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REVIEW ARTICLE

Comprehensive Insights into Neuropathy: Types, Management, and Promising Approaches

Gurvinder Singh, Ravinder Kumar*, Shruti Sharma, Dileep Singh Baghel, Saurabh Singh, M. R. Sumanthmayur and Rupali

Department of Pharmaceutical Sciences, School of Pharmaceutical Sciences, Lovely Professional University, Phagwara – 144411, Punjab, India; ravindervardhan278@gmail.com

Abstract

In recent times, there has been significant discussion surrounding neuropathic pain, which manifests as a general condition characterised by an abnormal increase in sensitivity to stimuli and nociceptive responses, even in the absence of harmful stimuli. For centuries, herbal plants have been utilised in treating neurological and psychiatric ailments, and present-day research further substantiates the effectiveness of plant-based products in addressing neurological disorders. Herbal plants have long been a cornerstone in treating neurological conditions, and current work highlights their role in managing peripheral neuropathy. Combining these traditional remedies with modern medical techniques may offer a comprehensive approach to managing and potentially alleviating the unbearable symptoms associated with this condition. Peripheral neuropathy is an ailment which affects or damages nerves, thereby impairing sensation, movement, and gland and organ functions. Patients diagnosed with cancer, AIDS, diabetes, multiple sclerosis, and stroke are predominantly prone to experiencing peripheral neuropathy. The term peripheral neuropathy encompasses two types: Mononeuropathy and Polyneuropathy. Mononeuropathy refers to the condition where a single nerve is affected, while Polyneuropathy refers to the condition where multiple nerves are affected. Peripheral neuropathy is distinguished by specific characteristics and manifestations such as loss of sensation, increased response to painful stimuli, pain, tingling, crawling, and itching.

Major Findings: The present work is focused on the key points about neuropathy, its classification, causes, treatments, the effectiveness of the medicinal plants and modern techniques available to address neuropathy.

Keywords: Minerals, Natural Alternatives, Pain, Peripheral Neuropathy, Vitamins, *Yoga*

1. Introduction

Neuropathic pain may endure even after the underlying nerve damage has healed, manifesting as heightened sensitivity to stimuli (hyperalgesia), the experience of abnormal sensations (hyperpathia), and pain response to ordinarily non-painful stimuli (allodynia)[1]. Peripheral neuropathy represents the impairment, damage, or disease that affects nerves, potentially leading to diminished sensation, movement, gland and organ functions[2]. Peripheral neuropathy mostly prevails in patients with cancer, AIDS, diabetes, multiple sclerosis and stroke[3-5]. The term peripheral neuropathy encompasses two types: Mononeuropathy and Polyneuropathy. Mononeuropathy refers to the condition where a single nerve is affected, while Polyneuropathy refers to the condition where multiple nerves are affected[6]. Peripheral neuropathy is attributed to sensation loss and increased response to painful stimuli, pain, tingling, crawling, and itching[7,8]. The prevalence of peripheral neuropathy is generally recorded at 2.4%. However, among individuals aged 55 years and older, the occurrence escalates to 8%[9]. Peripheral neuropathy is a widespread neurological disorder with an annual count of 77 per 1,000,000 individuals. It impacts a significant segment of the population across all age groups, ranging from 1% to 12%. In older individuals, the prevalence of this disease is up to 30%[10]. In diabetic patients, the prevalence rate

*Author for correspondence

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is between 6-51% approximately depending on age[11]. Diseases like diabetes, viral infections major surgeries or trauma, spinal cord injury, and stroke cause direct damage to the nervous system. The key causes of neuropathy include alcoholism, autoimmune diseases, exposure to poisons, infections, diabetes, and inherited disorders[12]. In contrast to various forms of chronic pain, neuropathic pain presents greater difficulties in its management, as the efficacy of treatment remains limited due to a lack of widespread administration of recommended medications at optimal dosages[13].

There is a link between sensory neuropathy and autonomic neuropathy. Autonomic neuropathy is characterized by orthostatic hypotension whereas abnormal nerve conduction defines sensory neuropathy. Chronic constriction of the sciatic nerve is a widely adopted animal model for studying neuropathic pain because it is the most reliable and easily reproducible[14]. The sciatic nerve holds the distinction of being the longest nerve within the human body. Following a nerve injury, various sites along the neural axis undergo alterations[15]. There can be numerous factors contributing to the occurrence of pain along the sciatic nerve. Sciatica of radicular origin, *i.e.*, pain that spreads along the sciatic nerve to down the back of the thigh and sometimes foot is caused due to the compression of L5 or S1 root and is usually separated from truncular or peripheral sciatica[16]. Radicular sciatica is categorized into two types: mechanical sciatica and inflammatory sciatica[17]. Accurate statistics regarding the occurrence and frequency of sciatica are not readily available. Typically, it is estimated that approximately 5% to 10% of individuals suffering from lower back pain also experience sciatica. This is in contrast to the reported lifetime occurrence of lower back pain, which ranges from 49-70%. The annual occurrence of sciatica related to disc issues in the general population is roughly estimated at 2.2%[18]. Recent studies show that constriction of the sciatic nerve further leads to intraneural edema, focal ischemia and behavioural alterations such as mechanical and thermal hyperalgesia, chemical hyper-reactivity and cold allodynia[14]. Neuropathic pain is characterized as pain that arises from disorders or abnormalities within the nervous system. Neuropathic pain is defined as "pain arising as an immediate consequence of any lesion or illness affecting the somatosensory system"[19]. This pain might be classified into the two categories as per the anatomical site of the lesion or illness: peripheral neuropathy and central neuropathy. The peripheral nervous system consists of peripheral nerves and dorsal root ganglia, while the central nervous system comprises the spinal cord and thalamus. Diseases like diabetes, viral infections, major surgeries or trauma, spinal cord injury, and stroke cause direct damage to the nervous system. This pain encompasses a range of conditions such as carpal tunnel syndrome, trigeminal neuralgia, post-herpetic neuralgia, radiculopathy, phantom limb pain, complex regional pain syndromes, and diverse forms of neuropathic pain associated with chemotherapy[20].

