Nanotechnology Perceptions
ISSN 1660-6795
www.nano-ntp.com

Plant-Derived Bioactive Molecules in the Management of Diabetic Neuropathy: Insights and Future Prospects

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Diabetic neuropathy is considered as frightening complications of diabetes mellitus that is being faced by healthcare providers and researchers all over the world. Number of diabetic people in increasing in an alarming rate and the prevalence of diabetic neuropathy also increasing proportionally. Patients can have a wide variety of symptoms as a consequence of the illness, which may responsible for mortality and morbidity. Diabetic neuropathy may not be apparent for several years after diabetes has been diagnosed, the prognosis for this condition is not virtuous. Increased generation of free radicals may lead to oxidative stress which is considered as a major pathological factor for diabetes neuropathy. Uncontrolled hyperglycemia leads to the development of diabetic neuropathy. Hyperglycemia activates many metabolic pathways and produces significant oxidative stress, possibly leading to cell death. This paper shed light on the possible molecular role that plant metabolites that may play key role in managing diabetic neuropathy, as well as the potential significance of several different pathways and processes in the progression of the condition. Additionally, a putative mechanism that involves a flavonoid component scavenging reactive oxygen species was described in the paper.

Keywords: Hyperglycemia, Diabetic neuropathy, Pain, Plant metabolites.

1. Introduction

Diabetic neuropathy (DN) is considered as major healthcare challenge caused as diabetic complications including developed and developing nations [1]. It is believed that diabetes mellitus (DM) is the primary cause of the other complications that may cause amputation of a lower limb [2]. The development of DN is a devastating consequence of DM that occurs over time [1]. In a recent study, it was found that approximately twelve percent of people who had DM also had DN. Diabetic neuropathy can be caused by DM that has been present for an extended period [2,3]. This condition can cause damage to peripheral nerves, impairments in

function, and other consequences. Diabetic neuropathy is a condition that affects several parts of the nervous system and is characterized by a wide range of symptoms, such as tingling, burning, and numbness [4,5,6]. Hyperglycemia is a crucial factor that leads to the progression of diabetic neuropathy; however, the exact cause of this condition is yet unknown [7]. Microvascular complications that are brought on by hyperglycemia in diabetic patients may have a pathophysiology that can be explained by several different causes [8]. Lack of proper diabetes care services, rising healthcare expenditures, poor management of blood glucose levels, inadequate screening and diagnostic resources, and a delay in diagnosis are some causes underlined the increased number of DN. People with DN experience significant pain [7], chronic sleep disruptions [8], decreased work productivity, higher treatment costs due to more extended hospital stay [9], physical limitations that hinder their ability to work, and frequent hospitalizations [10,11] that negatively impact on their social and psychological well-being. The development of DN is associated with several risk factors, the most prevalent of which are age, hypertension, body mass index (BMI), and fasting blood sugar level [12,13]. Cross-sectional studies have been used in the majority of the prior research on diabetic neuropathy in India, in particular, to attempt to estimate the prevalence of the neurological condition. In order to prevent DN, it is necessary to identify risk factors promptly and with a high degree of accuracy, as well as to have accurate time estimations for the development of the illness [16]. As a result, the purpose of this article is to provide answers to the concerns of when exactly diabetic neuropathy can become apparent in people who have type 2 diabetes mellitus and what factors contribute to the development of this condition. There is a microvascular consequence of diabetes that can affect as many as 50% of those who have type 1 or type 2 diabetes [18]. This condition is known as diabetic neuropathy (DN). The presence of DN is characterized by a modest inflammatory reaction, which is one of its markers [19]. To a large extent, activated immune cells are responsible for the production of a variety of pro-inflammatory cytokines (CKs), including C-reactive protein (CRP), monocyte chemoattractant protein-1, interleukin (IL)-1, interleukin-6, interleukin-8, and tumour necrosis factor-alpha (TNF-A). It is also important to note that local adipocytes and macrophages make significant contributions to the inflammatory cascade, and as a result, they are responsible for their development. According to the findings of previous studies [20-21], the presence of E-selectin (both locally produced and circulating), vascular cell adhesion molecule-1 (ICAM-1), and intracellular adhesion molecule-1 (ICAM-1) can be utilized to identify subclinical chronic inflammation. This type of inflammation has been linked to complications associated with diabetes. In addition, endothelial cells increase the synthesis of adhesion molecules and chemokines in response to the chemokines produced by tissues that have been wounded or suffering from disease [27, 28].

One of the most significant problems that can arise from diabetes mellitus is diabetic neuropathy (DN), which is quite similar to diabetic nephropathy (DN); for example,[29] The prevalence of diabetes mellitus is high among the top preventable causes of blindness among people of working age around the world. The development of diabetic neuropathy in some form or another is a possibility for around one-third of those who have diabetes [30]. Proliferative diabetic neuropathy and diabetic macular oedema are also included in this medical condition. These are two of the consequences that might potentially cause blindness, and they affect 10% of persons who have diabetes. A cascade of adhesion molecules and inflammatory mediators is involved [31-32]. This is in addition to the low-grade inflammation

that is occurring. According to the findings of research [33], the onset of diabetic neuropathy (DR) and other long-term consequences of diabetes can be attributed to the presence of subclinical chronic inflammation. It would be helpful to understand the inflammatory pathways [34, 35] to control or prevent diabetes and its repercussions before they cause irreversible harm to organs. Diabetic nephropathy, often known as DNP, is a condition that affects people who have diabetes and is linked to renal impairment that is caused by dementia. Among the many mechanisms that contribute to the development of DNP, two of the most important are managing blood pressure and glucose levels [36]. The incidence of diabetic neuropathy (DNP) is increasing in unison with the number of people who are diagnosed with diabetes around the world [37]. It is hypothesized that inflammatory and immunologic pathways contribute to the start and progression of DNP [38]. This is even though DNP is widely considered a disease not caused by the immune system. The following are some of the procedures that are included in the DNP: nuclear factor-κB (NF-κB) [39], a variety of growth factors (e.g., transforming growth factor beta (TGF-β); insulin-like growth factor (IGF) [40]; growth hormone, vascular endothelial growth factor (VEGF)[41-42]; several enzymes (e.g., nitric oxide synthase and cyclooxygenase-2) [43-44]; adhesion molecules (ICAM-1 [35,36]); chemokines (e.g., monocyte chemoattractant protein-1 [45]; and various cells (e.g., macrophages, monocytes, and leukocytes the number. Metformin is an example of an oral anti-diabetic medication; however, there are many other medications available on the market, such as dopamine agonists, dipeptidyl peptidase IV inhibitors, alpha-glucosidase inhibitors, thiazolidinediones, meglitinides, and sulfonylureas [46]. Insulin therapy and oral anti-diabetic drugs that are currently accessible, on the other hand, are not without their fair share of complications. In addition to their high pricing and poor tolerability, medications can produce a wide variety of unfavourable side effects, including hypothyroidism, tachycardia, weight gain, hepatic failure, and lactic acidosis [44, 45, 46]. These are just some of the many adverse side effects that medications can cause. Because of these problems, many people are looking for non-traditional remedies complementary to conventional medicine yet safer and more successful than conventional treatments. There is a long and illustrious history behind employing medicinal plants to treat various ailments. Bioactive compounds derived from plants have been utilized in therapeutic settings for a considerable time. During this time, patients have shown a greater tolerance and acceptance for these drugs [47, 48]. Research suggests that natural bioactive compounds could be a viable alternative to pharmaceuticals manufactured in a laboratory [49]. One of the reasons for this is that natural bioactive chemicals provide more potential in the treatment and prevention of various microvascular issues associated with diabetes.

MECHANISTIC INSIGHTS OF DIABETIC NEUROPATHY

The presence of diabetic neuropathy is associated with both microvascular damage and metabolic issues. There is a correlation between the two. Alterations in the connections between the immune and nervous systems and the activation of glial cells are examples of pathogenic pathways [50-51]. Among the vast majority of cases of diabetic neuropathy, it is considered that issues with metabolism are the underlying cause of the condition. The hyperglycemic state that is characteristic of type 1 diabetes mellitus, which is characterized by impaired insulin secretion, is the reason for enhanced polyol pathway stimulation (Figuring 1) in this disease [52]. This condition is characterized by impaired insulin secretion due to

hyperglycemia, and the affinity of aldose reductase for glucose increases, increasing the amount of sorbitol produced. Sorbitol concentrates intracellularly in brain tissue because it cannot pass through cell membranes. This is because sorbitol is a monosaccharide. This is the point at which it produces osmotic stress, an increase in the molarity of the intracellular fluid, an influx of water, damage to Schwann cells, and the degeneration of nerve fibres [53]. The induction of the NADPH oxidase complex results in the development of oxidative stress through three different mechanisms: an increase in reactive oxygen species, a drop in nitric oxide levels, and a reduction in glutathione synthesis [54].

