Review Article

A review on treatment and management of neuropathic pain with herbal folk drugs

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Abstract

Objective: Neuropathic pain condition is generally definite as a chronic pain state resulting from peripheral or central nerve injury also due to acute events (e.g., amputation, spinal cord injury) or systemic disease (e.g., diabetes, viral infection and cancer) and categorized by pathological symptoms, such as hyperalgesia and allodynia to mechanical and thermal (heat or cold) stimuli, as well as spontaneous pain. **Method**: Bibliographic information were collected and analysed from text books and peer reviewed journals, consulting worldwide accepted scientific databases from the libraries and internet sources. Peripheral processes in neuropathic pain engage production of intermediaries (cytokines, protons, nervegrowth factor), alterations of calcium channels, sodium channels, hyperpolarisation-activated nucleotide-gated ion channels, potassium channels, phenotypic switches and sprouting of nerves endings, and involvement of the sympathetic nervous system. **Results and conclusion**: Neuropathic pain has been treated by the two major classes of drug like analgesics, opioids and nonsteroidal anti-inflammatory drugs. Moreover, both opioids and nonsteroidal anti-inflammatory drugs generate difficult side effects, particularly with prolonged use as may be necessary in the treatment of chronic pain, which noticeably limit the clinical utility of these two classes of longer term use, but also produce side effects, ranging from dry mouth to the potential for cardio toxicity, which can limit their clinical utility. This review covered all herbal drugs which have been reported for the treatment of neuropathic pain.

Keyword: Neuropathic pain, herbal medicine, Neuroprotective, Nonsteroidal anti- inflammatory drugs

Introduction

As per The International Association for the Study of Pain (IASP) define neuropathic pain (NP) as initiated or caused by a most important lesion or dysfunction of the nervous system" (Merskey and Bogduk et al., 1994). Neuropathic pain is not based on a single pathophysiological procedure. resulting from peripheral or central nerve injury either due to acute events (like spinal cord injury) or systemic disease (like diabetes, alcoholism, kidney or thyroid diseases, viral infection and cancer, Poor nutrition or vitamin deficiency, AIDS etc.) and characterized by pathological symptoms, such as hyperalgesia and allodynia to mechanical and thermal (heat or cold) stimuli, as well as spontaneous pain (Childers et al., 2007; Carber et al., 2006). Types of neuropathic pain is 1.Mononeuropathy 2.Polyneuropathy .management of neuropathic pain, to the nervous system, is a clinical challenge because the essential mechanisms of neuropathic pain improvement remain poorly understood (Kehlet et al., 2006; Tsuda et al., 2005). Peripheral processes in neuropathic pain creation of mediators (cytokines, protons, and nerve growth factor), alterations in calcium channels, sodium channels, hyperpolarisation-activated nucleotide-gated ion channels, and potassium channels, phenotypic switches and developing of nerves endings, and involvement of the sympathetic nervous system. Stimulation of the NMDA receptor, establishment of microglia, oligodendrocytes, and astrocytes, increased production of nerve growth factor and brain-derived neurotrophic factor together with loss of spinal inhibitory control are responsible for central neuron hyperexcitability and maintenance of neuropathic pain (Vranken et al., 2012). The defense mechanisms involve pain signal transduction from the nociceptors-peripheral nervous system-spinal dorsal horns-thalamus-cortex and the pain control system from the cortex-periaqueductal grey matter-nucleus raphe magnus-spinal dorsal horn. In common individual the transduction system and the pain

