DETERMINING THE EFFECTS OF INDIAN MEDICINAL PLANTS IN THE TREATMENT OF NEUROPATHIC PAIN RELIEF

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Abstract

Health care providers face a tremendous difficulty in dealing with the widespread, substantial, and disabling condition of chronic neuropathic pain. Although there are several pharmaceutical options, no standard treatment currently exists for neuropathic pain that is effective in the long-

term. The science of medication research has shifted its focus away from synthetic chemicals and toward herbal formulations in recent years. As a result, we evaluated all the available data regarding the effectiveness of herbal medicines and plants in relieving neuropathic pain. The beneficial effects of each plant are described, including their use in animal and human models of neuropathic pain. Additionally, the probable mechanisms contributing to the protective effects are investigated. Furthermore, the most well-studied mechanisms in herbal pain therapy include the antioxidant activity, anti-inflammatory, anti-apoptotic, neuroprotective, and calcium inhibitory actions. For the management of neuropathic pain, this article contains a list of TIMPs and isolated compounds that have shown promise in clinical trials. Researchers receive help in their search for a viable therapy for neuropathic pain.
Keywords: Medicinal plants, neuropathic pain, herbs, health care

Introduction

The unpleasant physical and emotional experience we call pain serves an important purpose in our daily lives: it alerts us to tissue injury so we may take preventative measures [1]. Acute pain is a self-limiting response to an injury and serves a beneficial biological purpose. However, chronic pain may qualify as an actual medical condition. When coupled with an illness or injury, it might prolong rehabilitation time [1, 2]. Pain that is a "direct result of a lesion or disease which affects the sensorimotor system" is what is meant by "chronic neuropathic pain" [3]. Depending on where the damage is located, we can classify it as either central or peripheral. Metabolic conditions, viruses, trauma, severe ischemia insults, and autoimmune disorders are among the leading causes of chronic neuropathic pain [4-6]. It is difficult to find an effective treatment for neuropathic pain because of its many causes and intricate pathophysiology. Furthermore, the undesirable side effect profiles of currently available medicines severely restrict their application [7].

When left untreated, chronic pain can have far-reaching effects on an individual's quality of life as well as on their community [8]. Addressing this public health crisis presents a major challenge for contemporary medicine everywhere. Inflammatory and neuropathic pain are two distinct types of chronic pain that are defined by their etiology. Common sensory abnormalities in neuropathic pain include dysesthesia, hyperalgesia, and allodynia. Brain or spinal cord trauma can induce intense neuropathic pain (PNS) [9-10]. People with chronic illnesses may be unable to do routine tasks. Since the source of neuropathic pain is in non-neural sick tissues, it is often distinguished from other types of pain. These so-called nociceptive pain entities include disorders like osteoarthritis and inflammatory pain caused by diseases like MS, diabetes, stroke, trauma, and cancer. Neuropathic pain is widespread in cancer patients due to peripheral nerve injury or as a side effect of several chemotherapy drugs [10-12]. There could be as many as eight percent of Europeans who are adversely impacted.

Mechanisms of neuropathic pain

Recent years have revealed many neuropathic pain pathways. Nociceptors become hypersensitive in herpes zoster, postherpetic neuralgia, and complicated regional pain syndrome. These neuropathic pain disorders illustrate pain's complexity. Nociceptors are found at the nerve terminals of unmyelinated C fibres and minimally myelinated Ad fibres [13]. Endogenous

peptides affect the activity of painful mechanical, thermal, or chemical sensors (CGRP). Localized mechanical stress triggers mechanosensitive nociceptors [14]. Lysophosphatidic acid (LPA) and other lipid metabolites have been linked to neuropathic pain [15]. The production of LPA after tissue injury causes it to act on G-protein coupled LPA receptors. Damage to the axon and myelin sheath of a peripheral neuron leads to Wallerian degeneration [16-17]. After this, macrophages and other immune cells will begin to invade the area (neutrophils, T cells). Hormones of growth and development and inflammatory mediators such interleukins, tumor necrosis factor alpha, bradykinin, and prostaglandins are released (nerve growth factor, NGF). Allodynia and hyperalgesia are facilitated by these modifications [18].

Additionally, neuropathic pain is accompanied by a change in intracellular signalling. Structural and functional modifications that sustain the pain feeling are mediated by a wide range of second messengers [19]. Most secondary metabolites found in nature, such flavonoids, terpenoids, and alkaloids, have intricate structural frameworks and engage in a wide range of biological functions. Pain is controlled by these secondary metabolites because of their antioxidant properties, their ability to alter protein kinase C activity [20-23], and their ability to alter neurotransmitter systems in the central nervous system, which aids in the control of neuropathic pain [24-26].

Because of its varied causes and intricate physiology, neuropathic pain is notoriously challenging to treat [27- 29]. As a result of their widespread adverse effects, they also pose a threat to patients [29]. As a result, neuropathies remain a significant obstacle for both clinical practice and fundamental research. Because of this, studying the causes and mechanisms of neuropathic pain and looking into other therapeutic options is crucial.

Although the past 50 years have seen an explosion in the number of synthetic medicines available due to advances in combinatorial chemistry and screening techniques, natural products derived from plants and herbal remedies, and the characterization of their structures, continue to play an essential role in modern pharmacopoeias [30]. Natural products (NPs) or their secondary metabolites could be effective in the treatment and development of novel medications for the management of neuropathic pain due to their higher safety profile. In reality, NPs have historically served as the backbone of most medicines [31, 32], making significant contributions to the field of drug discovery. Analgesics that are currently often used to alleviate pain include morphine and derivatives of acetyl salicylic acid derived from plants.

Studies on neuropathic pain in animals and/or the role of drugs in its production and transmission

The evaluation of new treatments for chronic pain and the investigation of the underlying molecular mechanisms of pain have both benefited greatly from the use of animal models of neuropathic pain [34]. List of animal models used to study neuropathic pain.

The streptozotocin (STZ)-induced diabetes

For diabetic neuropathy research, scientists produced a STZ-induced pain model. Diabetes-related neuropathy is characterised by hyperalgesia, cold or heat allodynia, and hyperesthesia.

This may be attributed to high blood glucose-related oxidative and nitrosative damage [35-37]. Nociceptors are affected by reactive oxygen species (ROS) in two ways: they become more sensitive to noxious stimuli and they begin responding to stimuli that would normally be below their threshold. This sensitivity in the periphery not only causes pain directly, but it also indirectly contributes to pain by generating central sensitization in the spinal cord [33, 38]. When superoxide and nitric oxide are present in large amounts, they react to generate peroxynitrite, which has been linked to peripheral nerve energy insufficiency and impaired motor and sensory nerve conduction in people with diabetes [33, 39].

High-fat diet

High-fat diets are related with an increase in sorbitol pathway activity, oxidative nitrosative stress, and pro-inflammatory alterations in the peripheral nervous system (PNS), which can lead to nerve conduction velocity impairments and small-fiber sensory neuropathy [40,41]. Impaired glucose tolerance (IGT) and type 2 diabetes have both benefited from this paradigm, which has aided in the discovery of novel therapeutic approaches [42].

Sciatic nerve injury due to neuropathy

As the symptoms of neuropathy in animals with a sciatic nerve injury are like those in humans with a similar lesion, these animals are effective experimental models of neuropathy. Central sensitization in this model is characterised by persistent changes in neurotransmitter and receptor expression in response to the release of different inflammatory and pain mediators, which in turn increases the sensitivity of peripheral sensory afferents at the site of injury and in the CNS [33].

Neuropathy caused by chemotherapeutic drugs

Peripheral neuropathy is a common side effect of several classes of anti-cancer medications, including antitubulins, platinum analogues, and proteasome inhibitors (CIPN). These medications can cause pain in patients in a variety of ways, both directly and indirectly affecting sensory nerves. This is especially true for patients who have experienced nociceptive sensory loss because of cancer treatment [43, 44].

Plants used in neuropathic pain

Many modern pharmaceuticals found their way into widespread usage thanks to the ethno medical knowledge of indigenous peoples. This means that plants, both in their isolated active chemical forms and their more unrefined, raw pharmaceutical forms, are described as a fundamental source of medicine. Here, we talk about certain conventional pain-relieving plants that have undergone scientific evaluation for their effectiveness against neuropathic pain, and we provide a table of relevant mechanistic studies.

Aconiti tuber

Many different varieties of Aconitum have been used medicinally and for poisoning arrow tips in several different cultures since prehistoric times [76]. Aconitine and other alkaloids found in Aconitum species are used medicinally despite being powerful neurotoxins. Aconitum (Ranunculaceae) plant extracts have been used medicinally for a long time as pain relievers, anti-

inflammatories, rheumatism treatments, and neuro-protectants. A common pain reliever in developing countries is the traditional Oriental herbal medication Processed *Aconiti tuber* (PAT) [77]. Multiple doses of PAT showed protection against sciatic nerve damage-induced neuropathic pain due to chronic constriction injury (CCI) [27]. Aconitine, mesaconitine, and hypaconitine are examples of the diterpene alkaloids responsible for their poisonous effects. Using heat or alkaline treatment, these deadly alkaloids are converted into benzoylaconine, aconine, and pyroaconine. To lessen their toxicity (neurotoxicity), tubers have recently been autoclaved, which has gained a lot of favor [77].

Acmella oleracea

Acmella oleracea (Linn.), a plant in the Asteraceae family, is commonly referred to as "jambu" because of the delicious and spicy flavor it adds to local dishes. The plant's yellow blossoms and foliage can make your tongue feel numb and tingle [78]. In traditional medicine, toothache relief is achieved by applying a paste made of leaves or flowers [79, 80]. These drugs also have other pharmacological effects, such as being local anesthetics, analgesics, antipyretics, anti-inflammatories, antioxidants, diuretics, and vaso-relaxants [81, 82]. The analgesic and anti-inflammatory properties of the lipophilic alkylamides or alkamides in this plant have been the subject of substantial research [80, 83-84]. One such alkylamide is spilanthol. Several observable behavioral characteristics [85] suggested that A. oleracea ethanol extract significantly mitigated the neuropathic pain induced by partial sciatic nerve ligation (PSNL). This plant was not found to be harmful.

