International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2016): 79.57 | Impact Factor (2015): 6.391

The Role of Natural Products in Management of Neuropathic Pain

Putri Rossyana Dewi, I Putu Eka Widyadharma

Department of Neurology, Faculty of Medicine, Udayana University/Sanglah General Hospital, Bali-Indonesia

Abstract: ***Neuropathic pain as pain caused by lesion of the somatosensory nervous system, which causes unpleasant and abnormal sensation (dysesthesia), an increased response to painful stimuli (hyperalgesia), and pain in response to a stimulus that normally does not induce pain response (allodynia). As the prevalence of neuropathic pain is increasing in many countries, well management of neuropathic pain is necessary to develop. Despite the progress in recent years to develop the therapy, there is still need effective analgesic agent to manage neuropathic pain. Recently, the researchers have discovered some natural products and its derived compound that have an analgesic function and effective to manage neuropathic pain with limited adverse effects. In this review, some natural products and its function related to manage neuropathic pain will be explained.***

Keywords: Neuropathic pain, Analgesic agent, Natural Products

1. Introduction

Pain is one of the common health problems associated with many complications in various way. Normal pain stimulus is resulting from tissue damage is considered to be a normal physiological response to alert the body that tissue injury or damaged has occurred. It's called nociceptive pain. Nociceptive pain usually has well response to analgesics treatment and tends to relieve when the stimulus are removed or the tissue injury has healed. However, chronic pain particularly neuropathic pain involves an abnormal process of sensory input which has a long process compared than nociceptive pain. Chronic pain can be classified as inflammatory or neuropathic pain depending on its origin. Chronic pain defines as a problem that affects personal and their quality of life. The International Association for the Study of Pain (IASP) defines neuropathic pain as pain caused by lesion of the somatosensory nervous system, which causes unpleasant and abnormal sensation (dysesthesia), an increased response to painful stimuli (hyperalgesia), and pain in response to a stimulus that normally does not induce pain response (allodynia) [1,2,3].

Based on several studies, neuropathic pain affects about 1 in every 10 adults and makes the economic burden for treating this pain is increasing. It is estimated affects over 6 million patients in the U.S.A and Europe, also over 26 million patients worldwide which is cost $3 billion every year for the health care. The prevalence rate of chronic pain in France is 31.7% and that of chronic pain with neuropathic characteristics is 6.9% [1,3,4]. Neuropathic pain is widely recognized as one of the most difficult pain syndromes to manage and could be problematic due to multifactorial causes such as complicated underlying pathophysiology or heterogenous [1,5]. The available drugs to manage those symptoms are limited and the patient is increasing rapidly, the physicians are forced to give multiple drugs combination as the mainstay therapy [3,5].

Current pharmacological therapy for neuropathic pain usually combination of multiple drugs from several drug classes such as: opioids, tricyclic antidepressants, anticonvulsant agents, or non-steroid anti-inflammatory drugs. However, the neuropathic pain symptoms is relieved only 30-50% in 50 patients even with combination of multiple pharmacotherapy. Moreover, the therapy should be given for long term and cause some side effects and low compliance of the patients to take the medication regularly. These problems make those pharmacotherapy should be considered as first line management of neuropathic pain [1,3,5].

There are new trends to treat neuropathic pain with natural products which has either limited adverse effects or high efficacy. These facts make natural products emerge as interesting therapeutic agents to manage neuropathic pain. Food-derived natural compound have been used in treating many disorders since a century. In conclusion, natural products may present as therapeutic candidates for the development of new drugs to manage neuropathic pain [1,2,3,5].

2. Pathophysiology of Neuropathic Pain

The International Association for the study of Pain (IASP) defined neuropathic pain as pain initiated by a primary lesion or dysfunction of the nervous system. In general, pain perception for acute and chronic pain involves following several processes: transduction, transmission, modulation, and perception. The process is started when nociceptive receptors switch noxious stimulation into nociceptive signals, which are transported to central nervous system (CNS) by nerve fibers from site of injury. These nociceptive signals are modulated at synaptic sites and CNS by ascending or descending pathways resulted pain perception. Pain perception based on IASP is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage [1,3,6].

