Therapeutic Potential of Herbal Plants from North East India in Managing Diabetic Neuropathy: A Review

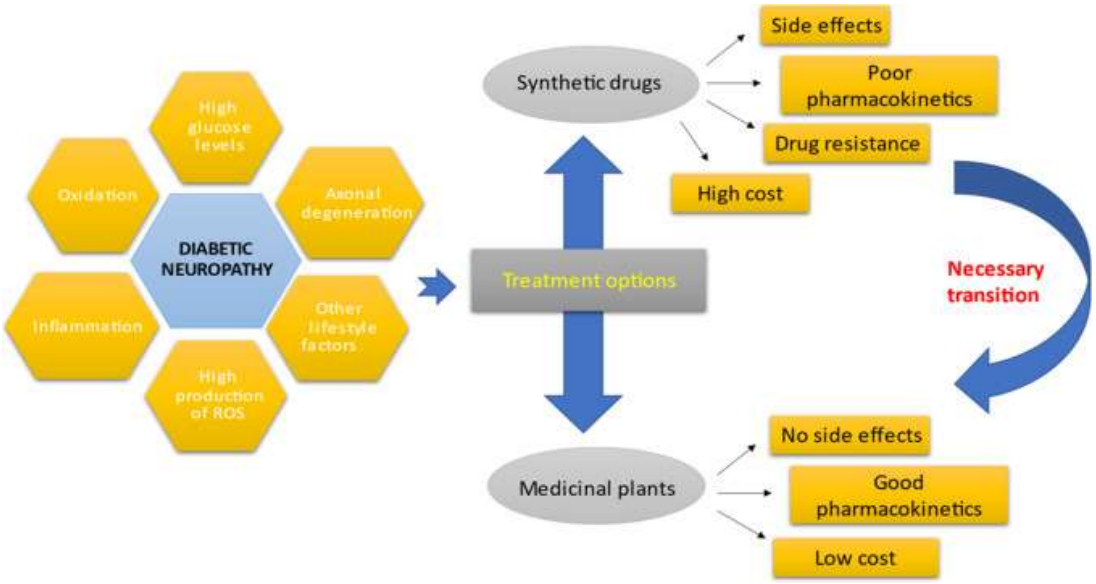
Karan Kumar Das[1,2], Biplab Debnath[3], Saikat Sen[4]*

[1]*PhD Scholar, Faculty of Pharmaceutical Science, Assam down town University, Guwahati, Assam, India.*
[2]*Assistant Professor of Bharat Technology, Uluberia, Howrah, West Bengal, India.*
[3]*Professor & Principal of Bharat Technology, Uluberia, Howrah, West Bengal, India.*
[4]*Professor & Dean, Faculty of Pharmaceutical Science, Assam down town University, Guwahati, Assam, India.*

***Corresponding author: Dr. Saikat Sen**

Faculty of Pharmaceutical Science, Assam down town University, Guwahati, Assam, India - 781068.
saikat.pharm@rediffmail.com ; saikat.sen@adtu.in

Graphical Abstract



Abstract

Diabetes mellitus is currently reaching pandemic proportions globally, being directly responsible for the dire consequences accompanying both diseases. Diabetes disrupts blood flow to the peripheral nervous system, potentially causing neuropathy—a frequent outcome. Neuropathy results in sensory loss, injuries, diabetic foot issues, and, in severe instances, even death. Diabetic neuropathy, typically linked to uncontrolled high blood glucose levels, also correlates with factors like advanced age, high body mass index (BMI), inflammation, elevated HbA1c levels, and heightened blood pressure, collectively heightening type 2 diabetes risk. Currently, the sole available treatment for diabetic neuropathy involves lowering the patient's overall

metabolic glucose levels. Medicinal approaches comprise anticonvulsants, N-methyl-D-aspartate receptor (NMDAR) antagonists, serotonin-norepinephrine reuptake inhibitors (SNRIs), and reactive oxygen species (ROS) inhibitors. Nevertheless, trust in synthetic pharmaceuticals has diminished due to their adverse effects—hallucinations, drowsiness, memory loss—coupled with high costs, suboptimal pharmacokinetics, and drug resistance development. Consequently, herbal medicine is undergoing a global resurgence. This article compiles medicinal plants like: *Acacia arabica*, *Aegle marmelos, Allium cepa , Aloe vera, Capparis deciduas, Momordica charantia, Ocimum sanctum, Phyllanthus amarus, Gingko Biloba, Atriplex hortensis, Clerodendrum colebrookianum, Curcuma longa*, *Verbena officinalis* etc. available in North East India that showcasing proven anti diabetic properties, analgesic and anti-inflammatory properties and their possible usefulness in diabetic neuropathy.