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management is under control but in PN imbalance between these two results in the neuropathy in persons. In NP the lesions are located at various locations in the body such as peripheral nerve dorsal root ganglion or dorsal root. PN may be due to compression, inflammation, ischemia, trauma, deficit nutrition or any degenerative disorder. Several treatment options are on hand by an interdisciplinary management team includes systemic medication, physical modalities (e.g., Physical rehabilitation), psychological modalities (e.g., behaviour modification, relaxation training), invasive procedures (e.g., Trigger-point injection, epidural steroids, sympathetic blocks), spinal cord stimulators, intrathecal morphine pump systems and various surgical techniques (e.g., dorsal root entry zone lesions, cordotomy and sympathectomy). But while contribution these options caution is warranted as it may improve underlying neuropathic support for the management of NP. The tri-cyclic anti-depressants, anticonvulsants (Pappagallo et al., 2003), local anaesthetics, corticosteroids, capsaicin or substance-p depletors (Collins et al., 2000), autonomic drugs (alpha-2 agonists (Clonidine) and alpha-1antagonists (prazosin, terazosin) and NMDA-antagonists including dextromethorphan, amantadine, memantine, and ketamine have been reported to relieve pain in various neuropathic pain states including phantom limb pain, central neuropathic pain, post herpetic neuralgia, and peripheral neuropathic pain (Arner et al., 1993). Neuropathic pain has been treated by the two major classes of drugs like analgesics, opioids and non-steroidal anti-inflammatory drugs, both opioids and non-steroidal anti-inflammatory drugs produce problematic side effects, particularly with prolonged use as may be required in the treatment of chronic pain, which markedly limit the clinical utility of these two classes of longer term use (Max et al., 1988). Evidence has been generated over the past few decades that various anticonvulsant agents provide relief of several chronic pain syndromes, and therefore, as an alternative to opioids, non-steroidal anti-inflammatory and tri-cyclic antidepressant drugs in the treatment of neuropathic pain (Backonja et al., 2003). However, common side effects associated with anticonvulsants are sedation, cerebellar symptoms (nystagmus, tremor and in coordination), haematological changes and cardiac arrhythmia (Jensen et al., 2002).

Preventive treatments

The defensive treatment available for neuropathy is grateful to reduce the frequency or severity. These drugs not only reduce the neurotoxic consequence of the chemotherapeutic agent, but also must maintain the anticancer effect. The agent includes drugs, vitamins, minerals, herbal remedies. Recently, some preclinical outcome have shown therapeutic efficacy of drugs from plant origin such as *Commiphora mukul*, *Cannabis sativa*, *Ocimum sanctum* and *Ginkgo biloba* in neuropathic pain (Pace et al., 2003; Moore et al., 2003). This is also supported by few clinical studies which have evidenced the beneficial effect of herbal medicines in neuropathic pain syndrome (Cascinu et al., 1995; Park et al., 2000). Therefore; scope of the new herbal medicine to combat the management of neuropathic pain syndromes is expected. Traditional herbal plants have been used throughout the world for the treatment of neuropathic pain. Glutamine could reduce the severity of peripheral neuropathy associated with high-dose paclitaxel induced. Trials are at present ongoing to assess its efficacy for standard-dose paclitaxel in breast cancer and other tumors for which peripheral neuropathy is the dose-limiting toxicity (Savarese et al., 2003; Vahdat et al., 2001).

Plant medicines used in the treatment of neuropathic pain

Herbal medicine has long been used to treat neural symptoms. While the precise mechanisms of action of herbal drugs, a number of them have shown to exert anti-inflammatory and/or antioxidant effects in a range of peripheral systems. Now, as growing evidence indicates that neuroglia-derived chronic inflammatory responses take part in a pathological role in the central nervous system, anti-inflammatory, herbal medicine and its constituents are being reported to be a potent neuroprotector against various brain pathologies (Moore et al., 2003;). Herbal remedies for such conditions have been known since time immemorial, and therapeutically useful for the treatment of various CNS disorders. Although all these herbal drugs the active principles and their formulations have not yet been precisely defined, and available data point towards that they could be useful sources to develop better, effective, safer, and cheaper drugs with novel modes of action. In the past few years, the number of reports on well-planned clinical trials using standardized herbal extracts has increased. Some phytoconstituents widely studied for the management of neuropathy in rats. Such as like caffeic acid, phenyl-ethyl ester, flavonoids like bioflavone, polyphenols Ghrelin , α-lipoic acid, playing crucial role in amelioration of neuropathy in animals, Glutamate carbopeptidase (Flatters et al., 2006). This review will underline the importance of phytochemicals on neuroprotective function and, in particular their mechanism of action and therapeutic potential (Lee et al., 2012).

