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REVIEW ARTICLE

Polyphenols for diabetes associated neuropathy: Pharmacological targets and clinical perspective

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Abstract

Objectives Diabetic neuropathy (DNP) is a widespread and debilitating complication with complex pathophysiology that is caused by neuronal dysfunction in diabetic patients. Conventional therapeutics for DNP are quite challenging due to their serious adverse effects. Hence, there is a need to investigate novel effective and safe options. The novelty of the present study was to provide available therapeutic approaches, emerging molecular mechanisms, signaling pathways and future directions of DNP as well as polyphenols' effect, which accordingly, give new insights for paving the way for novel treatments in DNP.

Evidence acquisition A comprehensive review was done in electronic databases including Medline, PubMed, Web of Science, Scopus, national database (Irandoc and SID), and related articles regarding metabolic pathways on the pathogenesis of DNP as well as the polyphenols' effect. The keywords "diabetic neuropathy" and "diabetes mellitus" in the title/abstract and "polyphenol" in the whole text were used. Data were collected from inception until May 2019.

Results DNP complications is mostly related to a poor glycemic control and metabolic imbalances mainly inflammation and oxidative stress. Several signaling and molecular pathways play key roles in the pathogenesis and progression of DNP. Among natural entities, polyphenols are suggested as multi-target alternatives affecting most of these pathogenesis mechanisms in DNP.

Conclusion The findings revealed novel pathogenicity signaling pathways of DNP and affirmed the auspicious role of polyphenols to tackle these destructive pathways in order to prevent, manage, and treat various diseases.

Keywords Diabetic neuropathy · Polyphenols · Therapeutic targets · Signaling pathways

Introduction

As one of the most chronic and common endocrine-metabolic disorders, diabetes mellitus (DM) is predicted to afflict up to 300 million people or more by the year 2025 [1, 2]. The elevated blood glucose concentration, in addition to macrovascular incidents (heart attack, stroke and peripheral vascular disease) also leads to microvascular complications in body organs specially kidney (diabetic nephropathy), eyes (retinopathy), and nerves (neuropathy) [1–3]. Diabetic neuropathy (DNP) has been considered the most common complication of diabetes resulting from prolonged periods of hyperglycemia, damaging fragile nerve fibers and the walls of their blood vessels [4]. The prevalence of DNP in diabetic patients ranges from 7% within 1 year of diagnosis, to 50% for those suffering from diabetes for more than 25 years [3]. DNP is divided into several subcategories, including; hyperglycaemia, generalized (autonomic neuropathy, sensorimotor polyneuropathy, and acute painful sensory neuropathy), focal and multifocal (thoracolumbar radiculoneuropathy,

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cranial neuropathy, proximal and focal limb DNP) neuropathies, and superimposed chronic inflammatory demyelinating polyneuropathy [5]. Diabetic sensory polyneuropathy or peripheral neuropathy is the most common form of DNP can present as sensory symptoms include hypesthesia, neuropathic pain, allodynia, paresthesias (tingling or pricking), dysesthesia and paresis [6]. Neurovascular insufficiency, autoimmune damage, neuro-hormonal growth factor deficiency and hyperglycemia-induced formation of advanced glycation end products (AGEs) are also among the multiple etiologies of DNP [7–9].

Despite clinical developments in the treatment of diabetes complications specially DNP, it still remained a clinical challenge with no effective solution. Thus, it rises the needs to develop novel multi-target therapeutics to regulate more involving destructive signaling pathways of individuals with DNP. As a heterogeneous and large group of phytochemicals containing phenol rings, polyphenols [10] are multi-target agents with the most antioxidants and anti-inflammatory effects have the potentials to combat several diseases like diabetes and its complications [11, 12]. Recently, polyphenols have also been introduced as potential neuroprotective agents in diabetes [13]. Understanding the signaling pathways underlying the progress of DNP and the way polyphenols prevent the progress of these destructive pathways, may lead to introduce polyphenols as new therapeutic agents in DNP.

The aim of the current review was to address available therapeutic targets, signaling pathways, molecular mechanisms, and future directions of DNP as well as polyphenols' effect, in order to pave the way for novel treatments.

Metabolic pathways involved in the pathogenesis of DNP

Different pathways have been reported as being involved in the development of DNP pathogenesis e.g., imbalances in peripheral nerves blood supply, the vascular system of the thalamic gland, gene expression of sodium and calcium channels, and autoimmune diseases characterized by activation of glial cells [14].

In terms of mechanism, polyol pathway, oxidative stress and advanced glycation, inflammation, trophic factors, channels, and glutamate pathway are the main mediators and signaling pathways associated with DNP [15–19].

Polyol pathway

Polyol pathway is present in several tissues like peripheral nerve and blood vessels and certainly contributes to the development of DNP [20]. Two main enzymes are involved in the polyol pathway; aldose reductase (AR, a rate-limiting enzyme) and sorbitol dehydrogenase which the first is found in various tissues, including nerve, lens, retina, glomerulus, and vascular cells [21]. High blood glucose level leads to the activation of AR that produces sorbitol from glucose. This reaction consumes nicotinic acid adenine dinucleotide phosphate (NADPH) and produces $NADP^+$. High consumption of NADPH reduces the level of reduced glutathione (GSH) and increases the level of oxidized glutathione (GSSG). Nevertheless, due to the inability of sorbitol to cross the cell membrane, the accumulated sorbitol elevates the blood osmolality resulting in the loss of electrolytes [17, 22]. High osmosis damages the cells surrounding peripheral neurons (Schwann cells) and causes the schwannopathy-related phenotype of DNP [22, 23].

The other key enzyme sorbitol dehydrogenase converts the accumulated sorbitol to fructose via oxidation and producing nicotinic acid adenine dinucleotide (NADH). However, the increase in both sorbitol and fructose leads to some deleterious effects on nerve cells due to several reasons, including the decrease in concentration of osmolality regulator (taurine or 2-aminoethanesulfonic acid, a bile component), and insulin sensitivity regulator (myoinositol), inhibition of Na^+/K^+ ATPase pump, accumulation of intracellular Na^+, ionic homoeostasis via diminution of Protein kinase C (PKC) activity which cause swelling of axon and axon-glia dysfunction, and reduction of nerve conduction velocity (NCV) [15].

The accumulated glucose enters the hexosamine pathway and produces fructose-6-phosphate which, in turn, is converted to uridine diphosphate-*N*-acetylglucosamine (UDP-GlcNac). GlcNac is one of the sugar moieties used in *N*- or *O*-glycosylation of such translated proteins (posttranslational modification) as the SP-1 transcription factor which leads to overexpression of plasminogen activator inhibitor-1 (PAI-1) and transformation of growth factor-β1 (TGF-β1). As a result, these factors cause the injury of nerves by producing mitochondrial superoxides [24]. Given that, AR inhibitors were highly effective in attenuating DNP in animal models [25]. In contrast, they were not as effective in human clinical studies [26], which was partly due to the administration of much lower doses than in animal *in-vivo* studies. Therefore, not adequate concentrations were reached to prevent the flux via the polyol pathway [25].

