-induced diabetic rats. The experiment reveals that diabetic rats have impaired Na⁺-K⁺-ATPase activity and alteration in PKC activity in the peripheral nerve which reduced nerve conduction as well as adversely affected nerve regeneration. This can be prevented by PKC agonists, suggesting the possible role of PKC in diabetic neuropathy (Kim *et al.*, 1991).

Pro-inflammatory processes

The above illustration pointed out that chronic hyperglycemia gives rise to oxidative stress of the endoplasmic reticulum (ER) and mitochondria. The increased accumulation of ROS leads to the activation of inflammatory processes such as NF- κ B, TNF- α , etc. (Cameron and Cotter, 2008). Kumar *et al.* (2012) illustrate the involvement of the NF- κ B inflammatory process in diabetic neuropathy using STZ-induced diabetic rats. BAY 11-7082 at two doses (1 and 3 mg/kg) and NF- κ B inhibitor were administered to two groups of diabetic rats. The result of BAY 11-7082 treatment indicates a dose-dependent decrease in the level of inflammatory markers (IL-6 and TNF- α) and inducible enzymes (COX-2 and iNOS), decreased MDA level, and improvement in GSH level along with improvement of sensory responses and nerve function compared to the non-BAY 11-7082 treated group. The result suggests that down-regulation of NF- κ B improved nerve function and prevents neuroinflammation by improving endogenous anti-oxidants and decreasing inflammatory cascades (Kumar *et al.*, 2012). These inflammatory cascades show mild intraneural inflammation resulting in degeneration of peripheral nerve fiber, associated with diabetic neuropathy. Further, the infiltration of macrophages in the nerve fiber induced the generation of pro-inflammatory cytokines and chemokines which are also associated with dysfunction of peripheral nerve fiber and inflammation (Baum *et al.*, 2021).

Cellular and trophic factor

Neurotrophin depletion is a major contributor to diabetic neuropathy (Azoulay *et al.*, 2020). The report found that diabetic mice model nerve growth factor release was inhibited in the skin, and nerve growth factor replacement improved peripheral diabetic neuropathic alterations of tiny fibers and autonomic disease (Schmidt *et al.*, 2003). Literature has discovered the pathophysiology of neuropathy, chimeric cells comprised of local Schwann cells or neuronal cells, and migratory proinsulin-producing cells from the bone marrow in diabetic nerves (Busik *et al.*, 2009).

Protective role of epicatechin in diabetic peripheral neuropathy

Epicatechin (flavon-3-ol monomer units) is a subclass of flavonoids known as flavanol monomers (Abdulkhaleq *et al.*, 2017), and is a plant-based bioactive compound. The most common source of epicatechin is cocoa, green tea, black tea, peanuts, grapes, berries, apple, and dark chocolate (Manach *et al.*, 2004). The chiral center on positions two and three of the plant-derived flavon-3-ol results in four diastereoisomers, namely (+)-epicatechin, (-)-epicatechin, (+)-catechin, and (-)-catechin (Bernatova, 2018). The chemical name of (-)-epicatechin is (2R, 3R). The 2,4-(dihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol shows significant anti-inflammatory and anti-oxidant properties. The natural flavonoids, epicatechin, have been associated with a number of health benefits such as improving the function of the heart, brain, and muscles. Furthermore, epicatechin has been shown to have significant effects on the management of diabetes (Table 1) and its associated complications such as neuropathy, retinopathy, obesity, cardiovascular complications, and retinopathy (Basu and Basu, 2020). Among the different

complications of diabetes, neuropathy is one of the insidious conditions in which nerve damage occurs throughout the body and adversely impacts the quality of life. The possible pathological involvement that modulates diabetic neuropathy includes decreased production of myo-inositol content in different autonomic nerves as well as increased oxidative stress, AGE, and PKC levels. Natural polyphenols have shown significant beneficial effects in the management of neuropathy. In this regard, an experimental finding indicates that the administration of catechin at the dose of 50 mg/kg body weight for the period of 28 days to STZ-induced diabetic rats exhibited a significant reduction of oxidative stress as well as neuronal damage in different nerves, suggesting flavonoids have a promising effect in the management of diabetic neuropathy (Addepalli and Suryavanshi, 2018). The anti-oxidant and anti-inflammatory properties of epicatechin are responsible for the reduction of damage to the pancreas, preventing diabetic-like conditions and improving the patient's life span. Si *et al.* (2011) studied the effect of epicatechin on the diabetic db/db mouse model. The results indicated that administration of dietary epicatechin (0.1–8 mmol/l) for 15 weeks reduced the concentration

Table 1. Source of different epicatechin and their anti-diabetic properties.

