**ANNALS OF MULTIDISCIPLINARY RESEARCH, INNOVATION AND TECHNOLOGY (AMRIT)**

**(A peer-reviewed open access multidisciplinary journal)**

www.adtu.in/amrit

**REVIEW ARTICLE**

DIABETIC NEUROPATHY MANAGEMENT

# Emerging Natural and Synthetic Compounds in the Management of Diabetic Neuropathy: Targeting Oxidative Stress and Inflammation

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Article Chronicle: Received: 14/06/24 Accepted: 28/06/24 Published: 30/06/24

**Abstract**

Diabetic neuropathy (DN) is a prevalent and threatening complication of diabetes, characterized by nerve damage resulting from chronic hyperglycemic conditions. Key factor in the pathogenesis of DN includes oxidative stress and inflammation, contributes to cellular damage (CD). Oxidative stress, chromatized by imbalance between pro-oxidants and antioxidants, leads to CD, while inflammation driven by pro-inflammatory cytokines, exacerbates the damage. Various factors, such as hyperglycemia-induced DNA damage, activation of transcription factors like NF-kB and Nrf2, and dysregulation of cytokine production contribute to the progression of DN. In this context, natural products and/or synthesized small molecules have garnered attention for their potential in mitigating oxidative stress and inflammation in DN. Natural products and synthesized small molecules have garnered attention for their potential in mitigrating oxidative stress and inflammation in DN. Compounds like sulforaphane, mangiferin, calpain, quercetin, curcumin, and resveratrol exhibit antioxidant and anti-inflammatory properties, thus showing promise in alleviating DN symptoms. Furthermore, various small molecules and herbal extracts have demonstrated efficacy in reducing oxidative stress, modulating cytokine levels, and improving nerve function in experimental models of DN. Combination therapies targeting multiple pathways involved in DN pathogenesis, such as the PARP inhibitor nicotinamide and the antioxidant melatonin, have shown promising results in ameliorating functional deficits and biochemical alterations associated with DN. This review aims to understanding the interplay between oxidative stress and inflammation and further exploration of natural products and synthesized small molecules as potential therapeutic agents for DN management.

**Keywords:** *Diabetic neuropathy (DN), Oxidative Stress, Inflammation, Natural products*

## List of Abbreviations

DN: Diabetic Neuropathy
ROS: Reactive Oxygen Species
MDA: Malondialdehyde
PARP: Poly ADP-Ribose Polymerase
NF-kB: Nuclear Factor kappa B
Nrf2: Nuclear factor erythroid 2-related factor 2
CCI: Chronic Constriction Injury
DRG: Dorsal Root Ganglion
AR: Aldose Reductase
AGEs: Advanced Glycation End products
RAGE: Receptor for AGEs
PKC: Protein Kinase C
GFAT: Glutamine Fructose-6-Phosphate Amido transferase
TGF-$\alpha$: Transforming Growth Factor alpha

TGF-$\beta$1: Transforming Growth Factor beta 1
NO: Nitric Oxide
DAG: Diacylglycerol
MNCV: Motor Nerve Conduction Velocity
IL: Interleukin
TNF-$\alpha$: Tumor Necrosis Factor alpha
IFN-$\gamma$: Interferon-gamma
LXs: Lipoxins
SNEDDS: Self-Nano Emulsifying Drug Delivery Systems
HO-1: Heme Oxygenase-1
NAC: N-Acetylcysteine
NPs: Nanoparticles