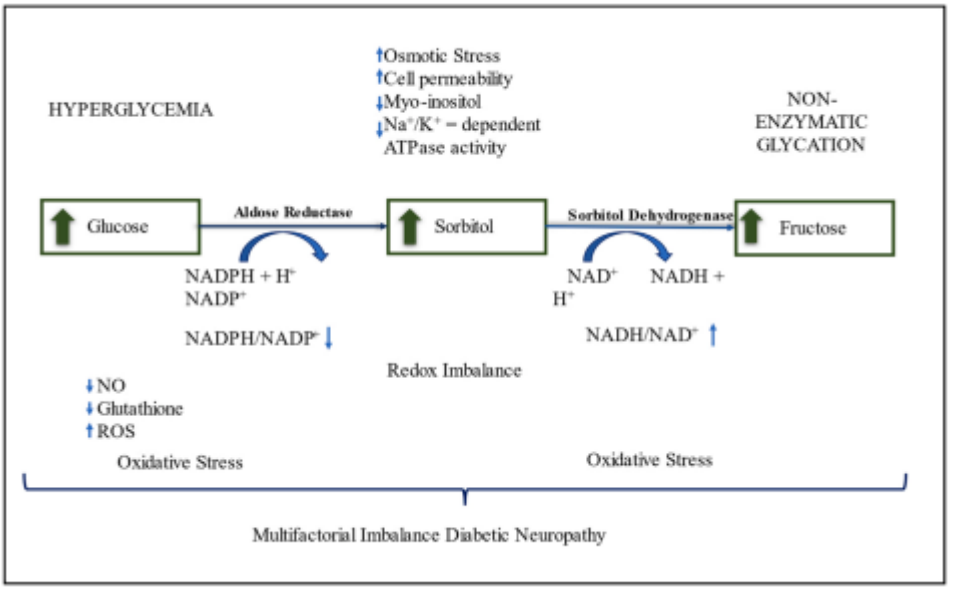


Figure 1: There is a wide range of potential causes that can be ascribed to the development of diabetic neuropathy. A situation known as hyperglycemia is responsible for an increase in the polyol pathway's activity. Damage is caused by oxidation and glycation that is not mediated by enzymes or other enzyme-dependent processes. A combination of these causes can cause diabetic neuropathy, or it can be caused by the impact of each of these factors on nerve tissues or vascular tissues individually. [54]

The proteins that have undergone modifications in glycation that do not involve enzymes, which is often referred to as oxidation in glycation processes, are a factor that contributes to the development of diabetic neuropathy [55]. With hyperglycemia, the increased concentration of glucose and fructose makes these sugars covalently linked to nucleotides, proteins, and lipid molecules [56]. This occurs because of the increasing concentration of glucose and fructose. An enzyme that controls the binding process does not need to exist for this binding to occur. These anomalies result from this process, which negatively impacts the structural proteins of nerves and the blood vessels that feed them with blood. These modifications, which are products of advanced glycation, bring about a change in the way that cells carry out their respective functions. Not only are AGEs responsible for the development of a variety of diseases, such as the formation of localized thrombus and vasoconstriction, but they are also accountable for the destruction of cellular DNA [57]. The fact that peripheral neurons also

contain glycation products and glycation receptors contributes to the intricacy of the issue. It is possible that the interactions between AGE-myelin and macrophages can also affect the demyelination of segments that occur in diabetic neuropathy [58]. AGEs are biomolecules that have been subjected to a lot of different molecular changes. These bio-molecules can be found both within and outside of human cells. Adducts of DNA and protein molecules are responsible for regulating cellular activity. These adducts move through the cells and are responsible for controlling the activity of the cells. Methylglyoxal, an excessively reactive dicarbonyl, has been shown to increase the susceptibility of endothelial cells to vascular injury [59]. This has been demonstrated through scientific research. The activation of the RAGE receptor is facilitated by extracellular proteins, such as plasma proteins, which impede the attachment of cells to one another. This phenomenon is referred to as [60]. The nuclear factor-kappa B (NF-B) transcription factor is activated if there is any interaction between the AGE and RAGE proteins. Several diverse processes, such as apoptosis and inflammation, are under the oversight of NF-B, which is responsible for their regulation [61].

Historical Prospectus

Inflammation in Diabetic Neuropathy

Both cranial neuropathies and neuropathy that affect the dispersion of nerve plexuses are examples of manifestations of diabetic polyneuropathy that are incredibly uncommon. Through nerve biopsies, it has been proven that inflammation is present in all cases [62]. An enhanced inflammatory response was observed in rats with experimental diabetes type 1 or type 2 with neuropathy, according to the findings of our experimental research [64]. As a consequence of this reaction, the sciatic nerve experienced an increase in the concentration of soluble cytokines, a slight infiltration of macrophages and T-cells and the proliferation of these cells. Furthermore, it was found that intraepidermal nerve fibres, classified as tiny nerve fibres, are frequently affected by axonal degeneration [65, 66]. As a consequence of this, we came up with the concept that normal diabetic neuropathy illnesses might perhaps involve inflammation of nerve tissue among their many different pathogenic components [67]. The peripheral nerves of rats with type 1 diabetes have been found to have higher levels of inflammatory markers, according to one discovery made by researchers [68]. One of these markers is an increase in the number of macrophages implanted and proliferated. According to the findings of our study, hyperglycemic ob/ob mice, which serve as a model for type 2 diabetes, exhibit a significantly higher level of macrophage infiltration in their sciatic nerves. An overt neuropathy was found to be linked with this [69], which manifested as axonal injury and the degradation of both myelinated and unshielded nerve fibres [70].

In more recent work, we explored prediabetes and metabolic syndrome using ob/ob mice that did not exhibit any indications of hyperglycemia. These mice were included in the investigation. [71] The existence of peripheral nerve inflammatory symptoms was not required for persistent hyperglycemia to occur.

An increased inflammatory response is connected with either type 2 diabetes or, obesity, or a combination of the two [72]. This has been demonstrated through research. The findings that were obtained are in agreement with the outcomes of the experiments that were carried out. It has been demonstrated that people who have been diagnosed with type 2 diabetes have elevated levels of inflammatory biomarkers in their blood, such as C-reactive protein (CRP),

interleukin (IL) 6, or IL 18 [73]. These biomarkers are a component of the inflammatory response. In addition, data suggests a relationship between inflammatory markers and a reduction in the heart's autonomic function in patients with type 2 diabetes [74].

