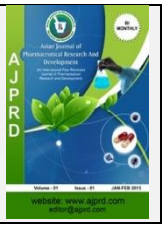
Available online on 15.10.2025 at http://ajprd.com

Asian Journal of Pharmaceutical Research and Development

Open Access to Pharmaceutical and Medical Research



Open Access

Review Article

Exploring the Role of Natural Agents in the Management of Diabetic-Induced Neuropathy

Darshan Anil Sonawane, Sunil K Mahajan, Chandrashekhar Patil, Durgesh Pagar, Gaurav Kasar

Department of Pharmacy, SSS's Divine College of Pharmacy, Satana, Nashik

A B S T R A C T

Nephropathy, retinopathy, cardiomyopathy, and peripheral neuropathy are some of the most common and serious complications of diabetes mellitus (DM), affecting around 50% of patients. These issues often arise due to poor blood sugar control or inadequate management of diabetes. Among these, diabetic peripheral neuropathy (DPN) is particularly troubling, as it's not only widespread but also the most painful. This work aims to explore the various approaches used to manage DPN, from traditional treatments to more alternative options. We'll dive into common medications, comparing the effectiveness of gabapentin and pregabalin, which are often used when regular painkillers like NSAIDs or opioids don't work. We'll also look at the wisdom of Oriental Medicine, which offers unique perspectives, and examine the potential of natural compounds that researchers suggest could be effective either alone or alongside current treatments. Lastly, we'll discuss ancient practices like acupuncture and electrostimulation as potential non-drug alternatives that may provide relief for those suffering from DPN.

Keywords:-Diabetes, Neuropathy, Peripheral, DPN, Gabapentin, Neuropathy.

A R T I C L E I N F O: Received 14 March 2025; Review Complete 12 May 2025; Accepted 19 August 2025. ; Available online 15 Oct. 2025

Cite this article as:
Sonawane D A, Mahajan SK, Patil C, Pagar D, Kasar G, Exploring the Role of Natural Agents in the Management of Diabetic-Induced Neuropathy, Asian Journal of Pharmaceutical Research and Development. 2025; 13(5):89-96,
DOI: http://dx.doi.org/10.22270/ajprd.v13i5.1633

*Address for Correspondence:
Darshan Anil Sonawane, Department of Pharmacy, SSS's Divine College of Pharmacy, Satana, Nashik

INTRODUCTION

Diabetes is one of the most prevalent and escalating metabolic disorders worldwide, posing significant health and economic challenges. Not only does the disease itself present a major concern, but its associated secondary complications are also grave and costly[1]. Among the complications that arise, microangiopathies—which affect small blood vessels—can lead to conditions like nephropathy and optic nerve damage, contributing to retinopathies. Diabetic peripheral neuropathy (DPN) is another major concern, and it often manifests as pain, tingling, or numbness in the hands, arms, feet, and legs, primarily due to poor diabetes control[2]. In more severe cases, uncontrolled diabetes can progress to macroangiopathies, leading to life-threatening conditions such as stroke[3].

Focusing specifically on the neurological damage caused by diabetes, this review aims to address the growing challenge of DPN. For those suffering from symptomatic DPN, the sensory symptoms can be intense and varied, including spontaneous sensations like tingling, burning, or a "pins and needles" feeling, as well as more negative symptoms like numbness or a loss of sensitivity to pain. These symptoms typically begin in the toes and, over time, may spread to the feet, legs, fingers, and hands. Neuropathic pain is often one of the first signs of DPN and can be debilitating, even when there are few other noticeable symptoms. Patients commonly describe their feet as feeling "tight" and experiencing stabbing, burning, or electric-like sensations, which can severely impact their quality of life[4].

In light of these challenges, this review provides a comprehensive look at conventional treatments for DPN, but it also emphasizes the importance of alternative approaches. Recent trends show that many individuals are turning to self-care methods, including complementary and alternative medicine (CAM), which are increasingly gaining attention for their potential to improve quality of life. CAM practices focus on a wide range of self-care activities, such as preventative measures, symptom management, and interactions with informal healthcare sources[4]. Research

indicates that patients often turn to CAM therapies not necessarily for their proven effectiveness, but because of their perceived safety and the more holistic approach they offer to managing their condition.

However, it's worth noting that many physicians may not be well-versed in CAM treatments, which often remain on the periphery of mainstream medical practice. This knowledge gap highlights the need for more widespread education on these therapies and their potential benefits. A concerted effort to increase awareness could foster a cultural shift within the medical community, encouraging a more integrative approach to managing diabetes-related complications[5].

Therefore, this review will also explore some of the most commonly used practices from Eastern medicine, as well as natural compounds believed to have therapeutic potential. While some of these treatments are still in the experimental stages, they offer promising possibilities for harnessing the healing properties of natural substances. These approaches could one day become integral to clinical practice, complementing conventional treatments and offering patients additional options for managing DPN and improving their overall well-being.

The Growing Impact of Diabetes Mellitus

The global statistics surrounding diabetes mellitus are significant and continue to rise at an alarming rate. According to the World Health Organization (WHO), the number of people diagnosed with diabetes has seen a dramatic increase since 1980. At that time, there were 153 million people living with diabetes worldwide[6]. By 2008, this number had nearly doubled to 347 million, and projections suggest that by 2025, the number of individuals with diabetes will soar to 380 million, accounting for about 7.1% of the world's adult population. These numbers highlight diabetes as a growing global health crisis affecting individuals across all income levels—high, middle, and low-income countries alike[7].