Oxidative stress and advanced glycation

The term oxidative stress is used in order to describe the state in which oxidation exceeds the antioxidant capacity in cells due to an imbalance of the enzymatic antioxidant catalase (CAT) and superoxide dismutase (SOD) or non-enzymatic factor glutathione (GSH). As mentioned above, the consumption of NADPH in the polyol pathway has a negative effect on the level of a reduced antioxidant key player, GSH. High level of reactive oxygen species (superoxide $O_2^{\cdot-}$, the hydroxyl radical $OH\cdot$, and hydrogen peroxide H_2O_2) damages the cells' lipid and

proteins. It has been reported that ROS leads to damage of lipids in the myelin sheath [27]. Edwards *et al.* showed that high level of nitrosative products (peroxynitrite $ONOO^-$ and nitrotyrosine NT) in diabetic patients are positively correlated with diabetic peripheral neuropathic pain [28]. Consequently, they would increase the lipid peroxidation, DNA and protein damage rate. Advanced glycation end products (AGEs) are made by non-enzymatic reactions between the damaged DNA, lipids or proteins and aldehyde groups of reducing sugars, which induce ROS production both during their interaction and formation with AGE receptor (RAGE) [7, 29]. Moreover, advanced lipoxidation end products (ALEs) are formed by increased oxidative stress-induced lipid per-oxidation coupled with altered lipid metabolism [30]. NADPH-oxidase, Na^+/H^+ exchanger, 12/15-lipoxygenase, and PKC-β are also among the enzymes involved in ROS production in DNP patients [31–33]. PKC-β plays a central role in nerve function and pathogenesis of DNP [34]. Streptozotocin (STZ)-induced diabetic rats showed the positive effects of PKC-β inhibitor on DNP in reducing free radicals [35].

Mitochondria is the also house for electron transport chain and normally produces a low level of free radicals which are neutralized by antioxidants. In hyperglycemia, the potential of the mitochondrial membrane is disrupted and it releases cytochrome c which activates procaspase 9 together with apoptotic protease activating factor-1 (Apaf-1) cause the activation of apoptotic executioner caspase 3 in neurons [36, 37]. In a study by Zherebitskaya *et al.* on STZ-induced diabetes rat model, high glucose decreased manganese-containing superoxide dismutase (MnSOD) and increased ROS level in axons which mainly caused the impairment in the axons outgrowth and dystrophic structures [38]. The aforementioned data on oxidative stress indicates that controlling ROS level in diabetic patients could be a plausible approach to prevent DNP.

Inflammation

Inflammation is a cellular process activated by an injury in the nerve, skin, spinal cord or dorsal root ganglion (DRG) leading to painful sensation. It is correlated with diabetes and high levels of inflammatory cytokines like C-reactive protein (CRP) and tumor necrosis factor α (TNF-α) in neuropathic patients [39]. Conti *et al.* found that the induction of diabetes with STZ led to the infiltration of immune cells (macrophages and monocytes), the neuronal overexpression of pro-inflammatory cytokines interleukin-1 beta (IL-1β) and expression of neurotrophin receptor p75 (p75 NTR) [40]. The involvement of inflammation in DNP was also confirmed in an animal model with STZ-induced diabetes. It was found that thiazolidinedione pioglitazone altered the expression level of protein kinase C-alpha, decreased phosphorylated extracellular signal-regulated kinases (ERK), and decreased the number of accumulated macrophages in Schwann cells [41].

As a transcriptional factor composed of two subunits of p65 and p50, nuclear factor kappa B (NF-κB) is localized in the cytoplasm in an inhibitory state bound to its inhibitor iκB. Upon simulation, iκB is tagged by ubiquitin for proteasomal degradation leaving NF-κB in an active state. The activated NF-κB is translocated to the nucleus where it promotes the expression of different inflammatory and survival genes. Andorfer *et al.* showed that the p65 subunit of NF-κB is up-regulated in the myelin sheath of neurons in demyelinating polyneuropathies [42]. Ha *et al* showed that hyperglycemia in glial cells activated NF-κB leading to an increase in the level of inflammatory genes (p38MAPK, TNF-α, IL-1β, IL-6, COX-2, iNOS) and cell adhesion genes (Endothelin-1, ICAM-1, and VCAM-1) [43]. Bierhaus *et al.,* localized NF-κBp65 subunit, advanced glycation end-product receptor and IL-6 in sural nerve biopsies collected from diabetic patients [16, 44]. All these findings prove that inflammatory signaling cascades play important roles in the pathogenesis of DNP and makes them interesting pharmacological targets by natural entities.

Trophic factors

Neurotrophic factors promote the normal physiological functions of surviving neurons, increase their resistance to injury, and stimulate nerve regeneration as well, which all improve the clinical condition of DNP patients [45]. Neurotrophin deficiency contributes to the pathogenesis of DNP. Brain-derived neurotrophic factor (BDNF), neurotrophin-3/4/5 (NT-3/4/5), ciliary neurotrophic factor (CNTF) and maybe insulin-like growth factors (IGFs) were all reduced in the muscle of DNP patients [46]. Nerve growth factor (NGF) could attenuate these neurotrophic imbalances [47]. In fact, preclinical studies support the notion that affecting neurotrophic factors by natural products might be effective treatments for many different types of peripheral nerve disease.

Peroxisome proliferator-activated receptors

Peroxisome proliferator-activated receptors (PPAR) belong to nuclear hormone receptor proteins. Bound to the lipophilic stimulant, PPAR, induces the expression of proximal genes involved in β-oxidation of fatty acids, proximal proliferation, lipid hemostasis and hepatocarcinogenesis [48, 49]. α, β/δ, and γ are the main three subtypes of PPARs which play a critical role in controlling the metabolism, storage, and mobilization of lipids, glucose, morphogenesis and inflammatory processes [50][49, 51]. PPARs cooperate with other cellular transcription factors such as NF-κB, signal transducer/activator of transcription-1 (STAT-1) and activated protein-1 (AP-1) [51]. PPARs repress the expressions of pro-inflammatory genes (IL-1β and TNFα), and chemokines (MCP-1 and CCR2) and reduce the pain sensation [52]. As

insulin-sensitizing drugs, PPAR gamma (PPARγ) agonists (e.g. pioglitazone and rosiglitazone), are widely recommended for the treatment of insulin resistance-hyperglycemia [53] and to attenuate spinal nociceptive neuron activation in type II diabetic rats [54]. The recent clinical application of PPARs agonist provides a promising future to evaluate their potential as novel analgesics in the treatment of different chronic pain conditions such as DNP. However, it is important to note their potential adverse effects while targeting the PPAR signaling system as analgesics [55]. These results make necessary the research for natural PPAR agonists in order to reduce the DNP.