According to prior research carried out by Herder and colleagues [75], systemic inflammatory indicators were discovered to be associated with the development and worsening of neuropathy in a diabetic older population throughout 6.5 years of follow-up. This was discovered during the study. The expression of inflammation-related genes has been elevated in macrophages produced from dorsal root ganglia in people with developmental neuropathy [76]. According to the authors, it is plausible that this process is one of the reasons why people are more sensitive to pain. This is something that may be considered likely. It was discovered that the expression levels of other genes associated with DRG neurons had reduced. The enhanced inflammatory gene profile and the concomitant downregulation of several DRG-neuronal genes [77] in patients with type 2 diabetes provide novel insights into the intraganglionic pathophysiology of DN [29]. These findings were found in patients with type 2 diabetes. This information is provided by the fact that these genes are simultaneously downregulated, which provides these insights. Significant investigations conducted in transgenic mice models of various inherited Charcot-Marie-Tooth (CMT) neuropathies were the first to indicate that a moderate inflammation of the nerves is involved in primary non-inflammatory peripheral nerve illnesses. This research was carried out to illustrate the nerves' involvement. The analysis of these investigations, which had been carried out more than thirty years ago, was included in the publication Martini and Toyka [79] wrote in 2004. According to the findings of these investigations, macrophages and CD8 T cell-mediated low-grade immune cell inflammation appear to be a substantial contributor to the pathogenic process, which indicates that they are responsible for the inflammation. Knockout mice models that were faulty in many cell-based immune mediator activators gave formal proof of the harmful activity of inflammatory pathways [80]. These models were used to study the adverse effects of inflammatory pathways. There were instances in which sural nerve samples obtained from individuals who were diagnosed with hereditary neuropathies revealed the presence of a low-grade inflammation [81]. On closer inspection, it was discovered that this inflammation was directly connected to axonal failure. In many cases of primary inflammatory neuropathies that are regarded as true, the source of nerve injury is the infiltration of macrophages and T cells into blood vessels in the sural nerve and skin biopsies. This, in concert with high levels of pro-inflammatory cytokines, is the cause of nerve injury. Diseases such as chronic idiopathic demyelinating polyradiculoneuropathy (CIDP), generalized basal ganglia syndrome, and vascular neuropathy are all examples of conditions that are included in this group. These are inflammatory neuropathies, disorders that affect the nerve fibres and the blood vessels inside the body. It has been observed that CD4-T cells are the primary cells in neuropathies that are induced by the immune system. Furthermore, the infiltration of immune cells is observed to be more severe in neuropathies caused by hereditary factors or diabetes [82,83]. Researchers have demonstrated that the cellular immune responses of experimental autoimmune neuritis models in rats and mice are distinct from those of transgenic CMT models [84,85]. The findings of our research, in conjunction with those of Nukada et al. [86], suggest that there is a potential that inflammation, in addition to the axonal degeneration of peripheral nerve fibres (figure 2),[87] plays a significant role in the multi-modal route that ultimately leads to diabetic neuropathy. This is the conclusion that can be drawn from the observations that we have

made.[87] Taking into account these inflammatory pathways is something that ought to be considered in order to come up with innovative remedies.

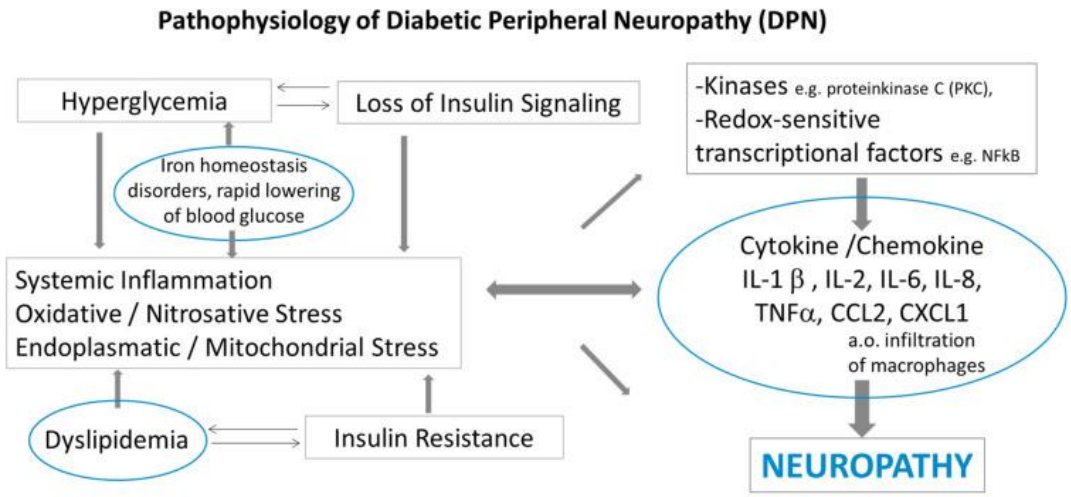


Figure 2: As modified in light of Pop-Busui (2016) [40], the processes and underlying mechanisms of peripheral neuropathy in diabetes individuals are discussed. Several factors contribute to the inflammatory connection that causes damage to peripheral nerve fibres in diabetic patients. These factors include hyperglycemia, insulin loss or resistance, dyslipidemia, and oxidative and nitrosative stress of the endoplasmic reticulum and mitochondria. These mechanisms may be partially responsible for developing inflammation, cellular damage, and reactive oxygen species (ROS). This will be discussed further in the following paragraphs. recognized to cause inflammation and damage to fibres, the mechanism by which macrophages infiltrate peripheral neurons and create cytokines and chemokines is responsible for either outcome. It would indicate that irregularities influence hyperglycemia in iron homeostasis and a quick decrease in glucose levels in the blood. In addition, the manifestation of the inflammatory process in the peripheral nerves is made to grow more severe [87]

Role of Inflammation in Diabetic Neuropathy

Even though the arteries of the Neuropathy are impacted before the development of vascular lesions [89], diabetic neuropathy was thought to be a microvascular consequence for a considerable time. This can be explained by the fact that the vasculature of the Neuropathy is related to and controlled by glia and neurons. This, in turn, explains the phenomenon. The neurovascular unit is a unique idea that has evolved within the arena of study on diabetic neuropathy from the field of neuropathy research. This unit comprises ganglion cells, glial cells, endothelial cells, and pericytes, all of which work together to form the blood vessels. Ganglion cells are responsible for creating the blood vessels. The notion of the neurovascular unit provides evidence that neurodegeneration occurs before the beginning of microvascular difficulties [90]. This is because the neurovascular unit represents the reciprocal requirement of vascular support and the dependency of regulating blood flow on glial cells, pericytes, and neurons. The results of recent investigations have revealed evidence that diabetes is linked to an increase in the expression of several different variables. The factors included in this

category are cytokines, which include IL-1β, IL-6, IL-8, TNF-α, and MCP-1. Additionally, chemokines, such as Cylco-oxygenase-2 and COX-2, are also included. Vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-1), basic fibroblast growth factor (bFGF), and hepatocyte growth factor (HGF) encompass these factors. To be more specific, it has been demonstrated that the concentrations of these compounds are much higher in the ocular fluid of diabetic patients [91-92]. It is believed that the accumulation of these cytokines, which are considered to induce the death of neuronal cells at an early stage, is the origin of the condition known as proliferative diabetic neuropathy. Furthermore, it is considered that these cytokines play a key role in the process of angiogenesis as well as the enhancement of VEFG expression [93]. It is well-established that Müller glial cells are extremely susceptible to metabolic abnormalities that are brought on by diabetes. This is the case even though it is known that they play a vital part in the metabolism of neuropathy. The early development of Neuropathy metabolic stress in animal models and tissues from diabetic patients who have little to no nonproliferative diabetic neuropathy is connected with the elevation of glial fibrillary acidic protein (GFAP) by Müller glial cells [94]. This is the case in both animal models and tissues from diabetic patients. This increases the production of pro-inflammatory mediators by the immune cells resident in the neuropathy, which are referred to as microglia. This is a consequence of the situation. Furthermore, this results in a more severe malfunction of the neuroglia and the vascular system [95]. The activation of microglia, which then results in the production of inflammatory mediators, is speculated to be the initial step in the process of neuroinflammation [96]. This is one of the various hypotheses on neuroinflammation. There is a possibility that the inflammatory response that takes place in diabetic neuropathy is the result of a shift in the metabolism. The death of cells was a potential explanation for the phenomenon they were causing. Through a process known as apoptosis, which ultimately leads to damage to mitochondria, diabetic neuropathy is responsible for the death of Neuropathy cells. This results in the mitochondria being damaged. The number of mutant non-coding RNAs, sometimes called mt-ncRNAs, is growing as a direct result of this phenomenon [97].

