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# Ginseng and its immuno-boosting properties: effects on fish immunity, mechanisms of action, and challenges in aquaculture

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Modern aquaculture is challenged by disease outbreaks caused by environmental stress and immune suppression in fish. The indiscriminate use of antibiotics has accelerated antimicrobial resistance and has demanded urgent need of natural and sustainable alternatives to enhance fish health. The present review is devoted to ginseng, a plant of the genus *Panax*, whose rich content of ginsenosides has well-documented antioxidant, anti-inflammatory, and immunomodulatory effects. This paper summarizes the mechanisms of ginseng in modulating the immune system of fish, highlighting the regulation of key signaling pathways, including NF-κB, JAK/STAT, MAPK, and PI3K/Akt, which results in balanced cytokine production, augmented antioxidant activity, and improved immune cell function. Evidence from trials in species such as tilapia, trout, and carp demonstrates that dietary supplementation with ginseng can increase resistance to bacterial pathogens and reduce dependency on antibiotics. However, challenges remain regarding dosage optimization, extract standardization, and evaluation of long-term effects. Overall, ginseng represents a promising natural immunostimulant for sustainable aquaculture, but further research is needed to establish standardized and effective application protocols.

KEYWORDS
**aquaculture, fish immune system, ginseng, immunomodulation, phytochemicals**

## 1 Introduction

Ginseng, primarily from the *Panax* genus, has long been revered in traditional medicine, particularly in East Asian cultures (Hu, 1976; Park et al., 2012). Known as a potent adaptogen, ginseng has been used for centuries to enhance vitality, boost immune function, and improve overall health (Kang and Min, 2012; Ratan et al., 2021). The two most common species, *Panax ginseng* (Asian ginseng) and *Panax quinquefolius* (American ginseng), are

rich in bioactive compounds known as ginsenosides, which are credited with their diverse therapeutic properties (Chen et al., 2019). In traditional Chinese medicine, ginseng is considered a tonic that can balance physiological functions, making it a versatile remedy for various ailments (Chen et al., 2019). In recent years, scientific research has supported many of these claims, revealing ginseng's anti-inflammatory, antioxidant, and immune-boosting properties (Kang and Min, 2012; Ratan et al., 2021), which have sparked growing interest in its use beyond human health, particularly in aquaculture. This interest stems from the pressing need to address health challenges in modern aquaculture.

Aquaculture, as one of the fastest-growing sectors of global food production, plays a critical role in meeting the increasing demand for seafood. However, the intensive nature of modern aquaculture has led to significant challenges, particularly in terms of fish health management. Disease outbreaks, often triggered by pathogens such as bacteria, viruses, and parasites, are major contributors to high mortality rates and economic losses in the industry (Cain, 2022). These diseases are exacerbated by immune suppression in fish, which can result from environmental stressors like poor water quality, overcrowding, nutrient imbalances, and high temperature (Meyer, 1991; Assefa and Abunna, 2018; Cain, 2022; Yousefi et al., 2025a). Conventional solutions to these challenges have relied heavily on the use of antibiotics and chemical treatments. However, the overuse of antibiotics has led to the emergence of antimicrobial resistance (AMR), creating a pressing need for alternative, sustainable solutions to promote fish health and enhance immune resilience (Bondad-Reantaso et al., 2023; Yousefi et al., 2025b).

The growing concerns over AMR and the environmental impact of chemicals in aquaculture have led to an increased focus on non-antibiotic strategies to improve fish health (Bhat and Altinok, 2023). Among these, the use of plant-based immunomodulators has emerged as a promising approach. Phytochemicals, derived from medicinal plants, possess a wide range of biological activities that can enhance immune function, improve disease resistance, and support overall fish health (Chakraborty and Hancz, 2011; Elumalai et al., 2020; Ahmadifar et al., 2021). Ginseng, with its potent bioactive compounds, has been highlighted as one of the leading candidates for this purpose. Its immunostimulatory properties make it an attractive alternative to conventional treatments (Kang and Min, 2012; Ratan et al., 2021), as it can enhance growth and both innate and adaptive immune responses in fish without the risk of promoting antibiotic resistance (El-Sayed et al., 2014; Bulfon et al., 2017; Yousefi et al., 2024, 2026). Moreover, ginseng's antioxidant effects help mitigate the oxidative stress that often accompanies immune suppression (Saba et al., 2018). This review presents an in-depth examination of the different species of ginseng, emphasizing their distinct phytochemical profiles and well-documented immunostimulatory activities. It highlights the specific ways in which ginseng modulates immune function in fish, with a focus on the molecular pathways. In addition, the article discusses the potential of ginseng as a sustainable alternative for antibiotics in aquaculture, while also outlining the key limitations and research priorities necessary to optimize its application in fish farming.

# 2 Types of ginseng and their phytochemical composition

## 2.1 Classification and types of ginseng

The genus *Panax* comprises several species of ginseng, each known for its unique medicinal properties and cultural significance. The most widely recognized types include *P. ginseng* (Asian or Korean ginseng), *P. quinquefolius* (American ginseng), *P. notoginseng* (Chinese ginseng), and *P. japonicus* (Japanese ginseng). Additionally, other species such as *Boesenbergia rotunda* (Thai ginseng) and *Eleutherococcus senticosus* (Siberian ginseng) are also valued for their medicinal properties, although they belong to different genera (Li, 2001; Seervi et al., 2010; Kim and Park, 2011; Jee et al., 2014). *P. ginseng*, also known as Korean or Asian ginseng, is the most commonly used species in traditional Chinese and Korean medicine, prized for its adaptogenic and immune-enhancing properties (Kiefer and Pantuso, 2003; Yousefi et al., 2026). *P. quinquefolius*, commonly referred to as American ginseng, is widely used in North American traditional medicine and is known for its cooling properties in contrast to the "warming" nature of Asian ginseng (Mancuso and Santangelo, 2017). *P. notoginseng* (also called Tienchi ginseng) is mainly used in Chinese medicine for its ability to stop bleeding, improve circulation, and reduce inflammation (Kim, 2012). *P. japonicus*, native to Japan and parts of China, is valued for its tonic effects and is often used in folk medicine to boost stamina and reduce fatigue (Chen et al., 2023; Wang et al., 2025). Thai ginseng, native to Southeast Asia, is valued for its energizing properties and is often used in traditional medicine to enhance physical performance and vitality (Eng-Chong et al., 2012). Siberian ginseng, indigenous to Northeastern Asia, is prized for its adaptogenic effects and is commonly used to increase resistance to stress and combat mental fatigue (Yan-Lin et al., 2011). Each species contains a variety of bioactive compounds, but the variation in these compounds results in different therapeutic effects across the types of ginseng. As a result, the classification of ginseng is not only based on geographical or botanical distinctions but also on the different pharmacological profiles they offer.