The global burden of diabetes-related deaths is also striking. In 2008, there were 57 million deaths worldwide, with 36 million (63%) attributed to non-communicable diseases (NCDs). These NCDs primarily include cardiovascular diseases, cancers, chronic respiratory conditions, and diabetes. Diabetes alone was responsible for 1.3 million deaths, underlining its severity as a public health issue[8].

Currently, the vast majority of diabetes cases—over 90%—are type 2 diabetes mellitus (T2DM), and its prevalence has been steadily rising in recent years. The increase is largely driven by the growing prevalence of risk factors such as obesity, physical inactivity, and an aging population[9]. Additionally, advancements in treatment and management have improved the survival rates of those living with T2DM. However, this improvement in longevity has also led to a surge in diabetes-related complications. Chronic conditions such as diabetic retinopathy, nephropathy, and the onset of diabetic peripheral neuropathy (DPN) are common among long-term diabetic patients[10]. While DPN affects about 8.3% of individuals newly diagnosed with T2DM, it can rise to as high as 50% in patients who have had diabetes for 25 years or more.

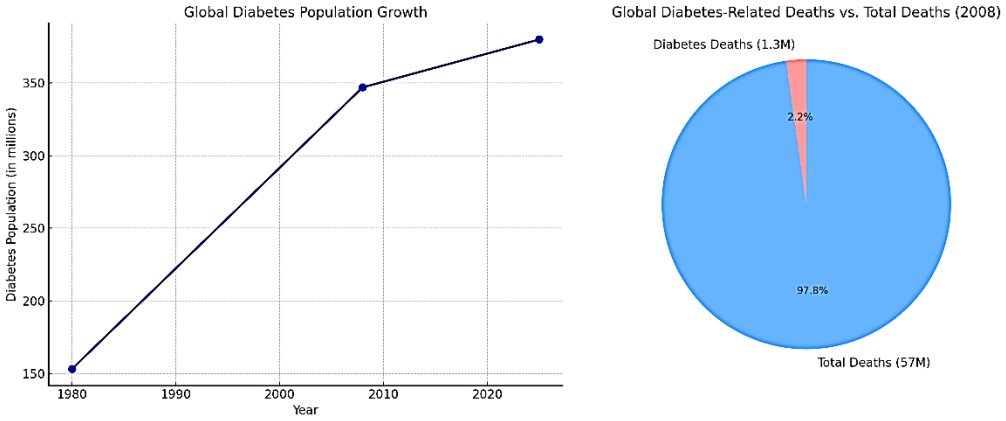


Figure 1: The visual representation of the global diabetes-related statistics

The financial cost of managing diabetes is staggering. In the United States, the economic burden of diabetes was estimated to be around $174 billion in 2007, based on healthcare costs for the 17.5 million adults living with the disease. This does not include indirect costs such as lost productivity or the societal impacts of the disease[11]. Across the globe, national healthcare systems and patients are grappling with the high costs of diabetes treatment and management.

In Italy, data from the AgenziaItaliana del Farmaco (AIFA) covering the period from 2002 to 2011 shows a steady increase in diabetes medication prescriptions, with an average annual increase of 1.9%. Notably, the prescription of metformin, a first-line treatment for T2DM, saw a significant rise of 14.3%. This suggests that metformin has become an increasingly popular and trusted medication for managing T2DM. With the rising incidence of diabetes, it's clear that efforts to improve prevention, treatment, and overall management are more critical than ever in tackling this global health challenge[12].

Recent data further emphasizes the growing problem of diabetes. According to the International Diabetes Federation (IDF) 2021 report, an estimated 537 million adults (20-79 years old) were living with diabetes globally in 2021, a number expected to reach 643 million by 2030 and 784 million by 2045. The rise in diabetes cases is linked not only to lifestyle factors but also to the aging global population and urbanization trends, particularly in developing nations[13].

The scale of this issue calls for increased awareness, better prevention strategies, and more effective treatments to manage the disease and its associated complications. As the numbers continue to grow, it's essential that healthcare systems worldwide are equipped to address the rising prevalence of diabetes and provide adequate care and resources to those affected[14].

Neuropathic Pain in Diabetic Peripheral Neuropathy (DPN) and Other Conditions

This section is not intended to be a comprehensive review of neuropathic pain, but rather an illustrative overview to show how pain—especially neuropathic pain—can link various diseases with different causes, particularly neurological and neurodegenerative disorders, alongside diabetic peripheral neuropathy (DPN), which is a common complication of diabetes mellitus (DM). It's important to understand that pain, particularly when it's neuropathic, can often be a common thread between conditions that, on the surface, seem unrelated but share a similar underlying mechanism of nerve damage[15].

Pain is often one of the first signs of inflammation in the body. Inflammatory pain occurs when tissues are damaged and immune cells infiltrate the area, contributing to pain sensations. This can be the result of trauma, burns, post-surgery recovery, or pain associated with certain diseases. Pain is a complex experience that varies in its intensity, duration, and the underlying causes. For example, it can be acute or chronic, localized or spread across larger areas of the body, and somatic (relating to the body) or visceral (relating to internal organs)[16]. The causes of pain can be grouped into three categories: nociceptive pain, inflammatory pain, and pathological pain.

- **Nociceptive pain** is a protective sensation that alerts the body to potential tissue damage. It's the kind of pain you feel when you touch something hot or get a cut—your body's way of saying, "move away to protect yourself."
- **Inflammatory pain** occurs when tissue damage leads to an immune response. This type of pain can persist as long as the underlying cause remains, such as in conditions like arthritis or infections.
- **Pathological pain**, as defined by the International Association for the Study of Pain (IASP), arises from damage to the nervous system, whether peripheral (in the nerves outside the brain and spinal cord) or central (in the brain and spinal cord). It includes neuropathic pain, which is caused by nerve damage that sends incorrect signals to the brain, or dysfunctional pain, where the body responds abnormally to normal signals, resulting in persistent pain sensations despite no real injury.

