

Neuropathic Pain: Literature Review and Recommendations of Potential Phytotherapies

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ABSTRACT

Introduction: One of the common syndromes that affect humanity is neuropathic pain (NP), yet poorly understood with no efficient treatment till now. Consequently, it is extremely crucial to seek further evidence for accurate diagnosis and optimum treatment. The aim of this work is to summarize the findings related to neuropathic pain in terms of etiology, types, diagnosis, current and future management prospective, and identify the gaps in neuropathic pain therapy. **Methods:** A literature investigation was carried out by analyzing classical peer reviewed papers and textbooks, taking into consideration worldwide well established scientific databases mainly PUBMED and SCOPUS to retrieve accessible published literature. The selection of phytotherapies was based upon their potentials in relieving NP in pre-clinical or clinical models. **Results:** One of the most critical points in this research is that recommendations of the future plans should be focused on the engagement of phytotherapy in the treatment regimen aiming at improving patients' quality of life and reaching optimum efficacy and minimum toxicity. Phytotherapies offer relatively low-risk options to NP patients and have an increasing evidence to be the future of neuropathic pain management. Patients suffering from neuropathy are depending increasingly on phytotherapies; however, they need more clinical trials in order to fully understand their mechanism of actions. **Conclusion:** Health-care specialists should be regularly informed about neuropathic pain current therapies and promising future phytotherapies, bearing in mind the risk/benefit profile of the utilization of these therapies in the amelioration of NP.

Key words: Neuropathy Pain, Current therapies, Diagnosis, Mechanisms, Recommendations, Phytotherapies.

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INTRODUCTION

Neuropathic pain (NP) is now a global health concern without adequate therapeutic approach. NP causes difficulties in daily activities, decreases performance and increases health care costs. Pain grading in NP is a crucial method for diagnosing NP.¹

Pain grading

NP is a syndrome and not a disease. It might be induced by a disease or a lesion of the peripheral or central-nervous system (CNS). The reason of NP might be either due to an infection, injury or metabolic disorder, or unknown cause. The same lesion or disease may induce the development of neuropathic, somatic or even psychogenic pain.²

The four criteria for grading NP diagnosis are as follows:

- I. Neuro-anatomical related pain.
- II. There is a related lesion or disease in the history of nervous system.
- III. The existence of positive or negative neurologic manifestations with the abundance of pain in neurological assessment or in the more objective confirmatory tests (quantitative sensory testing, laboratory tests).
- IV. The existence of related disease or lesion by no less than a single confirmatory test.

Consistent with this criteria NP can be classified into "defined" (all criteria present), "probable" (I and II, in addition either III or IV) or "possible" (I and II, with no confirmatory tests).³

Moreover, risk factors and epidemiology are cornerstones in understanding NP.

Risk factors and Epidemiology

The literature survey has shown fewer studies on the NP epidemiology. A study on patients evidenced neuropathic pain in 8.2% of adult patients having significantly higher pain intensity than others in a British study.^{1,4} Moreover, in a randomly selected adult population using the Douleur Neuropathique four Questions, neuropathic pain were identified in 6.9% of the examined persons in a French study.⁵ NP risk factors includes: females, elderly age, minor level of education, living in a rural area worse health (compromised physical, mental and social well-being).⁵⁻⁹

Pathomechanisms

Pathomechanisms causing the development of NP are divided into 3 groups: first, electrophysiological properties of the cellular membrane of the first

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sensory neuron changes, which include changes in nociceptor excitability, gene expression changes in neuronal cell body and in the release of neurotransmitters. Second, the alteration in impulse-processing in the spinal-cord dorsal-horns. Third, Disorders in the CNS such as disturbed balance between the activity of ascending excitatory systems and descending inhibitory systems. Moreover, the autonomic nervous system dysfunction might be also entangled with the NP development.^{1,10}

Screening

The screening scales can be used in identifying NP or the presence of a clear neuropathic factor in the pain syndrome. They may be used if medical history or physical examination reveals typical signs of neuropathic pain. The most widely used screening scales include: “Douleur Neuropathique 4 Questions” (DN4), “Leeds Assessment of Neuropathic Symptoms and Signs” (LANSS), NP questionnaire (NPQ) and NP DETECT.¹

Diagnosis and Current Therapies of Neuropathic Pain Postherpetic Neuralgia (PHN)

Diagnosis of PHN may be in patients complaining of severe unilateral pain in dermatomes where herpes zoster virus has caused lesions. This diagnosis is possible after the lesions have completely healed.^{11,12}

Opioids, amitriptyline, 5% lidocaine, gabapentin, pregabalin, and 8% capsaicin are the most efficacious first-line agents in treatment of PHN. Type and intensity of pain decide which of these agents is to be initiated. Recommendations suggest that monotherapy should be started. Switching to a combination is only recommended in case of failure of monotherapy.^{12,13}

Complex Regional Pain Syndrome (CRPS)

Diagnosis of CRPS should be performed by a specialist in neuropathy, which is a type of chronic pain affecting limbs.¹⁴

It is possible to give bisphosphonates, antispastic drugs, or invasive procedures in case of failure of medications of neuropathic pain.

