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Plants and Their Extracts Against Neurodegeneration: Ginseng (*Panax ginseng*)

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Abstract: Ginseng, particularly *Panax ginseng*, has been highly valued in traditional medicine for its health-promoting effects. Recent preclinical and clinical studies have highlighted its promising neuroprotective potential, mediated through multiple mechanisms of action. Among its diverse phytochemicals, ginsenosides are considered the principal bioactive compounds responsible for these neuroprotective effects. They contribute to the reduction of oxidative stress, inhibit the production of pro-inflammatory cytokines, and suppress microglial activation, thereby mitigating neuroinflammation. Ginseng also influences key neurotransmitter systems, including cholinergic, serotonergic, and dopaminergic pathways, which are critical for cognitive function and mood regulation. Studies in Alzheimer's patients have demonstrated improvements in memory, attention, and overall cognitive performance following ginseng supplementation. The neurogenic, anti-inflammatory, and antioxidant activities of ginseng further support its neuroprotective properties. Nevertheless, further rigorous scientific investigation is required to fully validate its therapeutic potential and identify possible side effects. This chapter provides a comprehensive overview of the physicochemical properties, phytochemical composition, pharmacological actions, and clinical evidence of ginseng, with a focus on its role in neuroprotection.

Keywords: Alzheimer's, Phytochemicals, Neuroinflammation, Clinical evidence, Cognitive function, Neuroprotective.

1. Introduction

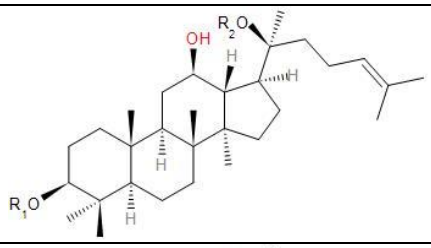
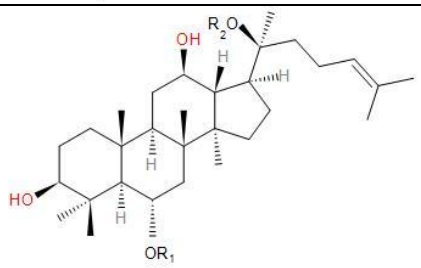
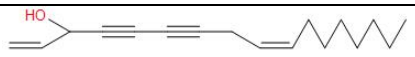
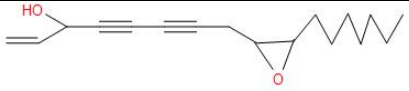
The human nervous system, a highly intricate and essential component of the body, plays a central role in regulating and coordinating diverse physiological functions to maintain homeostasis. Neurons, the fundamental units of the nervous system, are specialized cells responsible for signal transmission, information processing, intercellular communication, and the execution of motor and sensory functions. They also play a crucial role in cognitive processes, including memory and learning [1]. Various factors can impair the structure and function of neurons, leading to disruptions in nervous system control and contributing to the development of neurodegenerative conditions [2]. While synthetic drugs are commonly used to treat these disorders, they often cause adverse effects, prompting growing interest in alternative therapies that offer high therapeutic efficacy with minimal side effects. Herbal medicines have emerged as promising candidates for neurodegenerative disease management. Among these, ginseng is one of the most widely used natural medicines worldwide, valued for its neuroprotective properties and functional health benefits. The genus Panax comprises several ginseng species, including *Panax quinquefolius*, *Panax ginseng*, and *Panax notoginseng* [3]. Ginseng is primarily cultivated in temperate regions of the Northern Hemisphere, such as Japan, Korea, China, the United States, and Canada. It thrives in cooler climates with loamy, well-drained soil and prefers shaded conditions. The plant typically grows to a height of 6–18 inches, producing greenish-yellow corollas and 15–30 blooms that develop into light crimson, globular, pear-shaped fruits containing two seeds.