## 1 Introduction

Diabetes is linked to both macrovascular and microvascular issues, with diabetic neuropathy (DN) being a major microvascular complication affecting about 50-60% of patients with longstanding diabetes(1). DN, a prevalent and debilitating condition, arises from prolonged exposure to high blood glucose levels, leading to nerve damage and resulting in a range of sensory, motor, and autonomic dysfunctions. Among the several risk factors that lead to DN, oxidative stress and inflammation plays crucial roles by initiating and advancing nerve damage. The atypical rise in the blood glucose levels in diabetes are responsible for the overproduction of various ROS and the subsequent dysregulation of antioxidant defense systems, resulting in tissue damage through different signaling cascades. Additionally, obesity and dyslipidemia have been clinically reported to trigger systemic inflammation of peripheral nerves, associated with DN. Multiple pathways have been reported to contribute to oxidative stress and inflammation in DN, including hyperglycemia-induced DNA damage, activation of transcription factors like NF-kB and Nrf2, and irregular cytokine production(2). These mechanisms interconnect to create a complex web of molecular events culminating in nerve damage and dysfunction. The oxidative stress so developed in DN conditions, contribute to the peroxidation of fatty acids; producing reactive aldehydes like malondialdehyde (MDA). MDA serves as a reliable stress marker in diabetic individuals(3). Elevated MDA levels highlight the severity of oxidative damage and its role in the progression of DN associated complications(4). In recent years, there has been growing interest in exploring the therapeutic potential of small molecules and herbal extracts to alleviate oxidative stress and inflammation in DN. These compounds, have shown great promise in mitigating oxidative damage effects on nerve tissues through diverse pharmacological actions. Sulforaphane, quercetin, curcumin, and resveratrol have demonstrated efficacy in reducing oxidative stress, modulating cytokine levels, and enhancing nerve function in experimental DN models(5). Additionally, natural products like melatonin and quercetin have gained much attention over the years for their superior ability to modulate oxidative stress pathways and mitigate neuroinflammation, providing novel approaches to DN management(6). The primary objective of this review aims to comprehensively outline the role of oxidative stress in DN, emphasizing the significance of MDA as a marker of oxidative damage. This review also explores the therapeutic potential of small molecules and herbal extracts in alleviating inflammation and oxidative stress in DN. Furthermore, it discusses the emerging evidences supporting the combined use of natural products and PARP inhibitors as a synergistic approach to target multiple pathways implicated in DN pathogenesis. By elucidating these mechanisms, this review seeks to contribute to ongoing efforts to develop effective therapeutic strategies for DN management.

## 2 Risk Factors Associated with Diabetic Neuropathy

### 2.1 Oxidative Stress

Oxidative stress (OS) results from an imbalance between pro-oxidants and antioxidants, where pro-oxidants outnumber antioxidants, disrupting cellular functions. Pro-oxidants, such as free radicals or reactive oxygen species (ROS), aggressively target proteins, lipids, and nucleic acids for degradation, leading to cellular damage. Similarly, reactive nitrogen species (RNS) contribute to cellular damage alongside ROS. This oxidative assault on cellular components impairs biological activity and disrupts crucial metabolic processes, ultimately triggering cell death through apoptosis or necrosis(7). Antioxidants counteract oxidative stress by neutralizing free radicals. They can act as preventive agents, inhibiting the initiation of free-radical reactions, or as chain-breaking agents, suppressing free-radical chain reactions. While free radicals are generally detrimental, some play essential roles in normal physiological processes. For instance, superoxide (O2), hydrogen peroxide (H2O2), and nitric oxide (NO) are involved in regulating vascular function, inflammation, apoptosis, cell division, and bactericidal activity by neutrophils(8). In diabetes, oxidative stress contributes significantly to microvascular complications, primarily due to chronic hyperglycemia(9). Neuronal cells become more susceptible to damage due to facilitated glucose diffusion, leading to glucose flux. Prolonged exposure to glucose results in neurons having an increased number of mitochondria, phospholipids, and weakened antioxidant defenses. Studies on rats treated with streptozotocin, a diabetogenic agent, showed evidence of low antioxidant defenses in neurons, with minimal upregulation of antioxidant enzymes, except for catalase, after prolonged exposure(10).

#### 2.1.1 Malondialdehyde and Oxidative Stress

Oxidative stress leads to lipid peroxidation, resulting in the production of malondialdehyde (MDA), which serves as a marker for oxidative stress levels, often elevated in diabetic patients. Various inhibitors targeting different signaling pathways show potential for improving neuropathic conditions(11). For instance, in one study, treatment with MDL 28170, a Calpain inhibitor, significantly decreased neuronal MDA levels in diabetic rats compared to controls. Similarly, treatment with U83836E, an ROS scavenger, normalized MDA levels and antioxidant enzyme levels in diabetic rats after two weeks of treatment(12). Edaravone, a

specific scavenger for hydroxyl radicals, also showed promising results in reducing lipid peroxidation in the sciatic nerve of diabetic rats, with both curative and preventive effects observed. Additionally, treatment with BAY 11-7082, an IkB phosphorylation inhibitor, reduced nerve MDA levels and increased glutathione levels in diabetic rats, indicating antioxidant and anti-inflammatory properties(13). Hyperglycemia-induced DNA damage is mediated by peroxynitrite, and treatment with FeTMPyP, a peroxynitrite decomposition catalyst, restored peroxynitrite levels, preventing further DNA damage(14). FeTMPyP treatment also resulted in increased NAD and decreased MDA levels in the nerves of diabetic animals. Furthermore, plasma also exhibits elevated levels of stress markers such as MDA and peroxynitrite(11). Resveratrol, known for its potential to reduce DNA fragmentation, reduced the number of TUNEL-positive cells in the sciatic nerve sections of diabetic rats, thus alleviating complications associated with diabetic neuropathy(15).