Acorus calamus

Migraine, headache, physical discomfort, and inflammatory pain have all been treated with acorus calamus for a long time in Ayurvedic and Indian medicine. Researchers analysed the chemical makeup of the plant and isolated phytoconstituents. In addition to its sedative and hypotensive effects, this herb has numerous other uses, including as a carminative, expectorant, anti-fungal, psychedelic, and even a learning aid for the elderly [85, 86]. By numerous biochemical measures, A. calamus hydroalcoholic extract alleviated vincristine-induced neuropathic pain. The nociceptive pain threshold, sciatic functional, and biochemical abnormalities caused by CCI are also decreased by a plant extract high in saponin, and this effect is dose-dependent [87, 88]. The absence of morphological, biochemical, or behavioral alterations in wistar rats treated to an ethanolic extract of the plant provides conclusive evidence that the herb is non-toxic. The medicinal properties of this plant have also been widely recognized. This plant is toxic to humans since its primary ingredient, b-asarone, has been classified as a potent pesticide. Several countries, notably the USA, have explicitly banned it [88].

Alstonia scholaris

One of the traditional plants used to cure diarrhea, dysentery, malaria, fever, and cardiac and respiratory disorders is *Alstonia scholaris* (Linn.) R. Br. (Family Apocyanaceae) [89, 90]. In Hindi, it goes by the name Saptaparni. Its milky liquid can be applied to wounds and ulcers for pain relief, especially from rheumatic conditions [90]. This plant has been shown to be protective in several animal models of algesia and inflammation [91], including the formalin test and the air pouch model in rodents. The pharmacotherapeutic actions *of A. scholaris* are due to the presence

of alkaloids, coumarins, iridoids, flavonoids, leucoanthocyanines, steroids, tannins, phenolics, and saponins [92]. Physiological and behavioural alterations brought on by CCI are mitigated by a methanol extract of *A. scholaris* [92]. *A. scholaris* extract (ASE) was non-toxic at oral doses up to 2000 mg/kg; however, at intraperitoneal doses of 1100 mg/kg, organ damage occurred [93].

Butea monosperma

The Fabaceae species *Butea monosperma* prefers open areas, such as deciduous forests [94]. Muscle discomfort, joint pain, and severe headaches are commonly treated with a freshly produced decoction of *B. monosperma* in the Tamil Nadu and Madurai districts of India. An Ayurvedic concoction called Mahanarayanataila is taken for nerve pain [95]. Multiple biochemical assays confirmed that a dose-dependent protection against CCI and vincristine-induced neuropathic pain was provided by the ethanol extract of *B. monosperma*. For three months, rats were given an oral dose of 800 milligrams per kilogram of body weight (mg/kg bw) of the plant's seed powder. It is hazardous to rats because it changes the microstructure of many organs and the activity of numerous biochemical enzymes [96].

Cannabis sativa

There are more than 60 distinct cannabinoids, all of which are lipophilic chemicals extracted from Cannabis sativa. In terms of pharmacology, these phytocannabinoids cover a wide range, with components spanning full agonists to neutralizers of the cannabinoid receptor. A decrease in mechanical thermal pain sensitivity was observed after rats were given cannabis extract, suggesting that it helped treat the diabetic neuropathy caused by streptozotocin (STZ). The euphoric effects of the plant make it desirable for human consumption. The plant is rather harmless, with an LD50 of 3 g/kg. This plant's extract has been demonstrated to have varied effects on animals within 60 minutes. D-9-tetrahydrocannabinol [97] is the main psychoactive compound of this plant.

Crocus sativus

Saffron's primary biologically active compounds are picrocrocin, crocin, and safranal. Asthma, insomnia, pain, and cardiovascular disease are just few of the ailments for which saffron has been used traditionally as a treatment [35]. Changes in behavior caused by CCI-induced neuropathic pain were significantly reduced when ethanol, aqueous extract, and safranal were administered [35]. Even at high doses, this plant was shown to be barely hazardous to humans. There is no evidence that this plant is hazardous, according to the trials performed by several researchers [98].

Curcuma longa

The phenolic component curcumin, found in the spice *Curcuma longa*, is well-known. Animal studies have shown that it possesses analgesic properties, but the precise mechanisms responsible for this effect are still unclear [99]. Mechanical and thermal allodynia were greatly reduced and altered biochemical alterations in CCI-induced neuropathic pain were recovered after administration of curcumin [98]. As an extract, this medicinal herb has been shown to be safe for

use in guinea pigs, monkeys, and rats. However, curcumin, a molecule extracted from it, is dose-dependently poisonous [99].

Ecklonia cava

Edible brown seaweed, also known as Ecklonia cava, is widely harvested in Korea. It's a common component of many different products, including food, animal feed, and fertilizer. Treatment with *E. cava* extract markedly alleviated SNI-induced neuropathic pain, as evidenced by hyposensitive reactions. Even at 2000 mg/kg body weight, a single intake of this plant's extract did not cause any harm. Also, no biochemical or histological changes were seen after repeated dosing with this plant extract over a period of 4 weeks [100].

Emblica officinalis

Emblica officinalis is a potent natural antioxidant that is rich in helpful elements like minerals, vitamin C, and amino acids. Due to its high polyphenol content, it has numerous potential medical uses. *E. officinalis* aqueous extract considerably reduced STZ-induced diabetic neuropathy's behavioral and biochemical abnormalities and molecular modifications in a dose-dependent manner. Toxicity tests conducted on this plant over both short and long time periods found no evidence of biochemical or structural toxicity. Research on the safety of this vital medicinal herb has increased over the years [101].

Euphorbia tirucalli

Euphorbia tirucalli, which is a member of the Euphorbiaceae family. Latex has been used as a type of traditional medicine in Brazil for generations, and it is still widely used today. The tetracyclic triterpene alcohol euphol is the primary component of the plant's sap. The plant's bark also had anti-herpetic, anti-mutagenic, and molluscicidal properties. According to research, euphol prevents the production of inflammatory pain by controlling the endocannabinoid system and thereby inhibiting monoacylglycerol lipase (MGL) activity. Euphol treatment in a PSNL-induced neuropathic pain paradigm reduced mechanical hyperalgesia and reversed the metabolic alterations that had been generated. This plant's latex is extremely poisonous. As a result of its tendency to damage B cells and cause Burkitt's lymphoma, it can weaken the immune system. In addition, the latex of this plant reportedly had acute keratoconjunctivitis [102].

Gelsemium elegans

The Loganiaceae family, of which *Gelsemium elegans* (Benth.) is a member, are responsible for the hazardous plant that is native to southeast Asia. It's a favorite among the hill tribes because it thrives in the altitude. The use of G. elegans in Chinese medicine dates back centuries [103]. Extracts of the worm *C. elegans* have been shown to have analgesic and anti-inflammatory properties in animal tests. Gelsenicine and koumine, two substances derived from *G. elegans*, were used to reduce CCI- and PSNL-induced neuropathic pain and ameliorate inflammatory pain. Among the hilltribes of Southeast Asia, the suicide method of choice is the ingestion of this plant's very toxic substance. This plant's extract is toxic and can lead to respiratory failure and convulsions [104].

Ginkgo biloba

For thousands of years, people have turned to *ginkgo biloba* as a natural cure for a variety of health issues. There are a lot of flavone glycosides in it, and those are the compounds that have been associated to anti-inflammatory and free radical-scavenging properties [105]. In a rat model of acute inflammatory pain caused by formalin, carrageenan, and surgical incision, it was discovered to display anti-inflammatory and analgesic effects [106, 107]. The treatment of *G. biloba* extract markedly reduced mechanical hyperalgesia and cold allodynia and restored levels of antioxidant enzymes in patients with vincristine- and streptozotocin-induced diabetic neuropathy. This plant is often used as a blood-flow booster because of its medicinal value as a herbal remedy. Toxicological studies in male and female rats and mice confirmed the carcinogenic potential of this plant extract [108].

Hygrophila spinosa

It is a weed found in wet areas such as along the edges of tanks and ditches and in rice fields. Aphrodisiac, pain reliever, and malaria remedy are only few of the ancient uses for this plant [109]. In addition to its nervine tonic properties, the seeds also have hypoglycemic and antioxidant activities [110, 111]. With STZ-induced diabetic neuropathy, H. spinosa methanol extract treatment improved pain threshold and decreased sciatic nerve lipid peroxides. Even at 2000 mg/kg, this herb proved not harmful to rats [112].

Harpagophytum procumbens

Devil's claw, or *Harpagophytum procumbens*, is a medicinal plant native to South Africa's Kalahari Desert [113]. Some studies have shown that *H. procumbens* can reduce inflammation, both acute and chronic [114, 115]. Mechanical withdrawal threshold hypersensitivity responses caused by SNI-induced neuropathic pain were significantly reduced by *H. procumbens* ethanol extract. There was little evidence of harm at either the low or high doses tested for this plant extract. No harm was found in either the acute or chronic investigation in mice, as measured by biochemical parameters and histological analysis [116].

Momordica charantia

Momordica charantia, a member of the Cucurbitaceae family, is a highly promising therapeutic vegetable crop. The karela vegetable is known by several other names. The oil extracted from the seeds has been shown to help with the discomfort associated with rheumatoid arthritis, spondylitis, and diabetic neuropathy [117, 118]. Its effectiveness in suppressing acetic acid-induced writhings in mice has been demonstrated in subsequent studies [119]. The preventive effect of *M. charantia* extract was demonstrated by its ability to reduce the behavioral and biochemical changes associated with vincristine-induced neuropathic pain. Based on what we can tell from reviewing the available research, the plant extract has very little to no toxicity. The liver is a crucial organ, and according to toxicity studies, a dose of 2000 mg/kg bw of the plant extract causes a change in liver weight [120].

Nauclea latifolia

Behavioral difficulties in children with mental retardation, cerebral malaria, and nerve diseases like anxiety, sadness, and epilepsy are all treated with *Nauclea latifolia*, a traditional herbal remedy [121, 123]. The roots of *N. latifolia*, when brewed into a decoction, have been proven to reduce symptoms of inflammation, headache, neuropathic pain, and fever [122-125]. The alkaloid component of *N. latifolia* greatly decreased heat hyperalgesia and cold allodynia in rats with neuropathic pain due to CCI of the sciatic nerve. The toxicity of this plant was evaluated at 3200 mg/kg bw, and no toxicity was detected [126].

