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Medicinal herbs in the treatment of neuropathic pain: a review

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ABSTRACT

Chronic neuropathic pain is a common significant and debilitating problem that presents a major challenge to health-care. Despite the large number of available drugs, there are no curative conventional treatments for neuropathic pain. Nowadays, more attention has been focused on the herbal formulation in the field of drug discovery. Therefore, we performed an extensive review about herbal drugs and plants that exhibited protective effects on neuropathic pain. In this review, the beneficial effects of each plant in different neuropathic pain model, either in animals or in patients are reported. Moreover, the possible involved mechanisms for the protective effects are discussed. The more common plants which are used for the treatment of neuropathic pain are included as: *Acorus calamus, Artemisia dracunculus, Butea monosperma, Citrullus colocynthis, Curcuma longa, Crocus sativus, Elaeagnus angustifolia, Ginkgo biloba, Mitragyna speciosa, Momordica charantia, Nigella sativa, Ocimum sanctum, Phyllanthus amarus*, Pterodon pubescens Benth, Rubia cordifolia and Salvia officinalis. Furthermore, the most pathways which are known to be involved in pain relief by means of herbal remedies are anti-oxidant activity, anti-inflammatory, anti-apoptotic, neuroprotective and calcium inhibitory actions.
In conclusion, this review suggests that some herbal plants can be suitable candidates for the treatment of neuropathic pain.

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Introduction

Pain, an unpleasant sensation and emotional experience that in our daily life, is an alert of tissue injury to prevent further or impending tissue damage (1). Acute pain is a useful biologic purpose and self-limiting in nature that arises in response to a specific injury. Chronic pain, in contrast, may be considered as a disease state. It may outlast the usual duration of recovery, if accompanied with a disease or injury (1, 2). The definition of chronic neuropathic pain is "pain that comes from direct consequence of a lesion or disease which affect the somatosensory system" (3). It may be classified as central or peripheral, depending on the site of the lesion. The most causes of chronic neuropathic pain are metabolic disease, viral, trauma, severe ischemic insults, and autoimmune diseases (4-6).

Neuropathic pain usually does not have effective treatment, because of heterogeneous etiology and complex underlying pathophysiology, moreover, the unwanted side effect profiles limit the use of available drugs (7-9).

Neuropathic pain and underlying mechanisms

Neuropathic pain may be spontaneous or evoked in response to physical stimuli, that may manifest as increased sensitivity to pain (hyperalgesia) or as a pain evoked by a nonpainful stimuli (allodynia) (5, 10). Once injury occurs, inflammation and reparatory processes ensue, leads to a hyperexcitable state known as peripheral sensitization. Many types of peripheral mechanisms have been described, in most patients, this state resolves as healing occurs and inflammation subsides. But, stimulation from ongoing injury or disease lead to persist nociception, then the changes in primary afferent neurons may continue (11). Central changes can result from peripheral nerve lesions, which have been investigated in animals mainly at the spinal cord or sometimes at supraspinal levels (12, 13).

Several types of alterations can induce pathologic activation of central nociceptive neurons: such as neuroplasticity, microglial activation and hyper-excitability (central sensitization) of nociceptive neurons. Central sensitization possibly depends critically on intracellular changing that induced by the activation of N-methyl-D-aspartate (NMDA) and glutamate metabotropic receptors (12, 13). The stimulation of non-neuronal cells, microglia in central and macrophages in periphery, leads to production of a variety inflammatory cytokines and chemokines which play critical roles in neuropathic pain condition (14, 15).

Neuropathic pain and herbal medicinal products

The usage of natural products, principally herbal medicines is one of the ancient therapies used by humanity (16). During the recent years, people are eager to use herbal medicines due to their lower complications and fewer side effects than synthetic drugs (17). Regarding to the increasing demand for medicinal plants and related compounds the phytopharmaceutical studies and the use of these remedies for the management of painful neuropathy have been growing throughout the world (18).

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Animal models and/or pharmacological mechanisms of neuropathic pain

Animal models of neuropathic pain have been essential in the exploration of molecular mechanisms of pain also for the analysis of novel analgesics in the treatment of chronic pain (19). The animal models for studying neuropathic pain and a brief description of each model are as follows:

The streptozotocin (STZ)-induced diabetes

The STZ-induced diabetic neuropathic pain model mimics the diabetic neuropathy. This neuropathy is one of the most frequent peripheral neuropathies associated with hyperalgesia, cold or hot allodynia and hyperesthesia, the high blood glucose level induced oxidative and nitrosative stress which have been proposed to be an essential mechanism of neuronal injury related to diabetic neuropathy (20-22). Reactive oxygen species (ROS) enhanced nociceptors sensitization so that they not only respond more vigorously towards noxious stimuli, but also start to respond towards normally subthreshold stimuli. This peripheral sensitization not only induces pain directly but furthermore induces central sensitization in the spinal cord, which also indirectly contributes to pain (7, 23). In high concentrations superoxide combine with nitric oxide to form peroxynitrite, which is implicated in diabetes accompanied by motor and sensory nerve conduction deficits, in addition to peripheral nerve energy deficiency (7, 24).