Channels activation

The transient receptor potential vanilloid 1 (TRPV1) channel is involved in various modalities of nociceptive stimuli. In a STZ-induced painful DNP, TRPV1 expression was significantly increased in hyperalgesic compared to hypoalgesic and normoalgesic skin [56, 57]. Studies showed that early stages of DNP are due to up-regulation of TRPV1 by PKC and PKA [58]. It indicated the key role of TRPV1 channels in the expression of hyperalgesia [58]. Other TRPV receptors have not been yet investigated enough in DNP [59]. In general, TRPV might be considered as a promising therapeutic target to develop new treatments for DNP. Activation of TRPV1 evoked [Ca^{2+}] transients and also reciprocally alters in hyperalgesia [58]. Thus, calcium channels (Cav) are thought to be involved in painful DNP [60]. The alpha(2)delta subunits increase the expression and trafficking of these channels, but may also play a role in synaptogenesis within the central and peripheral nervous system [61]. In addition to Cav, voltage-gated sodium channels (Nav) have also been shown to increase at the site of neuronal damage in DNP [62]. Methylglyoxal, as an AGE, increased in the serum of painful DNP patients, and causes the thermal and mechanical hyperalgesia when injected into diabetic mice (not in sodium channel Nav1.8 knockout mice) [63]. These all show the importance of TRPV1, Nav and Cav channels by multi-target natural products on the development of DNP. Besides, targeting TRPV1 is co-expressed with glutamate receptors [64].

Glutamate pathway

Glutamate plays a crucial role such processes as the synapse plasticity, cell differentiation, cell migration, death [65] and peripheral transduction of sensory inputs in the central nervous system (CNS) [66]. Several studies have shown the involvement of glutamate-mediated toxicity in both acute and chronic neurodegenerative diseases of CNS and PNS [67]. Glutamatergic ligands cause nociceptive behaviors, which suggests that glutamate is involved in nociceptive pathways and peripheral sensory transduction. On the other hand, hyperglycemia significantly increased the expression of N-methyl-D-aspartate (NMDA) receptors in a mice model of type I diabetes [68]. The role of spinal NMDARs has also been demonstrated in nerve injury-induced pain [69]. Spinal NMDAR subunit 2B (NR2B) was upregulated in both protein and mRNA levels of STZ-induced DNP resulting in the hyperactivity of spinal cord dorsal horn neurons [70]. Glutamate, especially NR2B, trigger cascades of oxidative stress, inflammation, and apoptosis [71] which are among the important pathways involved in DNP. For the same reason, targeting the glutamate pathway and NR2B as upstream factors of oxidative, inflammatory and apoptotic pathways by natural entities is very promising to combat DNP.

Conventional pharmacotherapy of painful DNP

There are different drugs proposed for treating or controlling DNP complications. Conventional treatments for neuropathic pain include tricyclic antidepressants (TCA, e.g., nortriptyline or amitriptyline), serotonin-norepinephrine reuptake inhibitor (SNRI, e.g., duloxetine), anticonvulsants therapies (e.g., gabapentin, pregabalin), and the dual-effect drug tapentadol (an opioid receptor agonist and norepinephrine reuptake inhibitor) which are used to treat neuropathy induced disorders [72]. Other medications like opioids (e.g., Tramadol) are also prescribed but not recommended [19]. A recent systematic review and network meta-analysis of the randomized controlled trial confirmed the effectiveness of SNRIs, TCAs, anticonvulsants and topical capsaicin in painful DNP. Moreover, SNRIs had a greater effect on attenuating the pain than the opioids and anticonvulsants [73].

Nevertheless, there is no definitive treatment for DNP with most potency and less side effects. Thus controlling the blood sugar can significantly alter the course of neuropathy. Of another point of view, many of these agents have a number of serious adverse effects. This necessitates the search for effective and safe medications among which herbal medicine is a potential regimen for diabetes and diabetes-related complications such as neuropathy [74, 75].

Polyphenols as alternative therapies for DNP

The ethnobotanical data indicates that there are about 800 plants that may possess anti-diabetic properties. Several herbal treatments including curcumin, kaempferol, quercetin, naringenin, resveratrol, kolaviron, *etc* have been so far administered for DNP patients. But, first it is necessary to identify DNP syndromes some of which are potentially treatable by traditional herbal medicine.

Therefore, the current review has attempted to provide a helpful classification of herbal medicine used in the management of DNP. Most relevant pharmacological targets and cellular signaling involved in the therapeutic effect of polyphenols in diabetic DNP are as follows:

Enzymatic and non-enzymatic antioxidant performance

Hyperglycemia reduces the activity of antioxidant enzymes in diabetic animals with non-enzymatic glycosylation and causes oxidative stress [76]. Due to the induction of some damaging effects like free radical generation via ischemia, hyperglycemia, increased mitochondrial leak, catecholamine and leukocytes oxidation, decrease of glutathione peroxidase (GPx), glutathione-S-transferase (GST), Cu/Zn SOD and lower levels of GSH, oxidative stress plays a major destructive role in the development of DNP [76–79]. Several antioxidants specially polyphenols have shown some activities promising for the treatment of experimental DNP. Treatment with α-lipoic acid prevents neurovascular abnormalities in experimental DNP. It also attenuates reduced digital NCV, nerve blood flow and GSH levels in diabetic rats by enhancing oxygen free radical scavenging activity [80, 81]. On the other hand, probucol, as an LDL-oxidation inhibitor, and a powerful free radical scavenger, normalizes both nerve blood flow and electrophysiology [82].

Al-Rejaie *et al*. reported that naringenin possesses antioxidant activity. It also suppressed the levels of thiobarbituric acid reactive substances (TBARS) and nitric oxide (NO), and attenuated the reduced level of CAT, and GPx in STZ-induced diabetic rats [83, 84]. As another polyphenol, resveratrol protected neural tissues against diabetes-induced oxidative stress either by reducing NO, XO, MDA levels of the cerebellum, hippocampus, cortex, spinal cord and brain stem by enhancing GSH level in diabetic rats [85]. Curcumin and apocynin also attenuated the increased level of spinal H_2O_2 and MDA level and enhanced SOD level in STZ-induced diabetic rats, as indicated by Zhao *et al*. It has also been demonstrated that curcumin inhibited the activation of spinal NADPH oxidases, the main enzymes that produce ROS by reversing the upregulation of both phagocyte NADPH oxidase subunits ($p47^{phox}$ and $gp91^{phox}$) [86].

More relevant pharmacological targets and cellular signaling involved in antioxidant effect of polyphenols in DNP are shown in Table 1.

Prevention of pro-inflammatory cytokines and inflammatory reaction

Pro-inflammatory changes observed in diabetes play a major role in the pathogenesis of atherosclerosis, neuropathy, nephropathy, and retinopathy [87]. Generation of hyperglycemia-induced ROS is directly involved in the pathogenesis of DNP. These radical oxygen species may cause the production of TNF-α and IL-1β. Hyperglycemia and insulin resistance are associated with TNF-α system in the CNS which may induce pain and hyperalgesia in DNP [88–90]. Moreover, studies showed that inhibiting TNF-α reduced hyperalgesia in models of painful DNP [91]. Meanwhile, it has been demonstrated that intraplantar injection of TNF-α is associated with mechanical allodynia and thermal hyperalgesia in rats [17, 88, 92]. IL-1β is derived from many cell types, like fibroblasts, synoviocytes, mononuclear cells, schwann and endothelial cells, and plays a central role in the generation of mechanical hyperalgesia. It also neutralized IL-1 receptors, which in return, reduced the pain-associated behavior in mice model of experimental neuropathy [93–95].