Sl no	Source name	Quantity	Antidiabetic model	Expected outcome	Reference
1	Black grape	87.0 mg/kg	DRG neurons of rodents and hamsters	DRG primary cultures are also useful for tracing the time dynamics of molecular events that occur during oxidative stress-induced cell death	Tsanova-Savova <i>et al.</i> (2005), Vincent <i>et al.</i> (2002)
2	Cocoa beans	270–123.5 mg/100 g	Primary cultures of Schwann cells from Sprague-Dawley rat	DRG primary cultures are also useful for tracing the time dynamics of molecular events that occur during oxidative stress-induced cell death.	Othman <i>et al.</i> (2010)
3	Apple with skin	96.2 mg/kg	Neural crest cells	High glucose exposure lowers cell number and slows cell migration, suggests neuroprotective benefits	Suzuki <i>et al.</i> (1996)
4	Apple without skin	66.5 mg/kg	Cortical neurons	Establish an increase in apoptosis and a decrease in neurite production as a result of hyperglycemia to determine the cellular and molecular events underlying these deficits.	Guleria <i>et al.</i> (2006)
5	Apricot	60.6 mg/kg	Neuroblastoma cell line SHSY5Y	SHSY5Y cells have also been successfully used to illustrate signal transduction changes.	Shindo <i>et al.</i> (1996)
6	Avocado	5.6 mg/kg	Pheochromocytoma cell line	Effectively used to determine the NO-induced stress, involvement of pro apoptotic mitochondrial protein Bax, reactive oxygen species, carbonyl-induced stress and nerve growth factor signaling	Koshimura <i>et al.</i> (2003), Sharifi <i>et al.</i> (2007), Okouchi <i>et al.</i> (2005), Lelkes <i>et al.</i> (2001), Koshimura <i>et al.</i> (2002)
7	Blackberry	180.8 mg/kg	Schwann cell line	Increased glucose leads to intracellular sorbitol buildup as well enhanced activity of the enzyme AR, and activation of specific critical genes.	Sango <i>et al.</i> (2006)
8	Blueberry	11.1 mg/kg	Rodent whole embryo culture	This method is suitable for determining the teratogenic effects of hyperglycemia in the embryos of type-1 diabetic mothers.	Cockroft and Coppola (1977)
9	Grape	89.4 mg/kg	Shell-less cultures of chick embryos	Provides an idea about hyperglycemia-induced embryopathies, such as defects of the developing nervous system.	Datar and Bhone (2005)
10	Kiwi fruit	4.5 mg/kg	Embryonic stem cell line	Since they closely resemble the early developing embryo, human embryonic stem cell-derived embryoid bodies could be valuable in research into hyperglycemia-induced embryonic neuropathies.	Pouton and Haynes (2007)
11	Chocolate-black	327.4 mg/kg	BALB/cJ	Decrease the rate of motor nerve conduction velocity	Arts <i>et al.</i> (2000)
12	Raisins	7.1 mg/kg	Swiss mice	Decrease the rate of motor nerve conduction velocity	Arts <i>et al.</i> (2000)
13	Cocoa	2,037 mg/kg	MrgD	Decrease the rate of motor nerve conduction velocity	Risner (2008)

of insulin-like growth factor-1, serum cholesterol level, blunted fat deposition, and degeneration of aortic vessels significantly. In addition, it improved hepatic anti-oxidant parameters like glutathione and superoxide dismutase (SOD) levels as well as the activity of AMP-activated protein kinase- α . The results suggest the longer, healthier lifespan could be due to the anti-oxidant properties of epicatechin, which could be a promising food-derived anti-aging bioactive compound (Si *et al.*, 2011).

