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Panax Ginseng in Migraine Management: Dopaminergic and Neuroprotective Effects from Preclinical and Clinical Evidence

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ABSTRACT

Ginsenosides, the active components of *Panax ginseng*, show increasing potential for migraine management by modulating dopaminergic pathways, providing neuroprotection, and reducing neuroinflammation, which are key contributors to migraine pathophysiology. This review highlights the role of ginsenosides in inhibiting dopamine receptor desensitization, mitigating oxidative stress, and alleviating neuroinflammatory processes. Preclinical and observational studies suggest that ginseng is a safe and well-tolerated adjunctive therapy, particularly for treatment-resistant migraines. Despite its promise, the lack of standardized ginseng formulations and migraine-specific trials necessitate further investigation. If validated, *Panax ginseng* could emerge as a natural therapeutic option for migraine management, complementing existing treatments and addressing unmet needs in resistant patients.

Categories: Neurology, Complementary Medicine

Keywords: *Panax ginseng*; Migraine Management; Ginsenosides; Dopamine Modulation; Neuroprotection; Complementary Therapy

Abbrivations: SOD: Superoxide Dismutase; ROS: Reactive Oxygen Species; HPA: Hypothalamic–Pituitary–Adrenal; RCTS: Randomized Controlled Trials

Introduction

Migraine is a common, recurrent, often debilitating neurological disorder characterized by recurrent neurogenic headaches associated with alterations in pain sensitivity and increased vulnerability to sensitive stimuli [1]. Dysregulation of neurotransmitter systems, particularly dopamine, a fundamental component of migraine pathophysiology, has a special function in both pain perception and reward pathways [2,3]. The neurotransmitter levels of a critical mediator in the reward circuit of the brain, dopamine [1], have an important effect on the nucleus accumbens and the ventral tegmental area during migraine episodes, which is linked to changes in mood, motivation, and sensory responses. Dopamine dysregulation plays a significant role in the various phases of migraines. The prodrome phase, which occurs hours or days before the headache phase, is marked by early signs of dopamine imbalance, while the headache phase represents the peak of dysregulation. Targeting dopaminergic pathways early in the migraine cycle may help mitigate the severity of migraine attacks and improve patient outcomes [4,5]. As shown in Figure 1, dopamine levels fluctuate significantly during the migraine phases. The prodrome phase begins with relatively higher dopamine levels, which progressively decline during the aura phase and reach their lowest point during the headache phase, contributing to hypersensitivity and pain. Partial recovery is observed in the postdrome phase, further emphasizing the importance of dopamine regulation in migraine management [1,6,7].