Ocimum sanctum

Tulsi, or *Ocimum sanctum* (Linn.), is a popular plant in India. Animal studies have shown that it protects against ischemic brain injury, ischemia-reperfusion injury, and cardiac damage. Antiulcer, anti-diabetic, chemoprotective, anti-giardiac, anti-anxiety, and anti-stress properties of O. sanctum have also been documented [127, 128]. Several measures of pain relief, including assessments of behavior, oxidative stress, and calcium levels, all pointed plant extract as effective treatments for neuropathic pain. Studies in mice showed no evidence of acute or subacute toxicity at the doses used in these studies [129].

Olea europaea

The leaves of the plant, in addition to the oil, were included in the Pharmacopoeia because of their therapeutic value. High blood pressure and diabetes are treated with olive oil and olive leaves in several traditional cultures [130]. Oleuropein and its derivatives, including hydroxytyrosol and tyrosol, are responsible for the pharmacological actions of the leaves. Treatment with O. europaea (OLE) ethanol extract reduced hyperalgesia in STZ-induced diabetic neuropathy by decreasing the Bax/Bcl2 ratio and inhibiting caspase 3 activation. Moreover, OLE showed strong antioxidant capacity. Preliminary results from an animal study show that this herb is safe for human consumption.

Paederia scandens

There is a long history of using *Paederia scandens* as an analgesic and anti-inflammatory in East Asia. *Paederia scandens* MERRILL is a member of the family Rubiaceae, which has been approved by the FDA as GRAS (generally recognised as safe) for use in food and drugs. *P. scandens* main mechanism of action is an iridoid glycoside [131]; this group of compounds includes paederoside, scandoside, and asperuloside. SNI-induced mechanical hypersensitivity in neuropathic pain was reduced by treatment with iridoid glycoside from *P. scandens*.

Phyllanthus amarus

There are around 600 species of Phyllanthus (Euphorbiaceae), and they can be found across the tropics and subtropics. Based on pharmacological evidence [132-134], *Phyllanthus amarus* extracts may inhibit hepatitis B and related hepatitis virus DNA polymerase. Recent research suggests that *P. amarus* extracts can inhibit HIV-1 replication in HeLa CD4+ cells [135]. The progression of hepatocellular carcinoma has also been shown to be slowed when *P. amarus* extract was given orally with a carcinogen [136]. In mice, the hydroalcholic extract of *P. amarus* prevented the inflammatory and noxious effects of acetic acid, formalin, and capsaicin in a dose-

dependent manner [137,138]. Hypophyllantin, phyllantin, nirantin, nirtetralin, and phyloetralin are only a few of the lignans that have been identified thanks to extensive phytochemical analysis. *P. amarus* hexane extract and lignin fraction reduced mechanical allodynia and restored normal myeloperoxidase levels. Rats given an aqueous extract of *Phyllanthus amarus* showed various degrees of renal injury after treatment. Tubular necrosis, renal inflammation, and vascular enlargement can be seen in the animal's kidneys [139].

Pleurotus pulmonarius

There are several commercially grown Pleurotus species in China since the genus includes both edible and medicinal species. Recent research on hepatocellular cancer in mice has found that polysaccharides and extracts from the *Pleurotus pulmonarius* mushroom have anticarcinogenic action [140-142]. *P. pulmonarius* is useful in treating allergic rhinitis [143]. Mechanical allodynia following partial sciatic nerve ligation was reversed with GL therapy.

Punica granatum

Pomegranate, or *Punica granatum* (Linn.), is an edible ancient fruit that is a member of the Punicaceae family. Traditional Chinese medicine uses it as an astringent for parasite eradication, as well as an antipyretic and analgesic [144, 145]. It is also used in cooking. Pomegranate has several pharmacological and biological properties, such as those that fight free radicals [146], inflammation [144], diarrhea [145], tumors [147], hepatotoxicity [148], worms [149], lipoperoxidation [150], ulcers [151], and bacteria. According to the literature review, there were no reports of this plant being poisonous. Numerous experiments conducted by various researchers have confirmed the plant's safety.

Senna spectabilis

Studies on a wide variety of Senna and Cassia species have revealed the presence of many phenolic compounds with diverse biological and pharmacological action [152, 153]. *Senna spectabilis* flowers, fruits, and leaves are the primary source of the piperidine alkaloid known as (-)-cassine. Similar to other Senna and Cassia-derived heterocyclic amines, (-)-cassine's longaliphatic substituents give it a wide range of pharmacological properties.

Thymus caramanicus

Caramanicus thymus known as jalas (TCJ) is native to Iran, where it grows wild in a wide range of soil and climate conditions. The leaves of this plant have been used medicinally for centuries to treat anything from diabetes and rheumatism to skin disorders and bacterial infections [154]. Damage and apoptosis in PC12 cells brought on by excessive glucose were reduced by the hydro ethanol extract of *T. caramanicus* (TCJ). Also, in STZ-induced diabetic neuropathy, TCJ extract reduced hyperalgesia and prevented spinal apoptosis.

Nigella sativa

Ranunculaceae family member and annual bloomer *N. sativa* [155, 156]. The percentage of volatile oil is between 0.4% and 0.45%, while the percentage of fixed oil is over 30%. The thymoquinone (TQ) content of the volatile oil is 18.4%-24%. [157, 158]. A combination of N.

sativa and TQ significantly decreased high serum glucose and enhanced low serum insulin concentration. Along with that, they boosted the number of insulin-reactive -cells. TQ and *N. sativa* improved diabetes animal models in terms of histopathological assessment of tissues, showing less morphologic changes [158]. The oxidative and apoptotic consequences of neuropathic pain in CCI rats were reduced and their behavioral symptoms were dramatically improved after TQ treatment, according to another study [159]. Tewari et al. found that *N. sativa* significantly alleviated the neuropathic pain caused by cisplatin in mice [160].

Isolated natural compounds active against neuropathic pain
Goshajinkigan

As a complex drug, TJ-107 (Goshajinkigan) is highly recommended in Japan for the treatment of diabetic peripheral neuropathy symptoms as tingling, numbness, and paresthesias/dysesthesia. It contains ten distinct kinds of therapeutic herbs. Patients with colorectal cancer who were given TJ-107 orally in a randomised, double-blind, placebo-controlled trial showed promise in preventing or delaying the onset of oxaliplatin-induced peripheral neurotoxicity. Patients with type 2 diabetes who took Goshajinkigan over an extended period of time saw improvements in their macrovascular illnesses, retinopathy, or nephropathy, according to the results of a randomized, open-labeled clinical research [174].

Lappaconitine

Aconitum has been utilized in various forms since ancient times. The pharmacological effects of aconitine and similar alkaloids from Aconitum species included analgesic and anti-inflammatory properties [170, 171]. The aconitum alkaloid lappaconitine (LA) is harvested from the Aconitum plant's roots. Analgesic use of LA dates back centuries, particularly in China and Japan [172]. CCI-induced nociceptive behaviors in rats were suppressed by LA administration, which also reduced P2X3 receptor expression in DRG neurons and decreased the rapid IATP and Ia,-meATP [173].

Koumine

Gelsemium (G. elegans Benth.) has been used in traditional Chinese medicine for millennia to relieve pain, inflammation, and even cancer [175]. Gelsemium contains the alkaloid koumine [176]. STZ-induced diabetic rats had reduced tactile allodynia, sensory nerve conduction, and sciatic nerve pathology [177]. In rats with chronic constriction injury, koumine relieved heat hyperalgesia and mechanical allodynia better than gabapentin [176].

Quercetin

The phenolic chemical quercetin is found in many different plant species. Berrys, onions, apples, tea, and brassica vegetables are also good sources. Multiple therapeutic effects of quercetin on human health have been identified, including protection against cardiovascular disease and inflammation. After receiving quercetin, the tail-flick latencies of both diabetic and non-diabetic mice significantly increased. The opioid receptor antagonist naloxone reversed quercetin's elevated nociceptive threshold in both non-diabetic and diabetic rats. Quercetin's protective effect in STZ-induced diabetic mice most likely occurred through the modulation of opioidergic

pathway. Quercetin, according to another study, can protect Schwann cells against autophagy damage brought on by excessive glucose.

Genistein

As a replacement therapy for endogenous estrogens in hormonal diseases, neurological illnesses, inflammation, and pain, soy isoflavones have recently drawn the interest of various researchers. Soybeans contain the isoflavone genistein, a natural phytoestrogen. Inhibition of tyrosine kinases in general and estrogen receptors in particular. Recent years have seen a surge in interest in the possible neuroprotective effects of phytoestrogens in neurodegenerative disorders including Alzheimer's disease and ischaemia [178, 179].

Luteolin

The flavone luteolin is abundant in many edible and medicinal plants. Antioxidant, anticarcinogenic, and anti-inflammatory are only some of the many biological and pharmacological activities ascribed to it. [180, 181]. Lutein also demonstrated anticonvulsant, depressive, anxiolytic, and sedative effects.

Mangiferin

Higher plants, such as the Anacardiaceae family's Mangifera indica, contain the glucosylxanthone known as mangiferin (MG) (Linn.). There are several different biological actions [182-184] associated with the chemical, which explain why it is so often utilized in alternative medicine. Although glutamate causes neurotoxicity, MG has been shown to have neuroprotective characteristics [185, 186].

Naringin

Grape fruit and other citrus fruits contain the natural flavonoid naringin (40,5,7-trihydroxyflavanone-7-rhamnoglucoside) [187]. It can chelate metals, neutralize oxidants, and neutralize free radicals [188]. Data from experiments show that naringin is effective against cancer, inflammation, and even protects the heart [189]. It has been shown to reduce blood sugar and boost plasma insulin levels in rats with streptozotocin-induced diabetes [190,191].

Silibinin

Silymarin is a complex chemical derived from milk thistle seeds (Silybum marianum). Silibinin inhibits heme-mediated oxidative alteration of low density lipoproteins and neutrophil O2 generation [192, 193].

Oxymatrine

Oxymatrine (OMT) was found in *Sophora flavescens* plant roots. OMT protects neurons by inhibiting NR2B-containing NMDAR activity [194]. OMT reduces GAT-1 expression and increases $GABA_A$ Ra2 expression, causing neuropathic pain [195].

Tormentine

Hyptis capitata, *Ocotea suaveloens*, *Desfontainia spinosa*, and *Vochysia divergens* (Pohl) contain tormentic acid [196-199]. Acetic acid and formalin stimulate acute visceral, neurogenic, and inflammatory pain responses in rats, whereas *O. suaveolens* extract and tormentic acid from plant stem bark reduce these reactions [200].

