

Review

A Comprehensive Review of *Sanghuangporus* spp.: Unveiling the Multifaceted Therapeutic Potential of a Medicinal Fungus

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Academic Editor: Mehmet Ozaslan

Submitted: 10 September 2025 Revised: 25 January 2026 Accepted: 2 February 2026 Published: 21 October 2026

Abstract

Sanghuangporus spp. are treasured medicinal fungi prescribed for over a millennium. They produce diverse bioactive metabolites, including polysaccharides, polyphenols, triterpenoids, and others, with broad therapeutic potential spanning antitumor, immunomodulatory, antioxidant, and metabolic activities. Yet their transition from traditional remedy to modern therapy is hindered by tangled species boundaries, nonstandardized extraction protocols, poor bioavailability of key constituents, and scarce high-quality clinical evidence. Here we synthesize major advances in sanghuang research from 2020 to 2025. We chart the taxonomic clarification that now enables precise chemotaxonomic authentication, dissect the structures and modes of action of signature metabolites, and map the molecular circuits underlying their pharmacological effects. We further survey emerging green extraction and purification technologies, such as deep eutectic solvents and ultrasound–microwave synergistic systems, that raise yield while reducing environmental burden. Looking forward, we outline a translational roadmap that couples multi-omics standardization of chemotypes with nano-delivery strategies to enhance bioavailability, rigorously designed randomized controlled trials to validate efficacy, and sustainable biomanufacturing routes such as submerged fermentation. Only through such interdisciplinary convergence can sanghuang be transformed from an ancestral decoction into a rigorously evidence-based therapeutic and functional food for the twenty-first century.

Keywords: *Sanghuangporus*; polyphenol-rich polysaccharides; submerged fermentation optimization; metabolite standardization; sustainable cultivation

1. Introduction

“Sanghuang” traditionally refers to a group of wood-decay fungi that primarily grow on trees of the Moraceae family (especially *Morus* spp.), with a millennia-long history of use in East Asian medicine for treating gastrointestinal, inflammatory, oncological, and metabolic disorders. Historically, the taxonomy of these fungi has been highly ambiguous, leading to frequent misclassification under genera such as *Polyporus*, *Phellinus*, *Inonotus*, and *Tropicoporus*. This ambiguity was largely resolved by Shen et al. (2021) [1], who established the genus *Sanghuangporus* through multilocus phylogenetic analysis based on internal transcribed spacer (ITS), nLSU, *rpb1*, *rpb2*, and *tefl* gene regions. The genus currently comprises approximately 18 species, with *Sanghuangporus sanghuang* as the type species. Among these, *S. vaninii*, *S. baumii*, and *S. sanghuang* have been the focus of extensive pharmacological research [1,2].

Scientific interest in *Sanghuangporus* has resurged, driven by its remarkable chemical diversity and potent bioactivities. While many medicinal mushrooms are valued primarily for their polysaccharides or triterpenoids,

Sanghuangporus produces a broader array of bioactive compounds, including immunomodulatory polysaccharides (e.g., β -glucans), cytotoxic lanostane-type triterpenoids, antioxidative phenolics and flavonoids, and unique fungal melanins. Advances in omics and molecular techniques are gradually unveiling the mechanisms underlying these bioactivities, positioning *Sanghuangporus* as a promising source of novel therapeutics for cancer, neurodegenerative diseases, metabolic syndromes, and inflammatory conditions [3,4,5].

Beyond direct therapeutic applications, *Sanghuangporus* also holds significant potential as a functional food—defined as providing health benefits beyond basic nutrition [6,7,8]. Many edible mushrooms qualify as functional foods due to their palatability, rich bioactive constituents, and nutritional value [9,10]. Their secondary metabolites, such as polysaccharides, flavonoids, and triterpenoids, contribute to various health benefits, including hypoglycemic, antibacterial, antioxidant, anticancer, and immunoregulatory effects [11,12,13,14]. This stands in contrast to conventional pharmaceuticals, which often entail severe adverse effects [15,16]. Although direct clinical evidence cat-

egorizing *Sanghuangporus* products as functional foods remains limited, their notable bioactivities strongly support this potential [8,16,17]. A critical barrier, however, is the lack of standardized, clinically validated products and dosing regimens.

Overall, research on *Sanghuangporus* remains fragmented and hampered by non-standardized methodologies, inconsistent findings, and a lack of translational studies. This fragmentation hinders meta-analyses, direct comparison across studies, and ultimately, the development of evidence-based applications. To address these challenges and bridge existing gaps, this review synthesizes recent advances (2020–2025) in *Sanghuangporus* research. We critically examine its taxonomy, structural diversity and biosynthesis of bioactive compounds, pharmacological mechanisms, challenges in sustainable production, and clinical/nutraceutical applications. Furthermore, we identify key knowledge gaps and future research trajectories, calling for more rigorous, interdisciplinary approaches to unlock the full potential of these promising fungi.

