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Review Article

Herbs as positive modulator in neuropathic pain and their antinociceptive effect

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Abstract

Neuropathic pain arising from peripheral nerve injury is a clinical disorder characterized by a combination of spontaneous pain, hyperalgesia and tactile pain (allodynia), and remains a significant clinical problem since it is often poorly relieved by conventional analgesics. Despite the progress that has occurred in recent years in the development of therapy, there is still a need for effective and potent analgesics for neuropathic pain. This review summarizes the existing studies investigated the efficacy of herbs as a treatment for neuropathic pain. Recently discovered analgesic substances in neuropathic pain include alkaloids, terpenoids and flavonoid, this plant-derived substances have, and will certainly continue to have, a relevant place in the process of drug discovery, particularly in the development of new analgesic drugs. In this review, emphasis will be given to the important contribution of herbs and their compounds in the development of new analgesics.

Keywords: Neuropathic pain, Herbs, Analgesic, Anti-nociceptive, Plant metabolites.

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Neuropathic pain represents heterogenous conditions, which neither can be explained by one single aetiology nor by a particular anatomical lesion. This diversity in cause and site is reflected in entities such as peripheral nerve injuries due to trauma and poststroke pain due to ischaemic vascular lesions of the brain. Despite the different etiology and the multiple lesions giving rise to neuropathic types of pain, many of these conditions share common clinical phenomena like: no visible injury, paradox combination of sensory loss and hyperalgesia in the painful area, paroxysms and a gradual increase of pain following repetitive stimulation [1-3]. Neuropathic pain is widely recognized as one of the most difficult pain syndromes to manage, and outcomes often are unsatisfactory [4]. Epidemiological research in this area can be problematic, and the reasons for this are multifactorial. Patients experiencing pain may try numerous therapies, including traditional medicinal approaches for relief. Pain relief is the most frequently cited reason that people seek complementary and alternative medicine

(CAM) [5]. These therapies might be chosen because other conventional therapies were previously ineffective or produced side effects that were intolerable. Mostly drugs which are approved and authenticated by USFDA in neuropathic pain are Lyrica (Pregablin), Cymbalta (Duloxetine), Neurontin (Gabapentin), Lidoderm(5% lidocaine patch) & Qutenza (8% capsaicin patch). All these are associated with high incidence of side effects appealing for the more safe therapy [6].

The use of medicinal plants is a traditional form of providing relief from illness and can be traced back over five millennia in several civilizations. Over the years, natural products have contributed enormously to the development of important therapeutic drugs used currently in modern medicine [7,8]. The potential of higher plants as sources for new drugs is still largely unexplored. Among the estimated 250000 plant species existing world-wide, only a small percentage have been investigated phytochemically, and the fraction submitted to biological or pharmacological screening is even smaller [9]. In spite of the progress that has taken place in recent years in the development of therapy, the medical community still urgently needs effective and potent analgesics, especially for chronic pain. Thousand of patients with intense and unrelenting pain, such as that resulting from cancer or injury, have to depend on morphine, despite its well-known side effects [10]. This has renewed the interest of the major Pharmaceutical companies in higher plant-derived secondary metabolites as part of the search for new clinically useful drugs. In this review article we will focus on the contribution of plants to the development of modern analgesic drugs.

1. Herbs effective in Neuropathic pain

2.1 Papaver somniferum

Opium derives from the latex obtained by incision of the unripe capsules of *P. somniferum*, dried partly by spontaneous evaporation or by artificial heat. Opium contains about 25 alkaloids, including morphine, codeine, thebaine and papaverine. In 1805, the German pharmacist Sertu¨ner isolated the active ingredient in opium and named it ‘morphine’ [11-12]. Morphine was the first alkaloid to be discovered, and its isolation, therefore, was a breakthrough in organic chemistry. The pharmacological properties of morphine are quite complex and can vary depending upon the dose, site of action and administration route, and wide variation among animal species has been reported. The most relevant characteristic of morphine is its property of modulating the perception of pain, resulting in an increase in the threshold of noxious. Antinociception induced by morphine is now known to be mediated via activation of membrane opioid receptors, and therefore it can be inhibited by opioid receptor antagonists, e.g. naloxone [13].