High-fat diet

High-fat diet is an important risk factor for nerve conduction velocity deficit and small sensory fiber neuropathy with alimentary obesity, hyperinsulinemia, and impaired glucose tolerance develops neuronal damage resulting from oxidative stress of lipid metabolism and indicate increased sorbitol pathway activity, oxidative-nitrosative stress, and pro-inflammatory changes in peripheral nervous system (PNS) (25, 26). This model has been used in studies on pathophysiology of impaired glucose tolerance (IGT) and type 2 diabetes and for development of new treatments (27).

Neuropathy produced by sciatic nerve injury

The experimental model of neuropathy produced by sciatic nerve injury in animals mimic symptoms observed in human beings with nerve injury, and this model is widely used in behavioral examination. In this model, prolonged changes in neurotransmitter and receptor expression, lead to produce central sensitization in response towards the release of numerous inflammatory and pain mediators observed, which in turn enhances the sensitivity of peripheral sensory afferents at the site of injury and also in the CNS (7).

Chemotherapy-induced peripheral neuropathy

Peripheral neuropathy is a common side effect of many classes of anti-cancer drugs, the major classes of chemotherapy drugs that induce peripheral neuropathy (CIPN) including the antitubulins (paclitaxel, docetaxel, ixabepilone, and vincristine), platinum analogs (oxaliplatin, carboplatin, and cisplatin), and the proteasome inhibitors such as bortezomib and thalidomide. These drugs exert direct and indirect effects on sensory nerves to diminish the amplitude of action potential, slow conduction velocity and induce pain in patients, mainly those who experience nociceptive sensory loss through their cancer treatment (28, 29).

Research methodology

The current search was done in databases of Google Scholar, Medline and Scopus, using the following keywords: neuropathic pain, medicinal plants, phytotherapy and natural products. The search included literatures published as late as 31 April 2017.

In the present review, plants and some constituents of herbal medicine which have the potential to cure neuropathic pain have been discussed alphabetically.

For a summary of the selected experimental and human studies see Table 1 and Table 2.

Acorus calamus

A. calamus, belongs to Araceae family, it has been used for the management of several inflammatory disorders in Indian traditional medicine (30). The hydroalcoholic extract of *A. calamus* (HAE-AC) has been shown to significantly attenuate thermal hyperalgesia, thermal allodynia and mechanical hyperalgesia on neuropathic pain induced by tibial and sural nerve transection (TST) in rats. Moreover, a significant decrement in the superoxide anion, total calcium levels and myeloperoxidase (MPO) activity were also observed (31). Furthermore, HAE-AC decreased superoxide anion, total calcium levels and MPO activity in sciatic nerve chronic constriction injury (CCI). It also attenuated CCI induced development of painful behavioral changes including: thermal, radiant, mechanical hyperalgesia and thermal, chemical, tactile allodynia in rats (32). In other study, HAE-AC attenuated the development of painful behavioral (thermal and mechanical hyperalgesia and mechanical allodynia), biochemical (rises in the levels of superoxide anion, total calcium and myeloperoxidase activity) and histological changes in vincristine-induced neuropathy in rats (33). In a further study saponin rich extract of *A. calamus* (20 and 40 mg/kg) significantly improved CCI-induced nociceptive pain threshold, sciatic functional and electrophysiological changes in rats (34). These effects may have been exerted probably by multiple mechanisms containing antioxidative, anti-inflammatory, calcium inhibitory activity and neuroprotective actions (31-33).

Alstonia scholaris

A. scholaris belongs to Apocyanaceae family, it has been used for treating diarrhea, dysentery, malaria, fever and cardiac diseases as well as rheumatic pains in traditional medicine (35).

Singh *et al.* in 2017, showed that methanol extract of *A. scholaris* significantly attenuated heat hyperalgesia, mechanical hyperalgesia and cold allodynia as well as protection against oxidative stress and inflammatory activity in CCI rats (36). They have suggested that the therapeutic effect of this extract may be due to the presence of kaempferol and attributed to inhibit the inflammatory cytokines and ROS production (36).

Artemisia dracunculus

Artemisia species are beneficial herbal remedies with antioxidant and anti-inflammatory effects (25, 37). *A. dracunculus,* belongs to Asteraceae family, display anti-inflammatory and antinociceptive effects (25, 35). PMI-5011, is an ethanolic extract of *A. dracunculus*. PMI-5011 normalized glycemia, improved nerve conduction slowing and sensory neuropathy, and diminished 12/15-lipoxygenase upregulation and nitrated protein expression in peripheral nervous system in rats with high-fat diet-induced neuropathy of prediabetes and obesity, potentially, by multiple mechanisms that are including the inhibition of oxidative nitrosative stress and lipoxygenase activation (25). Another study demonstrated that *A. dracunculus* leaf aqueous extract diminished the acute and chronic pain on fructose fed male rats (38).

Butea monosperma

B. monosperma is distributed in deciduous forest and in open areas. It has been used in traditional medicine for various therapeutic effects such as diuretic, anti-diabetic, anthelmintic, antimicrobial, arthritis, wound healing in addition to treating burning sensation of the body (39, 40). Pretreatment with *B. monosperma* significantly increased the behavioral (i.e. hyperalgesia and allodynic pain sensation) changes and decreased thiobarbituric acid reactive substances (TBARS), total calcium levels besides increased the glutathione (GSH) levels in the sciatic nerve tissue when compared with the normal control group on vincristine-induced neuropathic pain model in rats, that may be due to its potential of neuroprotective, antioxidant and calcium channel inactivation (39). Another study investigated the ameliorative effect of ethanolic extract from leaves of *B. monosperma* in CCI model. Pretreatment of *B. monosperma* attenuated CCI induced development of histopathological, biochemical and behavioral alterations dose dependently, which is comparable to that of pregabalin pretreated group. This may be due to its potential anti-oxidative, neuroprotective and calcium channel modulatory effects of *B. monosperma* (40).