Vernonia cinerea

Vernonia cinerea belongs to the family Asteraceae which is a common wild plant of India. This plant is also called "Sahadevi", Naichette or Mukuthipundu. The ameliorative potential of ethanolic extract of entire plant of *Vernonia*

cinerea in the chronic constriction injury (CCI) of sciatic nerve induces neuropathic pain in rats. Biochemical changes in sciatic nerve tissue were lined out by estimating thiobarbituric acid reactive substances (TBARS), reduced glutathione (GSH) and total calcium levels. Reported that due to presence of flavonoids and other chemical constituents it gives anti-oxidative, neuroprotective and calcium channel modulator actions of its compounds (Thiagarajan et al., 2014).

Ocimum sanctum

Ocimum sanctum (L.), (Tulsi) is an home-grown plant generally found in all over Iplace, and used in the treatment of various diseases such as bronchial asthma, malaria, dysentery, skin diseases, arthritis, painful eye diseases, chronic fever. *Ocimum sanctum* is traditionally used by the people for the treatment of neuropathic pain. Reported that *Ocimum sanctum* has ameliorative potential in attenuating chemotherapy vincristine induced-painful neuropathic state with decrease in oxidative stress and calcium levels. The saponin phytochemical constituents' rich fraction of *Ocimum sanctum* may be responsible for its noted beneficial effect in neuropathic pain in rats (Kaur et al., 2010).

***Ferula hermonis* L. *and Sambucus nigra* L.**

The activity of *Ferula hermonis boiss* of ethylacetate (Ferula) and *Sambucus nigra* L. aqueous (Elder) extracts, and evaluated amelioration in alloxan-induced diabetic neuropathic pain on mice for longer period of time (8 weeks) and others models such as Tail-flick, hot-plate latencies (accessing thermal hyperalgesia), von Frey filaments test (accessing tactile allodynia) models, and reported that the isolated compounds from Ferula was ferutinin, and Kaempferol from Elder utilizing bio-guided fractionation and RP-HPLC steeping methods, and Compared to glibenclamide (GB) and tramadol (TRA), as positive controls, Suggested that Ferula Elder and their active isolates have shown significant results in ameliorating diabetic neuropathy (Raafat and Lakany, 2015).

Salvia officinalis

Isolated constituents of *Salvia officinalis* possess significant antioxidant activity in enzyme dependent and enzyme-independent systems. In addition to antioxidant activity, many salvia species and their isolated constituents showed anti-inflammatory properties. Reported the *Salvia officinalis* extract can have anti-inflammatory and also antinociceptive effects on chemical behavioral models of nociception in mice that involve an opioid mechanism. They studied that the effects of the *Salvia officinalis* hydroalcoholic extract on vincristine-induced neuropathic pain on mice and compared with morphine. Suggested that *Salvia officinalis* extract could be useful in the treatment of vincristine-induced peripheral neuropathic pain (Abad et al., 2011).

M. oleifera

M.oleifera leaves extract significantly reversed the activities of SOD and GSH-Px and the elevation of MDA level in the injured nerve. They reported that the *M. oleifera* leaves extract can assure for the management of neuropathic pain in diabetic condition. The potential underlying mechanism may occur partly via the decreased oxidative stress, *M. oleifera* leaves may be the possible novel adjuvant therapy for neuropathic pain management (Khongrum et al., 2012).

Harpagophytum procumbens

Harpagophytum procumbens, also identified as Devil's Claw, has traditionally been used to treat a wide range of circumstances, including pain and arthritis. They evaluated the pain-related behaviour, by the mechanical withdrawal threshold (MWT) test and measured by von Frey filaments and pain-related behaviour was also determined through, analysis of ultrasonic vocalization (USVs).They reported that the *H. procumbens* extracts have prospective analgesic effects in the case of acute postoperative pain and chronic neuropathic pain in rats (Lim et al., 2014).

