Original Article

Promising Flavonoids Against Neuropathic Pain: Their Mechanism And Therapeutic Opportunities

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Abstract

Neuronal damage results in neuropathy, a condition caused by irregular nerve function in the central or peripheral nervous systems. Since Neuropathic pain shows a heterogeneous profile and is often treated with psychoactive medications, such as benzodiazepines, it presents a great challenge in managing it. A variety of medications are used today to treat Neuropathic pain, including anticonvulsants, opioids, antidepressants, and lidocaine. However, they come with a varieties of side effects. Neuropathic pain needs alternative therapeutics to decrease the adverse effects. In folkloric medicine, Secondary metabolites which includes flavonoids are linked to benzodiazepine receptor affinity, which has been demonstrated in animal studies. Flavonoids have been shown that they reduce neuropathic pain in several animal models A potential role for flavonoids in treating neuritis is demonstrated in this paper. There is increasing evidence that flavonoids may have potential benefits in neuropathic pain. Flavonoids occur naturally in plants and can be found in various dietary sources. The benefits of this therapy have been demonstrated in numerous animal studies, including the reversal of hyperalgesia and allodynia. Neuropathic pain is also alleviated by flavonoids due to their anti-inflammatory effects which is evidenced by lowering multiple pro-inflammatory mediators, like IL-1β, IL-6, TNF-α, and NF-κB. According to preclinical studies, flavonoids may be able to treat neuropathic pain, but human trials are still in the early stages.

Keywords: Flavonoids, Neuronal injury, Neuropathic pain, Mechanism, Treatment

INTRODUCTION

Health systems around the world continue to struggle with chronic pain management as a prime conviction of disorder and disease (1). One of the most prevalent and disabling diseases in the US is chronic pain, which affects more than 100 million adults (2). Additionally, chronic pain accounts for an estimated $560 to $635 billion in healthcare costs and lost productivity, surpassing cancer, heart disease, and diabetes combined. (3). A lesion or disease of the somatosensory nervous system can cause neuropathy, a common type of chronic pain (4). Neuropathies often have multifactorial etiologies and are poorly understood pathophysiologically. Using a multidisciplinary approach to treat neuropathic pain is important to reduce pain, improve mood, and improve function (5). Neuropathy pain is less treatable with nonsteroidal anti-inflammatory drugs (NSAID), opioids, and other analgesics used to treat nociceptive pain (6). Among the first-line pharmacological treatments for neuropathic pain are tricyclic antidepressants, serotonin norepinephrine reuptake inhibitors (SNRIs), gabapentinoids, and topical medications. (7). It has been shown that there is a potential benefit from using phenytoin, mexiletine, dextromethorphan, tricyclic antidepressants, gabapentin, tramadol, pregabalin, opioids, and lamotrigine in the treatment of painful sensory neuropathy (8). However, because of their marked adverse effects, with presiding sedative effects, these treatments are often limited owing to their substantial pain-relieving effects. A wide range of chronic diseases are treated with natural products, including plant secondary metabolites, due to their restricted adverse effects and high effectiveness (9-10). Wine, cocoa, tea, and grapes all contain flavonoids, which are secondary metabolites (11). In addition to being antioxidants, flavonoids are also analgesics and anti-inflammatory substances (12). NF-kB-dependent suppression of proinflammatory cytokines, intercellular adhesion molecule suppression, signal transducer and activator of transcription 3, vascular endothelial growth factor suppression, as well as activation of antioxidant transcription factors like nuclear factor erythroid 2-related factor 2 (Nrf2) have all been implicated in these effects (13). In addition to treating neuropathic pain and oxidative stress, flavonoids are also considered safe natural alternatives to pharmaceuticals (14).

MECHANISM OF NEUROPATHIC PAIN

Afferent neurons respond ectopically to nerve damage through overexpression of the voltage-gated sodium channel messenger ribonucleic acid (mRNA). As a result, the action potential threshold is lowered, causing hypersensitivity due to clustering of these channels. This mechanism is also behind the pain relief effect of sodium channel blockers, such as lidocaine, in neuropathic pain (15). In addition to upregulation of receptor proteins, peripheral nerve injuries cause an increase in the number of these proteins. Physiological conditions partially express these receptors on primary afferent membranes. Vanilloid receptors, including the transient receptor potential cation channel subfamily V member 1 (TrpV1), play a major role in the observation of toxic heat increasing 43°C (16), while Several cold and menthol-sensitive transient receptor potential cation channels have been identified in the subfamily M (melastatin) member 8 of the transient receptor potential melastatin 8 (TRPM8) channel family which escalates at temperature ranges from 8° to 28°C. TRPM8 receptors are also expressed in neurons from the dorsal root ganglia that have a small diameter (17). A nerve injury can cause this channel to be upregulated, causing C-nociceptors to become more sensitive to cold, resulting in cold hyperalgesia (18).