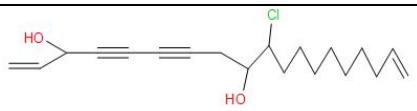
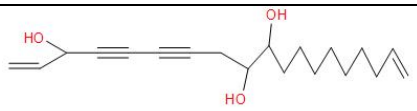
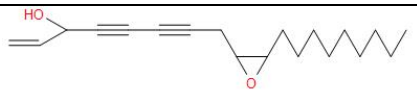
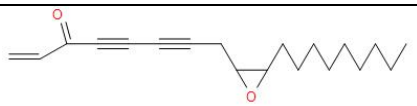
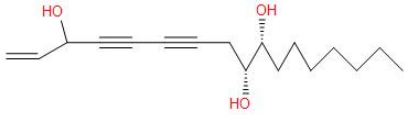
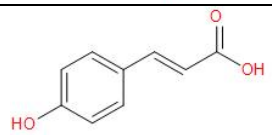
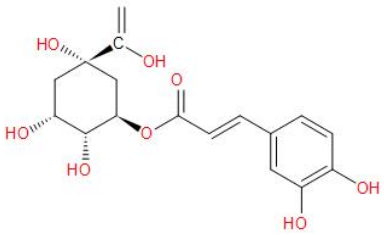
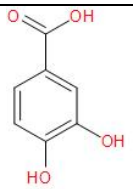
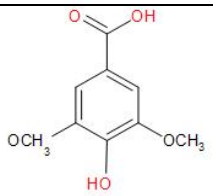
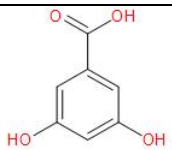
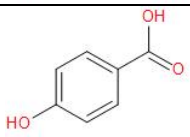
After drying, the roots become thick, subcylindrical, and fleshy, measuring approximately 25 cm in length and 2.5 cm in diameter, often with 1–2 large branches and a longitudinally wrinkled, spiral surface marked by root scars [4]. Ginseng species differ in root coloration: Chinese ginseng exhibits a yellowish-white hue, *Panax ginseng* is yellowish-brown, and *Panax quinquefolius* and *Panax notoginseng* are yellowish-white. The taste is mildly sweet, occasionally mucilaginous, and slightly bitter, with a subtle fragrance. The number of leaf scars on the rhizome can be used to estimate the plant's age [5]. The pharmacological effects of individual ginsenosides are influenced by variations in sugar moieties and their positions within the molecules. A single ginsenoside can elicit multiple actions in the same tissue, while each ginsenoside exhibits unique pharmacological activities. Based on these observations, scientists in Asia and the West have proposed a comprehensive pharmacological framework for *P. ginseng*, encompassing broad effects on multiple physiological systems. Recent studies have specifically highlighted the beneficial effects of ginsenosides on the nervous system, underscoring their neuroprotective potential [6]. This chapter provides a detailed overview of the chemical composition of ginseng, its historical significance in traditional medicine, and its evolving role in modern research focused on neurodegenerative diseases.

1.1 Physicochemical Characteristics of Ginseng

For decades, traditional East Asian medicine has utilized ginseng to treat a wide array of health conditions. Over the past three decades, it has become one of the most widely used herbal remedies globally [7]. Ginseng is applied not only in medicinal practices but also in agriculture, pharmaceuticals, dietary supplements, and health products. The primary bioactive constituents of ginseng are ginsenosides, which belong to the triterpene saponin class. However, ginseng contains additional bioactive compounds that contribute to its health-promoting properties. Recently, gintonin has been identified as another active component. Despite this, most pharmacological and therapeutic research on ginseng has focused on ginsenosides, of which approximately 200 different types have been identified [8]. Notable examples include Rb1, among others. The steroidal structure of ginsenosides underlies their diverse pharmacological effects. These compounds can influence cellular transcription and signaling by interacting with membrane-bound ion channels, extracellular and intracellular receptors, and cell membranes. A summary of the most common chemical constituents of ginseng is provided in **Table 1** [9].

Table 1: Chemical constituents of ginseng.

