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Letter to Editor

Use of Plant Derivatives, A New Approach to Enhance Peripheral Nerve Regeneration

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Throughout history, the use of plants has played a role in the development of medical treatments. As science and technology have advanced, the routes of administration, extraction processes, and research involving plant derivatives have improved, leading to the adoption of the term 'Flavonoids' to refer to a secondary metabolite in plants, which varies according to the species or fruit. Plants and their derivatives have been extensively investigated, revealing benefits in the treatment of a broad spectrum of diseases, including anticoagulants (warfarin), headache management (ergotamine), antiarrhythmics (digoxin), among others. The use of flavonoids in the central nervous system has been studied in models of nerve regeneration, prompting the extrapolation of studies focused on peripheral nervous system treatment, which is a novel topic of interest in the scientific community. The plant kingdom harbors a multitude of plants, each generating a vast array of flavonoids. Therefore, initiating research on these derivatives holds the potential for numerous benefits.

Peripheral nerve injury is a common pathology in emergency departments, with 1.5% to 4% of trauma cases presenting some degree of peripheral nerve injury. This poses several challenges in the management, treatment, and recovery of patients, as following a nerve injury, axons undergo a phenomenon known as Wallerian degeneration. In this phenomenon, the distal end of the nerve prepares to receive, under suitable conditions, axons growing from the proximal end of the injured nerve. The growth rate is approximately 1 mm per day, a crucial factor in preventing muscle atrophy due to prolonged denervation. Microsurgical nerve repair is an alternative; however, long-term outcomes in patients and the morbidity associated with the injury may lead to disabilities or motor and sensory impairments.

The molecular markers involved in nerve regeneration include GAP-43 (Growth Associated Protein-43), a bidirectional transport protein that regulates axonal regeneration in damaged peripheral nerves. It is localized in the growing axonal cone to promote synaptogenesis after injury. Other markers such as BDNF (Brain-Derived Neurotrophic Factor) and NGF (Nerve Growth Factor) induce the proliferation of Schwann cells, aiding in the survival and differentiation of neurons, ultimately contributing to axonal growth. NF200 is a marker found in myelinated neurons. These factors increase in the first week after injury and decline over time, leading to the hypothesis that this initial increase is due to the proliferation of Schwann cells in the early stages of peripheral nerve injury.

In the past two years, research in Asia has focused on assessing nerve regeneration in in vivo and in vitro animal models. One such study was conducted in Korea by Seo, T.-B., et al. [1], who evaluated the effects of Nobiletin (a polymethoxylated flavonoid extracted from citrus fruits) on neurite and axonal growth following sciatic nerve injury in rats. Rats were randomly divided into groups: a control group without any intervention, a second group with sciatic nerve injury treated with a placebo at 1 and 3 days post-injury, and finally, a sciatic injury group treated with Nobiletin at 1 and 3 days post-injury. It is noteworthy that in this study, Nobiletin was injected 10 mm distal to the injury, and the placebo was administered in the same location. For the in vitro study, dorsal root ganglia (DRG) were utilized to observe the expression of GAP-43 and BDNF in primary Schwann cell cultures through immunofluorescence and Western blot. The findings indicated that Nobiletin regulates DRG neurite growth at doses of 50 to 100 µM, increases GAP-43 expression both in vitro and in vivo, controls early-stage BDNF activation in nerve regeneration, and facilitates axonal growth from 5 to 10 mm two weeks after sciatic nerve injury.

Similarly, in China, Chen J., et al. [2] studied the use of green tea polyphenols (GTPs) in peripheral nerve regeneration. Rats underwent surgical sectioning of the sciatic nerve 0.8 cm from the piriform muscle, with subsequent epineural suturing and wound closure. Notably, in this study, the flavonoid was administered intraperitoneally with GTPs at a dose of 50 mg/kg/day for 2 weeks. Rats were evaluated electrophysiologically, based on triceps muscle weight, optical microscopy observation, transmission electron microscopy, RT-qPCR, and Western blot at 2, 4, 6, 8, and 12 weeks post-injury.

Results indicated an overall improvement in the treated group, displaying enhanced mobility, absence of plantar ulcers, reduced tissue adhesion in the periphery, and increased nutrient vessels. Electrophysiological tests in the GTPs group were statistically significantly better than the control group, though no significant difference was observed by week 12 post-injury. Triceps weight, the number of myelinated fibers, neural tissue morphology, and fiber diameter were all superior in the GTPs group. Notably, molecular markers of nerve regeneration were better expressed in the GTPs group at week 8 post-injury. However, by week 12, no significant difference was observed between the groups.

Other flavonoids, such as Quercetin, have been identified for their ability to induce neurite growth by promoting the expression of GAP-43. Isoquercetin, on the other hand, demonstrates the promotion of nerve regeneration and remyelination following nerve injury in rats. The ongoing exploration of novel flavonoids in peripheral nerve regeneration holds the potential for advancements that may complement surgical management, currently the cornerstone of nerve injury treatment. The demystification and implementation of these plant extract studies could lead to new discoveries, not only within the field of neuroscience but also in various other medical domains where phytotherapy is often met with skepticism due to limited scientific support. The continuous investigation of flavonoids in peripheral nerve regeneration may pave the way for novel therapeutic approaches and contribute to a broader understanding of their potential applications in diverse medical contexts.

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