### 2.1.2 Natural Products and Oxidative Stress

Natural products have attracted much attention for their potential in combating diabetes and alleviating neuropathic complications. Researchers have evaluated various parameters to gauge the effectiveness of these products. For example, studies have examined the effects of the aqueous extract of *Emblica officinalis* and its constituents, such as Quercetin, Sesamol, and Tocotrienol, on diabetic parameters associated with neuropathy(16). Treatment with E. officinalis extract restored lipid peroxide levels and antioxidant levels (glutathione and superoxide dismutase) in the sciatic nerve of diabetic rats, while also reducing nitrosative stress(17). Combining insulin with E. officinalis showed a synergistic effect in reducing nitrite and lipid peroxide levels(18). Sesamol and Tocotrienol, when administered with insulin, displayed antioxidant activity and prevented apoptosis, as evidenced by reduced reactive oxygen and nitrogen species stress and decreased caspase-3 activity(19). Naringin, a flavanone, exhibited neuroprotective effects by preserving endogenous antioxidants and membrane-bound inorganic phosphate enzyme levels, while also reducing oxidative-nitrosative stress and apoptosis in neural cells(20). When combined with insulin, naringin not only prevented diabetic conditions but also reversed neuropathic pain. Similar pain reduction was observed with insulin in combination with the antioxidants Resveratrol and Curcumin(21). N-Acetylcysteine (NAC), an antioxidant precursor, mitigated lipid peroxidation, restored phospholipid levels, and prevented cytochrome c release and caspase 3 activation in diabetic animals after seven weeks of treatment(22). Inhibiting protein glycation is crucial in managing diabetic complications. D-Limonene, a monoterpene, showed promise in improving neuropathic complications by inhibiting glycation(23). Limonene, present in Aegle marmelos, stabilized proteins by preventing the transition from alpha-helical to beta-sheet structure, protecting them from glycation(24). Human Serum Albumin (HSA) undergoes glycation in individuals experiencing chronic neuropathic complications due to oxidative stress. This glycation leads to secondary structure changes, such as the conversion from alpha helix to $\beta$-sheet, negatively impacting its functional properties. Additionally, reduced levels of thiol groups indicate decreased free radical scavenging capacity, indirectly increasing oxidative stress(25). High levels of protein carbonyls and fructosamine further indicate Amadori product formation in diabetic patients.

## 2.2 Inflammation

Inflammation is implicated in numerous diseases, with efforts aimed at curbing its effects. While inflammation serves as a protective mechanism, excessive or prolonged inflammation contributes to various chronic conditions, including neuropathic pain resulting from diabetic complications. The understanding of diabetic neuropathy (DN) has evolved from considering it a disease devoid of immune cells to recognizing a strong link between inflammation and DN progression, emphasizing the critical interplay between the immune system and DN advancement. Timely resolution of inflammation is crucial to halt the detrimental effects of cytokines on tissues. Pro-resolving mediators orchestrate resolution pathways, countering the inflammatory response and aiming to restore tissue homeostasis, thereby inhibiting further tissue damage. These mediators include cytokines, chemokines, and lipid mediators like lipoxins (LXs), resolvins, and protectins(26). Targeting untimely resolution processes presents potential therapeutic avenues for various diseases. A common symptom of diabetic neuropathy is the reduction in motor nerve conduction velocity (MNCV), with TNF-$\alpha$ administration into the sciatic nerve inducing pain by decreasing MNCV(27). Chronic inflammation associated with diabetes mellitus duration exacerbates neuropathy prevalence. Incidence of elevated serum concentrations of inflammatory biomarkers, e.g., C-reactive protein (CRP), interleukin (IL) 6, or IL 18 were found in humans with type 2 diabetes. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. Moreover, diminished cardiac autonomic function was reported to be associated with inflammation in type 2 diabetes. Subclinical inflammation and endothelial dysfunction are linked to cardiac autonomic neuropathy in type 2 diabetes. Inflammation, particularly the amplification of pro-inflammatory cytokines, plays a pivotal role in diabetic complications. Dysregulated cytokine production contributes to peripheral nerve complications observed in inflammatory diseases. A case-control study explored the influence of gene polymorphisms in pro- and anti-inflammatory cytokines on nerve damage in diabetic neuropathic patients. Functional SNPs of genes TNF-$\alpha$, IL-10, and IFN- were examined, revealing an association between IL-10-1082G/G polymorphism and susceptibility to diabetic neuropathy in Type 2 diabetes patients(28). Furthermore, the progression of DN involves oxidative stress intertwined with neuroinflammation. The interaction between transcription factors Nrf2 and NFB regulates oxidative stress and inflammation. Nrf2 activated by a reducing environment, upregulates antioxidant enzymes and detoxifying enzymes, thereby controlling inflammation(29). Conversely, oxidative stress activates NFB and AP-1, leading to endothelial dysfunction, altered NO levels, and macrophage migration, culminating in pro-inflammatory cytokine production and nerve tissue