2. Types of Neuropathy

2.1 Peripheral Neuropathy (PN)

PN is a cohort of diseases affecting peripheral nerves. There are multiple reasons leading to the occurrence of disease including hereditary, metabolic, infections, inflammatory, toxins, and traumatic. It encompasses both acute as well as chronic complications. Most cases of PN primarily result in reduced muscle strength and sensation loss, along with the presence of positive sensory symptoms and typically associated pain. Peripheral neuropathy, also known as polyneuropathy or mononeuropathy, is concluded by the specific location and anatomical distribution of sensory, motor, and autonomic impairments[9]. Polyneuropathy refers to the condition where multiple nerves are affected, while mononeuropathy describes neuropathy that either affects or originates from a single site Neuropathies affecting multiple nerves are called polyneuropathy whereas neuropathy affecting or originates from one site is called mononeuropathy. Prominent symptoms include altered thermal sensation accompanied by numbness, tingling, a sensation of pins and needles, burning, and an electric shock-like feeling. Polyneuropathy mainly influences myelin or axons and both although mononeuropathy affects the entire nerve particularly the connective neural tissue and nerve blood vessels[21] (Table 1).

2.2 Central Neuropathy (CN)

Central neuropathy arises from various causes such as injury in the central nervous system, vascular conditions, infectious diseases, demyelinating disorders, traumatic events, or neoplastic conditions. Calculus formation in

Table 1. Types, causes and symptoms of neuropathy

S. No.	Type of neuropathy	Causes	Symptoms
1	Peripheral neuropathy (PN)	Multiple reasons like hereditary factors, metabolic disorders, infections, inflammation, toxins and trauma.	Altered thermal sensation accompanied by numbness, tingling, a sensation of pins and needles, burning, and an electric shock-like feeling[21].
2	Central neuropathy (CN)	Injury in the central nervous system, vascular conditions, infectious diseases, demyelinating disorders, traumatic events, or neoplastic conditions.	Uncomfortable cold, swelling, squeezing sensation[22].
3	Hereditary neuropathy	Genetic abnormalities	Weakness, numbness, loss of sensation, and foot and ankle deformities[24].

the spinal cord or brain stem can result in CN also. It also includes post-stoke pain, multiple sclerosis or spinal cord injury[22]. Major symptoms are uncomfortable cold, swelling, and squeezing sensation. Central neuropathic pain originates from damaged nerves that can trigger central sensitization. This process promotes centrally dependent synaptic plasticity in the cortex and involves various synaptic modulators and excitatory amino acids further leading to alteration in channel mechanism and properties[23] (Table 1).

2.3 Hereditary Neuropathy

Hereditary neuropathy encompasses a variety of conditions that are linked to genetic causes of the disease. Typically, these conditions progress gradually over several years, ranging from mild to severe manifestations[21]. As a group, inherited neuropathies pose a common challenge, with a significant number of patients impacted by moderate types that remain undiagnosed. These neuropathies impact sensory, motor or autonomic fibres, with the genetic abnormalities primarily affecting either the myelin or axon. Prominent symptoms of hereditary neuropathies include weakness, numbness, loss of sensation, and foot and ankle deformities. Neuropathic pain, scoliosis, skeletal deformities, deafness, cognitive deficits, tremors, impaired speech and dysphagia, breathing difficulties, or structural changes of the central nervous system are also accompanied by the disorder[24] (Table 1).

3. Methods to Induce Neuropathy Experimentally

3.1 Peripheral Nerve Injury Models

Various models of peripheral nerve injury exist to induce experimental neuropathy in animals:

3.1.1 Complete Sciatic Nerve Transaction

This is the conventional animal model used to induce neuropathic pain. The sciatic nerve is subjected to a complete transection at the mid-thigh level in this model. The rat is subjected to anaesthesia prior to the surgical exposure of the common sciatic nerve. Connective tissue close to the sciatic nerve is removed with caution, and then using a nylon suture the sciatic nerve is securely tied at two locations, 1 cm apart, where it divides into the tibial and peroneal divisions. Subsequently, a complete transection of the nerve is performed amidst the ligatures and a 5 mm segment is excised to avoid nerve reconnection through regeneration. Furthermore, the adjoining saphenous vein is mutilated to cause complete denervation of the distal hind limb. A key limitation of this model is that complete nerve transections or lesions are uncommon in patients, and are typically associated with conditions like phantom limb pain[14].

3.1.2 Chronic Constriction Injury (CCI)

It is a commonly used animal model for investigating neuropathic pain. It induces mononeuropathy in rats. The rat is anaesthetized, and a blunt dissection of approximately 3 cm in length is performed on the skin between the gluteal muscles and biceps femoris. In the mid-thigh area, the sciatic nerve is uncovered, and nearly 7 mm of the nerve is dissected near its trifurcation. Three to four loosely spaced ligatures (approximately 1 mm apart) are then positioned around the sciatic nerve until a slight twitch is detected. Care must be taken to avoid disrupting the epineural circulation. Chronic Constriction Injury (CCI) is associated with intraneural edema, focal ischemia, and Wallerian degeneration. Behavioural indicators of spontaneous pain include excessive licking, guarding,

limping of the hind paw on the same side as the injury, and avoidance of placing weight on the injured side[14].