***Momordica charantia* L.**

The effect of *Momordica charantia* L. (MC) on the sural nerve transection (SNT)-induced neuropathic pain in rats. Investigated that administration of MC (200, 400, and 800 mg/kg) significantly attenuated SNT-induced behavioural and biochemical changes. Furthermore, pretreatment of BADGE (120 mg/kg, intraperitoneally) abolished the protecting effect of MC in SNT-induced neuropathic pain. They exposed, the PPAR-gamma agonistic activity, anti-inflammatory, and antioxidative potential is critical for antinociceptive effect of MC in neuropathic pain (Jain et al., 2014).

B. monosperma

The effects of ethanolic extract of *B. monosperma* leaves on vincristine-induced painful neuropathy in rats. Tissue thiobarbituric acid reactive substances (TBARSs), decrease glutathione (GSH) and total calcium levels were estimated to consider the biochemical changes in the sciatic nerve tissue. Microscopically, histopathological changes were also observed in the sciatic nerve tissue. They reported that the *B. monosperma* ameliorated vincristine-induced painful neuropathy; due to its potential of antioxidative, neuroprotective and calcium channel inactivation (Thiagarajan et al., 2013).

***Acorus calamus rhizome* (ACR)**

It is traditionally used to relieve the muscle, joint, vascular and nerve injury associated with severe inflammatory and neuropathic pain, Reported that on a rat model of hydroalcoholic extract of ACR rhizome has been exert favourable effect on neuropathic pain induced by tibial and sural nerve transaction. In a additional reported the study ACR extract attenuated sciatic nerve chronic constriction injury and induced ameliorated behavioural (hyperalgesia and allodynia), biochemical (superoxide anion, myeloperoxidase, and entire calcium), investigated the preventive effect of ACR Hydroalcoholic extracts on attenuated vincristine-induced behavioral and biochemical changes to an extent similar to pregabalin (positive control) and attenuated vincristine-induced painful neuropathy, which could be recognized its multiple effects together with antioxidative, anti-inflammatory, and calcium inhibitory activity (Muthuraman and Singh, 2011; Muthuraman , Singh et al., 2011).

***Punica granatum* L (PG)**

Fruit Extract of *Punica granatum* L (PG) [Ellagic acid (41.6%), Punicalagins (10%), Granatin (5.1%)] in Tibial and Sural Nerve Transection (TST) induced neuropathic pain in rats, and The administrations of PFE (100 & 300 mg/kg oral), significantly attenuate TST induced and biochemical changes. Pre-treatment of BADGE (120 mg/kg IP) a PPAR-γ antagonist and nitric oxide precursor L-arginine (100 mg/kg IP) abolished the defensive effect of PG. The results indicate that the PG shown to have attenuating effect in TST induced neuropathic pain which may be recognized to potential PPAR-gamma inhibition activity, nitric oxide inhibitory, anti-inflammatory and antioxidative actions (Jain et al., 2013).

***Commiphora mukul* (CM)**

The role of neuroprotective activity of *Commiphora mukul* (CM) (family Burseraceae), also well-known as CM were studied aligned with the chronic constriction injury of the sciatic nerve, CM was orally administered for 2 weeks and pain evaluation was performed by employing the behavioural tests such as thermal hyperalgesia (hot-plate and tail-flick tests), hot-plate and tail-flick latencies, and decreased paw withdrawal duration (in acetone test), and cold allodynia (acetone test). Reported that the significantly decreased the induced neuropathic pain (Mehta et al., 2015).

Ginkgo biloba

Investigated that the activity profiles of guggulipid at different doses, on CCI rats models, guggulipid (100 and 50 mg/kg) significantly ($p < 0.05$) reduced the spontaneous pain, mechanical allodynia and mechanical and thermal hyperalgesia responses and the LD50 of guggulipid was 1600 mg/kg. In SNL rats, both doses of guggulipid were found to be ineffective in reversing the sponataneous pain but showing antiallodynic and antihyperalgesic activity. They demonstrated that the guggulipid produce antinociception in the peripheral nerve injury (CCI and SNL) models of neuropathic pain and the underlying mechanisms are expected to be modulating microglial activation occurring due to peripheral nerve injury (Park et al., 2012).