The report found that the bioactive components of green tea play a significant role in the inhibition of AR, an enzyme that plays a vital role in the polyol pathway, one of the important pathological involvements of diabetic neuropathy. The experimental finding indicates strong inhibition of AR enzymes with IC₅₀ = 79 μ mol/l and 38 μ mol/l for epicatechin and epicatechin gallate, respectively, suggesting flavonoids have a promising effect in the management of diabetic neuropathy (Murata *et al.*, 1994). Another experiment evaluated the AR inhibitory activity using flavonoids. The result revealed that rich fractions obtained from *Pedaliium murex* showed effective non-competitive inhibition of AR in STZ-induced diabetic rats. This suggests that flavonoids could be useful in associated complications of diabetic individuals (Patel, 2021).

Many of the consequences of diabetes mellitus, including diabetic neuropathy, are linked to the buildup of AGEs. AGE inhibitors were developed to combat diabetes complications and age-related disorders. According to Vasan *et al.* (1996), the AGE-breakers are a new class of reagents that involve the breaking down of AGE cross-links between tissue proteins that have already formed (Vasan *et al.*, 1996). The use of botanical components, such as anti-AGE agents, has gained popularity as natural compounds have been demonstrated to be reasonably safer for human intake than synthetic substances (Lee *et al.*, 2007). One of the phytoconstituents, epicatechin, has shown effective prevention of oxidative stress in pancreatic beta cells (Martín *et al.*, 2014). Epicatechin is an anti-oxidant that protects lipids from oxidation and scavenges oxygen radicals (Ngawhirunpat *et al.*, 2010). Peng *et al.* (2008) studied the role of epicatechin in the inhibition of the production of AGE. The results found that phytoconstituents such as epicatechin, catechin, and procyanidin B₂ obtained from aqueous cinnamon bark exhibited significant inhibition of AGE production in the bovine serum albumin-glucose assay. The anti-oxidant and insulin-enhancing properties of bioactive compounds could be responsible for the entrapment of methylglyoxal and highly reactive carbonyl species, resulting in inhibition of AGE production and might be used as potential agents to alleviate diabetic complications (Peng *et al.*, 2008). Another article demonstrated the inhibition of accumulation of AGE of (-)-epicatechin using both *in vitro* glycated human serum albumin and *in vivo* rat models. Experimental findings indicate that the intraperitoneal administration of epicatechin at the dose of 50 and 100 mg/kg for 15 days reduced AGE in both models in a dose-dependent manner, which is confirmed using immunohistochemical and western blotting tests. This suggests that epicatechin could be applied in diabetic individuals for the management of neuropathy by depleting the level of AGE (Kim *et al.*, 2015). Similarly, the presence of anti-oxidant polyphenols such as (-)-epicatechin 3-O-gallate and (-)-epigallocatechin 3-O-gallate in green tea has exhibited a significant reduction in AGE production. Experimental findings indicate that administration of green tea extract at the dose of 300 mg/kg body weight to STZ-induced diabetic rats for the period of 1 month showed inhibition

of AGE formation. These findings conclude that epicatechin might be used as a promising agent in the management of diabetic neuropathy and other complications (Wu *et al.*, 2011). In normoglycemic rats injected with exogenous AGEs, the effects of epicatechin on retinal vascular impairment were also investigated; *in vitro* results revealed that epicatechin eliminates preformed antigenic AGEs (Kim *et al.*, 2015). From these findings, we can conclude that by inhibiting the formation of AGE, which is responsible for the pathogenesis of neuropathy, epicatechin may pose a potential therapeutic target to overcome both microvascular and macrovascular diabetic complications.

