

Review Article

Nerve Regeneration After Peripheral Nerve Injury, Are Flavonoids the Answer? A Scoping Review

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Introduction

Peripheral Nerve Lesions (PNL) are a group of entities that include sensory and motor nerve disorders. It has been estimated that 20 million people are affected in the US, generating an average cost of \$150,000 annually. This type of injury is associated with high disability depending on the location and type of injury, leading even to loss of the limb function. Among the most frequent mechanisms of injury are trauma, compression, iatrogenic lesions, metabolic and infectious alterations. It should be noted that trauma is the most frequent, with a prevalence of 1.3-2.8% [1,2].

There are different therapeutic options for its treatment, in which microsurgical reconstruction stands out. However, it must be considered that up to a third of the patients who receive the surgical intervention will have alterations in their functionality and quality of life related to incomplete recovery. Taking this into account, the need for new treatments that promote cell regeneration is imperative [3]. Among the available options, mesenchymal cells and bone marrow transplantation aim to promote cell differentiation processes, metabolic activity, and growth factors for post-injury repair [4,5]. Recently, flavonoids have been described as a novel tool to promote regeneration [6-10].

Abstract

Flavonoids are polyphenol compounds of plants origin with antioxidant, anti-inflammatory, immunomodulatory, and analgesic functions, among others. Peripheral nerve lesions represent a burden for patients and a high cost for the health systems. Although a diversity of surgical management is available, adjuvant therapies are required to improve regeneration time and prevent atrophy of the affected target organs. This review aims to synthesize the available information on the use of flavonoids in peripheral nerve regeneration. A review of the available literature was carried out, demonstrating that flavonoids are a therapeutic alternative that could favor axonal regeneration. However, clinical studies are required since the available works reviewed are experimental in murine models, and their extrapolation to humans is essential.

Keywords: Flavonoids; Peripheral nerve injury; Nerve regeneration; Schwann cell

Abbreviations: PNL: Peripheral Nerve Lesions; 7,8 DHF: 7,8-Dihydroxyflavone; BDNF: Neurotrophin Brain-Derived Neurotrophic Factor; trkB: Tropomyosin Receptor Kinase B; GDNF: Glia-Derived Neurotrophic Factor; BYHWD: Buyang Huanwu; GAP-43: Proteins Growth-Associated Protein 43; EGCG: Epigallocatechin-3-Gallate; NGF: Neural Growth Factor; SC: Schwann cells; Nrf2: Nuclear Factor Erythroid 2-Factor 2

Flavonoids are secondary metabolites of plant-based polyphenols, which promote pigmentation and herbal reproduction and are found primarily in fruits and vegetables [11,12]. Multiple benefits have been attributed to them since they have anti-inflammatory, immunomodulatory, and antioxidant effects, among others [12]. They are used in neurodegenerative diseases and as an adjuvant in central nervous system lesions. When discussing its use in nerve regeneration after a peripheral nerve injury, there is literature available describing its positive association, thus being a possible treatment option [6-10]. Considering the above, this review aims to synthesize the available information about the use of flavonoids in peripheral nerve regeneration.

Methods

A search of the literature was performed in the electronic databases PUBMED, EMBASE, COCHRANE, and LILACS with the terms "flavonoidal" OR "flavonoid" OR "flavonoids" OR "flavonoidic" OR "flavonoids" [MeSH Terms] OR "flavonoid" AND ("peripheral nerve injuries"[MeSH Terms] OR ("nerve regeneration"[MeSH Terms]). No discrimination was made based on study design or publication date. The articles found

were extracted to Rayyan software for later review, and duplicates were eliminated.

Eligibility Criteria

Articles included in this review had to use any molecule belonging to the flavonoid family as an intervention to assess its effect on peripheral nerve regeneration. When evaluating nerve regeneration, articles could use any measurement method, including different motor, sensory, and morphological evaluation tools. Articles had to be in Spanish or English. Articles that did not describe the methods used or for which the complete manuscript could not be obtained were excluded.

Article Selection Process

Three reviewers independently evaluated titles and abstracts of the manuscripts based on the eligibility criteria. Once discriminated, selection differences were resolved in a group reunion. Only those articles that the three reviewers approved were included. Subsequently, the complete manuscripts were analyzed, and data extraction was made. As a guide during the identification, review, and selection process, the PRISMA - ScR guidelines were followed [13].

