

Structure-function relationships of *Ganoderma* Polysaccharides: extraction, classification, bioactivities, and gut microbiota modulation

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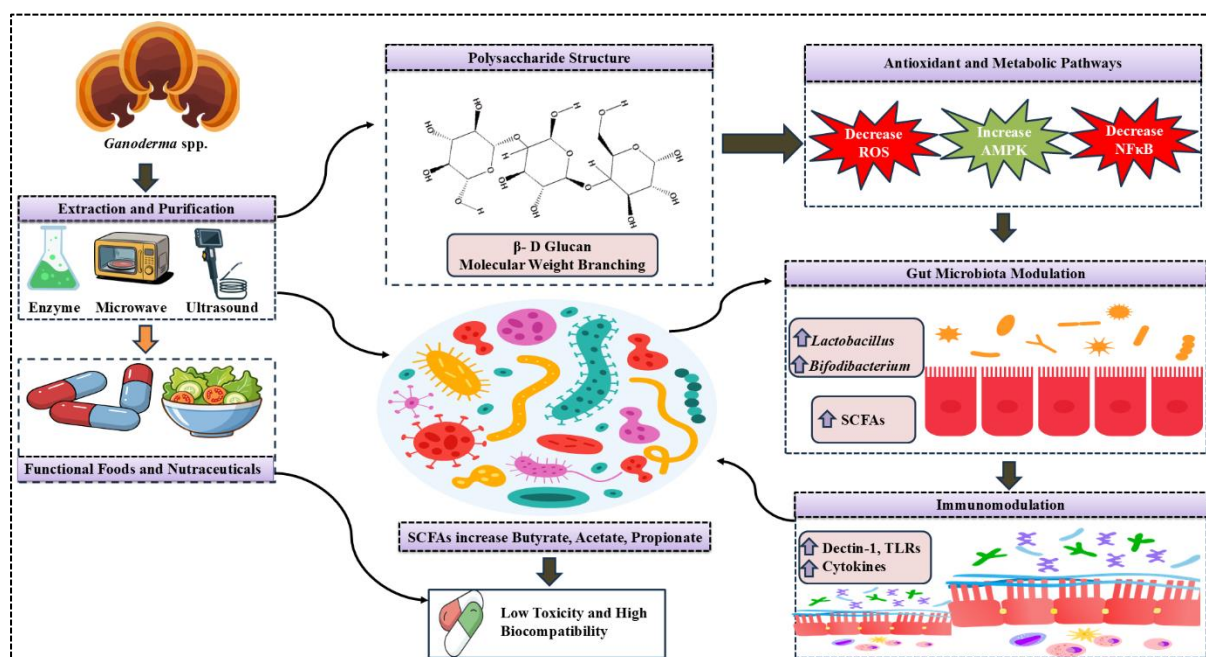
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Abstract

Ganoderma spp. Polysaccharides (GPs) are structurally diverse bioactive macromolecules with significant therapeutic potential, including antioxidant, antidiabetic, hepatoprotective, immunomodulatory, and prebiotic effects mediated through gut microbiota modulation. This review comprehensively summarises the extraction, structural characteristics, and biological activities of GPs, with a particular focus on their structure-function relationships and translational applications. Structurally, GPs are primarily composed of glucans along with heteroglucans and heterogalactans, where molecular weight and branching patterns play a crucial role in determining biological activity. Various extraction strategies, including enzymatic, ultrasound-assisted, and microwave-assisted procedures, have been developed to increase polysaccharide recovery yield and efficiency. Preclinical experimental evidence from in vitro and animal studies suggests that GPs have significant antioxidant and metabolic-regulating effects. GLP demonstrated strong antioxidant action with an IC_{50} of 0.56 mg/mL (ABTS assay), and antidiabetic investigations found a considerable drop in blood glucose levels to 162.8 ± 24.67 mg/dL at 50 mg/kg. Additionally, GPs enhanced gut microbial metabolism, with short-chain fatty acid levels reaching 361.37 μ g/mg, indicating improved intestinal homeostasis. Mechanistically, GPs regulate oxidative stress, immune responses, and gut microbiota composition, contributing to their multifunctional biological activities. Collectively, it highlights the integrated relationship between structural properties and biological functions of GPs and supports their potential application in functional foods and nutraceutical development targeting metabolic and gastrointestinal health.

Keywords: *Ganoderma* spp., polysaccharides, Gut microbiota modulation, Structure-activity relationship, bioactivity

Graphical abstract



1. Introduction

Edible fungi play a key role in both nutrition and health research around the world. They serve as food staples and are natural sources of unique bioactive compounds [1,2]. For example, *Lentinula edodes* and *Hericium erinaceus* are popular in cooking, while *Ganoderma* spp. are valued for their medicinal properties. These have been used for ages in traditional healing practices throughout East and Southeast Asia [3,4]. Growing evidence indicates that many of the health advantages linked to edible fungi are mediated through interaction with the gastrointestinal environment, namely through changes in the composition of the gut microbiota and microbial metabolism [5]. Consequently, growing recognition of edible fungi as modulators of host physiology has prompted renewed interest in elucidating their mechanism of action, particularly in relation to gut health, as outlined schematically in (Fig. 1).

Among edible and medicinal fungi, *Ganoderma* spp. represent one of the most extensively investigated genera owing to their diverse repertoire of bioactive metabolites, particularly polysaccharides, triterpenes, and sterols [6,7]. Although *Ganoderma* spp. have a long history of traditional application, increasing scientific attention has focused on elucidating the molecular mechanisms underlying their biological activities [8]. Among these metabolites,

Ganoderma Polysaccharides (GPs) are considered major functional components due to their immunomodulatory, antioxidant, anti-inflammatory, and metabolic regulatory properties [3]. Significantly, their structural characteristics, including molecular weight, monosaccharide composition, glycosidic linking patterns, degree of branching, triple-helix conformation, and polysaccharide-protein complex formation, greatly influence their biological activities [9]. Such structural heterogeneity is increasingly recognised as a critical determinant governing polysaccharide bioavailability, receptor interaction, microbial fermentation behaviours, and subsequent physiological responses [10].

In parallel, the gastrointestinal (GI) microbiota has emerged as a key regulator of host metabolism, immune function, and disease susceptibility [11]. Recent studies suggest that dietary polysaccharides can exert therapeutic effects indirectly through microbial biotransformation and modulation of the gut microbial ecology. GPs are resistant to digestion in the upper gastrointestinal tract, so they end up in the colon, where gut microbiota ferments them. This process increases the production of short-chain fatty acids (SCFAs) and other microbial metabolites linked to intestinal and systemic health, as well as beneficial taxa like *Bifidobacterium*, *Lactobacillus*, and *Akkermansia* [12,13].

In addition to gut microbiota modulation, GPs exhibit hepatoprotective, immunoregulatory, antioxidant and neuroprotective effects through mechanisms associated with oxidative stress regulation, inflammatory signalling pathways, and host-microbe interaction [14,15]. Given the increasing recognition of the microbe-gut-brain axis in GI and neurological disorders, the ability of GPs to modulate gut microbiota ecology suggests significant potential for their development as functional food and adjunct therapeutic agents [16,17].

This review provides a comprehensive and integrative overview of GPs with particular emphasis on the relationship between polysaccharides structural characterisation and their biological functions. Unlike previous reviews that primarily focus on general pharmacological properties, this article critically discusses how molecular weights, glycosidic configuration, branching patterns, and conformational features influence GP bioactivity and gut microbiota modulation. In addition, the review summarises current mechanistic evidence regarding GP-mediated regulation of microbial composition, SCFA production, immune signalling and GI homeostasis, while also addressing emerging applications in functional food and nutraceutical development. Specifically, this review aims to: (i) describe the structural classification and physicochemical properties of GPs; (ii) evaluate conventional

and advanced extraction methods and their effects on GP structure and bioactivity; (iii) analyse structure-activity relationships associated with antioxidant, antidiabetic, hepatoprotective, immunomodulatory and anticancer activities; (iv) elucidate the mechanism underlying GP-mediated gut modulation and SCFA production; and (v) assess translational potential and identify key gaps for future clinical research.

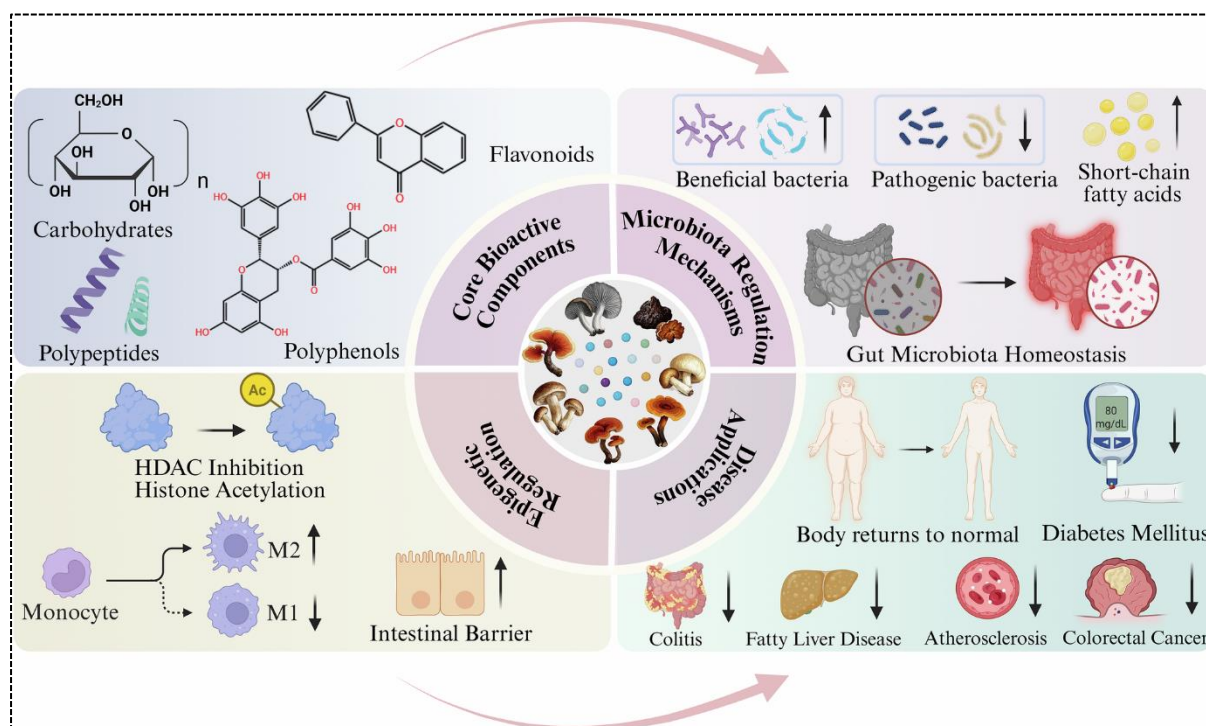


Fig. 1. This figure demonstrates the fundamental processes by which edible fungi's bioactive components (such as β -glucans and triterpenoids) alter the gut microbiota and treat illnesses: By restructuring the composition of the gut microbiota (e.g., encouraging the growth of beneficial bacteria like *Bifidobacterium* and *Lactobacillus* while suppressing pathogens like Enterobacteriaceae), these components increase the production of beneficial metabolites, especially butyrate and other SCFAs. On the one hand, by stimulating G protein-coupled receptors (GPR41/43, GPR109A) and blocking histone deacetylases (HDACs), SCFAs (Short-chain fatty acids) improve intestinal barrier integrity, reduce inflammation, and encourage the development of regulatory T cells (Tregs). However, they control epigenetic processes and host metabolism. Furthermore, components of fungi directly inhibit inflammatory pathways like TLR4/NF- κ B. These coordinated processes successfully address diseases associated with microbial dysbiosis, including colorectal cancer, metabolic syndrome (obesity/diabetes), and inflammatory bowel disease (IBD) [18].

2. Methods and strategies of reviewing

The literature search involved the use of electronic databases, which were selected through a combination of relevant keywords and the use of Boolean operators. The keywords and Boolean operators used were "*Ganoderma* spp.", "gut microbiota", "immunomodulatory", "extraction and purification methods", "biological activities", "beta-glucans", etc. The literature search process led to the identification of 250 articles through database searching and another 20 articles through other sources. However, the number of articles was reduced to 240 after the elimination of duplicates.

The articles were then screened using the title and abstract screening process, which led to the elimination of 20 articles that were considered irrelevant to the research study. Then, the remaining articles were subjected to the full-text screening process. During the full-text screening process, 10 articles were considered irrelevant to the research study. Hence, the final number of articles considered relevant to the research study is 210.

During the eligibility phase, 10 studies were excluded in the form of full-text articles based on reasons such as the absence of experimental data, insufficient methodology, duplication of data reported in the studies, and failure to meet the predefined inclusion criteria. Therefore, the qualitative synthesis was carried out with the inclusion of 200 studies. Of these studies included in the qualitative synthesis, 198 studies were further included in the quantitative synthesis in the form of meta-analysis. The reasons for the exclusion of the remaining studies were the absence of statistical data in the studies and insufficient reporting of key parameters, as shown in **Fig 2**.

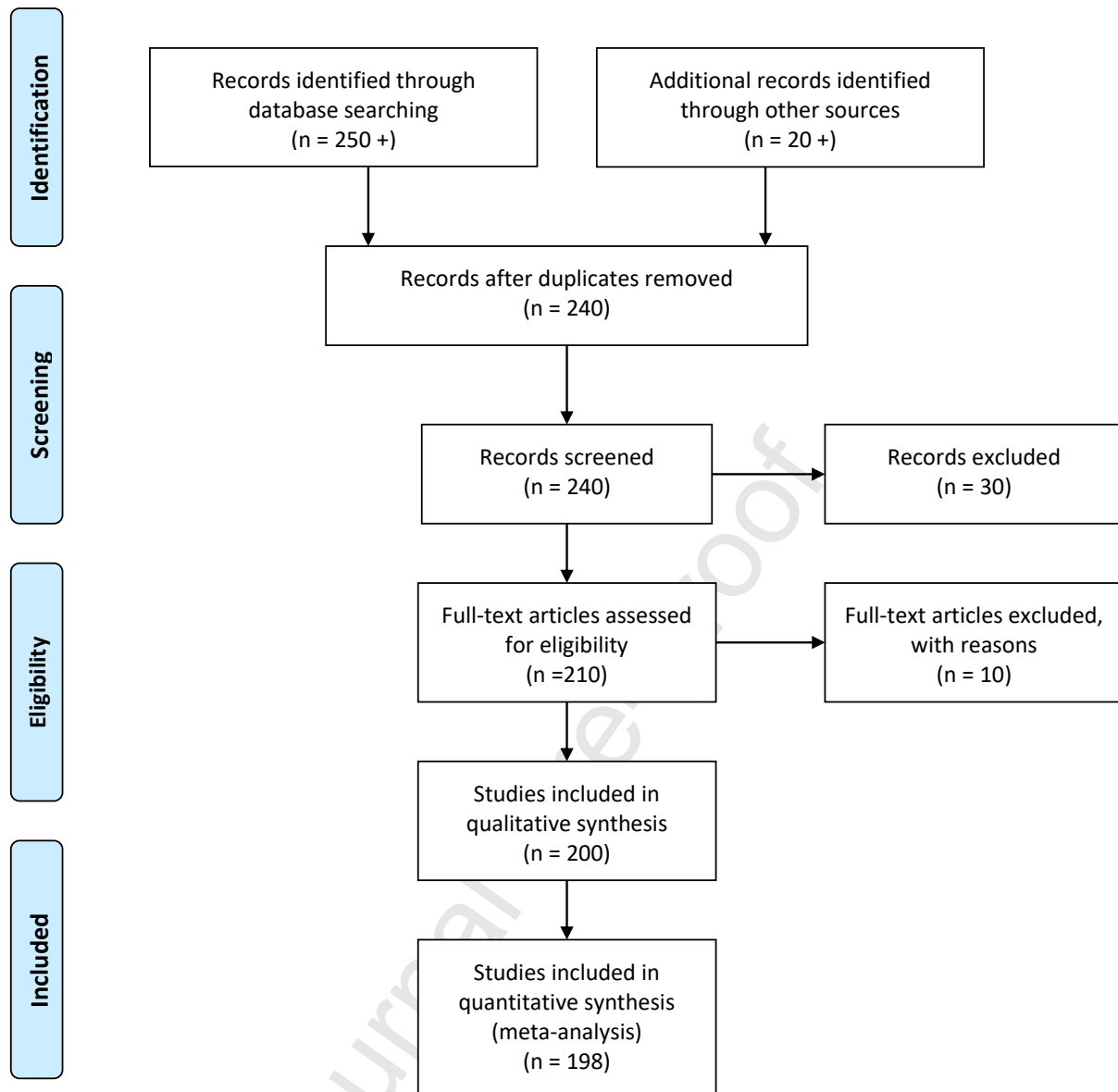


Fig. 2. PRISMA flow diagram

3. Structural Characteristics of GPs

The fruiting bodies, mycelium, spores, and fermentation broth of *Ganoderma* spp. have all been the subject of in-depth research on polysaccharides. The majority of these polysaccharides are crude extracts, and they frequently comprise diverse blends of glycoproteins, other macromolecules, and polysaccharides [19]. Natural polysaccharides generated from *Ganoderma* are broadly characterised as glucans, heteroglucans, heterogalactans, and heterogeneous main-chain polysaccharides based on the distribution and content of monosaccharides, as shown in Fig 3. [20]

3.1.1. Glucan

More than 40% of the overall polysaccharide composition is made up of glucans, a significant class of GPs [21]. A number of significant factors, including molecular weight, glycosidic types, degree of branching, and spatial conformation, control the structural complexity of glucans and ultimately affect their biological usefulness [22]. *Ganoderma*-derived polysaccharides predominantly consist of β -D-glucans with (1 $\rightarrow$ 3), (1 $\rightarrow$ 4), and (1 $\rightarrow$ 6) linkages, which are D-Glcp polymers with various conformations [23]. *Ganoderma* β -D-glucans are extensively distributed in various combinations with (1 $\rightarrow$ 3), (1 $\rightarrow$ 4), and (1 $\rightarrow$ 6) connections, and they show significant structural diversity and complexity beyond the conventional 1,3- β -D-Glcp backbone. For example, the main chain of GLSWA-I consists of 1,3- β -D-Glcp, 1,4- β -D-Glcp, and 1,6- β -D-Glcp residues, with branches consisting of β -D-Glcp-(1 $\rightarrow$ 4)- β -D-Glcp-($\rightarrow$) and β -D-Glcp-($\rightarrow$) residues coupled at the O-6 and O-4 positions. As a result, the degree of branching is 0.44 [24]. Structural modification has been shown to further enhance glucan bioactivity. Dong et al. [25] synthesised the selenium-enriched polysaccharide SeMPN, which contained 18.91 ± 1.8 μ g/g selenium, by enriching a *G. lucidum* mycelium polysaccharide fraction (MPN, a glucan).