Hyperglycemia and higher lipid level lead to NF-κB activation that plays a central role in TNF-α and ROS production inducing inflammatory demyelination. It has been reported that NF-κB may elevate in metabolic diseases like diabetes and initiates inflammation [96]. P65 and IκB-α are among the subunits of NF-κB which are overexpressed in sural nerve macrophages in acute and chronic inflammatory demyelinating polyneuropathies [42, 97].

Kumar and Sharma demonstrated that resveratrol possessed anti-inflammatory activity by decreasing the expression of p65 and IκB-α and ameliorating the elevated levels of TNF-α, COX-2, IL-6, and NF-κB in STZ-induced DNP in rats [98]. In addition, resveratrol significantly decreased the serum glucose level, atherogenic index, and the expression of cerebral MDA and COX-2 [99].

As revealed by Deng *et al*., carvacrol (25, 50, and 100 mg/kg) diminished STZ-induced DNP via decreasing the level of NF-κB p65 subunit, IL-1β, caspase-3, and TNF-α [100]. As another polyphenol, kaempferol attenuated STZ-induced DNP by decreasing the levels of IL-1β and TNF-α and suppressing the formalin-induced nociceptive behavior. It also ameliorated LPS-induced inflammatory mediators (NO, prostaglandins, TNF-α, IL-1β, ROS and phagocytosis) in the microglial cells [101, 102]. More relevant pharmacological targets and cellular signaling involved in the anti-inflammatory effects of polyphenols in DNP have been shown in Table 1.

Anti-nociceptive effects

Hyperglycemia-triggered lipid peroxidation and ROS generation in sciatic nerves, accelerated the dysfunction of sciatic nerves and reduced endoneurial blood flow in diabetes-induced neuropathy. Painful DNP can occur as spontaneously, hyperalgesia or allodynia. Neuropathic pain is one of the most common diabetic complications induced by abnormal function of the peripheral or central nervous system and results in sensory abnormalities, changes of primary afferent nerves, and central sensitization. Studies have demonstrated the effectiveness of γ-aminobutyric acid (GABA) and opioids, TCAs,

Table 1 Polyphenols as alternative therapies for DNP

Polyphenol name	Animal models and Tests	Dosage/day	Outcome	References
Astragaloside IV	STZ-induced diabetes rats	3, 6 & 12 mg/kg BID for 12 weeks, p.o.	↑Myelinated fiber area, myelinated fiber density & segmental demyelination ↓HbA1C levels ↑MNCV & GPx ↓AR in erythrocyte ↑ Na^+/K^+ ATPase activity in both the nerves and erythrocytes	[120]
Bacosine	Mechanical & thermal hyperalgesia, tactile allodynia & hot plate test in STZ-induced diabetes rats	5 & 10 mg/kg for 30 days, p.o.	diabetes-associated cognitive deficit ↓Hyperalgesia ↑MNCV ↓ AGEs & ROS	[190]
Carvacrol	Morris water maze and biochemical evaluations in STZ-induced diabetic rats	25, 50 & 100 mg/kg for 7 weeks, i.p.	↓MDA ↑SOD ↓IL-1β &TNF-α	[100]
Chlorogenic acid	Formalin-induced pain model in STZ-induced diabetic rats	100 mg/kg, i.p.	↑Mechanical hyperalgesia threshold ↓Formalin-induced nociceptive behavior	[108]
Chromane	Tail-immersion test and hot-plate test in STZ-induced diabetic rats	5 & 10 mg/kg for 30 days, p.o.	↓Thermal hyperalgesia & mechanical allodynia, ↑paw withdrawal threshold ↑MNCV ↓AGEs & ROS	[107]
Curcumin	Mechanical allodynia, Hot plate & tail flick test in STZ-induced diabetic rats	100 mg/kg, p.o. for 6 weeks	↓Thermal nociception ↑Paw withdrawal threshold & tail flick latency ↓TNF-α & IL-10	[111]
	Hot plate test, allodynia and Rota-rod test in STZ-induced diabetic rats	200 mg/kg, p.o. for 3 weeks	↓Thermal hyperalgesia & mechanical allodynia ↑Paw withdrawal threshold ↓COX & prostaglandin peroxidase ↓AR	[112]
	Mechanical allodynia in STZ-induced diabetic rats	200 mg/kg, p.o. for 14 days	↑Paw withdrawal threshold ↓MDA, H_2O_2 in the spinal cord ↑SOD	[86]
Curcumin & gliclazide	Hot-plate & tail-flick test in STZ-induced diabetic rats	100 mg/kg, p.o. for 5 weeks	↑Mechanical hyperalgesia threshold ↑Hot-plate & tail-flick latencies ↓peroxynitrite, LPO & TNF-α	[110]
Curcumin & resveratrol	Tail-immersion test & hot- plate test in STZ-induced diabetes	Resveratrol 20 mg/kg & curcumin 60 mg/kg, p.o. for 4 weeks	↑Nociceptive threshold ↓TNF-α ↓brain nitrite level	[191]
Diosmin	Tail immersion test & walking function test in STZ-induced diabetes	50 & 100 mg/kg p.o. for 4 weeks	↑Tail flick latency, ↓duration for traveling ↑SOD & GSH ↓MDA & NO	[114]
Epigallocatechin-gallate	Tactile allodynia & mechanical hyperalgesia in STZ-induced diabetes	2 g/L, p.o.	↓Thermal hyperalgesia & mechanical allodynia ↑Paw withdrawal pressure ↓8-OHdG immunoreaction, numbers of Fos-immunoreacted neurons & co-localization of 8-OHdG and Fos in laminae I–III	[192]
Epigallocatechin-gallate	Tail immersion test & formalin-induced pain in STZ-induced diabetic rats	20 & 40 mg/kg, p.o. for 7 weeks	↑Tail flick latency & nociceptive threshold ↓Formalin-induced nociceptive behavior ↓Nitrite ↓TBARS, MDA & ↑SOD	[106]
Grape seed proanthocyanidins	Hot plate test in STZ-induced diabetic rats	125, 250 & 500 mg/kg, p.o.	↑Hot-plate latency ↑Nerve conduction velocity ↓Concentration of free Ca^{2+}, ↑ATPase activities in sciatic nerves	[121]
Hydroxytyrosol	Hot plate paw withdrawal and Randall–Selitto paw withdrawal tests in STZ-induced diabetes	10 & 100 mg/kg, p.o. for 6 weeks	↓Thermal nociception ↑Paw withdrawal threshold ↑MNCV ↑ Na^+/K^+ ATPase activity	[193]

Table 1 (continued)

