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Antiradiation effects of ginseng polysaccharide and its application prospects in future food

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ABSTRACT

Panax ginseng, a foundational herb in traditional East Asian medicine, has been extensively studied for its therapeutic and nutritional properties. Among its bioactive constituents, ginseng polysaccharides (GPs) stand out for their potent antioxidant, anti-inflammatory, and immunomodulatory effects. These polysaccharides, primarily composed of monosaccharides such as glucose, galactose (Gal), and arabinose (Ara), demonstrate promising potential in alleviating oxidative stress and immune suppression. With increasing exposure to ionizing radiation from medical and industrial sources, the demand for effective radioprotective agents has grown. Ionizing radiation induces DNA damage and excessive reactive oxygen species (ROS) production, resulting in oxidative stress and immune dysfunction. Research suggests that GPs mitigate radiation-induced cellular damage by enhancing antioxidant enzyme activity, suppressing inflammatory cytokines, and regulating immune responses. Despite these encouraging findings, further investigations are needed to elucidate their mechanisms of action and optimize their clinical applications. This review provides a comprehensive analysis of the composition, biological activities, and radioprotective mechanisms of GPs, highlighting their potential as functional agents for safeguarding human health against radiation-induced damage.

1. Introduction

Panax ginseng has been a cornerstone of traditional East Asian medicine for centuries, celebrated for its therapeutic and nutritional benefits. Classical Chinese texts, such as Shen Nong's Materia Medica and the Compendium of Materia Medica, emphasize its role in invigorating vitality, regulating qi, and enhancing blood circulation. Traditionally, it has been used to address weakness, fatigue, and immune deficiencies, while promoting balance between yin and yang and boosting physical resilience[1-2]. In East Asia, ginseng is often consumed as soups or teas, particularly in colder months, to enhance vitality and well-being[3-5]. Scientific research has validated these traditional uses, highlighting ginseng's antioxidant, anti-inflammatory, and antifatigue properties. Bioactive compounds such as ginsenosides and polysaccharides are central to these effects[6-7]. Ginseng polysaccharides (GPs), composed primarily of glucose, galactose (Gal), and arabinose (Ara), have drawn attention for their potent antioxidant and anti-inflammatory activities, which contribute to their therapeutic potential[8].

With the rise in radiation exposure due to advances in medical and industrial applications, concerns about its potential harmful effects have also increased. Radiation is broadly categorized into ionizing

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and non-ionizing forms, with ionizing radiation being particularly damaging, as it directly interacts with biological molecules, resulting in DNA damage, apoptosis, and genetic mutations. These alterations contribute to a range of health issues, including cancer, cardiovascular diseases, and neurodegenerative disorders[9]. Ionizing radiation exposure also leads to an overproduction of reactive oxygen species (ROS), which induces oxidative stress—a key factor in the development of various diseases[10]. Radiotherapy, a common treatment modality for cancer, is known to cause a spectrum of side effects, from acute reactions such as skin damage to chronic conditions such as radiation pneumonitis and gastrointestinal discomfort[11-12]. A significant number of cancer patients undergoing radiotherapy are reported to experience fatigue and immune suppression after prolonged exposure[13]. Therefore, there is a pressing need for effective radioprotective agents to mitigate the damage caused by radiation. Given ginseng's well-established antioxidant and anti-inflammatory properties, polysaccharides derived from ginseng have emerged as promising candidates for radioprotection. Studies have shown that these polysaccharides can enhance the activity of antioxidant enzymes, reduce oxidative stress, and protect cells from radiation-induced damage[14-15]. In addition, bioactive polysaccharides have been shown to modulate immune responses, suppress the release of inflammatory cytokines, and alleviate immune suppression caused by radiation exposure[16-17]. These findings provide strong evidence for the potential application of polysaccharides derived from ginseng in radioprotection, offering a theoretical foundation for their use in mitigating radiation-induced injury. Further research is needed to fully elucidate their underlying mechanisms and optimize their clinical applications. This review aims to examine the composition, properties, and radioprotective effects of bioactive polysaccharides derived from ginseng, discuss their mechanisms of action, and explore potential future research directions. By doing so, we hope to provide valuable insights into the development of these polysaccharides as functional agents for promoting human health and protecting against radiation damage.

2. Historical consumption and therapeutic effects of ginseng

Ginseng is a highly regarded medicinal plant native to East Asia, with significant cultivation areas in China, Korea, and the Far East region of Russia. These regions are key producers and exporters of ginseng, contributing substantially to the global supply. In China, the provinces of Jilin and Heilongjiang, particularly in the northeastern region, have a long-standing tradition of ginseng cultivation, positioning them as leading centers of production worldwide. The Changbai Mountains in Jilin, renowned for their favorable climate and soil conditions, is considered an optimal environment for ginseng growth[18]. In Korea, ginseng is particularly esteemed, especially the red ginseng variety, which is produced by steaming or drying the root to enhance its bioactive components. This processing not only increases the medicinal value of the ginseng but also contributes to its high demand and recognition in international markets[19]. The Far East region of Russia is also home to wild ginseng, which is regarded as a rare resource due to its high medicinal value[20]. In North America, *Panax quinquefolius*, or American ginseng, is cultivated primarily in the United States and Canada and is widely exported, especially to East Asia, where it is popular for its tonic effects and reduced stimulating properties compared with Asian ginseng[21]. As research into the medicinal properties of ginseng continues, its cultivation and sales have extended beyond East Asia to global markets, particularly Europe and North America, where demand has consistently grown. The pharmacological effects of ginseng, including its immunomodulatory, antifatigue, antioxidant, and anticancer properties, have solidified its role as a significant medicinal herb worldwide. While ginseng has long been utilized as a traditional herbal remedy in East Asian medicine, its methods of consumption, including the use of its polysaccharides, vary widely across cultures. In traditional Chinese medicine (TCM), ginseng is prized for its qi-invigorating properties and is commonly used to address conditions such as weakness, immunodeficiency, and fatigue. The ways in which ginseng is consumed have evolved over time, with early practices involving fresh and dried roots, which later expanded to include sliced ginseng, infused liquors, soups, and more modern preparations such as capsules, tablets, and oral liquids. The nutritional composition and uses of fresh and dried ginseng differ significantly. Fresh ginseng, which retains a high moisture content, is rich in bioactive compounds, making it especially effective for immune enhancement, antifatigue, and antioxidant applications. Dried ginseng, on the other hand, undergoes a dehydration process that enhances its shelf life and makes it ideal for use in medicinal soups and stews, often consumed as long-term tonics[22]. While fresh ginseng is typically sliced or brewed to preserve its natural nutrients, dried ginseng is suited for slow-cooking methods such as soups, teas, and porridges, which facilitate the release of its active compounds. Additionally, processes such as steaming and fermentation can enhance the bioavailability of certain ginseng constituents[23]. Research indicates that both the frequency and duration of ginseng intake are closely linked to health outcomes, with long-term ginseng consumption associated with a reduction in all-cause mortality[24].