## 2.2 Phytochemical composition of ginseng

The medicinal properties of ginseng are primarily attributed to its rich phytochemical composition, with ginsenosides being the most studied and biologically significant group of compounds (Vindas et al., 2021). Ginsenosides are a class of steroidal saponins unique to the *Panax* species, and they exhibit a wide range of pharmacological effects, including immunomodulatory, anti-inflammatory, antioxidant, and anti-cancer activities (Shi et al., 2019). Key ginsenosides include (Lu et al., 2009): Rg1, which is known for its stimulatory effects on the central nervous system and its ability to enhance cognitive function, Rb1, which is associated with neuroprotective and anti-inflammatory activities; Rc, which has been found to possess anti-inflammatory properties, and Rg3, a potent antioxidant and anticancer agent that is more abundant in processed forms of ginseng like red ginseng. In addition to

ginsenosides, ginseng contains other bioactive compounds such as: polysaccharides, which have demonstrated immune-boosting and anti-tumor effects; flavonoids, which contribute to the plant's antioxidant activity; peptides, essential oils, vitamins, and minerals, which further enhance ginseng's therapeutic value (Lu et al., 2009; Ratan et al., 2021). These compounds work synergistically to provide the wide array of health benefits traditionally associated with ginseng. The biological effects of ginseng are largely determined by its ginsenoside profile, which varies significantly across different *Panax* species (Liu et al., 2016; He et al., 2025). Each species of ginseng has a unique combination of ginsenosides that contribute to its specific therapeutic properties. For example, *P. ginseng* typically contains higher concentrations of Rg1 and Rb1, which are associated with cognitive enhancement and anti-inflammatory effects (Asafu-Adjaye et al., 2003). *P. quinquefolius* is richer in Re and Rd, giving it stronger antioxidant and sedative properties, aligning with its traditional use as a cooling tonic in contrast to the more stimulating Asian ginseng (Chen et al., 2008). *P. notoginseng* is particularly abundant in Rg1 and Rb1, which contribute to its hemostatic and anti-inflammatory effects (Liang et al., 2024; Zeng et al., 2014). The variation in ginsenoside profiles not only affects the pharmacological effects of each species but also its suitability for specific applications. For instance, the high concentration of Rg3 in red ginseng makes it more effective in anticancer and antioxidant therapies (Sun et al., 2017; Wang et al., 2022), whereas the immune-modulating properties of Rb1 and Rg1 make white ginseng extracts more appropriate for enhancing immune function (You et al., 2022). Understanding these variations is critical for selecting the appropriate type of ginseng for specific therapeutic applications, particularly in fields like aquaculture, where species-specific ginseng extracts may offer tailored benefits for improving fish health and immunity.

## 2.3 Methods of extraction and processing

The extraction and processing of ginseng play a critical role in determining the concentration and efficacy of its bioactive components. Traditional methods of ginseng processing include drying and steaming, which lead to the production of different forms of ginseng, such as white ginseng (air-dried) and red ginseng (steamed and dried) (Nam, 2005; He et al., 2018). White ginseng is typically dried without additional processing, which preserves more of the natural ginsenoside profile but may have lower concentrations of certain bioactive compounds. Red ginseng undergoes a steaming process that alters the ginsenoside profile by converting certain compounds, such as the transformation of ginsenoside Rg1 to Rg3, which is known to increase antioxidant and anticancer properties (Jegal et al., 2019). Various modern extraction techniques have also been developed to maximize the yield of bioactive compounds: 1) Solvent extraction, using ethanol or methanol, is commonly employed to extract ginsenosides and polysaccharides, 2) Supercritical fluid extraction (SFE) offers a more environmentally friendly approach, utilizing $CO_2$ to extract high-purity ginsenosides without the need for harsh chemicals. 3) Ultrasonic and microwave-assisted extraction techniques have been explored to increase the efficiency of ginsenoside extraction, reducing time and energy consumption (Jegal et al., 2019). The choice of processing method influences the final phytochemical composition, and the resulting ginseng extract may vary in its biological activity depending on how it is processed.

# 3 Overview of the fish immune system

The immune system of fish is comprised of two primary components: the innate immune system and the adaptive immune system (Firdaus-Nawi and Zamri-Saad, 2016). The innate immune system serves as the first line of defense against pathogens, providing immediate but non-specific responses. This system includes physical barriers, such as mucosal surfaces, as well as cellular components, such as macrophages and neutrophils, that recognize and eliminate a broad range of pathogens. Additionally, the innate immune response involves various soluble factors like antimicrobial peptides, cytokines, and complement proteins that facilitate pathogen recognition and destruction (Aoki et al., 2008; Firdaus-Nawi and Zamri-Saad, 2016).

In contrast, the adaptive immune system develops a specific response against particular pathogens and relies on the recognition of unique antigens. This system involves the proliferation and activation of lymphocytes, including T and B cells, which provide long-term immunity through the production of specific antibodies (Tort et al., 2003; Kordon et al., 2021). Although the adaptive immune response in fish is not as well developed as in mammals, significant advancements in understanding fish immunology have revealed the presence of memory cells and more complex mechanisms than previously thought. Fish possess a variety of immune cells that play critical roles in both innate and adaptive immune responses (Tort et al., 2003; Aoki et al., 2008; Firdaus-Nawi and Zamri-Saad, 2016; Kordon et al., 2021). Macrophages are phagocytic cells that are vital for pathogen clearance. Macrophages are responsible for engulfing and digesting pathogens in fish, presenting antigens to lymphocytes, and secreting pro-inflammatory cytokines that activate other immune cells (Mokhtar and Abdelhafez, 2021). Similar to mammals, neutrophils in fish are short-lived phagocytes that respond rapidly to infection. They play a key role in the early stages of immune response by migrating to sites of infection, where they phagocytize pathogens and release antimicrobial substances (Neumann et al., 2001; Havixbeck and Barreda, 2015; Speirs et al., 2024). Lymphocytes include T cells and B cells, which are central to the adaptive immune response. T cells are further divided into helper T cells (CD4+) and cytotoxic T cells (CD8+), while B cells are responsible for antibody production (Alam and Gorska, 2003). Both types of lymphocytes contribute to immunological memory, which enables faster and more effective responses upon re-exposure to pathogens (Ratajczak et al., 2018). Natural Killer (NK) Cells are part of the innate immune system and play a critical role in identifying and destroying virus-infected cells and tumor cells. NK cells use various cytotoxic mechanisms, including the release of perforin and granzymes, to induce apoptosis in their target cells. Fish possess several specialized organs that are integral to their immune function (Prager and Watzl, 2019). Thymus is important for the development of T cell (Chilmonczyk, 1992). Spleen is a site for B cell

maturation and antibody production, as well as a reservoir for immune cells (Zapata, 2024). Also, kidney plays a crucial role in both osmoregulation and immunity. The head kidney, in particular, functions similarly to the bone marrow in mammals, serving as a site for hematopoiesis (the production of blood cells) and the maturation of immune cells (Geven and Klaren, 2017; Kondera, 2019). Liver in fish is essential for producing various immune factors, including complement proteins and acute-phase proteins. It also participates in filtering blood and removing pathogens and toxins (Bruslé and i Anadon, 2017; Causey et al., 2018).