Citrullus colocynthis

C. colocynthis (cucurbitaceae), endemic in Southern Tunisia, in folk medicinal used as an analgesic and anti-inflammatory agents (41). Aqueous extracts of the plant in acetic acid writhing test in mice and the carrageenan-induced paw edema assay in rats had analgesic and anti-inflammatory effects (41). More recently, in a two-arm double-blind randomized placebo-controlled clinical trial using a parallel design, sixty painful diabetic polyneuropathy (PDPN) patients were randomly allocated to treat either with a topical formulation of *C. colocynthis* or placebo, after 3 months the results showed that administration of a topical formulation of *C. colocynthis* fruit extract diminished pain in patients with PDPN (42).

Curcuma longa

C. longa, a perennial herb of the ginger family, is cultivated widely in south and southeast tropical Asia. It has been used medically for thousands of years (43). As a main constituent of *C. longa*, curcumin has a variety of pharmacological properties such as antioxidant and anti-inflammatory activities (43, 44). Curcumin improved mechanical allodynia and thermal hyperalgesia in CCI mice along with increasing spinal monoamine (or metabolite) contents. 6-Hydroxydopamine (6-OHDA) totally abolished the effects of curcumin on mechanical allodynia and p-chlorophenylalanine (PCPA) completely blocked the antinociceptive influence of curcumin on thermal hyperalgesia. Chronic co-treatment with the β2-adrenoceptor antagonist ICI 118,551, or by acute co-treatment with the delta-opioid receptor antagonist naltrindole blocked the anti-allodynic action of curcumin on mechanical stimuli. However, co-treatment with the irreversible mu-opioid receptor antangonist β-funaltrexamine acutely or with the 5-HT_{1A} receptor antagonist WAY-100635 chronically completely abrogated the anti-hyperalgesic effect of curcumin on thermal stimuli. According to these results, the descending monoamine system (coupled with spinal β_2-adrenoceptor and 5-HT_{1A} receptor) for antinociceptive properties of curcumin in neuropathic pain is crucial. Delta- and mu-opioid receptors are likely rendered as downstream targets (44). In another study, curcumin reduced mechanical and cold allodynia and attenuated the serum concentration of cyclooxygenase 2 (COX-2) in CCI model of neuropathic pain in rats, that may be mediated, at least partially, by reducing the inflammatory effects of COX-2 enzyme activity (45).

Crocus sativus

C. sativus commonly known as saffron, belongs to the Iridaceae family and extensively cultivated in Iran and other countries such as India and Greece (46, 47). It is used traditionally as food and remedy for several disorders including bronchospasm, insomnia, asthma, menstruation problems, pain relief and cardiovascular disorders (48). Chemical studies have shown that most important bioactive constituents of *C. sativus* are crocin, crocetin, safranal and picrocrocin (49, 50). The ethanolic and aqueous extracts of saffron as well as safranal attenuated the behavioural symptones of neuropathic pain in CCI model in rats (48). Besides, the ethanolic and aqueous extracts of *C. sativus* attenuated malondialdehyde (MDA) and increased GSH levels in CCI animals (51). Safranal showed an anti-nociceptive effect in chemical (formalin and acid acetic tests) methods of nociception in mice (52). Stigma extracts of *C. sativus* exerted anti-inflammatory effects (53). A recent study showed that saffron and crocin (30 mg/kg) reduced thermal hyperalgesia and mechanical allodynia, but crocin at lower dose (15 mg/kg) was ineffective to produce protective effects (54). Ethanolic and aqueous extracts of *C. sativus* as well as safranal diminished allodynia and hyperalgesia induced by (CCI) of the sciatic nerve, besides *C. sativus* extracts significantly decreased the lumbar spinal cord contents of MDA and proinflammatory cytokines (TNFα, IL-1β, IL-6) (55). A more recent study showed that, saffron as an adjunctive therapy in combination with amitriptyline lead to improvement of the therapeutic outcome in the management of neuropathic pain (56).

Elaeagnus angustifolia

E. angustifolia (Elaeagnaceae) is cultivated from the northern areas of Asia to the Himalayas and

Europe because of its ability to grow in a wide range of environmental conditions (57, 58). In Iranian traditional medicines, *E. angustifolia* fruit has been used as an analgesic agent for decreasing of pain in rheumatoid arthritis (59). *E. angustifolia* showed muscle relaxant (60) and anti-inflammatory (61) activity. Administration of different doses of this fruit showed significant analgesic effect on nerve ligated mice in hot plate test (57). Flavonoids have been considered the most essential components in *E. angustifolia* that have been related to antinociceptive and anti-inflammatory activities (62). Recently in a randomized controlled trial study *E. angustifolia* extract reduced the symptoms of osteoarthritis with an efficacy comparable to that of ibuprofen. It was also safe and well tolerated during the course of trial and no adverse effect was seen (63).