Interestingly, even while the monosaccharide composition and carbohydrate amount remained unchanged, SeMPN (9.689kDa) had a lower Mw than MPN (10.259). SeMPN has more immunostimulatory qualities and stronger antioxidant activity than MPN, according to in vitro experiments. It is possible that adding selenium was essential for increasing its biological activity. Enhancing the biological activity of polysaccharides can be achieved through both chemical modification and glucan DS enhancement. In addition to chemical modification, enzymatic processing is widely employed to improve glucan solubility and functionality; β -glucans are frequently hydrolysed into their soluble forms using enzymes, including glucanase, lichenase, and viscozyme L. Research on *G. lucidum*, for instance, showed that high-pressure steaming and viscozyme L enzymatic hydrolysis produced up to 8.05 g/100 g of beta-glucan. A temperature of 50°C, a pH of 5, and a reaction duration of four hours were the ideal parameters for enzymatic hydrolysis [26].

3.1.2. Heteroglucans

Heteroglucans found in *Ganoderma* are primarily made up of Glc and smaller sugars like Ara, Gal, and Xyl. One prominent example is GLP-1, which has an inserted 1,6- α -D-Galp

residue and a main chain of 1,3- β -D-Glcp and 1,4- β -D-Glcp. The presence of two complex side chains at the O-2 and O-4 locations of the Galp residues complicates this sequence [27]. A high-molecular-weight GPs fraction (RGLP-1) was isolated from the fruiting bodies of *G. lucidum* by Liu et al. [28]. The molar ratios of fucose (Fuc), mannose (Man), glucose (Glc), and galactose (Gal) in this β -pyran polysaccharide are 0.13: 0.05: 0.72: 0.10. A mixture of (1 $\rightarrow$ 3), (1 $\rightarrow$ 3,6), (1 $\rightarrow$ 4), and a tiny quantity of (1 $\rightarrow$ 6)-linked glucose with a triple helix conformation makes up the backbone. It's interesting to note that RGLP-1 has the strongest immunomodulatory function in vitro and a significantly larger Mw (3978 kDa) than GLSWA-I (157 kDa) and MPN (10.259 kDa). This shows that, depending on their structural characteristics, both high and low molecular weight polysaccharides can have immunomodulatory effects [24,25]. Furthermore, Li et al. [29] described the structure of a heteroglucan GP fraction (GLP-1) containing $\rightarrow$ 6)- β -D-Glcp-(1 $\rightarrow$, $\rightarrow$ 3)- β -D-Glcp-(1 $\rightarrow$, and $\rightarrow$ 6)- α -D-Galp-(1 $\rightarrow$) residues that had a flexible random linear conformation and demonstrated greater immunomodulatory activities compared with a β -D-glucan fraction (GLP-2). This enhanced bioactivity was reflected in improved thymus and spleen protection as well as more successful haematopoietic and serum immunoglobulin A (IgA) levels, potentially attributable to the greater complexity of its monosaccharide composition [30].

3.1.3. Galactans and heterogalactan

GPs include polysaccharides called Galactans and heterogalactans. 1,6- α -D-Galp units make up their backbone, and side chains containing non-reducing sugars such T- α -L-Fuc, T- α -D-Galp, T- α -D-Manp, and T- α -D-Galp-(1 $\rightarrow$ 6)- α -D-Galp-(1 $\rightarrow$ 4)- β -D-Glcp-(1 $\rightarrow$) linked to the O-2 positions [31,32]. According to Zhang et al. [33], reported that heterogalactans were also isolated from *G. lucidum* and *G. atrum*. PSG-2, a heterogalactan fraction recovered from *G. atrum* fruiting bodies, has a mass of 69 kDa and a backbone of α -1,6-linked Galp. It branches at the O-2 position, contains Gal (75.87%), Fuc (11.83%), Glc (6.02%), and has a low Man content [34]. Future research must, however, confirm the distinction between PSG-2 and GLP-2 bioactivities. The fruiting body of *G. atrum* yielded another neutral (1 $\rightarrow$ 6)-linked-heterogalactan fragment (Fw, Mw of 16.1 kDa). It exhibited very little antioxidant activity, perhaps because it contains very low levels of phenols and no uronic acid and protein (about 95.70 per cent carbs) [35]. In addition, *in vitro* cell-based studies demonstrate that LZ-D-1 enhances the growth of mouse splenic lymphocytes, suggesting that it may improve immunological function. The primary chain comprising 1,3- β -DGlc, 1,4,6- β -D-Glcp, and

1,6- α -D-Galp residues was identified as LZ-C-1. T- α -L-Fucp connections formed branches at the O-2 position of the 1,6- α -D-Galp residues [36]. Furthermore, glycopeptides produced from *Ganoderma* have heterogalactan sugar chains; the primary chains are 1,6- α -D-Galp, 1,4,6- β -D-Glcp, and 1,4- β -D-Glcp; two examples are GL-PWQ3 and GLPCW-II, with molecular weights of 2.4×10^4 Da and 1.2×10^4 Da, respectively [37]. Collectively, these findings align with reports indicating that many GPs contain varying levels of uronic acid or occur as polysaccharide conjugates with proteins, peptides, and phenol compounds [27,38,39]. Consequently, the biological activities of GPs fractions are strongly influenced by purification steps, including deproteinisation, depigmentation, and removal of small-molecular conjugates from crude extracts.

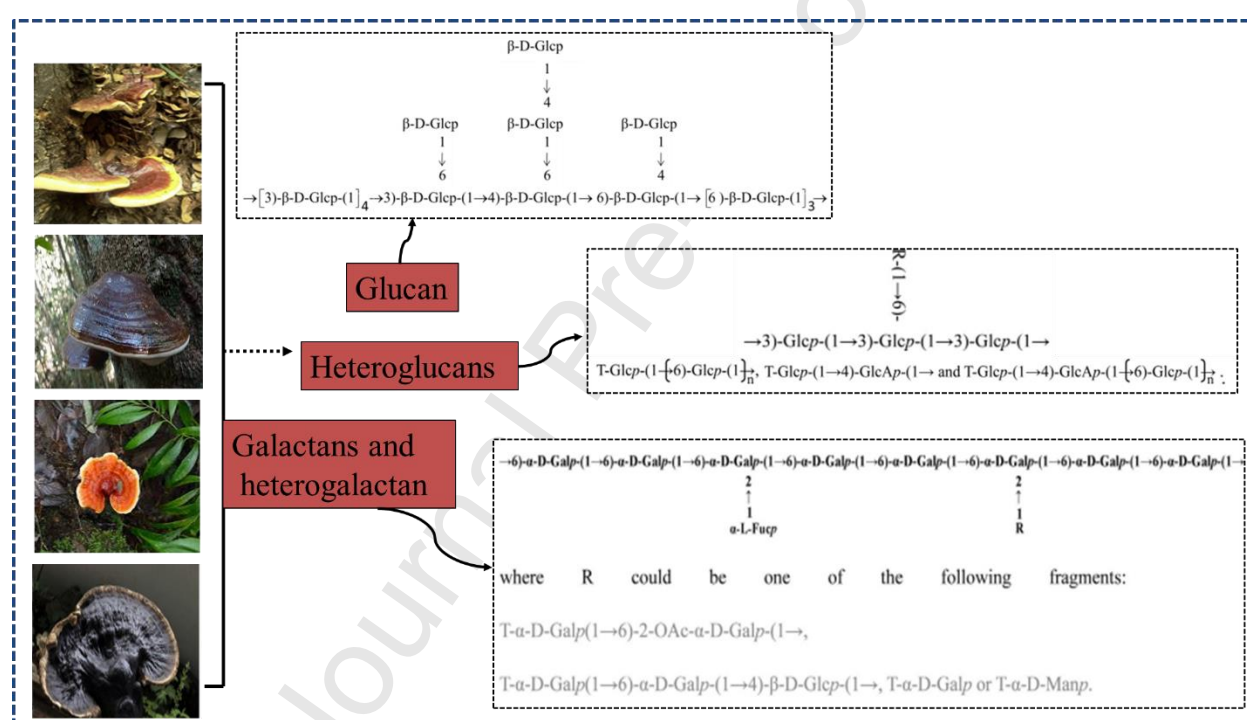


Fig. 3. The fruiting bodies of different species of *Ganoderma* spp. [6,40–42] and the typical structure of GPs. Glucan (GLSWA-I) [24], Heteroglucan (PSG-1-F0.2) [43], Heterogalactan (PSG-2) [34].

3.2. Integrated Structure-Activity Relationship (SAR) Framework of Polysaccharides

The chemical structures and properties of GPs, including monosaccharide composition, glycosyl linkage type, branch structures, molecular weight, and chain topologies, have been investigated using spectral analysis, chemical analysis, and chromatography. GLPs are acknowledged as significant biological response modifiers (BRMs), and as fig. 4 illustrates, structural characteristics such as molecular weight, glycosidic bond type, branching topology,

and substituent makeup significantly impact their bioactivities. Along with mannan and galactosan-containing structures, α -(1 $\rightarrow$ 3), α -(1 $\rightarrow$ 6), and β -(1 $\rightarrow$ 3), β -(1 $\rightarrow$ 6) glucans are the main glycosidic linkages frequently seen in GLPs. The structure-activity connection of polysaccharides from various *Ganoderma* species is summarised in Table 1, and the bioactivities that go along with them.

GPs' complete structural elucidation is achieved via the synergistic use of four main analysis techniques, all of which provide unique and critical structural information impossible to obtain via any other means. FTIR allows quick determination of the anomeric configuration and functional groups. During GPs studies, it has been established that β -glycosidic bonds give an FTIR signal near 890 cm^{-1} , whereas α -glycosidic bonds show peaks near 918 cm^{-1} and 874 cm^{-1} , while highly overlapped C-O-C, C-O, and C-C stretching vibrations near 1154, 1105, 1072, 1044, and 995 cm^{-1} correspond to the carbohydrate ring structure; carbonyl groups near 1078 cm^{-1} are characteristic for β -glucosides and utilised for quantitative determination of β -glucans in *Ganoderma* mycelium [44,45]. Moreover, NMR spectroscopy, including not only 1D spectroscopy of ^1H and ^{13}C nuclei but also advanced 2D spectroscopy, such as COSY, HSQC, HMBC, and NOESY spectroscopies, continues to be the benchmark in the assignment of fine structures. The detection of signals characteristic of anomeric protons in ^1H spectrum in 4.4 - 4.9 ppm region indicates the presence of β -anomeric bonds in GPs, while signals of ^1H - ^{13}C HSQC experiment in 4.95/100.9 ppm (H-1/C-1) were associated with starch and dextrin contamination, and the signal detected in 105.0 ppm in ^{13}C spectrum indicated the presence of the β -GlcP bond in polysaccharide fractions of *G. lucidum* before and after fermentation [46,47]. Furthermore, the solid-state CP-MAS NMR further revealed that the fungal cell wall is predominantly composed of β -1,3-glucans and chitin rigid cores surrounded by mobile outer layers enriched with β -1,4-glucans, α -1,3-glucans, arabinose, galactofuranose, and α -mannose residues [48]. GC-MS coupled with the analysis of PMAA methylation elucidates accurate information about linkage position and branching of glycosidic linkages. For instance, linkage types of PSG-1 extracted from *G. atrum* included 1,3-linkage, terminal linkage, and 1,3,6-linkage of GlcP [49]. However, comparative studies carried out on polysaccharide extracts of *G. lucidum* and *G. sinense* established that the $\rightarrow$ 3)-GlcP-(1 $\rightarrow$ linkage was the common linkage type responsible for immunostimulant and antitumor properties [50]. Further characterisation of size exclusion chromatography (SEC), especially the HPSEC-MALS-RI-VS method, specifically reveals molecular weight distribution, polydispersity index, and chain conformation attributes related to biological function. Glucan fractions of *G. lucidum* showed triple-helical chain conformation with

higher molecular weights, while PSG-1-F0.2 of *G. atrum* possessed hyper-branched coiled chains with spherical conformations. Moreover, confirmation on triple-helical conformation was established for RGLP-1 by Congo red assay with bathochromic shift of absorption spectra [51–53]. Collectively, the bioactivities of GPs are governed by their linkage type, branching pattern, and molecular weight. Integrated FTIR, NMR, GC-MS, and SEC-MALS analysis, therefore, provides a robust framework for establishing GP structure-activity relationships.

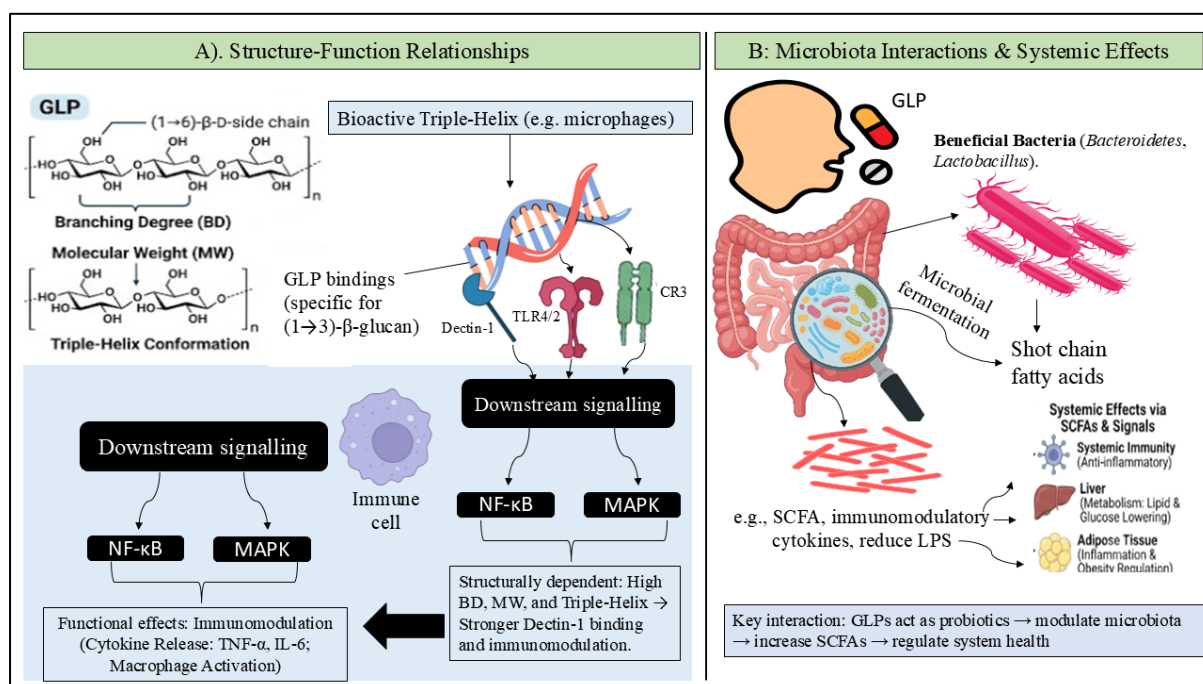


Fig 4. Structure-function relationships and gut microbiota-mediated systemic effects of GPs.

Abbreviations: GPs, *Ganoderma* polysaccharides; Mw, molecular weight; BD, branching degree; SCFAs, short-chain fatty acids; LPS, lipopolysaccharides; Nf-κB, nuclear factor kappa B; MAPK, mitogen-activated protein kinase; TLR4, toll-like receptor 4; CR3, complement receptor 3.