***Crocus sativus* L (CS)**

The ethanolic and aqueous extracts of *Crocus sativus* L (CS) and safranal (0.025, 0.05 and 0.1 mg/kg, i.p.) and crocin, in chronic constriction injury (CCI)-produce neuropathic pain in rats, attenuated the behavioural symptoms of neuropathic pain in a dose dependent manner. Crocin even at the high dose (50 mg/kg) failed to produce any protective role. gabapentine (100 mg/kg) as a reference drug significantly alleviated behavioural manifestations of neuropathic pain compare to control group. They revealed that the ethanolic and aqueous extracts of saffron and safranal could be useful in treatment of different kinds of neuropathic pains and as an adjuvant to conventional medicines (Amin et al., 2012).

***Cymbopogon martinii* (Roxb.)**

Cymbopogon martinii (Roxb.) Watson (Family: Graminae), generally known as Palmarosa, is traditionally used for central nervous system (CNS) disorders like as neuralgia, epileptic fits anorexia and neuroprotective action. They investigated neuroprotective effect of essential oil of *Cymbopogon martinii* beside global cerebral ischemia/reperfusion (I/R)-induced oxidative stress in rats. *Cymbopogon martini* increase in LPO and diminish in superoxide dismutase (SOD), catalase (CAT), total thiols and GSH, they reported that the potent neuroprotective effect of *Cymbopogon martinii* against global cerebral I/R-induced oxidative stress in rats (Buch et al., 2012).

***Sinomenium Acutum* (SA)**

Sinomenine is a chief ingredient of traditional Chinese medicine, which has been reported to have a variety of pharmacological effects including anti-rheumatism and immunomodulation. They examined the property of sinomenine in rats that received chronic constriction injury (CCI), a model of peripheral neuropathic pain. They reported that sinomenine exerts considerable antinociceptive property for neuropathic pain via GABAa-mediated mechanism, and it could be useful for the management of chronic painful conditions such as neuropathic pain (Zhu et al., 2014).

***Euterpe oleracea* (EA)**

Hydroalcoholic extract from *Euterpe oleracea* Mart. (Açaí) in a rodent model of acute and neuropathic pain.

Antinociceptive activities were evaluated by the administration of cholinergic, adrenergic, opioid, and L-arginine-NO antagonists. Oral administration of ASE (30, 100, or 300 mg.kg−1) dose-dependently, reduced nociceptive responses to acute/inflammatory pain in mice, including thermal hyperalgesia, acetic acid-induced writhing, and carrageenan-induced thermal hyperalgesia. The reported that the ASE showed significant antinociceptive result via a multifactorial mechanism of action, indicating that the extract may be useful in the development of new analgesic drugs (Sudo et al., 2015).

Matricaria chamomilla (MC)

This is frequently used herb in western as well as in eastern phytopharmacological. *Matricaria chamomilla* (MC) have main constituents such as alpha- bisabolol or chamazulene have anti-inflammatory effects. In a mouse model it was revealed that MC extract-treated mice had a significant decrease of cisplatin-induced peripheral pain. Reported that the MC hydroalcoholic extract able to decrease cisplatin-induced pain and inflammation better than morphine (Abad et al., 2011).

***Nigella sativa* L. (NS)**

Thymoquinone (TQ) active constitute of *Nigella sativa* L. (NS) (family of Ranunculaceae). Evaluation of the tissues in the diabetic animals showed fewer morphologic alterations, and myelin stop working decreased significantly after treatment with NS and thymoquinone. They investigated the possible beneficial effects of NS and TQ on histopathological changes of sciatic nerves in streptozotocin (STZ)-induced diabetic rats, and a significant decrease in the area of insulin immunoreactive β-cells ($P<0.0001$). NS and TQ treatment resulted in increased areas of insulin immunoreactive β-cells ($P<0.001$, $P<0.01$) (Kanter et al., 2008).