Fish exhibit both humoral and cellular immunity, although the mechanisms differ somewhat from those in mammals. Humoral Immunity involves the production of antibodies by B cells in response to specific antigens. The antibodies circulate in the bloodstream and bind to pathogens, neutralizing them or marking them for destruction by other immune cells. Additionally, fish produce various other humoral factors, including lysozyme and complement proteins, which help to enhance the immune response and eliminate pathogens (Yano, 1995; Ye et al., 2013). Cellular immunity primarily involves T cells and other immune cells like macrophages and NK cells. T cells recognize infected or abnormal cells and mount a targeted immune response. This involves the activation of cytotoxic T cells that directly kill infected cells and helper T cells that facilitate the activation of B cells and other immune components (Fischer et al., 2013). The interplay between humoral and cellular immunity in fish is crucial for an effective immune response to a wide variety of pathogens.

# 4 Immunomodulatory effects of ginseng on fish

## 4.1 Innate immune system modulation

Ginseng (*Panax* species) is known for its diverse biological activities, particularly its immune-modulating effects (Figure 1). One of the key indicators of innate immunity in fish is lysozyme activity, which plays a crucial role in the defense against bacterial infections. Studies have shown that ginseng as powder, byproduct, and extracts can significantly enhance lysozyme levels in various fish species (Choi et al., 2010; Won et al., 2008; El-Sayed et al., 2014; Bulfon et al., 2017; Van Doan et al., 2019; Yousefi et al., 2026), leading to improved antibacterial defenses. Increased lysozyme activity helps in the breakdown of bacterial cell walls, facilitating the elimination of pathogens. Respiratory burst activity in fish immune cells is another immune component stimulated by ginseng in fish (Won et al., 2008; Choi et al., 2010; Bulfon et al., 2017; Van Doan et al., 2019). The respiratory burst is a rapid release of reactive oxygen species (ROS) by phagocytic cells, such as macrophages and neutrophils, upon encountering pathogens (Forman and Torres, 2002). Therefore, enhanced respiratory burst activity following ginseng treatment can indicate an elevated capacity of immune cells to respond to infections. This response is crucial for the effective killing of bacteria and other pathogens. The complement system is an integral part of the innate immune response of fish, providing a first line of defense against invading pathogens (Holland and Lambris, 2002). Studies investigating the effects of ginseng on complement activation have shown promising results. Ginseng extracts have been observed to enhance complement activity in fish, leading to improved opsonization and lysis of bacteria (Van Doan et al., 2019; Liu et al., 2025).

Phagocytosis, the process by which immune cells engulf and digest pathogens, is another critical component of innate immunity that is influenced by ginseng (Kang and Min, 2012; He et al., 2018). In fish, as in other vertebrates, phagocytic activity is mainly performed by macrophages and neutrophils, which are essential cells that identify, ingest, and break down pathogens (Grayfer et al., 2018; Kordon et al., 2018). These cells are critical to the innate immune system, playing a major role in clearing pathogens and debris through processes like recognition, engulfment, and digestion (Grayfer et al., 2018; Kordon et al., 2018). The elevated phagocytic activity of macrophages and neutrophils has been also observed in fish following ginseng supplementation (Choi et al., 2010; Won et al., 2008; Van Doan et al., 2019). Such increased phagocytosis can improve the overall ability of the immune system to clear infections, contributing to better health and survival rates in aquaculture settings. Research indicated that ginsenosides, the principal bioactive compounds found in ginseng can stimulate both macrophages and neutrophils, enhancing their functionality and overall immune response (Azike et al., 2011; Nguyen and Rhee, 2016; He et al., 2017, 2018; Ratajczak-Wrona et al., 2020). Ginsenosides such as Rg1, Rb1, and Rg3 have been shown to promote the proliferation and activation of the immune cells, leading to increased production of cytokines and chemokines that are essential for orchestrating immune responses (Kim et al., 2017; Mohanan et al., 2018; You et al., 2022; Im, 2020; Lee et al., 2022; Jang et al., 2023). Ginseng seems to increase the phagocytic activity of cells through stimulating Toll-Like Receptors (Kang and Min, 2012), cytokine production (Pannacci et al., 2006), ROS regulation (Morshed et al., 2023), upregulating phagocytic receptors (Nguyen and Nguyen, 2019) and improving antioxidant enzyme activity (Im Chung et al., 2016).

Pathogen-associated molecular patterns (PAMPs) are molecules commonly found on the surface of pathogens, like bacteria, viruses, and fungi, but are not present in host cells. They serve as "red flags" that are recognized by the immune system's pattern recognition receptors (Abouelmaatti et al., 2013). Macrophages and neutrophils recognize PAMPs using receptors such as TLRs and phagocytic receptors (Akira, 2003). TLRs are a crucial component of the innate immune system, responsible for recognizing PAMPs and initiating immune responses of fish (Fan et al., 2015; Tanekhy, 2016) and other vertebrates (Kawasaki and Kawai, 2014). Ginsenosides have been shown to enhance TLR signaling pathways, thereby amplifying the immune responses (Su et al., 2012). However, we found no evidence in the literature supporting this role in fish.

Ginseng is known to modulate the expression of cytokines such as tumor necrosis factor-alpha (TNF-α), interleukins (IL-1, IL-6), and interferon-gamma (IFN-γ) (Kim et al., 2017). These cytokines play critical roles in activating macrophages and neutrophils, enhancing their ability to recognize, engulf, and destroy pathogens.