Polyphenol name	Animal models and Tests	Dosage/day	Outcome	References
Kaempferol	Formalin-induced and tail immersion test in STZ-induced diabetic mice	25, 50 & 100 mg/kg, p.o.	↓Formalin-induced nociceptive behavior in phase 1, phase 2 & edema size ↓Hyperalgesia, ↑thermal pain threshold, ↓IL-1β, TNF-α, LPO & nitrite	[102]
Kolaviron	STZ-induced diabetic rats	100 & 200 mg/kg, p.o. for 6 weeks	↓Oxidative stress ↓IL-1β & TNF-α ↑GSH, CAT & GPx ↓MDA, TBARS	[194]
Morin	Tail flick test in STZ-induced diabetic rats	15 & 30 mg/kg, p.o. for 3 weeks	↑Paw-withdrawal & tail flick latency ↑NGF & IGF-1 in sciatic nerves ↓IL-1β, TNF-α & LPO	[118]
Mulberry flavonoids	ALX- induced diabetic rats	0.3 & 0.1 g/kg, p.o. for 8 weeks	↓Peripheral nerve injury & numbers of extramedullary fiber of sciatic nerves ↓myelin breakdown & myelinated fiber cross-sectional area	[195]
Naringenin	Tail-flick, Randall & Selitto tests in STZ-induced diabetic rats	25 & 50mg/kg, p.o. for 5 weeks	↑Paw-withdrawal & tail-flick latency ↑NGF & IGF-1 in sciatic nerves ↓IL-1β & TNF-α ↑CAT, GSH & GPx	[84]
Naringin	Mechanical hyperalgesia, tactile allodynia & tail-immersion test in STZ-induced diabetic rats	40 & 80 mg/kg, p.o. for 4 weeks	↓Mechano-tactile allodynia ↑Nociceptive threshold & tail flick latency ↑MNCV ↑SOD ↓oxidative-nitrosative stress & TNF-α	[83]
Oryzanol	Hot-plate test & Tail-immersion test in STZ-induced diabetic rats	50 & 100 mg/kg, p.o.	↑Pain threshold & hot plate latency ↓Flinching in diabetic rats during both quiescent phase & phase 2 but not in phase 1 ↓Nitrite, MDA ↑GSH Attenuating Na+-K+ ATPase	[113]
Pepino polyphenolic extract	STZ-induced diabetic mice	0.5 or 1% for 12 weeks	↓TNF-α & IL-6 ↑GSH & GPx ↓AGEs &ROS ↑fascicle with numerous small myelinated fibers	[196]
Quercetin	Tail-flick test, Hot-plate method & the walking function test in STZ-induced diabetic rats	40 mg/kg, p.o. for 2 weeks	↑Tail-withdrawal latency & hot plate and cold allodynia latency ↓Number of foot slips	[75]
	Mechanical hyperalgesia, tactile allodynia & tail immersion test in STZ-induced diabetic rats	10, 20 & 40 mg/kg, p.o. for 8 weeks	↓Thermal hyperalgesia & mechanical allodynia, ↑MNCV ↑SOD & GPx, ↓TNF-α &IL-1β	[103]
	Tail-immersion assay in STZ-induced diabetic rats	10 mg/kg, p.o. for 4 weeks	↑Tail-flick latencies & nociceptive threshold in both diabetic and non-diabetic mice	[104]
	Tail-immersion assay & hot-plate test in STZ-induced diabetic rats	10 mg/kg, p.o. for 4 weeks	↓Thermal nociception ↑tail-withdrawal latencies & nociceptive threshold	[197]
Resveratrol	Cold immersion & hot immersion tests in STZ-induced diabetes rats	10 & 20 mg/kg, i.p. for 2 weeks	↑Tail flick latency & paw withdrawal pressure ↑MNCV ↓MDA ↑CAT	[98]
	STZ-induced diabetic rat	10 & 20 mg/kg, i.p. for 2 weeks	↑MNCV ↓MDA ↓p65, IκB-α & NF-κB ↓TNF-α, IL-6 & COX-2	[198]
	Cerebral ischemia-reperfusion in STZ-induced diabetic rats	20 mg/kg, p.o. for 6 weeks	↓Cerebral MDA & COX-2 ↑cerebral IL-4 ↑cerebral GSH contents	[99]
	STZ-induced diabetic rats	10 mg/kg, i.p. over 6 weeks	↓MDA, XO & NO	[85]

Table 1 (continued)

Polyphenol name	Animal models and Tests	Dosage/day	Outcome	References
			↑GSH in hippocampus, cortex, cerebellum, brain stem & spinal cord	
	Tail-immersion test in STZ-induced diabetes	20 mg/kg, p.o. for 2 weeks	↑Tail withdrawal threshold & tail withdrawal latencies	[199]
Silymarin	Tail-immersion test & formalin-induced pain test in STZ-induced diabetic rats	100 & 200 mg/kg, i.p. for 8 weeks	↑Tail flick latency ↓Nociceptive scores in both phases of the formalin test	[200]
6-Methoxyflavanone	Hot plate test in STZ-induced diabetic rats	10 & 30 mg/kg, i.p.	↓Thermal nociception, ↑paw withdrawal threshold & latency ↑flinching response threshold & latency by a preference for the δ- & κ-opioid receptors, involvement of GABA receptors	[109]
7-Hydroxy-3,4-dihydrocadalin	Formalin-induced pain & tactile allodynia in STZ-induced diabetic rat and mice	0.3–30 and 30-300 mg/kg, p.o.	↓Mechanical hyperalgesia and allodynia & formalin-evoked hyperalgesia ↑withdrawal threshold ↓MDA	[116]

DNP Diabetic neuropathy; *STZ* Streptozotocin; *ALX* alloxan; *TNF-α* Tumor necrosis factor-α; *IL-10* Interleukin-10; *MDA* Malondialdehyde; *GABA* Gamma-Amino Butyric Acid; *GPx* Glutathione Peroxidase; *CAT* Catalase; *GSH* Glutathione; *NGF* Nerve growth factor; *IGF-1* Insulin-Like Growth Factor; *XO* Xanthine oxidase; *NO* Nitric oxide; *NOS* neuronal Nitric oxide synthase; *SOD* Superoxide dismutase; *MNCV* Motor nerve conduction velocity; *AGEs* Advanced glycation end products; *AR* aldose reductase; *ROS* Reactive oxygen species; *8-OHdG* 8-hydroxy-2′-deoxyguanosine; *LPO* Lipid peroxidation; *TBARS* thiobarbituric acid reactive substances; *COX* Cyclooxygenase; *p.o.* per-oral; *i.p.* intraperitoneal

gabapentin, pregabalin, phenytoin, lamotrigine, dextromethorphan, and tramadol on painful sensory neuropathy. Although these therapies would relieve the pain 30–50%, they are often restricted due to significant side effects [87]. So, it raises the needs to polyphenols as alternative therapies.

As concluded by Kandhare *et al*., quercetin inhibited a significant increase of paw withdrawal threshold (PWT) in STZ-induced diabetic rats in a plantar heat hyperalgesia test that was evaluated by Hargreaves' test. In addition, it significantly increased the mechanical PWT, compared to STZ-diabetic control rats on a Randall-Selitto paw pressure device [103]. It has also been shown that quercetin (100 mg/kg, p.o) increased the tail withdrawal latency in both diabetic and non-diabetic mice [104]. Besides, it has significantly increased the tail and paw withdrawal latency and decreased the number of foot slips of STZ-induced diabetic rats in a dose-dependent manner, compared to normal control [75, 105, 106].