***Phyllanthus amarus* (PA)**

A hexane extract of *Phyllanthus amarus* has been reported to be effective for the following activity such as neuropathic pain management, anti-inflammatory actions, which are may be linked to the presence of lignans, and the hexanic extract of PA produces pronounced anti-allodynia (Kassuya et al., 2003).

Artemisia dracunculus

Artemisia dracunculus phytochemical constituents are essential oil, coumarins, flavonoids and phenolcarbonic acids. These species are also reported for their anti-inflammatory and antinociceptive properties. The essential oil consist estragole, methyleugenol and other monoterpenoids. Methyleugenol is a powerful pain reducer that inhibits transient receptor potential cation channels. An ethanolic extract of *A. dracunculus* compressed high fat diet induced neuropathy; mice were fed high-fat diets for 16 weeks. They increased obesity, moderate nonfasting hyperglycemia, nerve conduction deficits, thermal and mechanical hypoalgesia, and tactile allodynia. *A. dracunculus* proved to be a safe and nontoxic botanical extract, and reported that it can be use for the prevention of neuropathic changes (Watcho et al., 2010).

Aconiti tuber

The herbal analgesic medicine has been investigated for the relief of neuropathic pain in the rat CCI model. Additional groups received oral *Aconiti tuber*, 2 g/kg, after pretreatment with intraperitoneal naloxone, or intrathecal. The result indicated that the oral *Aconiti tuber* can alleviate mechanical allodynia and thermal hyperalgesia, dose-dependently, via spinal kappa-opioid receptor mechanisms in a rat CCI neuropathic pain model (Xu et al., 2006).

E. officinalis

Reported that treatment with the *E. officinalis* aqueous extract (250, 500 and 1000 mg/kg daily) significantly attenuated all the behavioural and biochemical alterations in a dose dependent manner. The major ending of the study is that insulin alone corrected the hyperglycemia and partially reversed the pain response on diabetic rats. The combination of insulin with *E. officinalis* extract not only attenuated the diabetic condition but also reversed neuropathic pain through modulation of oxidative-nitrosative stress in diabetic rats (Tiwari et al., 2011).

Allium sepa and Allium sativum

Are bulbous herbs belonging to the family Alliaceae. *A. sepa*, a effective antioxidant, due to its rich source of flavanoids and organo sulfur compounds and *A. sativum* contains non-volatile sulfur compounds such as S-allyl cycteine and S-allyl mercaptocysteine, which have powerful antioxidant activities and others like immunomodulatory, antidiabetic neuroprotective activities. Reported that the methanol extract of the both *A. sepa* and *A. sativum* were administered at a dose of 200 mg/kg p.o. for 21 days to mice. Treatment with the extracts reduced loss of body weight, decreased plasma glucose level, and drastically ameliorated the hyperalgesia, thiobarbituric acid reactive substance, serum nitrite and reduced glucothione levels in mice (Bahnot and Shri, 2010).

Conclusion

There are a numeral of herbal plants which are traditionally used, usually pharmacologist should study traditional systems of medicine in technical way and validate by screening plant/plant extracts for pharmacological activity. This review purposeful on the pharmacological reports of herbal plant/plant extracts screens the soluble extracts in the development of an acceptable neuropathic pain preparation and management, which if validated properly and proven scientifically can act as substitute or may even replace the modern neuropathic pain agent. Bearing in mind the

principle drawbacks, associated with synthetic compounds, herbal plants which are the gift from nature having long-established knowledge, provides excellent raw material for the treatment of different diseases and disorders. As in the allopathic system of medicine, neuropathic pain are available but traditional facts in the form of literature provides number of traditional and household preparations for those purposes. Preliminary scientific investigations on herbal plants point out those natural products could be exploited to discover some novel neuropathic pain agent.

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