Conclusion

Among the various kinds of pain, neuropathic pain is extremely difficult to relieve. Our inadequate knowledge of the processes underlying the development and maintenance of neuropathic pain makes its management a pressing therapeutic concern. Conventional drugs used to treat neuropathic pain have undesirable side. Researchers turned to traditional medicinal plants in their search for a viable pharmacological therapy for neuropathic pain. Herbs discussed here have a long history of usage as pain relievers and inflammation fighters, both in conventional medicine and in alternative and complementary treatment modalities. They are also tested pharmaceutically for their efficacy in relieving neuropathic pain. This analysis provides context, compiles the Indian medicinal herbs and isolated compounds that have shown promise in treating this painful brain disorder, and contributes to the ongoing quest to identify an effective innovative treatment agent for neuropathic pain.

References

1. Wang LX, Wang ZJ. Animal and cellular models of chronic pain. Adv Drug Deliv Rev 2003;55:949-965.
2. Razavi BM, Hosseinzadeh H. A review of the role of orexin system in pain modulation. Biomed Pharmacother2017; 90:187-193.
3. Treede RD, Jensen TS, Campbell J, Cruccu G, Dostrovsky J, Griffin J, et al. Neuropathic pain redefinition and a grading system for clinical and research purposes. Neurology 2008; 70:1630-1635.
4. Mulla SM, Buckley DN, Moulin DE, Couban R, Izhar Z, Agarwal A, et al. Management of chronic neuropathic pain: a protocol for a multiple treatment comparison meta-analysis of randomised controlled trials. BMJ open. 2014; 4(11):e006112.
5. Gilron I, Watson CPN, Cahill CM, Moulin DE. Neuropathic pain: a practical guide for the clinician. Can Med Assoc J 2006;175:265-275.
6. Forouzanfar F, Amin B, Ghorbani A, Ghazavi H, Ghasemi F, Sadri K, et al. New approach for the treatment of neuropathic pain: Fibroblast growth factor 1 gene-transfected adiposederived mesenchymal stem cells. Eur J Pain 2018; 22:295-310.
7. Quintans JS, Antoniolli AR, Almeida JR, Santana-Filho VJ, Quintans-Junior LJ. Natural Products Evaluated in Neuropathic Pain Models-A Systematic Review. Basic Clin PharmacolToxicol2014; 114:442-450.
8. P.O. Nguelefeck, R.C. Dutra, F.A. Paszcuk, E.L. Andrade, L.A. Tapondjou, J.B. Calixto, Antinociceptive activities of the methanol extract of the bulbs of Dioscoreabulbifera L. var

sativa in mice is dependent of NO–cGMP–ATPsensitive – K+ channel activation, J. Ethnopharmacol. 128 (2010) 67–574.

9. A.Z. Burakgazi, W. Messersmith, D. Vaidya, P. Hauer, A. Hoke, M. Polydefkis, Longitudinal assessment of oxaliplatin-induced neuropathy, Neurology 77 (2011) 980–986.
10. K.E. Schmader, Epidemiology and impact on quality of life of postherpetic neuralgia and painful diabetic neuropathy, Clin. J. Pain. 18 (2002) 350–354.
11. L. Werhagen, C.N. Budh, C. Hultling, C. Molander, Neuropathic pain after traumatic spinal cord injury relations to gender, spinal level, completeness, and age at the time of injury, Spinal Cord 42 (2004) 665–673.
12. S. Verma, L. Estanislao, D. Simpson, HIV-associated neuropathic pain: epidemiology, Pathophysiology and management, CNS Drugs 19 (2005) 325– 334.
13. D. Julius, A.I. Basbaum, Molecular mechanisms of nociception, Nature 413 (2001) 203–210.
14. R. Schmidt, M. Schmelz, C. Forster, M. Ringkamp, E. Torebjork, H. Handwerker, Novel classes of responsive and unresponsive C nociceptors in human skin, J. Neurosci. 15 (1995) 333–341.
15. H. Ueda, Peripheral mechanisms of neuropathic pain involvement of lysophosphatidic acid receptor-mediated demyelination, Mol. Pain. 4 (2008) 11.
16. G. Moalem, D.J. Tracey, Immune and inflammatory mechanisms in neuropathic pain, Brain Res. Rev. 51 (2) (2006) 240–264.
17. J. Scholz, C.J. Woolf, The neuropathic pain triad: neurons, immune cells and glia, Nat. Neurosci. 10 (2007) 1361–1368.
18. C. Sommer, M. Kress, Recent findings on how proinflammatory cytokines cause pain: peripheral mechanisms in inflammatory and neuropathic hyperalgesia, Neurosci. Lett. 361 (2004) 184–187.
19. T. Hucho, J.D. Levine, Signaling pathways in sensitization: toward a nociceptor cell biology, Neuron 55 (2007) 365–376.
20. M. Anjaneyulu, K. Chopra, Quercetin a bioflavonoid, attenuates thermal hyperalgesia in a mouse model of diabetic neuropathic pain, Prog. Neuropsychopharmacol. Biol. Psychiatry. 27 (2003) 1001–1005.
21. F.C. Meotti, F.C. Missau, J. Ferreira, M.G. Pizzolatti, C. Mizuzaki, C.W. Nogueira, Anti-allodynic property of flavonoid myricitrin in models of persistent inflammatory and neuropathic pain in mice, Biochem. Pharmacol. 72 (2006) 1707–1713.
22. M. Anjaneyulu, K. Chopra, Quercetin attenuates thermal hyperalgesia and cold allodynia in STZ-induced diabetic rats, Indian J. Exp. Biol. 42 (2004) 766– 769.
23. T. Hagenacker, I. Hillebrand, A. Wissmann, D. Busselberg, M. Schafers, Antiallodynic effect of the flavonoid myricetin in a rat model of neuropathic pain: involvement of p38 and protein kinase C mediated modulation of Ca (2+) channels, Eur. J. Pain 14 (2010) 992–998.
24. P.A. Batista, M.F. Werner, E.C. Oliveira, L. Burgos, P. Pereira, L.F. Brum, Evidence for the involvement of ionotropic glutamatergic receptors on the antinociceptive effect of ()-linalool in mice, Neurosci. Lett. 440 (2008) 299–303.
25. D.F. Lima, M.S. Brandão, J.B. Moura, F.A. Leitão, L.M. Miúra, Antinociceptive activity of the monoterpene a-phellandrene in rodents: possible mechanisms of action, J. Pharm. Pharmacol. 64 (2012) 283–292.

26. T. Sakurada, H. Mizoguchi, H. Kuwahata, S. Katsuyama, T. Komatsu, L.A. Morrone, Intraplantar injection of bergamot essential oil induces peripheral antinoci-ception mediated by opioid mechanism, Pharmacol. Biochem. Behav. 97 (2001) 436–443.
27. B. Amin, H. Hosseinzadeh, Evaluation of aqueous and ethanolic extracts of saffron, Crocus sativus L., and its constituents, safranal and crocin in allodynia and hyperalgesia induced by chronic constriction injury model of neuropathic pain in rats, Fitoterapia 83 (2012) 888–895.
28. M. Zimmerman, Pathobiology of neuropathic pain, Eur. J. Pharmacol. 429 (2001) 423–437.
29. C.J. Woolf, R.J. Mannion, Neuropathic pain aetiology, symptoms, mechanisms and management, Lancet 353 (1999) 1959–1994.
30. L.T. Okogun, W.R. Folk, 21 st century natural product research and drug development and traditional medicines, Nat. Prod. Rep. 30 (2013) 584–592.
31. M.S. Butler, Natural products to drugs: natural product-derived compounds in clinical trials, Nat. Prod. Rep. 25 (2008) 475–516.
32. J.W. Li, J.C. Drug, discovery and natural products: end of an era or an endless frontier? Science 325 (2009) 161–165.
33. Quintans JS, Antoniolli AR, Almeida JR, Santana-Filho VJ, Quintans-Junior LJ. Natural Products Evaluated in Neuropathic Pain Models-A Systematic Review. Basic Clin PharmacolToxicol2014; 114:442-450.
34. Mogil JS, Davis KD, Derbyshire SW. The necessity of animal models in pain research. Pain 2010; 151:12-17.
35. Mabley JG, Soriano FG. Role of nitrosative stress and poly (ADP-ribose) polymerase activation in diabetic vascular dysfunction. CurrVascPharmacol2005; 3:247-252.
36. Tiwari V, Kuhad A, Chopra K. Emblica officinalis corrects functional, biochemical and molecular deficits in experimental diabetic neuropathy by targeting the oxido-nitrosative stress mediated inflammatory cascade. Phytother Res 2011; 25:1527- 1536.
37. Drel VR, Pacher P, Vareniuk I, Pavlov I, Ilnytska O, Lyzogubov VV, et al. A peroxynitrite decomposition catalyst counteracts sensory neuropathy in streptozotocin-diabetic mice. Eur J Pharmacol2007; 569:48-58.
38. Wang ZQ, Porreca F, Cuzzocrea S, Galen K, Lightfoot R, Masini E, et al. A newly identified role for superoxide in inflammatory pain. J Pharm Exp Ther2004; 309:869-878.
39. Vincent AM, Brownlee M, Russell JW. Oxidative stress and programmed cell death in diabetic neuropathy. Ann N Y Acad Sci 2002; 959:368-383.
40. Watcho P, Stavniichuk R, Ribnicky DM, Raskin I, Obrosova IG. High-fat diet-induced neuropathy of prediabetes and obesity: effect of PMI-5011, an ethanolic extract of Artemisia dracunculus L. Mediators Inflamm 2010; 2010:268547.
41. Ozay R, Uzar E, Aktas A, Uyar ME, Gürer B, Evliyaoglu O, et al. The role of oxidative stress and inflammatory response in high-fat diet induced peripheral neuropathy. J Chem Neuroanat2014; 55:51-57.
42. Winzell MS, Ahrén B. The high-fat diet–fed mouse a model for studying mechanisms and treatment of impaired glucose tolerance and type 2 diabetes. Diabetes 2004; 53:S215-S219.
43. Schroder S, Beckmann K, Franconi G, Meyer-Hamme G, Friedemann T, Greten HJ, et al. Can medical herbs stimulate regeneration or neuroprotection and treat neuropathic pain in

chemotherapy-induced peripheral neuropathy? Evid Based Complement Alternat Med 2013; 2013:423713.