2. Taxonomic Background and Traditional Uses

2.1 Historical Continuity and Traditional Applications

The medicinal use of Sanghuang—referring to fungi now classified within the genus *Sanghuangporus*—is deeply rooted in traditional medicine systems across East Asia, particularly in China, Korea, and Japan, with a documented history spanning more than 1300 years. Its earliest recorded application appears in the Tang-dynasty text Yao Xing Lun (circa 7th–8th century CE), where it was prescribed for “fu zheng” (abdominal masses), conditions widely interpreted in modern contexts as gynecological tumors, including cervical cancer [18,19]. Traditional preparations typically involved decoctions (teas) or alcohol-based extractions used to treat inflammatory, gastrointestinal, and neoplastic conditions. Later historical records, including the Ming-dynasty *Compendium of Materia Medica* (*Bencao Gangmu*), further emphasized its detoxifying and “stasis-resolving” properties [20].

In recent decades, this enduring traditional knowledge has guided modern scientific inquiry. Contemporary pharmacological studies have validated many of these historical uses, revealing a broad spectrum of bioactivities that include antitumor, antioxidant, anti-inflammatory, immunomodulatory, hypoglycemic, antimicrobial, anti-aging, hepatoprotective, and neuroprotective effects [6,19,21,22,23,24,25,26]. The bioactive compounds underlying these activities—primarily polysaccharides, hispidin (a styrylpyrone polyphenol), flavonoids, and triterpenoids—have been isolated and characterized through rigorous preclinical research [1,22,27,28].

2.2 Taxonomic Clarification and Key Species

Persistent taxonomic confusion has long hampered the translation of traditional wisdom regarding Sanghuang into evidence-based applications. Early literature often misclassified these fungi under related genera such as *Phellinus* or *Inonotus*. Multilocus phylogenetic analyses (ITS, nLSU, EF1- α , RPB1, and RPB2) support *Sanghuangporus* as a monophyletic genus with 13 species, providing a framework for its taxonomy, origin, and biogeography [29]. Mitogenome-based analyses distinguish *Sanghuangporus* from Sanghuang-like fungi, confirming its monophyly and supporting the reclassification of *Phellinus gilvus* S12 as *Sanghuangporus vaninii* [30].

The genus *Sanghuangporus* currently comprises about 18 species, with *S. sanghuang* as the type species. The most widely investigated for medicinal uses include *S. sanghuang* (the type species), *S. baumii*, and *S. vaninii*. These species exhibit distinct host specificity: *S. baumii* primarily colonizes *Syringa* spp., *S. vaninii* is predominantly found on *Populus* spp., and *S. sanghuang* inhabits *Morus* tree [6,11]. This host specificity directly influences their metabolite profiles and, consequently, their bioactivity [30,31].

Fig. 1 illustrates the morphological characteristics of *Sanghuangporus* across key developmental stages, from early substrate colonization to mature fruiting bodies, which are typically used in medicinal preparations.

3. Chemical Diversity of Bioactive Compounds

3.1 Polysaccharides

As a major class of bioactive constituents in *Sanghuangporus* fungi, polysaccharides are primarily responsible for their broad-spectrum pharmacological activities. This section systematically reviews the research progress on the structure, extraction, purification, physicochemical properties, and structure-activity relationships (SAR) of Sanghuang polysaccharides.

3.1.1 Structural Diversity

Polysaccharides from *Sanghuangporus* exhibit remarkable structural heterogeneity, which is significantly influenced by the fungal source (fruiting body, mycelium, or fermentation broth) as well as the extraction and processing protocols employed. Structural characterization has historically focused on fruiting body polysaccharides from species such as *Phellinus igniarius* and *P. linteus* (now often classified under *Sanghuangporus*), whereas extracellular polysaccharides from fermentation broths remain comparatively underexplored. Mycelial polysaccharides typically display greater monosaccharide diversity, with elevated contents of fucose and mannose [32]. Molecular weight distributions also vary by source: those from fruiting bodies generally range from 10^4 to 10^6 Da, while extracellular polysaccharides often exceed 10^6 Da.