Ginkgo biloba

G. biloba is the popular herb that has shown some neuroprotective effects such as protective activity against transient and permanent focal cerebral ischemia (64) and dementia (65). The most unique constituents of the *G. biloba* extracts are the terpene trilactones, that are, ginkgolides and bilobalide. In a study, conducted by Kim, *et al.* , administration of *G. biloba* extract, EGb 761, lead to reduction of the paw withdrawal thresholds to mechanical stimuli and withdrawal frequencies to cold stimuli in the rat model of neuropathic pain induced by spinal nerve ligation (SNL). The beneficial effect of *G. biloba* extract on neuropathic pain was likely due to a combination of an anti-inflammatory, antioxidant effect, a platelet activating factor antagonist and a protective effect against NMDA induced neurotoxicity (66). Administration of EGb 761, a standardized extract of *G. biloba,* after the third week of STZ administration for 14 days reversed diabetes induced thermal hyperalgesia and mechanical allodynia on STZ-induced neuropathic pain in rats by inhibiting oxidative and nitrosative stress (67).

Mitragyna speciosa

M. speciosa (Korth.) belongs to Rubiaceae family, is endemic to tropical Southeast Asia (68). The leaves of *M. speciosa* have been used for medicinal purposes such as relieve muscle pain and fever (69), and has long been used in Thailand for its opioid-like effects (70). 7-Hydroxymitragynine is an indole alkaloid and was found to possess the most potent opioid agonistic effects among the components isolated from the traditional herbal medicine *M. speciose* (70). Matsumoto *et al.* developed dual-acting μ- and Δ-opioid agonists MGM-15 and MGM-16 from 7-hydroxymitragynine for the treatment of acute and chronic pain. MGM-16 exhibited a higher potency than that of 7-hydroxymitragynine and MGM-15 in *in vitro* and *in vivo* assays. Also MGM-16 exhibited a high affinity for μ- and Δ-opioid receptors both *in vitro* and *in vivo* tests. Systemic administration of MGM-16 caused antinociceptive effects in a mouse acute pain model and antiallodynic effects in a neuropathic pain model in mice (70). A recent study demonstrated that *M. speciosa* produced antinociceptive effects similar to the reference opioid agonists (69).

Momordica charantia

M. charantia (Cucurbitaceae) grows in Asia, Africa, and Latin America and is used traditionally as food and remedy for several disorders such as asthma and anaemia (71). Administration of *M. charantia* significantly attenuated TST induced behavioral alterations including cold, mechanical, and heat hyperalgesia, dynamic mechanical allodynia, and cold allodynia in rats. Furthermore, treatment of *M. charantia* also prevents TST-induced rise in nerve tissue TNF-alpha and TBARS contents. It is speculated that PPAR-gamma agonistic effect, anti-inflammatory, and antioxidative potential is critical for antinociceptive effect of *M. charantia* in neuropathic pain (72).

Nigella sativa

N. sativa is an annual flowering plant belonging to the Ranunculaceae family (73, 74). It consists of more than 30% fixed oil and 0.4%-0.45% volatile oil. The volatile oil have 18.4%–24% thymoquinone (TQ) (75, 76). *N. sativa* and TQ caused a significant reduction in elevated serum glucose and increased the lowered serum insulin concentration. They also increased the level of insulin immunoreactive β-cells. The histologic evaluation of the tissues in diabetic animals treated with TQ and especially *N. sativa* exhibited fewer morphologic alterations. The results are attributed to its direct and indirect antioxidant actions of TQ and especially *N. sativa* (76). Another study showed that administration of TQ significantly improved behavioral signs and apoptotic factors also oxidative effects of neuropathic pain in CCI rats (77). In a study conducted by Tewari *et al.* , *N. sativa* showed significant analgesic effects on cisplatin induced neuropathic pain in rats (78).

Ocimum sanctum

O. sanctum is an indigenous plant commonly found in India and is recommended in the Ayurveda to treat various diseases such as arthritis and painful eye diseases (79). Treatment with *O. sanctum* attenuated sciatic nerve transection-induced axonal degeneration, decrement of nociceptive threshold and motor in-coordination. Furthermore, it also attenuated axotomy-induced increase in TBARS, total calcium and diminution in GSH levels (80). In another study treatment with *O. sanctum* and its saponin rich fraction significantly attenuated vincristine-induced increase in the withdrawal duration of the hind paw in response to non-noxious cold stimuli and noxious mechanical stimuli and significantly decreased the vincristine-induced increase in oxidative stress markers and total calcium levels in vincristine-induced neuropathic pain in rats, which may be attributed to diminution in oxidative stress and calcium levels (79). A recent study showed that *O. sanctum* has potential effects in attenuating painful neuropathic state in CCI-induced peripheral neuropathy, and saponins may be the key chemical class responsible for its useful effect in neuropathic pain. Besides, the authors suggested that the pain relieving effects of *O. sanctum* and its saponin rich fraction may be via to attenuation of nerve injury inciting agent-induced increased contents of calcium and free radicals (81).