44. Jaggi AS, Singh N. Mechanisms in cancer-chemotherapeutic drugs-induced peripheral neuropathy. Toxicology 2012; 291:1-9.
45. H. Xu, H. Arita, M. Hayashida, L. Zhang, H. Sekiyama, K. Hanaoka, Painrelieving effects of processed Aconiti tuber in CCI-neuropathic rats, J. Ethnopharmacol. 103 (2006) 392–397.
46. E.C.O. Nomura, M.R.A. Rodrigues, C.F. da Silva, L.A. Hamma, A.M. Nascimento, L.M. de Souza, T.R. Cipriani, C.H. Baggio, M.F. de Paula Werner, Antinociceptive effects of ethanolic extract from the flowers of Acmella oleracea (L.) R.K., Jansen in mice, J. Ethnopharmacol. 150 (2013) 583–589.
47. A. Muthuraman, N. Singh, A.S. Jaggi, Protective effect of Acorus calamus L. in rat model of vincristine induced painful neuropathy: an evidence of anti-inflammatory and anti-oxidative activity, Food Chem. Toxicol. 49 (2011) 2557–2563.
48. A. Muthuraman, N. Singh, Neuroprotective effect of saponin rich extract of Acorus calamus L. in rat model of chronic constriction injury (CCI) of sciatic nerve-induced neuropathic pain, J. Ethnopharmacol. 142 (2012) 723–731.
49. M.S. Khyade, N.P. Vaikos, Phytochemical and antibacterial properties of leaves of Alstoniascholaris R. Br, Afr. J. Biotech. 8 (2009) 6434–6436.
50. V.R.K. Thiagarajan, P. Shanmugam, U.M. Krishnan, A. Muthuraman, N. Singh, Ameliorative potential of Butea monosperma on chronic constriction injury of sciatic nerve induced neuropathic pain in rats, An. Acad. Bras. Cienc. 84 (4) (2012) 1091–1104.
51. V.R.K. Thiagarajan, P. Shanmugam, U.M. Krishnan, A. Muthuraman, N. Singh, Antinociceptive effect of Butea monosperma on vincristine-induced neuropathic pain model in rats, Toxicol. Ind. Health. 29 (1) (2012) 3–13.
52. F. Comelli, I. Bettoni, M. Colleoni, G. Giagnoni, B. Costa, Beneficial effects of a Cannabis sativa extract treatment on diabetes-induced neuropathy and oxidative stress, Phytother. Res. 23 (2009) 1678–1684.
53. B. Amin, H. Hosseinzadeh, Evaluation of aqueous and ethanolic extracts of saffron, Crocus sativus L., and its constituents, safranal and crocin in allodynia and hyperalgesia induced by chronic constriction injury model of neuropathic pain in rats, Fitoterapia 83 (2012) 888–895.
54. X. Zhaoa, Y. Xuc, Q. Zhaod, C.R. Chena, A. Liub, Z. Huang, Curcumin exerts antinociceptive effects in a mouse model of neuropathic pain: descending monoamine system and opioid receptors are differentially involved, Neuropharmacology 62 (2012) 843–854.
55. J.G. Kim, W.D. Lim, S. Cho, D. Han, Y.T. Kim, The edible brown seaweed Ecklonia cava reduces hypersensitivity in postoperative and neuropathic pain models in rats, Molecules 19 (2014) 7669–7678.
56. V. Tiwari, A. Kuhad, K. Chopra, Emblica officinalis corrects functional, biochemical and molecular deficits in experimental diabetic neuropathy by targeting the oxido-nitrosative stress mediated inflammatory cascade, Phytother. Res. 25 (2011) 1527–1536.
57. R.C. Dutra, K.A.B.S. da Silva, A.F. Bento, R. Marcon, A.F. Paszcuk, F.C. Meotti, L.F. Pianowski, J.B. Calixto, Euphol, a tetracyclic triterpene produces antinociceptive effects in

inflammatory and neuropathic pain: the involvement of cannabinoid system, Neuropharmacology 63 (2012) 593– 605.

58. M. Liu, J. Shen, H. Liu, Y. Xu, Y. Su, J. Yang, C. Yu, Gelsenicine from Gelsemium elegans attenuates neuropathic and inflammatory pain in mice, Biol. Pharm. Bull. 34 (2011) 1877–1880.
59. Y. Xu, H. Qiu, H. Liu, M. Liu, Z. Huang, J. Yang, Y. Su, C. Yu, Effects of koumine an alkaloid of Gelsemium elegans Benth., on inflammatory and neuropathic pain models and possible mechanism with allopregnanolone, Pharmacol. Biochem. Behav. 101 (2012) 504–514.
60. R. Taliyan, P.L. Sharma, Protective effect and potential mechanism of Ginkgo biloba extract EGb 761 on STZ-induced Neuropathic Pain in Rats, Phytother. Res. 26 (2012) 1823–1829.
61. H.J. Park, H.G. Lee, Y.S. Kim, J.Y. Lee, J.P. Jeon, C. Park, D.E. Moon, Ginkgo biloba extract attenuates hyperalgesia in a rat model of vincristine-Induced peripheral, Neuropathy. Anesth. Analg. 15 (2012) 1228–1233.
62. V.S. Thorve, A.D. Kshirsagar, N.S. Vyawahare, P.A. Thakurdesai, A.M. Bhandare, H. spinosa T. anders ameliorates diabetic neuropathy in wistar albino rats, J. Complement. Integ. Med. 9 (2012).
63. D.W. Lim, J.G. Kim, D. Han, Y.T. Kim, Analgesic effect of Harpagophytum procumbens on postoperative and neuropathic pain in rats, Molecules 19 (2014) 1060–1068.
64. V. Jain, A. Pareek, Y. Ratan, N. Singh, Standardized fruit extract of Momordica charantia L protect against vincristine induced neuropathic pain in rats by modulating GABAergic action, antimitotoxic NOS inhibition, antiinflammatory and antioxidative activity, S. Afr. J. Bot. 97 (2015) 123–132.
65. G.S. Taiwe, E.N. Bum, E. Talla, T. Dimo, A. Dawe, V. Sinniger, B. Bonaz, A. Boumendjel, M.D. Waard, Nauclea latifolia Smith (Rubiaceae) exerts antinociceptive effects in neuropathic pain induced by chronic constriction injury of the sciatic nerve, J. Ethnopharmacol. 151 (2014) 445–451.
66. G. Kaur, A.S. Jaggi, N. Singh, Exploring the potential effect of Ocimum sanctum in vincristine-induced neuropathic pain in rats, Brachial Plex. Peripher. Nerve Inj. 5 (2010) 3.
67. A. Kaeidi, S. Esmaeili-Mahani, V. Sheibani, M. Abbasnejad, B. Rasoulian, Z. Hajializadeh, S. Afrazi, Olive (Olea europaea L.) leaf extract attenuates early diabetic neuropathic pain through prevention of high glucose-induced apoptosis: in vitro and in vivo studies, J. Ethnopharmacol. 136 (2011) 188– 196.
68. M. Liu, L. Zhou, Z. Chen, C. Hu, Analgesic effect of iridoid glycosides from Paederia scandens (LOUR.) MERRILL (Rubiaceae) on spared nerve injury rat model of neuropathic pain, Pharmacol. Biochem. Behav. 102 (2012) 465–470.
69. C.A.L. Kassuya, A.A. Silvestre, V.L.G. Rehder, J.B. Calixto, Anti-allodynic and anti-oedematogenic properties of the extract and lignans from Phyllanthus amarus in models of persistent inflammatory and neuropathic pain, Eur. J. Pharmacol. 478 (2003) 145–153.
70. C.H. Baggio, C.S. Freitas, D.F. Martins, L. Mazzardo, F.R. Smiderle, G.L. Sassaki, M. Lacomini, M.C.A. Marques, A.R.S. Santos, Antinociceptive effects of (1/3), (1/6)-linked b-glucan isolated from Pleurotuspulmonarius in models of acute and neuropathic pain in mice: evidence for a role for glutamatergic receptors and cytokine pathways, J. Pain. 11 (2010) 965–971.

71. V. Jain, A. Pareek, Y.R. Bhardwaj, N. Singh, Attenuating effect of standardized fruit extract of Punica granatum L in rat model of tibial and sural nerve transection induced neuropathic pain, BMC Complement. Alt. Med. 13 (2013) 274.
72. K.A.B.S. da Silva, M.N. Manjavachi, A.F. Paszcuk, M. Pivatto, C. Viegas Jr., V.S. Bolzani, J.B. Calixto, Plant derived alkaloid (_)-cassine induces antiinflammatory and anti-hyperalgesics effects in both acute and chronic inflammatory and neuropathic pain models, Neuropharmacology 62 (2012) 967–977.
73. N. Galeotti, E. Vivoli, A.R. Bilia, F.F. Vincieri, C. Ghelardini, St John's Wort reduces neuropathic pain through a hypericin-mediated inhibition of the protein kinase C, F and e activity, Biochem. Pharmacol. 79 (2010) 1327–1336.
74. Z. Hajializadeh, S. Nasri, A. Kaeidi, V. Sheibani, B. Rasoulian, S. EsmaeiliMahani, Inhibitory effect of Thymus caramanicusJalas on hyperglycemiainduced apoptosis in vitro and in vivo models of diabetic neuropathic pain, J. Ethnopharmacol. 153 (2014) 596–603.
75. R. Ranjithkumar, S.P. Balaji, B. Balaji, R.V. Ramesh, M. Ramanathan, Standardized aqueous Tribulus terristris (nerunjil) extract attenuates hyperalgesia in experimentally induced diabetic neuropathic pain model: role of Oxidative Stress and Inflammatory Mediators, Phytother. Res. 27 (2013) 1646–1657.
76. A. Ameri, The effects of Aconitum alkaloids on the central nervous system, Prog. Neurobiol. 56 (1998) 211–235.
77. Ha-Na Lyu, Ho-Young Kwak, Dae-Young Lee, Kyong-Tai Kim, Se-Young Kim, Nam-In Baek, Isolation of flavonoids from processed aconiti tuber, J App. Biol. Chem. 51 (4) (2008) 165–168.
78. A.M. Nascimento, L.M. deSouza, C.H. Baggio, M.F. Werner, D. Maria-Ferreira, L. M. da Silva, G.L. Sassaki, P.A. Gorin, M. Iacomini, T.R. Cipriani, Gastroprotective effect and structure of a rhamnogalacturonan from Acmella oleracea, Phytochemistry 85 (2013) 137–142.
79. H. Villachica, J.E.U. Carvalho, C.H. Muller, S.C. Diaz, M. Almanza, H.P.A. Frutales, C.A.S.P.L. Tratado, O. Wongsawatkul, S. Prachayasittikul, C. Isarankura-Na-Ayudhya, J. Satayavivad, S. Ruchirawat, V. Prachayasittikul, Vasorelaxant and antioxidant activities of SpilanthesacmellaMurr, Int. J. Mol. Sci 19969 (2008) 2724–2744.
80. S.K. Tiwari, An updated review on medicinal herb genus Spilanthes, Zhong Xi Yi Jie He Xue Bao 9 (2011) 1170–1178.
81. O. Wongsawatkul, S. Prachayasittikul, C. Isarankura-Na-Ayudhya, J. Satayavivad, S. Ruchirawat, V. Prachayasittikul, Vasorelaxant and antioxidant activities of Spilanthesacmella, Murr. Int. J. Mol. Sci. 9 (2008) 2724–2744 (9).
82. A. Chakraborty, B.R. Devi, R. Sanjebam, S. Khumbong, I.S. Thokchom, Preliminary studies on local anesthetic and antipyretic activities of Spilanthesacmella Murr.in experimental animal models, Indian J. Pharmacol. 42 (2010) 277–279.
83. J.P. Ley, G. Krammer, J. Looft, G. Reinders, H. Bertram, Structure-activity relationships of trigeminal affects for artificial a naturally occurring alkamides related to spilanthol, Dev. Food Sci. 43 (2006) 21–24.
84. L.C. Wu, N.C. Fan, M.H. Lin, I.R. Chu, S.J. Huang, C.Y. Hu, S.Y. Han, Antiinflammatory effect of spilanthol from Spilanthesacmella on murine macrophage by down-regulating LPS-induced inflammatory mediators, J. Agri. Food Chem. 56 (2008) 2341–2349.