Studying the anti-nociceptive effect of other polyphenols, Kaur *et al*., showed that chromane significantly corrected the decreased PWT of STZ-induced diabetic rats in tail-immersion and hot-plate tests, compared to the control group [107]. Chlorogenic acid and 6-methoxy flavanones also increased the thermal and mechanical PWT in diabetic rats, respectively [108, 109].

As Attia *et al*. articulated, the combined administration of curcumin and gabapentin caused a significant increase in the mechanical PWT as well as hot-plate and tail-flick latencies in STZ-induced diabetic rats [110]. Curcumin showed significant pain threshold elevations, increased reaction times and tail-flick response latencies [111]. Treatment with curcumin also enhanced the anti-nociceptive activity in hot-plate and allodynia- tests in STZ-induced DNP via increasing pain threshold level compared to untreated diabetic rats [112]. Oryzanol and diosmin both significantly increased the tail-flick latency in tail-immersion test and reduced the thermal hyperalgesia in STZ-induced diabetes [113]. In addition, diosmin treatment significantly improved shortening of time on walking function test in diabetic rats [114].

Kumar *et al*., demonstrated that the decrease of PWT and tail flick latency in cold and hot immersion performance was significantly corrected by resveratrol treatment at 10 and 20 mg/kg [98]. As two other polyphenols, silymarin and 7-hydroxy-3,4-dihydrocadalin caused a significant decrease in pain scores of the formalin-test [115, 116].

More relevant pharmacological targets and cellular signaling involved in anti-nociceptive effects of polyphenols in DNP are shown in Table 1.

Improvement of nerve growth factors

There are complex mechanisms behind the DNP involving several molecule alterations and sensory modalities.

Several neurotrophic factors have been found to effects the population of specific neurons in the nervous system, among the most promising ones is NGF [45]. Evidence suggests that DNP could be modulated by neurotrophins like transient receptor potential ion channels, including vanilloid receptor 1 (VR-1) in one hand and nerve growth factor (NGF), such as its receptors p75 and tyrosine kinase A (TrkA) as well as their down streams on the other hand. It has been well-documented that NGF has an important neuroprotective function and causes axonal growth. Pathological conditions that alter the levels of NGF can cause neurons to lose their function and die. After inflammation and nerve injury, NGF increases in the nervous system and facilitates hyperalgesia and pain that can be reduced by anti-NGF therapy. The complex of TrkA and NGF sensitizes VR1 thereby elevates pain. Following the binding of NGF to TrkA as related receptor, nerve regeneration, cell survival, and neurite-growth pathways will begin [117].

As a structurally similar hormone to insulin, IGF-1 plays an auspicious anabolic role in cellular proliferation and growth. It has also been considered as a strong inhibitor of apoptosis. It also controls the growth and development of nerve cells and DNA synthesis, as well [118]. It has been demonstrated that sciatic nerve levels of NGF and IGF-1 in morin treated diabetic animals significantly elevated in comparison with the negative control group [118].

As indicated by Song-Tao *et al*., mulberry flavonoids and methycobal alleviated the suppression of the average optical density of myelin sheath and myelinated extramedullary fiber cross-sectional area in diabetic rats. Furthermore, animals pretreated with 0.3 g/kg mulberry flavonoids showed ultrastructural features of myelin, remarkable axonal improvement and considerable decrement of myelin breakdown [119]. Astragaloside IV, as another polyphenol, suppressed a decrease in myelinated fiber area and density and segmental demyelination in diabetic rats by decreasing the hemoglobin A1c (HbA1C) and AR levels in erythrocytes, increasing the plasma insulin levels, and GPx activity in nerves. Moreover, astragaloside IV elevated Na^+/K^+-ATPase activity in both nerves and erythrocytes in STZ-induced diabetic rats [120].

Ding *et al*., showed that grape seed proanthocyanidins treatment (500 mg/kg dose) improved the abnormal function of peripheral nerve and impaired nerve tissues. They also showed that it reduced the NCV level and concentration of free Ca^{2+}, elevating Ca^{2+}-ATPase activity in sciatic nerves [121]. Diabetic rats treated with curcumin attenuated the reduction of sciatic nerve Na^+/K^+ ATPase activity compared to normal control. In addition, curcumin treatment of diabetic rats has shown a gradual recovery of cyclooxygenase activity in sciatic nerve [122].

Glutamate pathway and NMDA receptors

As previously mentioned, glutamate receptors and ligands are thought to be involved in nociceptive behaviors in experimental models of DNP. It seems that glutamate and the NMDA receptor are involved in nociceptive pathways and peripheral sensory transduction [123]. NMDA receptors are coupled to mitogen-activated protein kinase (MAPK) and ERK phosphorylation and activation in the superficial laminae of the spinal cord which can be suppressed by NMDA receptor antagonist treatment [124–126]. In painful DNP, NMDA receptor ion channel-mediated calcium entry play a key role for the activation of MAPK and ERK pathways [123].

Resveratrol prevents glutamate damages by blocking the NMDA receptor and suppressing glutamatergic neurotransmission [127, 128]. To prevent diabetic retinopathy, it significantly decreased glutamine synthetase, transportation, and expression, [129]. Resveratrol inhibits microglia activation, mitochondrial dysfunction, intracellular ROS production and impairments in Na^+/K^+-ATPase [130, 131]. It also down-regulates a glutamate-induced tissue plasminogen activator via ERK and AMPK/mammalian target of rapamycin (m-TOR) pathways and decreases MAPK activation, which subsequently suppresses the voltage-dependent Ca^{2+} channel activity and inhibits evoked glutamate release [132, 133]. Similar to resveratrol, piceatannol induces the expression of nuclear factor erythroid 2–related factor 2 (Nrf2)-dependent and heme oxygenase-1 (HO-1) and thereby, protects HT22 neuronal cells against glutamate-induced cell death [134].

As another polyphenol, chlorogenic acid in coffee protects neurons from glutamate neurotoxicity through its caffeoyl acid group, and its hydrolysate, the caffeic acid by regulating Ca^{2+} entry into neurons [135, 136].

Protection of motor neuron by epigallocatechin-3-gallate is associated with regulating glutamate level [137]. It inhibits glutamate dehydrogenase in pancreatic ß-cells and activates AMPK to positively affect diabetes [138]. It also reduces the glutamate-induced Ca^{2+} increase by attenuating PKC and ionotropic Ca^{2+} influx [139, 140], as quercetin does [141].

Curcumin attenuated NMDA receptor-mediated excitotoxicity in diabetic rats [142], ameliorated both glutamate level and gene expression of NR2B [143, 144], and prevented intracellular Ca^{2+} elevation [145]. In addition, it affected PI3K/AKT pathway and downstream signaling through TrKβ and BDNF, possibly by decreasing MAPK/ERK activation [146, 147].