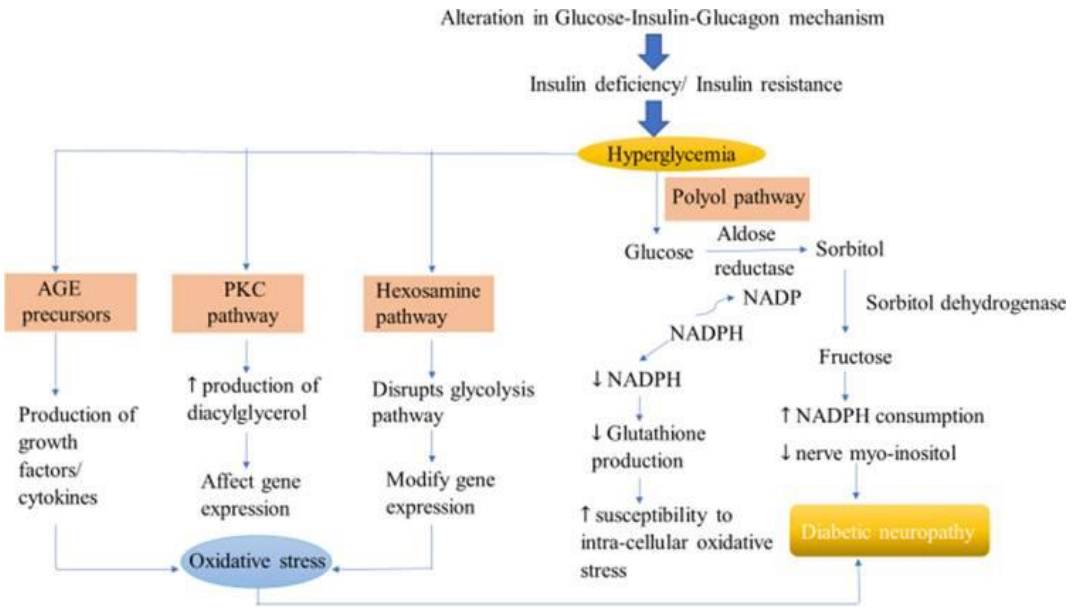


Figure 3: A conceptual frame work for the progression of diabetic neuropathy is illustrated. As an example of metabolic problems brought on by glial dysfunction, hyperglycemia, dyslipidemia, and insulin resistance are all included in this category. Inflammation, abnormal signaling of trophic factors, metabolic dysregulation, and neuronal death are other symptoms that glial dysfunction can bring on. Because immunocompetent cells in the neuropathy are thought to recognize deposited AGEs as foreign materials, which results in inflammatory reactions in diabetic neuropathy, AGE accumulation is a key trigger for creating inflammation in neuropathy. This is because AGE accumulation is a critical trigger for producing inflammation in the Neuropathy. The accumulation of AGEs has been the primary cause of inflammation in Neuropathy, as indicated by this. This category of molecules includes long non-coding RNAs, reactive oxygen species, advanced glycation end products, and other similar substances. [97]

Inflammatory Pathways in the Neurovascular Cells of Diabetic Neuropathy

The coordinated degenerative abnormalities in the cells that comprise the neurovascular unit in diabetic neuropathy are thought to be caused by anomalies in glial cells, which include astrocytes, microglia, and Muller cells (figure 4). Researchers are finding more and more evidence that diabetic animal models show many cell death pathways, such as ferroptosis, necroptosis, and pyroptosis [98]. Despite the widespread belief that early-stage diabetic neuropathy cells undergo apoptosis, this remains the case. Neuropathy tissues disperse damage-associated molecular patterns (DAMPs), which hastens the inflammatory response [99]. Inflammation contributes to the production of these regulated necrotic cell deaths. Figure 4 depicts the distribution of DAMPs in diabetic neuropathy and the inflammatory reaction's cellular and molecular pathways. Neuroinflammation and oxidative stress may have a link, as seen in figure 4.

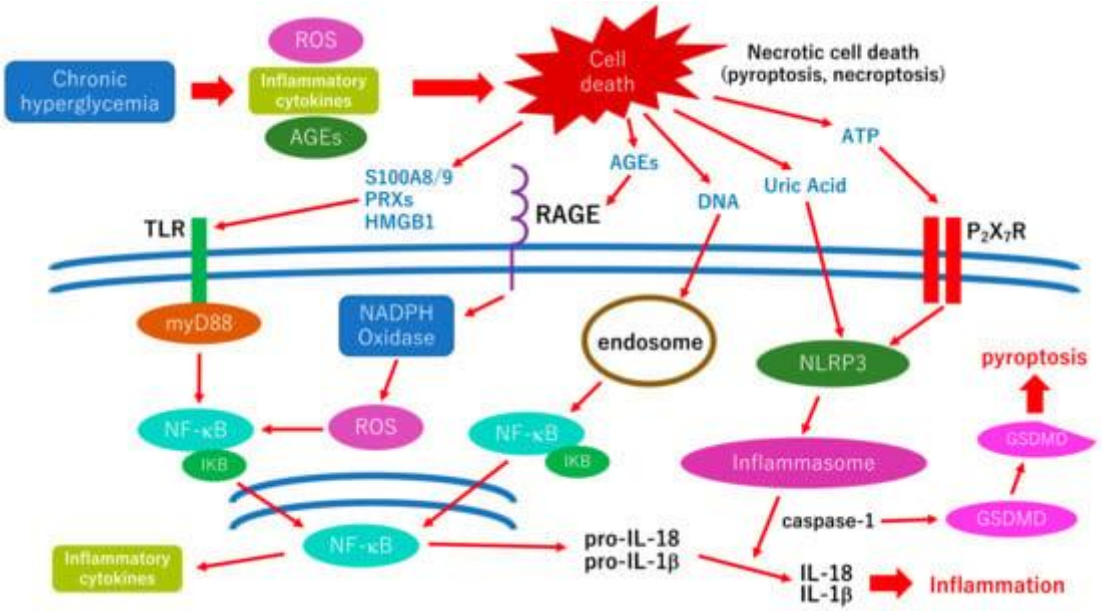


Figure 4: Shows a model of the cellular and molecular mechanisms that cause diabetic neuropathy's inflammatory response. The following is a picture of this model in action. Scientists think that oxidative stress caused by inflammatory cytokines, advanced glycation end products (AGEs), and reactive oxygen species (ROS) is what kills off neuropathy cells in diabetic neuropathy. It is believed that apoptosis or regulated necrotic cell death, which includes processes like pyroptosis, ferroptosis, and necroptosis, kills the Neuropathy cells impacted by diabetic neuropathy. Numerous DAMPs, such as HMGB1, ATP, uric acid, DNA, AGEs, S100A8/9, PRXs, and necrotic cell death, are abundant in neuropathy tissue. These diaminoacids (DAMPs) set off additional inflammatory reactions because they are identified by every pattern recognition receptor and activate every intracellular pathway. In the AGE-RAGE axis, reactive oxygen species (ROS) generation is increased after NADPH oxidase activation, the initial step. When intracellular reactive oxygen species (ROS) levels rise, the NF-κB pathway gets activated, generating inflammatory cytokines. It is important to note that diabetic neuropathy causes a permanent loss of vision due to the death of neuronal cells. The progression of diabetic macular edoema and vascular permeability should also involve the demise of vascular cells. Hence, it is reasonable to assume that anti-inflammatory medications can help prevent diabetic neuropathy and its related vascular and neurological complications. The following acronyms are frequently used: ROS, AGEs, TLR, RAGE, P2X7R, Myd88, NADPH, NLRP3, inhibitor of κB, and Gasdermin D[99]

Nutritional Consequences of Hyperglycemia

The condition known as hyperglycemia can have several significant repercussions, including alterations in nutritional status brought about by the changing levels of trace elements. Throughout the field of biology, minerals and trace elements play an essential part in a wide variety of processes, including the stabilization of enzymes and proteins as well as the actions of cofactors [99]. They bind themselves to the receptors on the cell membrane or change the receptor's structure [100]. This allows them to regulate essential biological processes. There is

a clear correlation between these critical micronutrients and diabetes mellitus, and significant physiological repercussions are connected with their presence [101-102]. Numerous studies [103] have demonstrated that individuals with diabetes mellitus have distinct metabolic processes for magnesium, copper, zinc, and iron. Several investigations have established a connection between the development of diabetes mellitus and alterations in the metabolism of trace elements. A few trace elements have the potential to enhance the effectiveness of insulin [104]. These elements include chromium, selenium, vanadium, zinc, manganese, etc. Proposed mechanisms for the enhancement of insulin action include activating the insulin receptor site; serving as cofactors or components for enzyme systems involved in glucose metabolism; [105] enhancement of insulin sensitivity; and [106] trace element antioxidant function to prevent tissue peroxidation. All of these mechanisms are aimed at enhancing insulin action. The functions of essential trace elements, such as zinc [107], are impacted when hyperglycemia is present. When it comes to insulin manufacturing, storage, and maintaining its structural integrity, zinc is an essential component. Zinc crystals are secreted, which is the procedure that ultimately culminates in the metabolic processes that involve glucose and the phosphorylation activities that involve glucose. An insufficient amount of magnesium has been linked to problems associated with diabetes, insulin resistance, dyslipidemia, carbohydrate intolerance, and other consequences that are associated with these conditions [109]. As a result of the far-reaching consequences that hypomagnesemia has on diabetic treatment, there is a significant association between diabetes mellitus and hypomagnesemia. There is a direct or indirect connection between trace element shortages and oxidative stress, which can result in insulin resistance and diabetes. There appears to be a correlation between the absence of certain trace elements and an increased risk of acquiring diabetes, as well as a worsening of the condition [110].