S. No.	Chemical constituent	Example	Chemical Structure	Uses
1.	Ginsenosides	20(S)-protopanaxadiol (PPD)		As an immunity booster. Used in the treatment of Parkinson's
		20(S)-protopanaxatriol (PPT)		Neurodegenerative disease treatment
		Panaxynol		Tumor and inflammation
		Panaxydol		Over inflammasome activation.
		Ginsenoyne A		Neurodegenerative disease

2.	Polyacetylene	Ginsenoyne B		COX overproduction
		Ginsenoyne C		Inflammation
		Ginsenoyne D		Autophagy
		Ginsenoyne E		Anti-inflammatory
		Panaxytriol		Alzheimer disease
3.	Phenolic compounds	p- coumeric acid		Neuro-inflammatory disease
		Chlorogenic acid		Hippocamal neurons degradation
		Protocatechuic acid		Alzheimer's disease and Parkinson's disease
		Syringic acid		Neuro damage
		Gentisic acid		Neuro damage
		p-hydroxybenzoic acid		Neurodegradation

Ginsenosides exhibit a wide range of biological activities, including antifungal, antiviral, antibacterial, and antioxidant properties. They have also demonstrated therapeutic potential in managing conditions such as stress, hypertension, and various neurodegenerative disorders, including Alzheimer's disease (AD), Parkinson's disease, and Huntington's disease [10]. Plant-derived materials serve as essential natural resources for the development of pharmaceuticals. Many modern drugs trace their origins to traditional plant-based therapies, highlighting the importance of botanicals in clinical medicine [11].

Ginseng, in particular, has been extensively used in clinical settings worldwide and holds promise as a foundation for the development of novel therapeutic agents. Evidence from multiple in vitro and in vivo studies supports the pharmacological and therapeutic potential of ginseng and its ginsenosides in treating a broad spectrum of disorders [12].

1.2 Ginseng in Folklore Medicine to Drug Discovery

For over 2,000 years, ginseng, derived from the root of Panax species, has been widely utilized for its health-promoting properties. The term Panax originates from the Greek word "panacea," meaning "cure-all," reflecting the traditional belief that ginseng can maintain and enhance overall health. In traditional Chinese medicine (TCM), ginseng is considered a "superior" herb, signifying its efficacy and safety for long-term use.

2. Traditional Uses in Asia

Ginseng is traditionally used in Chinese, Korean, and Japanese cultures to enhance physical strength, improve cognitive performance, boost immunity, and promote longevity. It is commonly recommended for managing conditions such as fatigue, respiratory infections, and digestive disorders.

2.1 Native American Medicine

Indigenous tribes, including the Iroquois, Cherokee, and Creek, also recognized the medicinal value of ginseng. They used it as a general health tonic, valued its cooling properties, and employed it to alleviate headaches.

2.2 Folklore

Throughout history, ginseng has often been surrounded by tales of nearly supernatural properties, including its purported ability to ward off misfortune and evil spirits. The root's human-like shape contributed to its high value, as it was believed to embody potent, life-giving qualities, leading to its frequent use in ceremonial practices across various cultures [13]. Ancient civilizations possessed extensive knowledge of medicinal plants, understanding both their therapeutic potential and toxicity. The renowned physician Dioscorides Pedanius emphasized that the dosage of a substance determines its effect—capable of healing or causing harm depending on its administration [14].

3. Pharmacological Impact and Chemical Make-Up

The health benefits of ginseng are primarily attributed to a unique group of compounds found in Panax species known as ginsenosides. These bioactive saponins exhibit a wide range of biological effects, including anti-inflammatory, antioxidant, anticancer, and neuroprotective activities [15].

3.1 Ginsenosides

Among the numerous ginsenosides, Rb1, Rg1, Rg3, and Rh2 have been the most extensively studied. These compounds contribute to ginseng's therapeutic effects by modulating cellular signaling pathways, regulating immune responses, and protecting against oxidative stress [16].