Since, Apigenin 8-C-glucoside, chlorogenic acid, and naringin regulate glutamate pathway [148, 149] and astragaloside IV and kaempferol attenuate glutamate-induced toxicity and oxidative stress [150, 151], they could be good options for preventing DNP complications (Table 1).

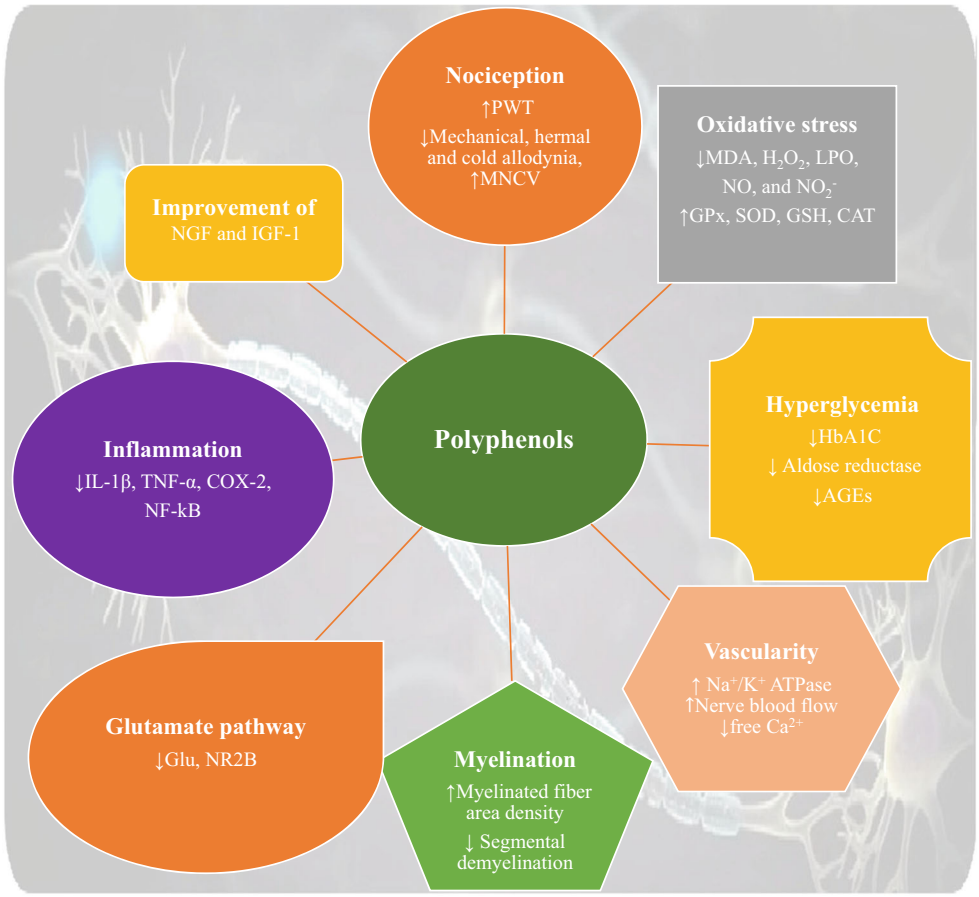

Fig. 1 General effects of polyphenols on DNP. PWT: Paw withdrawal threshold, NGF: Nerve growth factor, IGF-1: Insulin-like growth factor-1, MDA: Malondialdehyde, H_2O_2: Hydrogen peroxide, LPO: Lipid peroxidation, NO: Nitric oxide, XO: Xanthine oxidase, GPx: Glutathione peroxidase, SOD: Superoxide dismutase, GSH: Glutathione, CAT: Catalase, IL: Interleukin, TNF-α: Tumor necrosis factor-α, COX: Cyclooxygenase, HbA1C: Hemoglobin A1C, Glu:Glutamate, NMDA: n-methyl-D-aspartate, NR2B: NMDA type 2B, MNCV: Motor nerve conduction velocity, AGEs: Advanced glycation end products

More relevant pharmacological targets and cellular signaling involved in the therapeutic effect of polyphenols in DNP have been shown in Table 1, Figs 1 and 2.

Therapeutic applications and health benefits of polyphenols: Diabetes, DNP and beyond

Polyphenols benefit human health status and play promising roles in the management, prevention and treatment of several chronic diseases, including cardiovascular disease, cancer, obesity, pancreatitis, gastrointestinal problems, osteoporosis, lung damage, neurodegenerative diseases, and gut microbiota based on their antioxidant and anti-inflammatory effects [152–157]. Polyphenols have an auspicious role against several inflammation-mediated diseases through inhibiting inflammatory mediators and signaling pathways [158], as we described previously. Polyphenols also induce cell apoptosis and arrest cellular growth in order to be tumor suppressors [159].

Several studies reported that resveratrol prevents platelet aggregation and decreased blood pressure and low-density lipoprotein (LDL) cholesterol as well [11, 160–163]. Of the compounds contain the polyphenol curcumin, it was hypothesized to contribute to the low incidence of cognitive impairment and Alzheimer's disease in individuals with a high rate of consumption [164]. Randomized-controlled trial studies reported that polyphenolic compounds reduce the differentiation, proliferation and genesis of adipocytes [165]. Catechin polyphenols, have been linked to antioxidant, anti-inflammatory, and anti-mutagenic properties and thought to prevent weight gain by promoting greater fat oxidation and energy expenditure [166–169]. Resveratrol has also shown anti-obesogenic properties in both animal and human studies [170]. Curcumin has been shown to reduce adiposity through suppressed angiogenesis, reducing inflammation, and increasing energy metabolism [171]. Of the gastrointestinal benefits, polyphenol may inhibit invasive species while promoting beneficial gut bacteria, may promote beneficial actions of probiotics with unknown mechanisms [172–174]. Evidence