Studies indicate that ginseng exhibits a wide range of biological activities, particularly in its antioxidant and immunomodulatory properties. The soluble dietary fiber extracted from ginseng residues is highly water-soluble, with an impressive oil retention capacity, and demonstrates notable antioxidant and enzyme inhibitory effects[25]. Furthermore, fermented GPs have shown promise in enhancing immune function[26]. Regular, long-term consumption of ginseng allows individuals to benefit from its health-promoting effects, particularly when incorporated into their daily diet. Ginseng-based soups, for example, are commonly recommended during post-radiotherapy recovery to support physical restoration and boost immune function[27]. The primary active compounds in *P. ginseng* are polysaccharides and ginsenosides. Bioactive polysaccharides from ginseng have been shown to protect myocardial cells by scavenging free radicals, enhancing the activities of antioxidant enzymes, and suppressing lipid peroxidation and DNA oxidative damage[28]. Oxidative stress is closely linked to the onset and progression of many chronic diseases, and red ginseng has shown robust antioxidant effects[29]. As a widely used dietary supplement, ginseng is also known for its immunomodulatory benefits. Natural supplements such as ginseng are often preferred over synthetic products because of their relative safety and cost-effectiveness; synthetic alternatives can cause side effects, including anaemia, nausea, vomiting, and alopecia[30]. Extensive *in vitro* and *in vivo* studies have highlighted the immunoregulatory properties of ginseng. For example, ginsenoside

Rb1 inhibits the lipopolysaccharide (LPS)-stimulated production of TNF-α in RAW264.7 cells[31]. In 2006, Rhule et al.[32] reported that *Panax notoginseng* extract inhibits the LPS-induced production of TNF-α and IL-6 in RAW264.7 macrophages in a dose-dependent manner. Additionally, ginsan, a GPs extract, exerts immunomodulatory effects by inhibiting the p38 MAP kinase and NF-κB pathways[33]. Red ginseng extract has been shown to enhance the activities of surface costimulatory molecules (including CD80, CD40, and CD86) and major histocompatibility complex (MHC) class II in bone marrow-derived dendritic cells (BMDCs) *in vitro*, which promotes the proliferation of allogeneic T cells, syngeneic $CD4^+$ T cells, and $CD8^+$ T cells and increases IL-2 and IFN-γ production[34]. Similarly, GPs have consistently exhibited immunoregulatory properties *in vitro*. Polysaccharides found in ginseng, such as vitispiranoside, and furanoglucoside, promote BMDC maturation by increasing the production of markers such as CD86 and MHC class II, as well as IL-12 and TNF-α[35]. Acidic polysaccharides (200 mg/mL, purity > 99%) enhanced BMDC proliferation, morphologically promoted differentiation towards dendritic cells, and reduced phagocytic activity *via* differentiation[36]. Ginseng has also demonstrated anticancer efficacy, as studies have shown its dose-dependent inhibition of RMA cell viability and suppression of proinflammatory cytokines such as IL-4 and IL-5[37]. Liu et al.[38] reported that ginsenoside 20(*R*)-Rg3 significantly inhibits ovarian cancer cell viability by downregulating hypoxia-inducible factor. Additionally, ginseng can enhance the immunogenicity of drugs or vaccines when used as an adjuvant. Studies have shown that combining ginseng with vitamin C increases the number of NK and T cells, inhibits the viral lytic cycle, and reduces lung inflammation caused by H_1N_1 infection[39]. Furthermore, ginseng berry extract as an adjuvant promotes BMDC and Th1 and Tc1 cell activation, increasing CD86, MHC class I and II, IL-6, IL-12, and TNF-α production in spleen-derived dendritic cells[40]. With the continued development and application of ginseng as a functional food, increasing attention has been given to the potential of its bioactive polysaccharides. As primary functional components, these compounds exhibit significant immunomodulatory, antioxidant, and anti-inflammatory activities, making them valuable for development and use as daily dietary supplements[41]. As a functional food product, ginseng-derived polysaccharides can be incorporated into beverages, foods, and capsules to provide consumers with daily antioxidant and immune enhancement. This safe, natural ingredient has promising applications in health and wellness, facilitating the further use and popularization of ginseng-based products in health-related fields. Fig. 1 illustrates the history of ginseng consumption and its associated health benefits.