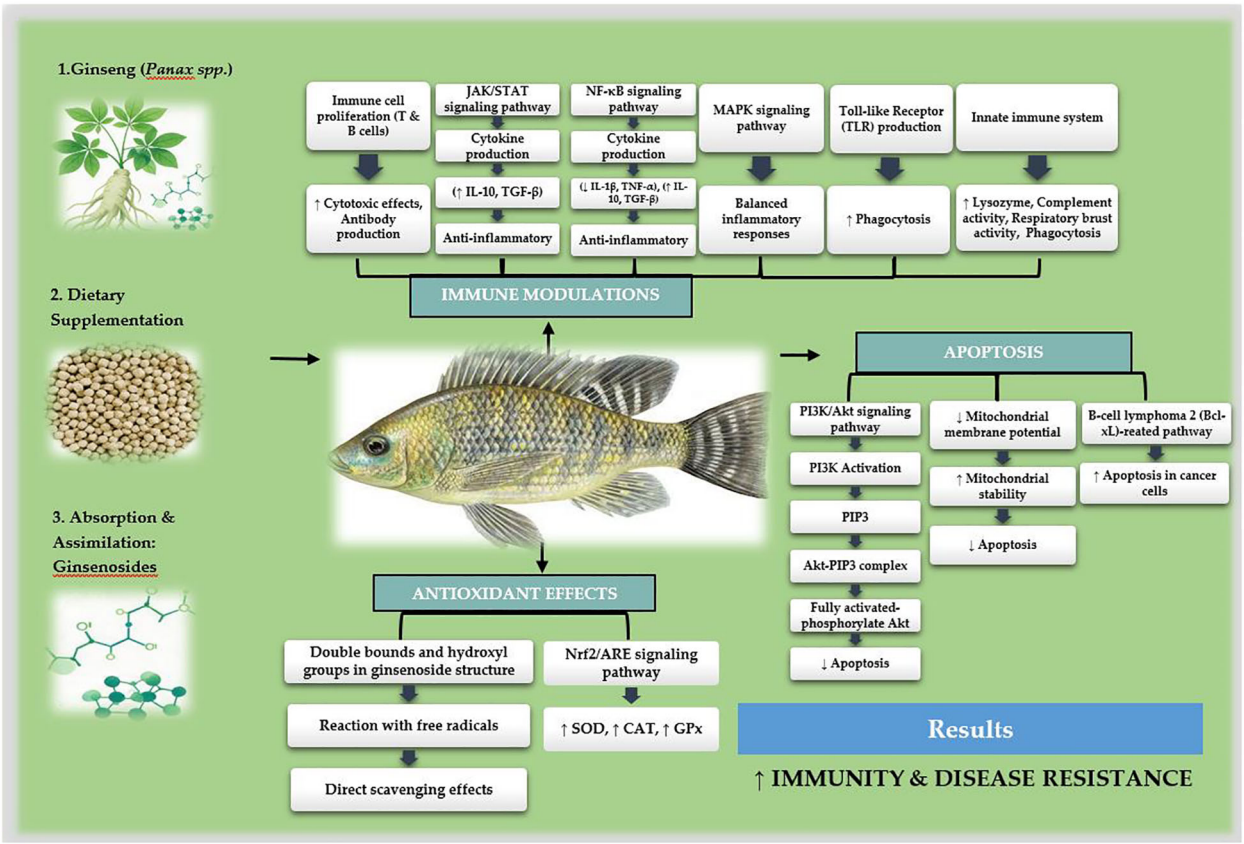


FIGURE 1
Mechanisms of the immune-boosting effects of ginseng. NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; JAK/STAT, Janus kinase/signal transducer and activator of transcription; MAPK, Mitogen-activated protein kinase; Nrf2/ARE, Nuclear factor erythroid 2-related factor 2/antioxidant response element; PI3K/Akt, Phosphoinositide 3-kinase/protein kinase B; TLR, Toll-like receptor; TGF-β, Transforming Growth Factor-beta; IL-1β, Interleukin-1 beta; TNF-α, Tumor Necrosis Factor-alpha; PI3K/Akt, Phosphoinositide 3-Kinase/Protein Kinase B; PIP3, Phosphatidylinositol (3,4,5)-trisphosphate; SOD, Superoxide Dismutase; CAT, Catalase; GPx, Glutathione Peroxidase; ↑, Increased/Enhanced/Upregulated; ↓, Decreased/Reduced/Downregulated.

There are some studies indicating the role of ginseng and their derivatives on cytokine production in fish. For example, in crucian carp, *Carassius auratus* fed with ginseng stem and leaf saponins (GSLS) dietary supplementation at 8 g/kg significantly upregulated the expression of immune-related cytokines including TNF-α, IL-10, and IFN-γ in the liver, spleen, and intestinal tract (Wang et al., 2024).

In channel catfish (*Ictalurus punctatus*), dietary supplementation with ginseng polysaccharides (GP) at 200–800 mg/kg significantly modulated cytokine expression, as evidenced by upregulation of anti-inflammatory mediators (TGF-β1, TGF-β2, TGF-β3, and IL-10) and suppression of pro-inflammatory cytokines (IL-1β, IL-8, and TNF-α) (Fu et al., 2025). In yellow catfish (*Pelteobagrus fulvidraco*), dietary supplementation with an astragalus–ginseng mixture at 500–2000 mg/kg significantly modulated cytokine expression, with IL-10 (anti-inflammatory) upregulated and pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) downregulated at lower concentrations, while higher doses increased pro-inflammatory responses (Lin et al., 2025). Dietary supplementation with ginseng polysaccharides (GP) at 500 and 1000 mg/kg significantly counteracted the pro-inflammatory effects of a high-cottonseed meal diet in grass carp (*Ctenopharyngodon idella*). The GP-supplemented diets suppressed the NF-κB/TLR pathway, leading to decreased expression of pro-inflammatory cytokines (TNF-α, IL-1B, IL-6) and increased anti-inflammatory markers (IL-10, TGF-β1) (Shi et al., 2025).

Neutrophils and macrophages use ROS to kill pathogens after engulfment (El Benna et al., 2016; Winterbourn et al., 2016; Canton et al., 2021; Herb and Schramm, 2021). Macrophages exposed to ginsenosides exhibit enhanced phagocytic activity and increased production of ROS, which are crucial for pathogen elimination (Xin et al., 2019). Additionally, ginsenosides have been reported to increase the expression of surface markers associated with natural killer cell activation, further demonstrating their role in enhancing innate immune responses (Lee et al., 2022; Jang et al., 2024). It was reported that dietary supplementation with ginseng can enhance neutrophil and macrophage activities. Dietary supplementation of rainbow trout (*Oncorhynchus mykiss*) with Red Ginseng (*P. ginseng*) powder at levels of 25–30 g/kg significantly enhanced myeloperoxidase (MPO) activity, indicating a boost in neutrophil activity (Liu et al., 2025). Dietary supplementation with 3% Siberian ginseng (*Eleutherococcus senticosus*) residuum extract significantly enhanced phagocytic and respiratory burst activity in olive flounder (*Paralichthys olivaceus*), indicating heightened macrophage and neutrophil function (Won et al., 2008). Table 1 presents the changes in immune parameters in detail in fish in response to dietary ginseng.