Under normal circumstances, pain is an unpleasant but vital sensation that helps protect the body. For example, it encourages us to avoid dangerous situations or take care of injuries promptly. However, when pain becomes chronic or is the result of nerve damage, as in neuropathic pain (NP), it can be much harder to treat and can seriously affect a person's quality of life. Chronic pain accounts for a significant portion of primary care visits, with about 40% of patient appointments in these settings being related to pain, and 20% of those patients suffering from pain lasting for six months or more[18].

When we focus specifically on chronic pain, particularly neuropathic pain, we see that it can develop as a secondary issue, often following another primary disease or injury. The onset, timing, and severity of neuropathic pain can vary widely, and in many cases, identifying the exact cause can be challenging. This type of pain is difficult to manage because it is often severe, persistent, and unresponsive to standard pain medications. Neuropathic pain arises when nerve fibers become damaged, often due to conditions like DPN, multiple sclerosis, or even chemotherapy[19]. These damaged nerves send incorrect signals to the brain, causing pain sensations even in the absence of any actual harm. In some cases, surrounding areas near the damaged nerves also become highly sensitive to pain, even though they aren't directly injured.

What makes neuropathic pain so difficult to treat is that it's not just about numbing pain signals like with typical pain relief methods. It's about addressing the underlying nerve dysfunction, which is why simple analgesics often don't work. This form of pain requires a more specialized approach, combining medications that target nerve signals and therapies that address the broader nervous system dysfunction[20].

Neuropathic pain is a complex condition, but understanding its origins and mechanisms is key to improving treatment strategies. Whether it's caused by diabetes, trauma, or other neurological disorders, addressing neuropathic pain requires a multi-faceted approach, one that not only focuses on pain relief but also on treating the nerve damage and restoring proper function. Nearly one-third of individuals with diabetes mellitus are diagnosed with neuropathic pain (NP), with diabetic peripheral neuropathy (DPN) being one of the most common and debilitating complications[21]. Studies show that between 16% and 26% of diabetic patients experience DPN, characterized by sharp, stabbing, or burning pain in the feet. This pain is often accompanied by other sensations such as tingling, numbness, or a "pins and needles" feeling, all of which reflect some degree of inflammation in the affected nerves[22]. In fact, DPN is a direct result of either macro- or microscopically identifiable nerve damage or disease processes that affect the somatosensory system. The pain experienced in DPN can include spontaneous pain, parasthesia (abnormal sensation), and heightened sensitivity to mechanical and thermal stimuli, leading to a phenomenon called hyperalgesia (exaggerated pain response) or allodynia (pain from stimuli that are not normally painful)[23].

While diabetes is primarily a metabolic disorder, the link between neuropathic pain and other non-communicable diseases (NCDs), particularly neurodegenerative disorders, is

increasingly recognized. Conditions like Multiple Sclerosis (MS), Guillain-Barré Syndrome (GBS), and Parkinson's Disease (PD) are known to often lead to neuropathic pain. These disorders trigger neuroinflammatory mechanisms in the body, which involve the activation of glial cells in the brain and spinal cord. These cells make up about 70% of the total cell population in the central nervous system and play a key role in the development of pain and nerve dysfunction[24].

Interestingly, the onset of neuropathy in some patients with neurodegenerative diseases can also be linked to the side effects of their treatments. For example, patients with Parkinson's Disease (PD) treated with levodopa—a common medication for PD—often experience a higher prevalence of neuropathic pain. This has been associated with elevated levels of fasting methylmalonic acid (MMA), which have been linked to sensorimotor neuropathy. This highlights the complex relationship between neurodegenerative diseases, their treatments, and the development of neuropathic pain, which often complicates both the condition and its management[25].

Overall, neuropathic pain is a challenging aspect of both diabetes and neurodegenerative diseases, and understanding the mechanisms behind it is crucial for improving treatment strategies and enhancing the quality of life for patients.

Conventional Treatments for Diabetic Peripheral Neuropathy: A Comparison of Gabapentin and Pregabalin

Monitoring blood sugar levels in both Type 1 and Type 2 diabetes is essential for preventing complications such as diabetic peripheral neuropathy (DPN). DPN is one of the most common and disabling complications of diabetes, yet effective treatments remain elusive. Pain management for DPN often involves common analgesics like non-steroidal anti-inflammatory drugs (NSAIDs) and opioids, but these medications are not always sufficient and can cause significant side effects[26]. Tramadol, a semi-synthetic opioid, is frequently used as a second-line treatment. It works by interacting with opioid receptors and affecting serotonin and norepinephrine levels. However, tramadol is not without its risks, including seizures and psychiatric side effects, even at low doses. Moreover, long-term use of opioid-based medications can lead to additional complications such as gastrointestinal issues, osteoporosis, depression, and cognitive decline[27]. Given the limitations of these traditional painkillers, doctors often turn to medications originally designed for other conditions, such as anti-epileptic drugs, to treat DPN. One of the most commonly used medications for neuropathic pain is gabapentin, which is prescribed widely in the UK for managing both general neuropathic pain and DPN symptoms. Since gabapentin's patent has expired, generic versions are now available, making it an affordable option. It has largely replaced carbamazepine in DPN treatment, offering significant relief from pain without the harmful side effects of earlier treatments like bone marrow suppression and osteoporosis[27].