Phyllanthus amarus

The plants belonging to the genus *Phyllanthus*

(Euphorbiaceae) have more than 600 species, which are extensively distributed in most tropical and subtropical countries (82). Several species from the genus *Phyllanthus* are extensively used in traditional medicine, in several countries, to treat of numerous diseases including flu, dropsy, diabetes, jaundice and bladder calculus (82). The hexanic extract of *P. amarus* inhibited the mechanical allodynia in mice after the partial ligation of the sciatic nerve, with a quite similar efficacy to that obtained with gabapentin. Administration of hexanic extract inhibited the increase of MPO activity, either following intraplantar injection of complete Freund's adjuvant (CFA) or after partial sciatic nerve ligation (PSNL) partly via the anti-inflammatory actions (82). It has been suggested that the antihyperalgesic and anti-inflammatory properties of *P. amarus* in a model of chronic musculoskeletal inflammatory pain are mediated through spinal or supraspinal neuronal mechanisms, principally by inhibition of PGE2 (73).

***Pterodon pubescens* Benth.**

P. pubescens Benth. (Leguminosae) is a tree native to central Brazil that has been used in folk medicine for its anti-inflammatory, anti-rheumatic and analgesic activities (83).

The hexane fraction of the ethanolic extract of the fruits of *P. pubescens* Benth induced anti-inflammatory effects in two animal models including: carrageenan-induced inflammatory reaction in the pleural cavity and complete Freund's adjuvant-induced arthritis (84). Administration of ethanolic extract from *P. pubescens* fruits (EEPp) causes significant inhibition of mechanical and thermal (heat and cold) hyperalgesia induced by PSNL in mice (83). Also, oral administration of EEPp diminished nociceptive behavior induced by intrathecal injection of TRPV1 and TRPA1channels activators (capsaicin and cinnamaldehyde, respectively). The treatment with EEPp inhibited the nociceptive behavior responses induced by the following intrathecal injections with glutamate, kainate, NMDA and trans-ACPD. In addition, EEPp also inhibited the nociceptive behavior responses induced by intrathecal injection of proinflammatory cytokines (TNF-α andIL-1β). These effects may be mediated at least in part, by the inhibition of proinflammatory cytokines, glutamatergic receptors as well as TRPV1 and TRPA1 channels (83).

Rosmarinus officinalis

R. officinalis commonly known as rosemary, belongs to Labiatae family. This plant has been used in traditional medicine for several disorders such as dysmenorrhea and rheumatic pain (85). Rosemary is rich in caffeic acid, rosmarinic acid, ursolic acid, carnosic acid and carnosol compounds (86). Administration of rosmarinic acid and ethanolic extract of *R. officinalis* decreased contents of spinal inflammatory markers comprising matrix metallopeptidase 2 (MMP2), COX2, IL-1b and PGE- 2 in CCI rats (87). The ethanolic extract of aerial parts of *R. officinalis* significantly diminished the amounts of glial activity, inflammation, and apoptosis markers in CCI rats (88).

Rubia cordifolia

R. cordifolia (Rubiaceae) is an ayurvedic herb. Common names of this plant are Indian madder, majit and manjishtha. It is distributed all over the lower hills of Himalayas in the North and Western Ghats in the Peninsula, Ceylon, South India, Japan, Indonesia, Java and in tropical Africa moist temperate and tropical forests (89). Generally root, leaves, fruits, stem etc. of the plant *R. cordifolia* are used for their therapeutic properties such as analgesic and anti-inflammatory activities (89). Patel *et al.* investigated the analgesic and anti-inflammatory activities of this plant. They showed that methanolic extract of the root of *R. cordifolia* significantly reduced in the paw edema produced by the carrageenan and increased the reaction time in tail flick test (89). In a further study, administration of alcoholic extract of roots and rhizomes of *R. cordifolia* significantly decreased withdrawal latency in cold allodynia method and withdrawal latency in the hot plate method in paclitaxel-induced neuropathic pain in rats. The results may be because of the involvement of GABA or antioxidant mechanism (90).

Salvia officinalis

S. officinalis (sage, also called garden sage, or common sage) (family: Lamiaceae) can be found worldwide. This plant is suitable to relive of unilateral headaches and headaches with neurological origin (91). The different extracts of *S. officinalis* in enzyme dependent and enzyme-independent lipid peroxidation systems showed an antioxidant activity (92) and anti-inflammatory properties (28). Qnais and colleagues demonstrated that the aqueous and butanol extracts of *S. officinalis* increased the latency on hot-plate assay and showed antinociceptive response in both phases of formalin and the carrageenan-induced paw oedema in rats (93). The hydroalcoholic extract of *S. officinalis* leaves presents significant anti-inflammatory as well as antinociceptive effects on chemical behavioral models of nociception that involves an opioid mechanism. Furthermore, carnosol and ursolic acid/oleanolic acid contained in this plant appears to contribute for the antinociceptive effect of the extract, probably via a modulatory effect on TRPA1-receptors (94). In another *in vivo* study the hydroalcoholic extract of *S. officinalis* elicited anti-inflammatory effects and decreased pain response on vincristine-induced peripheral neuropathic pain in mice (95). Salvigenin (5-Hydroxy-6,7,4′-trimethoxy flavones) is one of the active flavonoids found in this plant. Salvigenin in a dose dependent manner demonstrated a significant analgesic effect like morphine (91).