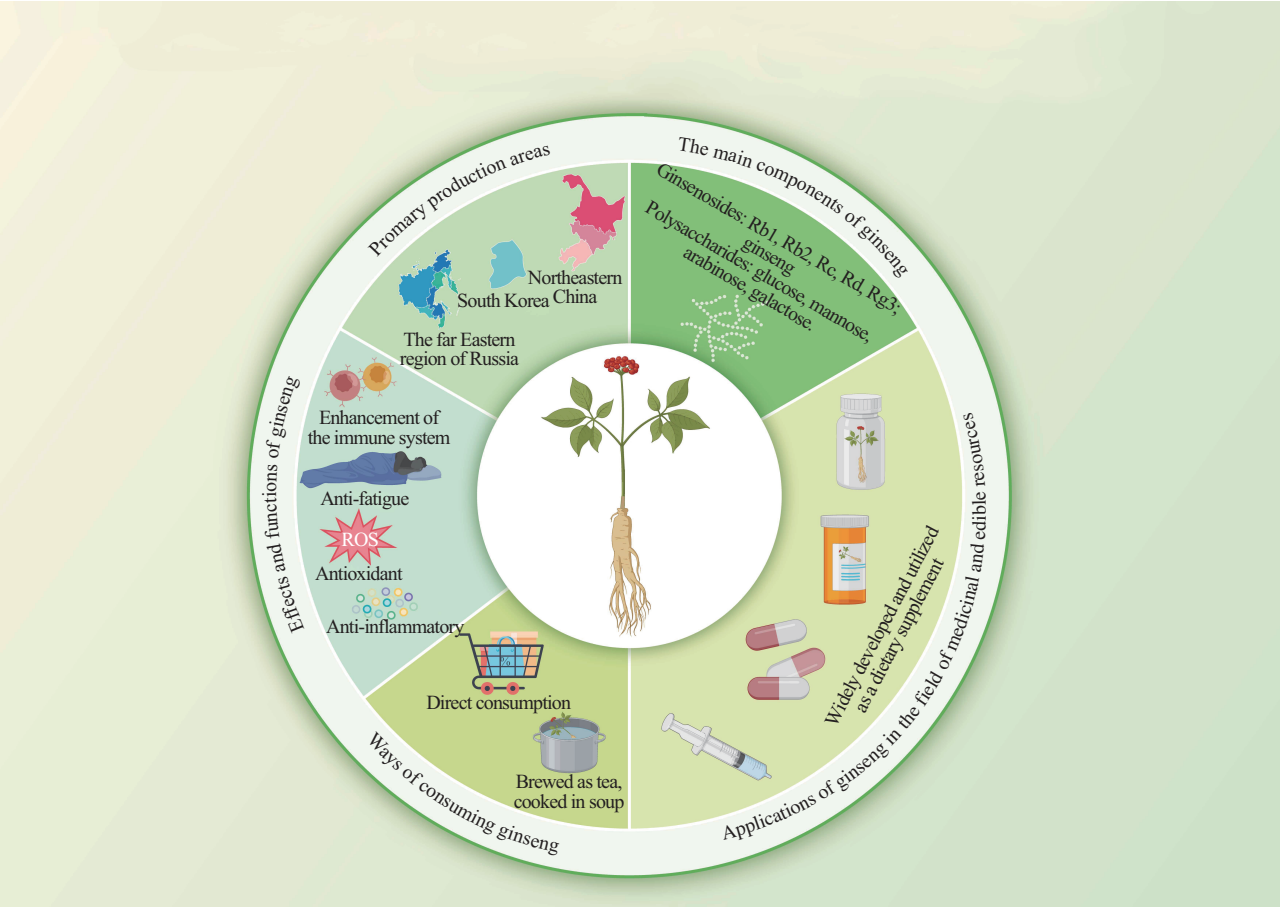

Fig. 1 History of ginseng consumption and research on its use as a medicinal and edible resource.

3. Composition and characteristics of GPs

P. ginseng contains a wide variety of bioactive compounds, including ginsenosides, essential oils, peptides, polysaccharides, nitrogenous compounds, fatty acids, and phenolic compounds[42]. These components have long been integral to traditional Chinese medicine due to their pharmacological properties. Among them, GPs are particularly notable for their immunomodulatory effects. The structure and composition of GPs play a crucial role in determining their biological activities. GPs are composed of various monosaccharides, such as rhamnose (Rha), galacturonic acid (GalA), Gal, and Ara[43]. Notably, rhamnogalacturonan I (RG-I), a form of pectin identified in ginseng, consists of a backbone of α-1,5-linked Ara and β-1,4-linked Gal side chains. These structural features are essential for its longevity-promoting effects[44]. The molecular weight and structural characteristics of GPs significantly impact their biological functions. Studies have shown that low-molecular-weight oligosaccharides, whether self-extracted or commercially obtained, exhibit superior antioxidant, hypoglycemic, and immunomodulatory activities[45]. In addition, combining fermented feed with GPs enhances gut morphology and microbiota composition, further boosting their bioactivity[46]. For instance, Cho et al.[47] identified an acidic GP, Y-75, that significantly enhanced NK cell activity, demonstrating its immunomodulatory potential. Additionally, research by Zhang et al.[48] revealed that GPs' immunomodulatory properties make them promising vaccine adjuvants for enhancing immune responses. Arabinogalactan (AG), a polysaccharide from ginseng composed of Ara and Gal, is known for its immunomodulatory and anti-inflammatory effects. Ramberg et al.[49] demonstrated that AG reduces inflammatory responses by regulating cytokines (e.g., IL-6 and TNF-α) and enhancing immune cell activities, including T cells and macrophages. Ginseng pectin, which is highly soluble in water, forms gel-like substances in the gastrointestinal tract, benefiting gut health by influencing microbiota composition and function. The fermentation of pectin produces short-chain fatty acids (SCFAs) like acetate, propionate, and butyrate, which act as prebiotics to regulate gut microbiota, promoting the growth of beneficial bacteria like *Bifidobacterium* and *Lactobacillus*[50]. The molecular weight and methoxylation degree of pectin directly affect its fermentation efficiency and its impact on the gut microbiota. High methoxy-modified pectins enhance SCFA production, while low methoxy-modified pectins are more effective in modulating gut microbiota, especially in promoting beneficial bacteria such as Lachnospiraceae. This modulation not only improves the gut microenvironment but also contributes to anti-inflammatory and antitumor effects[51-52]. Xie et al.[53] reported that ginseng pectin resists human digestive enzymes, supporting the metabolism of beneficial bacteria and inhibiting pathogenic bacteria, thereby improving gut health and boosting immune function. These properties underscore the significance of ginseng pectin in regulating the gut microbiota balance and enhancing overall health. In a pioneering study by Guo et al.[54], 2 homogeneous GPs, GPII and GPIII, were isolated, exhibiting substantial bioactivities, including antioxidant, anti-inflammatory, immunomodulatory, and gut microbiota-regulating effects. These polysaccharides scavenge free radicals and enhance antioxidant enzyme activity, reducing oxidative stress-induced cellular damage[55-56]. GPII and GPIII also show strong anti-inflammatory properties by inhibiting the production of pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-1β, and modulating inflammatory pathways like NF-κB and MAPK. These effects position GPs as potential therapeutic agents for chronic inflammatory diseases like colitis and arthritis[57]. Moreover, GPII and GPIII enhance immune responses by activating immune cells such as macrophages, T cells, and NK cells. Studies indicate that these polysaccharides significantly increase $CD4^+$ T cells and IgA-secreting cells, restoring immune functions that may be compromised by chemotherapeutic agents like cyclophosphamide. Additionally, GPII and GPIII regulate lymphocyte subpopulations in the spleen and peripheral blood, bolstering immune defense mechanisms[58]. Notably, these GPs also influence gut microbiota composition, promoting the growth of beneficial bacteria like *Bifidobacterium* and *Lactobacillus* while suppressing the growth of pathogenic bacteria such as *Escherichia coli* and *Shigella*. These effects contribute to restoring intestinal microecological balance, improving gut barrier function, and alleviating intestinal damage caused by inflammatory bowel disease or chemotherapy[59-60]. Table 1 provides a summary of the key active components in GPs, along with research findings related to their antioxidant, anti-inflammatory, and inflammation pathway inhibitory effects.