3.1.3 Partial Sciatic Nerve Ligation (PSL)

This model is widely utilized in studying neuropathic pain. It involves shaving the left hind paw of a rat and performing a dissection at the upper thigh to expose the sciatic nerve. The dorsal portion, approximately one-third to half, of the sciatic nerve is securely ligated using an 8-0 silk suture at the branching point of the posterior biceps-semi tendinosus nerve. Spontaneous pain is manifested through behaviours such as paw guarding and licking on the side of the injury. Cold allodynia, chemical hyperalgesia, and mechanical hyperalgesia can be observed within one week following the surgery, and these alterations typically endure for a period of 6 weeks. The PSL nerve model is the most relevant model for understanding neuropathic pain injury as partial nerve injury is the main cause of pain disorders in humans[14].

3.1.4 Spinal Nerve Ligation (SNL)

Spinal Nerve Ligation (SNL) is an experimental model used to induce peripheral mononeuropathy in animals. In this model, rats are anaesthetized and positioned for shaving the lower back. Next, a 2 cm incision is created at the level of the posterior iliac crest to reach the left lumbar spinal nerve. The spines; L5 and L6 are located and gently dissected, separating them from the neighbouring L4 spinal nerve. Subsequently, a tight ligation is applied to the Dorsal Root Ganglia (DRG). Within 24-48 h, behavioural changes such as thermal hyperalgesia, mechanical allodynia, cold allodynia, and spontaneous pain are reported and persist for a duration of 10-16 weeks[14].

3.1.5 Sciatic Nerve Cuffing-Induced Pain

Neuropathic pain in rats is induced in this model by surgically placing a polyethylene cuff around the common branch of the sciatic nerve. In this particular model, neuropathic pain is characterized by heat, hyperalgesia persists for three weeks and mechanical allodynia continues for two months. Recent studies report that there is a short-term diminution in the number of unmyelinated and small myelinated axons and a maintained decrease in the number of large myelinated axons[14].

3.1.6 Photochemical-Induced Sciatic Nerve Injury

Here, photosensitizing dye, erythrosine B dye (32.5 mg/kg) induced intravenously via the tail vein followed by surgical exposure of vertebrae to an argon ion laser, which causes excitation and leads to localized occlusion of blood vessels[25]. Reports suggest that the nerve injury in this model is not caused by the heat generated by the laser but rather by a photochemical reaction that leads to the formation of thrombosis in the small vessels supplying the nerve. The photochemical reaction causes a significant reduction in blood flow within the spinal cord. Consequently, spinal ischemia occurs, leading to necrosis of the parenchymal tissue at the spinal cord level. Autonomic, mechanical, and cold allodynia or hyperalgesia are the prominent characteristics of neuropathic pain observed in this model[14].

3.2 Drug-Induced Neuropathy Models (DIPN)

DIPN is characterized by harm to the peripheral nervous system resulting from exposure to a chemical substance[26]. The majority of drug-induced peripheral neuropathies lead to injury within the dorsal root ganglia. The six mechanisms associated with peripheral nerve damage have been identified in connection with peripheral neuropathy: metabolic imbalances, covalent alterations, organelle impairment, intracellular inflammatory signalling, issues with axonal transport, and channelopathies[27].

3.2.1 Resiniferatoxin (RTX)

An analogue of capsaicin, Resiniferatoxin, is commonly employed to induce small-fibre neuropathy in rodent models[28]. Hsieh *et al.*,[28] conducted studies to establish a small-fibre neuropathic pain model through the administration of a single dose of RTX. In this investigative setup, mice exhibited pure small-fibre neuropathy in one week after receiving a 50 µg/kg dose of RTX via intraperitoneal injection[29].

3.2.2 Acrylamide

Acrylamide is among the neurotoxic substances that affect the central as well as peripheral nervous systems[30]. Upon repeated, low-dose exposure to accumulated acrylamide (ranging from 35 to 140 mg/kg), experimental animals exhibited thermal

hyperalgesia and mechanical allodynia, while motor function remained unaffected[31].

3.3 Cancer Chemotherapeutic Agents

3.3.1 Vincristine Induced Neuropathy

Multiple cancer chemotherapy drugs are allied with neurotoxicity and PN. Vincristine is an alkaloid extracted from the plant *Vinca rosea* Linn. Family: *Apocynaceae*[32]. Vincristine is used as a chemotherapeutic agent for treating several malignancies such as leukaemia, breast cancer, lymphomas and brain tumours. Recent studies report that vincristine is linked with the advancement of neurotoxicity of peripheral nerve fibres resulting in sensory-motor neuropathy. Painful paresthesias is the major symptom in large no. of patients with pinprick and temperature sensations being more significantly impacted than the sense of vibration. During the later stages of the disease, loss of axons and motor functions become more eminent[33]. Vincristine does not penetrate the blood-brain barrier; however, its effect on the peripheral nervous system further leads to microtubule disorganization and endoneural swelling in myelinated as well as in unmyelinated sensory axons alongside hyperactivity in C fibre nociception neurons. Due to these changes, dorsal horn neurons are sensitized which leads to central sensitization[14].

3.3.2 Cisplatin Induced Neuropathy

Cisplatin is an anticancer drug that has effective action against multiple malignancies such as testicular, ovarian, head, colon, neck, and lung cancers. Anorexia, emesis, nephrotoxicity, ototoxicity, and peripheral neuropathy are the major symptoms associated with the use of cisplatin.[14] Cisplatin causes mainly large fibre neuropathy. The high cumulative dose of cisplatin results in the incidence of peripheral neuropathy. Cisplatin leads to impaired DNA mechanisms resulting in peripheral neuropathy[33].

3.3.3 Oxaliplatin Induced Neuropathy

Oxaliplatin plays a vital role in the management of advanced metastatic colorectal, breast, ovarian and lung cancer. Neuropathy produced by oxaliplatin is severe, reversible and is categorized by dysesthesia, paresthesia of the feet, hands and peroral region[14]. Platinum drugs have been found to trigger reactive oxygen species production, leading to neuronal cell death[33].