damage(30). Nrf2 activation holds great promise in protecting peripheral nerves from stresses associated with hyperglycemia, as decreased Nrf2 expression leads to increased inflammation and oxidative stress(31).

### 2.3 Role of Small Molecules in Reducing Inflammation

- **Curcumin**
  Curcumin, a compound abundant in turmeric, exhibits various beneficial properties, including antioxidant and anti-inflammatory effects. Clinical studies have demonstrated its potential in managing diabetic neuropathy by reducing thermal hyperalgesia through inhibition of proinflammatory cytokines like TNF-$\alpha$ and nitric oxide release(32). However, bioavailability and poor hydrophilicity of curcumin has remained a topic of concern since decades. This has encouraged researchers to develop formulations like self-nano emulsifying drug delivery systems (SNEDDS) to enhance its drug targeting efficacy.

- **Quercetin**
  Quercetin, a bioflavonoid, offers neuroprotection by modulating oxidative-nitrosative stress, proinflammatory cytokines, and DNA damage(33). Treatment with quercetin effectively inhibits elevated levels of TNF-$\alpha$ and IL-1$\beta$ in diabetic neuropathy, demonstrating its potential in mitigating inflammation associated with this condition.

- **Sulforaphane**
  Elevated NF-B activity during hyperglycemia is associated with overproduction of proinflammatory cytokines viz., IL-6, TNF-$\alpha$, COX-2 and iNOS. These proteins and enzymes are quintessential for the initiation and amplification of inflammatory progress in neuronal cells(8). Diminished Nrf2 activity leads to impaired antioxidant defence which is characterized by reduced levels of superoxide dismutase (SOD), catalyses to glutathione (GSH). Moreover, the production of detoxifying enzymes such as, haemoxygenase-1 (HO-I) and NADPH quinone oxidoreductase (NQO1) also gets decreased, resulting in nitrosative and oxidative stress(13). Neuroinflammation caused due to enhanced NF-B may also activate microglia and astrocytes, which further boosts the release of proinflammatory mediators, thereby developing a fierce cycle of inflammation. Neuroinflammation results in the release of algogenic mediators, such as prostaglandins, bradykinins, and chemokines which can sensitise the nerve fibres to painful stimulus, ending up in sensorimotor alterations. Neuroinflammation mediated by NF-B can also result in endoneurial hypoxia owing to the reduced blood supply to the nervous tissue and ganglion. This neuronal hypoxic condition eventually results in dysfunction of mitochondrial electron transport chain, reduced efficiency of mitochondria, and increased ROS production. Sulforaphane, a prominent isothiocyanate found in broccoli, exhibits antioxidant and anti-inflammatory properties. Studies investigated its effects on high glucose-induced alterations in Nrf2 and NF-b signaling pathways in Neuro 2a cells. Sulforaphane activates Nrf2 and inhibits NF-B, thereby inducing enzymes regulated by Nrf2 and modulating inflammatory mediators. These actions protect against pancreatic $\beta$-cell damage induced by IL-1$\beta$ and interferon- by inhibiting NF-B and its downstream signaling pathway(34).