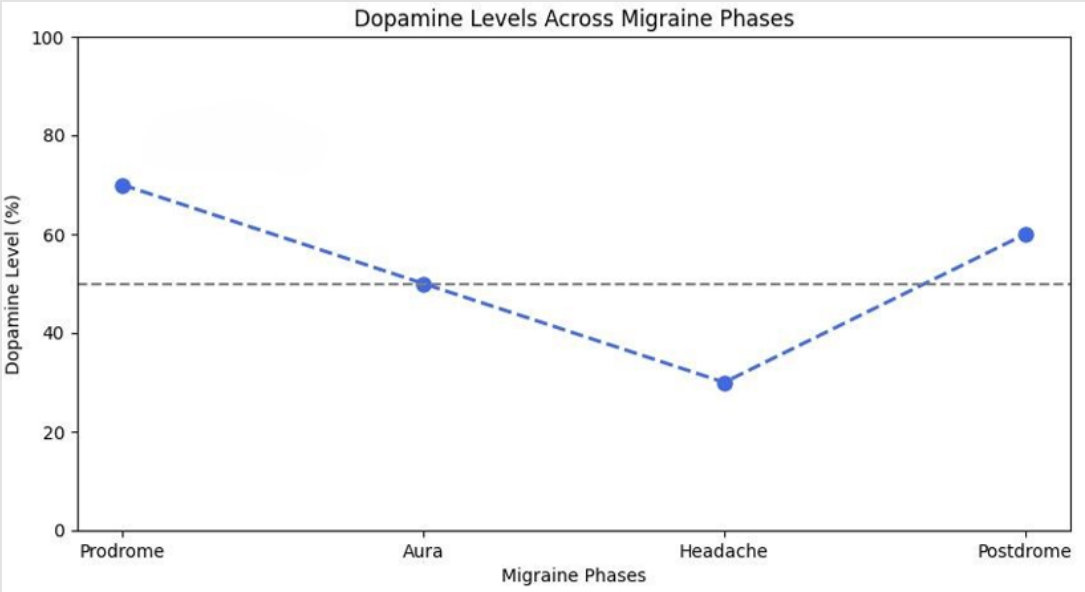

Figure 1: Dopamine Levels across Migraine Phases.

However, current migraine treatments target restoring balance to these systems by stabilizing neurotransmitters. Among acute interventions, triptans act primarily via serotonin receptors [1], whereas preventive treatments include beta-blockers, anticonvulsants, and antidepressants, which modulate the levels of the neurotransmitter. While these treatments are effective for many patients, many patients do not receive relief with these treatments, making alternative approaches necessary that target the underlying foundational neurobiological mechanisms of migraines [8-10]. The goal of this study was to determine how ginsenosides supplied by *Panax ginseng* affect dopamine levels and whether ginsenosides influence migraine symptoms in the prodromal or established phases. This study also aims to explain how ginsenosides act as neuroprotectants and anti-inflammatory agents in restoring healthy brain function in patients with migraine. Ultimately, this study aims to analyze the possibility of the use of ginseng as a therapy for migraine patients who fail adequately in response to conventional therapy.

Pharmacological Profile of Ginseng

The active compounds of *Panax ginseng*, which are traditionally used in East Asian medicine, are ginsenosides that have neuroprotective, anti-inflammatory, and even neurotransmitter-modulating effects. These bioactive components induce interactions with central nervous system pathways and modulate the dopaminergic and other neurotransmitters implicated in migraine pathophysiology [6,11]. Research has shown that ginsenosides, especially Rg1, Rb1, and Rg3, have important effects on dopamine signaling. For example, ginsenoside Rg1 increases dopamine release, enhances receptor sensitivity, and therefore counteracts dopaminergic dysregulation in migraine patients [12]. Furthermore, similar to the neuroprotective needs of chronic migraine patients, ginsenosides are also well known to attenuate neuroinflammatory responses [11], which are relevant to migraine management, as are ginseng's adaptogenic (stress-managing) properties. Migraine can trigger stress, and as ginsenosides affect the hypothalamic pituitary adrenal axis, ginseng may attenuate the frequency or intensity of stress-induced migraine episodes [4]. Table 1 provides a summary of the primary and secondary effects of the main ginsenosides on dopaminergic pathways, showing how they positively influence migraine-related neurotransmitter activity.

Table 1: Summary of the effects of ginsenosides on dopaminergic pathways.

Ginsenoside	Primary Effect	Secondary Effect
Rg1	Increases dopamine release	Enhances receptor sensitivity
Rg3	Improves receptor binding	Neuroprotection
Rb1	Reduces oxidative stress	Anti-inflammatory

Clinical Implications

Ginseng can be a promising alternative for patients who do not adequately respond to conventional treatments and can help alter neurobiological events such as dopamine modulation and neuroinflammation [13]. Since ginsenosides seem to have stable dopaminergic and counter-inflammatory effects, they may be especially useful in treating resistant migraine sufferers. Its potential as an adjunctive option to reduce symptoms is further emphasized by its compara-

tive effectiveness (see Figure 2) over conventional treatments. This review explores the intersection between migraine pathophysiology and ginseng pharmacological properties, especially the potential of ginsenosides to modulate dopamine and contribute to more comprehensive migraine management strategies [1,6].