3.3.4 Paclitaxel Induced Neuropathy

Paclitaxel-induced neuropathy refers to the development of nerve damage caused by Paclitaxel; an effective anti-cancer drug derived from the bark of the *Taxus brevifolia* tree. Frequently included in chemotherapy regimens, paclitaxel is used to treat cancers of the breast, ovary, head and neck, and lung[34]. Paclitaxel induces sensory neuropathy, which is distinguished by tingling, numbness, mechanical allodynia, and cold allodynia. Studies report that in an experimental model of neuropathy, a low dose of paclitaxel 1 or 2 mg/kg i.p. arouses pain syndrome or motor impairment. Neuropathy due to paclitaxel is categorized by cold allodynia, long-lasting tactile allodynia, and endoneural edema of the sciatic nerve. A high dose of paclitaxel to induce neuropathy develops with two different dose regimens, *i.e.*, 16mg/kg i.p. once a week for 5 weeks or a single injection of paclitaxel with a dose of 32 mg/kg[14].

3.3.5 Docetaxel Induced Peripheral Neuropathy

Docetaxel is a broadly used anti-cancer drug for breast, ovarian, and lung cancer treatment. Docetaxel induces neuropathy in rats with the weekly i.v. Injection of 5-10 or 12.5 mg/kg for 4 weeks. Docetaxel-treated rats reveal reduced tail nerve conduction velocity, thermal threshold changes, and deterioration of skin nerves in the foot pad[14].

3.3.6 Thalidomide

Thalidomide is employed in the management of multiple myeloma, and a significant risk factor for drug-induced peripheral neuropathy is the use of higher doses over an extended duration. The incidence rate of peripheral neuropathy with thalidomide treatment falls within the range of 23% to 70%. Although both conditions primarily result in sensory neuropathy, thalidomide-induced neuropathy is distinguished by pronounced tingling sensations in the hands and feet, along with numbness and mild motor impairment[35,36].

3.4 Diabetes Induced Neuropathy

The administration of pancreatic ß-cell toxins, such as streptozotocin and alloxan, is the prevailing method for inducing diabetic neuropathy in experimental

models. The clinical manifestations of this neuropathy encompass an escalation in vibration and thermal perception thresholds, which subsequently lead to sensory loss, paresthesias, allodynia, hyperalgesia, and the impairment of normal sensory functions[37]. The clinical presentation of neuropathy comprises heightened thresholds for vibration and thermal perception, which gradually advance to sensory loss, paresthesias, allodynia, hyperalgesia, and the impairment of normal sensory functions. Studies report that rat models of subcutaneous STZ-induced diabetes develop hyperalgesia and hyper-responsiveness of C-fibers during approximately 2-3 weeks. A new model has been developed to induce diabetes by an intravenous injection of STZ (50mg/kg) through a tail vein. The i.v. Injection of STZ documented to produce early hyperglycemia, and glycosuria, without ketosis, weight loss. Recent studies report, that mechanical and thermal hyperalgesia develops within 3 days and the behavioural alterations persist for 2-3 weeks after STZ administration[14].

3.5 Human Immunodeficiency Virus (HIV) Induced Neuropathy

The utmost collective manifestation of chronic pain in patients infected with HIV is distal symmetrical polyneuropathy characterized by painful sensory abnormalities. The frequency of neuropathy is suggestively correlated with the extent of immune deficiency and malnutrition. PN linked with AIDS resembles PN triggered by vitamin B12 deficiency[33]. Studies report that HIV-1 appears to interact with the nervous system via binding of the external envelop protein gp120, to the chemokines receptors CXCR4/CCR5 expressed on neurons and glial cells further leading to neurotoxicity and peripheral axonal damage[14].

3.6 Lipid Lowering Drugs Induced Neuropathy

Peripheral Neuropathy (PN) is the prevailing adverse effect observed in association with lipid-lowering drugs that inhibit 3-hydroxy-3-methyl-glutaryl-coenzymeA (HMGCoA) reductase. The mechanism by which lipid lower drugs result in PN is that these drugs interrupt cholesterol synthesis, resulting in disruption of cholesterol-rich neuronal membranes, or inhibition of coenzyme Q10 synthesis leading to neuronal mitochondrial damage[33].

3.7 Chronic Ethanol Consumption/ Withdrawal Induced Neuropathy

Recent studies documented that long-term alcohol consumption induces small fibre neuropathy and is categorized by distal axonal degeneration, *i.e.*, dying back neuropathy. Regular alcohol drinking leads to malnutrition and other B-vitamin deficiencies including folate deficiency have also been associated with PN[33]. Neuropathy by ethanol in rats has been developed by administering 6.5% ethanol daily over a period of 12 weeks or by daily escalating dosage schedule, *i.e.*, first to third day: 2.2% w/v, fourth to sixth day: 4% w/v, seventh to 16th day: 4.4 w/v, and from 17th to 70th day: 5% w/v respectively[14].

3.8 Pyridoxine (Vitamin B6) Induced Neuropathy

Vitamin B6 serves a crucial part in regulating various biological reactions within the body[38]. Pyridoxine, an essential form of vitamin B6, is used in the treatment of conditions such as premenstrual or carpal tunnel syndromes. When administered orally in the dosage range of 50-300 mg/kg/day, pyridoxine can induce sensory abnormalities associated with neuropathy. In rat models, neuropathy can be induced by pyridoxine through the utilization of three dosage regimens: A short-term/high-dose regimen of 1200 mg/kg/day for 1-15 days, an intermediate dose regimen of 600 mg/kg/day for 1-15 days, and a long-term/low-dose regimen of 100-300 mg/kg/day for 12 weeks[14].