3.2.1. Molecular weight and bioactives

In general, GLPs' bioactivity increases with their molecular weight. GLPs with varying MW are produced by hot water extraction and ultrasound-assisted extraction. Larger GLPs are more effective at reducing power, scavenging DPPH and hydroxyl radicals, and shielding yeast cells from UV light [39]. Considerable variation in the molecular weight of GLPs have been reported, reflecting their structural diversity and biological significance. Two heteroglycans (PL-1 and PL-4) and one glucan (PL-3) isolated from *G. lucidum* had

molecular weights of 8.3×10^3 , 2.0×10^5 , and 6.3×10^4 Da, respectively, according to Bao et al. [54]. Similarly, Chen et al. [55] discovered PSG-1 with a significantly higher average molecular weight of 1013 kDa using HPSEC analysis, whereas Ye et al. [36] found a water-soluble polysaccharide with a molecular weight of 7×10^3 Da. Sui et al. [56] further demonstrated that submerged-cultured intracellular GLPs (GLPs-In) possessed a higher molecular weight ($>10^6$ Da) than fruiting body-derived GLPs (GLPs-Fr), while extracellular GLPs (GLPs-Ex) exhibited relatively low molecular weight ($\sim 10^3$ Da). These high-molecular-weight GLPs showed enhanced stimulation of RAW264.7 macrophage viability, nitric oxide release, and inhibitory activity against HepG2 cells. In contrast, Xu et al. [38] reported that ultrasonic degradation-induced reduction in molecular weight improved the hypolipidemic and antioxidant activities of GLPs without altering their primary structure. Similarly, *Azadirachta indica* leaf polysaccharides with relatively low molecular weight (28.15 kDa) demonstrated strong antioxidant activity and tyrosinase, suggesting that lower molecular weight fractions may enhance solubility, diffusibility, and cellular interaction in tropical applications [57]. Recent studies on star anise polysaccharides (SAPs) further demonstrated that low-molecular weight fractions (21.64-29.35 kDa) with higher esterification degree, viscosity and branching complexity showed stronger inhibitory activities against lipase, ACE and α -glucosidase [58]. Despite the general association between higher molecular weight and enhanced immunomodulatory activity, contradictory findings have been reported regarding the optimal molecular weight range for specific biological function [28]. These discrepancies may partly arise from variation in raw *Ganoderma* materials, including species differences, development stages, cultivation conditions, and use of fruiting bodies, spores, mycelia, or fermentation-derived polysaccharides. Furthermore, extraction parameters, particularly temperature and processing intensity during hot-water, ultrasound-assisted, or alkaline-assisted, can substantially modify polysaccharides' structure through depolymerisation, conformational alteration, or selective enrichment of a specific fraction [59]. Consequently, differences in source material and extraction methodology may contribute significantly to the inconsistent activity profiles reported for the GP fraction across studies. Collectively, these findings indicate that molecular weight is a critical yet complex determinant of polysaccharides' bioactivity, with its effects varying according to biological targets, extraction methods, structural conformation and application-specific mechanisms.

3.2.2. Tertiary structure and bioactivities

GLPs are stabilised by side chains and have a tertiary structure, or triple helix, created by hydrogen bonding in the second carbon position. Like biopolymers like DNA and RNA, GLP bioactivities are frequently associated with their tertiary structure (the β -structure). High-molecular-weight β -D-glucans ($2.5 \times 10^4 \times 10^4$ Da) have a stable triple-helical structure that is directly linked to increased bioactivity, as shown by Synytsya et al. [60]. However, the ordered triple-helical conformation was disturbed by exposure to hostile environments such as alkaline solution, carbamide, or dimethyl sulfoxide, which led to the production of random coils and decreased biological activity. A conformational transition from ordered structures to random coils occurred at NaOH concentrations ranging from 0.19 to 0.24 M, whereas concentrations above 0.24M caused dissociation of one chain from the triple helix, ultimately leading to a complete random coil structure [61].

Similarly, GLP20, a purified β -(1 $\rightarrow$ 3)-d-glucan with β -(1 $\rightarrow$ 6)-linkage side branches isolated from *G. lucidum* fruiting bodies, exhibited a molecular weight of 3.75×10^6 Da and a polydispersity index of 1.36. Structural characterisation confirmed that GLP 20 possessed a rigid triple-helical chain conformation in aqueous solution and significantly stimulated nitric oxide production in RAW264.7 macrophages. Conformational transition of GLP 20 occurred at NaOH concentration greater than 0.15M, while helical structural into single chains, as confirmed by DSC analysis. Furthermore, GLP20 existed as random coils in DMSO, demonstrating the sensitivity of tertiary structure to environmental conditions [51]. Another study on β -d-glucan fractions from *G. lucidum* demonstrated rigid chain conformations with p-values greater than 2.06 and exponent values of $v=0.72$ and $\alpha=1.05$, confirming stable triple-helical organisation. The glucan fraction exhibited a persistence length of 128 nm, contour length of 2150 nm^{-1} . Fractions with molecular weights higher than $1.82 \times 10^6 \text{ g.mol}^{-1}$ exhibited stronger stimulation of lymphocyte proliferation and enhanced secretion of IL-6 and TNF- α , indicating that stable triple-helical conformations and rigid tertiary structure are strongly associated with enhanced immunomodulatory activity [62]. Overall, a stable triple-helical tertiary conformation is closely associated with enhanced GLP bioactivity, whereas disruption into a random coil structure significantly reduces their biological efficacy.

3.2.3. Monosaccharide units and bioactivities

The monosaccharide content of GLPs is usually consistent. D-glucose, D-fructose, D-galactose, D-mannose, D-xylose, L-fucose, L-rhamnose, and L-arabinose make up the majority of GLPs. Additionally, the monosaccharide composition of fruiting bodies varies. Bioactivities can vary according to monosaccharide concentration. High galactose, high

rhamnose N, and high glucosamine are the monosaccharide concentrations of exopolysaccharides (EPS) that influence their anti-inflammatory properties against macrophages [63]. Si et al. [64] used Plackett-Burman design (PBD) and response surface methodology (RSM) to optimise the medium composition in order to manufacture *G. lucidum* mycelium exopolysaccharide (GLEPS). Through transition metal catalyst chelation, radical scavenging, and reductive capacity, they concluded that the GLEPS with a higher uronic acid concentration had increased in vitro antioxidant activity. Furthermore, a polysaccharide having a main chain of 1→4 linked arabinose and 1→6 linked glucose showed a superior ability to scavenge DPPH radicals [65]. Overall, the bioactivity of GLP is highly dependent on its physical structure, such as molecular weight, backbone of β -(1→3)/ (1→6)-glucan, branching ratio, monosaccharide content, and tertiary structure. Triple-helix high molecular weight GLP normally possesses a good immunomodulatory effect, while low molecular weight GLP display more potent antioxidant and antilipemic activity because of better water solubility and diffusion ability. Collectively, current evidence demonstrates that the biological activities of GPs are strongly governed by their structural characteristics, including molecular weight, monosaccharide composition, glycosidic linkages, branching architecture, and tertiary conformation. β -(1→3)/ (1→6)-glucan backbones, appropriate branching patterns, and stable triple-helical structure are particularly associated with enhanced immunomodulatory and therapeutic activities. Advances in structural characterisation techniques have significantly improved understanding of these SAR, providing a foundation for the rational development of *Ganoderma*-derived functional food and therapeutics. However, the interpretation of SAR findings remains challenging because polysaccharide structures are highly influenced by biological sources and processing conditions. Variation in *Ganoderma* spp., tissue origin, cultivation practices, and extraction parameters can substantially modify structural features, thereby contributing to the inconsistent activity trend reported across studies.

Table 1.

Cross-species comparative structure-activity relationship of GPs fractions

Species	fraction	Mw(kDa)	Tertiary conformation	Monosaccharide composition	Bioactivity type	SAR inference	References
<i>Ganoderma sinense</i>	GSP-6B	1860	ND	Low- primarily glucose (homoglucan), with only trace galactose and mannose	Immunomodulatory	(1→6)-β-glucan backbone, dense O-3 branching, mixed (1→3)/ (1→4) side chains; branching density + covalent protein (~10%) likely drives Dectin-1/TLR-2 activation	[66]
<i>Ganoderma lucidum</i>	GLPL-1	5.2	ND	Low-glucose only (homoglucan)	Antioxidant	(1→3) (1→4) (1→6)-β-glucan, ~24% branching at C-3/C-6; lower Mw → more exposed hydroxyl groups → superior radical scavenging and Fe ²⁺ chelation	[67]
<i>Ganoderma leucocontextum</i>	GLP-3	159.7	Triple-helix	Heteropolysaccharides	Immunomodulatory	(→4)-α/β-D-Glcp mixed backbone structure with β-branching and triple-helix globular shape allows TLR2	[68]

						to recognise and activate downstream signaling by MAPK	
<i>Ganoderma atrum</i>	PSG-2	69	Linear (no helix)	Heteroglucan: Gal (75.87%), Fuc, Glc, Man	ND	1,6-galactan chain with O-2 branches (1,2,6-Galp) and acetylated units; heterogalactan composed mainly of galactose and fucose but with various end groups increases heterogeneity and binding capabilities.	[34]
<i>Ganoderma lucidum</i>	GLP1-GLP4	2.5->10	ND	Glucose + galactose-rich	Antioxidant, antiproliferative	Fractionation analysis reveals Mw-dependent bioactivity; the intermediate-high Mw fractions (8-10 kDa and >10 kDa) are the most active due to ideal chain length, hydroxyl group availability, and ability to act as a radical scavenger, whereas the very low Mw	[69]

						fractions display low activity.	
<i>Ganoderma sinense</i>	GSPA60-3	9.448	ND	β -GlcP, Manp, GlcA	immunomodulatory	β -glucan having acidic property and the residues of (1 $\rightarrow$ 6), (1 $\rightarrow$ 3,6)-GlcP and terminal GlcA activate the pathways of MAPK/Akt/NF- κ B mediated by TLR2/TLR4 to increase immune response in macrophages	[70]
<i>Ganoderma lucidum</i> (spores)	WGLP	15	ND	Homoglucan (β -D-glucose only)	Antitumor	Glucan polymer with (1 $\rightarrow$ 3)- β -D-glucan as the backbone and (1 $\rightarrow$ 6)- β -D-glucopyranosyl branches and end glucose; small molecular weight branched glucans improve cancer inhibition through the action of bioactive receptors, inhibiting the growth of the S180 tumour	[71]

Note: Molecular weights (Mw) are uniformly expressed in kilodaltons (kDa). ND indicates that the tertiary conformation or biological activity was not determined or reported in the original studies. Structure-Activity Relationship (SAR) inferences are based on reported associations between Mw, monosaccharide composition, branching patterns, glycosidic linkages and biological activities.

4. Extraction techniques

Polysaccharides obtained from *Ganoderma* species, either from the fruit body, spore, mycelium, or culturing broth, have varying structures and activities depending on how they are extracted [72]. Many traditional and modern extraction methods have been applied in obtaining GPs. These methods vary in terms of effectiveness, time taken, and amount of solvent required. They also vary in terms of structure preservation and eco-friendliness. Different methods are employed to obtain these polysaccharides, and the effectiveness of these methods is presented in Table 2.

The conventional hot water extraction (HWE) technique continues to be the best choice because of its simplicity, safety, low toxicity and environmentally friendly approach [73]. Normally, the HWE process takes place at 70-100°C with material to liquid ratios of 1:10 to 2:40 for 1-4 hours. Multiple steps are usually required to extract maximum from polysaccharides [27,74]. High temperature promotes cell wall disintegration and enhances solubility. Nevertheless, overheating might cause degradation of β -glucan, which will affect its conformation and biological activity. The pressurised hot water extraction technique proved to increase the recovery of β -glucan, which is considered one of the active components responsible for the immunomodulatory and therapeutic activities of GPs [75]. Other than water, GPs are soluble in diluted alkalis and weak acids, however not soluble in organic solvents such as alcohols. Alkaline-assisted extraction might improve efficiency and sugar purity through increasing cell wall permeability and polysaccharide release. In one study, the hot-water extraction process in alkaline media resulted in 8.30% polysaccharides yield with 95.67% sugar purity [76]. However, the excessive use of alkaline extraction may affect glycosidic bonds, side chains and triple helix conformation.

The conventional extraction begins with elimination of fats from fungi through the use of organic solvents followed by extraction of the residues using hot water, saline solution or dilute alkali in certain conditions [77]. It influences the yield, purity, molecular weight, and structure of polysaccharides. Hot water extraction preserves the natural conformation of polysaccharides, but it is not as effective as new techniques, which are quicker [27].

However, various modern and eco-friendly techniques for extraction have been developed to enhance the extraction efficacy and decrease energy use and extraction time. Ultrasound-assisted extraction (UAE) has drawn much attention owing to fast extraction, low temperature requirements, minimal solvent use and mass transfer efficacy. The cavitation

process occurring during UAE treatment helps break down the fungal cell wall and speed up the release of polysaccharides. Optimal UAE parameters of 40-81°C and 590-600W have resulted in GP contents of 0.52%-2.7% [21,78]. Interestingly, polysaccharides obtained by means of UAE had a capacity to scavenge the DPPH radical equal to that of vitamin C and higher than other methods of polysaccharide's isolation, such as HWE. At the same time, too intense ultrasound and long exposure could lead to low molecular weight and breaking of β -(1→3)/ (1→6)-glucan molecules. Also, the UAE is often used together with enzyme treatments. For example, UAEE technique with viscozyme and chitinase application under optimal conditions of pH 5.5, 45°C for 30 min and 480W resulted in polysaccharides extraction from Vietnamese red reishi mushroom with 3.2% efficiency [79]. Moreover, ultrasonic circulation extraction together with ultrafine grinding (UCE) increased GLP content up to 47.87 mg/ml [80]. These combined techniques improve cell wall degradation and facilitate the release of intracellular polysaccharides while reducing extraction duration.

Recent advancements in extraction technology have further enhanced GP recovery and structural preservation. Mechanochemical-assisted extraction (MCAE) increases yield to 5.92% while reducing extraction time by 45.8% compared with conventional hot reflux extraction. Continuous phase transition extraction (CPTe) produced 3.34-fold higher yields than HWE and 2.68-fold higher yields than UAE while simultaneously generating higher-molecular-weight polysaccharides with improved immunoregulatory properties. Microwave-assisted extraction (MAE) has also emerged as a highly effective approach, increasing GP yield to 7.7% while reducing extraction time by nearly 90% [81]. MAE utilises dielectric heating to rapidly disrupt fungal matrices and enhance solvent penetration. However, excessive microwave intensity may lead to thermal degradation and conformational instability of polysaccharides. More recently, deep eutectic solvent (DES)-based extraction systems have been recognised as promising green extraction alternatives because of their biodegradability, tunable polarity, low toxicity, and superior solubilisation capacity. Optimised ternary DES systems have achieved GP yields of up to 9.5% while reducing reliance on hazardous organic solvents [82,83]. Collectively, advanced extraction technologies demonstrate superior extraction efficiency, shorter processing times, lower solvent consumption, and improved environmental sustainability compared with conventional techniques. In particular, the greatest improvement in polysaccharide extraction was observed for CPTe and DES-assisted methods, while UAE and MAE provided fast extraction with lower energy consumption. However, over-extraction, such as prolonged ultrasound

treatment, higher microwave power, or too strong alkalinity, can cause depolymerisation of the polysaccharides, breaking down of the β -glucan branching structure, as well as the loss of triple-helix conformations. This can affect biological activity, hence the need for optimal extraction conditions to maintain the biological activity of the GPs.

4.1. Influence of extraction conditions on polysaccharides structure and biological activity

Extraction and purification conditions critically influence the structural characteristics and biological activities of fungal and other plant polysaccharides [84]. Recent studies on *Cornus officinalis* polysaccharides have highlighted that extraction and purification strategies can affect polysaccharide yield, structural characteristics, emphasising the importance of process optimisation for functional application [85]. Similarly, Gao et al. [86] reported that *Rubus idaeus* L. polysaccharides exhibit diverse biological activities, including immunomodulatory, anti-inflammatory, antioxidant, antitumor, and gut microbiota-regulating effects, which are closely associated with their structural properties. Likewise, a study on *Pseudostellaria heterophylla* polysaccharides demonstrated that molecular weight, monosaccharide composition and structural modification are key determinants of their immunomodulatory, antioxidant and antitumor activities, underscoring the significance of extraction and processing method in defining bioactivity [87]. Collectively, these studies emphasise the importance of the conditions used during extraction on polysaccharide structure and function. Likewise, for GPs, the conditions during the extraction process, including temperature, time, pH, ultrasonic power, microwave power, and purification method, have been found to affect the molecular weight, monosaccharide content, degree of branching, glycosidic bond linkages, and higher order structures, and consequently, their antioxidant, immune, anti-inflammatory, and anti-ageing activities [88,89]. For example, alkaline extraction of *G. lucidum*, optimised at 60.1°C, 77.3 min, 5.1% NaOH, and a substrate-to-liquid ratio of 1:21.4, enhanced delayed-type hypersensitivity responses, hemolysin antibody production and natural killer (NK) cell activity, suggesting preservation of immunologically active β -glucan domains [69]. Similarly, ultrasonic/microwave-assisted extraction (UMAE) significantly increased polysaccharides yield by 115.56% compared with hot-water extraction under optimised conditions of 50W ultrasonic power, 284W microwave power, and 701s extraction time, while also improving immune organ protection and NK cell activity [90]. UAE further demonstrated that the extraction condition strongly influences molecular weight distribution and antioxidant activity. Under optimised conditions (320W, 70°C, 34min), polysaccharides exhibited strong antioxidant capacity with an ORAC value of 1956 μ mol trolox/g, and the

higher-molecular-weight fraction (GLP1 and GLP2) showed stronger antioxidant and antiproliferative activities than the lower-molecular-weight fraction [91].