A significant proportion of patients with peripheral as well as central neuropathy experience hypersensitivity and allodynia as a result of dominant synaptic facilitation (19). Furthermore, peripheral nerve damage alters the neuromodulators, and neurotransmitters, synthesis as well as the density of calcium channels in the pre-synaptic region (20). NMDA (N-methyl-D-aspartate) receptor phosphorylation and increased synthesis of ion channels are responsible for post-synaptic changes, while ion channels in neurons are not affected (21). As a result of these changes, the mitogen-activated protein kinase system and Nav1.3 are aberrantly expressed (22). In addition to their role as anti-inflammatory, antioxidant, and tumour-preventative agents, flavonoids have also been extensively studied for their anti-tumour properties (23). Polyphenols are naturally occurring compounds found in plants, vegetables, and legumes, among other dietary sources. It is possible to categorize flavonoids into different groups according to modifications to their carbon skeleton. They contain more than 4000 compounds in total. The presence of carbonyl groups on C-4, an unsaturated carbon ring, and a lack of glycosylation are thought to cause greater anti-inflammatory activity. The antioxidant activity of flavonoids, as well as the inhibition of protein kinases and transcription factors, has been implicated in neuroinflammation cascades. Inhibition of protein kinases and transcription factors is thought to be a key factor in their anti-inflammatory properties (24). There is strong evidence that flavonoids inhibit the mitogen-activated protein kinase (MAPK) pro-inflammatory signalling cascade and, in particular, are related with decreased levels of IL-1β, TNF-α, and IL-6 (24,25).

DIFFERENT NEUROPATHIC PAINS AND FLAVONOIDS:

Neuropathy associated with diabetes and flavonoids

A significant impairment of health conditions and economic consequences result from the treatment of neuropathic pain (26). Among 382 million people around the world Diabetic neuropathy is the most common cause of neuropathy (27). It has also been shown that genistein, luteolin, catechin, rutin, and pelargonidin reduce malondialdehyde (MDA) levels in animal models of diabetes. Free radical-induced oxidative stress as well as lipid damage can be detected by MDA (28, 29). Experimental evidence of diabetic neuropathy has commonly been based on behavioral assessments of chemical, mechanical, thermal, and tactile hyperalgesia in animal models (30). The effects of flavonoids on thermal, mechanical, chemical, and tactile hyperalgesia have been demonstrated in models of diabetes with significant reductions in allodynia. A number of flavonoids including fisetin, baicalin, naringenin, pelargonidin, rutin, naringin, hesperidin, and luteolin reduced diabetes mediated thermal hyperalgesia, although kaempferol, epigallocatechin gallate, luteolin and morin attenuated mechanical hyperalgesia (Table:1) (31-34). Naringenin's potential role in treating diabetic neuropathy has been studied in multiple studies. A streptozotocin injection was used in these studies to induce diabetes in these patients. Naringenin was injected intraperitoneally into rats for 25 or 50 mg/kg/day, which reversed both clinical and biochemical measures of diabetic neuropathy in a study (35). Through the reduction of p38MAPK signaling, which is implicated in the induction of pro-inflammatory mediators, quercetin reduced mechanical pain and hyperalgesia in a diabetic neuropathy model (36).

EFFECT OF FLAVONOIDS ON CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY

A study found that rutin and quercetin suppressed mechanical and cold nociception thresholds mediated by oxaliplatin (37). Routine and nanoemulsions of quercetin were effective in alleviating oxyliplatin-mediated mechanical allodynia (38). A rat model of chemotherapy-induced peripheral neuropathy showed antinociceptive activity in 6-methoxyflavone (Table:1) (39). Many studies on quercetin have been focused on chemotherapy-induced neuropathy caused by platinum-based agents such as cisplatin, paclitaxel, and oxaliplatin. Allodynia and hyperalgesia are also common complications of chemotherapy-induced neuropathy (40).