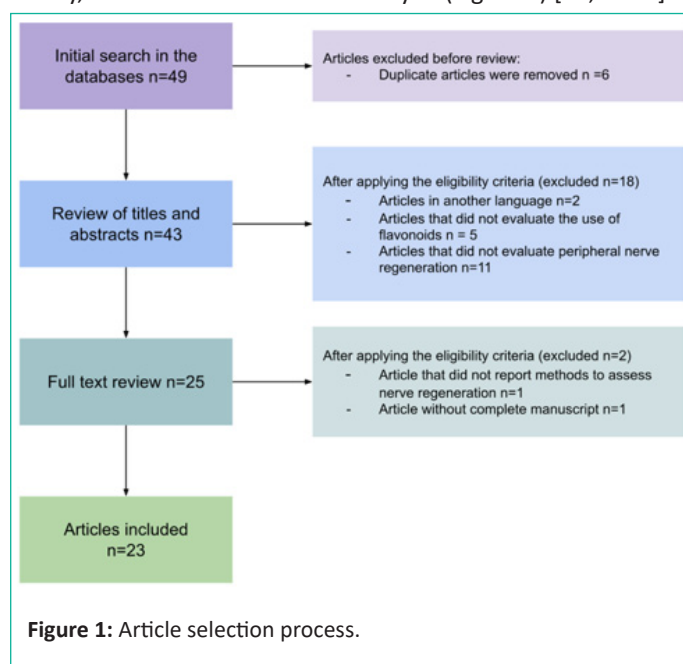
Data Extraction

Three reviewers independently assessed the full articles and extracted the title, authors, year of publication, study design, country, and research objectives. Additionally, the type of flavonoid used in the intervention, the study subjects, the methodology and tools for measuring nerve regeneration, results, conclusions, and limitations of each study were recorded. All this information was recorded in Excel © 2022 Microsoft.

Results

Selection of Sources of Evidence

After searching for articles in the electronic databases, 49 articles were obtained. Six duplicate articles were found. Subsequently, the review of titles and abstracts was carried out by applying the eligibility criteria, where 25 papers were selected that met all the characteristics. After reviewing the complete articles, those that did not have the entire manuscript or did not report the method for evaluating regeneration were excluded. Finally, 23 articles remained for analysis (Figure 1) [10,14-35].



Characteristics of Sources of Evidence

Intervention

In the selected medical literature, 12 different types of flavonoids were found to favor peripheral nerve regeneration, 7,8-dihydroxyflavone (7,8 DHF), baicalin, bogijetong, buyang huanwu, epigallocatechin-3-gallate, epimedium, myricetin, naringin, pueraria lobata, quercetin, red propolis, and silymarin.

7,8-Dihydroxyflavone (7,8 DHF)

One of the essential growth-promoting molecules used for axonal regeneration in peripheral nerves is the neurotrophin Brain-Derived Neurotrophic Factor (BDNF), which promotes Schwann Cell (SC) transformation and stimulates neurite elongation by binding to receptors from the tropomyosin receptor kinase B (trkB). In vitro experiments show that this molecule binds to the trkB receptor with high affinity, producing tyrosine phosphorylation and activating the same cascade of BDNF signaling components. The magnitude of these molecular changes is like those observed in rodents with sciatic nerve lesions treated with recombinant human BDNF, neurotrophin 4/5, electrical stimulation, or treadmill exercise, which share the mechanism by which they increase trkB signaling in regenerated axons. It has been shown that injections or topical application of 7,8 DHF at the time of nerve repair promote axonal regeneration, increasing the elongation of regenerated axons and improving muscle reinnervation [34].

Baicalin

Scutellaria baicalensis Georgii is a plant used to treat inflammatory processes, fever, ulcers, cancer, prophylaxis and treatment of cardiovascular, gastrointestinal, and immune diseases [36]. Clinical observations have shown its effectiveness in treating nervous system excitability conditions, neurosis, and insomnia [37]. Results of recent studies report that the flavonoids present in its leaves and roots have neuroprotective effects, specifically Baicalin, with a wide variety of biological functions, with anti-inflammatory, antioxidant, and anti-apoptotic effects [38]. Previous studies have reported its neuroprotective effect in rats, with the ability to promote neuronal differentiation of neural stem cells [39]. It has been demonstrated that significantly improves SC survival and function in vitro via upregulation of the S100 protein, a potentially critical factor contributing to neuronal development and stimulating the expression of Glia-Derived Neurotrophic Factor (GDNF), BDNF and Ciliary Neurotrophic Factor [15]. In other studies, the addition of Baicalin to culture media modulates the growth of cells derived from the dorsal root ganglion in the number and length of their neurites, accompanied by migration of SC, which suggests better survival of the cultured neurons and greater branching of the regenerated neurites, probably dependent on the presence of antioxidant flavonoids [35].