Structural characterisation studies further confirm a strong structure-activity relationship influenced by extraction conditions. Polysaccharide fractions isolated using ethanol precipitation and ion-exchange chromatography displayed distinct conformations and immunological activities; GLP-1, a D-galactoglucan with a flexible linear conformation, exhibited stronger spleen and thymus protection [29]. Likewise, the higher-molecular-weight fraction RGLP-1 (3,978 kDa) demonstrated superior immunomodulatory activity due to its β -glucan-rich composition and stable triple-helical conformation, as confirmed by SEM, AFM and Congo red analyses [28]. In addition, three-phase partitioning extraction of *G. Leucocontextum* spores yielded the polysaccharide GLSP-A1, which significantly reduced IL-6 and IL-1 β expression and decreased reactive oxygen species and lipofuscin accumulation in *Caenorhabditis elegans*, indicating potent anti-inflammatory and anti-aging properties [92]. These findings showed that extraction conditions affect polysaccharides in multiple ways. They change their molecular weight and branching, alter monosaccharide makeup and glycosidic linkages, and even tweak their triple-helical stability. High-temperature or alkali-assisted extraction may partially depolymerise polysaccharide chains, reduce molecular weight and alter branching architecture, whereas controlled ultrasonic or microwave-assisted extraction can improve extraction efficiency while preserving biologically active β -(1 $\rightarrow$ 3)/ (1 $\rightarrow$ 6)-glucan structures. These structural alterations subsequently influence their pharmacological activities.

Overall, the extraction approach is critical in defining the yields, structure, and bioactivity of GPs. Even though the classic HWE method continues to be popular due to its ease and safety, new technologies, including the use of ultrasound, microwave, mechanochemical, continuous phase transition, and deep eutectic solvent-based extraction methods, have been developed that increase efficiency and reduce processing time. It is worth noting that the extraction process parameters affect the molecular weight, the degree of branching, and the triple helix formation, thus affecting the antioxidant, immunomodulatory, and anti-ageing functions of the extracted polysaccharides.

Table 2

Extraction techniques, structural feature, yields and biological activities of polysaccharides from *Ganoderma* spp.

Species (Source)	Extraction Method	Key Conditions	Structural/ compositional features	Process Highlights	Biological Activity	Yield (%)	References
<i>Ganoderma lucidum</i> (mycelium)	HWE	100 °C, 2 h, 1:20	Water-soluble polysaccharides rich in β -glucans	Eco-friendly extraction	Immunomodulatory	2.59	[93]
<i>Ganoderma tsugae</i> (mycelium)	AE	2% NaOH, 25 °C	Alkali-soluble polysaccharide fractions with improved solubility	Improved solubility	Functional biomaterial	2.1	[94]
<i>Ganoderma lucidum</i> (fruiting bodies)	UAE	320-600 W, 40-80 °C	Low-molecular-weight polysaccharide fractions	Reduced time and energy	Strong antioxidant activity	0.52-2.78	[21,78,91]

<i>Ganoderma lucidum</i> (Mycelium and Fruiting Bodies)	AE	Temp: 100 °C, Time: 3 h, 6% NaOH c, Liquid- solid ratio: 20 ml/g	Alkali-extracted polysaccharides with high recovery efficiency	High yield under optimal conditions	-	4.96	[95]
<i>Ganoderma leucocontextum</i> (fruiting bodies)	HWE	Temperature: 90 °C; Time: 2 h; Solid: liquid ratio: 1:20.	Fraction-specific polysaccharides with distinct physicochemical properties	Fraction- specific extraction	Antioxidant activity	0.05- 0.26	[27]
<i>Ganoderma lucidum</i> (fruiting bodies)	HWE	90 °C, 2 h, 1:15	Crude polysaccharides containing β - (1→3)/(1→6)- glucans	Simple, scalable method	Antioxidant, anti- inflammatory	0.21- 1.85	[96]

<i>Ganoderma lucidum</i> (fruiting bodies)	AE	60.1 °C, 77.3 min, 5.1% NaOH, 21.4 mL/g	Alkali-soluble bioactive polysaccharides	High extraction efficiency	Immune activation (NK cells)	8.21	[69]
<i>Ganoderma lucidum</i> (Vietnamese Red strain)	UAEM	Enzyme concentration: 3%; pH: 5.5; Temperature: 45 °C; Time: 30min; Power: 480 W	Enzyme-assisted ultrasonically extracted polysaccharides	-	Showing the anticancer activities with the half-maximal inhibitory concentration (IC ₅₀) value of > 512 µg/ml	0.0320	[79]

Note: yields are presented as (%) of the polysaccharides extracted under particular extraction conditions. Variations in yield among different studies could be due to varying *Ganoderma* species, source materials (fruits, mycelium or spores), extraction methods, solvent systems used, and processing conditions. Hot Water Extraction (HWE), Alkaline Extraction (AE), Ultrasound-assisted extraction (UAE), Ultrasound-assisted enzymatic Extraction (UAEE), Ultrasound-assisted enzymatic Method (UAEM). IC₅₀ is the concentration that inhibits 50% of the target cell viability

5. Purification of GLP

GPs are always accompanied by impurities such as proteins and pigment. Therefore, the aim of getting an active compound is to separate these impurities [97]. Purification is done through various processes after the extraction process.

The GPs are large biomolecules made up of β -glucans with branch points. The molecules need to have their characteristic helical form to become active biologically. For this reason, they are soluble in water but insoluble in alcohol. Hence, the process of extracting them involves the use of hot water followed by alcohol to precipitate them, since the latter helps in clumping the polysaccharides [98]. Fractionation of raw GPs is done using the method of alcohol precipitation using solvents such as ethanol, methanol, or propanol [99]. For Further purification, column chromatography remains the most widely used approach. Techniques like anion exchange chromatography, e.g., DEAE-Sepharose Fast Flow, gel permeation (also known as size exclusion) chromatography, and microporous resin chromatography are commonly employed. Anion exchange chromatography is an effective tool in the separation of polysaccharides according to their charge, with high flow rates and chemical stability, though subsequent gel permeation chromatography is often needed to produce homogeneous products according to their size [100].

In addition to this, ultrafiltration has also come to represent an efficient membrane separation technique for the removal of small molecules/solvents under pressure. Though column chromatography on cellulose columns is capable of producing highly purified polysaccharides, it is limited by low flow rate and efficiency in handling highly viscous samples [101]. This is in contrast to DEAE-Sepharose Fast Flow anion exchange column chromatography, which is more suitable in terms of high flow rate and stability to purify GPs samples [102]. To obtain highly homogeneous polysaccharide samples, further purification by gel permeation chromatography is usually necessary [102]. Overall, to obtain highly purified GPs with specific structural and functional characteristics, extraction techniques in combination with graded precipitations and advanced chromatography techniques, as shown in Table 3.

Table 3.

Purification techniques and structural characterisation of GPs Fraction isolated from different *Ganoderma* spp.

Species	Fraction/Name	Purification Method	Mw (kDa)	Structural Features	Biological Activity	Purity/ total sugar content (%)	Deproteinisation and recovery rate (%)	References
<i>Ganoderma lucidum</i>	GLP _{UD}	DEAE-52+ Sephadex G-100	13.6	Modified structure	Hypolipidemic, antioxidant	76.83 ± 1.52	NA	[38]
<i>Ganoderma atrum</i>	-	Gel-filtration chromatography with Superdex-G 200	1010	β-(1-3)-, (1-6)-Glucose, with α-(1-4)- galactose, α-(1-2)-, α- (1-4)-mannose	-	73.1	NA	[49,103]
<i>Ganoderma lucidum</i>	GLP100	Ultrafiltration + DEAE-Sephacrose + gel filtration	322	β-glucan-rich fraction	Anti-fatigue, antioxidant	NR	NA	[74]

	GLP10	Membrane filtration + DEAE chromatography	18.8	Lower Mw fraction	Moderate bioactivity	NR	NA	
	GLP1	Ultrafiltration + DEAE chromatography	6.4	Low Mw polysaccharide	Reduced activity	NR	NA	
<i>Ganoderma leucocontextum</i>	GLP-1	DEAE + Sephacryl S-300	6.31	Non-triple helix	Strong antioxidant	73.36 ± 1.35	NA	[27]
	GLP-2	Chromatographic purification	14.07	Heteropolysaccharide	Moderate activity	72.45 ± 0.49	NA	
	GLP-3	Gel filtration	159.7	Triple-helix conformation	Immunomodulatory (MAPK, NF-κB)	NA	NA	
<i>Ganoderma sinense</i>	GSPB70-S	DEAE-Sepharose	2.87	Contains N-	α-glucosidase inhibition	95.67	NA	[76]

				acetylglucosamine				
<i>Ganoderma tsugae</i>	GM3	DEAE-Sephacrose CL-6B.	83.5	-	-	NA	Fraction I: 10.8%; Fraction II: 89.2% recovery content	[104]
<i>Ganoderma resinaceum</i>	-	freeze-thawing, dialysis and ultrafiltration	26	High branched β -(1-3)-glucan	-	NA	NA	[105]
<i>Ganoderma lucidum</i>	GLP _{UAE}	DEAE-52 chromatography	465.6	Similar linkage pattern	Antioxidant	84.3 (total sugar); phenolics: 0.17%	NA	[39]

Note: Mw values are expressed as kilodaltons (kDa). Purity and total sugar contents are (%) whenever available from the original studies. NR = not reported; NA = not available.

6. Biological activities

6.1. Antioxidant

GPs have garnered considerable attention owing to their strong antioxidant properties and their potential to combat oxidative stress. Bioactive macromolecules have shown appreciable free radical scavenging, reducing, and chelating properties, thus preventing oxidative damage to cellular components [106,107]. Their potential as therapeutic and nutraceutical agents is further enhanced by emerging research that links antioxidant activity with immunomodulatory and prebiotic-probiotic effects. For instance, polysaccharides from *G. tsugae* demonstrated high antioxidant activity in an in-vitro linoleic acid oxidation system evaluated using the conjugated diene assay, with EC values <0.1 mg/mL and radical scavenging activity ranging from 78.3 and 87.8%, at 0.1 mg/mL, comparable to standard antioxidants such as BHA (89.2%) and α -tocopherol (88.9%). Additionally, DPPH radical scavenging reached 93.7 and 100% at 20 mg/mL, while reducing power ranged from 0.87 to 1.14, indicating a strong electron-donating capacity [16].

GPs exert antioxidant actions via directly scavenging ROS, inhibiting lipid peroxidation, and enhancing endogenous antioxidant defences. Studies have indicated that GPs improve antioxidant enzyme activity, such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), while lowering malondialdehyde (MDA) levels. In differentiated PC12 neuronal cells exposed to H₂O₂-induced oxidative stress, pretreatment with 100µg/ml GL-LPP for 24h significantly reduced intracellular ROS levels, measured using a DCFH-DA fluorescence assay, from 112 ±12 to 101 ±6 fluorescence units compared with the H₂O₂ + PBS-treated control group (p<0.01) [108]. Furthermore, low-molecular-weight β -1,3-glucan (LMG) isolated from *G. lucidum* significantly protected RAW264.7 macrophages against oxidative damage induced by 20µM H₂O₂. Using an MTT assay, co-treatment with 100µg/ml LMG for 24h increased cell viability from 40% to 80% in a dose-dependent manner, while DCFDA fluorescence analysis confirmed a marked reduction in intracellular (ROS) generation compared with H₂O₂-treated control cells [109]. Also, Yang et al. show in their study that GLP, a polysaccharide peptide from *G. lucidum*, assist in the protection of organs during sepsis via the regulation of the Nrf2/NF- κ B signalling pathway. *G. lucidum* polysaccharides increase antioxidant capacity via the Nrf2 signalling pathway, leading to an enhanced antioxidant response with high levels of NQO1 and HO-1. On the other hand, GLP reduce inflammation via the inhibition of the NF- κ B signalling pathway,

leading to decreased TLR4/MyD88 signalling, reduction of NF- κ B p65 phosphorylation, and stabilisation of I κ B α , as shown in **Fig. 5** [110].

Similarly, another *Ganoderma* Spp., *G. leucocontextum*, polysaccharides (GL) GLP-1 (Mw 6.31 kDa, 73.36% carbohydrate) and GLP-2 (Mw 14.07 kDa, 72.45% carbohydrate), exhibited dose-dependent antioxidant activities, with GLP-1 demonstrating superior efficacy. In multiple in vitro cell-free antioxidant assays using vitamin C as the positive control, GLP-1 showed lower IC₅₀ values of 0.56 mg/mL (ABTS), 1.32 mg/mL (hydroxyl radical), and 0.76 mg/mL (superoxide anion), than GLP-2 (1.18, 2.78, and 1.34 mg/mL, respectively $p < 0.05$), although the radical scavenging activity of vitamin C remained comparatively higher. Moreover, GLP-1 exhibited higher TEAC values of 6.85 μ mol/g (FRAP) and 84.8 μ mol/g (ORAC) assay compared with GLP-2 (3.59 and 52.6 μ mol/g, respectively). In NIH3T3 fibroblast cells subjected to tert-butyl hydroperoxide (tBHP)-induced oxidative stress, treatment with GLP-1 (0.5-2mg/ml) significantly enhanced CAT/GSH-Px/GSH/GSSG levels while reducing LDH leakage, intracellular ROS, and MDA accumulation. These protective effects were comparable to those of 80 μ M Trolox, and significantly restored cell viability from 54.4% to approximately 90.5% ($p < 0.05$), as determined using a CCK-8 cell viability assay following 24h incubation [27].

Additionally, a study conducted by Zangeneh et al. (2025) shows that polysaccharides from *G. lucidum* possess a significant association between antioxidant and prebiotic-probiotic activities. Polysaccharides exhibit dose-dependent antioxidant activity; scavenging activity of DPPH was recorded at 92% at 1 mg/mL, which is almost comparable to that of ascorbic acid 97% ($p < 0.05$), and hydroxyl radical inhibition was recorded at levels > 15 mg/mL. On the other hand, the prebiotic activities of the polysaccharides involve the promotion of probiotic bacteria such as *Lactobacillus* and *Lactococcus*; optical density is increased during the initial incubation period (0-12 h). The polysaccharide content was found to be high at 361.37 μ g/mg, and this was found to possess better bioactivity. Overall, this study proves that polysaccharides from *G. lucidum* possess symbiotic activity, which includes antioxidant activity and probiotic activity [111]. Based on *in vitro* tests and animal studies, GPs are strong natural antioxidants. They work in multiple ways, scavenging free radicals, boosting cell defences, and helping gut microbiota to fight oxidative stress.

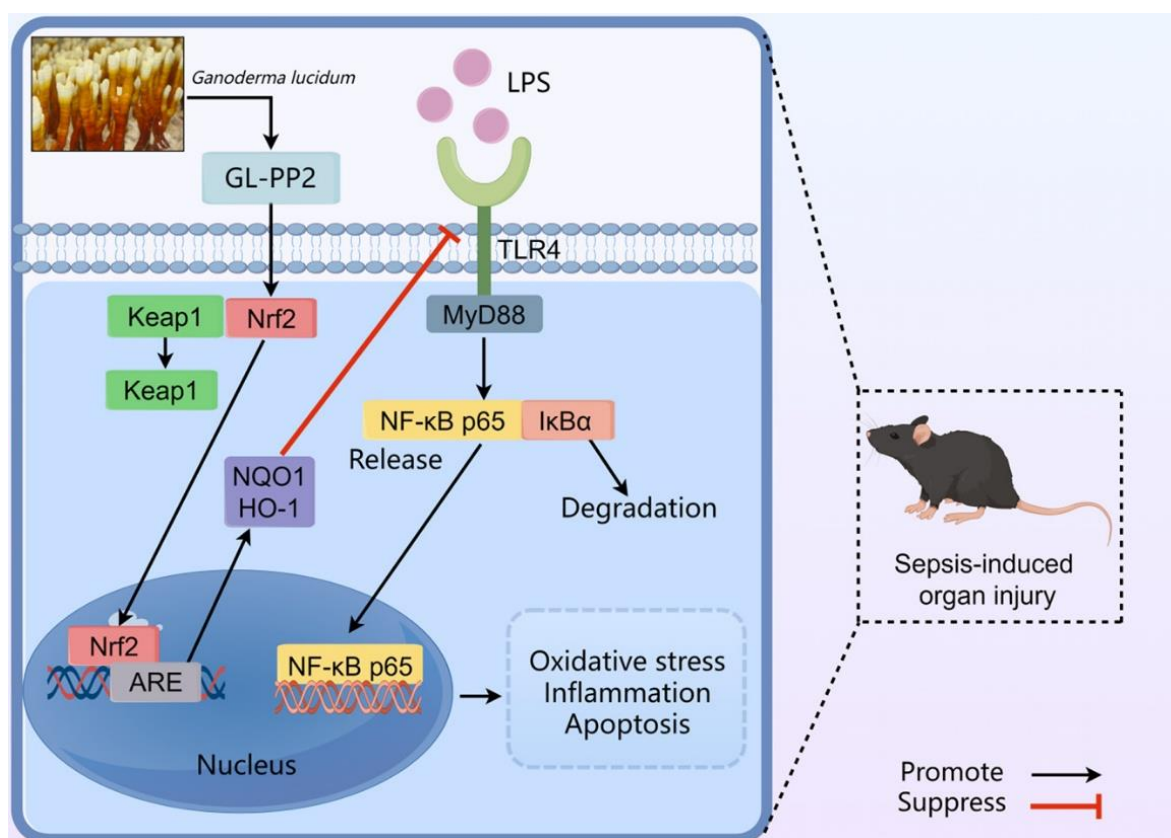


Fig. 5 Protective mechanism of GLP against sepsis-induced organ injury through modulation of the Nrf2 and TLR/MyD88/NF-κB signalling downstream antioxidant enzyme, including NQO1 and HO-1, while suppressing TLR4-mediated inflammatory signalling, thereby reducing oxidative stress, inflammation and apoptosis. Reprinted with permission from Ref. [110]. Abbreviation: LPS, lipopolysaccharide; tlr4, toll-like receptor 4; MyD88, myeloid differentiation primary response protein 88; NF-κB, nuclear factor kappa B; IκBα, inhibitor of κB alpha; Nrf2, nuclear factor erythroid 2-related factor 2; Keap 1, Kelch-like ECH-associated protein 1; ARE, antioxidant response element; NQO1, NAD(P)H quinone oxidoreductase 1; HO-1, heme oxygenase-1.