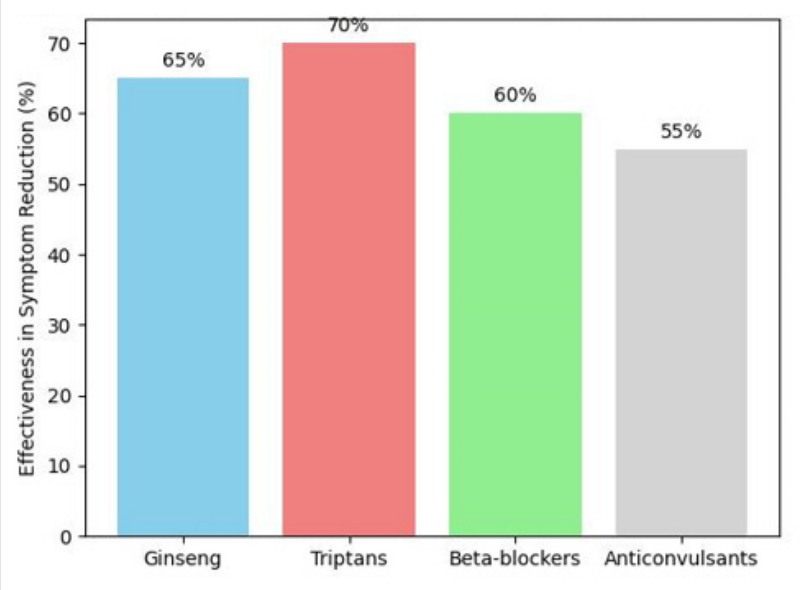

Figure 2: Comparative effectiveness of ginseng vs. conventional migraine treatments

Mechanisms of Dopamine Modulation by Ginseng

Panax ginseng has been investigated as a modulator of dopamine synthesis, receptor sensitivity, and neuroprotection in many ways. The primary bioactive compounds in ginseng, ginsenosides Rg1, Rg3, and Rb1, have been shown to stabilize dopamine levels and protect dopamine neurons from inflammatory damage, which is consistent with the pathophysiology of migraine [14,15].

Dopamine Release and Receptor Sensitivity

Research on *Panax ginseng* revealed a multidimensional effect on dopamine synthesis, receptor sensitivity, and neuroprotection. The primary bioactive compounds for ginseng, ginsenosides Rg1, Rg3, and Rb1, have been shown to stabilize dopamine levels and stabilize dopamine neurons from inflammatory damage, which is relevant to migraine pathophysiology [14,15]. Dopamine release and the modulation of receptor sensitivity by ginsenoside Rg1 are especially relevant in regions that respond to pain and reward. Rg1 increased dopamine receptor density [11,15], and in dopamine-efficient models, Rg1 was shown to increase dopamine receptor density in brain regions such as the prefrontal cortex and striatum, suggesting that the stabilizing effect of dopamine transmission could counteract dopamine variations observed during migraine phases. A reduction in oxidative stress within dopaminergic neurons is caused by ginsenoside Rb1 in the context of recurrent neuroinflammatory episodes, which is important, as these patients often do not respond to treatment. In dopamine-rich regions such as the substantia nigra and hypothalamus, Rb1 promotes the activity of antioxidant enzymes (e.g., superoxide dismutase (SOD)) to reduce cellular stress [16]. This protection may aid in maintaining the dopaminergic tone and anti-chronic pain sensitization [17,18]. Ginsenosides have been shown to improve dopamine receptor binding in the striatum, a brain area involved in the pain of migraine, and trigeminal pain pathways, and can modulate neurotransmission in the brain. These compounds could improve dopamine stability and alleviate hypersensitization via these pathways, preventing symptoms such as nausea and sensory sensitivity [19]. Taken together, these findings suggest that ginseng modulates dopaminergic pathways that both contribute to dopamine receptor sensitivity and stabilize dopamine levels through regulation of its release. Owing to their multifaceted (i.e., both prodromal and acute pain phases) action, ginsenosides are promising candidates for alleviating dopamine-related migraine symptoms. [20] Figure 3 shows the comparative analysis of migraine symptoms before and after ginseng treatment. These findings suggest that ginseng treatment has a high potential for alleviating the symptoms of dopamine-related migraine.