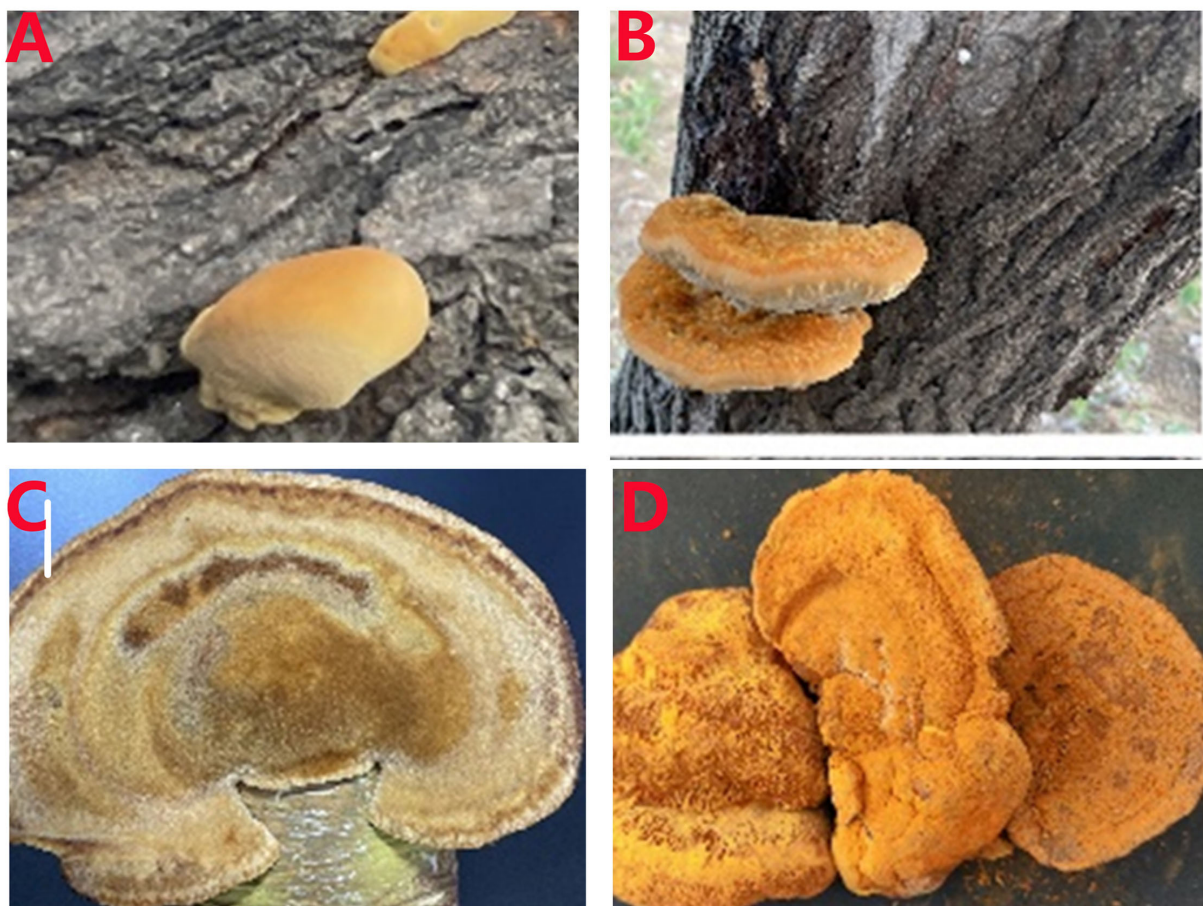


Fig. 1. Morphological characteristics of *Sanghuangporus* across developmental stages. This composite illustrates key life-cycle stages of the medicinal fungus *Sanghuangporus*. (A) Early-stage colonization on the host tree substrate. (B) Intermediate development showing bracket formation and structural differentiation. (C) Mature, fully formed fruiting body (bracket). (D) Dried specimens, representing the material typically used in medicinal preparations.

Two distinct β -D-glucans have been isolated from *P. ribis*. Liu et al. [33] subsequently isolated PRG and characterized it as a homogeneous β -D-glucan with a (1 $\rightarrow$ 3)-linked backbone, bearing at C-6 a branch of two (1 $\rightarrow$ 6)-linked glucoses and one terminal glucose every three residues along the main chain. Liu and Wang [34] identified a water-soluble polysaccharide with a (1 $\rightarrow$ 4), (1 $\rightarrow$ 6)-linked backbone, bearing a single β -D-glucose at C-3 of the (1 $\rightarrow$ 6)-linked glucosyl residue every eight residues along the main chain. SHPS-1, a 46 kDa heteropolysaccharide isolated from the fruiting bodies of *P. baumii*, exhibited anti-inflammatory activity by decreasing STAT-1 phosphorylation and iNOS/TNF- α expression while promoting IL-10 and CD206 expression in LPS-stimulated RAW 264.7 cells, and alleviated ulcerative colitis in mice by decreasing pro-inflammatory genes and increasing anti-inflammatory and tissue-repairing genes, suggesting its potential for IBD treatment [35].

Fruiting body polysaccharides are predominantly heteroglucans, composed of 50–70% glucose along with man-

nose, galactose, xylose, arabinose, and rhamnose. A common structural motif is a $\rightarrow$ 3)- β -D-Glcp-(1 $\rightarrow$ backbone featuring (1 $\rightarrow$ 3), (1 $\rightarrow$ 6), and (1 $\rightarrow$ 3,6) glycosidic linkages. Notably, 3(4)-O-Methyl-hexose has been identified in *P. ignarius* polysaccharides. For instance, a 46-kDa heteropolysaccharide from *Phellinus baumii* fruiting bodies (purified via hot water extraction, ethanol precipitation, DEAE-Sephadex, and Sephadex G-200 chromatography) contains a backbone of 1,3-linked β -D-Glcp and 1,6-linked α -D-Galp residues. Branching occurs at the C-6 position of specific Glcp residues through oligosaccharide side chains composed of Araf, Manp, and Galp. This polysaccharide demonstrated significant anti-inflammatory activity in LPS-stimulated RAW 264.7 macrophages by down-regulating STAT1 phosphorylation and upregulating tissue repair genes. It also ameliorated dextran sodium sulfate-induced ulcerative colitis in mice, effects attributed to its highly branched architecture and characteristic $\rightarrow$ 3)- β -D-Glcp-(1 $\rightarrow$ linkages [27,36].