In neuropathic pain, nerve injury alters expression of genes encoding cytokines and chemokine receptors thus induce nociceptive signaling in the peripheral and central nervous system. This complex process makes the neuropathic pain occurred. In addition, the injury of nerves will induce

immune reaction in the peripheral and CNS, including activation of mast and glial cells. These processes induce peripheral sensitization, which enhanced excitability of the primary afferent nociceptive receptors that convert peripheral stimulus into action potentials in the CNS. Simultaneously, after the peripheral nerve injury, microglia which are in resting state are activated through a cellular and molecular changes involves monocyte chemo attractant protein 1/C-C motif chemokine ligand 2 (MCPI/CCL2) [1,6].

Peripheral Mechanism of Neuropathic Pain

The following processes of pathological changes have been described in peripheral axons and dorsal root ganglia after nerve injury have been postulated to play a role in mechanism of neuropathic pain [1,6]:

1. Ectopic discharges in lesion fibers and their corresponding ganglia.

This refers to the spontaneous production of action potentials, in general within sites of axonal demyelination due to altered distribution of Na^+ channels in the demyelinated segments of the membrane. The newly inserted channels include Nav1.7, a channel linked to hereditary pain syndromes (if the activity is increasing) and insensitivity of pain (if loss its function) and Nav1.3, a channel normally expressed in sensory neuron during embryonic development, as well as β subunit. That condition is combined with a decrease in K^+ channels and an increase in nonselective hyperpolarization- and cyclic nucleotide-modulated (HCN) channels, these changes can result membrane instability sufficient for the emergence spontaneous activity.

High-frequency stimulation of small myelinated fibers (Aδ) generates pain and several studies said the implication of large Aβ fibers in touch allodynia and secondary hyperalgesia. The mechanism enabling normally non-nociceptive (Aβ) input to engage nociceptive circuitry may rely on both pre- and post-synaptic mechanism. A post-synaptic decrease γ-amino butyric acid (GABA)-ergic tone in dorsal horn is also a probable mechanism of nociceptive engagement by activities in Aβ fibers after nerve injury. Further to these mechanisms, a number of Aβ fibers undergo phenotypic changes and express neurotransmitters, such as calcitonin gene-related peptide (CGRP).

2. Abnormal activity in axons undamaged by injury.

Lesion distal to dorsal root ganglia lead to Wallerian degeneration, with the development of inflammatory phenomena, edema, and macrophage activation in the axonal segment. The timing of this process parallels that of hyperalgesia in rat models of chronic sciatic constriction and Wallerian degeneration may favor the development of abnormal activity including neurochemical abnormalities in the contiguous intact root ganglion with over expression of transient receptor potential vaniloid receptor 1 (TRPV1), neurotrophic factors such as brain-derived neurotrophic factor (BDNF), and mRNA for nociceptive neurotransmitters such as CGRP, in fibers spared by the lesion.

3. Alterations in the expression and regulation of intracellular Ca^{2+} ion and modulatory receptors on primary afferent terminals.

Neurotransmitter released by nociceptive terminals is triggered by Ca^{2+} entry and therefore depends on voltage-dependent channels. Spinal nerve ligation in rats induces over expression of the α2/δ Ca^{2+} channel subunit in the corresponding dorsal ganglia, which might entail an enhanced neurotransmitter release (in particular glutamate) by these terminals. This phenomenon also occurred in the dorsal horn, may be at the basis of the clinical efficacy of drugs, such as gabapentin and pregabalin, that selectively block the α2/δ Ca^{2+} channel subunit based on data suggest these drugs may decrease neurotransmitter release by linking specifically to the α2/δ Ca^{2+} channel subunit.