TABLE 1 Summary of the immunomodulatory effects of dietary ginseng and its derivatives in various fish species.

| Supplement name | Dietary level | Fish species | Duration | Immune parameters | Reference |
|---|---|---|---|---|---|
| Red Ginseng Byproduct (RB) | 0.5%, 1%, 2% | Olive flounder | 8 weeks | Lysozyme activity: ↑ (at 0.5%, 1%); Serum glucose: ↓; Serum GPT: ↓ (except 2%); Serum TG: ↓ | Choi et al. (2010) |
| Siberian Ginseng Residuum Extract (SG-RE) | 3%, 7% | Olive flounder | 8 weeks | At 3%: Phagocytic ratio (PR): ↑; Phagocytic index (PI): ↑; Respiratory burst (NBT): ↑; Serum lysozyme: ↑; Skin mucus lysozyme: ↑; Neutrophil count: ↑<br>at 7%: PR: ↔; PI: ↑; NBT: ↓; Serum lysozyme: ↔; Skin mucus lysozyme: ↔; Neutrophil count: ↑ | Won et al. (2008) |
| Ginseng Extract | 0.6 g/kg diet | Nile tilapia | 8 weeks | Total leukocytic count: ↑; Lysozyme activity: ↑; NBT activity: ↑; Serum bactericidal activity (SBA): ↑; Total globulin: ↑ | El-Sayed et al. (2014) |
| Ginseng Ethanolic Extract (*Panax ginseng*) | 0.01%, 0.02%, 0.03% | Rainbow trout | 10 weeks | Serum lysozyme: slight ↑; Leukocyte NBT: slight ↑; Serum antiproteases: ↔; Leukocyte MPO: ↔ | Bulfon et al. (2017) |
| Thai Ginseng (*Boesenbergia rotunda*) Powder | 5, 10, 20, 40 g/kg diet | Nile tilapia | 8 weeks | Lysozyme activity (SL): ↑; Peroxidase activity (SP): ↑; Alternative complement (ACH50): ↑; PI: ↑; NBT: ↑ | Van Doan et al. (2019) |
| Red Ginseng Powder (RGP) (*Panax ginseng*) | 5, 10, 15, 20, 25, 30, 35 g/kg diet | Rainbow trout | 60 days | Systemic (serum): Lysozyme: ↑; ACH50: ↑; Total Ig: ↑; MPO: ↓<br>Mucosal (mucus): Total Ig: ↑; Alkaline phosphatase (ALP): ↑; Protease: ↑; Lysozyme: ↑ | Liu et al. (2025) |
| Ginseng Stem and Leaf Saponins (GSLS) | 1, 2, 4, 8 g/kg diet | Crucian carp | 5 weeks | IgM: ↑; Complement C4: ↑; ALP: ↑; Gene expression (liver, spleen, intestine): *tnf-α, il-10, ifn-γ*: ↑ | Wang et al. (2024) |
| Ginseng Polysaccharide (GP) | 200, 400, 800, 1600 mg/kg diet | Channel catfish | 56 days | Epithelial barrier genes (zo-1, zo-2, occludin): ↑; Anti-inflammatory genes (*tgf-β1, tgf-β2, tgf-β3, il-10*): ↑; Pro-inflammatory genes (*il-1β, il-8, tnf-α*): ↓ | Fu et al. (2025) |
| *Astragalus-Ginseng* Mixture | 500, 1000, 2000 mg/kg diet | Yellow catfish | 6 weeks | Immune genes: Anti-inflammatory (*il-10*): ↑; Pro-inflammatory (*il-1β, il-6, tnf-α*): ↓; Lysozyme: ↑ | Lin et al. (2025) |
| Ginseng Polysaccharides (GP) | 500, 1000 mg/kg diet | Grass carp | 8 weeks | Pro-inflammatory cytokines (*tnf-α, il-1β, il-6*): ↓; Anti-inflammatory markers (*il-10, tgf-β1*): ↑ | Shi et al. (2025) |
| *Panax notoginseng* Extract (PNE) | 0.5, 1, 2, 4, 10 g/kg diet | Hybrid grouper | 8 weeks | Total protein: ↑; ALP: ↑; Immunoglobulin (Ig): ↑; Complement C3: ↑; Complement C4: ↑; Gene expression: *il-10* (↑), *tgf-β1* (↑), *tor* (↑), *mhc2* (↑), *tlr3* (↑) | Sun et al. (2018) |
| Red Ginseng Powder (RGP) (*Panax ginseng*) | 0.5, 1.0, 1.5, 2, 2.5, 3, 3.5 mL/kg diet | Rainbow trout | 8 weeks | Serum: Lysozyme: ↑; ACH50: ↑; Total Ig: ↑; MPO: ↑; NBT: ↑<br>Mucosal: Total Ig: ↑; Protease: ↑; Lysozyme: ↑; ALP: ↑ | Yousefi et al. (2026) |

↑ = Significant increase.
↓ = Significant decrease.
↔ = No significant change.

## 4.2 Adaptive immune system modulation

Ginseng, particularly its bioactive compounds known as ginsenosides, has shown significant potential in modulating the specific immune responses, particularly through the enhancement of antibody production (Qu et al., 2011; Park et al., 2015). Immunoglobulins, specifically IgM and IgG, are critical components of the adaptive immune response in fish (Kordon et al., 2021). IgM is the predominant antibody present during the initial immune response, while IgG is associated with long-term immunity and memory (Firdaus-Nawi and Zamri-Saad, 2016; Kordon et al., 2021). Some studies have demonstrated that ginseng supplementation can lead to increased levels of these immunoglobulins in various fish species (Sun et al., 2018; Wang et al., 2024; Liu et al., 2025). The enhanced production of these antibodies is vital for improving the overall immune defense against bacterial and viral infections, thus contributing to better health and survival rates in aquaculture.

The adaptive immune response in fish also relies heavily on the activation and proliferation of lymphocytes, including T-cells and B-cells, which are essential for specific immune recognition and response (Fischer et al., 2013; Mutoloki et al., 2014). Researches indicate that ginsenosides can induce the activation of T-cells, promoting their proliferation and enhancing their ability to mount an effective immune response (Lee et al., 2004; Son et al., 2010; Kim et al., 2018). T-cells are responsible for orchestrating the fish immune response and providing cell-mediated immunity, particularly against intracellular pathogens (Nakanishi et al., 2015). Additionally, ginseng has been shown to enhance the activation of B-cells, which are responsible for producing antibodies (Kang and Min, 2012; Park et al., 2015). The stimulation of B-cell proliferation leads to an increase in the generation of plasma cells, which secrete antibodies necessary for combating infections. Studies have also shown that ginseng supplementation can upregulate the expression of key surface markers associated with T-cell and B-cell

activation, such as CD4, CD8, and CD19 (Kang and Min, 2012; Alam et al., 2023). This upregulation indicates an enhanced capacity of these immune cells to respond to antigens and mount a robust immune response. However, according to our research review, the specific and direct effects of ginseng on the adaptive immunity of fish have not yet been comprehensively studied. While evidence from other biological models is promising, the fundamental mechanisms and efficacy in piscine systems remain a significant knowledge gap.