2.2 Cannabis sativa

Throughout history, *Cannabis sativa* L. has been used as a natural therapeutic herb. Usage of marijuana for medical purposes can be traced back 5000 years. In 1842, O’Shaughnessy, an army physician in India, published an extensive treatise on the use of cannabis in various medical conditions including as an analgesic. As a result, *Cannabis* was introduced into European medicine and subsequently into other areas of Western medicine, including the United States. Preparations such as tincture and extract of *Cannabis* were recognized for a long time as official drugs and were listed in the US Pharmacopoeia from 1850 until 1942. The *Cannabis* plant contains a complex mixture of substances that include at least 60 different cannabinoids, many of which have been shown to present pharmacological

activities [14]. Until 1964, it was generally assumed that the active principles of *Cannabis* were an unidentified mixture of isomers of tetrahydrocannabinols (THC). The major active constituent of *Cannabis*, THC, has been shown to possess antinociceptive properties when assessed in several experimental models, and this effect is attenuated by a CB1 receptor antagonist. The ethanol extract of the herb, and the cannflavones isolated from it, have been shown to possess analgesic action [15].

2.3 Capsicum species

The *Capsicum* species belong to the family of Solanaceae and originated in Central and South America. About 20 *Capsicum* species are included in this family. They are distributed throughout the world, but only five species are widely cultivated: *C. annuum, C. frutescens, C. chinense, C. pendulum* and *C. pubescens*. Capsaicin was recognized as the major component, constituting about 70% of the total pungent acid amides contained in plants belonging to the *Capsicum* species, while dihydrocapsaicin, an analogue of capsaicin (capsaicinoid), amounted to 30% or less [16]. Capsaicin is a very important pharmacological tool, because it exerts a dual role in the nociceptive process. Locally applied, capsaicin elicits a series of nociceptive, hyperalgesic and inflammatory reactions, mediated by an increase in membrane cation permeability. Capsaicin excites the afferent sensorial neurons, specifically, the C and Ad fibres that conduct the nociceptive information to the central nervous system (CNS), where it stimulates, mainly through the calcium influx, the release of several neuropeptides including tachykinins, calcitonin generelated peptide (CGRP) and somatostatin, and also blocks the intra-axonal transport of macromolecules, such as the neural growth factor (NGF) [17]. A two-arm, double-blind, placebo controlled, crossover clinical study found topical capsaicin formulation decreases postsurgical neuropathic pain to a 3 to 1 margin over placebo [18].

2.4 Salix species

The genus *Salix* (Salicaceae), containing about 500 different species of plants, is known popularly as willow. The species *S. alba* L., *S. fragilis* L. and *S. purpurea* L. are the most regularly used for medicinal purposes. The principal active constituent of *Salix sp*. is salicin. However, studies have shown that a whole series of phenolic glycosides, such as salicortin, fragilin and tremulacin, are present in the bark of this plant [19, 20]. In 1829, Leroux isolated the active ingredient, salicin, from the willow bark, and in 1838 salicylic acid was obtained. The first synthetically produced conversion of salicylic acid was acetylsalicylic acid, which Gilm synthesized in 1859. There is a considerable debate as to whether ASA or salicylate is the most effective analgesic [13].