6.2. Antidiabetic

Diabetes mellitus leads to high blood sugar, insulin resistance, and problems with how the body uses glucose, causing organ issues eventually. Recent studies show that oxidative stress is super important in causing diabetes, too. This stress makes ROS rise and causes redox imbalances in diabetic models [112]. Under normal conditions, the endogenous antioxidant system maintains equilibrium between ROS generation and scavenging. However, in streptozotocin-induced diabetes, both enzymatic (SOD, CAT, GPx) and non-enzymatic antioxidant defences are significantly compromised [113]. Hyperglycemia, insulin resistance,

and an inability to control the body's normal glucose metabolism are the major characteristics of type 2 diabetes [114]. GPs, a naturally occurring biomacromolecule, have been demonstrated to alleviate type 2 diabetes; this action is intimately linked to gut microbiota regulation.

In this context, polysaccharides derived from *G. lucidum* have demonstrated significant hypoglycemic potential. These compounds enhance plasma insulin levels while reducing blood glucose concentration [115]. Additionally, Xiao examined the effects of administering 50 and 100 mg/kg/day of GLP for seven days to mice with streptozotocin-induced diabetes. The concentration of fasting blood glucose, insulin, and epididymal white adipose tissue all sharply decreased. The amounts of mRNA in the liver were significantly reduced for glycogen phosphorylase (EC 2.4.1.1), fructose-1,6-bisphosphatase (EC 3.1.3.11), phosphoenolpyruvate carboxykinase (EC 4.1.1.49), and glucose-6-phosphatase (EC 3.1.3.9, G6Pase) [116].

Experimental studies using alloxan-induced diabetic Wistar rats have further confirmed their efficacy. For two weeks, the ethyl acetate and n-butanol fraction of *G. lucidum* aqueous extract was administered intraperitoneally at 50 mg/kg to alloxan-induced Wistar rats, with insulin (6IU/kg i.p.) serving as the positive comparator. Pre-treatment fasting blood glucose levels confirmed successful diabetes induction across all groups, ranging from 322.2 to 395.4 mg/dL on day 1, all exceeding the 200mg/dL inclusion threshold. After 1 and 2 weeks of treatment, fasting blood glucose in the ethyl acetate-treated group fell significantly ($p < 0.05$) to 188.8 ± 19.51 mg/dl and 162.8 ± 24.67 mg/dl, respectively. Similarly, the n-butanol fraction produced a significant ($p < 0.05$) reduction to 182.2 ± 56.09 mg/dl at week 1 and 148.8 ± 32.82 mg/dl at week 2. Notably, the insulin comparator group, while showing a significant reduction at day 7 (197.6 ± 31.56 mg/dl, $p < 0.05$), failed to maintain statistical significance at day 14 (210.6 ± 58.28 mg/dL), suggesting that both plant fractions achieved more sustained glucose lowering than the insulin control at the doses tested. However, these findings are derived from alloxan-induced rodent models and should be interpreted with caution, as animal models may not fully replicate human diabetic physiology. Clinical validation through randomised controlled trials is necessary before any therapeutic superiority can be claimed [117]. Beyond direct metabolic regulation, these polysaccharides also exert beneficial effects through modulation of gut microbiota. Notably, they enhance the abundance of beneficial microbes such as *Akkermansia*

muciniphila, which is associated with improved insulin sensitivity and reduced obesity-related metabolic dysfunction [118].

6.3. Hepaprotective

Polysaccharides that are obtained from *Ganoderma* mushrooms have been shown to have substantial hepatoprotective activity. It has been demonstrated that bioactive macromolecules have a protective role to play in liver injuries. This is done through various mechanisms that influence oxidative stress, inflammation, lipid metabolism, and fibrogenesis. The research findings have shown that GPs have a protective role to play in liver injuries.

6.3.1. Non-alcoholic fatty liver disease (NAFLD)

Two examples of chronic liver diseases include non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD), both of which are characterised by excessive fat deposition in the liver brought on by factors other than alcohol, medications, or hereditary problems. Hepatocellular carcinoma (HCC) or cirrhosis may occur as NAFLD gets worse [119]. NAFLD's pathophysiology is complicated and still poorly understood. NAFLD is caused by several factors, including oxidative stress, inflammation, dysregulated lipid metabolism, and an imbalance in the gut microbiota [120].

New research confirms that GLP helps treat NAFLD through various methods, like what's shown in Fig. 6. We know an off-balance gut microbiome and a weakened gut barrier can contribute to NAFLD. With NAFLD, these issues lead to more bacterial substances in the liver, causing chronic endotoxemia and messing up the gut-liver connection in the body [121]. The formation of fat in the liver and steatosis in hepatocytes, which are associated with the regulation of imbalance in gut microbiota and dysfunction in gut barrier function, were significantly reduced by using polysaccharides with a molecular weight higher than 3×10^5 Da from *G. lucidum* mycelia. These included a decrease in the Firmicutes/Bacteroidetes ratio, endotoxin-containing *Proteobacteria*, and metabolic endotoxemia [122].

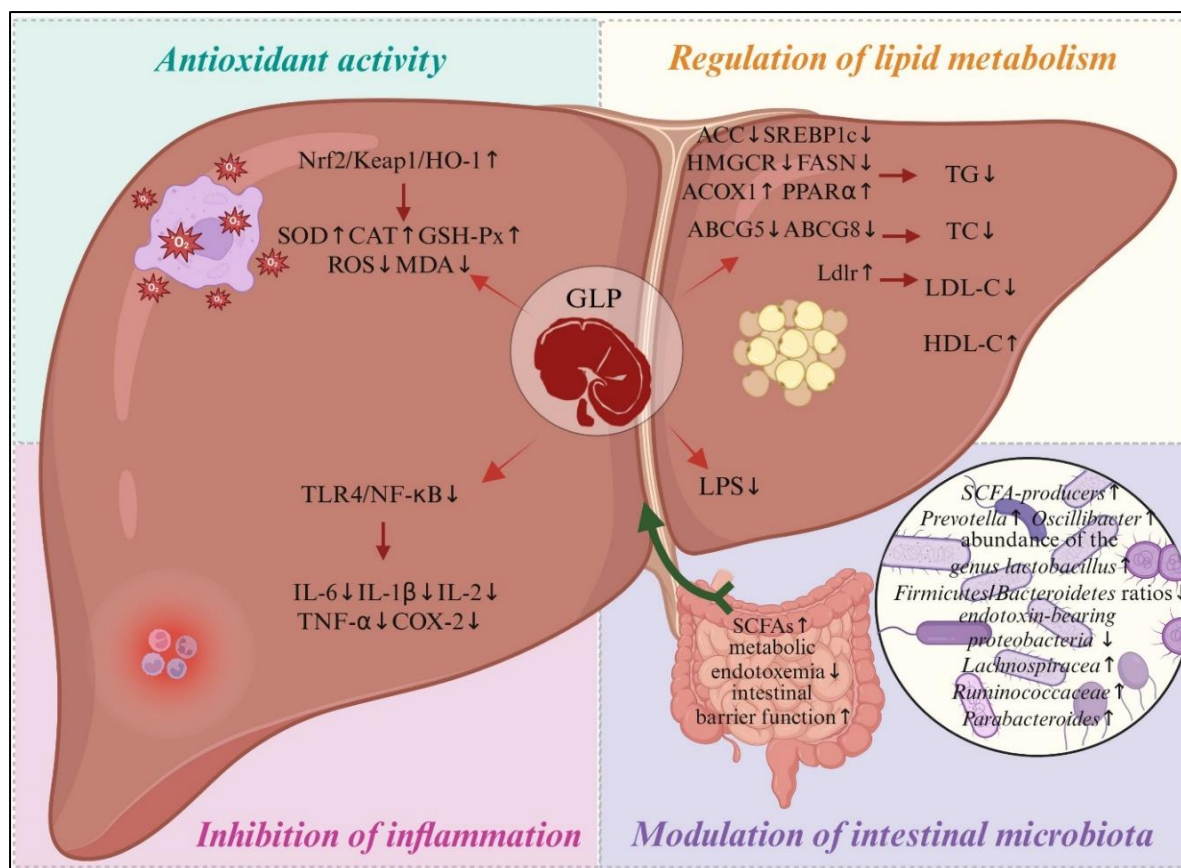


Fig. 6. Mechanisms of the underlying protective action of polysaccharides of *G. lucidum* concerning their antioxidative, anti-inflammatory, lipid metabolism, and probiotic effects. Isolation polysaccharides of *G. lucidum* are involved in the protective mechanisms in hepatocytes via several mechanisms: Nrf2/Keap1/HO-1 signalling pathways activation, production of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px), reducing ROS (reactive oxygen species) and MDA (malondialdehyde). Anti-inflammatory mechanism of isolated polysaccharides of *G. lucidum* is caused by affecting the TLR4 (toll-like receptor)/NF-κB (nuclear factor kappa B) pathway and also suppressing pro-inflammatory factors IL-6 (interleukin-6), IL-1β, TNF-α (tumour necrosis factor-alpha), and COX-2 (cyclooxygenase). The regulation of lipid levels in the liver with the help of isolated polysaccharides of *G. lucidum* happens through the regulation of ACC (acetyl-CoA carboxylase), Sterol Regulatory Element. Reprinted with permission from Ref. [123] (open access).

GPs control oxidative stress and lipid metabolism in addition to microbiota. Fudan-Yueyang *G. lucidum* (FYGL), a hyperbranched proteoglycan made of lipophilic protein and hydrophilic polysaccharide, has shown protective benefits against steatosis caused by palmitic acid in HepG2 hepatocytes [124]. By activating AMP-activated protein kinase

(AMPK) and acetyl-CoA carboxylase (ACC), which subsequently suppress the expression of fatty acid synthase and sterol regulatory element-binding protein-1 (SREBP1), FYGL significantly reduces levels of total cholesterol (TC) and triglycerides (TG). Additionally, FYGL increases the expression of CPT-1, which facilitates fatty acid oxidation. Additionally, it possesses antioxidant properties, increasing total antioxidant capacity and superoxide dismutase (SOD) activity while lowering levels of reactive oxygen species (ROS) and malondialdehyde (MDA) [125].

Other species within the genus *Ganoderma* also demonstrate hepatoprotective potential. For instance, polysaccharides isolated from *G. amboinense* (GAP) have shown protective effects against NAFLD in high-fat-diet-induced mouse models. Administration of GAP for eight weeks significantly reduced body weight, liver weight, and serum lipid levels while delaying NAFLD progression. Metabolomic analysis revealed that GAP regulates phosphatidylcholine metabolism and improves mitochondrial function, thereby promoting hepatic lipid catabolism and maintaining cellular energy homeostasis [126].

Moreover, abnormal lipid metabolism is a major contributor to NAFLD development and is considered a critical precursor to hepatic steatosis [127]. Several studies have shown that GLP administration (100-500 mg/kg) significantly reduced plasma triglycerides, TC, and LDL-C levels while increasing HDL-C levels in high-fat diet-induced Sprague-Dawley rats ($p < 0.05$). At 300mg/kg, serum TG, TC and LDL-C levels decreased to 1.73 ± 0.47 , 0.79 ± 0.12 , and 1.83 ± 0.11 mmol/L, respectively, whereas HDL-C increased to 1.83 ± 0.24 mmol/L, accompanied by reduced liver weight and hepatic lipid accumulation [128]. Furthermore, Xu et al. [38] isolated GLP ($M_w = 3.06 \times 10^6$ Da) and degraded polysaccharides fraction (GLP_{UD}, $MW = 13.6 \times 10^3$ Da) from the fruiting body of *G. lucidum*. Compared with GLP, GLP_{UD} significantly reduced TC, TG, and LDL-C levels by 98.5% ($p < 0.01$), indicating superior hypolipidemic activity. Overall, these findings suggest that GPs exert hepatoprotective effects against NAFLD through modulation of lipid metabolism, antioxidant defence system, gut microbiota, and mitochondrial function. Nevertheless, the majority of these findings are based on in vitro cell models and high-fat diet animal studies. Robust human clinical evidence supporting GPs as a hepatoprotective intervention for NAFLD remains limited, and further randomised clinical trials are warranted.

6.3.2. Liver fibrosis

Fibrosis is a pathological condition characterised by the excessive accumulation of extracellular matrix components (ECM) within tissue, which progressively disrupts normal organ structure and function and may ultimately result in organ failure and death. Fibrotic diseases are estimated to be responsible for nearly 45% of deaths in developed countries [129]. Hepatic fibrosis is an abnormal and progressive deposition of ECM proteins, especially collagen, within liver tissues. The incidence and mortality rates of hepatic fibrosis resulting from various etiological conditions are still on the rise globally. Despite advances in understanding the pathogenesis of hepatic fibrosis, effective pharmacological interventions are still not available, and liver transplant remains the only effective treatment option, which is still beset with numerous limitations and potential dangers to patients [130]. As shown in **Fig. 7**, GLP has been proven to play a role in the amelioration of hepatic fibrosis through various mechanisms.

In the normal liver tissue, the formation and breakdown of ECM components are in a balanced equilibrium; any alteration in this equilibrium leads to excessive ECM accumulation and fibrotic development. The extract of *G. lucidum* has demonstrated potential in the prevention and treatment of formaldehyde (FA)-induced liver fibrosis [131]. Biochemical markers such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP), where elevated enzyme levels are strongly linked to liver damage and fibrogenesis, were used to evaluate the hepatoprotective efficacy [132]. *G. lucidum* triterpenes significantly regulated liver injury markers, such as ALT, AST, superoxide dismutase (SOD), malondialdehyde (MDA), and glutathione (GSH), according to studies using D-galactosamine (D-GalN)-induced liver fibrosis. Histopathological analysis revealed that 180 mg/kg was the ideal hepatoprotective dose of total triterpene extract activity [133,134]. Similarly, by lowering the amount of fibrinogen (FIB) and collagen fibre deposition in the liver, GLP extracted from the fruiting body of *G. lucidum* was administered at 50, 100, and 200 mg/kg/day-1 for 8 weeks, successfully reducing carbon tetrachloride (CCl₄)-induced liver fibrosis [123]. GLP-extracted, sporoderm-removed *G. lucidum* spores were found to significantly reduce collagen deposition and hydroxyproline (Hyp) synthesis in CCl₄-induced rats, decreasing the degree of liver fibrosis [135].

In addition to regulating ECM accumulation, GLP also exerts anti-inflammatory effects, which are particularly important because hepatic fibrosis is frequently associated with inflammatory injury [136]. The immune system plays a critical role in mediating immune-cell infiltration that contributes to inflammation-driven fibrogenesis [137]. Oral GLP dosing (150

and 300 mg/kg day⁻¹) for six weeks considerably reduced pro-inflammatory cytokine levels, such as TNF- α , IL-1 β , and IL-6, in both serum and liver tissues in a CCl₄-induced mouse model, therefore attenuating hepatic fibrosis [135]. Overall, these findings suggest that GLP exerts antifibrotic effects through coordinated regulation of ECM remodelling, oxidative stress, and inflammatory signalling pathways, highlighting its potential as a promising therapeutic candidate for the prevention and management of hepatic fibrosis. It should be noted, however, that current evidence is largely confined to CCL₄-induced murine fibrosis models. Translation of these findings to clinical hepatic fibrosis treatment requires well-designed trials with standardised GP preparations.