# 5 Molecular mechanisms underlying ginseng's immune-modulating effects

## 5.1 Modulation of cytokine signaling pathways

It is well known that ginsenosides (as the primary active components of ginseng), play a pivotal role in modulating the immune response by regulating cytokine production (Kim et al., 2017). Cytokines are crucial signaling molecules in the immune system that mediate both pro-inflammatory and anti-inflammatory responses in fish (Zou and Secombes, 2016).) and other vertebrates (Shaikh, 2011). Among these, pro-inflammatory cytokines such as interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) are essential for initiating inflammatory responses and recruiting immune cells to sites of infection or injury. Conversely, anti-inflammatory cytokines like interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β) are critical for resolving inflammation and maintaining immune homeostasis (Shaikh, 2011).

Researches have demonstrated that ginsenosides can effectively modulate the production of these cytokines (Kim et al., 2017; Im, 2020). For instance, ginsenosides have been shown to down-regulate the expression of pro-inflammatory cytokines like IL-1β and TNF-α, thereby mitigating excessive inflammation that could lead to tissue damage and chronic inflammatory conditions (Kim et al., 2017; Im, 2020). Simultaneously, ginsenosides can enhance the expression of anti-inflammatory cytokines such as IL-10 and TGF-β (Im, 2020; Park and Cho, 2009), promoting a balanced immune response that favors healing and recovery. This dual regulatory effect underscores the potential of ginsenosides as therapeutic agents to manage immune responses. The research have shown that ginsenosides generally exert their regulatory effects on cytokine production through various intracellular signaling pathways. One of the most well-studied pathways influenced by ginsenosides is the nuclear factor kappa B (NF-κB) signaling pathway. By inhibiting the phosphorylation and degradation of the inhibitor of NF-κB, ginsenosides prevent NF-κB translocation to the nucleus, thus reducing the expression of pro-inflammatory cytokines such as IL-1β and TNF-α (Choi et al., 2007; Kim et al., 2017; Jang et al., 2023). Additionally, ginsenosides have been shown to modulate the janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, which plays a critical role in mediating the effects of cytokines (Jung et al., 2010; Qian et al., 2017). This pathway is particularly important for the signaling of IL-10 and TGF-β (Riley et al., 1999; Malemud and Pearlman, 2009). Ginsenosides can modulate the JAK/STAT signaling pathway, leading to increased expression of anti-inflammatory cytokines, thereby promoting an anti-inflammatory milieu (Jung et al., 2023). Furthermore, the mitogen-activated protein kinase (MAPK) pathway is another signaling cascade influenced by ginsenosides (Arafa et al., 2021). Activation of the MAPK pathway can lead to the production of various cytokines, including both pro-inflammatory and anti-inflammatory cytokines (Manzoor and Koh, 2012). Ginsenosides can fine-tune this pathway, allowing for a controlled inflammatory response (Saba et al., 2015; Lee et al., 2018). Unfortunately, our comprehensive review indicates a significant lack of evidence regarding the cytokine-related biochemical pathways modulated by ginseng in fish. The signaling mechanisms, such as the modulation of NF-κB or MAPK pathways, which are well-documented in *in vitro* and *in vivo* models. In a study by Nam et al. (2019), the MAPK signaling pathway was activated in zebrafish (*Danio rerio*) following supplementation with *P. ginseng* (Korea Red Ginseng). This constitutes a critical research gap that future research must address to fully understand ginseng's immune-boosting potential in aquaculture.

## 5.2 Modulation of antioxidant mechanisms

Ginseng, particularly through ginsenosides, plays a significant role in reducing oxidative stress within cells including immune cells (He et al., 2022; Paik et al., 2023). Oxidative stress arises when there is an imbalance between the production of ROS and the body's ability to eliminate these harmful byproducts through antioxidant mechanisms. Elevated levels of ROS can lead to cellular damage, dysfunction, and apoptosis, particularly in immune cells (Agostini et al., 2002) including fish immune cells (Gogal et al., 2000; Cheng et al., 2015; Biller and Takahashi, 2018). Scavenging ability of ginseng is particularly important in immune cells, which are often exposed to high levels of oxidative stress during inflammatory responses. Chronic inflammation can exacerbate oxidative stress, leading to further immune dysfunction (Khansari et al., 2009). By modulating inflammatory pathways and reducing the production of pro-inflammatory cytokines, ginseng can mitigate the inflammatory responses, thereby lowering the overall production of ROS (Kim et al., 2017). Therefore, given its established role in modulating cytokine signaling and inflammatory responses, ginseng is also likely to be a key regulator of oxidative stress in fish.

In addition to direct scavenging, ginseng also exerts protective effects by enhancing the endogenous antioxidant systems, which serve as the first line of defense against oxidative damage (Jung et al., 2005; Kim, 2012; Ramesh et al., 2012a). For instance, ginsenosides could promote the synthesis of important antioxidants such as glutathione, which plays a critical role in detoxifying harmful ROS and protecting cellular components, including proteins, lipids, and DNA (Kim et al., 2007; Liu, 2012). Researches indicate that ginsenosides can enhance the activity of key antioxidant enzymes, including superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx) (Chang et al., 1999; Ramesh et al., 2012a, b). SOD is crucial for converting superoxide radicals into hydrogen peroxide, while catalase and GPx subsequently reduce

hydrogen peroxide to water and oxygen, thus preventing oxidative damage (Bratovcic, 2020). By upregulating the activity of these enzymes, ginseng supplementation can effectively bolster the antioxidant defense system in immune cells, enhancing their resilience against oxidative stress. In fish, dietary ginseng supplementation in fish has been shown to elevate key antioxidant enzymes, a process, probably mediated by the nuclear factor erythroid 2-related factor 2 (nrf2)/Antioxidant Response Element (ARE) signaling pathway (Chaparala et al., 2020; Lu et al., 2023). However, such a mechanism of nrf2/ARE activation has not yet been studied in fish. In addition, some studies have indicated a significant reduction in malondialdehyde (MDA) levels, a robust indicator of mitigated oxidative stress in fish, following supplementation with ginseng (Ahmed et al., 2022; Li et al., 2022; Lin et al., 2025; Liu et al., 2025). Therefore, ginseng can play a crucial role in reducing oxidative stress in cells, particularly immune cells through the modulation of antioxidant enzyme activities and direct protection against ROS-induced damage. Table 2 presents the changes in antioxidant defense parameters in detail in fish in response to dietary ginseng.