Structural elucidation of an exopolysaccharide from *Phellinus pini* revealed a (1→2)-linked mannan backbone extensively substituted via (1→6) linkages with (1→3)-linked mannan side chains, terminating primarily in mannose with minor galactose and glucose residues. This polysaccharide activated macrophages, enhancing phagocytosis and stimulating the production of NO, ROS, and TNF- α [37].

Furthermore, a heteropolysaccharide from *Phellinus igniarius* fruiting bodies (isolated via hot water extraction, ethanol precipitation, and sequential chromatography) was characterized by methylation analysis and NMR spectroscopy. Its backbone consists of 1,6-disubstituted-3-O-methyl- α -D-Glcp, 1,3,6-trisubstituted- α -D-Manp, 1,4-disubstituted- α -D-Galp, and 1,2-disubstituted- α -D-Galp residues, with a terminal 1-substituted α -L-Fucp linked at O-3 of a Manp residue. *Phellinus* polysaccharides, important bioactive components with complex structures, exhibit multiple pharmacological activities, such as antitumor, immunomodulatory, antioxidant, hypoglycemic, and anti-inflammatory effects, making them promising for further research and application [38]. Similarly, Dictyophora polysaccharides, important bioactive macromolecules, possess diverse pharmacological activities, including antitumor, antioxidative, anti-obesity, anti-hyperlipidemic, hepatoprotective, immunomodulatory, anti-inflammatory, gut microbiota-regulating, antibacterial, and renoprotective effects, showing great potential for further research and application [39].

Collectively, these studies underscore the critical structure-activity relationships in *Sanghuangporus* polysaccharides [40,41,42]. Specifically, polysaccharides rich in $\rightarrow$ 3)- β -D-Glcp-(1→ linkages and those with extensive branching typically exhibit potent anti-inflammatory activity [40,43]. For example, structural analysis of an exopolysaccharide from a *Sanghuang* fermentation broth revealed a complex backbone. A novel extracellular polysaccharopeptide (SePSP) purified from the submerged fermentation broth of *Sanghuangporus lonicericola* CBS17 exhibited strong concentration-dependent antioxidant activity in vitro and effectively alleviated dextran sodium sulfate (DSS)-induced ulcerative colitis (UC) in mice by modulating inflammatory cytokines and inhibiting oxidative stress, supporting the development of sanghuang-derived functional foods for UC prevention and treatment [44]. Similarly, a novel D-mannose exopolysaccharide (SSEPS2) from *Sanghuangporus sanghuang* possesses a 1,3- and 1,2-linked α -D-Manp backbone substituted at O-6 by 1,6-linked and terminal α -D-Manp residues, adopts a flexible coil-like conformation, and exhibits in vitro antitumor activity against HepG2 and MCF-7 cells (IC_{50} = 365 and 340 μ g/mL) [45]. The structural diversity of bioactive polysaccharides from the medicinal mushroom *Sanghuangporus* is summarized in Fig. 2.

3.1.2 Extraction, Purification and Bioprocessing

The therapeutic efficacy conferred by *Sanghuangporus* is critically dependent on the efficiency and selectivity of downstream processing. The methods employed for isolating, purifying, and preparing its key bioactive compounds—notably polysaccharides—profoundly affect their structural fidelity, physicochemical characteristics, and ultimately, their biological potency. This section systematically compares contemporary and traditional methodologies, analyzing their underlying principles, respective advantages, limitations, and subsequent impact on bioactivity within the framework of SAR.

3.1.2.1 Extraction Technologies: Principles and Comparative Efficacy.

The choice of extraction method critically determines the yield, compositional profile, and preserved bioactivity of target compounds. Recent progress is characterized by a paradigm shift from conventional techniques toward advanced, integrated physical and green chemistry approaches.

Extraction methods significantly affect the physicochemical and biological properties of polysaccharides: compared with hot water extraction, ultrasound-assisted extraction yielded polysaccharides with lower molecular weight, higher protein and phenolic contents, stronger antioxidant and emulsifying activities, but lower α -glucosidase inhibition activity [46]. Hot water extraction (HWE) is a traditional, safe, and environmentally friendly method for extracting water-soluble polysaccharides from plants. It is widely used in current research because it has minimal impact on the chemical structure of polysaccharides [47], and it is a simple technique that produces high yields [48]. Furthermore, it often leads to the co-extraction of impurities (e.g., proteins, pigments), necessitating extensive downstream purification [49,50].

Ethanol extraction is the standard method for isolating medium- to non-polar bioactive compounds such as polyphenols (e.g., hispidin), terpenoids, and flavonoids. Ultrasound-assisted extraction (UAE) is frequently integrated to enhance efficiency via acoustic cavitation, which disrupts cell walls and improves mass transfer [51]. However, this method is unsuitable for polar polysaccharides, requires significant solvent volumes, and carries the risk of degrading thermolabile phenolic compounds if temperature is not meticulously controlled [52].