The chronic hyperglycemic condition of diabetes causes oxidative stress which might damage the nerve tissue of the autonomic nervous system leading to peripheral neuropathy. Agents having potential anti-oxidant properties, for example, natural polyphenols like epicatechin and catechin, obtained from different diet sources could be utilized in the management of hyperglycemia-induced oxidative stress in neuropathy. The report found that administration of polyphenol (catechin) at the dose of 50 mg/kg for 28 days improved the oxidative stress parameters such as MDA, reduced glutathione, SOD, and catalase in STZ-induced diabetic rat vagus nerves significantly in addition to the reduction of random plasma blood glucose level. Further, the treatment of polyphenol reduces multifocal proliferation of Schwann cells and fragmentation of myelin and axon cells which was confirmed using histopathology examinations of the vagus nerve. The finding suggests that polyphenol could have the ability to prevent neuronal degeneration in the peripheral nervous system by reducing oxidative stress in hyperglycemic animal models (Addepalli and Suryavanshi, 2018). Another research article cites the effect of polyphenols in the management of diabetic neuropathy by reducing oxidative stress using the *in vitro* Alamar Blue assay. Incubation of (-)-epigallocatechin-3-gallate (EGCG) in the concentration of 50 μ M in oxidative-stress-damaged cell lines of rat hippocampal neurons for 24 hours showed better cellular resistance to glucose oxidase by stimulating the protein expression of heme oxidase-1 enzymes via the Nrf2 signaling pathway. These results suggest the cytoprotective effect of EGCG is due to the reduction of oxidative stress in damaged cells and could be a key agent in the management of diabetic neuropathy (Romeo *et al.*, 2009). Similarly, the reduction of oxidative stress activity of EGCG was evaluated in an *in vivo* STZ-induced male Wistar rat diabetic model. Oral administration of EGCG (40 mg/kg) for 7 weeks to diabetic rats shows a significant reduction of diabetic-induced serum nitrite and MDA content and increases the level of erythrocyte SOD in serum. These results suggest the attenuation of the oxidative stress effect of EGCG could be utilized as a therapeutic agent in the treatment of diabetic hyperalgesia or neuropathy (Baluchnejadmojarad and Roghani, 2012).

Epicatechin has been considered a promising anti-inflammatory agent and shows strong action in the reduction of pro-inflammatory processes such as NF- κ B, iNOS, and c-JUN N-terminal kinase (JNK) which might be responsible for the progression of diabetic neuropathy. In this context, myristate 13-acetate was used to induce NF- κ B in Jurkat T cells 4.6-fold more. *In vitro* results show that pretreatment with epicatechin (20 nM) reduced the expression of NF- κ B to 78% via preventing the NF- κ B gene, suggesting the modulating properties of epicatechin could affect the immune function properties of diabetic neuropathy individuals (Mackenzie *et al.*, 2004). Recent discoveries demonstrate that ER stress plays a significant role in the

development of diabetic neuropathy and points to a potential new treatment target. Grape seeds proanthocyanidins (GSP) and their derivatives such as epicatechin and catechin obtained from grape seeds have been reported to mitigate pro-inflammatory markers which are involved in neuropathic pain in murine models. *In vivo* results have shown that oral administration of GSP at the dose of 250 or 500 mg/kg body weight to STZ-induced diabetic rats exhibited significant improvement in the level of nerve conduction velocity and morphology of myelin sheath along with increases in ER and mitochondria, suggesting GSP treatment could prevent neuropathy by mitigating Ca^{2+} content in sciatic nerves (Ding *et al.*, 2014). Similarly, flavonoids have shown considerable action in the alleviation of neurodegenerative disease by protecting the nervous system, which might be helpful in diabetic individuals. The proposed mechanism of the neuroprotective effect of epicatechin is the significant inhibition of Ca^{2+} -dependent JNK signal and caspase-3-like protease expression in neurons induced by oxidized low-density lipoprotein, which suggests epicatechin has strong neuroprotective properties (Schroeter *et al.*, 2001).