Bogijetong-Tang

Bogijetong-tang has been used in treating neuropathic pain and regulating serum glucose levels in diabetic patients in traditional Asian medicine [40]. It has been reported as a promoter of regenerative responses in spinal cord injuries, as well as in axonal regeneration after PNL and neuronal survival associated with Schwann cell activation [41-43]. Other studies show a protective effect in neuropathic lesions such as taxol injection or crush lesions in peripheral nerves [16].

Buyang Huanwu (BYHWD)

Overexpression of the Hsp27 protein in rodent studies have shown acceleration of axonal regeneration and motor recovery after prolonged injury, implying a potential application in human patients [44]. On the other hand, it has been reported that BYHWD protects SC from oxidative stress, mediates regenerative responses after spinal cord injury, and axonal regeneration in sciatic nerve injuries, acting on regenerated axons and SC [45,46]. It has been shown that treatment with BYHWD over-regulates proteins Growth-Associated Protein 43 (GAP-43) production in injured axons and activates Cdc2 signaling in SC. Sensory and motor activity results were significantly high in rats treated for prolonged periods. In humans, these results are lower, probably because the distances that regenerated axons must travel are much longer, and human SC at the distal ends of the lesions are less responsive, especially in prolonged denervation [22].

Epigallocatechin-3-Gallate (EGCG)

EGCG is the most abundant polyphenol in green tea, it has shown to have neurological effects, improve cognitive function and learning abilities, and prevent cardiovascular diseases and cancer. Other effects have shown that it slows the progression of neurodegenerative disorders due to a potential to inhibit neuronal apoptosis triggered by neurotoxic activities such as oxidative stress and neuroinflammation. In addition, it protects muscle fibers from cell death by activating anti-apoptotic signaling and inhibiting overexpression of the apoptotic factors as p53. It improves morphological recovery in skeletal muscle tissues after peripheral nerve injuries in rats, demonstrated by histological sections where reduced thickness and aggregate of connective tissue in the muscle fibers of treated animals is observed and significant progression of the response [17]. The administration of green tea extract to rats improves motor and sensitive reflexes and reduces hyperalgesia and allodynia in chronic compressive lesions of the sciatic nerve [47]. There is evidence that EGCG can reduce NADPH-d/nNOS reactivity and improve the survival of motor neurons in the injured hypoglossal nucleus and vagus nerve [48]. There is clear evidence that EGCG administration accelerates the recovery of motor and sensory function in sciatic nerve injuries, improving their regeneration *in vivo*, it significantly reduces the ultrastructural histological changes associated with nerve injury, indicating rapid cell regeneration with decreased signs of apoptosis, these characteristics suggest a neuroprotective mechanism against functional losses and neuropathological alterations seen in PNL [19]. The therapeutic effects are associated to the up regulation of various neurotrophic factors such as BDNF, GDNF, and NT3 [26]. Recent studies have demonstrated another effect of EGCG by finding an up regulation of glutathione reductase that supports the idea that it acts in an indirect pathway for the induction of enzymes and transcription factors of neuronal regeneration. In experiments with regenerative tubes to treat segmental losses of peripheral nerves, this compound has been added showing its antioxidant and anti-inflammatory effects during the whole recovery period [10]. Also, it improves the regeneration of the treated peripheral nerves and a good regenerative process of the gastrocnemius muscle affected in sciatic nerve lesions [20]. Less adhesion of nerves to surrounding tissues has been found, probably due to its anti-inflammatory effects. It also promotes the regeneration of blood vessels at the injury and around the nerve repair. Improvement of the muscle weight affected by nerve injury has been shown due to faster regeneration com-

pared to the control study groups and increased nerve conduction velocity in electromyography studies, indicating that it prevents muscle atrophy. The expression of the GAP-43 protein has been detected in animals. A more significant number of myelinated fibers of the repaired nerves was found, greater thickness of the myelin layer, and normal morphology of the SCs has been found [23].