Keywords: Medicinal plants, Diabetes mellitus, Diabetic neuropathy, Pain, Treatment

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Introduction

The global epidemics of diabetes mellitus are directly responsible for the severe complications associated with both diseases [1]. Neuropathy, a common diabetes complication, stems from disrupted blood flow to the peripheral nerve system. Neuropathy can result in sensory loss, injuries, diabetic foot issues, and even fatality. The condition known as diabetic neuropathy is most frequently linked to poorly controlled high blood glucose levels. However, other significant markers include advancing age, high body mass index (BMI), inflammation, elevated HbA1c levels, and high blood pressure [2].

Commonly recommended medications include anticonvulsants, N-methyl-D-aspartate receptor (NMDAR) antagonists, serotonin-norepinephrine reuptake inhibitors (SNRIs), and inhibitors of reactive oxygen species (ROS). However, public trust in synthetic drugs has been undermined due to their side effects (hallucinations, drowsiness, memory deficits), high cost, subpar pharmacokinetics, and drug resistance. This has prompted a global resurgence of herbal medicine [3].

The International Diabetes Federation (IDF) estimates that 425 million people worldwide have diabetes [1], making it the largest global epidemic of the 21st century [2]. China has 115 million people, India has 73 million, and the United States has 30 million individuals with diabetes [3]. These figures pale in comparison to those with prediabetes—estimated at 388 million in China [4], 133 million in India [5], and 85 million in the United States [6]. Diabetes and its complications account for 12% of global health expenditure, totalling $727 billion, a number steadily increasing at an unsustainable rate. Among diabetes complications, damage to the peripheral and autonomic nervous systems leads to a group of clinical syndromes, predominantly neuropathies. These syndromes encompass diffuse and focal nervous system damage and occur in up to half of all individuals with diabetes. The most prevalent form, diabetic neuropathy, presents as distal symmetric polyneuropathy, characterized by a 'stocking and glove' distribution affecting the hands and lower limbs. Other diffuse and focal neuropathies, including autonomic neuropathies and isolated mononeuropathies, can also arise due to diabetes-related nerve damage. Fig 1 represents the different forms of neuropathy. In recent times, there has been a notable increase in the utilization of medicinal plants for treating various ailments and discovering bioactive components for managing different diseases. This review is dedicated to

exploring the potential therapeutic applications of diverse medicinal plants indigenous to North East India, particularly in the context of managing diabetic neuropathy.

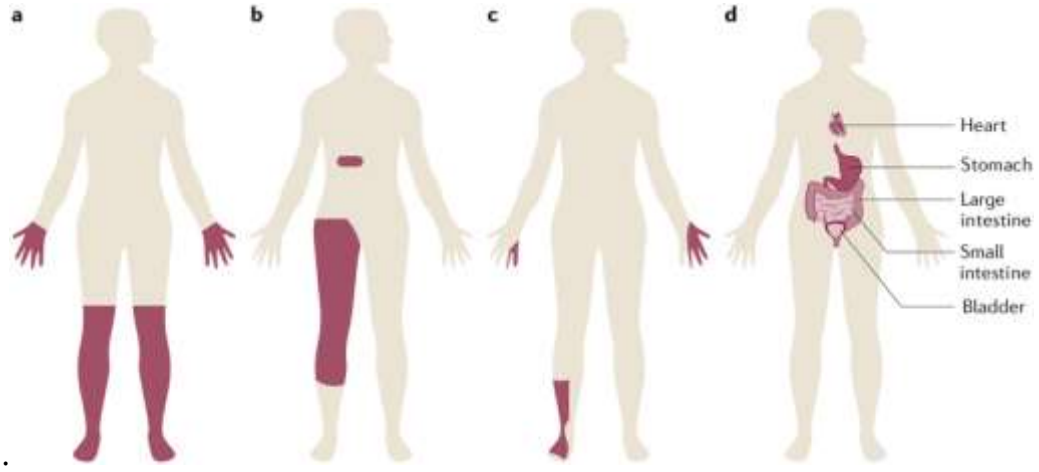

Fig: 1 People with diabetes may experience several distinct forms of neuropathy. Among these, distal symmetric polyneuropathy (DSP), also known as small-fiber-predominant neuropathy, stands as the most prevalent. Variations in neuropathy patterns include DSP, small-fiber-predominant neuropathy, treatment-induced neuropathy (part a); radiculoplexopathy or radiculopathy (part b); mononeuropathy (part c); and autonomic neuropathy or treatment-induced neuropathy (part d). While the neurological examination and nerve conduction velocity investigation results differ between patients with small-fiber-predominant neuropathy and those with DSP, both conditions share the same distribution. In contrast to various other nerve damage types associated with diabetes, diabetic radiculopathy and diabetic radiculoplexopathy respond well to immunotherapy and often show improvement over time. Treatment-induced neuropathy, triggered by overly stringent glycemic control, remains insufficiently acknowledged despite its diverse manifestations (parts a and d).