Enzyme-assisted extraction (EAE) employs specific enzymes (e.g., cellulase, pectinase) to selectively degrade structural cell wall components under mild conditions. This biocatalytic approach offers high selectivity and yield while aligning with green chemistry principles due to reduced energy and chemical consumption [53,54]. Its main drawbacks are the high cost of enzymes and the need for precise control of pH and temperature.

Physical field-assisted extraction techniques, namely Ultrasound-Assisted Extraction (UAE) and Microwave-

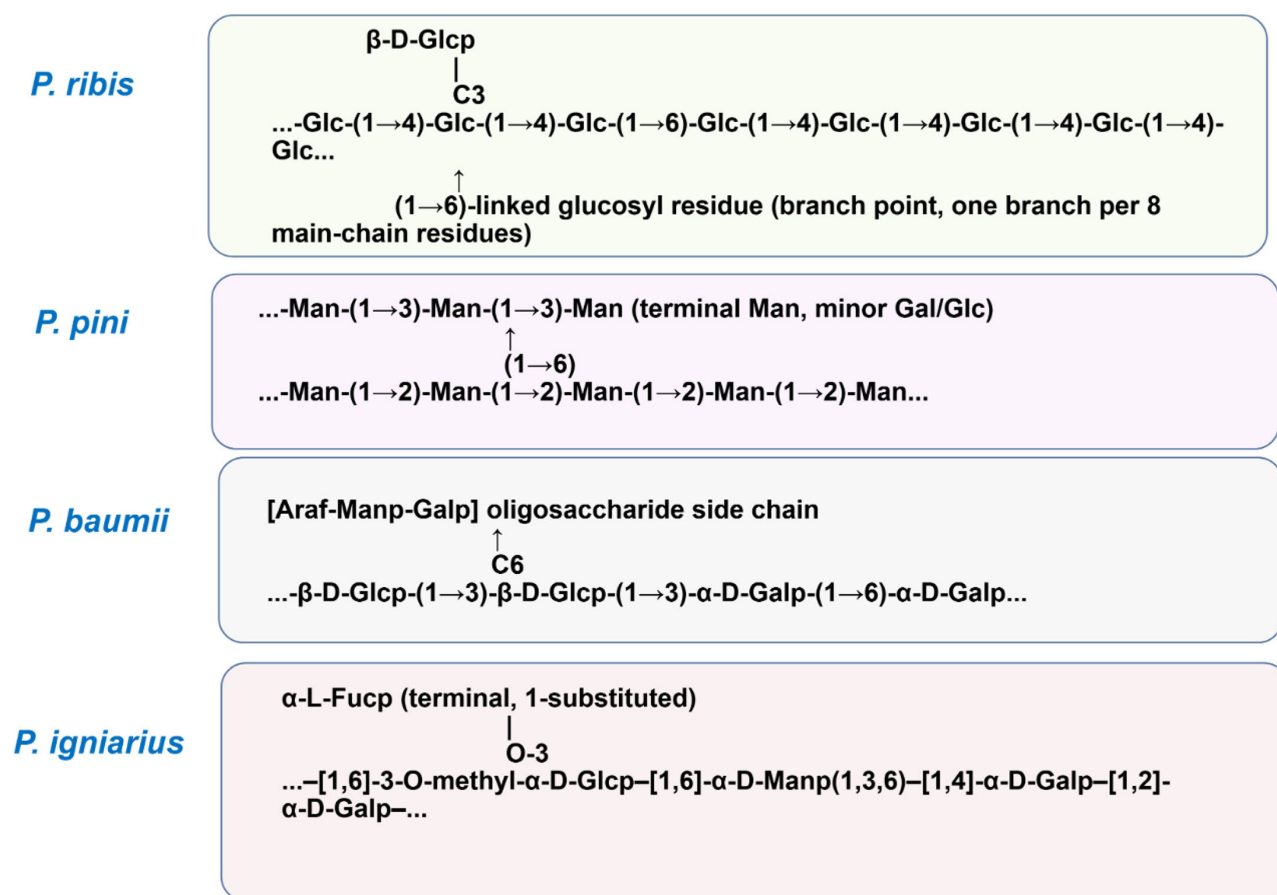


Fig. 2. Structural diversity of bioactive polysaccharides from medicinal mushroom *Sanghuangporus*.

Assisted Extraction (MAE), represent significant advances. UAE utilizes high-frequency sound waves to generate cavitation bubbles, whose collapse mechanically disrupts cells. While it increases yield and is energy-efficient, a major drawback is the potential induction of polysaccharide depolymerization, which significantly reduces molecular weight and intrinsic viscosity [54]. MAE employs microwave irradiation for rapid, volumetric heating, drastically reducing time and solvent consumption. However, it carries a risk of localized overheating and the consequent degradation of heat-sensitive compounds [55].

The synergy of these physical principles is harnessed in Ultrasound-Microwave-Assisted Extraction (UMAE), which combines ultrasonic cavitation with microwave irradiation under mild thermal conditions (<60 °C). This hybrid approach offers superior efficiency and speed, dramatically shortening processing time from hours to minutes while enhancing yield through effective cell wall disintegration [56,57]. The primary challenge lies in managing the combined sono-thermal stress to prevent compound degradation [55].