As experts say, an early multidirectional is found to be the most effective treatment, where physical therapy is a principle component of this therapy. Psychological therapy is also included in the treatment regimen if the pain is psychological in nature.^{1,15-18}

Diabetic Polyneuropathy

Diabetic polyneuropathy is caused by both types of diabetes mellitus (DM). Prevention of neuropathy in DM patients is achieved through maintaining a proper level of glucose in blood.^{19,20}

As for treatment, gabapentin, pregabalin, TCAs, venlafaxine ER and duloxetine are the first-line agents to treat diabetic neuropathy, while opioids and tramadol are the second-line agents.

Primarily patients are given a single first-line drug. Switching to a different drug from an alternate therapeutic group is done in case of failure of the first-line agent. Knowing that alleviation of pain is not achieved, we consider one of the following approaches: choose a second-line drug; choose a synthetic or natural drugs having other mechanism of actions; or use drug combinations.²¹⁻²⁴

Trigeminal Neuralgia (TN)

TN is diagnosed in patients who experience chronic NP in the trigeminal nerve area.^{25,26} The first-line agent for treatment of TN is carbamazepine. However, if carbamazepine is contraindicated, then the use of clonazepam, baclofen, or antiepileptics (gabapentin, lamotrigine or pregabalin) is indicated. Surgery is recommended in case of failure of pharmacotherapy, yet treatment with botulin toxin is advisable prior to a surgery.²⁷⁻³⁰

Post-amputation Pain

Phantom pain was incident in amputated patients with extremity and stump pain located surrounding the post-surgical stump scar.³¹

Due to the fact that strong opioids, tramadol, gabapentin, lidocaine infusions, calcitonin pregabalin or amitriptyline are recommended, evidence of effectiveness of these therapeutic agents is lacking. Other types of treatment have emerged, such as psychotherapy and physiotherapy. In phantom pain, spinal cord thermolesion and stimulations of the peripheral nerves are effective, while neurodestruction is possible in stump pain.³²⁻³⁴

Post-traumatic Pain (PTP) and Post-operative Pain (PPP)

PPP and PTP are chronic pathological pains which are associated with surgery or trauma and are present for more than normal tissue healing time, and their intensities, characters and localizations would not be explicated by the incident of other pathologies, for instance, disease recurrence, cancer or infection recurrence.³⁵

Prophylactic measures prior to surgeries are recommended to reduce the risk of nerve damage; for instance, techniques for epidural anesthesia; using local anesthetics for surgical wounds; pregabalin or gabapentin use in perioperative phase

Despite the lack of evidence, it's recommended to give lidocaine intravenous infusions in all risk groups (young patients, long duration surgeries, poor treatment of severe post-operative pain).

Despite the lack of evidence, treatment of post-operative pain is:

- Causative management
- Five-percent lidocaine patches alone or in combination with systemic drugs

In case of PPP refractory to therapeutic drugs, it's possible to consider interventional methods to relieve the pain.¹

Neuropathic Pain – Cancer Patients

Cancer patients' pain may have different causes and mechanisms (Table 1). Treatment choice depends on NP intensity where tramadol is administered in case of moderate intensity NP, while a strong opioid is given in cases of high intensity pain. Combination of the previous drugs with gabapentin and pregabalin helps in increasing effectiveness and reducing opioid doses. Venlafaxine and duloxetine are administered in treatment of neuropathy after chemotherapy.^{1,36}

Neuropathy – HIV Infection

Neuropathy experienced by HIV patient is either due to the virus itself, or due to the anti-retroviral therapy. A combination of 8% capsaicin patch, lamotrigine and gabapentin are recommended. Nevertheless, 5% lidocaine patches, pregabalin and amitriptyline lack effectiveness in treating such pain.^{1,40}

Central Pain (CP)

CP could be diagnosed in patients suffering from NP as a result of CNS injuries. It is crucial to indicate the etiology of such pain, e.g. Parkinson pain. The first-line agent in central pain therapy is pregabalin. However, in patients with depression or insomnia, the first-line treatment recommended are TCAs.^{1,3}

Nerve Injury and Neuropathic Pain

The appearance of peripheral nerve injury on somatosensory processing and pain is directly related to age at which damage took place.⁴¹ The mechanical hypersensitivity of the patients does occur but only late in life. This delay hypersensitivity could be observed by cold stimulation and weight bearing tests.⁴¹ This pain could be attenuated by pre-treatment with, an inhibitor of pro-inflammatory polarised microglia, minocycline.^{42,43}

Table 1: Causes and mechanisms of cancer patients pain, modified from [36].

	Cancer Patient Cause of Pain	Mechanism/Cause	Reference
I	Cancer Metastasis	Cancer infiltration to the PNS or CNS	[37]
II	Anticancer therapy	Nervous system intraoperative damage	[38]
III	Cancer related disease	Acute varicella zoster and post-herpetic neuralgia	[39]
IV	Disease(s) not related to cancer	Diabetic polyneuropathy	[1]

Neuropathic pain in osteoarthritis

The most common disorder of the muscle skeleton is osteoarthritis (OA), characterized by joint pain due to the central pain pathways and peripheral joint sensitization and the local joint inflammation done by nociceptive mechanism and changes in the bones.⁴⁴ Thus, medicines acting centrally can relieve osteoarthritic pain, although osteoarthritic pain causes are not completely understood.^{45,46} OA apparent mechanism of NP is due to increase in sodium channels, secondary hyperalgesia resulting from dorsal-horn sensitization of the NP modulation central point, and windup owing to the increase of calcium influx when NMDA receptors are activated.^{3,47,48}