Pathophysiology of Diabetic Neuropathy

Although there has been a significant advancement in our understanding of the pathophysiological mechanisms that contribute to the development of diabetic complications, the elusive nature of a plausible hypothesis for why some patients develop the painful form of the disease while others do not persist. While there has been significant advancement in our understanding of the pathophysiological mechanisms that contribute to the development of diabetic complications, this complexity is linked to neuropathy's involvement. It's important to note that pain is not always proportionate to the degree of neuropathy and can manifest even in the absence of nerve damage [4,5], presenting an intriguing phenomenon. A consensus exists that the toxic effects of hyperglycemia play a significant role in triggering this complication [6,7]. Diabetic neuropathy (DNP) affects various organ systems and is optimally managed by an interprofessional team. Given the absence of a cure, prevention becomes paramount. All individuals with diabetes should undergo a dietary consultation and receive education on suitable dietary choices, focusing on realistic plans that lower blood glucose levels. Engaging in a rehabilitation program or incorporating exercise aids in weight loss, facilitating blood sugar, blood pressure, and lipid control. A podiatry consultation is crucial for foot protection, and patients should be informed about avoiding trauma and any invasive foot procedures without prior endocrinologist clearance. Additionally, patients should avoid exposure to extreme cold or hot temperatures. A dedicated diabetic nurse should educate patients about all aspects of diabetes

and the significance of maintaining euglycemia. Patients should be instructed on blood glucose monitoring and the proper use of portable glucose monitors. Compliance with diabetic medications is vital. Finally, patients developing neuropathy often have concurrent nephropathy and retinopathy. As a result, all individuals with diabetes should be referred to a nephrologist and ophthalmologist. Effective communication within the interprofessional team ensures patients receive the available standard of care with minimal morbidity. Foot and nail care nurses monitor patients, provide education, and keep the team informed about the patient's condition. Pharmacists educate patients about medication usage and the significance of adherence.

Polyol- Pathway hyperactivity

Most often, metabolic disorders underlie diabetic neuropathy. The condition known as hyperglycemia, arising from impaired insulin secretion or insulin resistance, triggers increased activity in the polyol pathway [8]. This process involves the oxidation of nicotinamide adenine dinucleotide phosphate (NADPH) into NADP+, facilitated by sorbitol dehydrogenase, which converts sorbitol to fructose by altering oxidized nicotinamide adenine dinucleotide (NAD+) into its reduced form, NADH. During hyperglycemic states, aldose reductase exhibits higher glucose affinity, leading to sorbitol accumulation. However, the presence of negligible sorbitol concentrations in the nerves of diabetic patients suggests that this osmotic stress doesn't solely cause subsequent nerve damage [9]. This chain of events results in reduced glutathione regeneration, increased advanced glycation end product (AGE) production, and the activation of diacylglycerol and protein kinase C (PKC) isoforms [10]. The decline in glutathione, potentially the main instigator of oxidative stress, might be linked to toxic species accumulation, as described in [11]. While animal models have shown that aldose reductase inhibitors can prevent diabetic neuropathy, human trials have proved their ineffectiveness and dose-limiting toxicity [12].