Alkaline and acidic extraction serve as complementary strategies for isolating specific polysaccharide fractions. Alkaline extraction can modify polysaccharide struc-

ture, sometimes enhancing certain bioactivities, but it also risks inducing degradation (e.g., via β -elimination) and requires post-extraction neutralization [58,59].

Deep eutectic solvent extraction (DESE) has emerged as a pivotal green alternative. Natural deep eutectic solvents (NaDESS) are tailored, biodegradable solvent systems characterized by low toxicity and volatility, yet high solubilizing capacity for diverse phytochemicals [56,60]. Compared to traditional organic solvents, DESE is mild and helps preserve the polysaccharide structure [61]. Limitations include higher viscosity (which can hinder mass transfer), elevated cost, and a complex solvent recovery process.

A comparative summary of these methods, synthesizing their key advantages, disadvantages, and impacts based on literature-reported data, is presented in Table 1 (Ref. [49,50,51,52,53,54,55,56,57,58,59,60,62,63,64]).

3.1.2.2 Purification Strategies for Polysaccharides. Crude extracts contain proteins, pigments, and other impurities, necessitating purification to obtain homogeneous and bioactive fractions. Traditional laboratory protocols typically involve deproteinization using the Sevag reagent, followed by sequential chromatography. This commonly consists of anion-exchange chromatography (e.g., us-

Table 1. Extraction methods for *Sanghuangporus* polysaccharides: a comparative summary.

Extraction Method	Key Advantages	Key Disadvantages/Risks	References
Hot Water Extraction (HWE)	Simple, cost-effective, and industrially scalable. Effective for polar, thermostable polysaccharides and polysaccharide-protein complexes.	Prolonged time and high energy consumption.	[49,50,62,63]
Enzyme-Assisted Extraction (EAE)	High selectivity and yield under mild conditions. Aligns with green chemistry (low energy/chemical use). Preserves native structure and bioactivity.	High cost of enzymes. Requires precise control of pH and temperature.	[53,54]
Ultrasound-Assisted Extraction (UAE)	Enhanced efficiency and yield via cavitation. Energy-efficient and reduces extraction time.	Major risk: Can induce depolymerization of polysaccharides (reducing molecular weight & viscosity).	[51,52,54]
Microwave-Assisted Extraction (MAE)	Dramatically reduces time and solvent consumption via rapid, volumetric heating.	Risk of localized overheating and degradation of heat-sensitive compounds.	[55]
Ultrasound-Microwave-Assisted Extraction (UMAE)	Superior efficiency and speed; reduces processing time to minutes. Synergistic effect enhances cell wall disintegration and yield.	Challenge in managing combined sonothermal stress to prevent compound degradation.	[55,56,57]
Alkaline/Acidic Extraction	Effective for isolating specific polysaccharide fractions. Alkaline treatment can sometimes modify and enhance bioactivity.	Harsh conditions risk polysaccharide degradation (e.g., β -elimination). Requires post-extraction neutralization.	[58,59]
Deep Eutectic Solvent Extraction (DESE)	Green alternative: low toxicity, low volatility, biodegradable. High solubilizing capacity; better preserves native structure and bioactivity of sensitive polysaccharide-protein complexes.	Higher viscosity can hinder mass transfer. Elevated cost and complex solvent recovery process.	[56,60,64]

Footnotes: This table provides a concise summary of key extraction methods for *Sanghuangporus* polysaccharides based on current literature. It is noted that the selection of extraction method should be tailored to the target polysaccharide fraction, desired molecular weight, and intended bioactivity. Future research should focus on optimizing hybrid methods (e.g., DES-UMAE) and establishing standardized protocols to improve reproducibility, yield, and functional integrity of extracted polysaccharides. Comparative studies directly linking extraction parameters to specific structural features and *in vivo* efficacy are still needed.

ing DEAE-52 cellulose) and size-exclusion chromatography (e.g., using Sephacryl S-400), with elution typically performed using NaCl gradients or aqueous buffers [65,66,67,68]. Although this two-step approach remains a laboratory standard, it is labor-intensive, time-consuming, and can lead to polysaccharide degradation or the loss of bioactive components. These drawbacks raise significant concerns regarding reproducibility and industrial scalability [69].

Macroporous resin adsorption offers a more scalable alternative, primarily for decolorization and the removal of persistent pigments (e.g., certain flavonoids) that resist conventional treatments. Resins such as AB-8, characterized by high surface area and tunable polarity, facilitate efficient impurity removal and have been specifically optimized for *Sanghuangporus*-derived compounds [70,71]. However, critical process parameters—including pH, temperature, and contact time—are often empirically optimized and are system-specific. Consequently, the method requires rigorous validation for each polysaccharide type to avoid the unintended adsorption of bioactive fractions or their degradation [71,72,73,74].