2.5 Acorus calamus rhizoma

Acorus calamus (family: Araceae) is traditionally used in the treatment and management of various pain's which also includes severe inflammatory and neuropathic pain in Ayurveda. In a study using rat model, a hydroalcoholic extract of *Acorus calamus rhizoma* has been shown to exert beneficial effect on neuropathic pain induced by tibial and sural nerve transaction [21]. In a further study injury induced by sciatic nerve chronic constriction where therapy of *Acorus calamus rhizoma* extract has ameliorated behavioral (hyperalgesia and allodynia), biochemical (superoxide anion, myeloperoxidase, and total calcium), and histopathological (axonal degeneration) changes [22]. In another preclinical study, Hydroalcoholic extracts of *Acorus calamus rhizoma* attenuated vincristine-induced behavioral and biochemical changes to an

extent comparable to pregabalin (positive control). Use of hydroalcoholic extracts of *Acorus calamus rhizoma* has succesfully attenuated vincristine-induced painful neuropathy, which probably may be attributed to its multiple effects including antioxidative, anti-inflammatory and calcium inhibitory activity [23].

2.6 Yokukansan - Traditional Japanese medicine for neuropathic pain

Yokukansan is one of the traditional Japanese medicines called *kampo* in Japan. It is composed of seven kinds of medicinal herbs which includes *Atractylodis rhizoma, Poria sclerotium, Cnidium rhizome, Uncaria thorn, Japanese Angelica root, Bupleurum root, and Glycyrrhiza glabra.* Yokukansan has been approved by the Ministry of Health, Labor, and Welfare of Japan as a remedy for neurosis, insomnia, and irritability in children. In past studies it was observed that yokukansan clinically attenuates neuropathic pain due to postherpetic neuralgia, complex regional pain syndrome, and central cord syndrome and reported that yokukansan ameliorates neuropathic pain symptoms in patients [24]. In another study animal model of peripheral nerve injury was used to elucidate the mechanisms underlying protective effect of yokukansan in neuropathic pain associated with a blockade of glutamatergic neurotransmission via activation of glutamate transporters in the spinal cord [25].

2.7 Analgesic effect of Moutan cortex and Coicis semen on neuropathic pain

Moutan cortex, the root cortex of *Paeonia suffruticosa* Andrews, is an important Chinese crude drug used in many traditional prescriptions. One of the major constituents of Moutan cortex is 2-hydroxy-4-methoxy-acetophenone (paeonol) that has analgesic, antipyretic and antibacterial properties and used for the treatment of arthritis. When orally administered at 1 g/kg, paeonol markedly reduced the number of writhes in the acetic acid writhing test and increased the threshold by tail pinching of mice [26]. It also inhibited the rat paw edema induced by carrageenan, dextran and acetic acid with a potency similar to that of aspirin and was suggested to be largely responsible for the therapeutic effect of Moutan cortex [27]. However, since the extract of Moutan cortex blocked the PGF2-induced allodynia, the mechanism of action is different from the inhibition of prostanoid synthesis. On the other hand, a major constituent of Coicis semen is 6-methoxybenzoxazolone (coixol) but there are few reports on its analgesic effect on animal pain models [28]. Since the extracts orally administered 1 h before i.t. PGF2 blocked the allodynia, an active compound in the extracts could easily pass through the blood–brain barrier and exerted the action in the spinal cord. As compared with a single administration of the NOS inhibitor l-NAME whose effect was weak and short [29], the analgesic effect by the extracts of Moutan cortex and Coicis semen on neuropathic pain was observed over 24 h, suggesting that a long-lasting effect on neuropathic pain might be expected by continuous administration of the drugs. Whether paeonol or coixol is an active compound in the extracts and how the extracts exert the analgesic action on neuropathic pain remain unknown [30].