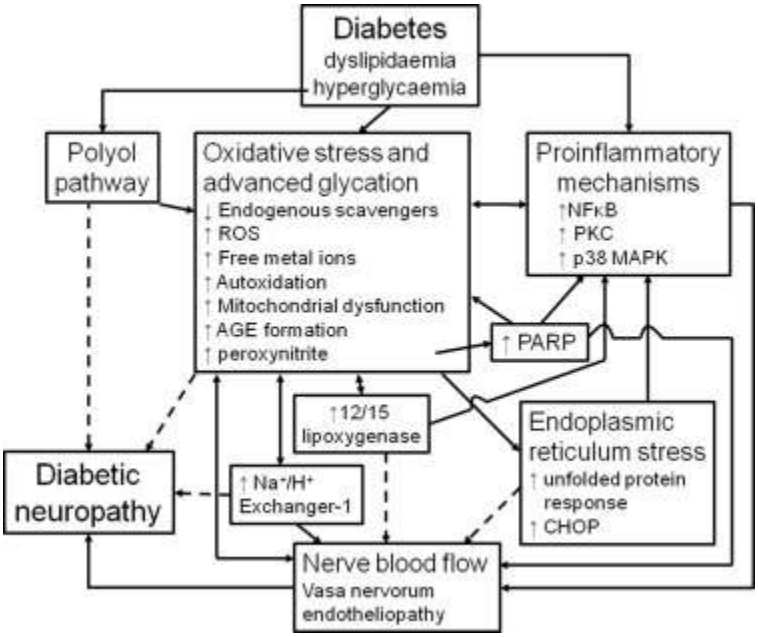

Fig: 2 Pathogenesis of diabetic neuropathy

Pathogenesis of diabetic neuropathy

Neuropathic pain is defined as pain arising from a lesion or disorder of the somatosensory nervous system. Approximately 30–50% of diabetic neuropathy patients experience neuropathic pain, which primarily presents as spontaneous (i.e., stimulus-independent) burning pain in the feet. Additional positive sensory symptoms include brush-evoked allodynia (pain induced by non-noxious stimuli) and paresthesias. These positive sensory symptoms often coincide with sensory loss, prompting patients to remark on the paradox of continuous foot pain despite insensitivity to touch. The reasons why some individuals with diabetic neuropathy experience neuropathic pain while others do not remain uncertain. This likely results from a multifaceted interplay of vulnerabilities, encompassing genetic factors, somatosensory circuitry, psychological elements under stressors like diabetes-induced metabolic dysfunction, and neuropathy severity. Most studies evaluating neuropathic pain risk factors in diabetic neuropathy are cross-sectional, lacking prospective analysis and often employing univariate rather than multivariate analysis. Additionally, these studies may not consistently specify the comparator, ideally involving a comparison between painful and painless diabetic neuropathy cases. Fig. 2 represents the pathogenesis of diabetic neuropathy.

Nonetheless, despite these considerations, several intriguing factors have recently come to light, as summarized. In alignment with risk factors typical of many neuropathic pain disorders, female gender poses a risk for painful diabetic neuropathy. Furthermore, although neuropathic pain can manifest across various neuropathy severities, a consistently higher prevalence of pain has been reported among patients with more pronounced neuropathy, as determined by clinical scoring scales and quantitative sensory testing for sensory loss.

Various metabolic factors associate painful diabetic neuropathy with painless diabetic neuropathy, encompassing inadequate glycemic control, impaired renal function, and elevated body mass index (BMI). While these factors might coincide with neuropathy progression, some could contribute to sensory neuron hyperexcitability and pain development. Injured sensory neurons, characteristic of diabetic neuropathy, develop hyperexcitability, generating action potentials even without external stimuli (spontaneous activity), and exhibit altered stimulus-response functions (Figure 3). This atypical activity is pivotal for sustaining neuropathic pain, persisting even in cases of longstanding pain. In fact, a study demonstrated that a localized anaesthetic block targeted at nerves innervating the lower limb in patients with neuropathic foot pain led to pain resolution and cessation of evoked pain during the nerve block. This observation suggests that primary afferent hyperexcitability constitutes a fundamental pathophysiological catalyst for pain, necessitating a comprehensive understanding and the development of therapeutic approaches to counter it.