85. M. Ghosh, Antifungal properties of haemperoxidase from Acorus calamus, Ann. Bot. 98 (2006) 1145–1153.
86. R. Hazra, K. Ray, D. Guha, Inhibitory role of Acorus calamus in ferric chlorideinducedepileptogenesis in rat, Hum. Exp. Toxicol. 26 (2007) 947–953.
87. A. Muthuraman, N. Singh, A.S. Jaggi, Protective effect of Acorus calamus L. in rat model of vincristine induced painful neuropathy: an evidence of antiinflammatory and anti-oxidative activity, Food Chem. Toxicol. 49 (2011) 2557–2563.
88. D.P. Shah, M. Ghag, P.B. Deshmukh, Toxicity study of ethanolic extract of Acorus calamus rhizome, Int. J. Green Pharmacy 6 (1) (2012) 29–35.
89. A.K. Nandkarni, K.M. Nadkarni, The indianmateria medica, with ayurvedic, unani and home remedies, popular prakashan, Bombay 1 (1976) 80–83.
90. S. Arulmozhi, P.M. Mazumder, L.S. Narayan, P.A. Thakurdesai, In vitro antioxidant and free radical scavenging activity of fractions from Alstoniascholaris Linn. R.Br, Int. J. Pharm. Tech. Res. 2 (2010) 18–25.
91. J.H. Shang, X.H. Cai, T. Feng, Y.L. Zhao, J.K. Wang, L.Y. Zhang, M. Yan, X.D. Luo, Pharmacological evaluation of Alstoniascholaris: anti-inflammatory and analgesic effects, J. Ethno. 129 (2) (2010) 174–181.
92. H. Singh, R. Arora, S. Arora, B. Singh, Ameliorative potential of Alstoniascholaris (Linn.) R. Br. against chronic constriction injury-induced neuropathic pain in rats, BMC Comp. Alt. Med. 17 (1) (2017) 63.
93. M.S. Baliga, G.C. Jagetia, J.N. Ulloor, M.P. Baliga, P. Venkatesh, R. Reddy, K.M. Rao, B.S. Baliga, S. Devi, S.K. Raju, V. Veeresh, The evaluation of the acute toxicity and long term safety of hydroalcoholic extract of Sapthaparna (Alstoniascholaris) in mice and rats, Toxicol. Lett. 151 (2) (2004) 317–326.
94. M.S. Lavhale, S.H. Mishra, Evaluation of free radical scavenging activity of Butea monosperma Lam, Indian J. Exp. Biol. 45 (2007) 376–384.
95. Anonymous, the Ayurvedic Pharmacopoeia of India, Government of India, New Delhi, 2006, pp. 128–130.
96. Shilpa Donga, Chronic toxicity study of Butea monosperma (Linn.) Kuntze seeds in albino rats, Int. Q. J. Res. Ayurveda 32 (1) (2011) 120.
97. K.T. Fitzgerald, A.C. Bronstein, K.L. Newquist, Marijuana poisoning, Top. Companion Anim. Med. 28 (1) (2013) 8–12.
98. Alireza Milajerdi, K. Djafarian, B. Hosseini, The toxicity of saffron (Crocus sativus L.) and its constituents against normal and cancer cells, J. Nutr. Intermed. Metab. 3 (2016) 23–32.
99. T.N. Bhavani Shankar, Toxicity studies on turmeric (Curcuma longa): acute toxicity studies in rats, guinea pigs and monkeys, Indian J. Exp. Biol. 18 (1) (1980) 73–75.
100. Hwang Hyejeong, M. Terada, S. Hyeon-Cheol, Single dose oral toxicity and 4- weeks repeated oral toxicity studies of ecklonia cava extract, SEIKATSU EISEI, J. Urban Living Health Assoc. 5 (2008) 282–289.
101. S. Kumar Middha, et al., Toxicological evaluation of Emblica officinalis fruit extract and its anti-inflammatory and free radical scavenging properties, Pharmacog. Mag. 11 (3) (2015) S427.
102. Aldo César Passilongo Silva, et al., Toxicological screening of Euphorbia tirucalli L.: developmental toxicity studies in rats, J. Ethnopharmacol. 110 (1) (2007) 154–159.

103. L. Zhang, J. Lin, Z.J. Wu, Chin. Med. Mater. 26 (2003) 451–453.
104. C. Rujjanawate, D. Kanjanapothi, A. Panthong, Pharmacological effect and toxicity of alkaloids from Gelsemium elegans Benth, J. Ethnopharmacol. 89 (1) (2003) 91–95.
105. J. Hibatallah, C. Carduner, M.C. Poelman, In-vivo and in-vitro assessment of the free-radical-scavenger activity of Ginkgo flavone glycosides at high concentration, J. Pharm. Pharmacol. 51 (1999) 1435–1440.
106. O.M. Abdel-Salam, A.R. Baiuomy, S. El-batran, M.S. Arbid, Evaluation of the anti-inflammatory, anti-nociceptive and gastric effects of Ginkgo biloba in the rat, Pharmacol. Res. 49 (2004) 133–142.
107. L.B. Thorpe, M. Goldie, S. Dolan, Central and local administration of Ginkgo biloba extract EGb 7611 inhibits thermal hyperalgesia and inflammation in the rat carrageenan model, Anesth. Analg. 112 (2011) 1226–1231.
108. V. Cynthia Rider, et al., Toxicity and carcinogenicity studies of Ginkgo biloba extract in rat and mouse: liver, thyroid, and nose are targets, Toxicol. Pathol 42 (5) (2014) 830–843.
109. S.K. Jain, Dictionary of Indian Folk Medicine and Ethnobotany, Deep Publications, New Delhi India, 1991 (pp. 105).
110. M. Vijayakumar, R. Govindarajan, G.M. Rao, C.V. Rao, A. Shirwaikar, S. Mehrotra, P. Pushpangadan, Action of Hygrophila auriculata against streptozotocin- induced oxidative stress, J. Ethnopharmacol. 104 (2006) 356– 361.
111. A. Patra, S. Jha, P.N. Murthy, Phytochemical and pharmacological potential of Hygrophila spinosa T. anders, Pharmacog. Rev. 3 (2009) 330–341.
112. V.S. Neharkar, S. Kshirsagar, R. Pandhare, Acute toxicity study of Hygrophila auriculata L. leaves methanolic extract in albino rats, J. Pharma. Chem. Biol. 3 (3) (2015) 388–395.
113. M.I. Georgiev, K. Alipieva, I.E. Orhan, Cholinesterases inhibitory and antioxidant activities of Harpagophytum procumbens from in vitro systems, Phytother. Res. 26 (2012) 313–316.
114. B. Baghdikian, M.C. Lanhers, J. Fleurentin, E. Ollivier, C. Maillard, G. Balansard, F. Mortier, An analytical study, anti-inflammatory and analgesic effects of Harpagophytum procumbens and Harpagophytumzeyheri, Planta Med. 63 (1997) 171–176.
115. M.L. Andersen, E.H. Santos, L. SeabraMde, A.A. da Silva, S. Tufik Evaluation of acute and chronic treatments with Harpagophytum procumbens on freund's adjuvant-induced arthritis in rats, J. Ethnopharmacol. 91 (2004) 325–330.
116. N.O. Al-Harbi, R.M. Al-Ashban, A.H. Shah, Toxicity studies on Harpagophytum procumbens (Devils claw) capsules in mice, J. Med. Plant. Res. 7 (42) (2013) 3089–3097.
117. P. Khanna, Oil from Momordica charantia L., its method of preparation and uses, US Patent 6964786 B1, (2005).
118. P.V. Nerurkar, L.M. Johns, L.M. Buesa, G. Kipyakwai, E. Volper, R. Sato, P. Shah, D. Feher, P.G. Williams, V.R. Nerurkar, Momordica charantia (bitter melon) attenuates high-fat diet-associated oxidative stress and neuroinflammation, J. Neuroinflamm. 8 (2011) 64.
119. M. Ullah, M. Showkat, N.U. Ahmed, S. Islam, N. Absar, Evaluation of Momordica charantia L. fruit extract for analgesic and anti-inflammatory activities using in vivo assay, Res. J. Med. Plant. 6 (2012) 236–244.
120. R.N. Husna, A. Noriham, H. Nooraain, A.H. Azizah, O.F. Amna, Acute oral toxicity effects of Momordica charantia in spraguedawley rats, Int. J Biosci. Biochem. Bioinfo. 3 (4) (2013) 408.