3.2 Additional Bioactive Compounds

In addition to ginsenosides, ginseng contains flavonoids, polysaccharides, peptides, and polyacetylenes, all of which contribute to its medicinal properties. Collectively, these bioactive compounds provide a wide array of health benefits.

3.3 Polysaccharides

Complex carbohydrates in ginseng, particularly polysaccharides, constitute approximately 10–20% of the plant's dry weight. These polysaccharides exhibit significant antioxidant and immunomodulatory properties [17]. Among them are:

3.3.1 Ginsan

Ginsan is a high-molecular-weight polysaccharide with branched chains found in ginseng. The starch component of ginseng consists of a combination of amylopectin and amylose. These polysaccharides contribute to ginseng's immunomodulatory and adaptogenic properties, playing a crucial role in enhancing immune function and promoting resilience to physiological and environmental stressors.

3.3.2 Phenolic compounds

Phenolic compounds constitute approximately 1–2% of ginseng's dry weight [18] and are largely responsible for its antioxidant and anti-inflammatory properties. Key phenolic constituents include kaempferol, vanillic acid, isorhapontigenin, quercetin, salicylic acid, and ferulic acid. These phenolic compounds play a central role in mediating ginseng's protective effects against oxidative stress and inflammation.

3.3.3 Alkaloids

Ginseng contains small amounts of alkaloids, which exhibit potential therapeutic effects. The primary alkaloids include ginsengine, a pyridine derivative with antioxidant properties, and ginsenamide, a peptide-like compound whose specific biological functions are not yet fully understood. Research into the roles of these alkaloids in mediating ginseng's pharmacological effects is ongoing.

3.3.4 Volatile oils

Volatile oils, which are responsible for ginseng's characteristic aroma, constitute approximately 0.1–0.5% of its dry weight. The major constituents include sesquiterpenes such as caryophyllene, humulene, and patchoulene, as well as monoterpenes including bornyl acetate, pinene, and limonene. While these volatile oils are believed to contribute to some of ginseng's biological effects, their precise mechanisms of action remain unclear [19].

4. Pharmacological effect

The pharmacological effects of ginseng [20] can be divided into multiple categories:

4.1 Adaptogenic and Anti-fatigue

Promotes better mental and physical function, lessens weariness, and raises stress tolerance.

4.2 Immunomodulatory

Promotes immunity, boosting defenses against illnesses and infections.

4.3 Antioxidant and Anti-inflammatory

Offers defense against cell damage, inflammation, and oxidative stress.

4.4 Cardiovascular

Prevents cardiac remodelling, lowers blood pressure, and enhances lipid profiles.

4.5 Anti-cancer

Promotes apoptosis, inhibits tumor development, and amplifies the effects of chemotherapy.

4.6 Neuroprotective

Enhances memory, cognitive function, and the prevention of neurodegenerative diseases.

4.7 Anti-diabetic

Promotes glucose absorption, insulin sensitivity, and glycemic management.

4.8 Gastrointestinal

Promotes gut health, aids digestion, and guards against ulcers.

5. Current Drug Development and Clinical Uses

The transition of ginseng from traditional medicine to scientifically validated therapeutic applications has sparked a new wave of research into its potential health benefits [20-21]. Current investigations focus on the following areas:

5.1 Anti-Cancer Properties

Ginseng has attracted significant research interest for its potential as an anti-cancer agent. Ginsenosides contribute to their therapeutic effects by inhibiting cancer cell proliferation, inducing apoptosis, and enhancing the efficacy of conventional chemotherapy agents.

5.2 Enhancement of Cognitive Performance and Neuroprotection

Multiple clinical trials have demonstrated that ginseng can improve cognitive performance, particularly in patients with Alzheimer's disease. Ginsenosides are believed to enhance memory and learning abilities while providing neuroprotective effects by shielding neurons from oxidative stress and related cellular damage.

5.3 Immune Modulation

Ginseng possesses immunomodulatory properties that enhance the immune system's ability to combat infections. It has been widely used in both conventional and alternative medicine as a natural immune booster, particularly during cold and flu seasons.