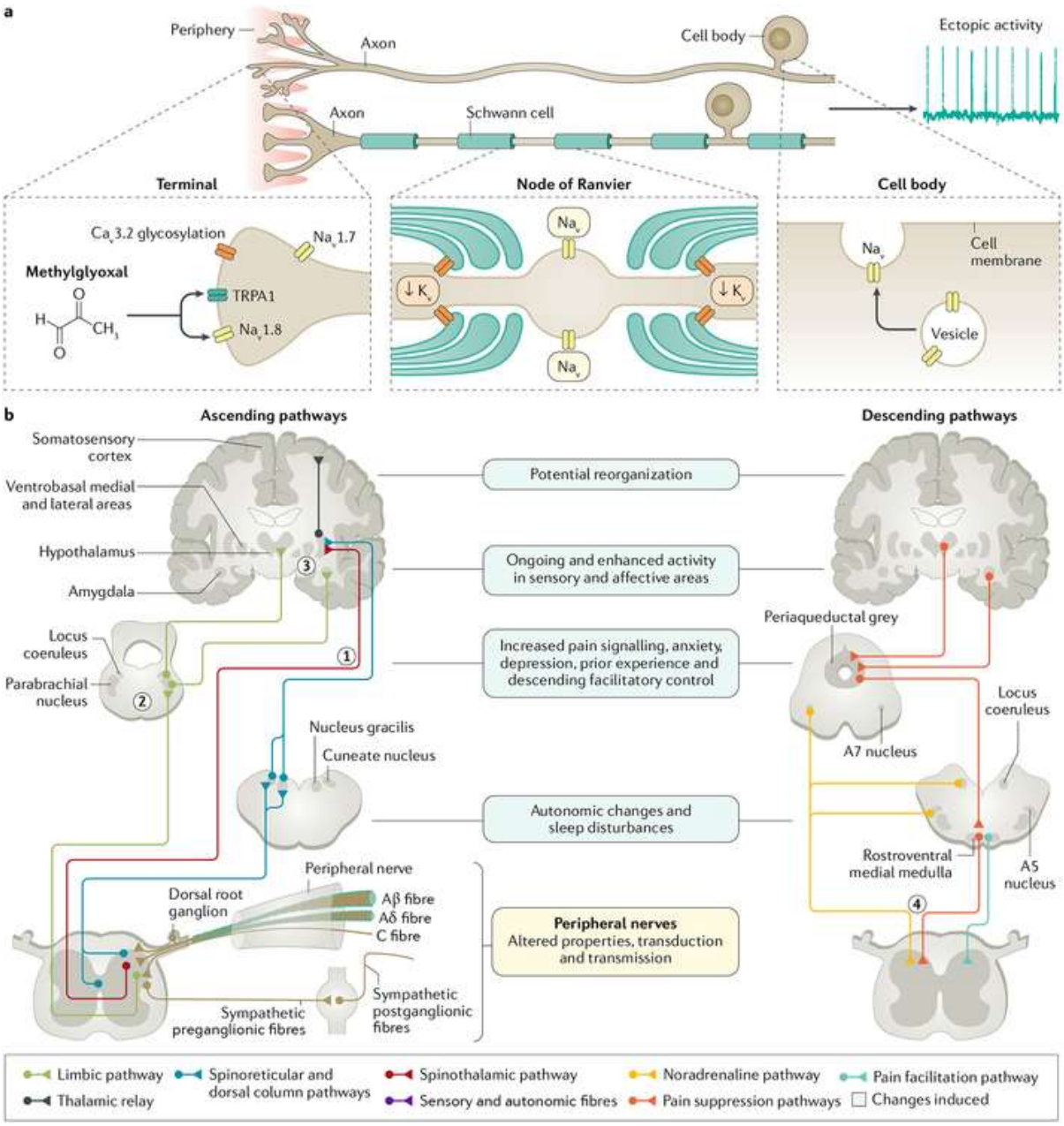

Fig:3 Figure 3a: demonstrates that the pathophysiology of painful diabetic neuropathy is caused by several different changes that occur in both peripheral and central neurons. Ion channels at the terminals of nociceptors can undergo glycation when methylglyoxal is added to the mix. This results in the formation of advanced glycation end-products (AGEs), which can contribute to increased neuronal hyperexcitability and gain of function in the channels themselves. Increased expression of voltage-gated sodium channels, such as Nav1.8, can contribute to hyperexcitability and is one of the changes that take place at the perikaryon. The expression of shaker-type potassium (Kv) channels is decreased in myelinated axons, which can also contribute to hyperexcitability. The hyperexcitability of neurons causes greater stimulus responses as well as ectopic neuronal activity, which in turn causes an excessive amount of nociceptive information to be received by the spinal cord. When activated, microglia in the dorsal horn of the spinal cord contribute to an increase in that region's level of excitability.

Figure 3b: Pain perception and the psychological changes associated with pain are both influenced by multiple ascending pathways. These ascending pathways include, for example, the spinothalamic pathway (1), which is implicated in pain perception, and the spinoreticular tract. In addition, autonomic function, fear, and anxiety are all associated with ascending pathways that pass from the parabrachial nucleus (2) to the hypothalamus and amygdala (3). The transmission of nociceptive

information at the spinal level can either be inhibited or facilitated by pathways that descend from the spinal level. Peripheral neuropathy has caused the changes that are illustrated in the boxes.

Possible Therapeutic Benefit of Medicinal Plant in Diabetic Neuropathy

***Acacia arabica*:**

Its natural habitat spans the entirety of India. *Acacia arabica* extract is effective in treating diabetes because it stimulates the body to restore the production of insulin due to the presence of tannins. Moreover, it shows antioxidant properties due to the presence of quercetin, which exhibits various activities including scavenging oxygen radicals. This can be beneficial for the pain management of diabetic neuropathy. [13].

***Aegle marmelos*:**

Its natural habitat encompasses the entirety of the Indian subcontinent. Because it encourages the body to produce more insulin, the plant extract is an effective medication for the treatment of diabetes. In rats with normal physiology, it leads to hypoglycemia, whereas in rats with alloxan-induced physiology, it has no effect. As a result, rabbits exhibited lower blood sugar levels. Moreover, the plant extract shows significant efficacy in reducing oxidative stress, which can contribute to alleviating the pain of diabetic neuropathy. [14].

***Allium cepa*:**

The anti-hyperglycemic effect was seen in diabetic rabbits when various ether-soluble fractions of dried onion powder were administered to them in addition to insoluble fractions. In addition, there is evidence that *Allium cepa* possesses antioxidant and hypolipidaemic activity. Administration of a sulfur-containing amino acid from *Allium cepa*, S-methyl cysteine sulphoxide (SMCS) (200 mg/kg for 45 days) to alloxan-induced diabetic rats significantly controlled blood glucose as well as lipids in serum and tissues and normalized the activities of liver hexokinase, glucose 6-phosphatase and HMG Co A reductase. Moreover, its antioxidant property helps to manage the pain of diabetic neuropathy [15,16].

***Allium sativum*:**

The entire country of India cultivates this perennial herb, more popularly known as lahsun. Its unpleasant odour comes from a sulphur compound called allicin, which also happens to have significant hypoglycemic activity [17]. It is hypothesized that enhanced hepatic metabolism, enhanced insulin release from pancreatic beta cells, and/or an insulin-sparing effect are responsible for this phenomenon [18].