121. J.M. Dalziel, the Useful Plants of West Tropical Africa, the Crown Agency for the Colonies, London, 1937.
122. J.E. Adjanohoun, N. Aboukakar, K. Dramane, M.E. Ebot, J.A. Ekpere, E.G. EnowOrock, D. Focho, Z.O. Gbile, A. Kamanyi, K.J. Kamsu, A. Keita, T. Mbenkum, C.N. Mbi, A.L.I.L. Mbome, N.K. Mubiru, W.L. Nancy, B. Nkongmeneck, B. Satabu, A. Sofowora, V. Tamze, C.K. Wirmum, Traditional medicine and pharmacopoeia, Contribution to Ethnobotanical and Floristic Studies in Cameroon, Centre de Production de ManuelsScolaires, Porto-Novo (Rep. Du Benin), 2016 (pp.133).
123. M. Arbonnier, ArbresAfriquedel'Ouest, Trees, Shrubs and Lianas of West Africa Dry Zones, Mali, Ouagadougou, first ed., Centre de Coopération International een Recherche Agronomique pour le développement/Muséumnationald' histoire naturelle/Union mondialepour la nature, 2000 (CIRAD/ MNHN/UICN).
124. M. Biholong, Contributionàl'étude Dela FloreDuCameroun: Les Astéracées. ThèseDedoctorat, UniversitédeBordeauxIII, Bordeaux, France, 1986, pp. 10– 50.
125. S. Amos, J. Abbah, B. Chindo, I. Edmond, L. Binda, B. Adzu, S. Buhari, A.A. Odutola, C. Wambebe, K. Gamaniel, Neuropharmacological effects of the aqueous extract of Nauclea latifolia root bark in rats and mice, J. Ethnopharmacol. 97 (2005) 53–57 (97).
126. O.A. Akinloye, M.O. Olaniyi, Nephrotoxicity and hepatotoxicity evaluation in wistar albino rats exposed to nauclea latifolia leaf extracts, Pertanika J. Trop. Agri. Sci. 35 (3) (2012) 593–601.
127. I. de Almeida, D.S. Alviano, D.P. Vieira, P.B. Alves, A.F. Blank, A.H. Lopes, C.S. Alviano, M.S. Rosa, Antigiardial activity of Ocimumbasilicum essential oil, Parasitol. Res. 101 (2007) 443–452.
128. D. Bhattacharyya, T.K. Sur, U. Jana, P.K. Debnath, Controlled programmed trial of Ocimum sanctum leaf on generalized anxiety disorders, Nepal Med. Coll. J. 10 (2008) 176–179.
129. M.K. Gautam, R.K. Goel, Toxicological study of Ocimum sanctum Linn leaves: hematological, biochemical, and histopathological studies, J. Toxicol. 2014 (2014).
130. S.N. El, S. Karakaya, Olive tree (Olea europaea) leaves: potential beneficial effects on human health, Nutr. Rev. 67 (2009) 632–638.
131. S.C. Kapadia, H. Tokud, H. Nishino, S. Ueda, Inhibitory effect of iridoids on Epstein–Barr virus activation by a short-term in vitro assay for anti-tumor promoters, Cancer Lett. 102 (1996) 223–226 (102).
132. P.S. Venkateswaran, I. Millman, B.S. Blumberg, Effects of an extract from Phyllanthus niruri on hepatitis B and woodchuck hepatitis viruses: in vitro and in vivo studies, Proc. Natl. Acad. Sci. 84 (1987) 274–278.
133. D.W. Unander, G.L. Webster, B.S. Blumberg, Records of usage or assays in phyllanthus (Euphorbiaceae): I. subgenera isocladus, kirganelia, cicca and emblica, J. Ethnopharmacol. 30 (1990) 233–264.
134. B. Wang, Treatment of chronic liver diseases with traditional Chinese medicine, J. Gastroenterol. Hepatol. 15 (2000) 67–70.
135. F. Notka, H.J. Linde, A. Dankesreiter, H.H. Niller, N. Lehn, AC terminal 18 amino acid deletion in Mar R in a clinical isolate of Escherichia coli reduces Mar R binding properties and increases the MIC of ciprofloxacin, J. Antimicrob. Chemother. 49 (2002) 41–47.

136. N.V. Rajeshkumar, R. Kuttan, Phyllanthus amarus extract administration increases the life span of rats with hepatocellular carcinoma, J. Ethnopharmacol. 73 (2000) 215–219.
137. A.R. Santos, R.O. De Campos, O.G. Miguel, V. Cechinel Filho, A.C. Siani, R.A. Yunes, J.B. Calixto, Antinociceptive properties of extracts of new species of plants of the genus Phyllanthus (Euphorbiaceae), J. Ethnopharmacol. 72 (2000) 229–238.
138. J.B. Calixto, A.R. Santos, V. Cechinel Filho, R.A. Yunes, A review of the plants of the genus Phyllanthus: their chemistry, pharmacology, and therapeutic potential, Med. Res. Rev. 18 (1998) 225–258.
139. A.O. Eweka, A. Enogieru, Effects of oral administration of Phyllanthus amarus leaf extract on the kidneys of adult wistar rats-a histological study, African J. Trad. Comp. Alt. Med. 8 (3) (2011).
140. P. Manzi, A. Aguzzi, L. Pizzoferrato, Nutritional value of mushrooms widely consumed in Italy, Food Chem. 73 (2001) 321–325.
141. M. Zhang, S.W. Cui, P.C.K. Cheung, Q. Wang, Antitumor polysaccharides from mushrooms: a review on their isolation process, structural characteristics and antitumor activity, Trends Food Sci. Technol. 18 (2007) 4–19.
142. C.G. Wasonga, S.A. Okoth, J.C. Mukuria, C.O. Omwandho, Mushroom polysaccharide extracts delay progression of carcinogenesis in mice, J. Exp. Ther. Oncol. 7 (2008) 147–152.
143. R. Yatsuzuka, Y. Nakano, S. Jiang, Y. Ueda, Y. Kishi, Y. Suzuki, E. Yokota, A. Rahman, R. Ono, I. Kohno, I. Kamei, Effect of usuhiratake (Pleurotuspulmonarius) on sneezing and nasal rubbing in BALB/c mice, Biol. Pharm. Bull. 30 (2007) 1557–1560.
144. L. Chia-Jung, C. Lih-Geeng, L. Wen-Li, W. Ching-Chiung, Anti-inflammatory effects of Punica granatum linne in vitro and in vivo, Food Chem. 118 (2010) 315–322.
145. M.S. Mudzhiri, Punica granatum bark extract as a therapeutic agent in tapeworm infection, Med. Parazitol 4 (1954) 311–313.
146. M.I. Gil, F.A. Tomas-Barberan, B. Hess-Pierce, D.M. Holcroft, A.A. Kader, Antioxidant activity of pomegranate juice and its relationship with Phenolic composition and processing, J. Agric. Food Chem. 48 (2000) 4581–4589.
147. N. Khan, F. faq, M.H. Kweon K. Kim, H., Mukhtar, Oral consumption of pomegranate fruit extract inhibits growth and progression of primary lung tumors in mice, Cancer Res. 67 (2007) 3475–3482.
148. G. Kaur, Z. Jabbar, M. Athar, M.S. Alam, Punica granatum (pomegranate) flower extract possesses potent antioxidant activity and abrogates Fe-NTA induced hepatotoxicity in mice, Food Chem. Toxicol. 44 (2006) 984–993.
149. M.K. Reddy, S.K. Gupta, M.R. Jacob, S.I. Khan, D. Ferreira, Antioxidant, antimalarial and antimicrobial activities of tannin-rich fractions, ellagitannins and Phenolic acids from Punica granatum, L. Planta Med. 73 (2007) 461–467.
150. K.B. Ajaikumar, M. Asheef, B.H. Babu, J. Padikkala, The inhibition of gastric mucosal injury by Punica granatum L. (Pomegranate) methanolic extract, J. Ethnopharmacol. 96 (2005) 171–176.
151. N.S. Al-Zoreky, Antimicrobial activity of pomegranate (Punica granatum L.) fruit peels, Int. J. Food Microbiol. 134 (2009) 244–248.
152. M. Pivatto, A.E.M. Crotti, N.P. Lopes, I. Castro-Gamboa, A. Rezende Jr., C. Viegas, M.C.M. Oung, M. Furlan, V.S. Bolzani, Electrospray ionization mass spectrometry

screening of piperidine alkaloids from Senna spectabilis (Fabaceae) extracts: fast identification of new constituents and cometabolites, J. Braz. Chem. Soc. 16 (2005) 1431–1438.

153. C. Viegas Jr., V.S. Bolzani, M. Furlan, E.J. Barreiro, M.C.M. Young, D. Tomazela, M.N. Eberlin, Further bioactive piperidine alkaloids from the flowers and green fruits of Cassia spectabilis, J. Nat. Prod. 67 (2004) 908–910.
154. J. Safaei-Ghomi, A.H. Ebrahimabadi, Z. Djafari-Bidgoli, H. Batooli, GC/MS analysis and in vitro antioxidant activity of essential oil and methanol extracts of Thymus caramanicusJalas and its main constituent carvacrol, Food Chem. 115 (2009) 1524–1528.
155. Amin B, Hosseinzadeh H. Black cumin (Nigella sativa) and its active constituent, thymoquinone: an overview on the analgesic and anti-inflammatory effects. Planta Med 2016; 82:8-16.
156. Javidi S, Razavi BM, Hosseinzadeh H. A review of neuropharmacology effects of Nigella sativa and its main component, thymoquinone. Phytother Res 2016; 30:1219- 1229.
157. Forouzanfar F, Fazly Bazzaz BS, Hosseinzadeh H. Black cumin (Nigella sativa) and its constituent (thymoquinone): a review on antimicrobial effects. Iran J Basic Med Sci 2014; 17:929–938.
158. Kanter M. Effects of Nigella sativa and its major constituent, thymoquinone on sciatic nerves in experimental diabetic neuropathy. Neurochem Res 2008; 33:87-96.
159. Amin B, Taheri M, Hosseinzadeh H. Effects of intraperitoneal thymoquinone on chronic neuropathic pain in rats. Planta medica 2014; 80:1269-1277.
160. Tewari S, Salman M, Thadani S, Singh S, Ahmad A. A study of pregabalin, tramadol, their combination and Nigella sativa in neuropathic pain in rats. Int J Pharm Sci Res 2015; 6:4406.
161. Rog DJ, Nurmikko TJ, Young CA. Oromucosal Δ 9-tetrahydrocannabinol/cannabidiol for neuropathic pain associated with multiple sclerosis: an uncontrolled, openlabel, 2-year extension trial. Clin Ther2007; 29:2068-2079.
162. Ellis RJ, Toper off W, Vaida F, Van Den Brande G, Gonzales J, Gouaux B, et al. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. Neuropsychopharmacology 2009; 34:672-680.
163. Johnson JR, Burnell-Nugent M, Lossignol D, Ganae-Motan ED, Potts R, Fallon MT. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC: CBD extract and THC extract in patients with intractable cancer-related pain. J Pain Symptom Manage 2010; 39:167-179.
164. Johnson JR, Lossignol D, Burnell-Nugent M, Fallon MT. An open-label extension study to investigate the long-term safety and tolerability of THC/CBD oromucosal spray and oromucosal THC spray in patients with terminal cancerrelated pain refractory to strong opioid analgesics. J Pain Symptom Manage 2013; 46:207-218.
165. Serpell M, Ratcliffe S, Hovorka J, Schofield M, Taylor L, Lauder H, et al. A double-blind, randomized, placebocontrolled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. Eur J Pain 2014; 18:999-1012.
166. Hoggart B, Ratcliffe S, Ehler E, Simpson K, Hovorka J, Lejcko J, et al. A multicentre, open-label, follow-on study to assess the long-term maintenance of effect, tolerance and safety of THC/CBD oromucosal spray in the management of neuropathic pain. J Neurol2015; 262:27-40.