4. Guidelines for the Treatment of Neuropathic Pain

The primary objective in the management of peripheral neuropathy is to treat the symptoms[39]. First-line treatment for neuropathic pain includes tricyclic antidepressants (amitriptyline, gabapentinoids (gabapentin and pregabalin), selective Serotonin-Norepinephrine Reuptake Inhibitors (SNRI) (duloxetine and venlafaxine). The second-line treatment includes capsaicin, lidocaine, tapentadol and tramadol whereas for the third-line treatment morphine, oxycodone and botulinum toxin – A are included. The pharmacologic effects of antidepressants involve binding to noradrenaline and serotonin (5-HT) transporters. The analgesic effects of tricyclic

antidepressants primarily stem from their ability to inhibit the reuptake of serotonin and noradrenaline. However, these medications also exhibit blocking activity on other receptors like histamine and sodium channels[40]. The inhibition of neurotransmitter reuptake results in elevated levels of noradrenaline and 5-HT within the synaptic gap[41]. Increased levels of these neurotransmitters in the synaptic gap, and prolonged pain trigger feelings of anxiety, followed by a gradually worsening state of depression and heightened perception of pain. As a result, the impact of antidepressant drugs on improving the depressive condition suggests their potential effectiveness in managing chronic pain. Moreover, these antidepressants can alleviate neuropathic pain, even in instances where the patient isn't experiencing depressive symptoms[42]. Gabapentinoids, including gabapentin and pregabalin, operate by obstructing presynaptic alpha-2-delta calcium channels located in the dorsal horn of the spinal cord. As a result, they lead to a reduction in the release of neurotransmitters[43]. SNRIs, along with topical treatments like the lidocaine patch, offer viable options for pain management, which provides pain relief by impeding the activity of voltage-gated sodium channels in peripheral nerves[44]. Naltrexone, an antagonist of opioid receptors, has demonstrated synergistic effects with gabapentinoids in preclinical investigations, resulting in the alleviation of allodynia[45]. Furthermore, there is some evidence of its effectiveness in addressing Complex Regional Pain Syndrome (CRPS), although the available data is restricted[46] (Table 2).

5. Alternative Treatment Options for the Treatment of Peripheral Neuropathy

5.1 Alpha-Lipoic Acid (ALA)

Alpha-lipoic acid is a type of antioxidant that the body naturally produces. It is present in every cell, where it helps convert glucose into energy[47]. ALA leads to the normalisation of nitric oxide metabolite levels and improves the clinical symptoms of neuropathy. The increased production of nitric oxide further promotes blood circulation to the neurons. Studies report that ALA results in a significant reduction in lipid

Table 2. Treatment Guidelines for neuropathic pain

First-line treatment options for PN			
S. No.	**Treatment**		**Mechanism of Action**
	Class	**Drugs**	
1	Tricyclic antidepressants	Amitriptyline	Binds to noradrenaline and serotonin (5-HT) transporters lead to inhibition of neurotransmitter reuptake resulting in elevated levels of noradrenaline and serotonin in synaptic gap[41].
2	Antiepileptics	Gabapentin and Pregabalin.	Obstruct presynaptic alpha-2-delta calcium channels located in the dorsal horn of the spinal cord resulting in a reduction in the release of noradrenaline and serotonin[43].
3	Selective serotonin-norepinephrine reuptake inhibitors (SNRI)	Duloxetine and Venlafaxine).	Impedes the activity of voltage-gated sodium channels in peripheral nerves[44].
Second-line treatment options for PN			
S. No.	**Class**	**Drugs**	**Mechanism of Action**
1	Topical	Capsaicin and lidocaine Patches	Impedes the activity of voltage-gated sodium channels in peripheral nerves[44].
Third-line treatment options for PN			
S. No.	**Class**	**Drugs**	**Mechanism of Action**
1	Opoids	Morphine	Opoids bind to opoid receptors resulting in complex cellular changes and inhibiting injury-induced nociception activation[40].

Table 3. Alternative treatment options for the treatment of PN

S. No.	Drug	Mechanism of action
1	Alpha-Lipoic Acid (ALA)	ALA normalised nitric oxide metabolite levels lead to increased production of nitric oxide further promoting blood circulation to the neurons[33].
2	Acetyl-L-Carnitine (ALC)	Facilitates the transport of free fatty acids across the mitochondrial membrane[48]. ALC reduces malondialdehyde of the sciatic nerve and normalizes myo-inositol level[33].
3	Methylcobalamin	Methylcobalamin normalizes the B12-dependent enzyme methionine synthase and increases the S-Adenosylmethionine (SAM) to S-adenosylhomocysteine ratio[49]. Increase in SAM resulting in methylation processes within the myelin sheath.
4	Qutenza	Functions as an agonist for the Transient Receptor Potential Vanilloid (TRPV1) receptor. TRPV1 receptor detects pain and temperature[50].

peroxidation also decreases protein glycosylation and increases Na+/K+ ATPase activity[33] (Table 3).

5.2 Acetyl-L-Carnitine (ALC)

It is an antioxidant that facilitates the transport of free fatty acids across the mitochondrial membrane, thereby improving cellular energy metabolism and either correcting a deficiency or enhancing the response to nerve growth factor[48]. Recent studies report that the ALC reduced malondialdehyde of the sciatic nerve and normalised myo-inositol level without reducing nerve sorbitol level[33] (Table 3).

5.3 Methylcobalamin

Deficiency of methylcobalamin is associated with the PN. The hypomethylation process in the central nervous system is associated with vitamin B12 deficiency and its resulting neuropathy. Inhibition of the B12-dependent enzyme methionine synthase causes a decline in the S-Adenosylmethionine (SAM) to S-adenosylhomocysteine ratio[49]. A reduction in SAM hinders methylation processes within the myelin sheath. Recent studies elucidate some of the potential mechanisms involved in vitamin B12 deficiency-associated neuropathies. A deficiency of vitamin B12 results increase in the levels of neurotoxic cytokine Tumor-Necrosis-factor α (TNFα) and a decrease in the levels of neurotrophic epidermal growth factor and neurotrophic cytokine interleukin-6[33] (Table 3).

