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Emerging role of genipin as a therapeutic in diseases of the peripheral nervous system

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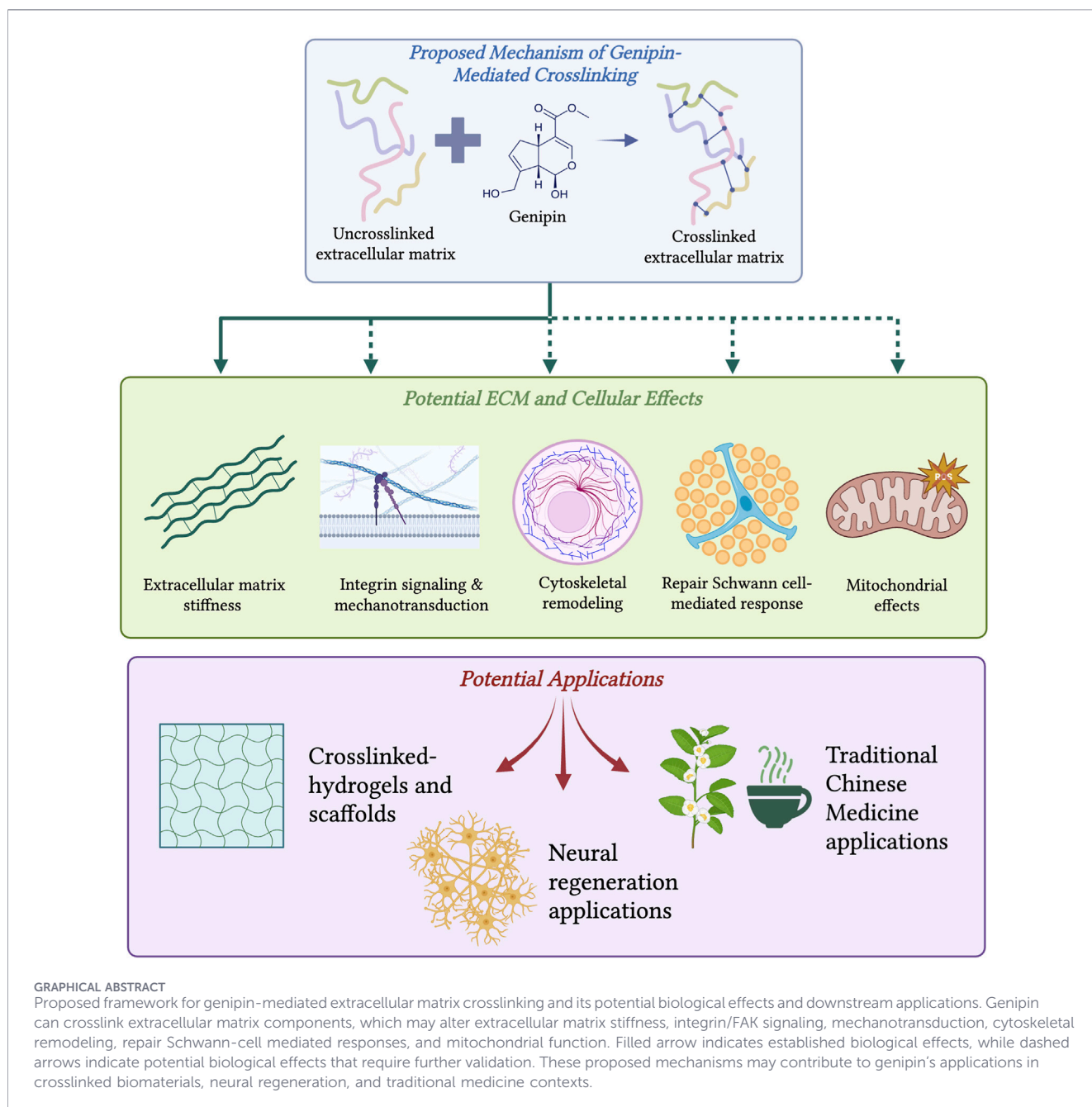
Genipin is bioactive compound derived from the fruit of *Gardenia jasminoides* that has been implicated in three primary contexts. First, as the active component of Traditional Chinese Medicine, genipin has been used for centuries to treat various inflammatory conditions. Second, genipin is widely employed in bioengineering as a low-cytotoxicity crosslinking agent to stabilize and stiffen extracellular matrices and biomaterials. Third, purified genipin has been reported to confer therapeutic benefits across a broad spectrum of disease models, including metabolic, inflammatory, and neurodegenerative conditions. The breadth of these applications raises a possible mechanistic question: does genipin exert multiple independent molecular effects, or do its diverse biological outcomes arise from a single upstream mechanism? We propose that genipin's extracellular matrix (ECM) crosslinking activity may represent an important and underexplored upstream mechanism of action. Specifically, we hypothesize that ECM crosslinking alters the biophysical microenvironment in a manner that subsequently modulates mitochondrial function and inflammatory signaling pathways, ultimately leading to the reported therapeutic effects. We further posit that this mechanism is particularly relevant within the peripheral nervous system. In both human cell-based and murine models, genipin protects against neurodegeneration and enhances regeneration following axonal injury. Chemical abrogation of genipin's crosslinking capability removes these effects, supporting a causal relationship between matrix crosslinking and neuroprotection. Collectively, these observations suggest that inhibition of genipin's crosslinking activity abrogates its therapeutic efficacy. We therefore propose that genipin's ECM crosslinking capacity may constitute an upstream biological function, explaining its wide-ranging applications and positioning it as a promising biologically derived therapeutic agent.