Constituents of herbal medicine with protective effect against neuropathy

A9-Tetrahydrocannabinol/Cannabidiol (THC/CBD)

Cannabis sativa has a long history of use as a medicinal agent (96). THC/CBD is derived from strains of *C. sativa* plant developed to produce high and reproducible yields of THC and CBD, with trace quantities of other cannabinoids and terpenes in a solution having ethanol, propylene glycol, and peppermint oil flavoring. THC and CBD contain ≥ 90% of the total cannabinoid content of the extracts (97). THC/CBD display many pharmacologic effects such as anti-inflammatory, appetite stimulant and antiemetic effects (96). THC/CBD has been approved in Canada as adjunctive treatment for the symptomatic

improve of neuropathic pain in multiple sclerosis (MS) in adults (97). The standardized extract of *C. sativa* evoked a total relief of thermal hyperalgesia, in CCI model in rat, that was mediated by vanilloid receptors TRPV1 (96). A phase II randomized clinical trial study showed that administration of active cannabis ranging in potency between 1 and 8% D-9-tetrahydrocannabinol significantly reduced neuropathic pain intensity in HIV-associated distal sensory predominant polyneuropathy (DSPN). These results showed that cannabinoid therapy may be an effective choice for pain relief in patients with medically intractable pain due to HIV-associated DSPN with mild and self-limited side effects (98). Moreover, in randomized controlled trials THC/CBD was effective in patients with central neuropathic pain and MS who completed -2 years of treatment with no evidence of tolerance (97). Also Johnson *et al.* in a double-blind, randomized, placebo-controlled, parallel-group trial study showed that THC/CBD is a useful adjunctive treatment for relief of pain in patients with intractable cancer-related pain who experience inadequate analgesia despite chronic opioid therapy (99). Same authors in an open-label extension study showed that long-term use of THC/CBD spray relieved cancer-related pain and generally well tolerated in advanced cancer patients. Moreover, patients who kept using the study medication did not seek to increase their dose of THC/CBD spray over time (100). Recently, in a double-blind, randomized, placebo-controlled, parallel group study administration of THC/CBD oromucosal spray in patients with peripheral neuropathic pain clinically improved their pain, sleep quality and global impression of change in the severity of their condition (101). More recently in a multicenter, open-label, follow-on study THC/CBD spray was beneficial for the majority of patients that have peripheral neuropathic pain associated with diabetes or allodynia. THC/CBD spray was well tolerated during the study period and also patients did not seek to increase their dose over time, with no new safety concerns arising from long-term use (102).

Lappaconitine

Since ancient times, preparations of various species of *Aconitum* have been widely used. *Aconitine* and related alkaloids, derived from *Aconitum* species, had various pharmacological effect such as analgesic and anti-inflammatory (103, 104). Treatment with *Aconitum* (including both Radix *aconite preparata* and *Radix aconite kusnezoffii*), mixture with Huangqi Guizhi Wuwu Tang (i.e., astragalus, cassia twig, white peony root, and spatholobi) in the four diabetic peripheral neuropathic pain subjects, lead to remarkably reduction of pain and the EMG profile was also improved. Adverse reactions were not observed during the therapy (105). Lappaconitine (LA) is aconitum alkaloid that extracted from the root of the plant Aconitum species. LA has been used as analgesic for centuries in the world, especially in China and Japan (106). Administration of LA showed inhibitory effect on the nociceptive behaviors induced by CCI, diminished the expression of the $P2X_3$ receptors in the dorsal root ganglion (DRG) neurons and inhibited the fast I_{ATP} and $I_{a,\beta\text{-meATP}}$ in the DRG neurons of the CCI rats via regulating the purinergic signaling system at DRG level (107).

DA-9801

DA-9801 is a botanical drug, extracted from *Dioscorea* species including: *D. rhizoma* and *D. nipponica* Makino (108). Many species of *Dioscorea* have traditionally been used clinically in Asia to treat numerous syndromes associated with metabolic disorders. Besides, the extracts of the *Dioscorea* species had antidiabetic and antiobesity effects (108-110).

Administration of DA-9801 improved damage produced by diabetic neuropathy by increasing the levels of NGF in plasma and the sciatic nerve and showed improvement on nerve conduction velocity and recovery from neuronal degeneration in STZ rat/mouse diabetic models and in db/db mouse model (111). Another study demonstrated that oral treatment with DA-9801 decreased the blood glucose contents and increased the withdrawal latencies in hot plate procedures. Furthermore, it prevented nerve injury based on increased nerve conduction velocity and ultrastructural changes (108).

Goshajinkigan

In Japan, TJ-107 (Goshajinkigan) is a complex drug containing 10 medicinal herbs that has been commonly prescribed to improve symptoms of diabetic peripheral neuropathy for example numbness, cold sensation, and paresthesias/dysesthesia. In a phase 2 randomized, double-blind, placebo-controlled study, oral administration of TJ-107 had acceptable margins of safety and tolerability and a promising influence in delaying the onset of grade 2 or greater oxaliplatin-induced peripheral neurotoxicity in colorectal cancer patients treated with oxaliplatin (112).

In a randomized open-labeled clinical trial study, long-term administration of Goshajinkigan showed beneficial effects on macrovascular diseases, retinopathy or nephropathy in type 2 diabetic mellitus patients (113).