Table 1 summarizes the key bioactive components of ginseng and their effects on antioxidant activity, anti-inflammatory responses, and the inhibition of inflammation pathways. For instance, ginsenoside Rb1 exhibited a concentration-dependent inhibition of UVB-induced ROS generation, suppressed MMP-2 activity, and enhanced GSH and SOD levels. These findings support current antioxidant theories, suggesting that ginsenoside Rb1 strengthens cellular antioxidant defenses, reducing oxidative stress and cellular damage caused by UVB. Oxidative stress is a key factor in skin aging, inflammation, and cancer. Thus, Rb1 may have potential not only for skin protection but also as a therapeutic target for anti-aging and anti-cancer treatments. American GPs significantly reduced TNF-α and IL-1β levels in the skin and blood of mice, preventing epidermal damage and hyperplasia. This result is consistent with theories of chronic inflammation and immune tolerance, indicating that GPs modulate immune responses to suppress excessive inflammation, thereby improving skin damage and hyperplasia. The modulation of NF-κB and MAPK signaling pathways further underscores the role of GPs in inflammation regulation. Additionally, GPs protect the intestinal barrier by reducing inflammatory cytokines such as IL-1β and IL-6 and modulating the NF-κB pathway, thereby mitigating intestinal barrier disruption. This mechanism supports the gut-immune axis theory, highlighting the link between intestinal integrity and systemic immune responses. GPs could therefore offer an effective strategy for regulating gut health and preventing intestinal inflammation. These findings demonstrated that GPs and their active components exert broad biological effects in immune regulation, antioxidant defense, anti-inflammatory responses, and gut protection. These effects align with established biological models, providing strong theoretical support for their potential clinical applications.

Table 1
Applications of the active ingredients in GPs.

Component	Disease or condition	Study overview	Findings	References
Ginsenoside Rb1	Ultraviolet B (UVB) radiation-induced oxidative stress in human dermal keratinocytes	Before irradiation, HaCaT cells were pretreated with different concentrations of ginsenoside Rb1, followed by detection of the ROS levels and determination of the survival rate.	Rb1 exhibited concentration-dependent inhibition of the UVB-induced increase in ROS levels; reduced the activity of MMP-2 induced by UVB; and increased the activities of glutathione and superoxide dismutase (SOD).	[61]
American GPs	UVB-induced skin cancer	SKH1 hairless mice were pretreated with American GPs before conducting photoaging experiments.	Pretreatment with American GPs significantly reduced the production of TNF-α and IL-1β in both the skin and blood of mice and effectively prevented epidermal damage and hyperplasia.	[62]
Ginseng polysaccharide	Oxidative damage to red blood cells (RBCs)	Three different research models were established: an *in vitro* model of RBCs exposed to H_2O_2 (40 mmol/L), an *in vivo* model of RBCs from rats subjected to exhaustive swimming, and an *in vitro* model of BRL-3A cells exposed to H_2O_2 (25 μmol/L).	Ginseng polysaccharide protects RBCs from oxidative stress damage by promoting RBC glycolysis and gluconeogenesis pathways in the liver.	[63]
Rg1 and Rs3	Inflammatory	Evaluation of the anti-inflammatory mechanism and identification of the key molecules in *in vivo* and *in vitro* models.	Rg1 and Rs3 inhibited macrophage migration and regulate ROS levels; promoted the M2 to M1 polarization of macrophages; and inhibited the overphosphorylation of signal transducer and transcriptional activator.	[64]
Korean black ginseng	Inflammation, pain, nociception	This study investigated the anti-inflammatory and anti-nociceptive effects of Korean black ginseng extract (KBGE) in *in vivo* and *in vitro* models. It evaluated the extract's effect on inflammation and pain perception.	Korean black ginseng showed significant anti-inflammatory and anti-nociceptive effects. It reduced inflammation markers such as TNF-α and IL-1β in animal models and exhibited pain-relief effects comparable to analgesic drugs.	[65]
Novel neutral polysaccharide PPQN	Inflammation	Nitric oxide (NO), TNF-α, IL-6, and IL-1β secretion were detected after LPS stimulation of PPQN-pretreated RAW264.7 macrophages.	PPQN significantly inhibited the secretion of NO, TNF-α, IL-6, and IL-1β after pretreatment and has therapeutic potential for the treatment of inflammation and inflammation-related diseases.	[66]
GPs	Inflammatory bowel disease	Effects of the isolated and characterized GPs on rat intestinal inflammation.	GPs significantly modulated the structure of the gut microbiota and restored mTOR-dependent autophagic function, leading to the inhibition of inflammation. The GPs suppress NF-κB activation, reduce oxidative stress levels, and decrease proinflammatory cytokine release.	[67]
High-grade (HG)-rich ginseng pectin	Colon cancer	MTT assays were used to evaluate the effects of the GP components and their temperature-modified products on HT-29 cell proliferation. Flow cytometry was used to evaluate the effect of GPs on cell cycle progression. Effects of GPs on Caspase-3 activation.	HG-rich ginseng pectin significantly inhibited cell proliferation; induced cell cycle arrest in G2/M phase; and displayed improved antiproliferative, apoptosis and Caspase-3 activation effects upon enrichment.	[68]
Water soluble GPs (WGP)	Type 2 diabetes	Urinary metabolomics based on rapid resolution liquid chromatography/mass spectrometry (RRLC/MS) to investigate the effects of WGP on type 2 diabetes in rats. Principal component analysis (PCA) was performed for pattern recognition to differentiate between type 2 diabetic rats and those receiving WGP treatment.	Eight potential biomarkers were identified and characterized. WGP regulates DNA metabolism, organic acid metabolism, and steroid hormone metabolism.	[69]
GPs	Aging	Validate the functionality of GPs on galactosamine-induced liver injury and cyclophosphamide-induced immunosuppression. Proteomic analysis was conducted on the spleen and liver to assess the immunomodulatory, anticancer, and hepatoprotective functions of the polysaccharides.	GPs enhanced the immune system, inhibited melanoma cell metastasis to the lungs, and effectively reduced liver damage.	[70]
GPs and the effective subfraction	Colitis	Evaluate the protective effects of GPs and the effective subfraction on dextran sodium sulfate (DSS)-induced colitis.	GPs reduced colon damage; restored the integrity of the intestinal barrier by modulating tight junction proteins (ZO-1 and Occludin); downregulated inflammatory cytokines such as IL-1β, IL-2, IL-6, and IL-17; and inhibited the TLR4/MyD88/NF-κB signalling pathway.	[71]
Ginseng extract G115®	Depression	Detection of depression status and BDNF and TrkB levels in rats continuously gavaged with G115® for 14 days *via* behavioural and Western blot assays.	Fluoxetine combined with Ginkgo extract G115® significantly alleviated depressive behaviours in SD rats.	[72]
P. ginseng extract (PGE)	Depression	Antidepressant effect and underlying mechanism of PGE in a chronic restraint stress (CRS)-induced mouse model of depression.	Oral administration of PGE ameliorated depression-like behaviours in mice induced by CRS. PGE elevated the messenger RNA expression levels of brain-derived neurotrophic factor in the amygdala of mice with induced CRS.	[73]
Ginsenoside Rb1	Depression	Detection of the antidepressant effect of Rb1 using behavioural analyses and ELISA kits to detect neurotransmitter levels.	Ginsenoside Rb1 improved the behaviours of depressed mice and increased the levels of 5-HT, 5-HIAA, NE, and DA in the brain.	[74]
Ginseng oligopeptides (GOPs)	Inflammation	Anti-inflammatory effects in SD rats.	Oral administration of GOPs inhibited inflammation in rats caused by cotton pellets and dextran. GOPs significantly inhibited oedema formation my modulating MAPK and NF-κB.	[75]
Ginseng extract fermented by *Lactobacillus brevis* (FGE)	Dermatitis	Anti-dermatitis effects were evaluated by Western blot to determine the levels of NO, IL-6, TNF-α, IL-10, and COX-2.	FGE inhibited the activation of macrophages to produce anti-dermatitis effects, which were associated with suppressing the nuclear translocation of NF-κB.	[76]