Molecularly Imprinted Polymers (MIPs) represent an advanced, high-specificity approach. MIPs are synthesized to contain three-dimensional binding cavities that are structurally complementary to a target molecule (the template). They exhibit superior selectivity and reusability, as demonstrated by morin-based magnetic MIPs (Morin-MMIPs) developed for enriching specific bioactive compounds [75]. Despite their promise for isolating rare glycoforms or high-value components, MIPs face notable translational barriers. These include complex, target-specific synthesis protocols; batch-to-batch variability; and high costs, which currently confine their application largely to proof-of-concept studies [75,76,77].

3.2 Impact of Extraction and Processing on Physicochemical Properties and Bioactivity

The extraction method profoundly influences the physicochemical and structural features of the resulting polysaccharides, which in turn dictate their biological activity.

3.2.1 Molecular Weight (MW) and Distribution

Polysaccharides exhibit considerable MW heterogeneity (10^4 – 10^8 Da), directly influenced by the extraction process. For instance, HWE tends to yield higher MW polysaccharides, while UAE and MAE often cause depolymerization, producing lower MW fragments [78,79]. This has direct bioactivity implications: high-MW fractions (>100 kDa) are generally more potent in immunostimulation and direct antitumor effects via mechanisms like Dectin-1 receptor engagement, while low-MW fractions (<50 kDa) often exhibit superior antioxidant activity, bioavailability, and hypoglycemic effects [78,80,81,82,83,84].

3.2.2 Structural Characteristics

Methods like alkaline extraction can alter monosaccharide composition and glycosidic linkage patterns. For example, alkaline-extracted PL-N had a distinct Ara/Xyl/Glc/Gal ratio and higher uronic acid content compared to hot water-extracted PL-W, which correlated with differences in solubility and bioactivity [85]. The preservation of a β -(1→3)-D-Glcp backbone with β -(1→6) side chains and triple-helix conformation, crucial for immune recognition, is highly dependent on using mild extraction conditions [86].

3.2.3 Structure-Activity Relationships (SAR)

The bioactivity of Sanghuang polysaccharides is closely related to their physicochemical properties, including molecular weight, monosaccharide composition, glycosidic linkage type, degree of branching, and higher-order structures (e.g., the triple helix).

High-molecular-weight polysaccharides (>100 kDa) generally exhibit stronger immunostimulatory and direct antitumor activities *in vitro*, primarily by activating pattern recognition receptors such as Dectin-1 and triggering immune cascades [79,80,81,82,83]. In contrast, low-molecular-weight polysaccharides (<50 kDa) often demonstrate greater antioxidant activity, higher bioavailability, and are more effective in conferring hepatoprotection and hypoglycemic effects [86,87,88].

3.2.3.1 Immunomodulation and Antitumor Activity. A β -(1→3)-glucan backbone is critical for binding to receptors on immune cells (e.g., Dectin-1, TLR-2). β -(1→6) Branching optimizes solubility and receptor-binding efficiency, while a triple-helix conformation is crucial for maintaining potent immunomodulatory activity [79,80,81,82,83]. Polysaccharide-protein complexes (proteoglycans) often exhibit enhanced immunomodulatory effects [80,89,90].

3.2.3.2 Antioxidant Activity. Low molecular weight, high uronic acid content, and greater accessibility of active groups generally correlate with stronger free radical scavenging and metal chelating capacities [86,91,92].

3.2.3.3 Hypoglycemic Activity. *P. linteus* polysaccharide extract (PLPE) exerts its hypoglycemic effect by modulating gut microbiota composition, increasing short-chain fatty acid (SCFA) production, maintaining intestinal barrier function, and reducing blood lipopolysaccharide (LPS) levels, thereby alleviating systemic inflammation and improving insulin resistance [88]. Similarly, PLP ameliorates type 2 diabetes by regulating gut microbiota and bile acid metabolism, promoting SCFA production and GLP-1 secretion, and ultimately increasing insulin release and lowering blood glucose [93].

In conclusion, the bioactivities of Sanghuang polysaccharides, which possess complex and diverse chemical structures, arise from the interplay of multiple structural features. Future research should prioritize the standardization of extraction and purification protocols, elucidate quantitative structure-activity relationships, and facilitate the rational development of polysaccharide-based drugs or functional foods.

3.3 Key Small-Molecule Bioactives in Sanghuang

Below the section on polysaccharides, the diverse pharmacological activities of *Sanghuangporus* fungi—stem from a wide array of other small-molecule metabolites. These compounds, which accumulate differentially in fruiting bodies and mycelia, constitute the core chemical basis for its antitumor, immunomodulatory, and other therapeutic effects. To date, 48 major metabolites have been identified and are systematically listed in Table 2 (Ref. [94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124]), and their corresponding chemical structures are presented in Figs. 3,4,5. They primarily belong to classes such as phenylpropanoids, terpenoids, furans, and other phenolic compounds.

3.3.1 Phenylpropanoids: A Predominant and Multifunctional Class

Phenylpropanoids are the most abundant class of small molecules in *Sanghuangporus* and are also the most pharmacologically diverse. Isolated from both fruiting bodies and mycelium, they exhibit a broad spectrum of bioactivities, ranging from well-documented antitumor, anti-inflammatory, and antioxidant effects to antidiabetic, antimicrobial, antiviral, anti-complementary, cardioprotective, and gastroprotective properties.