- **BAY-11-7082**
  The NF-kB protein complex plays a significant role in inflammatory responses. BAY-11-7082, an IkB phosphorylation inhibitor, was utilized to demonstrate the involvement of the NF-kB inflammatory cascade in diabetic neuropathy pathophysiology(35). Inhibition of NF-kB expression and downstream pro-inflammatory mediator expression helps mitigate nerve damage associated with inflammation and oxidative stress.

- **Calpain**
  Inflammation, oxidative stress, and neuronal apoptosis exacerbate diabetic neuropathy. Hyperglycemia elevates neuronal intracellular calcium levels, activating calpain, a calcium-dependent protein ubiquitously expressed in organisms. Calpain activation alters Na+ channels and affects the function of TTX-R sodium channels in sensory neurons(36). MDL 28170, a calpain inhibitor, has shown promising results in halting inflammation, suppressing TTX-R sodium current, and improving nerve conduction velocity and perfusion, ultimately alleviating sensory perception alterations and hyperalgesia in diabetic neuropathy.

- **Mangiferin**

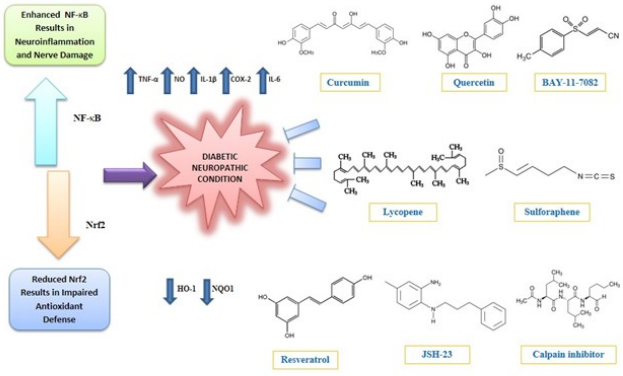


Figure 1: NF-KB and Nrf2 Imbalance Leading to Diabetes Neuropathy and Targeting with Natural and Synthetic Compounds

Recent research has revealed that mangiferin, derived from *Swertia chirayita*, offers significant benefits in alleviating diabetic neuropathic pain(37). This compound works through multiple mechanisms: it reduces inflammation, provides antioxidant protection,

and regulates nerve growth factors. These discoveries highlight the potential of mangiferin as a natural remedy for managing the symptoms of diabetic neuropathy.

- **Quillaic acid**
  Recently a study was conducted to demonstrate that the extract of *Saponaria officinalis* exhibits significant anti-diabetic neuropathy, and anti-inflammatory effects, with Quillaic acid identified as its most abundant and biologically active compound(38).

- **Resveratrol**
  Resveratrol known for its anti-inflammatory properties, decreases levels of inflammatory mediators like TNF-$\alpha$ and IL-6, contributing to the inhibition of NF-kB(39). By curbing NF-kB expression and impeding its activation, resveratrol helps mitigate inflammatory changes associated with diabetic neuropathy.

- **Lycopene**
  Lycopene, an organic pigment known as carotene, when administered to streptozotocin-induced diabetic mice, inhibits the release of pro-inflammatory mediators TNF-$\alpha$ and NO dose-dependently, suggesting its potential efficacy in attenuating diabetic neuropathic-pain(40). These natural remedies could be valuable additions to existing therapies for managing diabetes-related complications, offering new avenues for further investigation and development in diabetes management strategies.

- **JSH-23**
  JSH-23, a novel antioxidant and a NF-kB inhibitor, hinders the nuclear translocation of p65/p50 subunits, thereby reducing inflammatory damage in the sciatic nerve(31). Additionally, JSH-23 increases levels of the antioxidant defense marker Nrf2 and hemeoxygenase-1 (HO-1), suggesting its potential in enhancing antioxidant defenses.

- **ZnO NPs**
  The correlation between diabetes and an imbalance in zinc homeostasis suggests zinc-based therapy as an attractive therapeutic proposition. Over the years, the role of nanoparticles have drawn much attention in environmental and medicinal research owing to their superior properties at nano-dimension Studies on streptozotocin-induced diabetic mice revealed that small-sized ZnO nanoparticles (NPs) exhibited superior anti-diabetic effects compared to larger particles. ZnO-NPs stimulated the function of Th1 and Th2 cells, and the expression of insulin receptors and pancreatic genes associated with diabetes(41). Furthermore, ZnO-NPs restored altered levels of pro-inflammatory cytokines to near-normal levels. Synthesized green ZnO-NPs demonstrated anti-diabetic activity by restoring blood glucose levels through insulin secretion, with smaller particles exhibiting greater effectiveness due to enhanced penetration and higher surface-to-volume ratio. The mechanism behind ZnO-NP-induced insulin secretion warrants further investigation, with Zn ions potentially playing a role in augmenting insulin release from pancreatic islets.