Table 1 (*continued*)

Component	Disease or condition	Study overview	Findings	References
Ginsenoside Rg5	Cognitive dysfunction	Assessment of cognitive deficits, determination of the levels of the inflammatory cytokines TNF-α and IL-1β in the brain, measurement of the acetylcholinesterase (AChE) activity in the cortex and hippocampus of STZ-induced AD rats, and evaluation of Aβ deposition.	STZ-induced learning and memory impairments in rats were improved by Rg5, which was associated with attenuating neuroinflammatory responses.	[77]
Ginseng	Alzheimer's disease (AD)	Network pharmacology was used to evaluate the effects of ginseng in AD on the basis of the pathogenesis of Aβ.	Ginsenoside Rg3 targeted MAPK8, FLT1, and CCR5, while ginsenoside Ro targeted MAPK8, MAPK9, FLT1, and CCR5 for potential anti-AD efficacy.	[78]

4. Extraction of GPs

GPs can be extracted *via* several methods, and each method affects extraction efficiency and bioactive component preservation in different ways. Water extraction is the traditional and most widely used approach and generally involves prolonged heating at high temperatures. Water is commonly used as a solvent to disrupt the cell walls of the ginseng plant, facilitating the dissolution of its polysaccharides. However, this extraction method presents several limitations, including low efficiency and the risk of structural degradation of the polysaccharides due to prolonged heating. Heat-sensitive components, in particular, are susceptible to breakdown under these conditions, which can result in a significant reduction in the bioactivity of the final extract[79-80]. To overcome these challenges, enzymatic extraction has emerged as a more effective technique. This method leverages the high efficiency of enzymes, such as amylases and cellulases, to break down plant cell walls under milder conditions, thereby releasing larger quantities of GPs. Enzymatic extraction offers several advantages, including higher extraction efficiency, gentler processing conditions, and minimal disruption to the polysaccharide structure, resulting in high-quality extracts. For instance, studies have shown that GPs (FGEP-CA) extracted using a combination of cellulase and *α*-amylase exhibit enhanced immune-stimulating activity, significantly increasing cytokine production. Compared to traditional water extraction, enzymatic extraction yields a higher proportion of pectic polysaccharides with lower molecular weights and greater heterogeneity[81]. Despite these advantages, enzymatic extraction still faces challenges, such as enzyme activity and pH sensitivity, and the specific conditions required by different enzymes can add operational complexity and cost[82-83]. Microwave-assisted extraction (MAE) is another advanced, high-efficiency technique. By directly applying microwave energy, MAE rapidly heats the sample to disrupt cell walls, dramatically reducing extraction time. This method not only improves the extraction rate of polysaccharides but also preserves their bioactivity by maintaining lower temperatures, minimizing the degradation of heat-sensitive components[84]. Research has demonstrated that MAE at 145 °C and 1 600 W, using water as the solvent, can efficiently extract nine rare ginsenosides in just 15 min[85]. Compared to traditional methods, MAE significantly improves the yield of rare ginsenosides. However, the application of MAE is limited by high equipment costs and the need for precise control over temperature and extraction time, especially in industrial-scale operations where such precision is essential.In addition to the methods mentioned above, other innovative techniques, such as ultrasound-assisted extraction (UAE) and supercritical fluid extraction (SFE), are gaining attention for their effectiveness in polysaccharide extraction. UAE utilizes ultrasonic mechanical vibrations and cavitation effects to disrupt plant cell walls, enhancing the release of bioactive components and improving extraction efficiency[86]. On the other hand, SFE uses supercritical carbon dioxide as a solvent, offering benefits such as high selectivity and minimal solvent residue[87]. The combination of UAE and SFE has been shown to further improve both extraction efficiency and the purity of GPs. Studies indicate that ultrasound treatment significantly increases polysaccharide yield, particularly when extraction conditions such as temperature, time, and solvent ratios are optimized[88]. Furthermore, SFE effectively removes impurities, resulting in higher-purity polysaccharide extracts[89]. The synergy between UAE and SFE also enhances the bioactivity of the extracted compounds, with research showing that polysaccharides obtained through UAE exhibit superior antioxidant activity, significantly increasing free radical scavenging capacity compared to those extracted via conventional methods[90]. SFE, on the other hand, preserves more bioactive components, further enhancing the pharmacological effects of the extracts[91]. Given the diverse bioactivities of GPs, the extraction method plays a crucial role in determining both their yield and potency. Thus, further comprehensive research on optimizing extraction techniques is essential to fully elucidate the therapeutic potential of GPs (Fig. 2).