## 5.3 Modulation of apoptosis and cell survival pathways

Ginseng and its main compounds, ginsenosides, have also garnered attention for their role in modulating apoptosis in immune cells, particularly through the phosphoinositide 3-kinase (PI3K)/Akt signaling pathway (Qiu et al., 2014). This pathway plays a critical role in regulating cell survival and apoptosis by mediating various intracellular signaling cascades (Duronio, 2008). When the PI3K/Akt pathway is activated, Akt promotes cell survival by inhibiting apoptotic signals and enhancing anti-apoptotic mechanisms (Shimamura et al., 2003; Seol, 2008). Ginsenosides have been shown to activate this pathway in various immune cell types, leading to increased cell viability and reduced apoptosis, especially under conditions of oxidative stress or inflammation (Wang et al., 2014; Ghafouri-Fard et al., 2022; Tang et al., 2024). However, it seems that there is a dual role for ginsenosides, as some studies have reported apoptosis-inducing effects for these compounds, especially in relation to cancer cells. Ginsenosides induced apoptosis by regulation of B-cell lymphoma 2 (Bcl-xL) (Wang et al., 2002; Luo et al., 2015). By modulating the PI3K/Akt pathway, ginseng effectively enhances the survival of immune cells, regulates apoptosis, ensuring that they remain functional during immune responses. Furthermore, the activation of the PI3K/Akt pathway can promote metabolic reprogramming in immune cells, enhancing their ability to respond to stressors (Weichhart and Säemann, 2008; Jellusova and Rickert, 2016). Although some *in vitro* and *in vivo* studies (Wang et al., 2014; Ghafouri-Fard et al., 2022; Tang et al., 2024) have reported the influence of ginseng on programmed cell death, this mechanism remains uninvestigated in fish. Thus, this unexplored area regarding its role in fish warrants future research.

## 5.4 Influence on mitochondrial stability and reduction of immune cell death under stress conditions

Mitochondrial health is paramount for the survival and function of immune cells, as these organelles play a crucial role in energy production and the regulation of apoptosis (Walker et al., 2014; Xie et al., 2020). Ginseng has been shown to influence mitochondrial stability, thereby reducing immune cell death under stress conditions, such as oxidative stress or exposure to inflammatory cytokines (Wang and Roh, 2020; Iqbal and Rhee, 2025). Ginsenosides contribute to mitochondrial stability by promoting the expression of proteins that regulate mitochondrial dynamics and biogenesis. For instance, they enhance the expression of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), a key regulator of mitochondrial biogenesis, which supports the production of new mitochondria (Huang et al., 2022; Xin et al., 2024). This process is essential for maintaining the energy demands of immune cells, particularly during periods of heightened activity. Additionally, ginseng exhibits protective effects on mitochondrial function by reducing mitochondrial membrane potential loss and preventing the release of cytochrome c, a pro-apoptotic factor (Leung et al., 2007; Zhou et al., 2014).

The protective role of ginseng in maintaining mitochondrial stability and preventing immune cell death has not been established in fish. Key mechanisms such as its influence on PGC-1α-mediated biogenesis and the inhibition of apoptotic pathways in piscine mitochondria represent a critical knowledge gap. Future studies

TABLE 2 Summary of the antioxidant effects of dietary ginseng and its derivatives in various fish species.

| Supplement name | Dietary level | Fish species | Duration | Antioxidant parameters | Reference |
|---|---|---|---|---|---|
| Red Ginseng Powder (RGP) (*Panax ginseng*) | 5, 10, 15, 20, 25, 30, 35 g/kg diet | Rainbow trout | 60 days | SOD: ↑; CAT: ↑; GPx: ↑; MDA: ↓ | Liu et al. (2025) |
| Ginseng Stem and Leaf Saponins (GSLS) | 1, 2, 4, 8 g/kg diet | Crucian carp | 5 weeks | SOD: ↑; GSH-Px: ↑ | Wang et al. (2024) |
| Astragalus-Ginseng Mixture | 500, 1000, 2000 mg/kg diet | Yellow catfish | 6 weeks | CAT: ↑; SOD: ↑; GSH: ↑; MDA: ↓ | Lin et al. (2025) |
| Siberian Ginseng Water Extract (ASW) | 0.1‰, 0.2‰, 0.4‰, 0.8‰, 1.6‰ | Nile tilapia | 8 weeks | SOD: ↑; CAT: ↑ | Li et al. (2022) |
| *Panax notoginseng* Extract (PNE) | 0.5, 1, 2, 4, 10 g/kg diet | Hybrid grouper | 8 weeks | SOD: ↑; T-AOC: ↑ | Sun et al. (2018) |
| Red Ginseng Powder (RGP) (*Panax ginseng*) | 0.5, 1.0, 1.5, 2, 2.5, 3, 3.5 mL/kg diet | Rainbow trout | 8 weeks | CAT: ↑; SOD: ↑; GSH: ↑; GPx: ↑; MDA: ↓ | Yousefi et al. (2026) |

↑, Significant Increase; ↓, Significant Decrease; ↔, No Significant Change.

are needed to elucidate these functions to fully appreciate ginseng's potential in in fish.

### 5.5 Modulation of immune gene expression

Studies have shown that ginsenosides can modulate the expression of genes involved in various immune pathways. In fish, dietary ginseng has been shown to activate immune genes that encode for cytokines, antimicrobial peptides, and enzymes involved in oxidative defense mechanisms. For instance, crucian carp fed diets supplemented with up to 8 g/kg ginseng stem and leaf saponins for 5 weeks showed significant upregulation of cytokine genes (*tnf-α, il-10, ifn-γ*) in liver, spleen, and intestine (Wang et al., 2024). Ginseng's immunostimulatory effect in fish has been also linked to its influence on gene expression within innate immunity pathways. This includes genes associated with TLR signaling, which detects PAMPs and triggers downstream immune responses (Ratan et al., 2021; Xu et al., 2022). Ginseng appears to modulate the expression of genes encoding *tlrs*, leading to enhanced pathogen recognition and subsequent activation of immune defenses (Nakaya et al., 2004; Ahn et al., 2006; Xu et al., 2022). This modulation likely aids fish in faster and more effective responses to infections, such as bacterial and viral pathogens commonly encountered in aquaculture settings. Ginseng has been shown to upregulate genes coding for antioxidant enzymes such as SOD, CAT and GPx, which help mitigate oxidative damage during immune responses, thereby enhancing cellular integrity and immune efficiency under stress (Chang et al., 1999; Lee et al., 2012; Hassan et al., 2015). Supplementation with ginseng and its derivatives has been consistently shown to upregulate key immune and antioxidant genes in various fish species (Sun et al., 2018; Wang et al., 2024; Fu et al., 2025; Lin et al., 2025). According to studies, this includes enhancing the expression of cytokine genes (e.g., *tnf-α, il-10, ifn-γ*), genes for antioxidant enzymes (e.g., SOD, CAT), and receptors involved in pathogen recognition (e.g., TLRs). This genetic reprogramming strengthens the fish's innate immune response and cellular defense against oxidative stress.