***Aloe vera*:**

Aloe vera, a common houseplant, has a long history of being utilized to treat a wide range of ailments in various settings [19]. Gel and latex are the two basic extracts that can be obtained from the plant. While aloe vera gel is the mucilage or pulp of the leaves, aloe latex, also referred to as "aloe juice," is an exudate that is bitter and yellow in colour that comes from the pericyclic tubules that are located beneath the leaves' outer skin[20]. When diabetic and normal rats were given aloe gum extracts, the diabetic rats showed significant improvements in their ability to tolerate glucose [21]. *Aloe vera* and its bitter principle are known to stimulate insulin production and/or its release from pancreatic beta cells [22]. This plant not only can speed up the healing process of wounds in diabetic mice, but it also has dose-dependent anti-inflammatory effects, which are helpful for the pain management of diabetic neuropathy [23].

***Azadirachta indica*:**

This effect is due to increased glucose uptake and glycogen deposition in isolated rat hemidiaphragm [24,25], which causes hydroalcoholic extracts of this plant to have anti-hyperglycemic activity in streptozotocin-treated rats.

***Caesalpinia bonducella*:**
Caesalpinia bonducella is a species found all along India's coast and is known for its ability to regulate blood sugar levels when consumed by India's indigenous tribal population.[26]. When tested on chronic type II diabetic animals, both the aqueous and ethanolic extracts demonstrated significant hypoglycemic efficacy. Two fractions, BM 169 and BM 170 B, could increase insulin secretion from isolated islets. Anti hyperglycemic and hypolipidemic activities were observed in streptozotocin (STZ)-diabetic rats when they were given either an aqueous or an ethanolic extract of *Caesalpinia bonducella* seeds containing 50% ethanol [27]. Limiting glucose absorption by the seed extracts makes them effective against hyperglycemia[28].

***Capparis decidua*:**
The plant is found all over India but is most common in arid regions. In alloxanized rats, a hypoglycemic effect was observed after the rats were fed a diet consisting of 30% extracts of *Capparis decidua* (C. decidua) fruit powder for a period of three weeks[28]. This extract also significantly decreased the lipid peroxidation caused by alloxan in erythrocytes, kidneys, and hearts. It was discovered that C. decidua can change the levels of the enzymes superoxide dismutase and catalase, which helps reduce oxidative stress and is very effective in reducing diabetic neuropathic pain [29].

***Coccinia indica*:**
Patients with diabetes were given dried extracts of *Coccinia indica* (C. indica) at a dosage of 500 milligrammes per kilogramme of body weight for a period of six weeks. These extracts restored the activities of the enzyme lipoprotein lipase (LPL), which had been reduced in untreated diabetics [30], as well as glucose-6-phosphatase and lactate dehydrogenase, which had been raised.

***Eugenia jambolana*:**
As a home remedy for diabetes, a decoction made from the kernels of the *Eugenia jambolana* plant is commonly used in India[31]. This also makes up a significant portion of many different herbal remedies that are intended to treat diabetes. The anti hyperglycemic effect of the lyophilized powder, as well as the aqueous and alcoholic extracts, shows a reduction in the blood glucose. This varies depending on the individual's diabetes level. It shows a reduction of 73.51% in mild diabetes, which has a plasma sugar level of more than 180 mg/dl. However, in moderate diabetes (plasma sugar >280 mg/dl) and severe diabetes (plasma sugar >400 mg/dl), it is reduced to 55.62% and 17.72% respectively [31]. Upon incubation of plant extract with isolated islets of Langerhans from normal as well as diabetic animals, it was discovered that insulin secretion was boosted[32].

Mangifera indica:
In traditional Nigerian medicine, the leaves of this plant are used as an anti-diabetic agent, even though an oral administration of an aqueous extract of the plant did not affect the blood glucose level in either normoglycemic rats or rats that had been streptozotocin-induced to develop diabetes[33]. On the other hand, anti diabetic activity was observed both when the extract and glucose were given to the rats at the same time as well as when the extract was given to the rats sixty minutes before the glucose[34].

***Momordica charantia*:**
In India and many other Asian nations, *Momordica charantia* is frequently used to treat diabetes and hyperglycemia. In several different animal models, it was discovered that extracts of the fruit pulp, seed, leaves, and whole plant had a hypoglycemic impact. When administered subcutaneously to langurs and humans, polypeptide p, which was isolated from the fruit, seeds, and tissues of *M. charantia*, exhibited a significant hypoglycemic effect. The extract of *Momordica*

charantia shows significant antioxidant activity, which helps to protect against oxidative damage due to diabetic neuropathy [35].

***Ocimum sanctum*:**

Tulsi is the common name for this plant. Since ancient times, people have recognized this plant for its medicinal properties. Both normal rats and diabetic rats induced by alloxan showed a significant reduction in the amount of sugar in their blood when they were given an aqueous extract of the leaves of *Ocimum sanctum* [36]. In diabetic rats, tulsi was shown to have hypoglycemic and hypolipidemic effects, as indicated by a significant reduction in fasting blood glucose, uronic acid, total amino acid, total cholesterol, triglyceride, and total lipid [37]. The extract of *Ocimum sanctum* shows great efficacy in reducing the calcium level and oxidative stress in vincristine-induced rats. As a result, it proves its efficacy against diabetic neuropathy. [38].