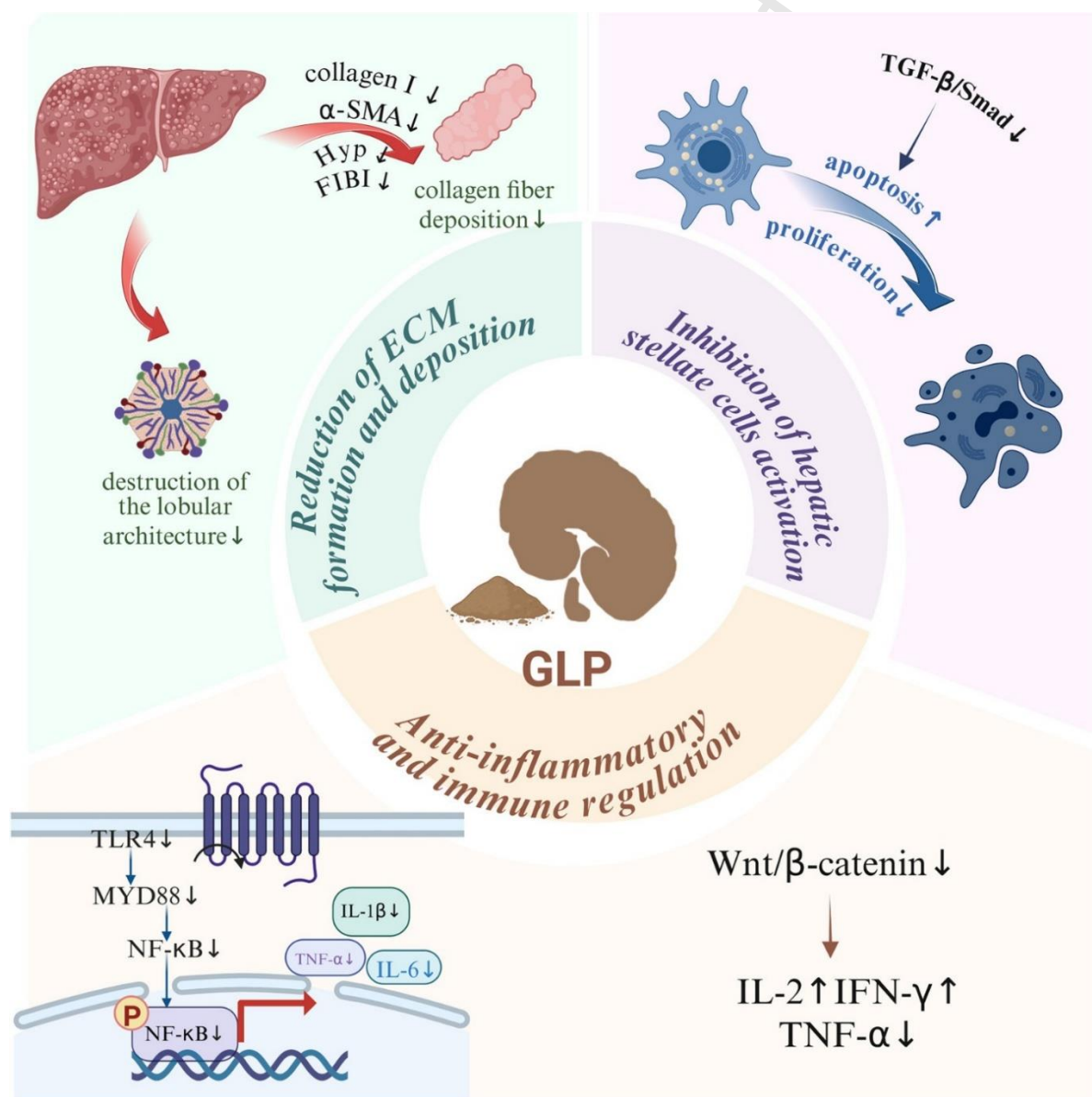


Fig. 7. Proposed anti-fibrotic mechanism of GLP. It attenuates liver fibrosis by suppressing extracellular matrix (ECM) formation and collagen deposition, inhibiting hepatic stellate cell

activation through modulation of the transforming growth factor-beta (TGF- β)/Smad signalling pathway, reducing inflammatory responses via inhibition of the toll-like receptor 4 (TLR4)/myeloid Differentiation Primary Response Protein 88 (MyD88)/nuclear factor kappa B (NF- κ B) pathway, and regulating immune response through the wntless-related integration site (Wnt)/ β -catenin signalling pathway. These effects collectively contribute to the prevention of hepatic fibrogenesis and restoration of liver architecture. Reprinted with permission from Ref. [123] (open access). Abbreviation: GLP, *Ganoderma lucidum* polysaccharides, α -SMA, alpha-smooth muscle actin; Hyp, hydroxyproline; FIBI, fibrosis index; IL, interleukin; TNF- α , tumour necrosis factor- α .

6.4. Immunomodulation activity

GPs have received much attention for their multifunctional roles in immunological modulation. GPs have received much research interest because of their potential to influence the immune system via multiple pathways **Fig. 8**. GPs have a high affinity for immunological receptors, including Dectin-1, MR, CR, TLR2, and TLR4, suggesting their potential for immunomodulation [138]. Structurally, β -glucans such as β -1,3-D-glucan with β -1,6-glucose side chains, derived from *Ganoderma* spores, play a crucial role in receptor binding and activation of downstream signalling cascades. Specifically, the rigid triple-helical conformation and high molecular weight of these β -glucans are critical for optimal Dectin-1 engagement, as they present repetitive β -glucans epitopes that promote receptor clustering and Sky-mediated CARD9 activation. This leads to NF- κ B nuclear translocation, AP-1 activation via MAPK cascades (p38, JNK, ERK), and subsequent transcription of pro-inflammatory cytokines, including TNF- α , IL-6, and IL-2, collectively enhancing immune cell activation and cytokine production [139,140].

At the cellular level, Lin et al. found that GLP have been reported to activate and promote the maturation of human monocyte-derived dendritic cells through NF- κ B and MAPK signalling pathways, a process mechanistically dependent on TLR2/MyD88 engagement that upregulates co-stimulatory molecules (CD80, CD86) and MHC-II expression, thereby bridging innate and adaptive immunity. GLPs also enhanced neutrophil chemotaxis and phagocytic activity via phosphorylation of p38 MAPK, Src, PI3K, and protein kinase C, which collectively reorganise the actin cytoskeleton and activate NADPH oxidase-driven respiratory bursts for pathogen killing. Additionally, *G. lucidum* cell-wall polysaccharides significantly stimulated TNF- α , IL-2, and IFN- γ production in human peripheral blood

mononuclear cells (PBMCs) at 100µg/ml ($p<0.05$), with extracellular fraction A-g inducing up to 4348 pg/ml IL-2, and 7534 pg/ml IFN- γ , while β -glucan fraction B- β produced the highest TNF- α level (2413 pg/ml) [141]. Similarly, β -d-glucan from *G. sinense* has been shown to stimulate B-cell proliferation, inflammatory cytokine production from mononuclear and dendritic cells, and nitric oxide production from RAW264.7 cells [68]. Moreover, GLP-3, a water-soluble polysaccharide from *G. leucocontextum* with a molecular weight of 159.7 kDa, significantly stimulated RAW264.7 macrophage activity at 50-200µg/ml without cytotoxicity (cell viability remained above control levels up to 400µg/ml). It enhanced phagocytosis, nitric oxide production and cytokine secretion while increasing JNK, ERK, p38MAPK and Akt phosphorylation by 3.455-10.57fold ($p<0.05$) [142].

In vivo and clinical studies further support these findings. Administration of β -d-glucan has been reported to increase total lymphocyte counts in the peripheral blood of asymptomatic children aged 3-5 years following 12 weeks of supplementation (4433.6 ± 1266.5 vs. 3876 ± 1252.1 cells/ μ L; $p=0.0015$) without causing significant adverse haematological or biochemical effects [143]. GPs β -d-glucan supports spleen and thymus function and boosts IgA levels in cyclophosphamide-induced immunosuppressed mice ($p<0.01$), indicating notable immunostimulatory activity [29]. Collectively, these findings demonstrate that GPs exert immunomodulatory effects through a well-defined receptor-signalling axis, GP binding to Dectin-1, TLR2/TLR4, and CR3 activates Syk, CARD9, and TRIF adaptors, which converge on NF- κ B, MAPK (ERK/JNK/p38), and PI3K/Akt pathways to drive pro-inflammatory cytokine transcription and enhance both innate and adaptive immune cell functions. These mechanistically diverse and interrelated pathways emphasise GPs as prospective immune regulators, with further research needed to investigate their therapeutic uses and synergistic potential with existing immunotherapies in inflammatory and autoimmune illnesses. It should be noted that clinical evidence supporting GP-mediated immunomodulation in humans is minimal; the majority of mechanistic data comes from in vitro and animal investigations, with limited support from small-scale clinical studies.

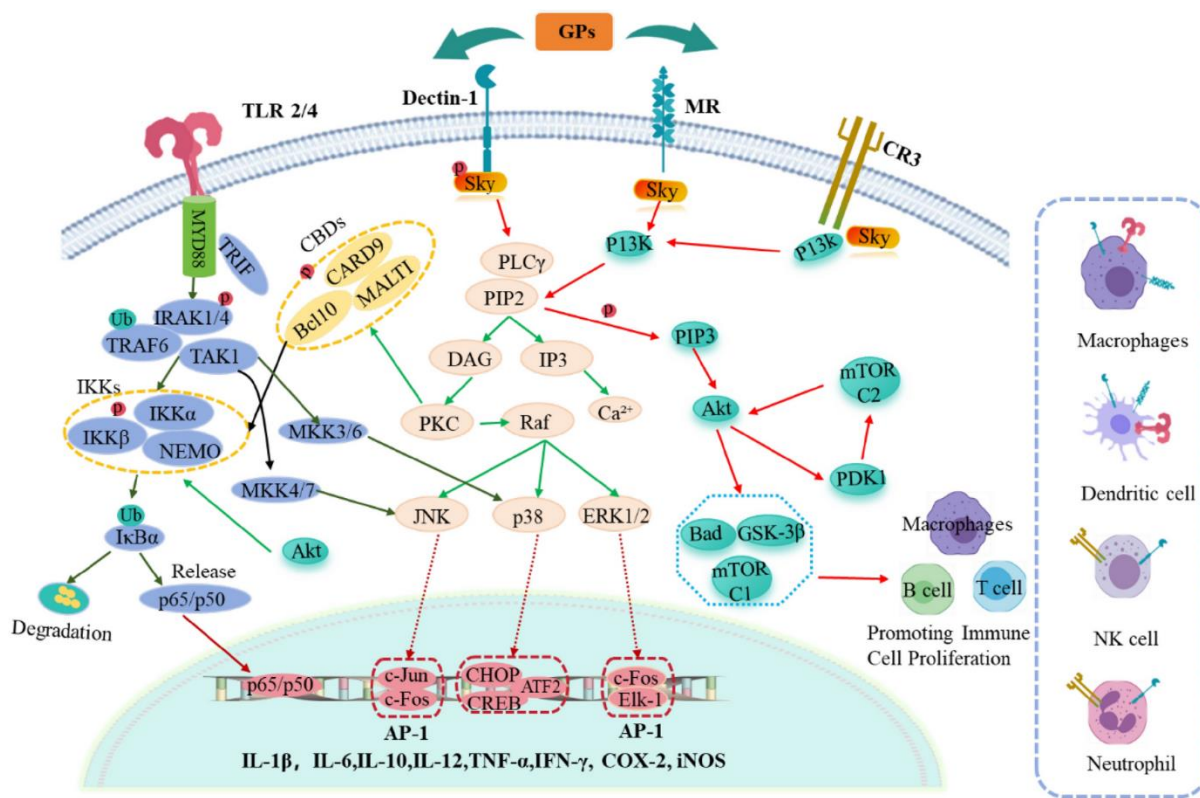


Fig. 8. Possible immunomodulatory mechanisms of GPs. The interaction of GPs with immune receptors, Dectin-1(dendritic cell-associated C-type Lectin-1), MR (mannose receptor), CR3 (complement receptor 3), and TLRs (toll-like receptor), has been demonstrated. The receptors activate immune cells via various pathways, like NF- κ B (nuclear factor kappa B), MAPK (mitogen-activated protein kinase), and PI3K/Akt (phosphoinositide 3-kinase/protein kinase B) [144]. The activation of immune cells like macrophages, DCs (dendritic cells), T cells, B cells, NK (natural killer) cells, neutrophils, etc., has been shown. The immune cells that are activated express pro-inflammatory cytokines like TNF- α , IL-1 β , IL-6, and IFN- γ . These cytokines activate immune cells for growth, activation, and phagocytosis. These cytokines are produced by immune cells like macrophages and DCs. In addition, pro-inflammatory cytokines activate tumour cell growth inhibition through apoptosis and angiogenesis. For example, Gl-BSP, a polysaccharide from *G. lucidum*, has been shown to significantly enhance the cytotoxicity of NK cells and T cells. This enhances tumour cell growth inhibition through the upregulation of IFN- γ and TNF- α . IFN- γ activates macrophages and NK cells to enhance their cytotoxicity. Also, TNF- α induces apoptosis in tumour cells and disrupts vascular structure.ir cytotoxicity. Moreover, TNF- α induces apoptosis in tumour cells and disrupts the vascular structures in tumours. In addition, the PI3K/Akt pathway is related to T cell and B cell growth and survival. Furthermore, activation

of the mTOR (mammalian target of rapamycin) C1 pathway is related to immune cell growth. All these signalling pathways activate immune cells, which induce a strong immune response to modulate the tumour microenvironment to induce antitumor immunity [23].

6.5. Anticancer activity

Polysaccharides from *Ganoderma* spp., particularly GLPs, have exhibited potential therapeutic benefits in the management and treatment of cancer. GLPs exhibited anti-cancer potential against different cancer cell lines. GLPs exhibited anti-proliferative potential against different cancer cell lines. GLPs exhibited anti-migration and anti-invasive potential against different cancer cell lines. GLPs exhibited anti-proliferative potential against human osteosarcoma cell lines MG-63 and U2-OS. GLPs exhibited anti-proliferative potential against aggressive human cancer cell lines, such as human triple-negative breast cancer cell lines MDA-MB-231. GLPs exhibited anti-proliferative potential against aggressive human cancer cell lines, such as human melanoma cell lines B16-F10. GLPs exhibited strong anti-cancer potential against human gastric and hepatic cancer cell lines MKN28, AGS, NCI-N87, HepG2, BEL-7402, and Huh-7. GLPs exhibited anti-apoptotic potential against different cancer cell lines. GLPs exhibited cell cycle arrest in the G1 phase. GLPs exhibited enhanced anti-proliferative potential, particularly the sulfated polysaccharide fractions of GLPs [145–147]

These findings are further supported by in vivo data showing substantial antitumor activity of GLPs. GLPs are found to show dose-dependent tumour growth inhibition and tumour weight reduction in sarcoma-bearing mice after oral administration. Moreover, studies using Hepa1-6 allograft tumour models further show that GLPs can suppress tumour growth while increasing immune activation markers such as CD86 [148]. Mechanistically, GLPs regulate multiple intracellular signalling pathways associated with tumour cell survival and apoptosis **Fig. 9.** The process is activated intrinsically by mitochondrial membrane depolarisation, cytochrome c release into the cytosol, and formation of the apoptosome complex (cytochrome c / Apaf-1 / caspase-9), which results in the activation of the executioner caspases, caspase-3 and caspase-7. Extrinsically, GLP modulates the production of Fas/FasL and TRAIL death receptors, which activates caspase-8 and causes Bid cleavage for signal amplification. cAMP/PKA-regulated signal transduction impairs ERK signalling and promotes pro-apoptotic gene expression [149].

In addition to direct cytotoxic effects, GLPs exert pronounced immunomodulatory activities that contribute to tumour suppression. They promote macrophage polarisation toward the pro-inflammatory M1 phenotype while suppressing M2 polarisation via MAPK signalling, leading to increased expression of iNOS, IL-12, IL-23, IL-27, and TNF- α , and decreased expression of CD206, Arg-1, IL-10, and IL-6. Molecular Mechanism of Action GLP-induced activation of MAPK (ERK/p38) signalling in TAMs leads to the inhibition of STAT6 phosphorylation and IL-4/IL-13-driven M2 polarisation, whereas it stimulates the transcription by NF- κ B of M1-associated factors [148]. Furthermore, activation of CD68⁺ macrophages enhances the secretion of IL-6, IL-1 β , and TNF- α , while reducing IL-13-mediated immunosuppression by natural killer T (NKT) cells, thereby improving tumour immune surveillance and supporting synergistic therapeutic approaches such as photothermal immunotherapy [150]. Furthermore, TNF- α produced by activated M1 macrophages and NK cells triggers tumour cell apoptosis via the TNFR1/TRADD/FADD/caspase-8 signalling pathway and impairs tumour angiogenesis by blocking VEGF-dependent endothelial cell survival, while IFN- γ generated by NK and T lymphocytes stimulates JAK1/2-STAT1 signalling for improving cytotoxicity [23]. Collectively, these findings highlight GLPs as promising multifunctional agents for cancer therapy, integrating direct anticancer effects with immune-mediated tumour suppression. However, it is important to note that the majority of the anticancer evidence presented here derives from in vitro cell line studies and murine allograft models. No large-scale clinical trials have yet confirmed the efficacy of GLPs as a standalone cancer therapeutic in humans, and these findings should be regarded as preclinical.