In recent years, there has been a shift towards prescribing pregabalin (brand name: Lyrica®) in place of gabapentin in some regions, particularly in Italy. Pregabalin, a more potent analogue of gabapentin, was approved in 2005 for treating neuropathic pain associated with DPN, postherpetic neuralgia, and partial-onset seizures[28]. Despite its growing use, clinical studies have shown that pregabalin does not offer significant advantages over gabapentin in terms of efficacy or safety, especially considering its higher cost. globally, spending on neuropathic pain treatment reached €116.6 million, with pregabalin accounting for 0.9% of this total. Pregabalin's daily consumption is around 1.2 prescriptions per 1,000 people, reflecting its increasing prescription rates. In the last year, prescriptions for pregabalin grew by 13.5%, accompanied by a 13.8% increase in spending[29]. However, clinical trials suggest that pregabalin's benefits are limited compared to gabapentin, which is prescribed in much larger quantities and remains a more affordable option. Ultimately, while both gabapentin and pregabalin are commonly used to treat DPN, gabapentin continues to be the more cost-effective and clinically reliable choice. Pregabalin, though popular, has not proven to be more effective than gabapentin, underscoring the importance of ongoing evaluation of treatment options for DPN[30].

Alternative Medicine in the Management of DPN

Non-pharmacological and alternative therapies are increasingly being explored for managing diabetic peripheral neuropathy (DPN), particularly for alleviating neuropathic symptoms such as pain, paresthesia, and numbness[31]. While conventional treatments focus on managing the pathogenesis of DPN and preventing nerve damage, these therapies often come with significant side effects. As a result, many patients and healthcare providers are turning to complementary treatments, which have gained popularity in Europe and the Far East, either as standalone options or in combination with traditional pharmacological therapies[32].

Studies have shown that acupuncture can offer clear clinical benefits in reducing symptoms associated with neurological disorders. For example, one study found that six sessions of acupuncture, combined with ongoing nefazodone therapy, led to significant symptom improvement in two out of three patients with DPN. Another study involving 63 DPN patients showed that acupuncture improved symptoms and may even accelerate nerve regeneration. This suggests that acupuncture may play a role in both symptom management and promoting nerve recovery[33].

Another alternative approach to DPN management is **electrostimulation**, which has been explored for its effectiveness in treating chronic pain associated with peripheral neuropathy. The use of electrical currents to relieve pain dates back to ancient Egypt, Greece, and Rome, where it was observed that electric shocks from fish could provide pain relief. Modern studies have confirmed the benefits of electrostimulation in treating DPN[34]. In a study by Henson and colleagues, more than 50% of patients with DPN experienced significant pain relief after spinal cord stimulation, leading to improved quality of life and functional capacity. In an earlier trial conducted in 1998, patients with peripheral neuropathy showed an 83% improvement in pain levels after four weeks of transcutaneous electrical nerve stimulation (TENS). This study demonstrated that electrostimulation could reduce discomfort without any side effects, and suggested further

research to determine the optimal frequency of treatment for long-term pain relief[35].

Traditional Chinese Medicine (TCM) also offers promising alternative treatments for DPN, particularly through the use of natural compounds. Over centuries, Chinese medicine has developed a deep understanding of the healing properties of herbs and other natural products, which are increasingly being incorporated into modern treatment regimens. In China, herbal remedies are often used either alone or alongside conventional treatments to manage DPN symptoms. These herbal formulations can be taken orally or applied topically and may include self-prescribed herbal formulas, individual herbs, or patented Chinese herbal medicines[36].

In TCM, health is viewed as a state of balance between the forces of yin and yang, the flow of Qi (life energy), and the harmony of the five elements: wood, fire, earth, metal, and water. This holistic perspective informs the approach to treating DPN. According to TCM, the development of DPN can be attributed to several factors:

1. **Yin or Yang Deficiency**: Imbalances in these foundational elements can generate an internal "cold," contributing to symptoms of DPN.
2. **Prolonged Duration of Diabetes**: Chronic diabetes can lead to blood viscosity changes, microvascular coagulation, and impaired blood circulation, causing blood stagnation that affects the organs and tissues.
3. **Obesity**: Excess weight can impair the spleen and stomach, leading to further complications in DPN[37].
4. **Tissue Necrosis**: Damage to tissues, muscles, and sinews, often linked to liver and kidney deficiencies, contributes to the pathology of DPN.
5. Through these perspectives, TCM seeks to restore balance in the body, improve circulation, and strengthen the organs involved in managing blood flow, offering a comprehensive approach to managing DPN symptoms[38].

Phenolic Compounds

Diabetes is widely recognized as an oxidative stress disorder, resulting from an imbalance between the production of free radicals and the body's ability to neutralize them with natural antioxidants. Many studies have indicated that oxidative stress plays a crucial role in systemic inflammation, endothelial dysfunction, impaired pancreatic β-cell function, and decreased glucose utilization in peripheral tissues, which ultimately lead to long-term complications of diabetes[39].Recent research highlights the potential benefits of natural phenolic compounds in managing diabetic peripheral neuropathy (DPN). A variety of fruits and vegetables are rich in phenolic acids, which are known to have multiple physiological and pharmacological effects[40]. These compounds help combat oxidative stress by scavenging free radicals and protecting against photooxidation. Studies, both in vitro and in vivo, have shown that phenolic acids possess significant antioxidant properties, along with anti-inflammatory, antiallergic, and anti-mutagenic effects. Additionally, they have been found to support cardiovascular health. Certain phenolic acids, such as chlorogenic acid, syringic acid, and vanillic acid, have shown cytoprotective properties that may help prevent complications from diabetic neuropathy by inhibiting neuronal cell cycle dysfunction and apoptosis[41].