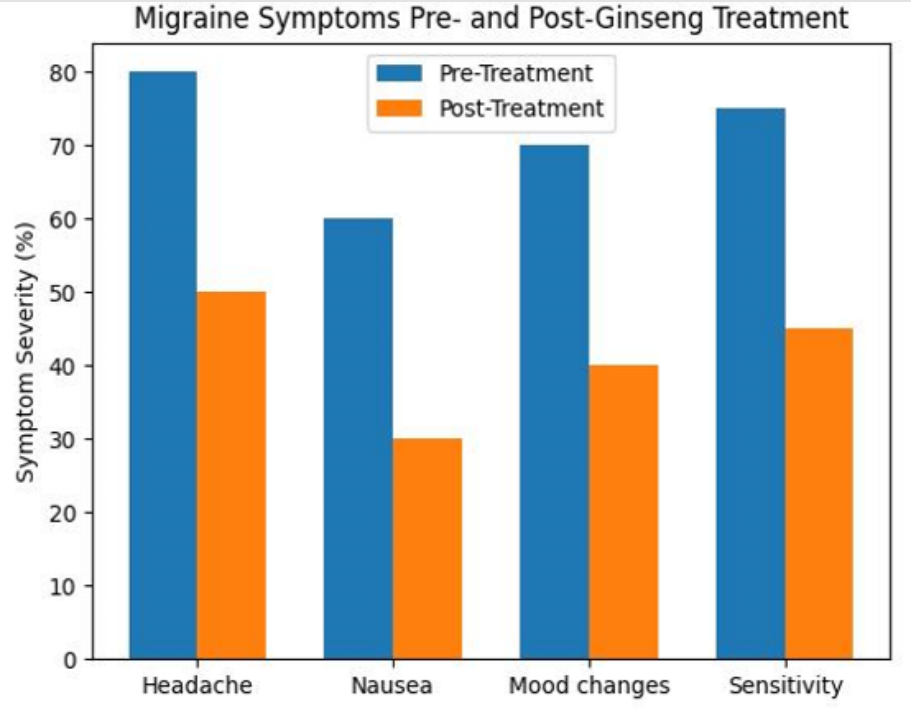

Figure 3: Migraine symptoms before and after ginseng treatment.

Preclinical and Clinical Studies: Ginseng's Effects on Dopaminergic Systems

Ginseng and its ginsenosides have been studied for their neuroprotective effects on dopaminergic activity and pain responses. Specifically, these studies are important because dopamine plays a key role in both initiating and advancing migraine. The neuroprotective properties of ginsenosides Rg1 and Rb1 include their ability to reduce reactive oxygen species (ROS) and downregulate the production of inflammatory cytokines such as TNF-α and IL-1β [21]. These actions protect dopaminergic neurons from inflammatory damage, which is hazardous in migraine since neuroinflammation is implicated in pain sensitization. Both Rg1 and Rb1 have also been shown to activate the Nrf2/HO-1 pathway, which enhances the antioxidant defense system, reduces mitochondrial stress, and promotes neuron resilience [17,18,22]. The preservation of dopamine receptors and new studies of ginsenoside Re revealed that it is capable of protecting dopamine neurons in the face of oxidative stress, which implies that ginseng might be able to prevent dopamine loss in certain migraine pathways. Ginsenoside Re enhances dopaminergic survival and supports mitochondrial health and ATP production, which are necessary traits for coping with stress conditions [23]. That is, ginsenosides Rg3 and Rh2 have been shown to reduce pain hypersensitivity, which is a characteristic of migraines [24]. Ginseng shows promise as a neuroprotective and anti-inflammatory agent [22] that stabilizes dopaminergic pathways and may reduce susceptibility to migraine attacks. Ginseng ginsenosides also promise to maintain dopamine neurons and increase receptor sensitivity to address chronic migraine symptoms and reduce the number of migraines [11].

Clinical Trials and Observational Studies in Migraine Patients

While direct clinical studies of the effects of ginseng on migraines are scarce, the dopaminergic modulation and neuroprotective properties of ginseng are of interest as potential aspects for the treatment of migration.