***Phyllanthus amarus*:**

It belongs to the family Euphorbiaceae and can grow to a height of up to 60 centimetres. Bhuiamala is the name that most people use to refer to it[39]. It can be found in small pockets across the warmer regions of India, particularly in the states of the Deccan, Konkan, and south India. Diabetes treatment has traditionally benefited from its application. Additionally, the plant exhibits activity that is anti-mutagenic, anticarcinogenic and antidiarrheal activity, and moreover, it shows anti-inflammatory activity also; thus, it exhibits efficacy for the pain management of diabetic neuropathy [40].

***Pterocarpus marsupium*:**

In India, the hilly regions are the primary habitat for this deciduous tree of moderate to big size. [41] demonstrated that the hypoglycemic activity of this extract is due to the presence of tannates in the extract. It has been demonstrated that a flavonoid fraction derived from *Pterocarpus marsupium* can cause degranulation of pancreatic beta cells [42]. The anti hyperlipidemic activity was demonstrated by marsupium, pterosupin, and liquiritigenin, all of which were extracted from this plant [43]. It has been discovered that epicatechin, the active principle of the plant, is insulinogenic, meaning that it increases insulin release and converts proinsulin to insulin in vitro[44].

***Atriplex hortensis*:**

It's a popular plant of north-east India , by and large in Assam, commonly known there as Pahari paleng, proves potential antioxidant activity with lofty antiradical activity [45]. That can be very effective for the pain management of diabetic neuropathy in upcoming future by reason of its above mentioned activity.

***Clerodendrum colebrookianum*:**

It's a popular plant of north-east India , by and large in Assam, commonly known there as Nephaphu, proves potential anti-inflammatory activity by means of free radical scavenging and suppression of both the COX enzymes [46]. That can be very effective for the pain management of diabetic neuropathy in upcoming future by reason of its above mentioned activity.

***Tinospora cordifolia*:**
It is a large climbing shrub that belongs to the family Menispermaceae. It has glabrous leaves and is deciduous. It is well known as Guduchi throughout India due to its widespread distribution [47]. After receiving oral administration of the extract of *Tinospora cordifolia* (T. cordifolia) roots for a period of six weeks, alloxan diabetic rats exhibited a significant decrease in the levels of glucose in their blood and urine as well as lipids in their serum and tissues. Additionally, the extract prevented a reduction in total body weight [48]. In traditional Indian ayurvedic medicine, T. cordifolia is frequently used to treat diabetes mellitus [49]. A significant decrease in both blood glucose and brain lipids was observed in alloxan diabetic rats after they were given an aqueous root extract of T. cordifolia through oral administration. Although the aqueous extract at a dose of 400 mg/kg elicited a significant anti-hyperglycemic effect in various animal models, its effect was only comparable to that of one unit/kg of insulin [50]. It has been demonstrated in rodents that decreasing the blood glucose level and increasing glucose tolerance can be achieved by giving them either an alcoholic or aqueous extract of T. cordifolia on a daily basis [51].

***Ficus religiosa*:**
In India, the name "peepal" refers to the flowering tree Ficus religiosa, which belongs to the family Moraceae. Using elements from the *Ficus religiosa* tree, the ancient Indian medical technique of Ayurveda has been linked to successful diabetic therapy [52]. Many other types of bioactive compounds, such as tannins, saponins, polyphenolic chemicals, flavonoids, and sterols, could be found in the plant. The *Ficus religiosa* tree bark contains a compound called sitosterol-d-glucoside, which has been hypothesized to cause hypoglycemic action in rabbits [53]. Leucocyandin 3-O-beta-d-galactosyl cellobioside and leucopelargonidin-3-O-alpha-L rhamnoside [54] are the bioactive components found in Ficus. Some research suggests that the focus phytoconstituents may help reduce blood sugar levels significantly. The furanocoumarin derivatives bergapten and bergaptol, as well as phytosterols and flavonoids, have been identified in it [55].The anti hyperglycemic activity of *Ficus religiosa* leaves has also been studied [56]. When an aqueous extract of *Ficus religiosa* was taken orally for 21 days, blood glucose levels dropped significantly, and insulin production went up. Insulin stimulates glucose absorption in many tissues, but skeletal muscle is particularly important for this process. Extract from the peepal tree has been shown to reverse the loss of glycogen in muscle and the liver due to diabetes [57,58].

***Gingko Biloba*:**
Ginko biloba is a very ancient plant to manage pain, and it is considered as a living fossil belonging to the family Ginkgoaceae. The leaf extract of this plant has shown a potential effect on human patients (age more than 18 years) with diabetic sensorimotor polyneuropathy. Which study was conducted at the Services Institute of Medical Sciences (SIMS), which was a Diabetic Management Centre, Lahore, Pakistan. [59].