4. Neuroimmune interactions resulting in enhanced and/or altered production of inflammatory signal molecules.

There is increasing evidence that nerve injury-induced activation of peripheral immune cells. Thus, the factors that they can produce can alter sensory processing and play critical roles in the development and maintenance of neuropathic pain. Cytokines and chemokines released by immune cells, such as tumor necrosis factor-a (TNF- α), interleukins (ILs), nerve growth factor (NGF), and chemokine ligands (CC). All of these products can cause sensitization of channels, such as TRPV1, result in firing of nociceptors at normal body temperature.

5. Sensory sympathetic coupling and other alterations in receptor signaling.

Nerve growth factor plays an important biological role in the development and maintenance of small-diameter somatic and sympathetic neurons. In rats, endoneurial administration of NGF induces neuronal sprouting and behavioral signs of thermal hyperalgesia. In humans, local injection of NGF has been shown to decrease thermal pain threshold and induce pressure allodynia.

Spinal Mechanism

Central sensitization exists at both spinal and supraspinal levels, but some studies concern in the spinal dorsal horn. Two abnormal phenomena develops after an inflammatory lesion of cutaneous tissues: primary hyperalgesia to mechanothermal stimuli at the level of the level of the lesion, and secondary hyperalgesia to mechanical stimuli over non affected sites around the lesion. These two types of hyperalgesia are dependent on the initial increase of peripheral nociceptive input because blockade of this input by local anesthetics can eliminate them completely [1,6].

The Brainstem

Projections of the nociceptive dorsal horn to brainstem and thalamic structures trigger descending loops back to the dorsal horn, which modulate the spinal transfer of nociceptive transmission. A several of studies suggest that some of these loops involve the brainstem participate in neuropathic pain. Feedback systems controlling pain involving brainstem have been known for many years; they involve descending serotonergic and noradrenergic input from the lower brainstem through the dorsolateral funiculus and are considered to underlie pain-relieving effects of tricyclic antidepressants [1,6].

3. The Role of Natural Products and its Derived Compounds in Neuropathic Pain

Several of studies suggest that natural products have analgesic effects to manage neuropathic pain. As explained above, neuroinflammation plays important role to induce neuropathic pain. As the result, decreasing neuroinflammation is a key process to relieve neuropathic pain through regulation of anti-inflammatory and inflammatory mediators. Based on systematic review of natural products, there are the five most researched natural compounds such as: flavonoids (28%), terpenoids (17%), alkaloids (14%), phenols (10%), and carotenoids (10%) [1,2,5].

Flavonoids are one of the most important secondary metabolites for pharmaceutical and cosmetics industries due to its biological properties, such as cancer-preventive component, anti-aging, antioxidant, anti-inflammatory and analgesic. Flavonoids manage neuropathic pain by modulating the activity of protein kinase C and its antioxidant activity. Ginkgetin, a biflavone isolated from *Ginkgo Biloba* leaves has been reported a an inhibitor of group II phospholipase A2. This compound strongly reduces arthritic inflammation, confirmed by histological examination of knee joint. Moreover, clical study showed *Ginkgo Biloba* extract (standardized to 21.0 mg flavonglycosids and 3 mg folic acid) treatment improved the nerve function and pain associated with autonomic neuropathic in ten patients. Qeercetin has been described as an antioxidant, antinociceptive and anti-inflammatory compound whose has preventive effects against oxaliplatin-induced painful peripheral neuropathy. Naringin, a flavonoid abundant in citrus fruits, such as grapefruits, has been reported to process anti-inflammatory agents. Naringin reversed the pain response in STZ-induced diabetic rats by altering expression of endogenous biomarkers [1,2,5,7].

Capsaicin is one of food-derived natural compound and well-known as TRPV1 agonist. Uniquely, capsaicin will induce pain by single treatment, but will relieve pain with repeated injection. Intrathecal capsaicin injection attenuates thermal hyperalgesia, but does not reduce mechanical allodynia in nerve-injured rats. It also exerts a dual role in nociceptive process. Capsaicin induce nociceptive processes which are hyperalgesia and inflammatory reactions mediated by increasing membrane permeability. Capsaicin excites the afferent sensorial neurons especially the C and Ad fibers which conduct the nociceptive information to the CNS. Capsaicin also blocks the intra-axonal transport of macromolecules such as NGF [1,5].