Dopaminergic Modulation in Human Studies

The common migraine symptoms of nausea, sensory sensitivity, mood fluctuations, and so on have been shown in clinical research to be at least in part the consequence of dopaminergic dysregulation. Dopamine antagonists, which are known to effectively relieve migraine-associated nausea, are thought to provide such benefits by acting on dopamine receptors, especially D2 receptors, either through agonist activity or the blockade of endogenous dopamine. With respect to the therapeutic potential of ginseng for its dopaminergic effects, studies of ginseng are not specific to migraine. For example, ginsenosides have been proven to enhance dopamine signaling and stabilize

mood in patients with dopaminergic disorders, such as ADHD [14,15]. Dopamine receptor agonists have also been shown in studies to stabilize dopamine in areas including the nucleus accumbens and ventral tegmental area to modulate neuroinflammation and protect against receptor hypersensitivity [25]. They are relevant to migraine because they affect reward and pain perception, which can be dysregulated in patients with migraine. Therefore, the ability of ginseng to stabilize dopamine function might have an effect on controlling mood disturbances and pain processing in migraine patients [26].

Observational studies on pain modulation

According to some studies, the anti-inflammatory and antioxidant properties of ginseng reduce pain intensity and frequency [27,28]. Although these studies are not migraine-specific, they show that ginseng is effective for managing neuroinflammation—the process linked to chronic pain—which has also been proposed as a pathway that contributes to the development of migraine. Proinflammatory cytokines such as TNF-α and IL-6 are upregulated in migraines and are reduced by ginseng, lowering inflammation and reducing pain sensitivity [24]. A systematic review of the effects of ginseng on neurological conditions revealed that dopamine modulation by ginsenosides was associated with increased pain response in patients with all types of neurological conditions, suggesting a similar application for migraine. Ginseng thus provides preliminary support for the adjunctive treatment of ginseng to improve the balance of dopamine, mitigate neuroinflammation, and manage migraine symptoms [18].

Dopamine and Mood Regulation: Insights from Observational Data

Ginseng has adaptogenic effects on the hypothalamic–pituitary–adrenal (HPA) axis, reduces cortisol levels, and improves stress responses in patients with stress-related disorders [28]. Stress, a major migraine trigger, may have a bearing on these patients. Stress disorder studies have shown that ginsenosides support dopamine stability during mood regulation, supporting the prevention of emotional stress that precedes migraine attacks [19]. Taken together, these observational findings support the notion that ginseng may be utilized to target multiple pathways that are associated with migraine. The supportive effect on dopamine function, improved stress resilience, and lowered neuroinflammation provided by ginseng may promote this as a likely alternative therapy for diminishing the frequency and acuity of migraine attacks.

Potential Clinical Implications and Safety Profile

Safety and Tolerability of Ginseng

Any complementary therapy is critically tested in terms of safety. Ginseng has a good safety profile with minor side effects in clinical settings. The results of ginsenoside studies, particularly those involving Rg1 and Rb1, used in observational studies have revealed a very low incidence of adverse effects even with higher doses and can be used as adjunctive(s) in the management of migraine. As with most drugs, typical side effects are generally mild, including minor digestive discomfort and/or mild headaches, and are well tolerated in chronic use contexts [14,29]. Table 2 provides an overview of these findings, emphasizing its tolerability for long-term use.

Table 2: Summary of the safety and tolerability profile of ginseng.

Side effects	Frequency	Severity	Resolution
Mild digestive discomfort	low	Mild	Usually, resolves with dose adjustments
Headaches	Low	Mild	Temporary
Mild sleep disturbances	Rare	mild	temporary

Ginseng has a broad spectrum of pharmacological actions and therefore represents an attractive alternative to conventional migraine treatments for patients' refractory to conventional migraine treatments. Ginsenosides of ginseng may indeed provide a multitarget therapeutic approach to migraine by targeting dopaminergic pathways, increasing anti-inflammatory responses, and increasing overall resilience to stress. While standard treatments are not effective at treating dopaminergic dysregulation, the particular effect of ginseng on dopaminergic stability may serve as an additional therapy to reduce symptoms and attack frequency [24]. Figure 4 outlines the pathways through which ginsenosides can contribute to migraine management. The study revealed ginseng to be a possible integrative therapy for patients desiring a natural, low-sided effect profile. Studies of dose optimization and long-term safety in migraine populations could add support for its use in migraine treatment plans.