One promising compound is hydroxytyrosol, a polyphenolic compound derived from olive oil. Known for its potent antioxidant properties, hydroxytyrosol has demonstrated beneficial effects both in human studies and experimental settings. For instance, in rat models of diabetes induced by streptozotocin, hydroxytyrosol was shown to mitigate secondary neuropathy associated with the condition[42].

Efforts to discover new compounds for treating DPN are a major research focus. For example, an ongoing study at Rajiv Gandhi University of Health Sciences is investigating the antioxidant properties of Terminalia bellericaRoxb, a plant known for its hypoglycemic effects in rats. Terminalia bellirica, which contains ellagic and gallic acids, has been a staple in traditional Indian medicine, particularly in Ayurvedic treatments for digestive and liver disorders[43].

Numerous natural compounds from plants continue to show promise as potential treatments for DPN. For instance, a methanol extract of **Allium cepa** (common onion) has been found to offer more significant improvement in treating diabetic neuropathy in mice than **Allium sativum** (garlic), likely due to its higher phenolic content. Similarly, an animal study on **Momordica Charantia Linn.** (bitter melon) has shown that its extract possesses antioxidant and neuroprotective properties, in addition to its well-established hypoglycemic effects[44]. This plant has long been used in traditional medicine and is gaining attention for its potential in managing DPN, especially in models of streptozotocin-induced diabetic neuropathy.

Fatty Acids and the Role of Evening Primrose Oil in Neuropathic Pain Management

Linoleic acid (LA) is a primary dietary essential fatty acid (EFA), crucial for various biological processes. In the 1950s, a study by Brenner and colleagues on diabetic rats led to the discovery of the enzyme Δ-6-desaturase, which converts linoleic acid into γ-linolenic acid (GLA). GLA is an essential component of myelin and neuronal cell membranes. This conversion is the first step in the production of prostaglandin E1 (PGE1), which has anti-inflammatory, antiplatelet, and vasodilating properties. Alternatively, when the conversion process is slower, linoleic acid can be metabolized into arachidonic acid and its by-products, including prostaglandin E2 (PGE2), leukotrienes, and thromboxane, which promote inflammation, vasoconstriction, and platelet aggregation[45].

The study revealed that diabetic rats had significantly impaired Δ-6-desaturase activity, which resulted in the need for much higher amounts of linoleic acid compared to normal animals. This impairment of the enzyme was later shown to occur in both type 1 and type 2 diabetes patients, leading to lower levels of PGE1 and higher levels of PGE2 and thromboxane, contributing to the inflammatory processes associated with diabetes. As a result, dietary supplementation with gamma-linolenic acid (GLA)-rich products, such as evening primrose oil, was suggested to help increase the

production of PGE1 and improve the inflammatory balance[46].

Evening Primrose Oilis derived from the seeds of *Oenotherabiennis* and is a rich source of omega-6 fatty acids, particularly GLA and LA[47]. Commercial evening primrose oil preparations typically contain 8% GLA and 72% LA. A recent study demonstrated the antioxidant benefits of a combination of α-lipoic acid and evening primrose oil, showing an improvement in neuropathic pain through the increased synthesis of PGE1. This suggests that evening primrose oil, by enhancing PGE1 production, could potentially help alleviate symptoms of neuropathic pain, making it an important consideration for managing diabetic neuropathy and related conditions[48].

Table 1: Summary of Alternative Therapies and Compounds for Managing Diabetic Peripheral Neuropathy (DPN)

Kind of Therapy/Class of Compounds	Genus/Species	Subclass of Compound
Alkaloids	*Papaver somniferum* (Poppy)	**Morphine**
	Erythroxylum coca	**Cocaine**
	Serotonin (found in roots, leaves, fruits, and seeds from species like dates, papayas, and bananas)	**Serotonin**
Cannabinoids	*Cannabis sativa*	**Δ9-Tetrahydrocannabinol (THC), Cannabidiol (CBD)**
Electrotherapy	-	**Electric Stimulation**
Acupuncture	-	**Needle Therapy**
Phenolic Compounds	*Allium cepa* (Onion), *Allium sativum* (Garlic)	**Sulfides, Allicin**
	Momordicacharantia (Bitter Melon)	**Phenolic Acids**
	Terminalia bellirica	**Ellagic and Gallic Acids**
	Coffea (Coffee), *Camellia sinensis* (Tea)	**Caffeine**
Essential Fatty Acids	*Oenotherabiennis* (Evening Primrose)	**Gamma-linolenic acid (GLA)**
Oriental Chinese Medicine	*Astragalusmembranaceus*	**Astragaloside IV**
	Piper longum	**Guineensine**
	Salvia miltiorrhiza (Danshen)	**Tanshinones**
	Hirudo	**Hirudin**
	Codonopsispilosula	**Polysaccharides**
	Angelica sinensis (Dong Quai)	**Ligustilide**
	Rehmanniaglutinosa	**Iridoid Glycosides**
	Paeonialactiflora	**Paeoniflorin**
Vanilloids	*Capsicum annuum* (Chili Pepper)	**Capsaicin**
Spatholobi Caulis	*Spatholobussuberectus*	**Flavonoids**
Cyathulae Radix	*Cyathulaeofficinalis*	**Triterpenes**

CONCLUSION:

Diabetic Peripheral Neuropathy (DPN) presents a significant challenge in the management of diabetes mellitus, leading to debilitating symptoms such as pain, numbness, and tingling. Despite the availability of conventional treatments like gabapentin and pregabalin, the effectiveness of these medications remains limited, with some patients turning to alternative therapies for relief. Complementary approaches such as acupuncture, electrostimulation, and the use of natural compounds offer promising benefits, particularly in symptom management and nerve regeneration. Furthermore, phenolic compounds and essential fatty acids like Gamma-linolenic acid from evening primrose oil show potential in addressing oxidative stress and inflammation associated with DPN. While these alternative treatments hold promise, more research and clinical trials are necessary to validate their efficacy and integrate them effectively with conventional treatments. Overall, a multifaceted approach that combines pharmacological and non-pharmacological strategies may offer the best outcomes in managing DPN and improving patients' quality of life.

REFERENCE:

1. Tomic D, Shaw JE, Magliano DJ. The burden and risks of emerging complications of diabetes mellitus. Nat Rev Endocrinol. 2022 Sep;18(9):525-539. doi: 10.1038/s41574-022-00690-7. Epub 2022 Jun 6. PMID: 35668219; PMCID: PMC9169030.
2. Parker ED, Lin J, Mahoney T, Ume N, Yang G, Gabbay RA, ElSayed NA, Bannuru RR. Economic Costs of Diabetes in the U.S. in 2022. Diabetes Care. 2024 Jan 1;47(1):26-43. doi: 10.2337/dci23-0085. PMID: 37909353.
3. Bodman MA, Dreyer MA, Varacallo MA. Diabetic Peripheral Neuropathy. [Updated 2024 Feb 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK442009