The report found that epicatechin and catechin obtained from the diet have significant actions in the protection of central neurons and preventing neuroinflammation. The result shows that 1-month administration of epicatechin (50 μ g) produces a significant reduction of pro-inflammatory cytokines. TNF- α and IL-6 suggest flavonoids as promising neuroprotective agents and could be considered a potential therapeutic approach in the management of diabetic neuropathy (Noll *et al.*, 2013). Al-Gayyar *et al.* (2011) investigated the function of pro nerve growth factor in neuroglial activation and the neuroprotective benefits of epicatechin, a specific inhibitor of tyrosine nitration in an experimental rat model of diabetes at a dose of 100 mg/kg body weight and found that epicatechin can successively restore neuronal survival (Al-Gayyar *et al.*, 2011). Quiñonez-Bastidas *et al.* (2013) suggested that in diabetic rats, daily or every other day pre-treatment with epicatechin (0.03–30 mg/kg, i.p.) for 2 weeks reduced formalin-induced nociception (Quiñonez-Bastidas *et al.*, 2013). Recently, in chronic constriction injury-induced neuropathic pain models, researchers looked at the antinociceptive efficacy and underlying mechanism of *Camellia japonica* leaf extract having epicatechin and rutin, and found *C. japonica* leaf extract and its active components might have antinociceptive benefits against CCI4-induced neuropathic pain, which may be mediated through DRG MAPK activation and spinal microglial activation (Lim *et al.*, 2022). Furthermore, epicatechin activates the NO-cyclic GMP- K^+ channel, 5-HT_{1A/1B/1D/5A} serotonin receptors, and opioid receptors to produce antinociception (Quiñonez-Bastidas *et al.*, 2018). Similarly, (-)-epicatechin has demonstrated significant anti-diabetic activity by altering the relative expression of the GLUT 3 and TNF- proteins in an *in vivo* high fat, STZ-induced diabetic model, suggesting that it may alleviate neuropathy (Gonzalez, 2014). Lopes *et al.* (2012) studied the mechanism of antinociceptive action of epicatechin isolated from the hydroalcoholic fraction of *Combretum leprosum* using Swiss albino mice model. Initially, the nociception was induced in the paw of animals by using 20 μ mol of glutamate. The use of epicatechin (50 mg/kg p.o.) to the nociceptive mice, after pretreatment with naloxone (2 mg/kg s.c.), glibenclamide (mg/kg s.c.), ketanserin (0.3 mg/kg s.c.), yohimbine (0.15 mg/kg s.c.), pindolol (1 mg/kg s.c.), and atropine (0.1 mg/kg s.c.) exhibited reverse antinociceptive effect. The result indicates the participation

of opioid receptors and potassium channels sensitive to ATP, as well as serotonergic (receptors 5HT_{1A} and 5HT_{2A}), adrenergic (α 2 receptor), and cholinergic receptors in the alleviation of pain receptors and might be useful in the management of diabetic neuropathy (Lopes *et al.*, 2012). The above findings suggest that epicatechin having anti-oxidant activity can be employed to ameliorate neuropathic pain by modifying the complementary biochemical processes. The stimulation of essential components in the Nrf2 pathway, NF- κ B pathway, NO pathway, PI3K/AKT system, and the particular regulation of mitochondrial activity, endothelial function, muscle growth, and inhibitors are all important for epicatechin's biological actions.

In addition to pre-clinical data on epicatechin in hyperglycemia, there are limited data on blood glucose control in pre-diabetic human patients. In this regard, a double-blinded, placebo-controlled, randomized, Phase I trial was conducted by using (+)-epicatechin with a dose of 30 mg/day for 7 days, and the result shows glycemic control in treated volunteers when compared to the placebo group (ClinicalTrials.gov, 2016). Another clinical trial was conducted for the testing of safety and effectiveness of synthetic prepared (+) epicatechin capsules at the dose of 25 mg thrice a day for 4 months in patients having Friedreich's Ataxia, a neurological disorder. The result showed enhanced mitochondrial biogenesis, resulting in neuroprotection (ClinicalTrials.gov, 2016).

CONCLUSION

We found that the plant-derived flavonoid, epicatechin, has a promising effect on the prevention and management of diabetic neuropathy by modulating different pathological processes. The presence of anti-oxidant properties of epicatechin prevents the polyol pathway and AGEs, improves autonomic nerve function, and prevents neuronal damage caused by diabetic-induced free radicals. Furthermore, the significant anti-inflammatory activity of epicatechin helps in the prevention of neuroinflammation and protects the central as well as peripheral neurons. The effect of epicatechin in improving various neuropathic pain conditions, including mechanisms with preclinical information, suggests that it has a significant role in the control of neuropathic pain. As a result, it can be concluded that epicatechin has a great deal of potential for the development of innovative neuropathic pain treatments. Nevertheless, more research is required.

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AUTHOR CONTRIBUTIONS

The authors confirm their contribution to the paper as follows: study conception and design: JD and GP; data collection: JD, BK; draft manuscript preparation: GG, GD, BK. All authors reviewed the results and approved the final version of the manuscript.

CONFLICT OF INTEREST

There are no conflicts of interest declared by the authors.

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This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included within this research article.

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