Terpenoids and steroids compounds are widely distributed as pharmacological properties. Terpenoids have some function as anti-inflammatory and antinociceptive properties, inhibit platelet aggregation and change transduction mechanism in the intracellular level. The monoterpenes found in essential oil of *Cymbopogon Citratus* exhibit anti-nociception function when assessed in different experimental models of pain. Myrcene, as its derived compound, has similar effect anti-nociceptive as peripheral acting of opiates (dypirone). β-Caryophyllene (BCP) is natural selective agonist of the peripherally expressed cannabinoid receptor 2 (CB2), an important receptor in neuropathic pain. BCP usually found in spices and food plants. The function of BCP is to relieve thermal hyperalgesia, mechanical allodynia, and reduced spinal neuroinflammation in mouse models of inflammatory and neuropathic pain [1,2,5].

Palmitoylethanolamide (PEA), an endogenous fatty acid amide has been known able to perform various biological function related to neuropathic pain and inflammatory process in clinical trial. PEA is an endogenous modulator usually found in some foods like eggs or milk. Some studies reported PEA has no adverse effects. PEA has function to relieve both thermal hyperalgesia and mechanical allodynia by regulating cannabinoid receptor γ (PPAR γ) and TRPV1 receptors in neuropathic model mice. PEA has good enough as analgesic compound to relieve neuropathic pain regardless of age, sex, and the pain trigger [1].

Acorus calamus rhizoma (family: Araceae) is natural compound traditionally use as analgesic agent to manage severe inflammatory and neuropathic pain. In a study using rat models, a hydroalcoholic extract of *Acorus calamus rhizoma* has been shown to exert beneficial effects on neuropathic pain. Some further studies suggest that injury induced by sciatic nerve chronic constriction where therapy of *Acorus calamus rhizoma* extract has relieved hyperalgesia and allodynia [5].

In recent years, alkaloids have been reported as anti-nociceptive agent to treat neuropathic pain. Dehydrocorybulbine (DHCB) is isolated from *Corydalis yanhusu*, a traditional pain relief plant. Synthetic DHCB has efficacy in acute pain, inflammatory pain, and neuropathic pain. These anti-nociceptive effects are reversed by a dopamine D2 agonist in the tail-flick test. DHCB exhibits affinity to dopamine receptors and display its highest affinity to the D2 receptor. Mitragynine, the major alkaloidal constituent found in young leaves of *Mytragina speciosa* exerts an opioid-like activity, but its selectivity for the opioid receptor subtypes differs from the morphine. Huperzine A (HUP-A), a naturraly occurring *Lycopodium* alkaloid, isolated from *Huperzia seerrata*, exerts potent reversible inhibition on acetylcholinesterase alleviating neuropathic pain without drug tolerance and dependence [1,5,7,8].

Crocus Sativus L, known as saffron, is an aboriginal plant growing in various part of the world. Crocin, picrocrocin, and safranal are three major biologically active ingredients of saffron. Saffron and its component have notable anti-nociceptive and anti-inflammatory activities. In rat model study, saffron and its main constitute crocin are able to alleviate both mechanical allodynia and thermal hyperalgesia suggesting these substances could have a therapeutic effect in the management of neuropathic pain [9].

Rubus fruticosus is belonging to the *Rosacae* family. The plant is found in many parts of the world and has some biological effects. Several studies showed that its phenolic compounds and anthocyanin have neuroprotective, analgesic, and sedative properties also can improve the age related

memory impairment and learning disability. In a rat model study, suggest that hydroethanolic extract of *Rubus fruticosus* has analgesic effect in diabetic rats especially with higher dose. Considering by thermal test such as Tail-Flick which used for pain assessment, central pathway is mainly assessed. There is a possibility that *Rubus fruticosus* can have analgesic effects by affecting central nervous system [10].