5. Effects of radiation on biological systems and the radioprotective effects of GPs

Radiation can be classified into 2 main types: ionizing and nonionizing. Ionizing radiation includes X-rays, gamma (γ) rays, alpha (α) particles, beta (β) particles, and neutron radiation, all of which possess enough energy to remove electrons from atoms or molecules, leading to the destruction of biological macromolecules such as DNA and proteins and ultimately causing cell death or mutations[92]. Although ionizing radiation is widely used for medical diagnostic and therapeutic purposes, exposure to high doses can result in severe tissue damage and radiation sickness[93]. Nonionizing radiation, which includes UV rays, microwaves, and radio waves, lacks the energy to ionize atoms or molecules but may still impact biological systems through thermal effects or other mechanisms, such as UV-induced DNA damage[94]. Among the various effects of ionizing radiation, DNA damage, which manifests as double-strand breaks (DSBs), single-strand breaks (SSBs), and base damage, is one of the most lethal. Among these, DSBs are considered the most deleterious; failure to repair these breaks can lead to genomic instability, cancer, or apoptosis. Ionizing radiation also generates ROS through direct and indirect mechanisms, further exacerbating DNA damage[95-96]. In recent years, research has focused on elucidating the DNA repair mechanisms activated by radiation-induced damage, particularly nonhomologous end joining (NHEJ) and homologous recombination (HR). The oxidative stress caused by radiation primarily results from the overproduction of ROS, which aggressively attack cellular components, such as membranes, DNA, and proteins, impairing cellular function or inducing cell death. Ionizing radiation promotes the ionization of water molecules, generating ROS such as hydroxyl radicals (•OH), superoxide anions (O_2^-•), and H_2O_2[97].

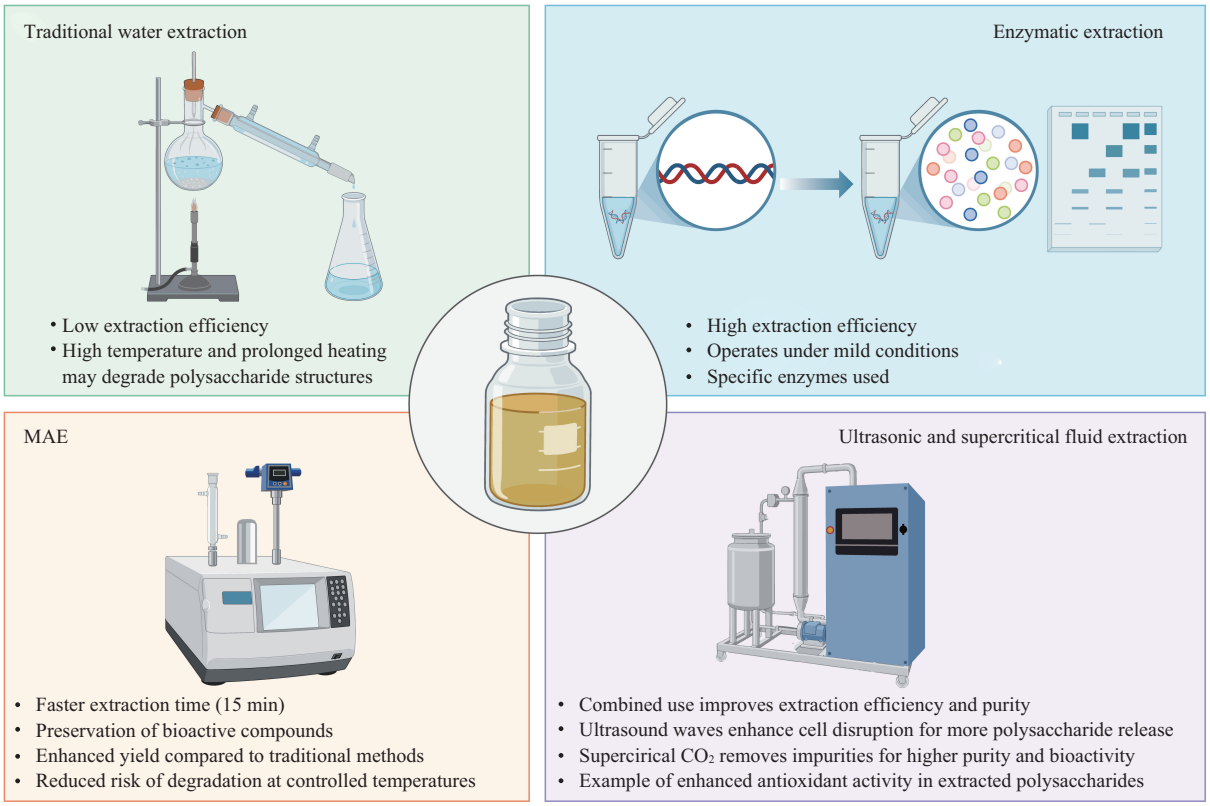

Fig. 2 Methods for extracting GPs.

These radicals readily diffuse and damage nearby molecular structures, initiating a cascade of cellular dysfunction. Furthermore, oxidative stress is associated with various pathologies, including ageing, cardiovascular diseases, neurodegenerative disorders, and cancer. Hence, investigating natural antioxidants derived from plants offers promising therapeutic potential for mitigating radiation-induced oxidative stress[98]. Ionizing radiation also inflicts significant damage to the immune system, impairing immune cells such as T cells, B cells, and macrophages and thereby weakening the body's immune response[99]. Ionizing radiation also disrupts haematopoietic stem cells, leading to a reduction in leukocyte counts, which severely impacts the regenerative capacity of the immune system. Chronic radiation exposure can result in sustained immunosuppression, increasing the individual's susceptibility to infections, tumours, and other diseases[100]. Interestingly, moderate radiation exposure, as in radiotherapy, may induce an antitumour immune response[101]. Therefore, it is imperative that ionizing radiation be used in a judicial manner, and strategies to mitigate radiation-induced tissue damage are essential. Furthermore, the development and utilization of natural antioxidants from plants to treat radiation-induced damage hold considerable promise[102-104].