Treatment of Diabetic Neuropathy

Because of the insufficient pain alleviation and the limited understanding of the aetiology of the ailment, there is still a treatment challenge linked with DNP. This is because the condition needs to be better understood. Only symptoms are treated by pharmacological therapies, except glycemic control therapy; these therapies do not address the pathophysiology that lies under the surface. Additionally, the potential for undesirable effects [3,121] and the development of tolerance [121] are two factors that contribute to the limitations of these therapies. It has been demonstrated through randomized controlled trials that a wide range of medications, either on their own or in combination, considerably lessen the severity of neuropathic pain in contrast to the placebo. However, this does not provide adequate relief from the misery that the vast majority of patients are experiencing [122]. In clinical studies, a treatment is considered successful if it not only decreases pain by fifty percent [123-125], but also has some extra good benefits on sleep, weariness, depression, and quality of life [125]. This is a basic rule that applies to all treatments. Consequently, the key goals of treating this condition are to eliminate the chance that other variables are contributing to painful peripheral neuropathy, use medicine to reduce pain and improve glycemic control as a preventative therapy [126]. Although there are multimodal and interdisciplinary approaches to treatment, the major strategy is pharmacologically based [127]. This is even though there are other treatment options. Pregabalin, duloxetine, and tapentadol are the three drugs that have been approved by the Food and Drug Administration of the United States of America for use in the

treatment of DNP. In order to treat post-traumatic stress disorder (PDPN) without the use of medicines, several non-pharmacological treatments can be utilized. These approaches include stress reduction, acupuncture, nutritional supplements, TENS, FREMS, and SCS. Although most non-pharmacological treatments have a limited body of data, SCS is an exception to this rule and may be considered for specific individuals.

TENS and FREMS

TENS, which stands for transcutaneous electrical nerve stimulation, is a method that does not require any intrusive treatments. It is a technique that involves the delivery of electrical current to nerve fibres through skin electrodes.[128] It is several possibilities, including the gate control theory, the dilation of blood vessels, and the release of endogenous opioids, are among those that have the potential to explain the observed reduction in pain levels. Furthermore, it is necessary to conduct additional prospective trials on a broad scale to determine whether transcutaneous electrical nerve stimulation (TENS) is useful in treating postpartum pancreatitis (PDPN). Another non-invasive therapy option, FREMS, involves applying electrical pulses to the patient's lower extremities through electrodes. This method reduces the risk of the patient experiencing any adverse effects [129]. FREMS has the potential to be introduced into the treatment algorithm for patients who have not responded effectively to two separate classes of neuropathic pain medicines, as indicated by the outcomes of a recent randomized controlled trial (RCT) pilot study project that was referred to as The FREMSTOP research. In addition, the research showed that patients who used FREMS reported feeling less pain and experienced a more significant impact from the treatment. This resulted from the fact that they used FREMS [130].

Spinal Cord Stimulation

During a technique that involves spinal cord stimulation, a pulse generator is surgically placed into the lower back [131]. After that, this generator is connected to percutaneous leads positioned in the epidural region. The SCS measurement method is susceptible to utilizing low frequencies (LF-SCS, 10–100 Hz) and high frequencies (HF-SCS, 1–10 kHz). Both of these frequencies are capable of being utilized. According to the findings of two randomized controlled trials (RCTs), 71% LF-SCS has been demonstrated to significantly lessen the pain experienced by individuals with PDPN and improve their quality of life. There is a possibility that LF-SCS will cause patients to experience paraesthesia, which can be a frightening and upsetting experience for them.[132]. The 75% using 10 kHz SCS in patients with PDPN has been proven to reduce pain (pain relief of at least 50% on the visual analogue scale) and increase health-related quality of life. These beneficial effects have been demonstrated through clinical trials. The results of a recent randomized controlled study (RCT) in the United States support this assertion. Six percent of the people who participated in the trial reported adverse effects related to the experiment.[133]. Infection, wound dehiscence, and slower healing were among the adverse events, and two percent of the individuals required treatment with explanation. Another recent systematic review and network meta-analysis of SCS in PDPN concluded that SCS alleviates pain and improves health-related quality of life [134]. A network of researchers conducted the meta-analysis. On the other hand, the relative advantages of LF-SCS compared to HF-SCS are not yet known because no head-to-head randomized controlled trials have been conducted in the field.71% [135].

Monochromatic Infrared Energy

Research has been conducted to determine whether or not monochromatic infrared energy, sometimes referred to as MIRE, could be used as a treatment for PDPN [136]. The MIRE technique uses light with a wavelength of 890 nm, and it is asserted that this particular wavelength can penetrate the skin and lead to tissue regeneration [137]. Various studies have been conducted to investigate the efficacy of MIRE for PDPN, and the findings of these studies have been diverse. Based on the results of two randomized controlled trials, it was discovered that the application of MIRE greatly enhanced peripheral sensation.[138]. It comes to 76,77 With regard to quality of life (QoL), the Michigan Neuropathy Screening Instrument (MNSI), vibration perception threshold (VPT), Semmes-Weinstein monofilaments (SWM), and nerve conduction velocities, a double-blind, randomized, sham-controlled trial discovered that there were no significant differences between MIRE and sham therapy for sensory neuropathy in DPN. This was the conclusion reached by the researchers. (F) Although there was no change in intraepidermal nerve-fiber density with short-term MIRE usage, there was a symptomatic benefit and an increase in quality of life, according to the findings of another randomized, sham-controlled research study that exclusively examined patients struggling with postpartum pulmonary hypertension (PDPN). The study was conducted on patients experiencing difficulties with their quality of life [139].

Psychological Therapy

Psychological treatment may be helpful for patients who are dealing with concurrent psychological suffering. [140] Psychological therapy comes in the forms of behavioural therapy, acceptance and commitment therapy (ACT), and cognitive behavioural therapy (CBT).81% Patients with post-traumatic stress disorder (PDPN) who received cognitive behavioural therapy (CBT) saw a significant decrease in the severity and intensity of their pain compared to those who received standard care, according to a pilot study of a randomized controlled trial (RCT).[141] According to a review carried out by the Cochrane Collaboration, cognitive behavioural therapy (CBT) has been demonstrated to have a tiny or very small therapeutic effect in people who suffer from chronic pain when it comes to the decrease of pain (moderate quality evidence), distress (moderate quality evidence), and disability (poor quality evidence).81% The data from behavioural treatment and acceptance and commitment therapy (ACT) are of extremely low to middling quality, making it impossible to draw any judgements on the advantages or disadvantages of either 81%

Phytoconstituents in diabetic neuropathy

Non-pharmacological therapies, including electrostimulation, acupuncture, and Traditional Chinese Medicine (TCM), are included in caring for patients with DPN. Natural compounds are defined as the chemical substances derived from living organisms. Plants are the main sources of natural chemicals. Plants produce a wide range of natural compounds known as secondary metabolites. Plants use these compounds as flavouring agents, glues, oils, waxes, dyes, glue substitutes, and perfumes. They are also recognized as possible sources of natural medicines, antibiotics, insecticides, herbicides, and other chemicals [142].

Plant secondary metabolites can be categorized into three main classes according to their metabolic origins: (i) phenolic compounds, (ii) terpenoids, and (iii) nitrogen-containing

alkaloids and sulfur-containing chemicals. Fruits, vegetables, cereals, and beverages are the main sources of naturally occurring phenolic compounds, which have been shown to positively impact human health compared to another group of secondary metabolites [143]. Environmental factors such as sun exposure, soil types, rainfall, and stress significantly impact a plant's polyphenol content [144]. Plant cell vacuoles contain soluble phenolics, whereas insoluble phenolics are found in the cell walls (Fig. 5) [145]. The amount of phenol rings in a compound determines which group it belongs to. The primary groups of phenols are phenolic acids, flavonoids, stilbenes, and lignans.