#### 2.3.1 Traditionally Available Herbal Extracts in Inflammation Control

Many modern drugs are often limited due to their high cost and potential side effects, prompting the exploration of herbal therapies that are traditionally believed to promote healthier living. In diabetic neuropathy, inflammation triggered by hyperglycemia is a key factor. Traditional medicinal plants with hypoglycemic properties hold great promise as sources for new anti-diabetic treatments, particularly those with antioxidant and anti-inflammatory properties. Therefore, efforts to control hyperglycemia by means of discovering novel herbal anti-diabetic agents should continue to prevent diabetes-related complications. Extracts from *Emblica officinalis*, a potent antioxidant, have been investigated for their ability to target oxidative stress-mediated nerve damage in diabetic rats(50). Treatment with *Emblica officinalis* extract significantly reduces oxidative stress, nitrite levels, and cytokines in both serum and sciatic nerves of diabetic rats, ultimately leading to an improvement in the nociceptive threshold. Fenugreek seed extract (IND01) offers sustained protection against thermal hyperalgesia in rat models of peripheral neuropathy, potentially through modulation of sensory pathways or inhibition of cytokine release(47). Bioactive fractions from *Annona reticulata* bark (ARB) and *Ziziphus jujuba* root bark (ZJ), when combined with insulin, demonstrate neuroprotective effects in diabetic neuropathy(51). These fractions alleviate thermal, mechanical hyperalgesia, and cold allodynia by reducing nerve oxidative stress, inflammatory cascade mediated by NF-kB and iNOS, and abnormal cytokine release, thereby ameliorating diabetic neuropathic conditions.

## 3 Natural Products in DN Treatment

### 3.1 Melatonin and Nicotinamide Treatment in Experimental Diabetic Neuropathy

DNA damage triggers the activation of PARP, initiating a cellular metabolic cycle that consumes energy and ultimately leads to cell death. A recent study investigated the combined treatment of the antioxidant melatonin and the PARP inhibitor nicotinamide for reducing the consequences of diabetic neuropathy (DN). After six weeks of diabetes induction, the drugs were administered either alone or in combination for two weeks, and functional, behavioral, and biochemical changes were studied in the drug treated animals(52). Both melatonin and nicotinamide, either used as monotherapy or in combination, significantly improved functional deficits and pain parameters. Moreover, the combinatorial therapy reversed biochemical alterations, including a significant decrease in nitrotyrosine and Poly ADP-Ribose (PAR) immunopositivity in sciatic nerve micro-sections of the drug treated group. Thus, simultaneous inhibition of the oxidative stress-PARP activation cascade may hold promise for the pharmacotherapy of DN(52). Another study investigated the role of oxidative/nitrosative stress-induced PARP overactivation following nerve injury

Table 1: Plants and Their Mode of Action on Diabetic Neuropathy

| Sl.No. | Plant name | Plant part(s) used | Mode of action |
|---|---|---|---|
| 1 | *Sesamum indicum* | Seed | Attenuation of oxidative stress by reducing xanthine oxidase activity, iNOSmRNA and p38 MAPK activation (42) |
| 2 | *Calotropis procera* | Root, shoot, and leaves | Anti-hyperglycemic activity through $\beta$-cell regeneration and increase in plasma insulin and HbA1C %, further research is required (43) |
| 3 | *Curcuma longa* | Rhizome | Reduces the expression of NF-$\kappa$B, IKK-$\kappa$, COX-2, iNOS, TNF-$\alpha$ and IL-6, nitric oxide synthase and cycloxygenase-2 (44) |
| 4 | *Urticadioica* | Leaves | The constituent scopoletin modulates the expression of PPAR-$\gamma$, which is involved in the neuronal insulin receptor functioning in the hippocampus of rodents with insulin resistance (45) |
| 5 | *Allium sativum* | Edible part | Significant protection through decrease in serum nitrite level, and increased GSH level in both preventive and curative groups. |
| 6 | *Allium cepa* | Outer scales | Outer bark of the onion is more potent due to the presence of high quantity of phenolic compounds (46) |
| 7 | *Emblica officinalis* | Fruit | Inhibits TNF-$\alpha$, IL-1$\beta$, TGF-$\beta$1 levels, reduces diabetes-inducednitrosative stress, and increases the expression of Reduced Glutathione (GSH) and Superoxide Dimutase (17) |
| 8 | *Trigonellafoenum-graceum* | Seed | Offered sustained protection against TH and deranged MFT scores (47) |
| 9 | *Annona reticulata* | Bark | |
| 10 | *Ziziphus jujuba* | Root, bark | Shows neuroprotective effect by inhibiting NF-$\kappa$B inflammatory cascade (48) |
| 11 | *Crocus sativus* | Stigma | Shows neuroprotective activity by reducing oxidative stress(49) |