## 6 Applications of ginseng in aquaculture

### 6.1 Disease resistance and reducing antibiotic dependence

Recent field studies have highlighted the beneficial effects of ginseng-enriched diets on disease resistance in various fish species, including tilapia, carp and trout (Table 1) (Abdel-Tawwab, 2012; Bulfon et al., 2017; Van Doan et al., 2019; Wang et al., 2024; Fu et al., 2025; Yousefi et al., 2026). The incorporation of ginseng, particularly its bioactive compounds such as ginsenosides, into aquaculture diets has shown promising results in enhancing the immune responses of these fish, thereby improving their overall health and resilience against infectious diseases (Abdel-Tawwab, 2012; Bulfon et al., 2017; Van Doan et al., 2019; Wang et al., 2024; Fu et al., 2025). In studies involving Nile tilapia (*Oreochromis niloticus*), Thai ginseng, *B. rotunda* and American ginseng *P. quinquefolium* supplementations have been linked to improved resistance against *Streptococcus agalactiae* (Van Doan et al., 2019) and *Aeromonas hydrophila* (Abdel-Tawwab, 2012) respectively. Fish fed diets enriched with ginseng exhibited enhanced levels of innate immune components (lysozyme, alternative complement ACH50, phagocytosis index, respiratory burst activities, peroxidase). These changes were associated with lower infection rates and reduced mortality, demonstrating the protective role of ginseng in enhancing tilapia's immune response (Abdel-Tawwab, 2012; Van Doan et al., 2019). Research on rainbow trout has also indicated that ginseng can bolster disease resistance. In controlled trials, trout receiving *P. ginseng* extract-enriched feed showed increased survival rates following exposure to pathogens like *Yersinia ruckeri* (Bulfon et al., 2017). In channel catfish challenged with *Y. ruckeri*, those fed a diet containing ginseng polysaccharide (GP) had higher survival rates than fish without supplementation (Fu et al., 2025). Moreover, rainbow trout fed with ginseng (*P. ginseng*) essential oil at 3 ml/kg diet exhibited the highest antioxidant enzyme activity and immune response, as well as the lowest mortality after *A. hydrophila* challenge (Yousefi et al., 2026).

The aquaculture industry has faced increasing scrutiny over the use of antibiotics due to concerns regarding antibiotic resistance and the potential impacts on human health and the environment (Rasul and Majumdar, 2017). Consequently, there is a growing interest in finding alternative approaches to enhance fish health and immunity without relying on conventional antibiotics. Ginseng, with its rich phytochemical profile and well-documented immunomodulatory properties, presents a promising alternative as an immune enhancer in aquaculture. Ginseng contains several bioactive compounds, particularly ginsenosides, polysaccharides, and flavonoids, which are known to exhibit immune functions (Ratan et al., 2021). As reviewed above, these compounds can enhance the innate and adaptive immune responses in fish, making them more resilient to infections (Abdel-Tawwab, 2012; El-Sayed et al., 2014; Van Doan et al., 2019). These effects are critical in reducing the incidence of diseases and promoting overall health, thus potentially decreasing the reliance on antibiotics.

### 6.2 Challenges in ginseng use

While ginseng has shown considerable promise as an immune enhancer in aquaculture, the current body of research on its effects in fish is still limited and presents several challenges. These limitations can impact the understanding of ginseng's efficacy, its practical application in aquaculture, and the establishment of guidelines for its use. One of the primary limitations in current research is the variability in ginseng's efficacy based on dosage, fish species, and environmental conditions (Abdel-Tawwab, 2012; El-Sayed et al., 2014; Van Doan et al., 2019). Although we found no study reporting dose-dependent toxicity of ginseng in fish, several studies have reported ginseng toxicity at high concentrations (Chan and Fu, 2007; Park et al., 2013; Lee et al., 2014; Paik and Lee, 2015; Park et al., 2018). Therefore, it is necessary to optimize the administered levels of ginseng for fish.

Another significant challenge is the lack of standardization in ginseng extracts used in research. Ginseng is a complex herbal product with varying profiles of active compounds, particularly ginsenosides (Harkey et al., 2001), which can differ based on factors such as the source of the plant, processing methods, and extraction techniques (Punja, 2011; Jegal et al., 2019; Piao et al., 2020). This variability makes it difficult to compare findings across studies and to establish a clear understanding of which specific ginsenosides contribute most significantly to immune enhancement. Therefore, standardizing ginseng extracts to ensure consistent levels of active compounds is essential for conducting reliable research and producing reproducible results. Establishing guidelines for the preparation and application of ginseng supplements in aquaculture could help in creating more uniform conditions for evaluating its effectiveness.

To address the limitations outlined above, future research should focus on several key areas. First, long-term studies are necessary to assess the sustainability of ginseng's effects on fish immunity. Most current studies are conducted over relatively short periods, which may not capture the long-term benefits or potential adverse effects of ginseng supplementation. Understanding how prolonged exposure to ginseng affects immune function, growth, and overall health will be vital for its integration into aquaculture practices. Additionally, exploring synergistic formulations that combine ginseng with other phytochemicals or probiotics could enhance its effectiveness. Research into how ginseng interacts with these compounds can lead to improved health benefits and disease resistance in fish. Identifying combinations that work synergistically may maximize the immune-stimulating effects of ginseng and provide a broader protective response against various pathogens.

## 7 Conclusion

This review highlights the significant findings on ginseng's impact on fish immunity, showcasing its potential as an effective immunomodulatory agent. Studies indicate that ginseng enhances both innate and adaptive immune responses in various fish species, leading to increased disease resistance and improved overall health. The ability of ginseng to stimulate immune cell activity, regulate cytokine production, and bolster antioxidant defenses underscores its promise in sustainable aquaculture practices. Ginseng-based supplements could play a crucial role in improving fish health, reducing disease outbreaks, and decreasing the reliance on antibiotics. By integrating ginseng into aquaculture diets, fish farmers can promote a more robust immune system in their stocks, ultimately contributing to healthier fish populations and improved yields. However, the need for continued research and development in this area is paramount. Further studies are essential to standardize ginseng formulations, determine optimal dosages, and explore potential synergistic effects with other phytochemicals. In conclusion, ginseng represents a valuable natural resource for enhancing fish immunity and promoting sustainable aquaculture practices. As the industry faces increasing pressures to reduce antibiotic use and enhance fish health, the potential of ginseng should be further explored to fully realize its benefits in aquaculture systems.

## Author contributions

MY: Conceptualization, Writing – original draft, Writing – review & editing. ZA: Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing. YB: Writing – original draft. GA: Writing – original draft. ZK: Writing – original draft. HG: Writing – original draft. EA: Writing – review & editing.

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## Conflict of interest

Author YB was employed by company LLP "NFT-KATU".

The remaining author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Generative AI statement

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## Publisher's note

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