However, non-pharmaceutical treatment, as physiotherapy, hydrotherapy, and most important the use of electrical stimulation of nerves and cold or heat packs are essentially equal. Consequently, the centrally acting medications might be used together with anti-inflammatory and analgesic drugs for some patients in the future. Additional options like strontium ranelate/bisphosphonates for methotrexate are still under investigation.⁴⁹

METHODS

Search strategy

The search in the primary literature has been performed by the lead-researcher (K. Raafat) between January and March 2016. A computerized based search has been accomplished in worldwide well established scientific databases mainly PUBMED and SCOPUS. Each database has been searched utilizing a search strategy developed of the combination of the keywords following: neuropathy or neuropathy pain or neuropathy diagnosis or neuropathy current therapies or neuropathy mechanisms or neuropathy extract or neuropathy phytotherapies or neuropathic pain therapy recommendations. The relevant research article citations have been investigated for the potential secondary and tertiary literature.

Exclusion and inclusion criteria

The following exclusion and inclusion criteria have been utilized; paper type: primary, secondary or tertiary literature, written in English, in peer-reviewed journals or published books; study design: studies employing pre-clinical or clinical models research methods were included. Full text manuscripts of the included publications have been retrieved. In case of studies with identical results and methodologies, the earlier publication has been selected. The selection of phytotherapies was based upon their potentials in relieving NP in pre-clinical or clinical models. The authors of relevant studies have been contacted for any missing information, and studies have been excluded if no communication has been established.

Quality assessment

The included studies quality has been examined utilizing a standardized tool. The tool consists of eight components: (I) participants have been representative to the targeted population, (II) design of the study, (III) confounding factors control (IV) clinical trials blinding (V) data-collection reliability, (VI) the exclusion and inclusion criteria, (VII) integrity of intervention and (viii) analyses of the intervention. The studies have been included in the current study if all criteria have been fulfilled. On the other hand, the fourth criterion has been considered not feasible when assessing some pre-clinical studies.⁵⁰

Data synthesis

In order to combine the data that have been included from the literature, a narrative synthesis method has been utilized. Electronic copies of manuscripts have been read by the lead-researcher to improve information extraction relevant to the inclusion and exclusion criteria and the manuscript characteristics, to examine their quality. At least two researchers have read each manuscript. The original research characteristics have been examined utilizing a pre-arranged scheme and the following information has been extracted: phytotherapy name and family, part used, aim of the study, most active constituents, highest dose utilized, analysis method, the route of administration, pre-clinical or clinical model, presence of positive control and its route of administration, results, neuropathic pain indication and limitations.

MECHANISMS

Literature has shown several mechanisms that cause the NP symptoms:

Sensitization of nociceptors

Exogenous or endogenous substances trigger the nociceptors. These substances involve inflammatory mediators (prostaglandins, bradykinin, and arachidonic acid different derivatives), neurotransmitters (neurokinins, stimulatory-amino acids, noradrenalin, histamine and 5-HT), and growth factors.⁵¹⁻⁵³

Upon the injury of peripheral nerve axon, degeneration takes place. Inflammatory mediators, growth factors, proinflammatory cytokines are released. As a result, hyperalgesia and allodynia occurs.⁵⁴⁻⁵⁶

Afferent neurons irregular ectopic excitability

Irregular excitability of A δ and C fibers result in stinging and burning pain. Sodium channels apparently cause these symptoms. Moreover, voltage-gated ion channels, Na_v (1.7, 1.8 and 1.9), are of particular role in pain perception.⁵⁷⁻⁵⁹

Spinal dorsal horn pronociceptive facilitation

Glutamate is a crucial stimulatory pain neurotransmitter caused by the CNS. The conduction of peripheral pain signals involves glutamate receptors.⁶⁰⁻⁶⁴ Calcitonin-gene related peptide and substance P are entangled in the disinhibition of the ionotropic-glutamate NMDA receptors. Moreover, metabotropic-glutamate receptors hinder the adenylyl-cyclase and decreases the conduction of pain signals.^{62,65,66}

Spinal inhibitory network disinhibition of pain

Thermal-grill illusion (TGI) has been provoked by the loss of inhibition through a non-noxious cold stimulus at the level of the spinal-cord.^{67,68} TGI was related to the loss of inhibition of central and peripheral toxic thermal responsive pathways.^{62,69,70}

Sympathetically controlled pain

Indirect and direct mechanisms are both involved in sympathetically controlled pain. Nociceptive input and efferent sympathetic signaling are coupled in neuropathic pain. The subcutaneous introduction of noradrenalin after continuous sympathetic block results in similar pain sensations. After sympathectomy, hyperalgesia and pain were the result of the sympathetic trunk stimulation.^{71,72}

Also, findings show that in a few NP cases, sympathetic-activity might lead to pain stimulation. Indirect mechanisms are related to elevated sympathetically-stimulated vasomotor activity leading to impaired nutrition and oxygen supply with altered microcirculation.^{62,73}

Central reorganization phenomena

Significant reorganization in imaging examinations of phantom-limb pain (PLP) patients was admitted. Pain intensity was strongly related to the quantity of cortical reorganization. This shows that the wider exposed body part that is not involved into extension field of the excised part, the higher the PLP.⁶²

CURRENT THERAPIES

From a pharmacodynamics perspective, drugs treating neuropathic pain classes includes, anticonvulsants, antidepressants and antiarrhythmics.⁷⁴ In spite of lack of information from controlled randomized trials, a number of drugs have shown clinically positive effects on specific NP symptoms (Table 2).