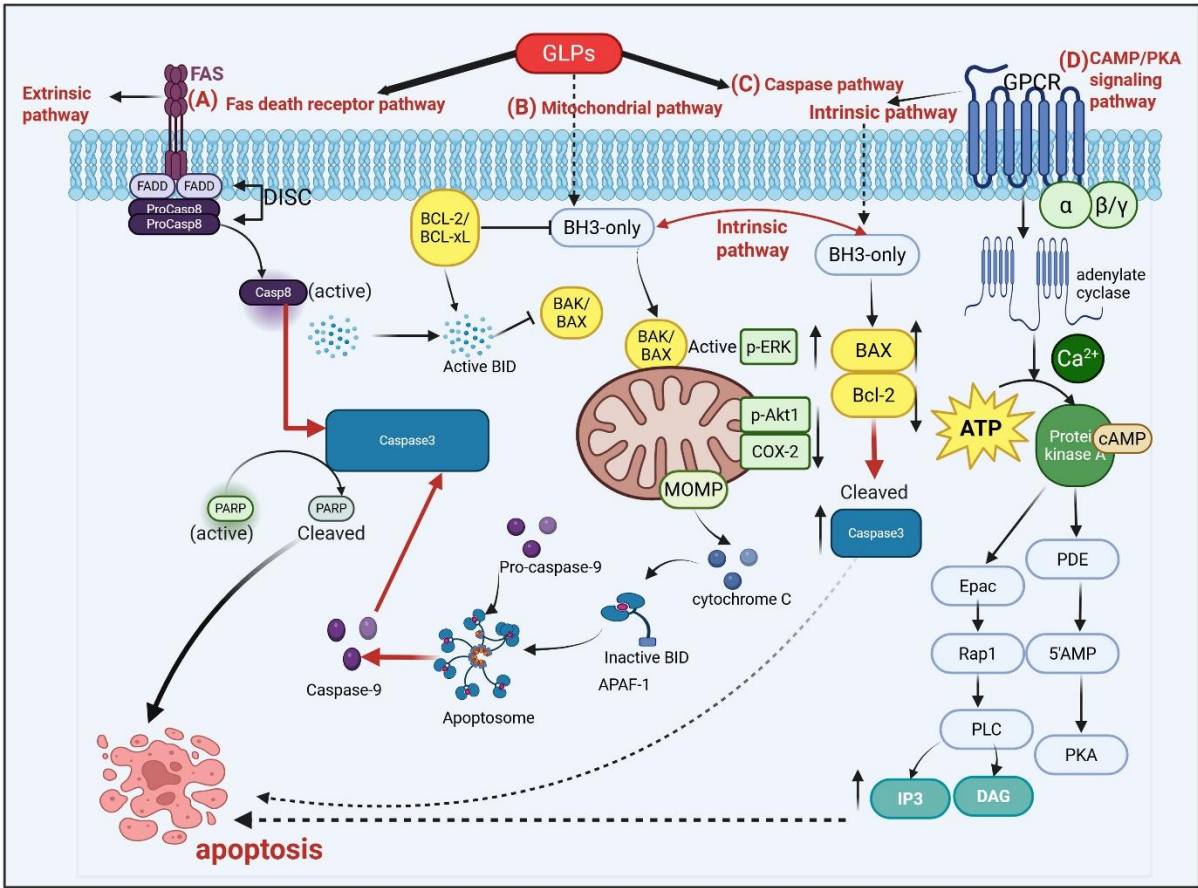


Fig. 9. Proposed molecular mechanisms underlying the anticancer and apoptosis-inducing effects of GLP through Fas receptor-mediated, mitochondrial, caspase-dependent, and cAMP/PKA signalling pathways. Reprinted with permission from Ref. [149] (open access). Abbreviations: Fas, Fas cell surface death receptor; FADD, Fas-associated death domain; DISC, death-inducing signalling complex; Bcl-2, B-cell lymphoma 2; BID, BH3 interacting-domain death agonist; BH3, Bcl-2 homology 3; BAK, Bcl-2 antagonist/killer; BAX, Bcl-2-associated X protein; MOMP, mitochondrial outer membrane permeabilization; APAF-1, apoptotic protease-activating factor1; PARP, poly(ADP-ribose) polymerase; GPCR, G protein-coupled receptor; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; PDE, phosphodiesterase; Epac, exchange protein directly activated by cAMP; PLC, phospholipase C; IP3, inositol 1,4,5-trisphosphate; DAG, diacylglycerol; ATP, adenosine triphosphate; COX-2, cyclooxygenase-2; ERK, extracellular signal-regulated kinase.

7. Gut Microbiota Modulation and Metabolic Utilisation of GPs

The human gut is a highly complex system with trillions of microbes, forming a dynamic microbial community with various axes of multidirectional communication with different

organs in the human body [151]. The microbiota of the gut refers to the diverse array of microbial species found in the GI tract, and the microbiome refers to the combined genetic material of all the microbes [152]. Among the dominant phyla of microorganisms, *Firmicutes* and *Bacteroidetes* are major populations in the gut. The modulation of these populations by prebiotics is increasingly being accepted as a potent approach to maintain gut homeostasis and to prevent disorders of metabolism and inflammation [153]. Furthermore, gut microbiota creates a variety of metabolites that play key functions in host physiology.

The microbiota-regulating activities of GPs involve both direct prebiotic effects and secondary immunometabolism response mediated by microbial metabolites. Resistance of GPs to enzymatic breakdown makes them a suitable substrate for selective fermentation by gut flora and leads to the increased growth of probiotics, such as *Bifidobacteria*, *Lactobacilli*, *Akkermansia* and so on, producing SCFAs, and hence makes GPs good candidates for prebiotics. This selection of microbes due to the introduction of GPs is considered to be one of the main prebiotic effects of GPs [154]. Furthermore, many of the physiological actions of GPs depend on their fermentation products, such as acetate, propionate, and butyrate, activating host mediators: G-protein-coupled receptors (GPR41/GPR43), NF- κ B and MAPK signalling pathways, and TLR-dependent immune response [155]. Several works have identified substantial associations between changes in gut microbiota induced by GPs and several physiological characteristics (metabolic and inflammatory) [156]. However, the evidence available currently still relies on correlations alone, and there have been no confirmed cases of causality between changes brought about by the gut microbiota and physiologic improvements [157]. Despite many scientific investigations on the relationship between the impact of GP modification on metabolic, immune and inflammatory results, the current literature mostly provides correlational data, without providing definitive causative proof. Consequently, future research involving germ-free and antibiotic depletion models, FMTs and multi-omics approaches is needed to determine the causative microbiota-host interactions associated with the physiological benefits mediated by GP manipulation. However, germ-free and gnotobiotic models are characterised by intrinsic interpretative difficulties, including immune system development abnormalities, altered gastrointestinal physiology, and lack of the complex multi-species interactions seen in the conventional microbiota [158]. The results obtained from these models might not completely reflect the interaction of the host-microbiota under physiological conditions, and human implications of rodent studies should be carefully inferred.

Compared with other well-studied bioactive polysaccharides such as Inulin, Pectin, and Fucoidan, GPs exhibit several distinctive structural and functional characteristics. Inulin has proven itself to be a classical fermentable prebiotic that selectively boosts beneficial commensal flora of the gut, including *Bifidobacterium* and *Lactobacillus* species, causing an increase in total concentration of SCFAs in in vitro and in vivo fermentation experiments [159,160]. Pectin has been known for its intensive production of SCFAs, including acetate and propionate, along with stimulation of the abundance of butyrate-producing bacteria and improvement of intestinal mucosal barrier function and decrease in postprandial plasma glucose concentrations [161,162]. On the other hand, fucoidan, being a sulfated marine polysaccharide composed of sulphur-containing chemical groups with molecular weights from 10-10,000 kDa, has relatively higher anticoagulant, antiviral, anti-cancer, and immunomodulating actions due to its marine nature and sulfated structure [163,164]. It has been proven that fucoidan significantly inhibits tumour growth and development of neo angiogenesis, which can be related to high biological activities caused by the degree of sulfation and molecular weights [165]. GPs have unique properties of selective prebiotics, and at the same time, they are direct immunomodulators via the mechanisms of Dectin-1, TLR, NF- κ B, and MAPK-dependent pathways [139,140].

Experimental studies increasingly support the microbiota-modulating potential of GPs in different metabolic and disease models. In a high-fat diet-induced hyperlipidaemic rat model, oral administration of *G. lucidum* polysaccharide peptides (GLPP; 150mg/kg/day for 8 weeks) significantly reduced body weight gain from 228.43 $\pm$ 16.68g to 166.08 $\pm$ 21.63g and altered gut microbial composition by increasing *beneficial* *Alloprevotella*, *Parabacteroides*, *Parasutterella*, *Alistipes*, *Barnesiella*, *Bacteroides* and *Bacteroidales* S24-7, while reducing dysbiosis-associated genera such as *Blautia*, *Enterorhabdus*, and *Roseburia*. These microbial changes were associated with increased SCFA production, particularly butyrate, together with reductions in serum triglycerides, TC, LDL-C, hepatic lipid accumulation and inflammatory injury markers [166]. In ovariectomised (OVX) mice, GLP supplementation (100-400mg/kg/day for 8 weeks) significantly attenuated abnormal weight gain, decreased fat mass, and improved serum lipid profiles while restoring gut microbiota dysbiosis associated with estrogen deficiency. OVX mice exhibited reductions in beneficial *Bifidobacterium* and *Lactobacillus* populations together with enrichment of pathogenic taxa, including *Klebsiella* and *Clostridioides difficile*, whereas GLP intervention partially restored microbial

homeostasis and improved liver metabolic parameters through modulation of the gut-liver axis [154].

Similarly, in high-fat diet-induced dyslipidaemia mice, GLP administration (400mg/kg/day for 16 weeks) significantly decreased the *firmicutes/Bacteroidetes* ratio and increased gut microbial richness, as reflected by the chao1 diversity index. LEfSE analysis identified 10 key microbial biomarker strains enriched following GLP treatment, which were associated with enhanced energy metabolism, amino acid metabolism, lipid metabolism and cell growth pathways. Structural characterisation showed that GLP has a molecular weight of 12.53 kDa and contains both α and β -glycosidic linkages. This suggests that its structure could help with selective microbial use and prebiotic activity [167]. In a study using a murine 4T1 breast cancer model, adding spore-derived GLP (SGP) at 200-400 mg/kg/day alongside paclitaxel changed the gut microbiota. It increased helpful bacteria like *Bacteroides* and *Ruminococcus*, while reducing cancer-linked ones such as *Desulfovibrio* and *Odoribacter*. These microbiota alterations were correlated with suppression of tumour metabolic reprogramming and improved antitumour immune responses, highlighting the broader systemic implications of GP-mediated microbiota modulation [168].

Mechanistically, bacteria belonging to the phylum *Bacteroidetes* dominate as degraders of complex polysaccharides in the gut, primarily because they contain starch utilisation system (Sus)-like transport systems, which enable efficient degradation of these complex carbohydrates [169]. The gut commensal bacterium *Bacteroides uniformis* JCM 13288T can utilise β -glucans and cross-feed them to other microbial populations, contributing to microbial equilibrium [170]. Carbohydrate-active enzyme (CAZyme) genes can be found in polysaccharide utilisation loci (PULs) that are involved in glycan identification and degradation in *Bacteroidetes*. PULs, such as PUL1,6- β -glucan in *Bacteroides thetaiotaomicron*, may recognise and break down fungal-derived 1,6- β -glucan is presented in (Fig. 10A) [171]. Furthermore, the enzyme composition within PULs reflects glycan structure, offering insights into substrate specificity and supporting prebiotic development (Lapebie et al., 2019). In addition, Gram-positive *Firmicutes*, like *Bacteroidetes*, are involved in polysaccharide metabolism, but at lower levels of CAZyme [173]. Although there have been significant breakthroughs in the mechanics of GPs fermentation and metabolism by gut bacteria, the mechanisms of GPs fermentation remain unclear, providing a promising research goal for the future (Fig. 10B). From the mechanistic perspective, the production of SCFA, including acetate, propionate, and butyrate, that occurs in GP fermentation serves as a

signaling mechanism as it acts through the activation of G-protein-coupled receptors (GPR41 and GPR43) and inhibition of histone deacetylase (HDAC). This leads to the regulation of NF- κ B-dependent signalling, increased intestinal barrier integrity, and modulation of metabolic and immune homeostasis [174,175]. In summary, GPs exert significant prebiotic effects by selectively modulating gut microbial communities and promoting the production of beneficial metabolites, particularly SCFAs. These microbiota-mediated interactions contribute to the regulation of metabolic homeostasis, immune responses, intestinal barrier integrity, and disease-related pathways. Recent animal studies demonstrate improvements in obesity, dyslipidaemia, estrogen-deficiency-associated metabolic disorders, and cancer progression. Mechanistically, the utilisation of GPs by gut microbes through specialised carbohydrate-active enzymes and polysaccharide utilisation loci highlights the importance of GP structural features in determining fermentation behaviour and biological outcomes. Nevertheless, the causal relationships between GP-driven microbiota changes and host physiological benefits remain incompletely understood, warranting future investigation using germ-free models, faecal microbiota transplantation, and multi-omics approaches to elucidate the underlying mechanism and support clinical translation.

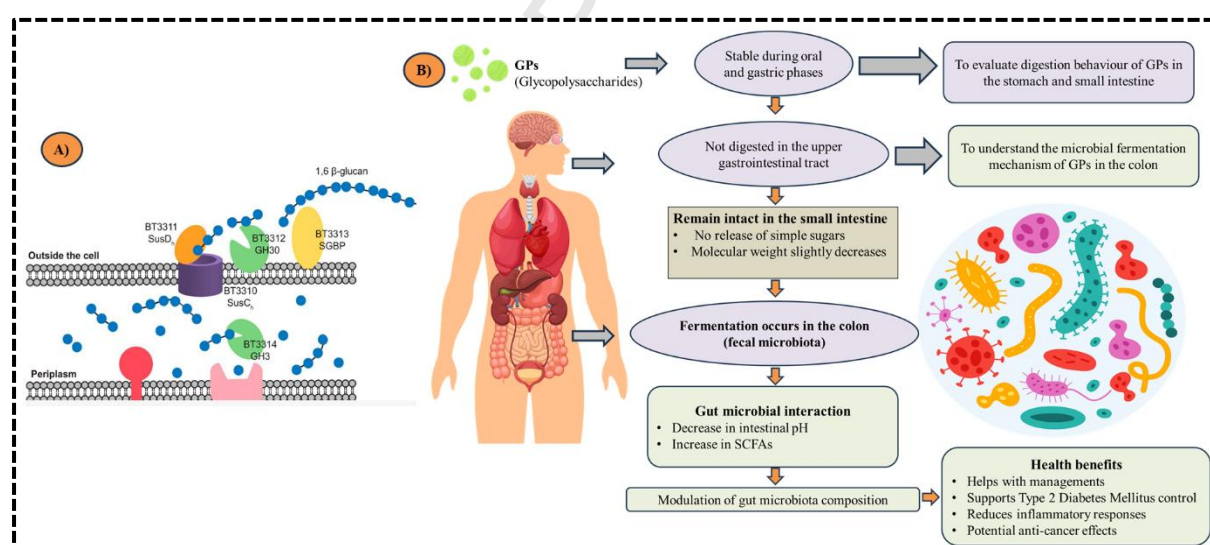


Fig. 10. The potential for GPs as prebiotics. (A) *Bacteroides thetaiotaomicron* degrades 1,6- β -glucan [171]. (B) Graphical review of the prebiotic potential of GPs and gaps in understanding regarding polysaccharide-Gut Microbiota-host interactions. Abbreviation: GPs, Ganoderma polysaccharides; Sus, starch utilisation system; SusC, starch utilisation system outer membrane transporter; SusD, starch utilisation system surface glycan-binding protein; GH3, glycoside hydrolase family 3; SGBP, surface glycan-binding protein; β -glucan, beta-glucan.

8. Safety and toxicity

Ganoderma spp. have long been utilised in traditional medicine and are generally regarded as safe due to their extensive history of consumption and therapeutic use [6]. Because these bioactive compounds have a variety of bioactivities, such as hepatoprotective, antidiabetic, anticancer, antioxidant, and microbiota-modulating activities, along with low toxicity and side effects, interest in *Ganoderma*-based polysaccharides as safe therapeutic alternatives has grown [3]. However, the complex pathogenesis of diseases like liver disorders remains a limiting factor in the effectiveness of the available clinical therapeutic interventions, most of which are accompanied by serious side effects. Although several pharmacological agents, like resmetirom, atezolizumab, sorafenib, and futibatinib, are in the pipeline for the treatment of diseases like NAFLD and liver fibrosis, their clinical application is hindered due to safety concerns [123].

Furthermore, earlier research have demonstrated that GLP, a water-soluble component of *G. lucidum*, has no substantial toxicity or safety issues. A 12-week randomised double-blind, placebo-controlled clinical experiment evaluated the efficacy and safety of a 200 mg/day β -glucan formulation from *G. lucidum* in healthy adults. The clinical research found that β -glucan was safe and well-tolerated, with no significant variations in renal or hepatic function between the treatment and placebo groups [176]. Furthermore, mice given *G. lucidum* HWE (5000 mg/kg/day) showed no changes in body mass, organ weight, or blood parameters [177]. Furthermore, a complete toxicological examination of GLP in Kunming mice and Wistar rats, which included acute, subchronic, and genetic toxicity testing, revealed that GLP is not hazardous [178].

Subchronic toxicity studies also support these findings. Administration of β -d-glucan at doses of 0-2000 mg/kg/day for 90 days had no deleterious effects on haematology, serum chemistry, urinalysis, or histopathological parameters and no treatment-related abnormalities were observed in clinical or physiological endpoints [179]. Clinical evidence further corroborates these findings; for instance, a 12-week study involving patients with urinary tract infections reported no sign of hepatic, haematological, or renal toxicity following GP administration [180]. Additionally, the genotoxicity assay, including Ames, micronucleus, and chromosome aberration tests, consistently yielded negative results, indicating no mutagenic potential [181]. Collectively, current evidence suggests that GPs possess a high safety margin and favourable tolerability, supporting their potential application in therapeutic and

nutraceutical formulations. Nevertheless, despite promising toxicological findings, large-scale multicentre clinical trials and long-term safety evaluation are still required to establish standardised dosage ranges, chronic safety profiles and potential herb-drug interaction in diverse patient populations.