5.4 Qutenza

Qutenza (8% Capsaicin patch) functions as an agonist for the Transient Receptor Potential Vanilloid (TRPV1) receptor. Originally approved for addressing post-herpetic neuralgia in 2009, an additional new drug approval for employing Qutenza to manage painful peripheral diabetic neuropathy was issued in July 2020[50] (Table 3).

6. Potent Medicinal Plants for the Management of Peripheral Neuropathy

6.1 *Artemisia dracunculus*

Artemisia dracunculus (Family: *Asteraceae*) possess anti-inflammatory and antinociceptiveactivities[51,52]. Watcho *et al.*,[51] study has documented the effectiveness of an ethanolic extract derived from *A. dracunculus* normalizes glycemia and improves nerve conduction in high-fat diet-induced neuropathy of prediabetes and obesity. Shahraki *et al.*,[53] reported that the aqueous extract obtained from the leaf of the *A. dracunculus* plant can effectively alleviate acute and chronic pain in male rats fed with fructose.

6.2 *Ginkgo biloba*

Ginkgo biloba (Family: *Ginkgoaceae*) possess neuroprotective, anti-inflammatory, antioxidant, a platelet-activating factor antagonist activities[54]. According to a study by Kim *et al.*[54], the administration of *G. biloba* extract demonstrated a reduction in paw withdrawal thresholds to mechanical stimuli and withdrawal frequencies to cold stimuli in rat models of neuropathic pain.

6.3 *Colchicum luteum*

Commonly known as *Suranjan* (Family-*Liliaceae*). *Unani* literature refers to two varieties used medicinally:

a bitter variety called Suranjan Talkh obtained from *Colchicum autumnale L.* (Meadow saffron) and *C. luteum* Baker (Indian Colchicum), and a non-bitter variety known as SuranjanShirin obtained from *Merendra persica*, commonly found in Persia. It acts as an anti-inflammatory and is used for the management of Sciatica, Gout, Impotence, Hemorrhoids, Nerve disorders, skeletal pain, and wounds). The chief chemical constituent of *C. luteum* is colchicine[55]. Ali *et al.,*[56] reported that the anti-inflammatory effect of *C. luteum* is attributed to its ability to decrease the expression of TNF-α receptors on the surface of macrophages and endothelial cells, thereby preventing the activation of macrophages induced by TNF-α.

6.4 *Bauhinia variegata*

Commonly known as *Kachnar* (Family-*Fabaceae-Leguminosae*). Various parts, *i.e.*, flowers, buds, stems, roots, bark, seeds, and leaves have been used since ancient times for the treatment of a wide range of diseases[57]. Mishra *et al.*[9] reported that leaf extract of *B. variegata* possesses antibacterial, anticancer and antioxidant activity. Recent studies have indicated that the presence of flavonoids in *B. variegata* exhibits notable antioxidant activity by effectively scavenging various free radicals[58].

6.5 Cannabis

Cannabidiol (CBD) is the primary non-psychoactive compound found in Cannabis, which is a physiologically important isomer of delta9-tetrahydrocanabinol. Recent studies suggest that cannabidiol has antianxiety, antipsychotic, neuroprotective, and anticonvulsant effects. It is a powerful antioxidant and also has anti-inflammatory and immunomodulatory effects[59]. Cannabidiol shows its pharmacological action by acting on two types of receptors: CB 1 and CB 2. CB 1 receptors act on voltage-gated calcium and potassium channels further leading to the inhibition of synaptic transmission. CB 2 receptors have a limited expression in the central nervous system these receptors are primarily expressed in the immune system[60].

6.5.1 *Acorus calamus*

Acorus calamus (Family: *Araceae*) has been traditionally used in the treatment of various inflammatory conditions based on ancient medicinal systems[61]. Research studies have reported that the hydroalcoholic extract derived from *A. calamus* exhibits a reduction in thermal hyperalgesia, thermal allodynia, and mechanical hyperalgesia associated with neuropathic pain. The hydroalcoholic extract of *A. calamus* exerts its effects through various mechanisms, including antioxidative, anti-inflammatory, calcium inhibitory activity, and neuroprotective actions[5].

6.6 *Alstonia scholaris*

Alstonia scholaris (Family: *Apocyanaceae*) is useful in the treatment of various diseases like diarrhoea, dysentery, malaria, fever, heart diseases and rheumatic pains in the traditional system of medicine. Studies report that the ethanolic extract of *A. scholaris* diminishes heat hyperalgesia, mechanical hyperalgesia and cold allodynia and protects against oxidative stress and inflammatory activity in CCI rat[62].

6.7 *Commiphora mukul*

Commiphora mukul (Family: *Burseraceae*), alias *Commiphora wightii* or guggul, is eminent in the Ayurvedic system of medicine. Studies report that due to its antioxidant activity, *C. mukul* decreases neuropathic pain, by exerting protective action on lipid peroxidation; increasing cellular antioxidant defense. Despite the antioxidant activity, studies also revealed that the phytoconstituents of guggul suppresses IL-1β- and IL-6-mediated inflammatory response by suppressing nuclear factor-κβ activation, TNF-α, and prostaglandin E2 (PGE2) production, NO formation, and phosphorylation of p38 map kinase[63].

6.8 *Boswellia serrata*

Acetyl-11-keto-beta-boswellic acid (AKBA), an effective phytochemical found in *B. serrata* (Family: *Burseraceae*), is widely used due to its anti-inflammatory properties and its capability to inhibit the nuclear factor-kappa B signaling pathway. According to a study by Wang *et al.*,[64], genomic sequencing was performed in a rat model with sciatic nerve crush injury after the administration of gastric AKBA for 30 days. The findings of the study demonstrated that AKBA promoted the repair of sciatic nerve injury in rats by increasing the expression of BDNF, NGFR, and NGF mRNA, thereby enhancing the expression of their corresponding proteins. Additionally, AKBA reduced the expression of MPO mRNA and protein in

the phagosome pathway, leading to the inhibition of inflammation.