SELECTED POTENTIAL PHYTOTHERAPIES

Currently, phytotherapies have been utilized as an adjunctive therapy for amelioration of NP.^{76,77} Many studies have provided evidence underling the beneficial effects of phytotherapy in NP (Figure 1).

Nowadays, many pre-clinical and clinical trials have tested and utilized phytotherapy as an adjunct therapy for NP.⁷⁶ Nevertheless, the efficacy of phytotherapy towards NP patients still been questioned. Therefore, we selected some frontline phytotherapies to review their efficacy towards NP (Table 3).

Rheum ribes

Rheum ribes (*R. ribes*), the Syrian rhubarb, is traditionally utilized in Lebanese traditional medicine for DM management. *R. ribes* aqueous extract was investigated pre-clinically for antidiabetic, antioxidant and antidiabetic-neuropathy activities in experimental animals.⁷⁸ *R. ribes* highest dose (50 mg/kg) significantly elevated serum-CAT levels. Bio-guided fractionation proved that the most active compound present in *R. ribes* is rutin. Prophylactic treatment with *R. ribes* before alloxination, guarded against provoking diabetic neuropathy (DN) in experimental animals. In another diabetic group, after eight weeks of treatment, *R. ribes* significantly ameliorated hyperalgesia in experimental animals. These data pave the way for a future promising drug for the amelioration of DN and a novel prophylactic-treatment intended for DN vulnerable groups.^{78,79}

Cannabinoids

Chemotherapy is known to have a lot of serious side effects. One of these effects is severe NP, that makes quality of life impairment. Moreover, Chemotherapy evoked NP poorly responds to the conventional analgesics.⁹⁴ Therefore, cannabinoid extract were tested for its effects on chemotherapy-induced NP treatment.^{95,96} The drug used is nabiximol (delta-9 tetrahydrocannabinol with cannabidiol as spray) on sixteen patients, and a (0-10) numeric points rating-scale for NP intensity has been utilized as the main result measure. The primary outcome that five participants experienced reduction of pain by 2.6-3.4 points. Ten participants continued an extension phase and reported modest improvement. This pain reduction makes nabiximol an important candidate to do larger randomized trials^{94,95,97} Furthermore, a meta analysis was done on inhaled cannabis and its effect on NP in 405 patients in an individualized form. This study showed a 30% reduction in chronic pain improvement at the individual patient level.⁸⁰ Therefore, cannabinoids open doors for a future treatment for NP.

Table 2: Neuropathic pain lines of treatment, modified from⁷⁵

Lines of Treatment	Treatment	Indication/ Neuropathic pain symptoms
	Tricyclic antidepressants (TCAs):	
	- Desipramine	BRP
	- Amitriptyline	STP; BRP
	- Imipramine	STP; BRP
I	Serotonin and noradrenalin reuptake inhibitors (SNRIs):	
	- Venlafaxine	STP
	Ca channel alpha 2 delta:	
	- Pregabalin	ADA; HPA; STP; BRP
	- Gabapentin	ADA; HPA; STP; BRP
	Local anesthetic:	
	- Topical 5% lidocaine patches.	ADA; HPA
II	Opioids	
	- Morphine	ADA
	- Tramadol	ADA
	Other anticonvulsants:	
III	- Carbamazepine	STP
	- Lamotrigine	STP
	Others:	
	- Topical capsaicin	ADA; HPA

ADA = Allodynia; HPA = Hyperalgesia; STP = Shooting pain; BRP = Burning pain.

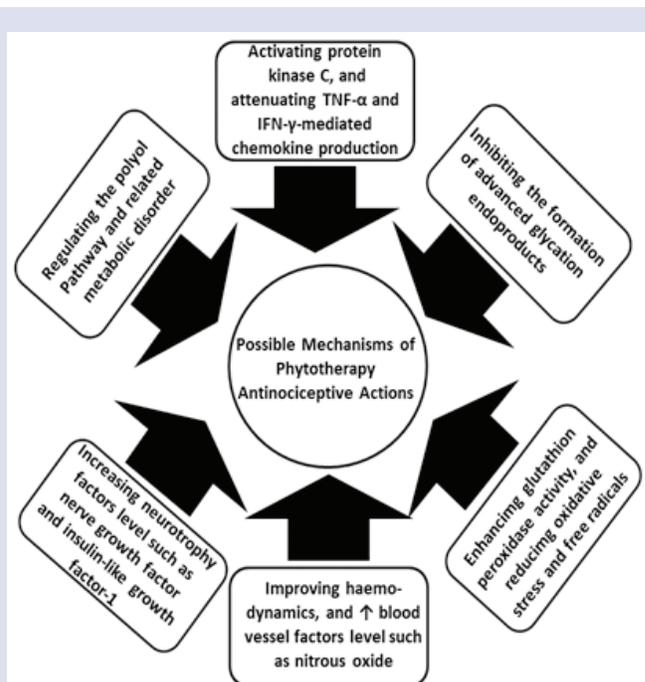


Figure 1: Possible mechanisms of phytotherapy antinociceptive actions modified from.^{76,77}