4. Syahriyani, St & Yusuf, Saldy&Syam, Yuliana. (2021). The effectiveness of complementary and alternative medicine therapy in reducing pain in diabetic neuropathy: A systematic review. Public Health of Indonesia. 7. 31-40. 10.36685/phi.v7i1.385.
5. Salih S, Jawahi TA, Al Salem RH, Alhazmi SA, Buayti AA, Alammari AH, Mashi HM, Dobea LA, Muaddi MA. Bridging the knowledge-practice gap: A cross-sectional survey assessing physician knowledge, attitude and practice toward complementary and alternative medicine. PLoS One. 2025 May 14;20(5):e0322613. doi: 10.1371/journal.pone.0322613. PMID: 40367283; PMCID: PMC12077789.
6. Al-Emadi S, Al-Shehhi F, et al. Undiagnosed diabetes mellitus in rural communities in Sudan: prevalence and risk factors. *Eastern Mediterranean Health Journal*. 2015;21(3):123-131. Available from: https://www.emro.who.int/emhj-volume-21-2015/volume-21-issue-3/undiagnosed-diabetes-mellitus-in-rural-communities-in-sudan-prevalence-and-risk-factors.html
7. *Diabetes in India*. Wikipedia [Internet]. Wikimedia Foundation; updated 2 months ago [cited 2025 Aug 19]. Available from: *Diabetes in India* article, Wikipedia.
8. Balakumar, P., Maung-U, K., &Jagadeesh, G. (2016). Prevalence and prevention of cardiovascular disease and diabetes mellitus. *Pharmacological research*, *113*(Pt A), 600–609. https://doi.org/10.1016/j.phrs.2016.09.040
9. Zheng, Y., Ley, S. H., & Hu, F. B. (2018). Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nature reviews. Endocrinology*, *14*(2), 88–98. https://doi.org/10.1038/nrendo.2017.151
10. Elendu, C., John Okah, M., Fiemotongha, K. D. J., Adeyemo, B. I., Bassey, B. N., Omeludike, E. K., &Obidigbo, B. (2023). Comprehensive advancements in the prevention and treatment of diabetic nephropathy: A narrative review. *Medicine*, *102*(40), e35397. https://doi.org/10.1097/MD.0000000000035397
11. American Diabetes Association (2018). Economic Costs of Diabetes in the U.S. in 2017. *Diabetes care*, *41*(5), 917–928. https://doi.org/10.2337/dci18-0007
12. Ingrasciotta, Y., Bertuccio, M. P., Crisafulli, S., Ientile, V., Muscianisi, M., L'Abbate, L., Pastorello, M., Provenzano, V., Scorsone, A., Scondotto, S., &Trifirò, G. (2020). Real World Use of Antidiabetic Drugs in the Years 2011-2017: A Population-Based Study from Southern Italy. *International journal of environmental research and public health*, *17*(24), 9514. https://doi.org/10.3390/ijerph17249514
13. Sun, H., Saeedi, P., Karuranga, S., Pinkepank, M., Ogurtsova, K., Duncan, B. B., Stein, C., Basit, A., Chan, J. C. N., Mbanya, J. C., Pavkov, M. E., Ramachandaran, A., Wild, S. H., James, S., Herman, W. H., Zhang, P., Bommer, C., Kuo, S., Boyko, E. J., &Magliano, D. J. (2022). IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes research and clinical practice*, *183*, 109119. https://doi.org/10.1016/j.diabres.2021.109119
14. Davies MJ, Gray LJ, Ahrabian D, et al. A community-based primary prevention programme for type 2 diabetes mellitus integrating identification and lifestyle intervention for prevention: a cluster randomisedcontrolled trial. Southampton (UK): NIHR Journals Library; 2017 Jan. (Programme Grants for Applied Research, No. 5.2.) Chapter 2, Systematic review. Available from: https://www.ncbi.nlm.nih.gov/books/NBK409310
15. Colloca, L., Ludman, T., Bouhassira, D., Baron, R., Dickenson, A. H., Yarnitsky, D., Freeman, R., Truini, A., Attal, N., Finnerup, N. B., Eccleston, C., Kalso, E., Bennett, D. L., Dworkin, R. H., & Raja, S. N. (2017). Neuropathic pain. *Nature reviews. Disease primers*, *3*, 17002. https://doi.org/10.1038/nrdp.2017.2
16. Jain, A., Gyori, B.M., Hakim, S. *et al.* Nociceptor-immune interactomes reveal insult-specific immune signatures of pain. *Nat Immunol* 25, 1296–1305 (2024). https://doi.org/10.1038/s41590-024-01857-2
17. Ras T. (2020). Chronic non-cancer pain management in primary care. *South African family practice : official journal of the South African Academy of Family Practice/Primary Care*, *62*(1), e1–e4. https://doi.org/10.4102/safp.v62i1.5203
18. Iannitti, T., Kerr, B. J., & Taylor, B. K. (2014). Mechanisms and pharmacology of neuropathic pain in multiple sclerosis. *Current topics in behavioral neurosciences*, *20*, 75–97. https://doi.org/10.1007/7854_2014_288
19. sante CO, Wallace VC, Dickenson AH. Mammalian target of rapamycin signaling in the spinal cord is required for neuronal plasticity and behavioral hypersensitivity associated with neuropathy in the rat. The journal of pain : official journal of the American Pain Society. 2010;11:1356–1367.
20. Attal N. (2019). Pharmacological treatments of neuropathic pain: The latest recommendations. *Revue neurologique*, *175*(1-2), 46–50. https://doi.org/10.1016/j.neurol.2018.08.005
21. Didangelos T, Doupis J, Veves A. Painful diabetic neuropathy: clinical aspects. In: Aminoff MJ, Boller F, Swaab DF, editors. *Handbook of Clinical Neurology*. Vol. 126. Amsterdam: Elsevier; 2014. p. 53-61. doi:10.1016/B978-0-444-53480-4.00005-9.
22. Bodman MA, Dreyer MA, Varacallo MA. Diabetic peripheral neuropathy [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan– [updated 2024 Feb 25; cited 2025 Aug 19]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK442009/
23. esfaye S, Boulton AJ, Dyck PJ, Freeman R, Horowitz M, Kempler P, et al. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care. 2010 Oct;33(10):2285-93. doi:10.2337/dc10-1303.
24. Dhir S, Derue H, Ribeiro-da-Silva A. Temporal changes of spinal microglia in murine models of neuropathic pain: a scoping review. *Front Immunol.* 2024 Dec 6;15:1460072. doi: 10.3389/fimmu.2024.1460072.
25. Toth C, Breithaupt K, Ge S, Duan Y. Levodopa, methylmalonic acid, and neuropathy in idiopathic Parkinson disease. Ann Neurol. 2010 Jul;68(1):28-36. doi:10.1002/ana.22021.
26. Pop-Busui R, Boulton AJ, Feldman EL, Bril V, Freeman R, Malik RA, et al. Diabetic Neuropathy: A Position Statement by the American Diabetes Association. Diabetes Care. 2017 Jan;40(1):136–54. doi:10.2337/dc16-2042.
27. Wiffen, P. J., Derry, S., Bell, R. F., Rice, A. S., Tölle, T. R., Phillips, T., & Moore, R. A. (2017). Gabapentin for chronic neuropathic pain in adults. *The Cochrane database of systematic reviews*, *6*(6), CD007938. https://doi.org/10.1002/14651858.CD007938.pub4
28. Cao, X., Shen, Z., Wang, X., Zhao, J., Liu, W., & Jiang, G. (2023). A Meta-analysis of Randomized Controlled Trials Comparing the Efficacy and Safety of Pregabalin and Gabapentin in the Treatment of Postherpetic Neuralgia. *Pain and therapy*, *12*(1), 1–18. https://doi.org/10.1007/s40122-022-00451-4
29. Mayoral V, Gálvez R, Ferrándiz M, Miguéns Vázquez X, Cordero-García C, Alcántara Montero A, Pérez C, Pérez-Páramo M. Pregabalin vs. gabapentin in the treatment of neuropathic pain: a comprehensive systematic review and meta-analysis of effectiveness and safety. Front Pain Res. 2025 Jan 7;5:1513597. doi:10.3389/fpain.2024.1513597.
30. Athanasakis, K., Petrakis, I., Karampli, E., Vitsou, E., Lyras, L., &Kyriopoulos, J. (2013). Pregabalin versus gabapentin in the management of peripheral neuropathic pain associated with post-herpetic neuralgia and diabetic neuropathy: a cost effectiveness analysis for the Greek healthcare setting. *BMC neurology*, *13*, 56. https://doi.org/10.1186/1471-2377-13-56
31. Pop-Busui R, Ang L, Boulton AJM, et al. Diagnosis and treatment of painful diabetic peripheral neuropathy. Arlington (VA): American Diabetes Association; 2022 Feb. Available from: https://www.ncbi.nlm.nih.gov/books/NBK580224/doi: 10.2337/db2022-01
32. Merghany, R.M., Saleh, R.A., Hamed, A.A. *et al.* Natural therapy proposed for the management of diabetic peripheral neuropathy (DPN). *Inflammopharmacol* (2025). https://doi.org/10.1007/s10787-025-01790-2
33. Ge, R., Liu, R., He, M., Wu, J., Zhang, F., & Huang, C. (2024). The efficacy of acupuncture for diabetic peripheral neuropathy: a systematic review and meta-analysis of randomized controlled trails. *Frontiers in neurology*, *15*, 1500709. https://doi.org/10.3389/fneur.2024.1500709
34. Nahm F. S. (2020). From the torpedo fish to the spinal cord stimulator. *The Korean journal of pain*, *33*(2), 97–98. https://doi.org/10.3344/kjp.2020.33.2.97
35. Henson, J. V., Varhabhatla, N. C., Bebic, Z., Kaye, A. D., Yong, R. J., Urman, R. D., &Merkow, J. S. (2021). Spinal Cord Stimulation for Painful Diabetic Peripheral Neuropathy: A Systematic Review. *Pain and therapy*, *10*(2), 895–908. https://doi.org/10.1007/s40122-021-00282-9