Radiation-induced apoptosis plays a pivotal role in tissue injury following exposure to ionizing radiation. Research has shown that radiation triggers apoptosis *via* the activation of several key signaling pathways, including the PTEN, PI3K/AKT, and p53 pathways[105]. Activation of these pathways leads to cell cycle arrest and enhances DNA repair mechanisms, ultimately influencing cell survival and tissue damage outcomes[106]. In the context of radiation-induced injury, natural compounds that regulate apoptotic signaling pathways have garnered increasing attention. As natural modulators, GPs have been shown to effectively inhibit radiation-induced apoptosis, potentially through the modulation of key apoptotic pathways. Studies suggest that GPs can reduce apoptosis rates induced by radiation by mitigating oxidative stress and inflammation[107]. Moreover, GPs may exert protective effects through the regulation of mitochondrial autophagy and the modulation of apoptosis-related proteins such as Bax and Bcl-2[108]. In one study, these polysaccharides significantly improved the survival rates of mice and reduced cellular damage caused by radiation exposure. These protective effects were likely linked to the stimulation of immune cells, particularly macrophages and T lymphocytes, which play crucial roles in immune defense[109]. The functionality of these immune cells is closely related to the stiffness of their cytoplasm and the deformability of their membranes, both of which influence their phagocytic capabilities[110]. By modulating these biophysical properties, these compounds may help restore macrophage function and enhance their resistance to radiation-induced damage[111]. Furthermore, they promote the secretion of cytokines such as TNF-α and IL-6, which are essential for regulating immune responses and mitigating radiation-induced damage[112]. Their structural features, including molecular weight and sugar composition, may also play a role in determining biological activity. Specific structures may exhibit a stronger affinity for immune cell receptors, enhancing immunomodulatory effects[113]. Additionally, enzymatically modified versions have been shown to exhibit enhanced antioxidant and immune activities, suggesting that structural modifications can further optimize therapeutic efficacy[114]. The radioprotective effects are summarized in Fig. 3.

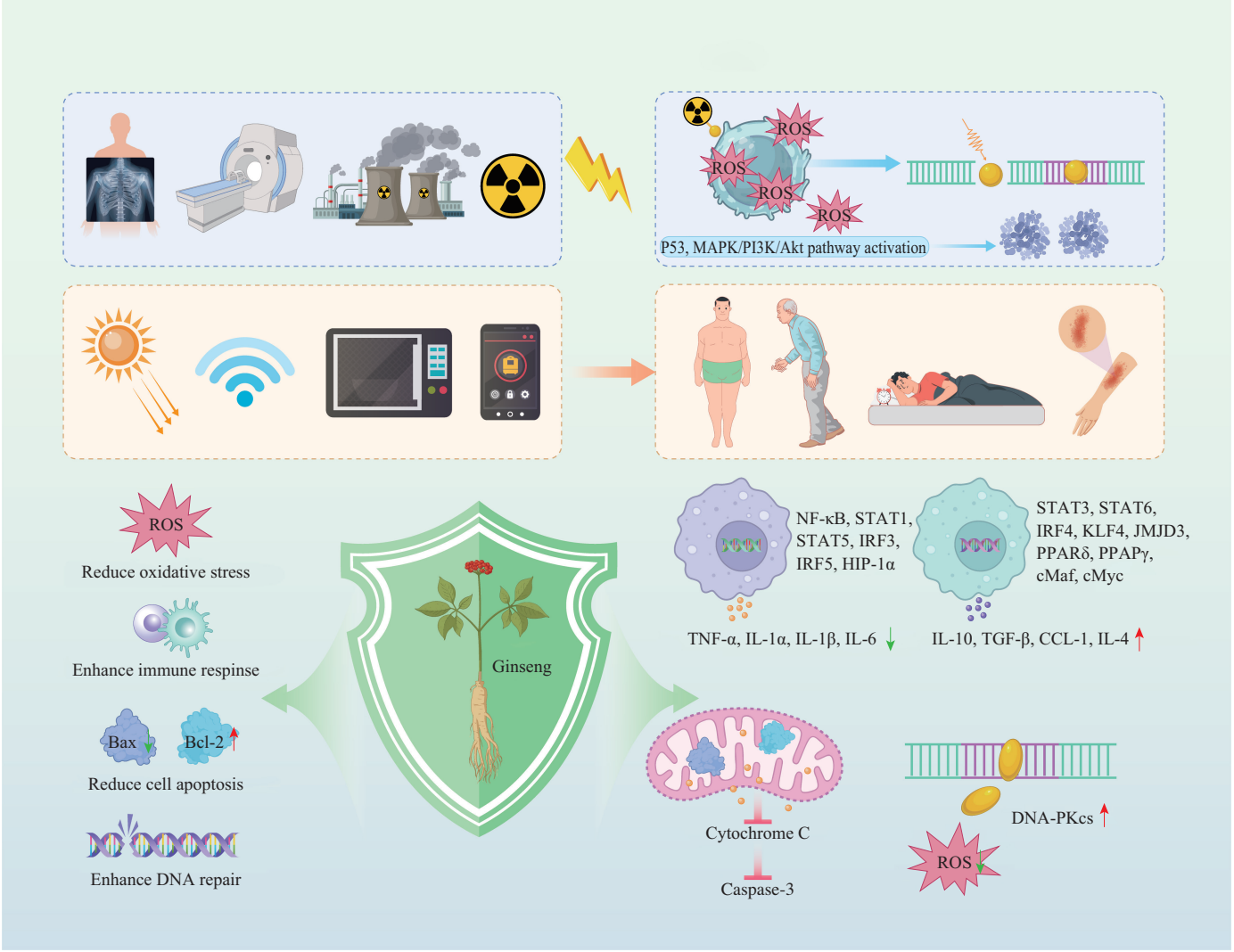

Fig. 3 Mechanisms of the antiradiation effects of GPs.

6. Future applications and perspectives of GPs

6.1 Further mechanistic and clinical research

Building on the established evidence of GPs' radioprotective properties, particularly their efficacy in mitigating oxidative stress and immune suppression caused by radiation exposure, it becomes imperative to delve deeper into their underlying biological mechanisms. These findings not only highlight the therapeutic potential of GPs but also underscore the necessity of translating these insights into clinically relevant applications. Therefore, advancing our understanding of the molecular interactions and optimizing these polysaccharides for therapeutic implementation represent critical next steps.

The radioprotective effects of GPs are intrinsically linked to their antioxidant, immunomodulatory, and anti-inflammatory activities. However, the precise mechanisms underlying these effects remain only partially understood. Future research should focus on elucidating the relationship between the molecular structures of GPs and their biological activity. Structural features, including molecular weight, sugar chain branching, and monosaccharide composition, may play critical roles in how these polysaccharides interact with immune cell receptors. Advanced analytical techniques, such as nuclear magnetic resonance (NMR) and infrared (IR) spectroscopy, could provide more detailed structural insights into GPs[115-116]. Moreover, investigating the mechanisms by which these polysaccharides exert their effects at the cellular level, such as their influence on DNA repair, redox homeostasis, and apoptosis, should be a key area of focus. Recent studies suggest that GPs may enhance the activity of antioxidant enzymes by modulating key signaling pathways, including the Nrf2/ARE, MAPK, and NF-κB pathways, which play a central role in mitigating radiation-induced oxidative stress[117]. Understanding these signaling pathways is essential for advancing our knowledge of the radioprotective mechanisms of GPs and may reveal new therapeutic targets. For instance, promoting the activation of the Nrf2/ARE pathway could elevate the expression of intracellular antioxidants like SOD and catalase (CAT), thus reducing free radical damage from radiation exposure[118]. Additionally, further fundamental research is necessary to explore the specific roles of GPs in immune cells, particularly in enhancing immune defense mechanisms by activating macrophages and T cells.