KEYWORDS

crosslinker, extracellular matrix (ECM), genipin, human pluripotent stem cell (hPSC), peripheral nerve injury

Introduction

Genipin is a naturally occurring small molecule iridoid compound derived primarily from the fruit extracts of *Gardenia jasminoides* and *Genipa americana* plants belonging to the Rubiaceae family. Known as *Zhi Zi* in TCM, the fruit of *Gardenia jasminoides* has been used for centuries as a treatment for its anti-inflammatory, choleretic, diuretic, and antipyretic effects (Li et al., 2016). Subsequent studies demonstrated that some of these pharmacological effects were mediated by genipin (Aburada et al., 1980; Aburada et al., 1978). Many formulations containing *Zhi Zi* have also demonstrated therapeutic potential for central nervous system (CNS) disorders, such as depression, stroke, and Alzheimer's



disease (Li et al., 2016). Beyond its widespread use in TCM preparations, genipin currently occupies two distinct and disconnected roles in modern biomedical research. First, it is commonly used as a biocompatible crosslinking agent in tissue engineering applications to stabilize ECM-based biomaterials such as collagen, gelatin, and chitosan (Xu et al., 2024). Second, it is studied as a bioactive small molecule with reported anti-inflammatory and antioxidant activities with potential therapeutic effects in various metabolic conditions (Sobolewska et al., 2025). Despite these parallel investigations into genipin's applications, there is an incomplete understanding of whether genipin's reported therapeutic effects are pharmacologically independent or a result of its chemical crosslinking reactivity. We contend this conceptual separation has limited the field's ability to fully

understand genipin's biological activity, as it isolates its chemical reactivity from its reported cellular effects. We propose that genipin's primary pharmacological activity originates at the level of the ECM, where its crosslinking activity reshapes the physical and structural properties of the microenvironment. This reshaping, in turn, affects downstream cellular signaling pathways, providing a mechanistic bridge between the historically disconnected structural and pharmacological roles.