Incarvillateine

Incarvillea sinensis is a big noniaceae plant distributed in Northern China. It has been widely used as a traditional herbal medicine for treatment of rheumatism, bruises and wounds. It also is effective in decreasing pain and inflammation in traditional Chinese medicine (114). Incarvillateine is considered the major active constituent of this plant. Administration of incarvillateine attenuated formalin-induced pain in mice with a higher potency than morphine (115). Furthermore, the antinociceptive action of incarvillateine attenuated by non-selective adenosine receptor antagonist, non-selective opioid receptor antagonist, and μ and κ opioid receptor antagonists (116). Administration of incarvillateine in a dose-dependent manner decreased acetic acid-induced writhing and also inhibited both thermal hyperalgesia and paw edema, and increased interleukin-1β levels in Complete Freund's Adjuvant model. Furthermore, incarvillateine reduced mechanical allodynia induced by SNI or paclitaxel. Additionally, incarvillateine-induced antinociception was reduced by theophylline, 1,3-dipropyl-8-cyclopentylxanthine, and 3,7-dimethyl-1-propargylxanthine, but not naloxone. It seems the mechanism of antinociceptive effects are mediated by adenosine receptors, but not the opioid receptor system

Table 1. Herbal medicines and their constituents tested for neuropathic pain in human studies

Substance	Neuropathic disorders	Study type	Results	References
A^9-Tetrahydrocannabinol/Cannabidiol (THC/CBD)	HIV-associated distal sensory predominant polyneuropathy	Phase II, double-blind, placebo-controlled, crossover trial	Reduced neuropathic pain intensity	(98)
THC/CBD	Central neuropathic pain in patients with multiple sclerosis	Randomized controlled trials	Improvement in neuropathic pain without evidence of tolerance	(97)
THC/CBD	Patients with intractable cancer-related pain	Multicenter, double-blind, randomized, placebo-controlled, parallel-group study	Reduced neuropathic pain	(99)
THC/CBD	Patients with terminal cancer-related pain refractory to strong opioid analgesics	An open-label extension study	Well tolerated and reduced pain	(100)
THC/CBD	Patients with peripheral neuropathic pain	A double-blind, randomized, placebo-controlled, parallel group study	Improvement in neuropathic pain	(101)
THC/CBD	Patients with peripheral neuropathic pain	A multicentre, open-label, follow-on study	Improvement in neuropathic pain	(102)
Aconitum	Patients with diabetic peripheral neuropathic pain	Controlled clinical trials study	Reduced diabetic peripheral neuropathic pain	(105)
Citrullus colocynthis	Painful diabetic polyneuropathy patients	Double-blind randomized placebo-controlled clinical trial	Reduced diabetic polyneuropathy pain	(42)
Goshajinkigan	Oxaliplatin-induced neuropathy patients	Phase 2, multicenter, randomized, double-blind, placebo-controlled trial	Delayed the onset of grade 2 or greater oxaliplatin-induced neuropathy	(112)

NMDA: N-methyl-D-aspartate; CNS: central nervous system; PNS: peripheral nervous system; STZ: streptozotocin; ROS: reactive oxygen species; CIPN: chemotherapy drugs that induce peripheral neuropathy; HAE-AC: hydroalcoholic extract of A. calamus; MPO: myeloperoxidase; TST: tibial and sural nerve transection; CCI: chronic constriction injury; TBARS: thiobarbituric acid reactive substances; GSH: glutathione; PDPN: painful diabetic polyneuropathy; 6-OHDA: 6-Hydroxydopamine; PCPA: p-chlorophenylalanine; COX-2: cyclooxygenase 2; MDA: malondialdehyde; SNL: spinal nerve ligation; NOS: nitric oxide synthase; PSNL: partial sciatic nerve ligation; EEPp: ethanolic extract from P. pubescens fruits; THC/CBD, A9-Tetrahydrocannabinol/Cannabidiol; DRG: dorsal root ganglion; 3α-HSOR: 3α-Hydroxysteroid oxidoreductase; SOD: superoxide dismutase

(114).

Koumine

Gelsemium is a genus of the family Loganiaceae, *G. elegans* Benth. has long been used in Chinese traditional medicine to relieve pain, inflammation, and cancer (117). Koumine is an alkaloid monomer found abundantly in *Gelsemium* plants (118). Koumine attenuated tactile allodynia, improve sensory nerve conduction, and mitigate the pathology of sciatic nerves in STZ-induced diabetic rats (119). In another study koumine suppressed thermal hyperalgesia and mechanical allodynia more potently than gabapentin in CCI rats (118).

Upregulation of allopregnanolone induced significant analgesia, indicating that allopregnanolone in the spinal cord (SC) may be an essential key modulator of neuropathic pain. 3α-Hydroxysteroid oxidoreductase (3α-HSOR) is responsible for allopregnanolone upregulation in the SC. The activity of 3α-HSOR in the SC of koumine-treated CCI rats increased by 15.8% as compared to untreated CCI rats. Also, the intrathecal injection of medroxyprogesterone acetate, a selective 3α-HSOR inhibitor, dose-dependently reversed the analgesic effect of koumine on CCI-induced mechanical pain perception. The authors suggested that koumine altered 3α-HSOR-regulated allopregnanolone levels in the SC of rat. Elevated allopregnanolone levels may exert analgesic effects through allosteric modulation of $GABA_A$ and by suppressing the release of microglia activation-induced inflammatory cytokines (118).

Naringin

Naringin, a flavanone-7-*O*-glycoside derived from grape fruit and related citrus species, has metal-chelating, antioxidant and free radical scavenging effects (120). Administration of naringin increased the level of nociceptive threshold, endogenous antioxidant and membrane bound inorganic phosphate enzyme. It also diminished the oxidative–nitrosative stress level, inflammatory mediators as well as apoptosis in neural cells in STZ induced diabetic neuropathic pain. The results may be due to antioxidant and antiapoptotic activity of naringin (120).