6.9 Lappaconitine

Lappaconitine is a natural substance found in the roots of Aconitum plants. For hundreds of years, it has been used to relieve pain, especially in China and Japan[65]. Aconitine and its associated alkaloids, sourced from Aconitum plants, exhibit diverse pharmacological effects, including analgesic and anti-inflammatory properties[66,67].

6.10 *Naringin*

A flavanone-7-O-glycoside, *Naringin*, is obtained from grapefruit and similar citrus plants. It exhibits actions such as metal chelation, antioxidation, and scavenging of free radicals. When *Naringin* is administered, it triggers an elevation in the nociceptive threshold level, boosts endogenous antioxidants, and enhances the activity of membrane-bound inorganic phosphate enzymes. Furthermore, it mitigates levels of oxidative and nitrosative stress, inflammatory mediators, and apoptosis within neural cells in diabetic neuropathic pain induced by STZ. These outcomes are likely attributed to Naringin's inherent antioxidant and anti-apoptotic properties[68].

6.11 *Incarvillea sinensis*

Incarvillea sinensis, a prominent member of the *Noniaceae* family, is native to Northern China. This plant has gained widespread usage as a folk medicine to treat ailments like bruises, rheumatism and wounds. Within the realm of traditional Chinese medicine, it has demonstrated effectiveness in alleviating both pain and inflammation. The primary active component of this plant is recognised as incarvillateine. The application of incarvillateine reduced pain in mice induced by formalin, exhibiting greater potency compared to morphine. Additionally, its pain-relieving effects were reduced by non-selective adenosine receptor antagonists, non-selective opioid receptor antagonists, and antagonists for μ and κ opoid receptors[64,69,70].

7. Role of Proteins, Vitamins in Neuropathy

7.1 Vitamin B12

Vitamin B12 or cobalamin, is naturally found in animal-derived and dairy products and synthesised by specific microorganisms[71]. Vitamin B12 serves a crucial part in two important biochemical reactions in the human body[72]. Firstly, it contributes to the methylation process of homocysteine to form methionine. This reaction generates tetrahydrofolate, a vital precursor to synthesize purines and pyrimidines, essential for DNA and RNA production. Secondly, vitamin B12 facilitates the alteration of L-methyl malonyl A to succinyl coenzyme A. This conversion is necessary to form the myelin sheath, a protective covering around nerve fibres that ensures proper nerve signal transmission. Certain drugs such as metformin, proton pump inhibitors and chronic exposure to nitrous oxide can contribute to vitamin B12 deficiency. Nitrous oxide specifically inactivates methyl-cobalamin, which hinders the alteration of homocysteine into methionine and also the production of Methyl Tetrahydrofolate (MTHF) and Tetrahydrofolate (THF). These substances are necessary to synthesize myelin sheath proteins and DNA[73].

7.2 Vitamin E

Vitamin E is an antioxidant or free radical scavenger. It is freely present in animal fat, nuts, grains and vegetable oils. In humans, the biologically active form of vitamin E is alpha-tocopherol[74]. It is fused into chylomicrons and passively absorbed in the intestines. Vitamin E is transported to tissues along chylomicrons and the remaining vitamin and chylomicrons are then transferred to Very Low-Density Lipoprotein (VLDL) through alpha-Tocopherol Transfer Protein (TTP). Deficiency of this vitamin results in severe diseases like loss of vibration, retinopathy, loss of deep tendon reflexes, muscle weakness, ataxia and shot lifespan of white and red blood cells. Vitamin E plays a crucial role in wound healing by promotingan enhanced immune response. It prevents the peroxidation of Polyunsaturated Fatty Acids (PUFA) in cell membranes by supporting the antioxidant defense system. However, it should be noted that higher doses of vitamin E can potentially lead to fibrosis and delay wound healing[75].

7.3 Vitamin B6

Vitamin B6 or pyridoxine, is essential for maintaining nerve health. Deficiency or excess of vitamin B6 can contribute to neuropathy. It can be obtained through dietary sources and is not synthesized by the human

body[76]. After absorption, it is converted into pyridoxal phosphate, serving as a vital co-factor in numerous metabolic reactions. Vitamin B6 deficiency is frequently observed in individuals undergoing treatment with drugs such as isoniazid, phenelzine, hydralazine, and penicillamine. Additionally, malnutrition caused by alcoholism can also contribute to vitamin B6 deficiency. The major symptoms associated with vitamin B6 deficiency include numbness, seizures, burning pain, ataxia, reduced deep tendon reflexes and mild weakness in the distal areas[73].

7.4 Vitamin B1

Vitamin B1, also known as thiamine, is a water-soluble vitamin predominantly found in both found in animal and plant tissues[77]. Thiamine is absorbed in the small intestine through a combination of active and passive diffusion and undergoes conversion to Thiamine Diphosphate (TDP). Thiamine diphosphate is a crucial co-factor in cellular respiration, ATP production, synthesis of glutamate and γ-aminobutyric acid or myelin sheath maintenance. Commonly observed conditions associated with thiamine deficiency include chronic alcohol abuse, AIDS, recurrent vomiting, eating-related disorders and weight reduction surgery. Neuropathy resulting from a deficiency of vitamin B1 is known as beriberi. Wernicke's encephalopathy and Korsakoff's syndrome are both caused by thiamine deficiency. Major symptoms associated with thiamine deficiency are fatigue, irritability, muscle cramps, burning pain, weakness of muscles in toes and feet, aching, and cramping in the lower legs[73].