Genipin as a crosslinker in peripheral nervous system (PNS) research

Genipin's function as a crosslinker is rooted in its chemical reactivity. Genipin was first proposed as a natural crosslinking agent

in 1988 based on initial observations of its ability to form an adduct with glycine (Fujikawa et al., 1988). While the precise mechanism of genipin's crosslinking is unknown, the widely accepted mechanism includes a nucleophilic attack by an amino group of a protein at its C-3 position, which opens the dihydropyran ring. This results in a reactive aldehyde intermediate that can undergo a second nucleophilic attack by a primary amine, which leads to the formation of stable covalent linkages between genipin and adjacent proteins (Butler et al., 2003). Genipin is most commonly crosslinked with biomaterials such as a collagen, gelatin, and chitosan, all of which contain several primary amine groups that readily react with genipin to form stable networks (Xu et al., 2024). Moreover, genipin-crosslinked scaffolds and hydrogels are mechanically and biologically superior to those using synthetic crosslinking agents, such as glutaraldehyde and formaldehyde, which exhibit higher cytotoxicity and poor biocompatibility (Xu et al., 2024). As a result, genipin has been increasingly used as a biomaterial crosslinker aimed at supporting regeneration across injury models in the CNS and the PNS.

The PNS consists of the afferent sensory nervous system and the efferent motor and autonomic nervous systems. The sensory nervous system detects and carries signals, such as pain, temperature, and touch, towards the CNS, whereas the autonomic nervous system carries signals from the CNS to organs and tissues to regulate their function (Murtazina and Adameyko, 2023). The autonomic nervous system operates largely unconsciously to maintain homeostasis and modulates involuntary responses, such as heart rate and blood pressure (Murtazina and Adameyko, 2023). Genipin's crosslinking capability becomes particularly relevant in disease models of the PNS, where axon stability, regenerative capacity, and ultimately, neuronal survival, are intimately linked to ECM composition and organization.

Peripheral nerve repair is a complex process involving coordinated interactions among different ECM components, signaling molecules, growth factors, and migratory Schwann cells (SCs) to guide axon regrowth (Jiang et al., 2024). The ECM is composed of many proteins, including collagen, fibronectin, laminin, as well as proteoglycans and glycosaminoglycans, providing structural support and facilitating communication between cells (Jiang et al., 2024). The composition, structure, and elasticity of the ECM heavily influence PNS homeostasis, injury response, and regeneration. SCs typically function to myelinate peripheral neurons, allowing for nerve impulses to be conducted; however, in the context of peripheral nerve injuries, these SCs are able to dedifferentiate into repair SCs to enable nerve regeneration (Jeanette et al., 2021). The ability of repair SCs to dedifferentiate, proliferate, and remyelinate axons in peripheral nerve injury is strongly regulated by the ECM stiffness as well as mechanotransducers, YAP (Yes-associated protein) and TAZ (PDZ-binding motif) (Jeanette et al., 2021; Xu et al., 2021). ECM-derived mechanical cues are translated to intracellular signaling responses through integrins, focal adhesions, and the actin cytoskeleton through a process called mechanotransduction (Xu et al., 2021; Metafune et al., 2025). Downstream activation of FAK (focal adhesion kinase) further regulates canonical signaling pathways involved in cell proliferation, migration, and axon regeneration, while also contributing to YAP/TAZ-mediated transcriptional responses important for SC-mediated repair (Metafune et al., 2025). These ECM-mediated processes are likely to differ across different types of PNS injuries, such as traumatic injury, diabetic neuropathy, and genetic neuropathies.

Historically, the application of genipin in PNS research has been limited to models of acute nerve injury, such as sciatic nerve transections, crush injuries, and short-gap severances, tears, and lacerations. The standard of treatment for such injuries is nerve autografts; however, this typically results in the loss of nerve function at the donor site. The Nerve Bridge Technique has emerged as a potential method to bypass nerve donation. This method uses a nerve conduit or a hollow, tubular scaffold to bridge nerve gaps and provide physical support for regenerating axons, Schwann cell migration, and ECM remodeling. In these contexts, genipin-crosslinked conduits have shown improvements in axonal regeneration and electrophysiological recovery in animal models (Chang, 2009).