***Curcuma longa*:**
The common name of *Curcuma longa* is turmeric belonging to the family Zingiberaceae. The motherland of this plant is India. The major active ingredient of this plant is curcumin having significant anti-hyperglycemic and antioxidant properties. Curcumin shows very potential activity against diabetic neuropathy in STZ-induced diabetic rats when curcumin was administered orally in the dose of (200 mg/kg body weight) for three weeks [60].

***Pterocarpus marsupium*:**
The Fabaceae family is home to the *Pterocarpus marsupium* tree, sometimes known as the Indian Kino Tree or the Bijasar. The most often utilized components of plants are the heartwood, leaves, flowers, bark, and gum. India, Nepal, and Sri Lanka are three countries where the *Pterocarpus marsupium* tree thrives. According to Ayurveda, it is one of the most adaptable medicinal plants, possessing a wide range of different types of biological activities. It is widely known that the tree, in its entirety, possesses potential medicinal value. This tree can reach a height of 30 meters in its lifetime. Studies on the chemical makeup of bijasar have revealed that this plant is an excellent resource for polyphenols. Terpenoids and phenolic substances, such as -sitosterol, lupenol, aurone glycosides, epicatechins, and isoflavonoids, can be found in P. marsupium [61,62].

***Trigonella foenum-graecum*:**
The plant known as fenugreek or methi, *Trigonella foenum-graecum*, is a member of the Fabaceae family. The components of the plant that are used the most frequently are the seeds and the leaves. Fenugreek, scientifically known as *Trigonella foenum-graecum* L., is grown as a semiarid crop in India and several other regions of the world [63]. In Indian cuisine, it is commonly consumed as both a vegetable and a spice. Fenugreek is used in the food industry as a flavouring agent, and it is well-known for its pungent, fragrant qualities [64]. Fenugreek has been shown to have powerful anti-diabetic characteristics, according to research conducted on a variety of animal models [65]. Fenugreek has been shown to benefit human subjects in terms of both glucose and cholesterol levels [66]. The anti hyperglycemic impact has been linked to a reduction in somatostatin levels as well as an increase in plasma glucagon levels [67]. It has been demonstrated that the powder made from fenugreek seeds can restore normal activity of the creatinine kinase enzyme in the liver, skeletal muscles, and heart of diabetic rats [68].

***Gymnema sylvestre*:**
The plant known as gurmar, or *Gymnema sylvestre*, is a member of the family Asclepiadaceae. It is a herb that grows naturally in the tropical woods of Sri Lanka and India. G. sylvestre is a big climber that puts down roots at the nodes it passes through. Ayurvedic remedies made from this plant make use of its powerful anti-diabetic properties. When coupled with acarbose, it is believed to inhibit intestinal transit of maltose in rats [69]. Its anti diabetic efficacy has been demonstrated in animal models by a number of researches, which may be found in [70]. In rats, there was also a decrease in the amount of free oleic acid that was absorbed [71]. There have been reports that an aqueous extract of G. sylvestre can elicit reversible increases in intracellular calcium and insulin secretion in mouse and human beta cells that are affected by type 2 diabetes [72].

***Verbena officinalis*:**
Verbena officinalis, commonly known as common verbena or common vervain, a popular member of the family Verbenaceae. This plant manifests very promising anti-inflammatory, antioxidant and analgesic efficacy [73,74]. Moreover the plant extract exerts anti-diabetic efficacy as a folk medicine [75]. The plant extract contains a variety of bioactive chemicals, the most prominent of which are iridoids, phenylpropanoid glycosides, flavonoids, and phenolic acids [74]. That can be very effective for the pain management of diabetic neuropathy in upcoming future by reason of its above mentioned activities.

Conclusion

The neuropathy associated with diabetes presents a challenging and debilitating condition strongly linked to lifestyle choices. Its incidence is rapidly increasing, with the potential to become one of the most prevalent global health issues. Contributing factors to elevated blood glucose levels include excessive sugar consumption, obesity, insufficient physical activity, and environmental influences. These elements contribute to the development of diabetic neuropathy, which damages peripheral nerves in the brain. Inadequate awareness of nutritional practices and various lifestyle factors also play roles in its emergence. These processes encompass anti-inflammatory, neuroprotective, antioxidant, anti-apoptotic, and calcium inhibitory activities.

While reports suggest the positive impact of plants in diabetic neuropathy treatment, clinical trials involving plants remain underexplored. Consequently, herbal preparations, like those discussed, require support and promotion to counter challenges related to synthetic pharmaceuticals. Exploring alternative and complementary therapies such as Ayurveda provides numerous treatment options for chronic conditions like type 2 diabetes. Ayurveda holds potential not only for diabetes patients but also for the healthcare system at large. It emphasizes the mind-body connection, nutrition, exercise, lifestyle adjustments, and medication use.

Lifestyle modifications are often the most effective approach for managing chronic illnesses. Despite Ayurveda's personalized treatment approach, limited research has been conducted due to its nature. This could be a crucial area for future research. The outcomes of such studies might lay the groundwork for drug development to treat diabetes neuropathy. The findings from this assessment might aid in achieving better diabetes neuropathy management.

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