FLAVONOIDS AND CHRONIC CONSTRICTION INJURIES OF THE SCIATIC NERVE

Flavonoids including hesperidin, diosmin , and grape seed proanthocyanidins reduced both thermal and mechanical hyperalgesia (41, 42). In compare, other flavonoids that includes genistein, epigallocatechin gallate, epigallocatechin gallate derived compounds, morin, and isoorientin decreased only thermal hyperalgesia (43,44). A remarkable deduction in mechanical and thermal hypersensitivity was noticed with quercetin in comparison with morphine and gabapentin. A pre-injury dose of quercetin lowered mechanical hypersensitivity for a long time, indicating quercetin has antinociceptive properties in chronic constriction injury models (45). Among the many chronic neuropathic pain models, chronic constriction injury is one of the most widely studied. In addition to hyperalgesia, allodynia, paraesthesia, dysesthesia, and

spontaneous pain, chronic constriction injuries have several other symptoms (46). The mRNA expression levels of IL-33/ST2, IL-1b were reduced after a single serum diosmin administration, while TNF-a along with IL-33, ST2, and IL-1b were decreased after chronic administration. As well as decreasing oligodendrocytes and microglia expression levels, a single administration decreased astrocytes together with oligodendrocytes and microglia (47). Astroglia and microglia that express ionized calcium-binding adaptor protein-1 and glial fibrillary acidic protein were also inhibited by phorarin. (48). In the Chronic constriction injury model-induced neuropathic pain model, morin decreased IL-6, TNF-a, phospho-NF-kB, NF-kB, COX-2, iNOS, and PARP levels (49). The most abundant and active component of green tea is epigallocatechin-3-gallate, which belongs to the flavan-3-ol subgroup of flavonoids. Inflammation is reduced, oxidative stress is inhibited, and tumor growth may be modulated by it, according to numerous studies (50,51). Numerous studies show that it is effective in treating neuropathic pain in various rat models, as we present here. Experimental studies in rats with chronic constriction injury measuring epigallocatechin gallate's effectiveness for reducing thermal hyperalgesia (52).

NEUROPATHIC PAIN SIGNALLING PATHWAYS AFFECTED BY FLAVONOIDS

The GABAA receptors in flavonoids are responsible for their anti-inflammatory and antioxidant effects (53). Oxidative stress causes most metabolic disorders. Reactive oxygen species (ROS) and free radicals created by regular oxygen metabolism inside tissues and cells endanger them in addition to exogenous factors (54). A number of chronic diseases, including cancer, neurodegenerative disease, diabetes, and atherosclerosis, have been shown to benefit from flavonoids due to their antioxidant properties (55-57). Additionally, certain flavonoids inhibit free radical formation by playing an important role in iron chelation (58). Hesperidin and quercetin also reduced partial sciatic nerve ligated neuropathic pain and protected nerves from injury (59). In the case of ischemic reperfusion, xanthine dehydrogenase converts into xanthine oxidase, which is a precursor of free radicals. The enzyme plays a critical role in the metabolism of xanthine into uric acid. Many flavonoids, including quercetin, silibinin, and luteolin, have antioxidant properties that stop xanthine oxidase from working (60). Additionally, reperfusion causes inflammatory mediators as well as cytotoxic oxidants to be released as leukocytes are mobilized, thereby provoking the complement system. Leucocytes are immobilized by many flavonoids, resulting in a decrease in the serum complement system and inflammation as a result (61). Both neuropathic pain of peripheral origin and inflammation are associated with the same pathophysiological mechanism. Allodynia and hyperalgesia are both manifestations of these pathologies (62).

Table:1 Promising finding of flavonoids in neuropathic pain management.