167. Feng L, Liu W-K, Deng L, Tian J-X, Tong X-L. Clinical efficacy of aconitum-containing traditional Chinese medicine for diabetic peripheral neuropathic pain. Am J Chin Med 2014; 42:109-117.
168. Kono T, Hata T, Morita S, Munemoto Y, Matsui T, Kojima H, et al. Goshajinkigan oxaliplatin neurotoxicity evaluation (GONE): a phase 2, multicenter, randomized, doubleblind, placebo-controlled trial of goshajinkigan to prevent oxaliplatin-induced neuropathy. Cancer ChemotherPharmacol2013; 72:1283-1290.
169. Heydari M, Homayouni K, Hashempur MH, Shams M. Topical Citrullus colocynthis (bitter apple) extract oil in painful diabetic neuropathy: A double-blind randomized placebocontrolled clinical trial. J Diabetes 2016; 8:246-252.
170. Taki M, Omiya Y, Suzuki Y, Ikeda Y, Noguchi M, Matuba T, et al. Quality and pharmacological investigation of processed Aconiti tuber (JT-3022). Nat Med 1998; 52:343-352.
171. Murayama M, Mori T, Bando H, Amiya T. Studies on the constituents of Aconitum species. IX. The pharmacological properties of pyro-type aconitine alkaloids, components of processed aconite powder 'kako-bushi-matsu': analgesic, antiinflammatory and acute toxic activities. J Ethnopharmacol1991; 35:159-164.
172. Singhuber J, Zhu M, Prinz S, Kopp B. Aconitum in traditional Chinese medicine—a valuable drug or an unpredictable risk? J Ethnopharmacol2009;126:18-30.
173. Ou S, Zhao Y-D, Xiao Z, Wen H-Z, Cui J, Ruan H-Z. Effect of lappaconitine on neuropathic pain mediated by P2X 3 receptor in rat dorsal root ganglion. Neurochem Int 2011; 58:564-573.
174. Watanabe K, Shimada A, Miyaki K, Hirakata A, Matsuoka K, Omae K, et al. Long-term effects of Goshajinkigan in prevention of diabetic complications: a randomized open-labeled clinical trial. Evid Based Complement Alternat Med 2014; 2014.
175. Jin G-L, Su Y-P, Liu M, Xu Y, Yang J, Liao K-J, et al. Medicinal plants of the genus Gelsemium (Gelsemiaceae, Gentianales)—a review of their phytochemistry, pharmacology, toxicology and traditional use. J Ethnopharmacol2014; 152:33-52.
176. Qiu H-Q, Xu Y, Jin G-L, Yang J, Liu M, Li S-P, et al. Koumine enhances spinal cord 3α-hydroxysteroid oxidoreductase expression and activity in a rat model of neuropathic pain. Mol Pain 2015; 11:1-13.
177. Ling Q, Liu M, Wu M-X, Xu Y, Yang J, Huang H-H, et al. Antiallodynic and neuroprotective effects of koumine, a Benth alkaloid, in a rat model of diabetic neuropathy. Biol Pharm Bull 2014; 37:858-864.
178. H. Sawada, S. Shimohama, Estrogens and Parkinson disease: novel approach for neuroprotection, Endocrine 21 (2003) 77–79.
179. L.J. Currie, M.B. Harrison, J.M. Trugman, J.P. Bennett, J.F. Wooten, Postmenopausal estrogen use affects risk for Parkinson disease, Arch. Neurol. 61 (2004) 886–888.
180. M.L. Neuhouser, Dietary flavonoids and cancer risk: evidence from human population studies, Nutr. Cancer 50 (2004) 1–7.
181. G. Seelinger, I. Merfort, U. Wölfle, C.M. Schempp, Anti-carcinogenic effects of the flavonoid luteolin, Molecules 13 (2008) 2628–2651.
182. D. García, R. Delgado, F.M. Ubeira, J. Leiro, Modulator effects of rat macrophage function by Mangifera indica L extract (Vimang) and mangiferin, Int. Immunopharmacol. 2 (2002) 797–806.

183. G. Garrido, R. Delgado, Y. Lemus, J. Rodríguez, D. García, A.J. Núñez, Protection against septic shock and suppression of tumor necrosis factor alpha and nitric oxide production on macrophages and microglia by a standard aqueous extract of Mangifera indica L (Vimang1): role of mangiferin isolated from the extract, Pharmacol. Res. 50 (2004) 165–172.
184. G.L. Pardo-Andreu, M.F. Barrios, C. Curti, I. Hernandez, N. Merino, Y. Lemus, Protective effects of Mangifera indica L. extract (Vimang) and its major component mangiferin, on iron-induced oxidative damage to rat serum and liver, Pharmacol. Res. 57 (2008) 79–86.
185. M. Gottlied, R. Leal-Campanario, M.R. Campos-Esparza, M.V. SánchezGómez, E. Alberdi, A. Arranz, Neuroprotection by two polyphenols following excitotoxicity and experimental ischemia, Neurobiol. Dis. 23 (2006) 374–386.
186. Y. Lemus-Molina, M.V. Sánchez-Gómez, R. Delgado-Hernández, C. Matute, Mangifera indica L. extract attenuates glutamate-induced neurotoxicity on rat cortical neurons, Neurotoxicology 30 (2009) 1053–1058.
187. G.C. Jagetia, T.K. Reddy, The grape fruit flavonone: naringin protects against the radiation-induced genomic instability in the mice bone marrow: a micronucleus study, Mutat. Res. 19 (2002) 37–48.
188. Y.T. Chen, R.L. Zheng, Z.J. Jia, Y. Ju, Flavonoids as superoxide scavengers and antioxidants, Free Radic. Biol. Med. 9 (1990) 19–21.
189. O. Benavente-Garcia, J. Castillo, Update on uses and properties of citrus flavonoids: new findings in anticancer, cardiovascular, and antiinflammatory activity, J. Agric. Food Chem. 56 (2008) 6185–6205.
190. M.M. Ali, M.A. Abd El kedar, the influence of naringin on the oxidative state of rats with streptozotocin induced acute hyperglycaemia, Z. Naturforsch. 59 (2004) 726–733.
191. V.R. Punithavathi, R. Anuthama, P.S. Prince, Combined treatment with naringin and vitamin C ameliorates streptozotocin-induced diabetes in male Wistar rats, J. Appl. Toxicol. 28 (2008) 806–813.
192. J. Post-White, E.J. Ladas, K.M. Kelly, Advances in the use of milk thistle (Silybum marianum), Integr. Cancer Ther. 6 (2007) 104–109.
193. M.L. Rothenberg, A.M. Oza, R.H. Bigelow, J.D. Berlin, J.L. Marshall, R.K. Ramanathan, L.L. Hart, S. Gupta, C.A. Garay, B.G. Burger, N. Le Bail, D.G. Haller, Superiority of oxaliplatin and fluorouracil leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil-leucovorin: interim results of a phase III trial, J. Clin. Oncol. 21 (2003) 2059–2069.
194. K. Zhang, Y.J. Li, Q. Yang, O. Gerile, L. Yang, X.B. Li, Y.Y. Guo, N. Zhang, B. Feng, S. B. Liu, M.G. Zhao, Neuroprotective effects of oxymatrine against excitotoxicity partially through down-regulation of NR2B-containing NMDA receptors, Phytomedicine (2012) 1–8.
195. H.Y. Liu, Y.X. Li, Y.J. Hao, H.Y. Wang, X.Y. Dai, T. Sun, J.Q. Yu, Effects of oxymatrine on the neuropathic pain induced by chronic constriction injury in mice, CNS Neurosci. Therap. 18 (2012) 1030–1032.
196. A. Beirith, A.R.S. Santos, J.B. Calixto, S.C. Hess, I. Messana, F. Ferrari, R.A. Yunes, Study of the antinociceptive action of the ethanolic extract and the triterpene 24-hydroxytormentic acid isolated from Ocotea suaveolens (Meissn) Hassler, Planta Med. 65 (1999) 50–55.

197. P.J. Houghton, L.M. Lian, Triterpenoids from Desfontainia spinosa, Phytochemistry 25 (1986) 1939–1944.
198. K.H. Lee, Y.M. Lin, T.S. Wu, D.C. Zhang, T. Yamagishi, T. Hayashi, I.H. Hall, J.J. Chang, R.Y. Wu, T.H. Yang, The cytotoxic principles of Prunella vulgaris, Psychotriaserpens, and Hyptis capitata: ursolic acid and related derivatives, Planta Med. 54 (1988) 308–311.
199. S.C. Hess, F.D. Monache, Divergioic acid, a triterpene from Vochysiadivergens, J. Braz. Chem. Soc. 10 (1999) 104–106.
200. L.B. Bortalanza, J. Ferreira, S.C. Hess, F.D. Monache, R.A. Yunes, J.B. Calixto, Anti-allodynic action of the tormentic acid a triterpene isolated from plant, against neuropathic and inflammatory persistent pain in mice, Eur. J. Pharmacol. 453 (2002) 203–208.