6. Therapeutic Potential of Ginseng in Neurodegenerative Diseases

Patent documents published between 2010 and 2018 have categorized the primary bioactive ingredients of ginseng and their pharmacological effects as follows:

- **Alzheimer's Disease (AD), Senile Dementia, and Cognitive Impairment:** Ginseng's therapeutic effects and its active constituents targeting these conditions.
- **Parkinson's Disease (PD):** Ginseng's medicinal properties and the bioactive compounds responsible for its activity in PD [21].
- **Cerebral Ischaemia:** Ginseng's pharmacological actions and the components contributing to its neuroprotective effects in cerebral ischaemia.
- **Other Neurological Disorders:** Ginseng's therapeutic potential and active ingredients in the management of various other neurodegenerative and neurological conditions [22].

7. Traditional uses in neurodegenerative diseases

Nature provides a vast array of molecular structures that serve as essential scaffolds for the development of novel and potent therapeutics targeting various illnesses. Natural products not only act as direct pharmacological agents but also serve as precursors for synthetic compounds, facilitating the discovery of new drugs with diverse mechanisms of action [23]. Due to their therapeutic potential, natural compounds—including ginseng—have been widely employed in the management of neuropsychiatric and neurodegenerative disorders. They generally exhibit good tolerability and a long history of clinical use, although certain adverse effects, such as hepatotoxicity and allergies have been reported [24]. Ginseng's preventive and therapeutic effects are primarily attributed to over 180 ginsenosides [25]. These compounds exert significant pharmacological effects on the central nervous system (CNS), including enhancement of

cognitive function, reduction of neurodegenerative pathology, prevention of neuroinflammation and oxidative stress, and regulation of nerve growth factor production [26].

7.1 Antioxidant and Neuroprotective Activities

Preparations of *Panax ginseng* exhibit moderate antioxidant activity. Aqueous extracts effectively scavenge carbon radicals, hydroxyl radicals, nitric oxide radicals, and superoxide radicals [27]. For instance, a 2 mg/mL extract completely scavenged DPPH radicals, while 0.5 mg/mL quenched 80% of carbon-free radicals, 0.1 mg/mL scavenged ~40% of hydroxyl radicals, and 2 mg/mL scavenged superoxide radicals [28].

7.2 Effects on Alzheimer's Disease (AD)

Ginseng and ginsenosides have demonstrated neuroprotective potential against AD. Black, red, and white ginseng exhibited IC50 values against acetylcholinesterase (AChE) of 1.72, 6.30, and 5.89 mg/mL, respectively, and butyrylcholinesterase (Bu-ChE) of 1.88, 1.84, and 2.56 mg/mL, respectively. Ginsenoside Re at 200 μmol/L inhibited β-secretase in N2a/APP695 cells, reducing Aβ synthesis by 26.82%. In transgenic AD mice overexpressing APP/Aβ, administration of 10 mg/kg Rg1 for three months ameliorated Aβ pathology, modulated APP processing, and improved cognitive function [29-30]. Korean red ginseng aqueous extract (10–500 μg/mL) suppressed tau aggregation (IC50 = 545 μg/mL) and dissociation (IC50 = 713 μg/mL), with the polysaccharide fraction being most effective in preventing tau aggregation (IC50 = 179.3 μg/mL) and the saponin fraction most effective in dissociating aggregated tau (DC50 = 100.2 μg/mL) [31].