Although significant radioprotective effects of GPs have been demonstrated in animal models, most of these studies remain preclinical. To substantiate these findings, future research should involve large-scale, multicenter, randomized controlled clinical trials. Such studies would provide more comprehensive data on the effects of GPs across diverse populations and variations in treatment responses, which are crucial for assessing their efficacy and safety. Demographic factors, such as age, sex, and overall health, may influence patient responses to GPs, and large-scale clinical trials would help identify these variations, contributing to the development of personalized treatment approaches. Clinical investigations should also address optimal dosing regimens and administration routes for GPs. While oral consumption is the most common method, alternative delivery systems, such as transdermal patches or localized injections, might be more effective in certain clinical contexts. Additionally, the potential for synergistic effects when GPs are used in combination with other antioxidants or immunostimulants during radiotherapy should be explored. Such combinations could enhance therapeutic efficacy while reducing side effects. Finally, safety evaluations are essential in clinical trials, particularly to determine whether long-term use of GPs could lead to any toxicity or adverse effects.

6.2 Development of ginseng polysaccharide formulations for personalized applications

The potential of GPs for radioprotection is evident; however, their clinical translation and widespread application require further development from the perspectives of formulation and personalized application. Traditionally, GPs have been administered in oral dosage forms, but challenges related to their stability and absorption in the gastrointestinal tract highlight the need to increase their bioavailability. Recent advancements in modern formulation technologies, such as nanotechnology and microencapsulation, offer novel approaches to improve the absorption of polysaccharides. Encapsulating GPs in nanoparticles or liposomes not only protects their active components from degradation in the digestive tract but also facilitates targeted release, thereby increasing their concentration and efficacy in specific tissues[119]. Future formulation development should focus on diverse administration routes, including oral, topical, and transdermal applications. Numerous researchers have developed GPs products, such as ready-to-drink tea bags, candies, and tablets, which not only increase the usability of these products but also facilitate their daily intake. Oral formulations are particularly suitable when combining GPs with other functional ingredients, such as additional antioxidants or immunostimulants, to create multifunctional compound formulations that enhance the overall therapeutic and preventative effects. Personalized application is an emerging trend in modern medicine. The biological activities of GPs may vary due to differences in the individual genotype, gut microbiota, or metabolic status. Future research could leverage genomic and metabolomic analyses to identify populations that would benefit most from GPs, as well as to determine the optimal formulations and dosages for precise therapeutic interventions. Studies have shown that GPs can modulate the gut microbiota balance, particularly by increasing the abundance of beneficial bacteria (such as bifidobacteria and lactobacilli), which are crucial for gastrointestinal health and immune modulation[120-121]. Therefore, when developing food-derived products, GPs could be combined with prebiotics to enhance their positive effects on gut health, thereby creating probiotic functional foods. By integrating formulation development with personalized applications, GPs can play a significant role not only in treating radiation-induced damage but also as a functional food, enabling the public to obtain health benefits in everyday life through their diet. This developmental direction necessitates further scientific research and clinical validation to ensure safety and efficacy and improve the standardization and regulation of different components and formulation types, thereby improving market competitiveness and the global recognition of GPs products.

6.3 Long-term safety, side effects, and clinical application of GPs in functional foods and radiotherapy support

GPs have demonstrated considerable promise in radioprotection and immune modulation, yet their long-term safety and potential side effects require thorough investigation, particularly regarding their use in functional foods and as adjuncts to radiation therapy. While GPs are generally regarded as safe for short-term use, their prolonged consumption, particularly in functional foods or as dietary supplements, necessitates further evaluation of their safety profiles. In the context of radiotherapy, GPs have been shown to mitigate radiation-induced oxidative stress and inflammation, enhancing tissue recovery and reducing radiation-related side effects. However, the interaction between GPs and other cancer treatments, including chemotherapeutic agents, remains insufficiently explored. Concerns about whether GPs might interfere with the mechanisms of action of certain chemotherapies or alter radiation therapy outcomes need to be addressed. Moreover, the prolonged use of GPs could lead to excessive immune stimulation, potentially causing inflammatory or autoimmune responses, thus highlighting the need for careful monitoring of immune function during long-term use. The incorporation of GPs into functional foods, such as teas, candies, and tablets, is gaining popularity due to their antioxidant and immune-enhancing properties. However, for widespread acceptance, the long-term impact of these products on organ health, particularly liver and kidney function, should be evaluated[122]. Furthermore, GPs' influence on gut microbiota, which has been shown to increase beneficial bacteria like Bifidobacteria and *Lactobacillus*, requires further investigation to ensure that their effects on the gut microbiome remain beneficial over time. Combining GPs with prebiotics or other bioactive ingredients may enhance their therapeutic effects but also necessitates safety testing to prevent potential interactions that could lead to adverse outcomes. The bioavailability and pharmacokinetics of GPs are key determinants of their clinical effectiveness and safety. To improve their absorption and targeted delivery, novel formulation technologies such as nanocarriers, liposomes, and microencapsulation have been employed. However, the safety of these formulations, especially with regard to long-term exposure, must be comprehensively assessed in clinical trials to ensure their overall safety.

While GPs hold significant therapeutic potential, particularly for radioprotection and as functional food ingredients, their long-term safety, potential side effects, and interactions with other treatments must be rigorously evaluated. Future clinical studies that address both efficacy and safety are crucial to advancing the clinical and dietary applications of GPs.

7. Conclusion

As traditional medicines with a history that dates back several thousands of years, GPs undoubtedly hold great promise for applications in modern medicine. However, to effectively translate these traditional remedies into scientifically validated therapeutic options, concerted efforts are needed in various areas, including scientific research, technological development, and industry collaboration. By integrating modern technological approaches, such as genomics, proteomics, and metabolomics, the mechanisms of action of GPs can be thoroughly analysed, thereby accelerating their application in drug development. In particular, collaborative efforts with global research institutions can facilitate comparative studies of GPs derived from different sources and preparation methods and explore the optimal production processes and usage strategies. Additionally, strengthening partnerships between the scientific community and pharmaceutical companies can promote the development of GPs products, ultimately achieving a true transformation from traditional herbal medicines to modern pharmaceutical applications.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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