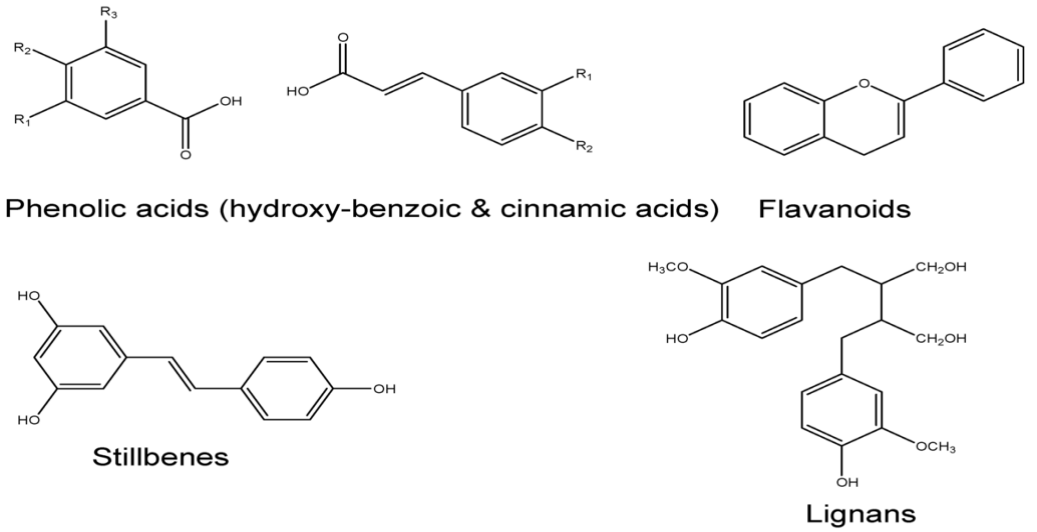


Figure 5: Chemical structures of the different classes of polyphenols

A naturally occurring flavonoid, diosmin is found in large amounts in the pericarp of different citrus fruits (Fig. 6) [149]. It has previously been demonstrated that hyperglycemia, or the overproduction of free fatty acids, induces inflammation that damages mitochondrial DNA and malfunctions pancreatic cells [150]. Tumour necrosis factor (TNF-α), interleukins (IL-1β and 6), macrophage chemotactic protein (MCP-1), and other NF-κB-associated pro-inflammatory chemokines and cytokines were deactivated as a result of antioxidant supplementation with diosmin [151].

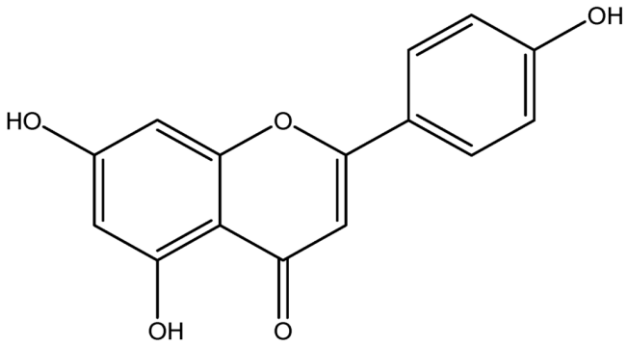


Figure 6: Chemical structure of Apigenin

A naturally occurring flavonoid, diosmin is found in large amounts in the pericarp of different citrus fruits (Fig. 7) [152]. It has previously been demonstrated that hyperglycemia, or the overproduction of free fatty acids, induces inflammation that damages mitochondrial DNA and malfunctions pancreatic cells [153]. Tumour necrosis factor (TNF-α), interleukins (IL-1β and 6), macrophage chemotactic protein (MCP-1), and other NF-κB-associated pro-inflammatory chemokines and cytokines were deactivated as a result of antioxidant supplementation with diosmin [154].

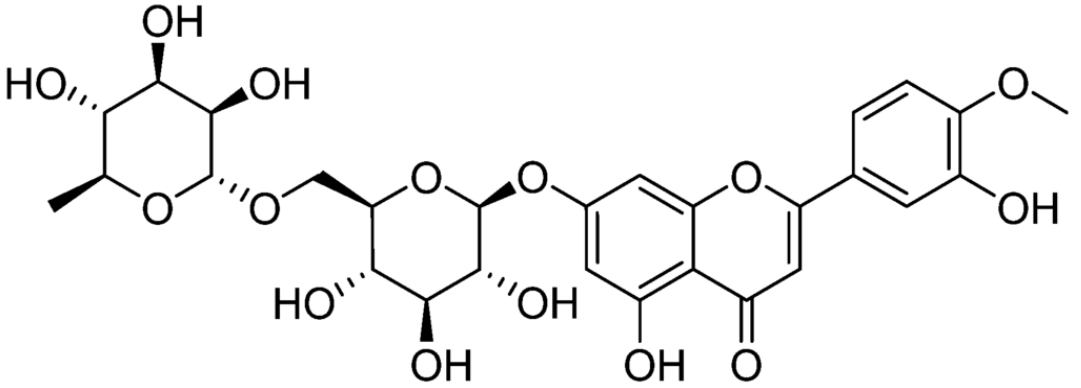


Figure 7: Chemical structure of Diosmin

Numerous foods contain quercetin, such as broccoli, red onions, apples, grapevines, tea, vegetables, and capers (Fig. 8) [155]. Inflammatory mediators activate numerous receptors, and this leads to altered vascular flow, impaired insulin signalling, pancreatic β-cell dysfunction, and endothelial dysfunction, all of which contribute to diabetic vascular problems [156]. Patients with type 1 and type 2 diabetes have been found to have elevated levels of CRP, a measure of systemic inflammation, and endothelial dysfunction indicators [157]. Administrations of quercetin guard against the hyperconstriction of vasoconstriction brought on by diabetes. In both diabetic models, aortic NF-kβ was inhibited and serum levels of TNF-α and CRP were reduced, which led to these results [158].

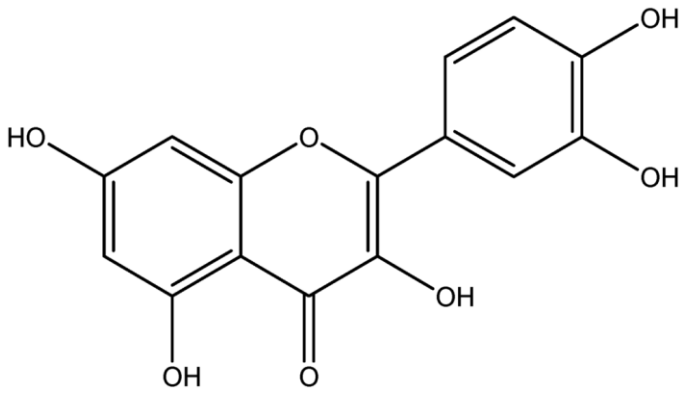


Figure 8: Chemical structure of Quercetin

Kaempferol is a natural flavonol, relatively abundant in grapefruit, tea cruciferous vegetables

and some edible berries (Fig 9) [159]. Previous findings showed that the antioxidant content of Kaempferol reduced IL-1β and TNF-α [160], and kaempferol was also reported to decrease fasting blood glucose and improve insulin resistance significantly. Anti-inflammatory and anti-diabetic kaempferol effects are mediated through AMPK activation [161].

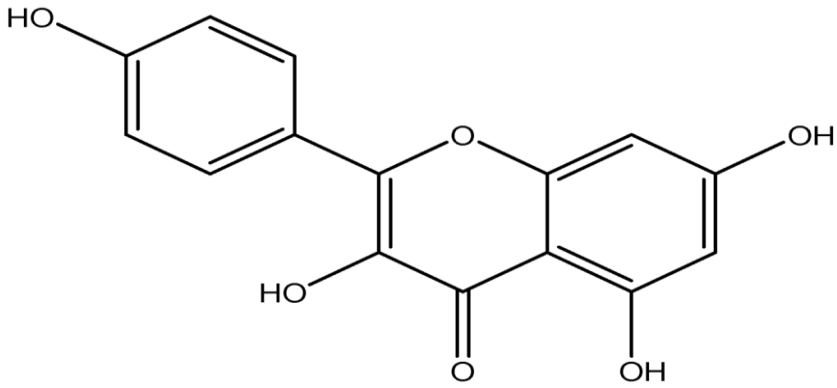


Figure 9: Chemical structure of Kaempferol

A bitter-masking flavanone called eriodictyol is isolated from rose hips, lemons, and Indian beech. According to reports, eriodictyol has anti-inflammatory qualities because it dramatically reduces endothelial NOS (eNOS), vascular endothelial growth factor (VEGF), TNF-α, and neuropathy (Fig. 10) [162]. Eriodictyol supplementation reduced diabetes by upregulating PPARγ2 protein levels in differentiated 3T3-L1 adipocytes and adipocyte-specific fatty acid-binding protein mRNA expression. Moreover, in HepG2 cells with HG-induced insulin resistance, eriodictyol reactivated Akt [163].