Conclusion

A review of the literature on *Panax ginseng* has shown that it may be a suitable complementary therapy for migraine treatment because of its dopaminergic modulation and neuroprotective and anti-inflammatory properties. Consistent with the pathophysiology of migraine, the pharmacological actions of ginsenosides, including Rg1, Rg3, and Rb1, support dopamine stabilization, increase receptor sensitivity, and reduce neuroinflammation. Together, these results suggest that ginseng can have a therapeutic benefit for patients with neurobiological and inflammation-based resistance to conventional treatment. Ginseng has proven to be a favorable option among natural adjunctive therapies with a good safety profile, as few, if any, adverse effects have been observed in preclinical and observational studies supporting its long-term use. Preliminary results are promising, however, the lack of migraine-specific clinical trials and variability in ginsenoside concentrations within current formulations underline the need for further research. Developing standardized formulations and conducting targeted clinical trials will be essential to confirm its effectiveness and optimize its role in migraine management. The underexplored mechanisms targeted by *Panax ginseng*, including dopamine modulation and stress resilience, could be used to complement what current migraine treatments have to offer and further expand options to improve the quality of life of patients. Further research could identify *Panax ginseng* as a mainstay of comprehensive migraine management, allowing patients to enjoy a natural and effective means of relief.

Discussion

This literature review highlights the potential of ginsenosides Rg1, Rg3, and Rb1 from *Panax ginseng* for the management of migraine symptoms via dopaminergic modulation, neuroprotection, and anti-neuroinflammatory effects. The pathophysiology of migraine is currently based on a neuroinflammatory paradigm that integrates dopamine homeostatic deviations [3]. While the mechanisms by which the direct effects of ginsenosides on dopamine synthesis, receptor sensitivity, and protection of dopaminergic neurons from oxidative stress might decrease the frequency and intensity of migraine attacks are not fully understood [11,15], they nonetheless provide insight. In addition to their adaptogenic properties, which modulate the release of stress-induced migraines, they help diminish stress [19]. Considering the combined properties of these qualities, ginseng is a viable adjunctive therapy for dopamine-related neuroinflammation, or perhaps an addendum to present treatments directed at serotonin pathways or pain relief. Despite these promising findings, significant challenges remain.

Despite these promising findings, there remain significant challenges and counterarguments. A major limitation is a shortage of migraine-specific clinical trials using ginseng; most evidence is gained from preclinical or non-neurologic studies. Therefore, rigorous clinical research is needed for ginseng to test its efficacy as a treatment option in migraine patients; well-designed trials of migraine patients are needed. Additionally, the variations in ginsenoside concentration with different formulations restrict the acquisition of consistent therapeutic results. This inconsistency raises concerns about whether ginseng provides reliable treatment. Establishing effective clinical use will require the formulation of standard protocols for formulation and dosing. The main limitation is that there are few migraine-specific clinical trials devoted to ginseng, as the evidence is limited to preclinical or non-neurological studies. This highlights that well-designed clinical trials on patients with migraine are needed and rely heavily on indirect evidence. Moreover, the variability in ginsenoside concentrations within and between different formulations presents challenges for achieving consistent therapeutic outcomes. The variations in ginsenoside concentration across different formulations present a challenge for achieving consistent therapeutic outcomes. Although standardization of extraction and dosing protocols is critical for clinical reliability, this review primarily focuses on the therapeutic potential of *Panax ginseng* in migraine management through mechanisms such as dopaminergic modulation, neuroprotection, and anti-inflammatory effects. Future studies addressing the standardization of ginseng formulations would significantly enhance its clinical applicability. Furthermore, developing uniform protocols could bridge the gap between preclinical evidence and real-world therapeutic outcomes, enabling more reliable integration into clinical migraine management strategies.