Table 3: Description of selected Phytotherapies and their effects on neuropathy

Phytotherapy	Family	Used plant part(s)	Most active constituent(s)	Highest dose-Administration route	Predlinical/Clinical Model	Positive control-Administration route	Indication/Neuropathic pain symptoms	Reference(s)
- <i>Rheum ribes</i>	Polygonaceae	Roots	Rutin	50 mg/kg-IP	Alloxan-induced neuropathy in mice	Tramadol 10 mg/kg-IP	HPA	[78, 79]
- <i>Cannabis sativa</i>	Cannabaceae	Flowers	Cannabinoids	32 mg THC per session-Inhaled	Double blind randomized clinical trials	—	ADA	[80]
- <i>Ferula hermonis</i>	Apiaceae	Roots	Ferutinin	50 mg/kg-IP	Alloxan-induced neuropathy in mice	Tramadol 10 mg/kg-IP	ADA; HPA	[24]
- <i>Sambucus nigra</i>	Adoxaceae	Inflorescence	Kaempferol	200 mg/kg-IP	Alloxan-induced neuropathy in mice	Tramadol 10 mg/kg-IP	ADA; HPA	[24]
- <i>Curcuma longa</i>	Zingiberaceae	Roots	Curcuminol	<i>Curcuma longa</i> 100 mg/kg and curcuminol 40 mg/kg-IP	Alloxan-induced neuropathy in mice	Tramadol 10 mg/kg-IP	ADA; HPA	[81, 82].
- <i>Punica granatum</i>	Punicaceae	Fruit rind	Gallic acid	100 mg/kg-IP	Alloxan-induced neuropathy in mice	Tramadol 10 mg/kg-IP	HPA	[83, 84].
- <i>Salvia libanotica fruticosa</i>	Lamiaceae	Roots	Flavonoids	50 mg/kg-IP	Alloxan-induced neuropathy in mice	Tramadol 10 mg/kg-IP	HPA	[84]
- <i>Centaurea horrida</i>	Asteraceae	Herb and root	Flavonoids	100 mg/kg-IP	Alloxan-induced neuropathy in mice	Tramadol 10 mg/kg-IP	HPA	[84]
- <i>Hordeum spontaneum</i>	Poaceae	Grains	Gluten	50 mg/kg-IP	Alloxan-induced neuropathy in mice	Tramadol 10 mg/kg-IP	HPA	[85] and [84]
- <i>Hypericum perforatum</i>	Hypericaceae	Seeds	Hyperforin and hypericin	60 mg/Kg-PO	STZ-induced diabetes in rats	—	HPA	[86]
- <i>Rhodiola rosea</i>	Crassulaceae	Roots	Glycosides	100 mg/kg-IP	STZ-induced diabetes in rats	Gabapentin-IP	HPA	[87]
- <i>Ficus racemosa</i>	Moraceae	Stem bark	Phytosterols	Aqueous extract 500 mg/kg and ethanolic extract 400 mg/kg	STZ-induced diabetes in rats	—	HPA	[88]
- <i>Gymnema sylvestre</i>	Apocynaceae	Leaves	Gymnemic acids	100 mg/kg/day-PO	STZ-induced diabetes in rats	—	HPA	[89]
- <i>Citrullus colocynthis</i> (Topical)	Cucurbitaceae	Fruit	Polyphenolics	Topical formulation	Double blind randomized clinical trials	—	STP; BRP	[90]
- <i>Dioscorea japonica</i>	Dioscoreaceae	Rhizome	Saponins	100 mg/kg, daily-PO	Type-2 Diabetic db/db Mice	Gabapentin-OP	HPA; STP; BRP	[91]
- <i>Cleome viscosa</i>	Capparaceae	Herb	Polyphenolics	400 mg/kg-PO	STZ-induced diabetes in rats	—	HPA	[92]
- <i>Camellia sinensis</i>	Theaceae	Leaves	Polyphenolic catechins: epigallocatechin-3-gallate (EGCG), epigallocatechin, gallic acid and epicatechin	300 mg/kg-PO	Oxaliplatin-induced NP in rats	—	ADA	[93]

ADA = Allodynia; HPA = Hyperalgesia; STP = Shooting pain; BRP = Burning pain; IP = Intraperitoneal; PO = Orally.

Ferula hermonis

Ferula hermonis (Ferula) or Zallouh roots, has been recognized for its sexual stimulant powers for many years. Ferula are known for the treatment of stomach disorders, skin infections, dysentery, fever and neurological disorders in the Asian folk medicine.⁹⁸

In a recent study, the most active isolate utilizing bio-guided fractionation from Ferula was ferutinin. Compared to tramadol (TRA), the highest doses of tested Ferula (50 mg/kg) exerted remarkable effect towards ameliorating allodynia and thermal hyperalgesia.²⁴

Sambucus nigra

Sambucus nigra (Elder) is another medicinal plant in which Elder is used in the management of diabetes neuropathic pain.²⁴ The inflorescences of Elder comprises valuable phenolic compounds, comprising flavonoids, phenolic acids, proanthocyanidins and catechins.⁹⁹ Moreover, Elder demonstrates immune-stimulating, anticancer,¹⁰⁰ antiallergic, antiviral, antibacterial, bronchodilatory, antitussive activity.¹⁰¹

Elder has shown significant effects towards amelioration of mechanical allodynia and hyperalgesia.²⁴ Elder were fractionated by RP-column chromatography and RP-HPLC, and showed that the most effective compound was kaempferol. Elder has shown high efficacy against tactile allodynia after a single-administration. However, for amelioration of hyperalgesia, needed repeated administration.²⁴