2. Substances derived from plants effective in neuropathic pain

3.1 Alkaloids

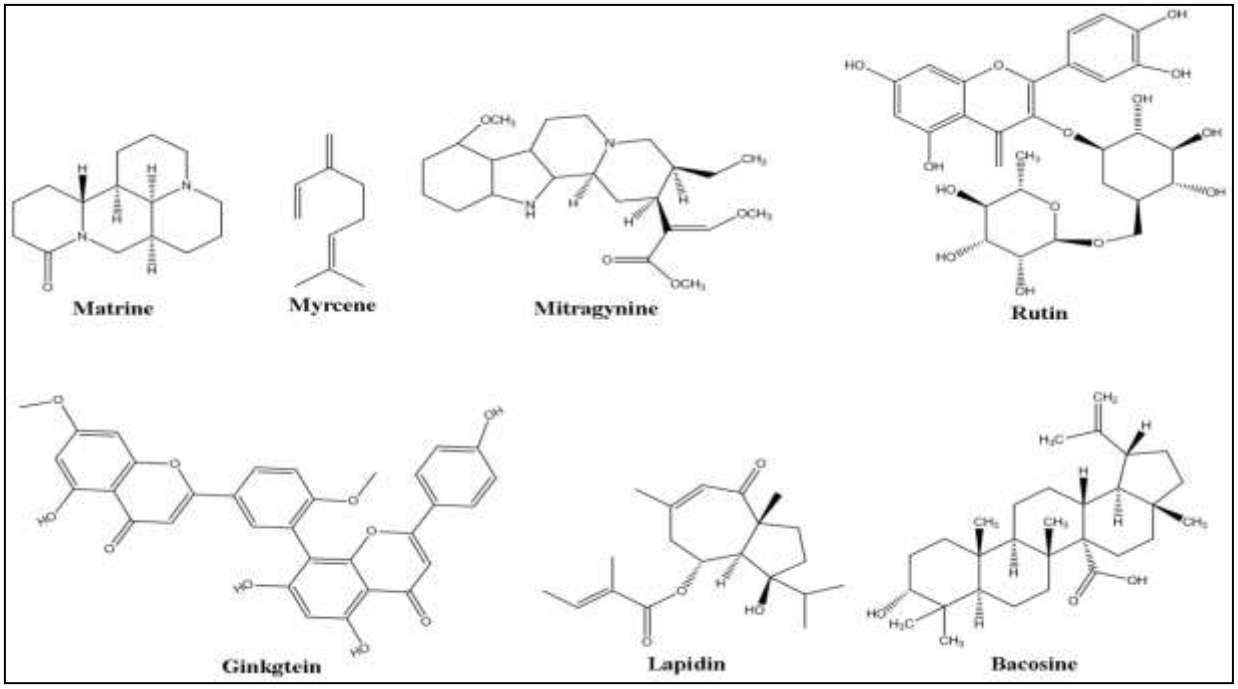
In recent years, a large number of different kinds of naturally occurring alkaloids with antinociceptive effect in neuropathic pain has been reported. Rios *et al.* (1989) reviewed the chemical structures and the main pharmacological actions of aporphinoid alkaloids and found that some of them exhibited antinociceptive effect in

neuropathic pain, namely pronuciferine, glaucine, nuciferine and pukateine [31]. A crude alkaloid extract from *Hunteria zeylanica* has been found to exert pronounced antinociception when assessed in several chemical (but not thermal) models of neuropathic pain in mice. This activity might be attributed to the presence of eburnamine and other derivatives and pleiomutinine [32, 33]. Two matrine type lupin alkaloids, allomatrine and matrine (Fig-1), isolated from *Sophora alopeculoides* exhibit antinociceptive effects, which are mediated through the activation of k-opioid receptors and both m- and k-opioid receptors, respectively [34]. Mitragynine (Fig-1), the major alkaloidal constituent found in young leaves of *Mitragyna speciosa*, exerts an opioid-like activity, but its selectivity for the opioid receptor subtypes differs from that of morphine [35, 36]. The alkaloids isolated from *Psychotria colorata* show a marked naloxone-reversible antinociceptive activity in animals [37]. Furthermore, these alkaloids have an inhibitory effect on [3H]-naloxone binding, providing a neurochemical basis for the opioid-like activity *in vivo* [38]. Isoretuline, but not O-acetyllisoretuline and Ndesacetylisoretuline, isolated from *Strychnos henningsii* Gilg, have antinociceptive and antiinflammatory action in animals [39].