9. Functional Food Application of GPs

Mushroom compounds are widely employed in various industries, including nutrition, pharmaceuticals, and cosmetics [182]. *Ganoderma* spp. has been utilised as a health supplement for thousands of years due to its inherent therapeutic properties. Prebiotics are commonly added to dairy products to enhance their functional and nutritional qualities [183]. Because of their various bioactive properties, GPs have shown great promise in the functional food industry. A number of studies have found that GPs' immune-regulating, anti-tumor, and prebiotic activities have resulted in a wide range of commercial applications in this field. GPs are commonly used in the formulation of various functional drinks, including herbal teas and energy drinks, particularly in the Asian market, due to their immune-boosting and fatigue-reducing properties [184]. Moreover, GPs play an important part in the worldwide dietary supplement market, particularly in the US and Europe. The capsules, tablets, or powders are believed to have immunomodulatory, anti-inflammatory, and anti-tumour activities [185]. GPs are being incorporated into functional snack foods, such as energy bars and cereals, as additives with probiotics [182]. GPs are promising bioactive compounds with diverse pharmacological properties, including immunomodulatory, gut microbiota-regulating, and supporting their application in nutraceuticals [186]. Currently, numerous *Ganoderma*-based commercial products, such as dietary supplements, functional beverages, and cosmetics, are available in the global market (Table 3), which shows the industrial importance of *Ganoderma* spp. In addition, polysaccharide-based biomaterials are increasingly explored for edible films and sustainable food packaging due to their biodegradability, film-forming ability, and capacity to incorporate bioactive compounds. Incorporation of natural extract, essential oils and protein has been shown to improve antioxidant activity, antimicrobial properties, food preservation and shelf-life extension [187].

Nevertheless, there are various challenges that hinder their optimal utilisation. First, the low extraction efficiency of water-soluble GPs, which ranges between 1-3%, makes them expensive. This has necessitated the use of modern technologies, such as biotechnology fermentation, to boost their extraction efficiency. Secondly, their stability during processing

and storage remains a concern. Microencapsulation using biopolymers such as maltodextrin, gum Arabic, alginate, protein, and polysaccharide-based carriers can improve the stability, solubility, controlled release, and bioavailability of GPs while protecting them from degradation during processing and storage [188]. Such approaches also facilitate their incorporation into beverages, dairy products, and nutraceutical formulations. This challenge has been addressed using various methods, such as microencapsulation techniques. Thirdly, sensory issues, such as inherent bitterness, are limitations to their utilisation. This has been addressed using flavour masking techniques. Practical bitterness-masking strategies include the use of natural sweeteners, flavour enhancers, aroma compounds, and encapsulation technologies that reduce direct interaction of bitter components with taste receptors [189]. These approaches improve consumer acceptance without substantially compromising the biological activity of GP-containing products. Finally, the lack of activity-based quality control has been a challenge to their efficacy. This has been addressed by determining some critical components, such as β -Glucans, to guarantee their effectiveness. This has been done to guarantee their efficacy, as discussed by Wu et al. [23].

Table 3

Commercial *Ganoderma*-based products and applications

Product	Bioactive constituent	Health/function al claims	Dosage from	Product class	manufacturer
Mahogany Reishi Mushroom Extract Capsules	Reishi Mushroom mycelium	Support longevity, boost immunity, body detox and anti-inflammatory	Capsules (2/day)	Nutraceutical	INDIA, mahogany organics
Royal King Lucid <i>Ganoderma</i> Tea	Ethanol extract of <i>Ganoderma lucidum</i>	Protection of the kidney, liver and pancreas, enhancement of cardiovascular functions,	Tea Bag	Functional beverage	China, Royal King

detoxification.

DXN Lingzhi Coffee	<i>Ganoderma lucidum</i> extract	-	powder	Functional beverage	Malaysia, DXN
Reishi Green Tea	Reishi extract	May help improve health, well known as an effective weight loss supplement.	Tea Bag (1 Sachet)	Functional beverage	USA, Eternal Spirit Beauty
Cosmeceuticals <i>G. Lucidum</i> Mask	Nourishing mask with mushroom extract and hyaluronic acid	Smoothens fine lines and wrinkles, with intense moisturisation.	Sheet	Cosmeceuticals 1	Korea, RNW
CAFÉ <i>GANODERMA</i> (REISHI) 4 in 1 Coffee	Reishi extract	Reduces fatigue, supports metabolism and immunity	Beverage (1 cup/day)	Functional beverage	USA
Nutraceutical Reishi Mushroom Capsules	<i>G. lucidum</i> extract (10:1)	Immune enhancement, cardiovascular and cognitive support	Capsules (2/day)	Nutraceutical	USA, pura sol
Ganozhi Toothpaste	<i>Ganoderma</i> extract	Cleansing, anti-bacterial, freshening up,	BOX	Personal care	Malaysia, DXN

protects the gums
(dental health is
related to heart
problems).

Multiple
applications for
emergency use:
internal
digestion, acidity,
vomiting, pain,
diarrhoea, and
insect bite.

V-Gano shampoo	<i>Ganoderma</i> extract + herbal blend	Promotes hair growth, improves scalp hydration, and maintains scalp health	Liquid shampoo	Cosmeceutica 1	India, Falcon Marketing
Reishi Mushroom	<i>Ganoderma</i> <i>lucidum</i> extract (3600 mg; 4:1)	Supports a healthy heart; supports healthy ageing; supports the immune system; helps support longevity.	Capsule (2 /day	Nutraceutical	USA, NusaPure

Note: Health claims associated with commercial Ganoderma products are primarily based on traditional use and preclinical studies, and lack consistent clinical validation for established therapeutic efficacy.

8. Challenges and future prospects

Despite the significant advances that have been reported regarding the elucidation of the biological activities of GPs, there are still several critical challenges that have continued to hinder the application of the compound in the management of GI health/diseases.

8.1. Structural heterogeneity and lack of standardisation

One of the major limitations in GP research is its high degree of structural heterogeneity, including differences in its monosaccharide content, glycosidic linkages, molecular weights, and branching. These structural characteristics are known to be highly species and culture-condition-dependent, and extraction protocol-dependent, causing inconsistencies in biological activities [190]. Additionally, a lack of standardised extraction and purification methods results in poor reproducibility of results. It is imperative to have standardised methods and reference standards, especially in relation to the quantification of β -glucan content, to ensure reproducibility in both academic and industrial use.

8.2. Incomplete understanding of structure-function relationships

While various studies have suggested that factors like molecular weight, triple helix structure, and β -(1 $\rightarrow$ 3) / (1 $\rightarrow$ 6) linkages impact GP bioactivity, it is still not well defined [191]. Interestingly, it has been found that high- and low-molecular-weight polysaccharides can show immunomodulatory and prebiotic activities, respectively, implying that several factors might be working in concert [192]. Structural properties such as molecular weight, branching degree, glycosidic linkage and triple-helical conformation likely influence microbial accessibility, PUL-mediated degradation, SCFA production, and host receptor interaction [88]. Several studies have reported enhanced immunomodulatory effects for higher-molecular-weight β -glucans and stronger antioxidant activities for the lower-molecular-weight fraction; the mechanistic relationship between GP structural characteristics and gut microbiota regulation remains poorly defined [28]. Future investigation should therefore integrate advanced molecular biology and system biology approaches, including metagenomics, transcriptomics, metabolomics, molecular docking and germ-free animal models to elucidate how specific structural features of GPs influence microbial fermentation behaviour, host signalling pathways, and gut-homeostasis-related therapeutic outcomes. Such mechanistic insights will support the rational development of structurally optimised GP-based functional food and microbiota-targeted nutraceuticals. The proposed molecular mechanism underlying the differential microbiota-modulating activities of high- and low-molecular-weight GPs is summarised in Fig. 11.

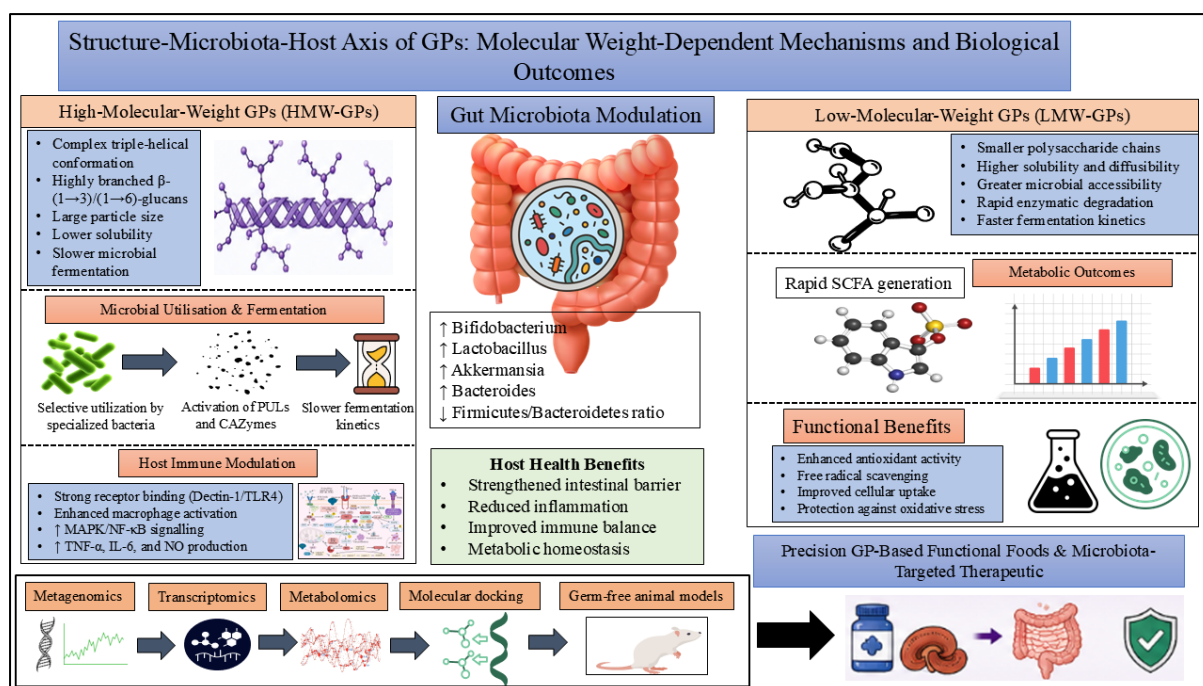


Fig. 11. Molecular weight-dependent mechanisms of GPs on gut microbiota modulation and host health. Abbreviations: GPs, *Ganoderma* polysaccharides; HMW-GPs, high-molecular-weight *Ganoderma* polysaccharides; LMW-GPs, low-molecular-weight *Ganoderma* polysaccharides; SCFAs, short-chain fatty acids; PULs, polysaccharide utilisation loci; CAZymes, carbohydrate-active enzymes; Dectin-1, dendritic cell-associated C-type lectin-1; TLR4, toll-like receptor 4; NF- κ B, nuclear factor kappa B; MAPK, mitogen-activated protein kinase; TNF- α , tumour necrosis factor-alpha; IL, interleukin; NO, nitric oxide.

8.3. Limited mechanistic insights into gut microbiota modulation

Although GPs have been identified as promising prebiotics, the exact mechanisms of the interaction of GPs with the microbiota are not well understood. However, the existing evidence indicates that the microbiota of the phylum *Bacteroidetes* uses polysaccharide utilisation loci and carbohydrate active enzymes to break down complex β -glucans [172,193]. In addition, the variability in the composition of the human gut microbiota plays an important role in GP metabolism. Such variability may be attributed to various factors like diet, age, and genetic differences. However, variability may pose a challenge to the general application of GPs. Future studies should be conducted using various “omics” approaches like metagenomics, metatranscriptomics, and metabolomics. In addition, the development of personalised prebiotic therapy is a promising approach.

8.4. Lack of robust clinical evidence

Although several research studies have demonstrated the potential of GPs in their therapeutic applications by conducting *in vitro* and *in vivo* research, studies in humans are limited. Most of the research studies have demonstrated limitations in their findings due to small sample size, limited duration of study, and differences in GP preparations and doses [194]. To further advance the clinical potential of GPs to the next step, future research studies should be designed in a randomised, double-blinded, and placebo-controlled manner. Long-term research studies should be conducted on chronic gastrointestinal disorders such as bowel disease and colorectal cancer.

8.5. Challenges in extraction, yield, and scalability

The low extraction yield of water-soluble GPs, which ranges between 1-3%, remains a major hindrance in large-scale GP extraction. Although recent technologies like UAE, MAE, and DES have shown encouraging results in terms of GP extraction yield, it is still important to further optimise their cost-effectiveness. The extraction conditions have a major impact on GP structure and bioactivity; thus, it becomes imperative to optimise them precisely. In this regard, recent computing techniques like Response Surface Methodology (RSM), Artificial Neural Networks (ANN), and Genetic Algorithm (GA) have received significant attention [195,196]. RSM is a powerful optimisation technique that requires fewer experiments to optimise the parameters. ANN is useful for modelling non-linear relationships. GA is another powerful optimisation technique that helps in the global optimum conditions.

8.6. Stability, bioavailability, and delivery limitations

GPs are prone to deterioration during processing and storage, especially under harsh conditions of temperature and pH. Moreover, their bioavailability is not direct, as they influence the system indirectly through microbial fermentation. To overcome these drawbacks, advanced drug delivery systems such as microencapsulation, nano-carrier systems, and controlled-release systems are under investigation for improving stability and targeting in the GI tract [106]. Such systems may also help in their incorporation into functional foods and nutraceuticals.

8.7. Regulatory and quality control issues

The proliferation of *Ganoderma*-based products in the global market is a key factor that points towards the development of effective regulatory and quality control measures. Currently, the lack of standardised guidelines for characterising and quantifying GP results in

variability in product quality and safety [197]. Future research in this field needs to be directed towards the development of activity-based quality control measures, including the standardisation of β -glucans and activity assays. It is also important to develop a uniform policy on regulating *Ganoderma*-based products in different markets of the world.

8.8 Integration into multi-target therapeutic strategies

GPs also possess potential for integration in multi-target therapy, especially in diseases related to the gut-liver and gut-brain axis [198]. However, their interaction with various drugs, probiotics, and dietary factors should also be explored. Future research in this field should be oriented towards the development of symbiotic, i.e., products containing *Ganoderma* and probiotics, for enhancing their potential and expanding their application.

In summary, future advancements made in multi-omics, artificial intelligence, nano-capsulation and systems biology are likely to provide better insights into host-microbiome interactions, which will help precision nutrition and personalised therapeutic interventions. The inclusion of polysaccharides derived from *Ganoderma* species in functional foods and nutraceuticals, through biotechnological advancements, will help their application. Furthermore, future clinical trials should incorporate standardised GP preparation with clearly defined molecular characteristics, including β -glucan content, molecular weight, and branching profiles. Randomised, double-blinded, placebo-controlled clinical studies should evaluate not only symptomatic improvement in GI disorders, but also microbiota-related biomarkers such as short-chain fatty acid production, microbial diversity indices, intestinal permeability markers, inflammatory cytokines, and metabolomic profiles. Safety assessment should include long-term safety and toxicity evaluation, allergenicity, drug-polysaccharides interactions, and dose-tolerance studies. Furthermore, stratification of participants based on gut microbiota composition may help establish personalised therapeutic responses to GPs in conditions such as inflammatory bowel disease, irritable bowel syndrome, colorectal cancer, and metabolic-associated gut disorders.

9. Conclusion

GPs have emerged as promising bioactive macromolecules with considerable potential for supporting GI and systemic health applications, particularly through modulation of the gut microbiota and host signalling networks. Accumulating evidence suggests that GPs may contribute to immune regulation, metabolic homeostasis, and oxidative stress mitigation, supporting their development as functional food ingredients and nutraceuticals.

However, several critical challenges continue to limit their translational and clinical advancement. Current evidence is dominated by *in-vitro* and animal studies, with a scarcity of well-designed human clinical trials. Substantial structural heterogeneity arising from differences in *Ganoderma* spp., cultivation conditions, extraction processes, and purification methods complicates structure-activity relationships analyses and hinders cross-study comparability. In addition, low extraction yields, limited standardisation of characterisation protocols, and insufficient understanding of causal microbiota-mediated mechanisms remain major barriers to industrial development and regulatory acceptance. The influence of inter-individual microbiome variability on GP responsiveness also remains largely unexplored. Further research should prioritise standardised extraction and analytical frameworks, integration of multi-omics, and system biology approaches, mechanistic validation using causality-oriented microbiome models, and rigorously designed clinical trials. Furthermore, investigation into personalised nutrition strategies, scalable production technologies, and formulation approaches that improve stability, bioavailability, and consumer acceptance will be essential for translating GPs from promising experimental compounds into evidence-based functional food and nutraceutical products.

CRedit authorship contribution statement

Aman Sharma: Conceptualisation, visualisation, Writing-original draft, Formal analysis, Data curation. **Divyesh Suvedi:** Writing-original draft, Data curation, and formal analysis. **Kaushiki Bhagat:** writing review and editing, and Formal analysis. **Mamta Chandel:** writing review and editing. **Rachna Verma:** Data curation. **Sonika Kalia:** writing review and editing. **Ashwani Tapwal:** Data curation. **Dinesh Kumar:** Supervision and Validation. **Lukas Peter:** writing review and editing. **Vinod Kumar:** Supervision and validation. **Avinash Sharma:** Formal analysis.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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