Curcumol

Turmeric (*curcuma longa* L.) contains curcumol, a guaiane-type sesquiterpenoid hemiketal. Curcumol could be used as antihepatic fibrosis, anti-inflammatory, antitumor and anti microbial effects.¹⁰²⁻¹⁰⁵ Increasing oxidative stress will increase diabetic neuropathy because the tissues will not use the glucose present in blood. Supplementation of antioxidant compounds, like curcumol, ameliorates diabetic neuropathy.^{81, 82}

Pre-clinically treatment of mice with turmeric extract show high improvement in the management of diabetic neuropathy. Same goes to curcumol. Furthermore, they improve tactile allodynia. Rapid onset medication (turmeric) may be better for acute management. However, curcumol is efficient for long term management.⁸¹

In conclusion, based on the previous results, curcumol decreases oxidative stress and ameliorates the nerve functions in tactile allodynia.

Punica granatum

Due to its safety and availability, herbal extracts are being used in the regulation of diabetic neuropathy.^{83,84} One of these herbal extracts, is *Punica granatum* ethanolic extract (*P. granatum*) and its dried spray biopolymeric dispersion of either chitosan (F2) or casein (F1) has *in vivo* antioxidant and improves diabetic neuropathy complications. Pre-clinical studies for diabetic neuropathy, using *P. granatum* extract (100mg/kg), F2, F1, and gallic acid (6mg/kg), clearly enhanced thermal and tail flick latencies and ameliorated oxidative stress.¹⁰⁶

Salvia fruticosa

Salvia or *Salvia libanotica fruticosa* (Lamiaceae) grows chiefly in Lebanon.¹⁰⁷ Pre-clinical studies suggests that Salvia improves peripheral nerve function in the diabetic mice.^{84, 108} These findings give clinicians promising drug-leads for the management of diabetic neuropathy symptoms.

Centaurea horrida

Centaurea horrida is another antioxidant rich plant. Extracts from leaves, flowers¹⁰⁹ and roots.⁸⁴ were reported to depress blood sugar levels and ameliorate thermal hyperalgesia in mice models of diabetic neuropathy.

Hordeum spontaneum

Hordeum spontaneum K. (Poaceae), known as wild barley is known for its hypoglycemic potentials.⁸⁵ Its high levels of beta-glucan which causes alleviation of insulin levels and decrease of oxidative stress might the underlying causes of wild barley diabetic neuropathy ameliorative effects.⁸⁴

Hypericum perforatum

Acute administration of *Hypericum perforatum*, St. John's Wort seed extract (SJW), containing hyperforin and hypericin, ameliorated mechanical hyperalgesia for a prolonged time. The antinociceptive efficacy of SJW was comparable to that of current therapies (carbamazepine and L-acetyllevocarnitine).⁸⁶ These results suggest that SJW might become a novel therapeutic perspective for painful diabetic neuropathy.

Rhodiola rosea

Golden root or *Rhodiola rosea* ethanol extract (*R. rosea*) (Crassulaceae) preclinical studies has shown a significant activity towards thermal and chemical antinociceptive activities, suggesting that *R. rosea* had anti-diabetic hyperalgesia potentials.⁸⁷

Ficus racemosa

Preclinical study showed *Ficus racemosa* had a significant antioxidant potential and marked improvement in hyperalgesia utilizing locomotion rise, tail flick and fall latency periods.⁸⁸ Further clinical studies are required to support these findings.

Gymnema sylvestre

Gymnema sylvestre treated diabetic animals had shown neuroprotective effects associated with antioxidant and anti-inflammatory activities.⁸⁹ It has proved to be one of most promising diabetic neuropathy future preventive therapies.

Citrullus colocynthis

Bitter apple or *Citrullus colocynthis* (*C. colocynthis*) is one of the fruits that has shown significant potentials against diabetic NP. In a double-blind placebo-controlled clinical randomized trial, *C. colocynthis* topical formulation had a significant antinociceptive effects against painful diabetic neuropathy.⁹⁰ More studies are required to establish *C. colocynthis* potentials on nerve function and overall quality of life.

Dioscorea japonica

Standardized *Dioscorea japonica* extract has shown to ameliorate, transgenic diabetic animals, thermal hyperalgesia and peripheral-nerve damage.⁹¹ These results might pave the way for preparation of a potential botanical therapy for diabetic neuropathy.

Cleome viscosa

In vivo subchronic treatment with *Cleome viscosa* ethanolic extract significantly attenuated nociceptive thresholds. It had also significant *in vivo* antioxidant activities.⁹² Additional work is suggested to know its antinociceptive mechanism of action.

Camellia sinensis

Green tea has been found to contain four major polyphenolic catechins: epigallocatechin-3-gallate (EGCG), epigallocatechin, gallic acid and epicatechin.¹¹⁰ Because of the antioxidant activity of its polyphenol catechins, *Camellia sinensis* has been found to be useful adjuvant to alleviate oxaliplatin-induced allodynic sensory symptoms in a rat model of neuropathic pain.⁹³ More clinical trials are required to strengthen these findings.

Finally, these data has shown that natural therapies have indeed significant potentials to be the future hope for NP patients. However, the management of neuropathic pain remains to be an ongoing battle in the

purpose of finding the optimum treatment with the best benefit on the patients' life quality.