in initiating neuro-inflammation and a bioenergetic crisis, which further leads to neurodegenerative changes. Besides PARP activation, oxidative/nitrosative stress also activates cascades like NF-kB and MAPK signaling pathways, hindering other signaling cascades, including the Nrf2 pathway. This study examined the combined therapeutic effect of the antioxidant quercetin and the PARP inhibitor 4-amino-1,8-naphthalimide (4-ANI) in reducing the effects of chronic constriction injury (CCI) neuropathy in rats(53). Quercetin and 4-ANI were administered either alone or in combination for 14 days to assess sciatic functional index, allodynia, hyperalgesia, oxidative/nitrosative stress, mitochondrial function, and levels of inflammatory markers(54). The results demonstrated that while quercetin and 4-ANI alone improved pain behavior and biochemical alterations, the combination therapy showed a more significant reversal of CCI-induced changes. Levels of nitrotyrosine and poly ADP-ribose (PAR) immune-positivity decreased, and nuclear factor erythroid 2-related factor (Nrf-2) levels increased significantly in micro-sections of the sciatic nerve and dorsal root ganglion (DRG) of the treatment group. These findings suggest that simultaneous inhibition of the oxidative stress-PARP activation cascade could be a potentially useful strategy for managing trauma-induced neuropathic pain(54).

## 4 Conclusion and Future Directions

Diabetes mellitus being a silent-killer gradually progress to neuropathy resulting in excruciating pain. Therefore, it becomes imperative to undertake certain therapeutic measures to regulate neuropathic pain effectively. Naturally available herbal agents possessing anti-diabetic, antioxidant and anti-inflammatory potential should be prioritized for reducing blood glucose levels and subsequently managing neuropathic pain, as synthetic agents pose numerous side effects and poor pharmacokinetics. Therefore, herbal extracts with medicinal values can thus be proposed as an alternative therapy to treat diabetic complications. This review potentially explores the comprehensive treatment of recent progresses in antioxidant-based strategies which includes those herbal agents that possess dual antioxidant/anti-inflammatory end-points. The role of MDA in oxidative stress and its elevation in diabetic subjects highlight the importance of targeting oxidative stress pathways in DN management. Small molecules such as MDL 28170, U83836E, Edaravone, and BAY 11-7082, along with herbal extracts like curcumin, quercetin, and *Emblica officinalis*, have demonstrated anti-inflammatory and antioxidant properties in preclinical studies. These compounds act through various mechanisms, including inhibition of NF-B signaling, modulation of Nrf2 activity, and

suppression of pro-inflammatory cytokines. Furthermore, natural products in combination with PARP inhibitors, such as melatonin and quercetin, show synergistic effects in reducing oxidative stress and inflammation in experimental models of DN. By targeting multiple pathways involved in oxidative stress and inflammation, these compounds display huge potential for the development of novel therapeutics for DN. In conclusion, targeting oxidative stress and inflammation pathways through naturally available herbal extracts and small molecules in combination with PARP inhibitors represents a promising approach for the management of DN. Further research is needed to holistically explore the underlying mechanisms and evaluate the clinical efficacy of herbal based antioxidants in mitigating the long-standing problem of diabetic neuropathy.

## Conflict of Interest

The authors declare no conflict of interest in this reported communication.

## Acknowledgment

SKS, AG, and NCT would like to acknowledge Assam down town University for their basic research support.

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