7.3 Effects on Parkinson's Disease (PD)

Ginsenosides Rb1 and Rg1 have shown neuroprotective effects in PD models. Rb1 increased PC12 cell viability and reduced apoptosis, while Rg1 administration (5–20 mg/kg, i.p.) in rats attenuated dopaminergic cell loss [32]. Rb1 (100 μmol/L) reduced α-synuclein aggregation by ~80%, whereas Rg3 inhibited ~25%. Western blot analysis demonstrated that Rb1 induced dose-dependent dissociation of α-synuclein fibrils [33]. Oral administration of Rg1 (10–40 mg/kg) in mice improved dopaminergic neuron survival, motor deficits, and ultrastructural alterations in the substantia nigra pars compacta, likely via anti-neuroinflammatory mechanisms [34]. Additionally, ginsenosides Rg1, Re, and Rd upregulate tyrosine hydroxylase expression, enhancing dopamine synthesis, reducing locomotor dysfunction, and preventing free radical-induced neuronal damage [35]. Rb1 also increases dopamine and serotonin levels in the brain by inhibiting both isoforms of monoamine oxidase (MAO), while stimulating enzymes involved in neurotransmitter synthesis [36].

7.4 Effects on Huntington's Disease (HD)

In vitro studies using YAC128 striatal neurons demonstrated that low-dose pretreatment with ginsenosides Rb1, Rc, and Rg5 (0.01–1 μmol/L) reduced glutamate-induced neuronal apoptosis via inhibition of intracellular Ca^{2+} elevation [37]. Similarly, in vivo studies using 3-nitropropionic acid (3-NP) models showed that ginsenosides (6.25–50 mg/kg, i.p.) alleviated behavioral deficits, increased survival, and prevented intracellular Ca^{2+} overload [38]. Overall, these findings highlight the multifaceted neuroprotective effects of ginseng and its ginsenosides, supporting their traditional use in the prevention and management of neurodegenerative diseases.

8. Relation between Structure of Ginseng and Anti-neurodegenerative Activity

Ginsenosides, the primary bioactive components of ginseng, undergo structural transformations under various conditions, including decoction, steaming, acidic gastric environments, and metabolism by intestinal bacteria. For example, steaming red ginseng generates partially deglycosylated saponins such as ginsenosides Rh1, Rg2, and Rg3 [39]. These structural modifications can significantly influence biological activity, as stereoisomers often exhibit distinct pharmacological effects, potencies, and pharmacokinetic profiles. For instance, 20(S)-Rg3 enhances insulin secretion in response to glucose, whereas 20(R)-Rg3 shows no such effect. Steaming ginsenosides Rb1, Rb2, Rc, and Rd causes the release of malonyl groups from their glucosyl moieties, leading to the formation of corresponding ginsenosides. The acetyl group in red ginseng saponins, such as Rs1 and Rs2, remains at the 6-position of the glucosyl moiety, likely due to the inactivation of the deacetylating enzyme during steaming [40]. Additionally, novel dammarane glycosides with modified side chains, including ginsenosides Rh4, Rg5, Rg6, 20(E)-ginsenoside F4, and Rf2, have been isolated from Korean red ginseng

following heat treatment [41]. Structural changes in ginsenosides also occur post-ingestion. Gastric juice, digestive enzymes, and intestinal microbiota contribute to the biotransformation of ginsenosides. The intestinal flora, in particular, cleaves terminal sugar moieties, modifying the glycosidic structure and potentially enhancing bioavailability and pharmacological effects [42]. Such structural modifications are believed to play a crucial role in ginseng's anti-neurodegenerative activity, influencing its ability to interact with molecular targets in the central nervous system.

9. Pre-clinical and Clinical Perspectives of Ginseng in Neurodegenerative Diseases

Clinical investigations have generally confirmed the safety of ginseng consumption. Key findings from these trials [43] are summarized as follows:

- A total of 44 studies were included, assessing ginseng's effects on cardiovascular health, psychomotor performance, glucose metabolism, antioxidant activity, anti-fatigue effects, and sexual health.
- Among these, 29 studies reported positive outcomes, while 15 studies found no significant effect.
- Adverse effects were documented in 16 studies, whereas 5 trials reported no adverse outcomes, and 23 studies did not mention any adverse events.
- The most commonly reported side effects of ginseng included dyspepsia, insomnia, and hot flashes.

These findings suggest that ginseng is largely safe for human consumption, supporting its potential use as a therapeutic agent in the management of neurodegenerative diseases.