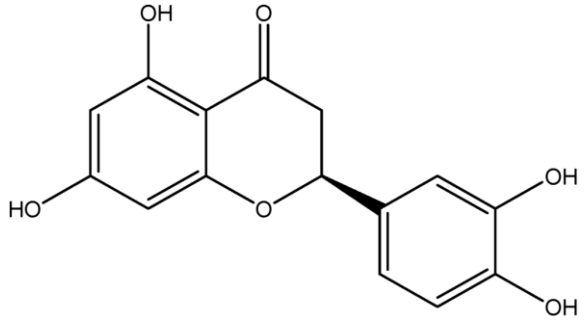


Figure 10: Chemical structure of Eriodictyol

Naringenin is a flavonoid with strong antioxidant potential, and it is present in grapefruit, oranges, and tomatoes (Fig. 11) [164]. Additionally, it was discovered that naringenin prevented reactivity in diabetics by upregulating both 5′ AMPK. High blood sugar stimulates the innate immune system, which causes inflammation and type 2 diabetes [165]. When naringenin is administered, the AMPK pathway is activated more, which improves insulin sensitivity and glucose tolerance [166].

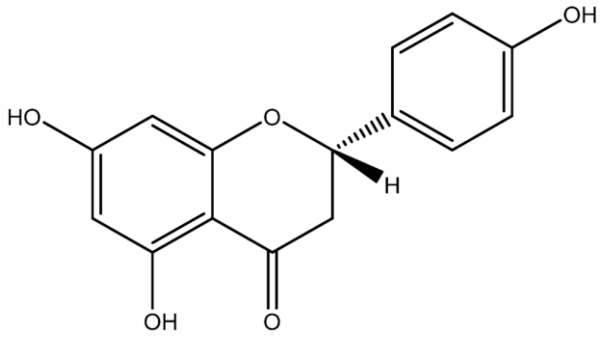


Figure 11: Chemical structure of Naringenin

Citrus fruits such as oranges and lemons contain hesperidin, a flavanone glycoside (Fig. 12) [167]. Hesperidin reduces the symptoms of diabetes by regulating blood sugar and cholesterol levels, reducing the production of free radicals, and releasing cytokines that promote inflammation. Because hesperidin has a great antioxidant capacity, it has also been shown to reduce oxidative stress, which helps prevent damage from oxygen free radicals to cellular organelles and associated enzymes and the development of insulin resistance [168].

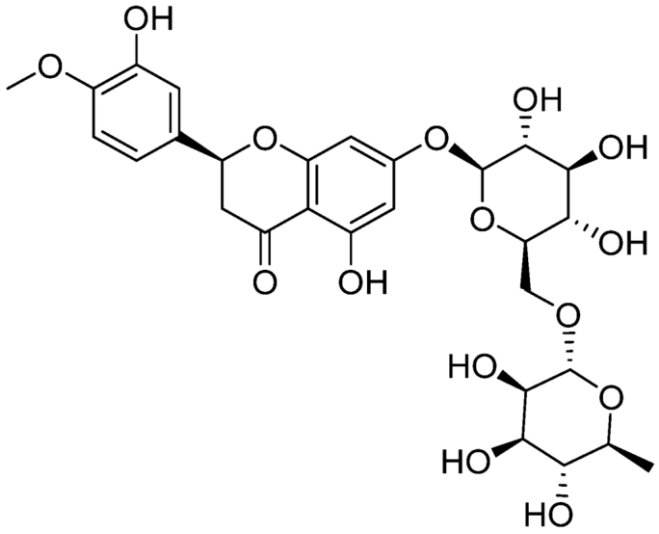
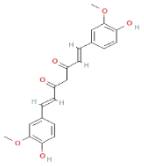
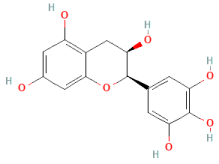
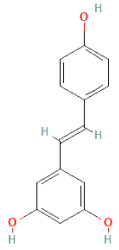


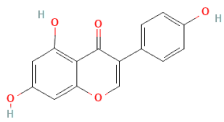
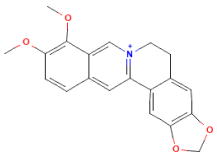
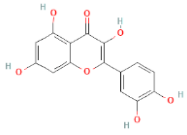
Figure 12: Chemical structure of Hesperidin

However, there are significant side effects linked to medications that attempt to prevent and repair nerve damage as well as treat the pathophysiology of DPN [169]. This makes treating neuropathic symptoms—symptoms brought on by damage to the nerves—like pain, paresthesia, and numbness, especially challenging. Complementary and alternative medicine is gaining popularity in nations like Asia and Europe as a way to manage the symptoms of diabetic poly neuropathy [170]. This holds regardless of whether the treatment is used in addition to or instead of standard pharmaceutical treatments. Many therapeutic modalities, such as laser treatment, magnet therapy, and acupuncture, are commonly used during these procedures [171]. Children and adults alike can benefit from this treatment by lessening their

symptoms of acute, chronic, and degenerative disorders and improving their general health. Very thin needles are inserted into specific anatomical locations during traditional acupuncture treatments in Asia to create a more harmonious flow of life force and help remove stagnant energy, also known as chi. When it comes to clinical efficacy, acupuncture is unquestionably better at relieving the symptoms associated with neurological disorders. In one study, for example, patients benefited more from a regimen of six acupuncture sessions plus continuous nefazodone medication in two out of three cases.[172] Furthermore, DPN patients were asked to participate in an alternative experiment. According to the protocols of traditional Chinese medicine, the patients in this trial received either acupuncture (n = 42) or no acupuncture (n = 21). Diagnostic palpation was used in this trial to identify sensitive areas. At the end of the clinical trial, acupuncture treatment alleviated the symptoms of diabetic peripheral neuropathy (DPN), suggesting that it may hasten the regeneration of nerve terminals.

Table 1: Bio active compound in an animal model for diabetic macro vascular complication[173]

Bio active compound	Study model	Duration	Study outcomes
Curcumin 	Rat model of diabetic neuropathy	12 week	It lowered the expression of toll-like receptor 4 (TLR4) and suppressed the production of renal inflammatory genes and the phosphorylation of caveolin-1 at Tyr14. Reduced production of proinflammatory CKs and TLR4 was another finding, as was the HG-triggered phosphorylation of caveolin-1.
Epigallocatechin 	Rat model of diabetic neuropathy	12 week	Decreased VCAM-1 and ICAM-1 expressions; enhanced glomerular enlargement and mesangial matrix expansion;
Resveratrol 	Mouse model of neuropathy	7 days	The phosphorylation and production of adenosine mono phosphate-activated protein kinase (AMPK) protein were significantly reduced, as were protein carbonyl oxidative stress (OS) indicators and super oxide anions.
Genistein	Rat model of diabetic neuropathy	2 weeks	TNF-α levels were decreased in both mRNA and protein; activated microglial cells were prevented from secreting TNF-α and phosphorylating P38 and extracellular signal-regulated kinase (ERK) through the suppression of tyrosine kinase; multiple

			inflammatory signaling pathways in activated microglia were disrupted, including P38 MAPKs and ERK mechanisms.
Berberine 	Mouse model of diabetic neuropathy	8 weeks	Deactivated the nuclear factor-κB (NF-κB) signaling, lowered the apoptosis of the retinal ganglion cell layer, and reduced the occurrence of diabetes-related ocular degeneration. HG-mediated effects on apoptosis and oxidative stress in Müller cells were reversed.
Quercetin 	Rat model of diabetic neuropathy	6 week	Increased levels of interleukin-1β and TNF-α were significantly improved, while the expressions of NF-κB, myeloid differentiation factor 88, and TLR4 were significantly reduced.