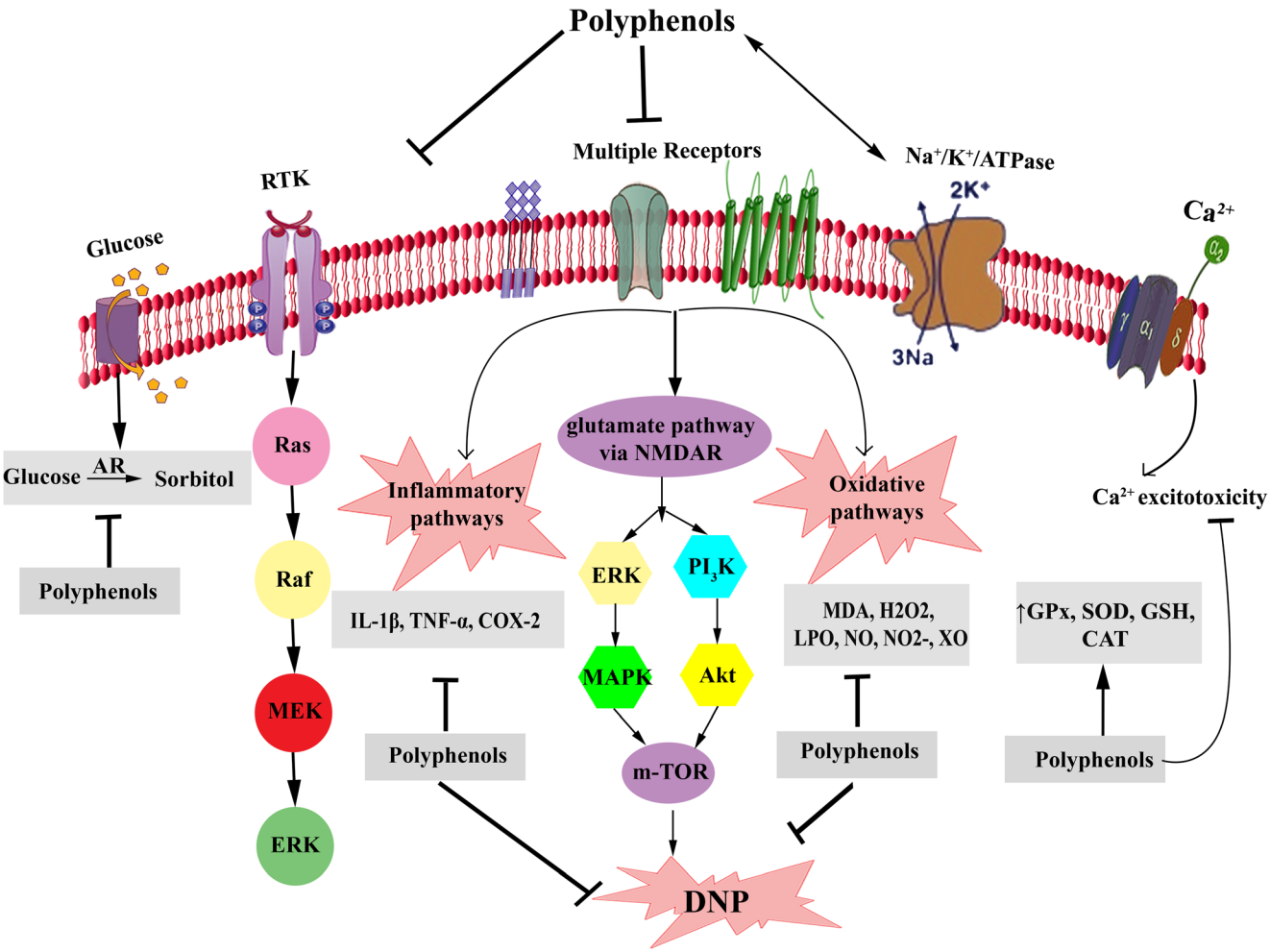

Fig. 2. Polyphenols mechanisms of action in DNP. DNP: Diabetic neuropathy, AR: Aldose reductase, RTK: Receptor tyrosine kinase, NGF: Nerve growth factor, IGF-1: Insulin-like growth factor-1, MDA: Malondialdehyde, H2O2: Hydrogen peroxide, LPO: Lipid peroxidation, NO: Nitric oxide, XO: Xanthine oxidase, GPx: Glutathione peroxidase, SOD: Superoxide dismutase, GSH: Glutathione, CAT: Catalase, IL: Interleukin, TNF-α: Tumor necrosis factor-α, COX: Cyclooxygenase, NMDAR: n-methyl-D-aspartate receptor, MAPK: mitogen-activated protein kinase, ERK: extracellular signal-regulated kinases, m-TOR: Mammalian target of rapamycin, Activation ↑, Modulation: ↕ Inhibition ⊥

suggests modulatory potential impacts of polyphenols on chronic disease risk, such as the hepatoprotective and atheroprotective effects and improving insulin sensitivity [175–177].

Although, there are yet limited human studies to tackle diabetic chronic complications by polyphenols, purified polyphenols, as well as diets rich in polyphenols, also prevent the progress of human chronic complications in diabetes like DNP [178, 179]. As inflammation, oxidative stress, trophic factors, channels, and glutamate pathway are the main signaling mediators and pathways associated with DNP, so polyphenols with anti-inflammatory and antioxidant effects could carry out their significant health benefits through tackling them in diabetes. In the clinical trial testing, curcumin attenuated inflammatory mediators like TGF-β and IL-8 [180] as well as oxidative stress markers including lipid peroxidation and MDA [181], thereby could be a promising polyphenol to combat DNP. In type II diabetic patients, resveratrol [182], berberine [183, 184] and catechin [185] resulted in a decrease in insulin resistant and an increase in insulin level. A meta-analysis of clinical studies in diabetic patients showed that cinnamon or cinnamon extracts decrease fasting blood glucose levels [186]. As high blood glucose level leads to the activation of AR enzyme of the polyol pathway in DNP [21], so resveratrol, catechin and cinnamon could be effective compounds to combat DNP. As another polyphenol, ginger in addition to blood glucose lowering effects it also decreased inflammation and oxidative stress in patients with type II diabetes [187, 188]. Growing evidence have revealed positive effects of various dietary polyphenols on blood glucose and polyol pathway, oxidative stress, and inflammatory mediators may also help prevent and control diabetes complication as DNP, however, more clinical trials are needed [189].

Conclusion and future perspective

As the most distressing complication of diabetes, DNP affects more than 30% of diabetic people worldwide. There are increasing types of diabetes-induced peripheral nerve injury, including autonomic and small fiber predominant neuropathy, diabetic amyotrophy, radiculopathy, mononeuropathy and mononeuritis multiplex. The pathogenesis of DNP is multifactorial with the main categories being metabolic and ischemic. Although opioid therapy and neuromodulating medications, including TCA and anticonvulsants have been found to be effective in the treatment of neuropathic pain, the high costs associated with social and personal healthcare of DNP in one hand, and lack of consistently effective and safe treatment for DNP on the other hand rise the needs to develop novel herbal therapies to improve the life quality of individuals with DNP [201]. Among natural entities, several evidence indicated that polyphenols possess protective effects via antioxidant and anti-inflammatory pathways. Polyphenols are multi-target agents [10] with different structures, signaling pathways and physiological roles possessing the rich antioxidants and anti-inflammatory effects. They have the potentials to combat several chronic diseases like diabetes and its complications with less toxicity *in-vitro* and in animal models, so play a vital role in human health [11, 12]. These features have made polyphenols an emerging area of interest in nutrition [202, 203]. The current review, introduced polyphenols as strong multi-target compounds to tackle DNP through affecting different signaling pathways with fewer side effects. The findings affirm that herbal treatments such as curcumin, kaempferol, quercetin, naringenin, resveratrol, kolaviron, and *etc* may positively effect in the management of DNP.

Further area of research on novel pathogenicity signaling pathways of DNP as well as the safety and efficacy of polyphenols in human, will expand the more potential applications of polyphenols in the management, prevention, and treatment of several diseases. However, more studies are still needed to introduce more effective treatments for DNP.

Compliance with ethical standards

Conflicts of interest The authors stated no conflicts of interest

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