3.2 Terpenoids and steroids

Terpenoid and steroid compounds are widely distributed pharmacological properties. Among other actions, naturally occurring terpenoids present antiinflammatory and antinociceptive properties, inhibit platelet aggregation, and interfere at the intracellular level with several steps of signal transduction mechanisms [40-41]. The monoterpenes found in the essential oil of *Cymbopogon citratus* exhibited antinociception when assessed in different experimental models of pain. Myrcene (Fig-1) was the most active component of the oil, having an antinociceptive effect similar to that described for peripheral-acting opiates or dypirone [42]. Lapidin, a bicyclic sesquiterpene from *Ferula linkii*, trans-dehydrocrotonin, a 19-nor-clerodane diterpene from *Croton cajucara*, and four triterpenes isolated from dichloromethane extract of *Ganoderma lucidum*, denoted ganoderic acids A, B, G and H, were effective in inhibiting acetic acid-induced abdominal constrictions in mice [13]. Bacosina (Fig-1), isolated from aerial parts of *Bacopa monnieri*, and 1,8-cineole, present in the essential oil of *Nepeta italica*, exhibited antinociception by interaction with opioidergic pathway [44,45]. The isolation and identification of several terpenes with antinociceptive effects have been demonstrated in preliminary studies. Kaurenoic acid, the major component of *Wedelia paludosa* , marrubiin, a furanolactone diterpene from *Marrubium vulgare*, the pholidotin and 24-methylenecycloartenal isolated from *Epidendrum mosenii*, moretenone and glutinol isolated from *Sebastiania schottiana*, a-amyrin and b- amyrin from *Aleurites moluccana*, a-amyrin acetate, b-amyrin acetate and glochidone isolated from *Ipomoea pes-caprae*, Ichigoside F1 from *Rubus imperialis* and 24-hydroxytormentic acid isolated from *Ocotea suaveolens* exhibited dosedependent and significant antinociception when assessed in acetic acid, formalin and capsaicin tests. Other structurally similar diterpenes to marrubiin also cause significant inhibition of the abdominal constrictions induced by acetic acid [13].

Fig 1- Bioactive compounds found effective in neuropathic pain and have anti-nociceptive effect.



3.3 Flavonoids

Preliminary studies have demonstrated that various flavonoids, including rutin (Fig-1) and quercetin, two common and abundant flavonoids in nature, luteolin isolated from *Wedelia paludosa* [46,47] and the luteolin derivative, luteolin-4'-O-neohesperidoside, isolated from *Caralluma attenuate* [48], quercetin 3-O-glycoside (isoquercitrin) isolated from many plants, taxifolin but not its glycoside derivative, astilbin, isolated from *Hymenae martiana*[49], two kaempferol glycoside derivatives isolated from *Hedyosmum bonplandianum* [50], pectolinarin isolated from aerial parts of *Cirsium subcoriaceum* [51], and gossypin all produced significant antinociception in the acetic acid-, formalinand capsaicin-induced nociceptive response. Hesperidin, a citrus flavonoid , 2@-O-rhamnosylswertisin, but not swertsin, isolated from *Aleurites moluccana*, and some biflavonoids, such as amentoflavone, volkensiflavone, GB-2a, fukugetin, fukugeside , and GB-1a [13,52,53] which are well-distributed in the families of Clusiaceae and Guttiferae, also exerted pronounced antinociception in mice against the nociception caused by i.p. injection of acetic acid. Quercetin-3-O-galactoside (hyperoside) possesses analgesic effects related to a reduction of calcium influx in afferent nerve endings without anaesthetic action [54]. Ginkgetin (Fig-1), a biflavone isolated from *Ginkgo biloba* leaves, has been reported as an inhibitor of group II phospholipase A2. This compound strongly reduces arthritic inflammation, confirmed by histological examination of the knee joint. In addition, ginkgetin showed antinociceptive activity in acetic acidinduced writhing, suggesting that this compound may be a potential antiarthritic agent having an analgesic effect [55]. Moreover, a clinical study showed that *Ginkgo biloba* extract (standardized to 21.0 mg flavonglycosids and 3 mg folic acid) treatment improved the nerve function and pain associated with autonomic neurophathy in ten patients [56].