One non-pharmacological alternative that may be explored for DPN therapy is electrostimulation [173]. Studies have indicated that electrotherapy may be a useful treatment for severe and persistent diabetic peripheral neuropathy [174].

Out of 52 patients with DPN who had spinal cord stimulation, 42 of them reported a reduction in leg pain of more than 50%, according to the research done [175]. These patients also reported improvements in their quality of life and functional ability. In 1998, Kumar carried out a study including thirty-one participants with peripheral neuropathy signs and symptoms. This was where the original data came from. Transcutaneous electrostimulation (TES) was used to provide electrotherapy to eighteen patients; the control group, which included thirteen patients, did not receive this treatment. This group received treatment at home for four weeks at the lower extremities using a four millisecond pulse with a frequency greater than two hertz for half an hour every day [176]. Peripheral neuropathy patients who received electostimulation reported less pain and discomfort [177], and none of the electostimulated patients experienced any negative side effects. Given that this is the case, more research is likely needed to see whether or not this treatment can be adjusted to be given once a week until the patient experiences no more pain, and then once a month thereafter. The part that natural materials play in acupuncture and traditional Chinese medicine as supplementary and alternative therapies for DPN patients is another crucial issue that has to be addressed. [178] The benefits of using all-natural medicines to cure disease and injuries have grown significantly over time. The current emphasis of research is to find novel, potentially effective medications that can offer a safe therapy without causing the ever-growing side effects that are being reported. Considering this viewpoint, traditional eastern medicine—especially Chinese medicine—was a trailblazing field of study. In China, herbal medications are utilized

alone or in combination with more traditional medical therapies when it comes to DPN [178]. Herbal therapies can be divided into three groups based on their use: patented Chinese herbal medications, self-prescribed formulations, and herbs used only once [179]. These groups include both oral and topical applications of herbs. Traditional Chinese medicine (TCM) holds that the elements of wood, fire, earth, metal, and water, as well as yin and yin, Qi (life energy) and Xue (blood), are in harmony with one another [71]. When each of these components is balanced with the others, a state of health of this kind is considered achieved. The well-known medications used in traditional Chinese medicine come from natural sources. Four bullet points are provided below to highlight the best theories held by Traditional Chinese Medicine (TCM) about the aetiology and pathophysiology of DPN [180].There is a deficiency of either yin (black) or yang (white), the two forms of energy. They are regarded as one of the eight principles of Traditional Chinese Medicine (TCM), along with excess and deficiency, heat and cold, internal and external, and internal and external medicine. There is a chilly feeling inside when these concepts are out of alignment. Prolonged diabetes mellitus, alterations in blood viscosity resulting in modifications to blood flow and absorption into organs and tissues (blood stasis, microvascular coagulation, obstruction of sinews and channels); obesity accompanied by damage to the stomach and spleen; changes in muscle, sinew, and channel physiology; changed physiology due to liver and kidney deficiencies; and tissue necrosis and altered physiology. Conversely, Feng and colleagues (2005) highlighted the positive attributes linked to natural products. Studies have demonstrated that aldose reductase inhibitors, which include several traditional medicinal herbs, can either stop or postpone the onset of diabetes-related complications, including diabetic nephropathy, peripheral neuropathy, vasculopathy, and neuropathy [181]. Several flavonoids from this class, including quercetin, silymarin, puerarin, baicalim, and berberine, have been found to have strong inhibitory effects [180]. Furthermore, if one searches Medline for "medicinal herbs and diabetic peripheral neuropathy," Pubmed returns sixteen hits. The most current of these, cited in reference [182], is an intriguing collection of plants with pharmacological qualities for DPN. It includes the following: Astragalus Radix (TCN: Huang Qi), Angelicae Sinensis Radix (TCN: Danggui), Pheretima (TCN: Dilong), Carthami Flos (TCN: honghua), Rehmanniae Radix (TCN: dihuang), Paeoniae Radix Rubra (TCN: chishao), Cyathulae Radix (TCN: chuanniuxi), Asari Radix and Rhizoma (TCN: xixin), and Scolopendra (TCN: wugong). Both functional deficiencies and diabetic neuropathy have been associated with low vitamin B12 levels. Furthermore, vitamin B12's pharmacological benefits against diabetic peripheral neuropathy (DPN) have been contrasted with vitamin B12. Metformin-using diabetic patients are particularly vulnerable to this [183]. Moreover, some data suggests the specific herb Astragalus Radix may have qi-tonifying properties [184]. It has been shown that the astragaloside herb family, which includes Radix Astragalus membranaceus Bunge (Astragaloside IV), is protective against DPN. This is usually the case. It has been discovered that Angelicae Sinensis Radix (Dang Gui) and Paeoniae Radix Rubra (Chi Shao) both have a blood-tonifying effect [185]. At the same time, Chuan Xiong Rhizoma is a treatment that has been shown to enhance blood circulation. Another well-known ingredient in traditional Chinese medicine (TCM) that seems to have therapeutic advantages against direct pulmonary hypertension (DPN) is guineasine, which is derived from Piper longum [186]. Lastly, but just as importantly, laboratory data supports TCM's efficacy. The most recent study on the subject of "diabetic peripheral neuropathy and alternative medicine" was published on Pubmed in 2013 and consists of six articles. The most

recent of these studies shows that streptozotocin-induced diabetic peripheral neuropathy (DPN) in rats was positively affected by Tang-Luo-Ning (TLN) [187]. Traditional Chinese medicine (TCM) has shown promising results when using TLN to treat acute pancreatitis [188]. According to the Traditional Chinese Medicine (TCM) theory, Huang Qi, Chishao, and Salvia miltiorrhiza Bge. (Danshen) are the three traditional Chinese herbs that are fundamentally needed for the TLN formula. For patients who are diagnosed with DPN, TLN may be a life-saving alternative therapy because the results show that it is quite effective in stopping the disease's progression [189,190].

Future Prospective

No drug that is both safe and effective for treating DN is currently on the market. One possible approach to managing DN and other neurological complications associated with diabetes is the use of bioactive chemicals, which have anti-inflammatory and neuroprotective properties. Contrarily, bioactive substances can modulate DN through various signaling pathways. Reversing diabetic eye damage is another possible use for them as a safe and efficient treatment option. Additional clinical and preclinical trials are needed to determine how well these bioactive chemicals regulate different signaling pathways. A further use for quantitative structure-activity relationship (QSAR) modelling is the synthesis of powerful analogues of naturally occurring pharmaceuticals. Therefore, safer and more cost-effective ways to treat DN could be to create and use plant bioactive molecules. More than that, diabetic rat models have retinas susceptible to neurotrophic effects, reduced oxidative stress, and decreased apoptosis, all of which are antidiabetic. Further research is needed to better understand how phytochemicals can help reduce microvascular complications of diabetes, such as DN. Bioactive chemicals may have neuroprotective, antioxidant, and antidiabetic effects, but this must be proven in clinical trials on DN patients.

2. Conclusion

Diabetic neuropathy is a complicated and significant ailment that is related to lifestyle choices. It is a condition that is continuously growing and has the potential to become one of the health epidemics shortly. An excessive quantity of sugar consumption, obesity, a lack of physical activity, and environmental variables are all contributing factors that cause elevated glucose levels. These elevated glucose levels, in turn, affect the peripheral nerves of the brain, which ultimately results in diabetic neuropathy. Different aspects of lifestyle and a lack of understanding regarding nutritional practices also play a significant part in developing this condition. As a result of their poor pharmacokinetics and adverse effects, the drugs that are currently accessible are not used very frequently. If sustained efforts to use therapeutic plants continue, herbal medicinal plants and the bioactive compounds they contain have the potential to be a solution for diabetic neuropathy with minimal or no adverse effects. This is because therapeutic plants are involved in the analgesic effects and pathways, which include anti-inflammatory, neuroprotective, antioxidant, anti-apoptotic, and calcium-inhibitory actions. Even though the therapeutic role of medicinal plants in managing diabetic neuropathy has been recorded, clinical trials have not yet been explored for their potential application. As a result, the herbal formulation that has been described ought to be promoted and supported to circumvent the problems related to conventional pharmaceuticals.

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