Epimedium

Epimedium extract has been used in China to treat erectile dysfunction, postmenopausal syndrome, and osteoporosis for hundreds of years, Icariin being its main component. It has been shown to promote bone formation and have neurotrophic effects in *in vivo* and *in vitro* experiments [49,50]. It has also been found to promote muscle function recovery after spinal cord injury in rats [51]. Other studies suggest that since nerve regeneration is a sum of factors, these compounds promote its development, although the details of their mechanisms of action are still unclear [21]. A more recent study found that local application of Icariin contributes to peripheral nerve regeneration, increasing the number of regenerated nerve fibers and nerve conduction velocity. Also, improving functional recovery measured and comparative histopathological changes [27].

Myricetin

It is a plant-based flavonoid (3,3',4',4,5,5',7-hexahydroxyflavon) present in various vegetables, fruits, nuts, and red wine. It has been reported to have antioxidant, antibacterial, cardioprotective, and antiproliferative properties [52]. A recent study investigated its effects after sciatic nerve injury in rats, showing significantly high values in the sciatic functional index and the arthroscopic position index and recovery of sensorimotor functions. The expression of BDNF and TrkB factors was also established, reflected in a more remarkable axonal regeneration and myelination [29].

Naringin (4',5,7-Trihidroxi Flavonone 7-Ramnoglucosida)

Naringin is a flavonoid glycoside in grapefruit, tomato, and citrus fruits. It has been shown to significantly increase SC proliferation after neurectomy of sciatic nerve [33]. Also, acute and chronic pain disorders such as hyperalgesia after PNL have been significantly reduced by treatment with naringin due to its antioxidant properties which act as a non-enzymatic cellular defense, maintaining cellular homeostasis by reducing oxygen radicals and by its inhibitory effect of neurotrophin p75, promoting axonal regeneration and functional recovery [53-55]. Other studies have found that it suppresses the activation of c-Jun N-terminal protein kinase, preventing cell damage, which is demonstrated in the improvement of sciatic function index tests [30].

Pueraria Lobata

Puerarin has been used in traditional Chinese medicine for treatment of various diseases, including nerve diseases, for its effects as a free radical scavenger, antioxidant, inhibition of inflammatory response and reperfusion, and improvement of cerebral microcirculation, suggesting that it may reduce the initial damage in PNL and facilitate their repair. GAP43 is a membrane-associated phosphorylated protein related to neuronal growth, neurite formation, and brain plasticity, in the study groups treated with puerarin, GAP43 overexpression was found in the injured segments, where it was observed that the number, integrity, and thickness of the myelin sheaths of the regenerated

axons were more significant, confirmed by histological findings, and the muscle mass index [31]. Its oral administration has been shown to promote regeneration of injured sciatic nerves and promoting axonal growth, metabolites of *Pueraria lobata* have shown nerve differentiation effects *in vitro*, increasing the number of neurite-bearing cells and expression of synapsin I in cell cultures supplemented with NGF. Quality of nerve regeneration and its morphology compared between study groups confirm that nerve structures are more mature with higher values of total nerve area, endoneuria area, and number of myelinated axons. Daidzein, principal metabolite, has been found to bind to estrogen receptors and exhibits estrogenic activity, markedly accelerating axonal growth, additionally, daidzein has an immune stimulatory effect, increasing phagocytic response of macrophages and altering prostaglandin synthesis, producing degeneration of the damage nerve, and releasing neurotrophic factors that accelerate the maturation of regenerated nerves [18].

Quercetin

Quercetin shows beneficial effects in several *in vivo* models of neural disorders, such as brain trauma, spinal cord injury, and cerebral ischemia [56]. *In vitro* studies also reveal increase neuronal survival and decrease of toxicity and neuroinflammation [57]. Also induces neurite outgrowth by promoting GAP-43 expression, increased cAMP expression, and remyelination after sciatic nerve injury in rats [25,58]. Intracellular cAMP levels are directly associated with activation of intrinsic axonal growth capacity, the overregulation of IL-6, which, through STAT3, induces regeneration-related genes, such as GAP43 [32]. Treatment with quercetin shows significant recovery after PNL, demonstrated by increased motor functional indexes, reflecting axonal integrity and number of reinnervated fibers in target muscles and the elongation of regenerated neurites stimulated by synaptotagmin-1, as well as increased diameter and thickness of the myelin sheath. More recent studies show that it promotes the expression of myelin-associated glycoprotein and peripheral myelin protein 22, which benefit remyelination, in addition to promoting SC proliferation and migration, which reflects the suppression of oxidative stress by reducing the production of Nox4 and Duox1 and promoting the expression of Nuclear Factor Erythroid 2-Factor 2 (Nrf2) and SOD2, both proteins involved with inhibition of free radical production [25,59]. It reduces oxidative stress and inflammatory response, attenuating neuronal autophagy and apoptosis [28].