36. Jin, D., Huang, W. J., Meng, X., Yang, F., Zheng, Y. J., Bao, Q., Zhang, M. Z., Yang, Y. N., Ni, Q., Lian, F. M., & Tong, X. L. (2017). Chinese herbal medicine TangBi Formula treatment of patients with type 2 diabetic distal symmetric polyneuropathy disease: study protocol for a randomized controlled trial. *Trials*, *18*(1), 631. https://doi.org/10.1186/s13063-017-2345-1

37. Piao, Y., & Liang, X. (2012). Chinese medicine in diabetic peripheral neuropathy: experimental research on nerve repair and regeneration. *Evidence-based complementary and alternative medicine :eCAM*, *2012*, 191632. https://doi.org/10.1155/2012/191632

38. Li, Y. Y., Guan, R. Q., Hong, Z. B., Wang, Y. L., & Pan, L. M. (2024). Advances in the treatment of diabetic peripheral neuropathy by modulating gut microbiota with traditional Chinese medicine. *World journal of diabetes*, *15*(8), 1712–1716. https://doi.org/10.4239/wjd.v15.i8.1712

39. Wang J, Ma Q, Li Y, Li P, Wang M, Wang T, et al. Research progress on Traditional Chinese Medicine syndromes of diabetes mellitus. *Biomed Pharmacother*. 2019;120:109565. doi: 10.1016/j.biopha.2019.109565

40. Sarkar D, Christopher A, Shetty K. Phenolic bioactives from plant-based foods for glycemic control. *Front Endocrinol (Lausanne)*. 2022 Jan 18;12:727503. doi: 10.3389/fendo.2021.727503

41. Rashedinia, M., Alimohammadi, M., Shalfroushan, N., Khoshnoud, M. J., Mansourian, M., Azarpira, N., &Sabahi, Z. (2020). Neuroprotective Effect of Syringic Acid by Modulation of Oxidative Stress and Mitochondrial Mass in Diabetic Rats. *BioMed research international*, *2020*, 8297984. https://doi.org/10.1155/2020/8297984

42. Ristagno, G., Fumagalli, F., Porretta-Serapiglia, C., Orrù, A., Cassina, C., Pesaresi, M., Masson, S., Villanova, L., Merendino, A., Villanova, A., Cervo, L., Lauria, G., Latini, R., & Bianchi, R. (2012). Hydroxytyrosol attenuates peripheral neuropathy in streptozotocin-induced diabetes in rats. *Journal of agricultural and food chemistry*, *60*(23), 5859–5865. https://doi.org/10.1021/jf2049323

43. Gupta A, Kumar R, Pandey AK. Antioxidant and antidiabetic activities of Terminalia bellirica fruit in alloxan induced diabetic rats. *S Afr J Bot*. 2020;130:308-315. doi: 10.1016/j.sajb.2019.12.010

44. Richter, E., Geetha, T., Burnett, D., Broderick, T. L., &Babu, J. R. (2023). The Effects of *Momordicacharantia* on Type 2 Diabetes Mellitus and Alzheimer's Disease. *International journal of molecular sciences*, *24*(5), 4643. https://doi.org/10.3390/ijms24054643

45. Xing, Y., Pi, M., Zhang, R., & Wen, T. (2021). Study on the TCM Syndromes Evolution and Chinese Herbal Characteristics of Type 2 Diabetes Patients with Different Courses of Disease in TCM "Heat Stage": A Real-World Study. *Evidence-based complementary and alternative medicine :e CAM*, *2021*, 1282957. https://doi.org/10.1155/2021/1282957

46. Li, Y. Y., Guan, R. Q., Hong, Z. B., Wang, Y. L., & Pan, L. M. (2024). Advances in the treatment of diabetic peripheral neuropathy by modulating gut microbiota with traditional Chinese medicine. *World journal of diabetes*, *15*(8), 1712–1716. https://doi.org/10.4239/wjd.v15.i8.1712

47. El-Kossi AA, Abdellah MM, Rashad AM, Hamed S. The effectiveness of evening primrose oil and alpha lipoic acid in recovery of nerve function in diabetic rats. *J Clin ExpInvestig*. 2011;2(3):245-253. doi: 10.5799/ahinjs.01.2011.03.0049

48. Won, J. C., Kwon, H. S., Moon, S. S., Chun, S. W., Kim, C. H., Park, I. B., Kim, I. J., Lee, J., Cha, B. Y., & Park, T. S. (2020). γ-Linolenic Acid versus α-Lipoic Acid for Treating Painful Diabetic Neuropathy in Adults: A 12-Week, Double-Placebo, Randomized, Noninferiority Trial. *Diabetes & metabolism journal*, *44*(4), 542–554. https://doi.org/10.4093/dmj.2019.0099.