In a recent study naringin in a dose dependent manner reduced the mechanical allodynia and thermal hyperalgesia induced by SNL, as well as markedly inhibited peripheral neuropathy-induced activation of glial cells (astrocytes and microglia) (121). Naringin significantly increased PPARγ expression and superoxide dismutase (SOD) contents, reduced MDA contents, and improved the activities of main inflammatory cytokines including TNF-α, IL-1β, and IL-6 in the STZ induced diabetic rats (122).

Quercetin

Quercetin is a phenolic compound extensively distributed in the plant kingdom. It is found in frequently consumed foods, including berries, onions, apples, tea and brassica vegetables. Quercetin has several beneficial effects on human health such as cardiovascular protection and anti-inflammatory effects (123). Administration of quercetin significantly increased in tail-flick latencies in both diabetic and nondiabetic mice. Quercetin-induced increase in nociceptive threshold was reversed by an opioid receptor antagonist (naloxone) in nondiabetic and diabetic mice. The protective effect of quercetin was probably mediated via modulation of opioidergic mechanism in STZ induced diabetic mice (123). Another study showed that quercetin can alleviate high glucose-

Table 2. Mechanisms of actions of herbal medicines against neuropathic pain in animal models

Substance	Animal model	Mechanisms of actions	References
Pterodon pubescens Benth	Partial sciatic nerve ligation (PSNL) in mice	Inhibition of proinflammatory cytokines, glutamatergic receptors as well as TRPV1 and TRPA1 channels	(83)
Shanzhiside methylester	Spinal nerve injury (SNI) in rat	Microglial β-endorphin expression via p38 MAPK signaling	(15)
Emblica officinalis	Streptozotocin (STZ)-induced diabetes in rat	Modulation of oxidative–nitrosative stress	(21)
PMI-5011	High-fat diet-induced neuropathy in mice	Inhibition of oxidative nitrosative stress and lipoxygenase activation	(25)
Rubia cordifolia	Paclitaxel-induced neuropathic pain in rat	Involvement of GABA or antioxidant mechanism	(90)
EGb 761	SNL in rat	Anti-inflammatory, antioxidant effect, a platelet activating factor antagonist and a protective effect against NMDA.	(66)
Ocimum sanctum	Vincristine-induced neuropathic pain in rat	Decrement of oxidative stress and calcium levels	(79)
Acorus calamus	Tibial and sural nerve transection (TST) in rat	Anti-inflammatory, antioxidant, and neuroprotective actions	(31)
Acorus calamus	Chronic constriction injury (CCI) in rat	Anti-oxidative, anti-inflammatory, neuroprotective and calcium inhibitory actions	(32)
Acorus calamus	Vincristine-induced neuropathic pain in rat	Anti-oxidative, anti-inflammatory, neuroprotective and calcium inhibitory actions	(33)
Salvia officinalis	Vincristine-induced neuropathic pain in mice	Anti-inflammatory effects	(95)
Koumine	CCI in rat	Elevated allopregnanolone levels through allosteric modulation of $GABA_A$ and by suppressing the release of microglia activation-induced inflammatory cytokines	(118)
Incarvillateine	Complete Freund's Adjuvant (CFA), SNI and paclitaxel induced neuropathic pain in mice	Activation of the adenosine system	(114)
Curcumin	CCI in mice	Descending monoamine system (coupled with spinal β2-adrenoceptor and 5-HT1A receptor)	(44)
Curcumin	CCI in rat	Decrement the serum level of COX-2	(45)
Phyllanthus amarus	CFA, PSNL in mice	Anti-inflammatory action	(82)
Cannabis sativa	CCI in rat	Mediated by vanilloid receptors TRPV1.	(96)
Momordica charantia	TST in rat	PPAR-gamma agonistic activity, anti-inflammatory, & antioxidative effects.	(72)
lappaconitine	CCI in rat	Regulating the purinergic signaling system at DRG level	(107)
Saffron's extracts and safranal	CCI in rat	Antioxidant effects.	(48)
MGM-16	PSNL in mice	Opioid agonistic effects	(70)
Nigella sativa and thymoquinone	STZ-induced diabetic in rat	Antioxidant actions	(76)
DA-9801	STZ induced rat/mouse diabetic, db/db mouse model	Increasing the NGF level	(111)
Naringin	STZ induced diabetic in rat	Antioxidant and antiapoptotic activity	(120)
Quercetin	STZ induced diabetic in mice	Modulation of opioidergic system	(123)

induced damage to Schwann cells by autophagy (124). In one study, quercetin reduced renal damage including: epithelial desquamation, swelling, intracytoplasmic vacuolization, brush border loss and peritubular infiltration in STZ-induced diabetic nephropathy rats (125). A recent study showed that the effect of quercetin was significantly superior to gabapentin and morphine in terms of improving mechanical and thermal hypersensitivity in a rat model of CCI (126).

Conclusion

The urgent need to find an alternative therapy which can improve neuropathic pain effectively with few side effects led scientists to find medicines from natural sources. This review suggests that herbal medicines are alternative options to relieve and manage neuropathic pain. Results from the current study suggest that the most pathways involved in the analgesic effects of herbal remedies are antioxidant, anti-inflammatory, anti-apoptotic, neuroprotective and calcium inhibitory actions.

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