DISCUSSION

In spite of the existence of guidelines and a number of effective drugs for the treatment of NP, there are still several cases that remain untreated or undertreated. This concern has highlighted the need of several research studies in the scientific field. One of these studies is the management of NP through phytotherapies.

Oxidative stress has been involved in the reactive oxygen species (ROS) release, responsible for many neurodegenerative disorders including NP.¹¹¹ The cellular defensive mechanism opposing ROS-mediated cellular injury has been ameliorated by the natural antioxidant enzymes. Phytotherapies such as *Rheum ribes*, *Cannabis sativa*, *Ferula hermonis*, *Sambucus nigra*, *Curcuma longa*, *Punica granatum*, *Salvia libanotica fruticosa*, *Centaurea horrida*, *Hordeum spontaneum*, *Hypericum perforatum*, *Rhodiola rosea*, *Ficus racemosa*, *Gymnema sylvestre*, *Citrullus colocynthis*, *Dioscorea japonica*, *Camellia sinensis* and *Cleome viscosa* had shown the ability to ameliorate NP by various mechanisms of actions. Most of these medicinal plants have shown to comprise bioactive constituents possessing antioxidant potentials.

R. ribes has shown to be one of the most potent phytotherapies. Bio-guided fractionation has proved that rutin, a key constituent of *R. ribes*, significantly decreased hyperalgesia (Table 3), and was suggested that this effect is due to elevation of natural antioxidant effect, catalase.⁷⁸ Nevertheless, there is no full clinical evidence for its use. On the other hand, a number of conventional drugs have shown clinically positive effects on specific NP symptoms (Table 2).

C. sativa has also shown potent neuroprotective effects. It has been investigated in terms of amelioration of NP in the literature review (Table 3). Double blind randomized clinical trials have shown that inhaled THC, a key constituent of *C. sativa*, significantly decreased allodynia, and was suggested that this effect is due to THC specific suppression of central and peripheral sensitization.^{80,96}

The third most potent herb was *F. hermonis*. Interestingly, there has been no detailed clinical studies investigating *F. hermonis* in the amelioration of NP reported in the English language. *In vivo* pharmacological investigation had shown that ferutinin, a constituent of *F. hermonis*, significantly decreased hyperalgesia and allodynia, and was suggested that this effect is due to elevation of natural antioxidant effect, catalase.²⁴ (Table 3).

S. nigra has shown potent antihyperalgesic and antiallodynic activity. Although no detailed clinical trial has been reported, the bio-guided fractionation has shown that kampferol was the most active constituent in the inflorescence of *S. nigra*. Literature review has shown that kampferol antioxidant potentials might be responsible for *S. nigra* neuroprotective effects.²⁴

The research performed on *C. longa* has indicated efficacy in NP amelioration. Pharmacological studies on mice have indicated that the antioxidant potentials of curcumol, *C. longa* key constituent, alleviated allodynia and hyperalgesia.⁸¹ (Table 3). Detailed clinical trials are required to fully understand curcumol mechanism of action.

Research on the utilization of *P. granatum* has shown to be a promising phytotherapeutic agent for amelioration of NP. The antioxidant potentials of gallic acid, *P. granatum* key constituent, has shown effective antihyperalgesic activity.¹⁰⁶ A much extended and larger clinical trials would be recommended to fully investigate *P. granatum* neuroprotective activities.

The potential significant role of ethnopharmacology in the evolution of herbal treatment for NP has been shown by research on three herbs. An *in vivo* investigation was performed by three traditional herbs, namely *S. fruticosa*, *C. horrida* and *H. spontaneum*. Among these herbs, *C. horrida*

has shown to possess the most potent antihyperalgesic activity. *C. horrida* has potentially elevated catalase levels suggesting that its antioxidant potential might be responsible for its neuroprotective effects.⁸⁴

H. perforatum has shown potent antihyperalgesic activity against NP in a diabetic rat model. Research so far has shown that hyperforin and hypericin, *H. perforatum* key constituents, might be responsible for its neuroprotective activity.⁸⁶ (Table 3). These results have been only demonstrated in rat model, however, the results appear as a promising future treatment.

The traditional use of *R. rosea* has led the scientists to discover its antihyperalgesic potentials. Preclinical studies has shown that *R. rosea* inhibited COX-1 and -2 and phospholipase A2, suggesting that this mechanism is responsible for antinflammatory and antinociceptive activities⁸⁷ (Table 3). These finding reflect positive outcomes for further investigation.

The protective role of *F. racemosa* against neurodegenerative NP has been demonstrated in a rat model. The antioxidant potentials of *F. racemosa* monitored in the significant elevation in catalase, superoxide dismutase, and amelioration of nitrite level, C-reactive protein and lipid peroxidation levels, which might be responsible for its potential antihyperalgesic activity.⁸⁸

Gymnemic acids, the active constituents in *G. sylvestre*, has proved to have antihyperalgesic activity in a preclinical model. The association of gymnemic acids antioxidant and antinflammatory activities might be responsible for its neuroprotective effects.⁸⁹ Further clinical studies are indicated for fully understanding gymnemic acids mechanism of action against NP.

Within the inclusion criteria of this study, *C. colocynthis* has been appropriately researched. In a double-blind placebo-controlled clinical randomized trial, *C. colocynthis* topical formulation had a significant antinociceptive effects against painful diabetic neuropathy.⁹⁰ Further studies are required to establish *C. colocynthis* potentials on overall quality of life.