In these studies, genipin's activity is interpreted mainly through a structural lens. Genipin is primarily regarded as a crosslinker that offers mechanical and structural stability to the biomaterial itself rather than as a biologically active compound capable of modulating regeneration. This limited interpretation largely assumes that the intrinsic repair mechanisms within the environment remain intact and that scaffold reinforcement alone is sufficient to enhance regeneration. We believe that this limits exploration into genipin's potential as a therapeutic in the setting of peripheral nerve regeneration and how it may influence and modulate cellular processes. Moreover, the experimental design of these studies only explores a subset of peripheral nerve injuries caused by physical trauma. However, this sharply contrasts the clinical reality of many peripheral nerve injuries and neuropathies, which arise from chronic, progressive disease states rather than traumatic injury. Peripheral nerve damage and neuropathies arise from a variety of insults including vascular issues, autoimmune diseases, infections, nutritional deficiencies, exposure to toxins, chemotherapy, and diabetes. These conditions can compromise the functional capabilities of the PNS. Notably, despite the prevalence and severe functional consequences of peripheral nerve injuries, the PNS has largely remained comparatively underappreciated within the broader neuroscience research landscape.

Genipin as a bioactive molecule in PNS research

The assumption that genipin functions solely as a crosslinker for hydrogels and scaffolds for PNS nerve regeneration may overlook its pharmacological effects. Emerging evidence from non-PNS-related studies show that genipin can regulate inflammatory signaling (Jaafar et al., 2024), mitochondrial function (Cho, 2022), and cellular stress responses (Luo et al., 2019), suggesting that genipin's role as a crosslinker may extend beyond mechanical stabilization.

Within the broader clinical context of peripheral nerve injuries, the regenerative improvements shown in genipin-crosslinked nerve conduits warrant reconsideration. Evidence supporting a broader biological role for genipin in the PNS emerges from disease modeling of chronic and progressive peripheral neuropathies. We have previously explored genipin as a bioactive small molecule therapeutic in a model of Familial dysautonomia (FD), a rare genetic disorder characterized by impaired development and function of sensory and autonomic neurons (Saito-Diaz et al., 2024). In *in vitro* models of FD using induced pluripotent stem cells (iPSCs), genipin administration reversed neurodegenerative and neurodevelopmental phenotypes, improving neuronal survival and

functional outcomes, thus providing foundational evidence that genipin may exert direct biological effects on peripheral neurons. Importantly, genipin treatment prevented degeneration of iPSC-derived FD neurons. We further showed that this occurred via genipin's crosslinking activity, since chemical modification of genipin into 1,10-anhydrogenipin lost its functional activity in those cellular assays (Saito-Diaz et al., 2024; Zhang et al., 2006). Finally, ECM crosslinking increased its stiffness, reorganized the cytoskeleton, and activated signaling pathways, linking crosslinking to genipin's pharmacological activities. Importantly, this study established genipin as a compound that rescues sensory deficits *in vivo*. In two independent FD mouse models, genipin rescued neurodevelopmental defects in embryos, increasing sensory neuron survival, reinnervation of target tissue, and rescued the behavioral fine touch response. This *in vivo* rescue of both development and degeneration highlights genipin's ability to modulate PNS pathology at a whole-organism level, in addition to isolated human *in vitro* models, strengthening the biological relevance of its activity in a system that closely models human PNS degeneration. Moreover, the study provided evidence that genipin enhances injury-based axon regeneration in both PNS and CNS neurons, including sympathetic, sensory, and prefrontal cortical neurons.

Beyond FD models, diabetic neuropathies, including its main subtypes distal symmetric polyneuropathy and diabetic autonomic neuropathy, represent a compelling next test case to test the potential regenerative and neuroprotective effects of genipin. Diabetes mellitus is a chronic metabolic condition characterized by hyperglycemia and is the leading cause for sensory and autonomic peripheral neuropathies in patients, with 50% and between 20% and 40% of patients experiencing progressive sensory and autonomic dysfunction, respectively (Yang et al., 2025). Investigating genipin in the context of diabetic neuropathies, in addition to existing research on FD models, would further validate whether genipin can promote axon regeneration of degenerating neurons or prevent degeneration as a prophylactic. Additional studies are needed to understand whether neuronal function remains intact and target-organ communication is preserved or restored in a metabolically hostile environment.