The current body of evidence is limited by the scarcity of migraine-specific clinical trials involving *Panax ginseng*, with most data derived from preclinical studies or observational research in non-migraine populations. This reliance on indirect evidence limits the generalizability of findings and underscores the need for rigorous clinical research to validate ginseng's efficacy and safety in migraine management. Without such trials, it remains challenging to confirm its effectiveness, establish dosing guidelines, and address potential interactions with conventional therapies. These limitations are significant but also present opportunities for further investigation. However, the present results suggest that *Panax ginseng* may serve as an adjunctive therapy for migraine, but additional research is necessary to fully understand its interactions with other neuroactive systems, such as serotonin and glutamate. A better understanding of these interactions could clarify its therapeutic potential. The proper efficacy of ginseng must be confirmed by standardized clinical trials and extensive long-term studies. It is hoped that as research progresses, *Panax ginseng* might play a role in migraine treatment, a natural, effective means by which patients can improve their quality of life.

Future Directions for Research

Randomized Controlled Trials (RCTs) in Migraine Populations: These trials should emphasize parameters that capture the full spectrum of ginseng's effects on migraine, including attack frequency,

prodromal symptoms such as mood shifts, and the intensity of the main complaint. Mechanistic studies on dopaminergic pathways: Additionally, further experiments should detail the effects of active principles on dopamine receptors, dopaminergic synthesis and release, and receptor binding. Information from imaging techniques such as PET applied to migraine models may provide insights into the in vivo effects of ginsenosides on the dopamine system. Exploring Long-Term Safety and Tolerability: While ginseng has shown promising effectiveness and safety in short-term clinical trials (trial number: ChiCTR1800016363) [30], long-term studies are needed to monitor potential side effects in chronic migraine patients (those receiving treatment over extended periods at high doses) and to compare outcomes with those of other alternative therapies [14,29]. Future research will prioritize the formulation and standardization of ginsenosides by developing consistent extraction methods and dosage protocols. They are critical to ensuring the reproducibility and reliability of findings, thereby enabling broader clinical implementation. Combination therapies with conventional treatments: Further studies should investigate whether the use of ginseng combined with standard migraine medications such as triptans and beta-blockers provides greater efficacy than the use of ginseng alone. Available evidence supports the potential of combined approaches to enhance pain reduction by stabilizing dopaminergic neurotransmission and reducing inflammation [3,15]. Potential barriers to clinical implementation: Although findings on ginsenosides are promising, regulatory barriers and standardization challenges remain. Inconsistent ginsenoside concentrations across formulations may affect therapeutic consistency, and regulatory frameworks may require comprehensive evidence before approval for clinical use. These findings on *Panax ginseng* and ginsenosides collectively support their potential use in migraine control, addressing barriers to integrating ginseng into standard migraine treatment plans. The ability of ginseng to stabilize dopaminergic neurons, prevent neurodegeneration, and suppress neuroinflammation aligns with contemporary approaches to migraine etiology. Continued research could secure its place in migraine management plans, offering a nonpharmacological, effective treatment for this disabling disorder.

Disclosures

This study did not involve any human or animal subjects; therefore, IRB approval and informed consent were not needed.

Conflicts of Interest

The authors declare that they have no conflicts of interest related to this work. No financial support, services, or third-party payments were received for any aspect of the submitted work. Additionally, the authors have no relevant financial activities outside of this work, patents, or other relationships that could be considered broadly relevant to the manuscript.

Consent For Publication

Not applicable

Availability Of Data and Materials

This article is based on previously published data and literature, all appropriately cited in the manuscript. No new datasets were generated or analyzed during the current study.

Authors' contributions

R.J.A.R. conceptualized the study, conducted the primary literature review, and drafted the manuscript. T.S.D. supervised the work, provided consistent guidance throughout the study, cross-checked the manuscript, and ensured scientific accuracy. All the authors have read and approved the final manuscript and agree to be accountable for the integrity and accuracy of the work.

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Data Access Statement

No new data were generated or analyzed during this study. Data sharing does not apply to this article, as it is a literature review.

Declaration of Interests

The authors have no competing interests.

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