D. japonica alleviated transgenic diabetic animals, thermal hyperalgesia and peripheral-nerve damage. Induction of nerve growth factor might be responsible for *D. japonica* extract ameliorative effects towards hyperalgesia, shooting and burning pains. Latest research has indicated that *D. japonica* standardized extract were being under investigation in a randomized clinical study.⁹¹ This study results might pave the way for validation of *D. japonica* use against NP.

The significant antioxidant activity was responsible of the choice of *C. viscosa* as a potential candidate in amelioration of NP. Preclinical studies have shown that *C. viscosa* possessed significant antihyperalgesic properties. Moreover, the amelioration of lipid peroxidation and oxidative stress in treated NP models, has suggested their association in *C. viscosa* mechanism of action.⁹²

In addition, even though green tea has shown temporary effect on neurotoxicity, it might be a useful future adjuvant therapy to ameliorate allodynic sensory symptoms in the primary stages of preclinical neurotoxicity with a good safety history.⁹³ Nevertheless, more in-depth clinical studies are required to validate green tea utilization in NP management.

Generally, herbal therapy appeared to be well tolerated by preclinical/clinical models with NP. Potential side effects of these natural plants had not shown as an emerging issue. However, these phytotherapies need more clinical evidence to demonstrate any underlying side effects, and to verify their promising neuroprotective properties.

Moreover, the study results have indicated the potential advantages of phytotherapy as a NP therapeutic option, utilized both alone or in combination with conventional treatment. This study also suggested that

further investigation into the utilization of phytotherapy in the treatment of NP was both needed and justified.

RECOMMENDATIONS IN MANAGEMENT OF NEUROPATHIC PAIN

I. Pain management should be headed by knowing the cause of NP and initiating a suitable treatment.

II. Relevant comorbidities should be identified as they may require analgesic dosage modification or constitute contraindications for treatment.

III. Patient education should be implemented (like; treatment and diagnosis).

IV. Specific NP syndromes according to lines of treatment (Table 2 and 3) should be managed with regards to the recent recommendations.

V. First-line treatment should be continued if it is effective (at least 50% pain reduction), in an adequate time.

VI. Lack of effectiveness of first-line drugs, used at appropriate doses either alone or in combination, designates the need for trying treatment with second-line and third-line drugs.

VII. Pharmacologic management should be accompanied with non-pharmacologic interventions.

VIII. Treatment efficiency should be measured with suitable frequency.

IX. Physicians consider spinal cord stimulation SCS, is a factor to block stimulus transmission, or intrathecal drug delivery systems when other pharmacological treatments fail.

X. Alternative treatments include phytotherapies are needed to decrease the dose and possible side-effects of the first line treatments.

XI. Phytotherapies need more clinical trials in order to fully understand their mechanism of action, to demonstrate any underlying side effects, and to validate their future use.

CONCLUSION

In spite of the presence of guidelines and a number of effective drugs for the treatment of NP, there are still several cases that remain untreated or undertreated. This issue has raised the concern of several research studies in the scientific field. One of these measures is the management of NP through phytotherapy. Therefore, this review discusses neuropathic pain and provides multiple recommendations on how to diagnose and manage this syndrome with a special emphasis on phytotherapy potentials. Phytotherapies, although not yet well studied, offering relatively low-risk options in neuropathic pain patients and having an increasing evidence to be the future of NP management.

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CONFLICTS OF INTEREST

There are no conflicts of interest.

ABBREVIATION USED

NP; neuropathic pain; CNS; central nervous system; TN; Trigeminal Neuralgia; CP; Central Pain; TCAs; Tricyclic antidepressants; OA; Osteoarthritis; TGI; Thermal-grill illusion; PLP; phantom-limb pain; ROS; reactive oxygen species; COX; Cyclooxygenase.

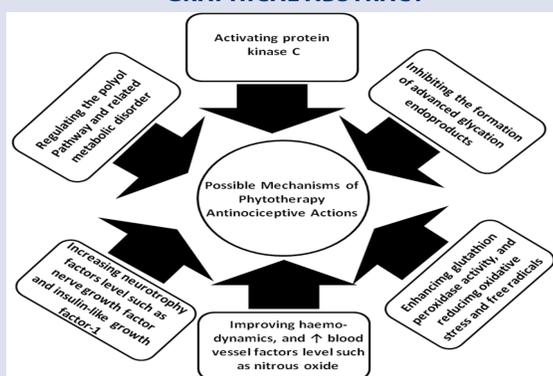
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GRAPHICAL ABSTRACT



- This review discusses neuropathic pain and provides multiple recommendations on how to diagnose and manage this syndrome with a special emphasis on phytotherapy potentials. Phytotherapies, although not yet well studied, offering relatively low-risk options in neuropathic pain patients and having an increasing evidence to be the future of NP management.

AUTHOR PROFILES



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Group Photo: Rawan El-Haj, Dania Shoumar, Rana Alaeddine, Yousra Fakhro, Natalie Tawil, Farah Shaer, Amani Daher, Natalie Awada, Ali Sabra, Khoulood Atwi, Malak Khaled, Raneem Messi, Nour Abouzaher, Mohamed Hourri and Samer Al Jallad: Phytotherapy Junior Research Team, coordinated by **Dr. Karim M. Raafat**, Associate Professor of Phytochemistry, with a main research focus on the separation and the isolation of medicinally important compounds from natural origin and testing their possible pharmacological and toxicological effects.



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