Red Propolis

Red propolis plant extract contains antioxidant agents, including phenols, flavonoids, naphthoquinones, and others. It has shown several biological activities, including cytotoxic activity against cell tumors and antimicrobial properties. These antioxidant agents help to clear myelin by macrophages and thus accelerate the regenerative process of the injured nerve [60]. Other studies evidence their neuroprotective effects, improving sensory and motor recovery, decreasing inflammation, and increasing myelin axons [24].

Silymarin

Silbum marianum fruit extract comprises one flavonoid, taxifolin, and seven flavones. Antioxidant effects are attributed to it, such as direct scavenging of free radicals and chelation of free Fe and Cu, preventing their formation and inhibiting specific enzymes producing them and protecting the integrity of

mitochondria under stress conditions, maintaining an optimal intracellular balance by activation of a variety of antioxidant enzymes and non-enzymatic antioxidants mainly through Nrf2 pathway [61]. These characteristics can be demonstrated with the improvement of axonal regeneration and CS, accompanied by the myelination process and structural recovery of the regenerated nerve fibers [14].

Discussion

Flavonoids have existed in nature for about a billion years, interacting with evolving organisms. They are defined as a broad compound of polyphenols, origin in the plant kingdom and found in vascular plants due to their secondary metabolism. They are low molecular weight compounds that carry numerous functions, among as protective agents against UV light, anti-inflammatory, analgesic, anti-allergic, venotonic action, and especially their potent antioxidant activity. Its function has recently been studied in other fields, such as mental health and the nervous system, with positive effects on nerve signaling and the function of molecular receptors in the central nervous system [62-64].

As a matter of fact, injured nerves in the peripheral nervous system can regenerate and reinnervate their target organs [65]. After an injury, approximately one-third of patients remain with incomplete functional recovery. Furthermore, it is associated with chronic pain, muscle atrophy, and weakness, resulting in lifelong disability and costs in medical follow-up [14]. Advanced microsurgical techniques have established effective treatment for this entity, but adjuvant therapies are required to improve regeneration times and prevent atrophy of the target organs. Recently, flavonoids have been extensively studied, finding beneficial effects to complement or improve different treatments, given their antioxidant and anti-inflammatory capacity [66].

The present study evaluated the available literature to determine if flavonoids after PNL could be a treatment that benefits nerve regeneration and improves outcomes. Many studies, both *in vitro* and *in vivo*, have shown the positive effect of flavonoids in the regeneration of the peripheral nervous system, evaluating sensorimotor recovery. These effects are related to cell signaling pathways that reduce neuroinflammation and oxidative stress and promote the expression of neurotrophic and axonal protection factors such as BDNF, NGF and TrkB. The molecular mechanisms are extensive and still not fully clarified; however, most studies have shown that flavonoids, due to their neuroprotective, anti-inflammatory, and anti-apoptotic effect, decrease the degree of inflammation and increase the number, integrity, and thickness of the pods of myelin, which improves functional recovery compared to placebo [24]. Recovery of normal neurological function remains a significant challenge, however, flavonoids could be an effective adjuvant therapy to improve axonal regeneration and sensorimotor recovery.

The diversity of evaluated studies and origin countries demonstrates the growing interest in flavonoids to improve axonal regeneration in PNL. China has the most studies, probably due to the massive consumption of flavonoids for different purposes. Most articles were experimental studies in a murine model, showing the ease of this type of study in these animals. Nevertheless, similar studies in large animals are necessary to explore the optimal treatment conditions, maximize the translational potential of these molecules, and extrapolate results to humans.

Limitations

To date, this article is the first review of the use of flavonoids in nerve regeneration available in the literature. Articles published in different languages were included, and multiple databases were searched to reduce publication bias. A possible limitation of this work is that no review of the gray literature was carried out.

Conclusions

PNL is associated with high costs to health system and high disability. Advances in nerve repair require adjuvant therapies to reduce care costs and improve sensory, motor, and proprioceptive recovery after the injury. Based on what has been observed, flavonoids are a therapeutic alternative that could favor nerve regeneration, given their anti-inflammatory and antioxidant function. Since the articles evaluated are experimental studies, additional controlled clinical studies are required to determine the effectiveness of the different types of flavonoids in nerve regeneration, their mechanisms of action, the factors involved, and their safety.

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Conflicts of Interest

None of the researchers declared any conflict of interest with the topic to be discussed.

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