7.5 Vitamin B3

Vitamin B3 or Niacin, is absorbed in the small intestine through simple diffusion[78]. Niacin and its analogs play a crucial part in carbohydrate metabolism. Niacin deficiency can lead to other nutritional deficiencies and subsequently result in neuropathy. It is commonly observed in patients with lower levels of Vitamin B12 or Thiamine[73].

7.6 Protein

The prolonged inflammation process may also contribute to poor wound healing due to Protein deficiency, detrimental collagen synthesis, and increased probability of wound extension, and leads to secondary edema due to hypoalbuminemia due to which protein malnutrition occurs[79]. Albumin, a protein found in blood, provides essential amino acids to help wounds heal. Cells can absorb albumin from the intravascular and extra-vascular compartments because it can easily pass through the cell membranes. In the injured location, there is more availability of plasma protein due to increased permeability, which facilitates wound healing[80].

8. Role of Minerals in Neuropathy

8.1 Copper

Copper is primarily present in Western diets and is abundant in copper-rich foods like seafood, nuts, wheat, and grains. Studies suggest that deficiency of this mineral is associated with peripheral neuropathy, myeloneuropathy, or myelopathy[81]. Copper plays a vital role in numerous oxidative reactions within the body[82]. These reactions have the potential to generate free radicals and can be toxic to cells, making it essential for the cell to tightly regulate both the absorption and elimination of copper. After entering the bloodstream, copper binds to plasma proteins then it is carried through the portal vein to the liver where it combines with ceruloplasmin, which facilitates its transport into cells[83]. Excessive intake of zinc, either through supplements or old zinc creams can lead to a deficiency of copper associated with neurological signs. Zinc and copper bind to metallothionein within the enterocytes. Overconsumption results in the upregulation of these complexes where copper has a greater affinity for these receptors than zinc. Then zinc is absorbed into the bloodstream and the copper metallothionein complex remains in the enterocytes and is excreted in faeces following normal discard of these cells. Copper insufficiency also arises from excessive iron consumption and malabsorption syndrome. Common complications associated with the deficiency of copper are vibrations, anaemia, myelodysplastic syndrome bladder dysfunction, motor neuron dysfunction, motor and sensory axonal abnormalities, and polyneuropathy[73].

8.2 Magnesium

In an animal experiment conducted by Hasanein *et al.*,[76] it was observed that administering oral magnesium

supplements to diabetic rats led to a reduction in pain, as assessed through thermal pain thresholds. Additionally, diabetic individuals have been reported to exhibit notably lower plasma magnesium levels when compared to non-diabetic controls[84].

8.3 Chromium

A deficiency in chromium can result in peripheral neuropathy linked to compromised glucose tolerance[85]. Verhage *et al.*,[86] reported that chromium infusion normalized nerve conduction within three weeks.

9. Role of *Yoga* in Neuropathy

It has been confirmed that practising Yogic exercises lead to a reduction in blood sugar levels[87]. Research has indicated a noteworthy decrease in both fasting and post-prandial blood sugar levels, contributing to improved blood sugar control[88]. This was accompanied by a substantial reduction in glycosylated haemoglobin levels and a decrease in the need for medications[89]. This leads to a reduction in serum lipid peroxide levels, resulting in a decrease in the harmful effects of oxygen free radicals[90]. Research has unveiled that *Yoga* promotes the efficient utilization of oxygen by nerves and a reduction in oxidative stress[91]. NP is a frequent result following spinal cord injury, affecting as many as 70% of individuals with SCI[92]. The utilization of *Yoga* as a complementary therapy within rehabilitation protocols has demonstrated the potential to improve pain tolerance in individuals with spinal cord injuries and other patients experiencing pain[93].

10. Conclusion

Neuropathy is a prevalent and challenging condition, with implications for both clinical practice and research. Understanding its causes, mechanisms, and treatment options is crucial for improving the life quality in individuals having neuropathic pain and related conditions. The current oral treatments for peripheral neuropathy provide less relief along with side effects such as blurred vision, weight gain, dizziness, and constipation. Additionally, these formulations may not effectively prevent nerve demyelination. To mitigate these side effects, it is crucial to explore alternative treatment approaches, such as topical application and combination therapies that minimize side effects while addressing all symptoms of neuropathy. The potent herbal plants used for the management of peripheral neuropathy have gained significant attention in the field of traditional and alternative medicine. These natural remedies offer promising therapeutic potential for alleviating the symptoms and discomfort associated with neuropathic conditions. *A. dracunculus, G. biloba, C. luteum, B. variegata, Cannabis, A. calamus, A. scholaris, C. mukul, B. serrata, Lappaconitine, Naringin,* and *I. sinensis* are among the medicinal plants with documented properties that include anti-inflammatory, antioxidant, and neuroprotective activities. These plants have shown promise in reducing pain, improving nerve conduction, and managing symptoms related to peripheral neuropathy. The diverse range of bioactive compounds found in these medicinal plants provides multiple avenues to manage neuropathic pain with its associated symptoms. Further research and clinical studies are essential to know about mechanisms of action and to establish standardized protocols for their relevance in the management of peripheral neuropathy. As natural alternatives have potential benefits, these medicinal plants offer hope for individuals suffering from neuropathic conditions and represent a valuable area of exploration for the future of neuropathic pain management. In addition, addressing nutrient deficiencies is crucial for managing neuropathy, with vitamins and minerals playing essential roles. B vitamins and minerals like copper, magnesium, and chromium have implications for nerve health. Lastly, the role of *Yoga* in neuropathy management is promising, offering a holistic approach to improving physical and mental well-being. However, consultation with healthcare professionals is recommended for a well-rounded treatment plan.

11. Author Contribution

Gurvinder Singh, Dileep Singh Baghel and Saurabh Singh: supervision and review; Ravinder Kumar and Shruti Sharma: Conceptualization; writing, review and editing; Sumanthmayur MR and Rupali: editing. All authors have read and agreed to the published version of the manuscript.

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