Opium derives from the latex obtained by incision of the unriped capsules of *Papaver somniverum.* Opium contains 25 alkaloids including morphine, codeine, thebaine, and papaverine. Morphine is the first alkaloid to be discovered. The most relevant characteristic of morphine is its properties of modulating and perception of pain resulting an increasing of the noxious threshold. Anti-nociception induced by morphine is mediated by activation of membrane opioid receptors, therefore it can inhibit by opioid receptor antagonist [5,8].

Liquiritigenin is a plant-derived compound and transient receptor potential melastatin 3 (TPRM 3) produced robust anti-hyperalgesia effect in rat model of peripheral neuropathic pain. Liquiritigenin has an impressive anti-nociceptive effect, mechanical hyperalgesia which reveals a broad spectrum activity to manage neuropathic pain [4].

There are many studies showing that omega-3 polyunsaturated fatty acids (PUFAs) have positive effects on mood, as well as analgesic effects. Omega-3 is effective against inflammatory and neuropathic pain. This compound does not interact with the pharmacodynamics or pharmacokinetics of commonly used analgesic drugs. Moreover, resolvin E1 derived from omega-3 also has analgesic effect to manage neuropathic pain [1,2,7].

In recent studies, isoflavones are phytoestrogen used for treating hormone deregulation like menopause and effective in diverse diseases. Genistein, a soy isoflavone, alleviate painful neuropathy by multiple mechanisms, regulating estrogen receptor-β, antioxidant, and anti-inflammatory disease [1].

4. Conclusion

Natural products and its derived compound have been considered becoming a new perspective to manage pain-related problems. In this review, it's become clear that so many natural products like plant-derived compound, extract foods have its function as anti-nociceptive agents. Some studies suggest that natural products are safe to use and has minimum adverse effects which need to confirm in further research. It's important to clarify pharmacodynamics and pharmacokinetics each compound to confirm its safety to human.

References

[1] Lim EY, Kim YT. Food-Derived Natural Compounds for Pain Relief in Neuropathic Pain. *Biomed Research International*. 2016

[2] Quintans J, Antoniolli AR, Almeida J, et al. Natural Products Evaluated in Neuropathic Pain Models – A Systematic Review. *Basic & Clinical Pharmacology & Toxicology, 114, 442-450*. 2014.

[3] Butera J. Miniperspectives: Recent Approaches in the Treatment of Neuropathic Pain. *Journal of Medicinal Chemistry volume 50, number 11*. 2007.

[4] Chen L, Chen Q, Qian X, et al. Liquiritigenin Alleviates Mechanical and Cold Hyperalgesia in a Rat Neuropathic Pain Model. *Scientific Reports 4:5676*. 2014

[5] Deshmukh R, Vij V, Sharma V, Kumar P, et al. Herbs as Positive Modulator in Neuropathic Pain and Their Antinociceptive Effect. *Innovations in Pharmaceuticals and Pharmacotherapy, Vol 2 (3), 378-387*. 2014

[6] Garcia-Larrea L, The Pathophysiology of Neuropathic Pain: Critical Review of Models and Mechanism. *Refresher Courses, 15th World Congress of Pain, IASP Press*. 2014.

[7] Mazzon E, Maria G, Sabrina G, et al. Use of Natural Compounds in the Management of Diabetic Peripheral Neuropathy. 2014

[8] Butler M. Natural Products to Drugs: Natural Product Derved Compounds in Clinical Trials. *The Royal Society of Chemistry Nat. Prod. Rep 22, 162-195*. 2005.

[9] Safakhah H, Taghavi, T, Rashidy-Pour A, et al. Effects of Saffron (*Croccus sativus L.)* Stigma Extract and its Active Constituent Crocin on Neuropathic Pain Responses in a Rat Model of Chronic Constriction Injury. *Iranian Journal of Pharmaceutical Research 15(1):253-261*. 2015.

[10] Ali G, Abdolkarim H, Naser M, et al. Effect of Hydroethanolic Extract of *Rubus fruticosus* on Neuropathic Pain in Wistar Diabetic Rats. *Caspian Journal of Neurological Sciences 1(1):27-34*. 2015.