Other applications and translational potential of genipin

One of genipin's intriguing features is its ability to produce a vibrant blue pigment following its reaction with primary amines (Neri-Numa et al., 2017). This property has made genipin particularly attractive in the food industry, where it has been used as a natural, non-toxic colorant alternative to synthetic dyes, such as Jagua (genipin-glycine) blue derived from *G. americana* and gardenia (genipin) blue derived from *Gardenia jasminoides*. These natural dyes are approved for use in the United States (US), after a recent push by the US government to encourage the development and adoption of safer, naturally derived substitutes in the food industry. Genipin's use as a food colorant is particularly informative in that it reflects preliminary regulatory acceptance of specific genipin-derived products for consumption. While regulatory acceptance in the food industry may not strictly inform safety and efficacy in therapeutic settings, especially in cases where larger doses are required for therapeutic effects, it provides initial support of genipin's good safety profile.

In preclinical FD mouse models, genipin has also been shown to be well-tolerated when administered to pregnant dams, showing no side effects in embryonic development, gestational weight, and litter size (Saito-Diaz et al., 2024). While the use of genipin is approved in defined parameters as a food additive and shows promise in preliminary preclinical models, there is a practical translational question that remains unaddressed: does genipin administration produce off-target pigmentation in organs and tissues, particularly with repeated dosing and long-term exposure? Additionally, does genipin-mediated crosslinking significantly or adversely affect non-target organs?

Several other key gaps remain in genipin's pharmacology that limit its adoption as a clinical intervention for peripheral nerve disorders and neuropathies. First, dosing and formulation parameters vary widely across studies, making it difficult to compare efficacy and safety. Second, the pharmacokinetics (PK) and pharmacodynamics (PD) profiles of genipin are understudied, and they play a substantial role in bioavailability, off-target effects, tissue distribution, and clearance. Third, toxicology studies must extend beyond short-term viability and include longitudinal assessments of organ function, potential cellular and extracellular interactions, and immunogenicity. These gaps are vital to address for peripheral neuropathies, where the clinical need is high and the disease biology differs from acute injury models.

Another critical consideration towards advancing potential therapeutics, such as genipin, for PNS disorders is ensuring the use of human-relevant systems that capture disease-relevant phenotypes. Human pluripotent stem cell (hPSC) technology provides an excellent platform for disease modeling and drug assessments in a controlled and scalable manner, especially for diseases of the PNS like FD or diabetic neuropathies, where it is difficult to access autonomic neurons. Uncovering the PK and PD profiles in hPSC or iPSC-derived peripheral neuron subtypes provides an opportunity to evaluate human-specific responses at an early stage and may reduce the extremely high failure rate of drug candidates.

Discussion

Taken together, these findings support a more integrated view of genipin not only as a multifunctional compound, but as a regulator of the ECM environment, whose crosslinking activity may unify its diverse reported effects. Additional studies in the PNS are required to validate alternative mechanisms of action, including inflammatory, antioxidant, mitochondrial, and cellular stress pathways, and to determine whether these effects occur independently, in parallel with, or as upstream or downstream consequences of ECM remodeling. Moving forward, the central question pertaining to genipin should focus on how it interacts with peripheral neurons and the surrounding extracellular environment and how it can be appropriately leveraged. Ultimately, addressing this question will shape the future use of genipin and expand approaches to treat complex PNS disorders.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical approval was not required for the studies on humans in accordance with the local legislation and institutional requirements because only commercially available established cell lines were used. Ethical approval was not required for the studies on animals in accordance with the local legislation and institutional requirements because only commercially available established cell lines were used.

Author contributions

AP: Visualization, Conceptualization, Writing – original draft, Writing – review and editing. NZ: Supervision, Conceptualization, Funding acquisition, Resources, Writing – original draft, Writing – review and editing.

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