10. Marketed formulations of Ginseng to treat neurodegenerative diseases

The leading producers of ginseng are South Korea, China, Canada, and the United States, collectively producing approximately 79,769 tonnes of fresh ginseng worldwide. The global ginseng market—including processed products and raw ginseng root—is projected to reach a value of USD 2,084 million. Ginseng is distributed in 35 countries, with major producers such as China and South Korea acting as both importers and exporters [44]. A variety of commercial ginseng products are available for consumer use, ranging from capsules and tablets to extracts, powders, and functional foods (see **Table 2**). However, current production methods are insufficient to meet the growing industrial demand, highlighting the need for the development of novel synthetic and large-scale production techniques [44-45].

Table 2: Marketed formulation of ginseng.

S. No.	Commercial ginseng product	Ingredients
1	Vitamin C-rich Korean red ginseng (KRG) candies	KRG (6-year-old) powder 2%, aspartame, magnesium stearate, glucose, dextrin, citrate, and vitamin C
2	Insam-ju	An alcoholic beverage made of ginseng
3	Qipi pills	*P. ginseng* extract
4	Shenlinbaizhu capsules	*P. ginseng* extract
5	KRG jelly	L-menthol, herbal flavours, sucrose, oligosaccharides, agar, and
6	KRG crunchy white chocolate	Sugar, milk, cocoa butter, palm oil, lecithin, vanilla, and red ginseng taste are combined with 1.2% KRG (6-year-old) extract.
7	KRG tea extract	KRG (6-year-old) extract 100%
8	Renshenguipi pills	*P. ginseng* extract

11. Safety Profile of Ginseng

Ginseng and its preparations have been extensively studied as both a nutritional supplement and a natural medicine. A total of 3,974 publications on *Panax ginseng* from authors across 64 countries were indexed in the Web of Science between 1959 and 2016. However, relatively few studies have systematically investigated ginseng toxicity; most research has focused on issues related to overuse or abuse. Recent studies indicate that standardized *P. ginseng* extracts can affect cardiac function, potentially lowering blood pressure, causing diastolic dysfunction, and, in extreme cases, leading to heart failure depending on the dose and duration of

consumption [46]. Ginseng has also been implicated in rare adverse reactions, including Stevens-Johnson syndrome, cerebral arteritis from ethanol-extracted preparations, and inflammatory skin eruptions, such as papules in older adults. Additionally, ginseng may interact with certain medications, which can pose health risks. For instance, concurrent use with warfarin may affect anticoagulant efficacy and increase the risk of thromboembolism or hemorrhagic events [47]. Pregnant and breastfeeding individuals are advised to exercise caution, as ginseng may be harmful during the first trimester and lactation. Overall, while ginseng is generally considered safe when used appropriately, further research is needed to fully elucidate its toxicity profile, drug interactions, and long-term safety of its active constituents [13].

12. Conclusion

Ginsenosides have demonstrated multifaceted effects on neurons and glial cells by modulating inflammation, oxidative stress, apoptosis, and cholinergic dysfunction. They also possess the potential to enhance synaptic plasticity and neurogenesis. Key signaling pathways implicated in these effects include PI3K/Akt, CREB/BDNF, Keap1/Nrf2, and NF-κB/NLRP3 inflammasome pathways. Despite these promising findings, data on the precise molecular targets of ginsenosides remain limited, and the underlying mechanisms are not yet fully understood. Advanced approaches such as high-throughput screening and molecular docking are needed to elucidate these targets more precisely. Furthermore, clinical trials investigating the efficacy of ginsenosides in neurodegenerative diseases are scarce, likely due to challenges such as low oral bioavailability, poor solubility, and limited membrane permeability. Recent research has explored innovative ginsenoside delivery strategies, including polymeric microparticles, proliposomes, and niosomes, which significantly enhance water solubility, bioavailability, and pharmacological activity. These approaches offer a promising avenue to optimize the therapeutic potential of ginsenosides in the management of neurodegenerative disorders.

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