Flavonoids	Model	Dose	Effects	References
Naringenin	Diabetic neuropathy	20, 40, and 80 mg/kg	Decrease neuropathic pain by down regulation of mediator cytokine including TNF-a	63
	Diabetic neuropathy	25,50, or 100 mg/kg/day	1.Dose dependent decrease in serum glucose level and HA1C levels 2.Decreased levels of TNF-α, TGF-β, and MMP-9	64
	Diabetic neuropathy	25 and 50 mg/kg/day	Improves diabetic neuropathy by its antioxidant and anti-inflammatory properties	63
Quercetin	Paclitaxel-induced neuropathy	20 or 60 mg/kg/day	Dose-dependent decrease in hyperalgesia and allodynia basing upon mechanical nociceptive thresholds and tail withdrawal latency	40
	Oxaliplatin-induced neuropathy	20 mg/kg/d	1.No change in mechanical allodynia caused by oxaliplatin 2.Reduction in c-Fos levels in DRG tissue samples	38
	Streptozotocin-induced diabetic	50 and 100 mg/kg	Antinociceptive activity through the opioidergic modulation mechanism that decreases diabetic neuropathic pain	65
Hesperidin	Diabetic neuropathy	50mg/kg and 100mg/kg	Significantly decrease hyperglycemia 1.Dose-dependent reduction in mechano-tactile allodynia and thermal hyperalgesia, with synergistic effect when combined with insulin	66
	sciatic nerve Chronic constriction injury	100mg/kg, 1000mg/kg	1.Hesperidin effect synergistically improved with coadministration of diosmin 2. Naloxone, bicuculline, and haloperidol variably inhibited antihyperalgesic	42

			effects of hesperidin/diosmin	
Epigallocatechin-3-gallate	Chronic constriction injury of sciatic nerve	10mg/kg, 30mg/kg, 50mg/kg,	1.Reduced thermal hyperalgesia 2.Reduction in FASN activity in dorsal horn of spinal cord 3.Reduced expression of TNF-α, IL-6, IL-1β, and NF-κB mRNA and protein in dorsal horn of spinal cord	67
	Chronic constriction injury	1 mg/kg	Ameliorates neuropathic pain through the suppression of TLR4 signal pathway that reduces the expressions of NF-kB, IL-1b and TNF-a	43
	Streptozotocin-induced diabetic	2 g/L	Ameliorates diabetic neuropathy by preventing oxidative stress	68
Luteolin	Streptozotocininduced diabetic	50, 100, and 200 mg/kg	Ameliorates diabetic neuropathy through the up-regulation of theexpression of Nrf2	69
Genistein	Chronic constriction sciatic nerve injury	1, 3, 7.5, 15, and 30 mg/kg	Ameliorate painful neuropathy by decreasing the mRNA expressions of IL-1b and IL-6 in sciatic nerve as well as protein expression of IL-1b in dorsal root ganglion and spinal cord	70
Catechin	Streptozotocin-induced diabetic	25 mg/kg and 50 mg/kg	Attenuation of diabetic autonomic neuropathy through the improvement in antioxidant enzymes in vagus nerves	28
Morin	Streptozotocin-induced diabetic	50 and 100 mg/kg	Reduces diabetic neuropathy by inhibiting NF□kB□mediated neuroinflammation and increasing Nrf2□mediated antioxidant defenses in high glucose induced N2A cells	71
Diosmin	Chronic constriction injury	1, 10 mg/kg	Ameliorates neuropathic pain by activating the NO/cGMP/PKG/KATP channel signaling	47
Fisetin	Chronic constriction injury	10 mg/kg	Relieves chronic neuropathy pain	31
Isoorientin	Chronic constriction injury	15, and 30 mg/kg	Provides relief from neuropathic pain By reducing IL-6 expression and TNF-a and IL-1b levels	44
Pelargonidin	Streptozotocininduced diabetic	10 mg/kg	Improve diabetic neuropathic hyperalgesia via attenuation of oxidative stress	72
Baicalin	Streptozotocin-induced diabetic	10, 20, and 40 mg/kg	Analgesic activity in diabetic neuropathic pain through transient receptor potential vanilloid 1	73
Kaempferol	Streptozotocin-induced diabetic	5 and 10 mg/kg	Reduces diabetic neuropathy by attenuating oxidative stress-mediated release of pro-inflammatory cytokines	74

CONCLUSION

The lack of treatment options and multifactorial nature of neuropathic pain make it difficult for patients and providers to manage. There have been numerous animal-model studies that demonstrate the potential value of flavonoids for treating neuropathic pain, as well as reversing hyperalgesia and allodynia in a variety of conditions, including diabetes, chemotherapy, and peripheral nerve injury. Flavonoids have been shown to improve many neuropathies pain conditions

in animal models as well as control various pain biomarkers. Agonists, such as GABA, can be altered by allosteric modulators at the GABAA receptors, thereby controlling their activity. Neuropathic pain may be managed effectively with flavonoids, which are strong allosteric modulators. As a result, there is a great deal of potential in flavonoids for the development of new therapeutic agents for Neuropathic pain, although more research is necessary.

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