3. Miscellaneous compounds

Several studies have shown that other classes of naturally occurring substances, including xanthones, tannins and saponins, possess antinociceptive properties. Nepetalactone, a lactone extracted from *Nepeta casearea*, is the main antinociceptive component of this plant, and shows a specific opioid receptor subtype agonistic activity [57]. Acteoside, a phenylethanoid glycoside, has been isolated as an antinociceptive principle from *Lipia triphylla*, a Peruvian medicinal plant, by activity-guided separation [58]. 1,7- Dihydroxy-2,3-dimethoxy-xanthone, isolated from *Polygala cyparissias*, produces dose-related inhibition of acetic acid-induced abdominal constriction in mice, being more active than some reference drugs [59,60]. Furthermore, 1,7-dihydroxy-2,3-dimethoxy-xanthone antagonizes, in a concentration-dependent fashion, several inflammatory mediator-mediated contractions in the guinea-pig trachea [61]. Recent studies conducted by our research group demonstrated that different components of *Croton urucurana*, such as acetyl aleuritolic acid, catechin, gallocatechin, etc. presented antinociceptive effects, but the potency of the isolated compounds was similar to or lower than those exerted by extracts or fractions, suggesting the existence of other minor active components or the existence of a synergistic effect [62]. Smilaxin B, a spirostanol glycoside isolated from *Smilax sieboldii* Miq., caused antinociception when administered i.c.v. and analysed in the tail-flick test. This effect was mediated by $GABA_A$ and N-methyl-Daspartate (NMDA) receptors, but not $GABA_B$ or non- NMDA receptors located at the supraspinal level. However, the antinociceptive effect may have been produced by activation of descending noradrenergic systems without affecting opioidergic or serotonergic pathways [63]. The 2-(4-bromobenzoyl)-3-methyl-4,6-dimethoxy benzofuran, a xanthoxyline derivative revealed interesting antinociceptive spinal and supraspinal actions when assessed in several chemical and thermal models of nociception [64]. In a recent study curcumin has shown its effect possibly through its inhibitory action on NO and TNF-α release and point towards its potential to attenuate diabetic neuropathic pain [65].

Conclusion

Although significant scientific progress has been made in recent decades on the elucidation of the neurobiology of neuropathic pain transmission, especially by application of modern techniques of electrophysiology and molecular biology, the need for new and more effective analgesics for clinical use, free as far as possible of undesirable side effects, are still urgently required. One of the most important analgesic drugs employed in clinical practice today continues to be the alkaloid morphine, in spite of its well-known undesirable side-effects. However, from this review it has become clear that there are many possible targets and available strategies that might permit the development of new and effective analgesic drugs from naturally occurring secondary metabolites derived from plants, and which may be expected to have therapeutic benefit in the management neuropathic pain. Plant-derived secondary metabolites have, over the years, greatly contributed to our current understanding of the process of pain transmission, and, especially, have permitted us to characterize the receptor types and endogenous ligands involved in the mechanism of nociception. Morphine, capsaicin and cannabinoids, among others, are good examples. Thus, this field of research has become the focus of intense interest, on the part of both academics and pharmaceutical companies, and efforts towards the identification of effective and

safe analgesics, direct from plants or from derivatives, will certainly reap great rewards in the near future. Thus, naturally occurring substances derived from plants currently have and will certainly continue to have a relevant place in the process of drug discovery, particularly in the development of new analgesic drugs.

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