Specifically, anti-inflammatory activity is notable in 3,4-dihydroxybenzalacetone (1) [94]. Potent antitumor effects *in vitro* and *in vivo* have been reported for compounds 1, meshimakobnol A (2), meshimakobnol B (3), hispidin (4), and phellifuropyranone A (5) [95,96,97,98]. The antioxidant capacity of sanghuang is primarily attributed to mycelium-derived compounds such as hispidin (4), inotilone (6), caffeic acid (7) [99,100]; among these, compounds 6 also exhibit antiviral properties [125]. Antidiabetic potential has been observed in multiple phenyl-

Table 2. Summary of bioactive constituents isolated from *Sanghuangporus*.

Chemical Class & Compounds	Reported Bioactivities	Reference(s)
Phenylpropanoids		
3,4-Dihydroxybenzalacetone (1)	Anti-inflammatory	[94]
Meshimakobnol A (2), B (3), Hispidin (4), Phellifuopyranone A (5), 3,4-dihydroxybenzalacetone (1)	Antitumor (<i>in vitro</i> & <i>in vivo</i>)	[94,95,96,97,98]
Hispidin (4), Inotilone (6), Caffeic acid (7)	Antioxidant (<i>in vitro</i> & <i>in vivo</i>)	[99,100]
Hispidin (4), Phelligrider A (8), Hypholomine B (9), Interfungin A (10), Protocatechualdehyde (11), Davallialactone (12), Inoscavin A (13)	Antidiabetic	[101,102,103,104,105]
Phellinstatin (14)	Antimicrobial (against <i>S. aureus</i> and MRSA)	[106]
Hispidin (4)	Cardioprotective	[107]
Caffeic acid	Beneficial health effects	[108]
Terpenoids and Sterols		
Gilvsins A–D, Igniarens A–C, Phellilins A–C (15–24)	(Structures reported, bioactivities implied for class)	[109,110,111]
Phellinignincisterols A–C (25–27)	Act as chemotaxonomic markers	[112]
Phellilane L (28), Phellidene E (29)	Antimicrobial (against <i>P. gingivalis</i>)	[113,114]
Atractylenolide I (30)	Antitumor	[115]
Phellinulin derivatives (31–41)	Hepatoprotective	[116,117,118]
Furans		
Phellinone (42)	Broad-spectrum Antimicrobial	[119]
Phellinusfurans A & B (43, 44)	Inhibit classical complement pathway (non-cytotoxic)	[120]
5-Hydroxymethylfurfural (45)	Antidiabetic	[121]
Other Constituents		
Ellagic acid (46)	Anti-hyperglycemic	[104]
Hispolon (47)	Anti-inflammatory, Antitumor	[122,123,124]
Ergothioneine (48)	Antidiabetic	[103]

Footnotes: This table organizes the bioactive compounds from *Sanghuangporus* by chemical class. Compound numbers in parentheses (e.g., 1, 2) correspond to identifiers used in the source text and figures (e.g., Fig. 3). For phenylpropanoids, please note that compounds 4 (hispidin) and 7 (4-(3,4-dihydroxyphenyl)-3-buten-2-one) are listed multiple times as they exhibit multiple, distinct bioactivities supported by different referenced studies. Bioactivities and associated references are summarized as reported in the primary literature.

propanoids, including hispidin (4), phelligrider A (8), hypholomine B (9), interfungin A (10), protocatechualdehyde (11), davallialactone (12), and inoscavin A (13) [101,102,103,104,105]. Antimicrobial activity is exemplified by phellinstatin (14), effective against *Staphylococcus aureus* and MRSA [106]. Other notable effects include the cardioprotective action of hispidin (4) [107] and Caffeic acid shows beneficial effects against cancer, diabetes, atherosclerosis, Alzheimer's disease, and bacterial and viral infections [108]. In total, fourteen distinct phenylpropanoids with significant pharmaceutical potential have been identified from *Sanghuangporus*.

3.3.2 Terpenoids and Sterols

Terpenoids, including sesqui-, di-, and triterpenes, represent another major class of bioactive small molecules in *Sanghuangporus*. Ten terpenoids, such as gilvsins A–

D [109], igniarens A–C [110], and phellilins A–C (compounds 15–24) [111], have been isolated from its fruiting bodies. These are accompanied by three unique steroids, phellinignincisterols A–C (26–28), which function as chemotaxonomic markers for this fungus (Figs. 4,5) [112]. The mycelium also produces diverse terpenoids, with fourteen pharmacologically active compounds reported [113,114,115,116]. Notable examples with antimicrobial activity against *Porphyromonas gingivalis* include phellilane L (28) and phellidene E (29) [113,114], while atractylenolide I (30) exhibits antitumor properties [115]. Furthermore, a series of phellinulin derivatives (31–41) demonstrate hepatoprotective effects, providing a basis for exploring SAR in liver protection [116,117,118]. Elucidating the precise SAR of these terpenoids, given their diverse pharmacological profile, remains a crucial research frontier for guiding the rational design of novel therapeutics.

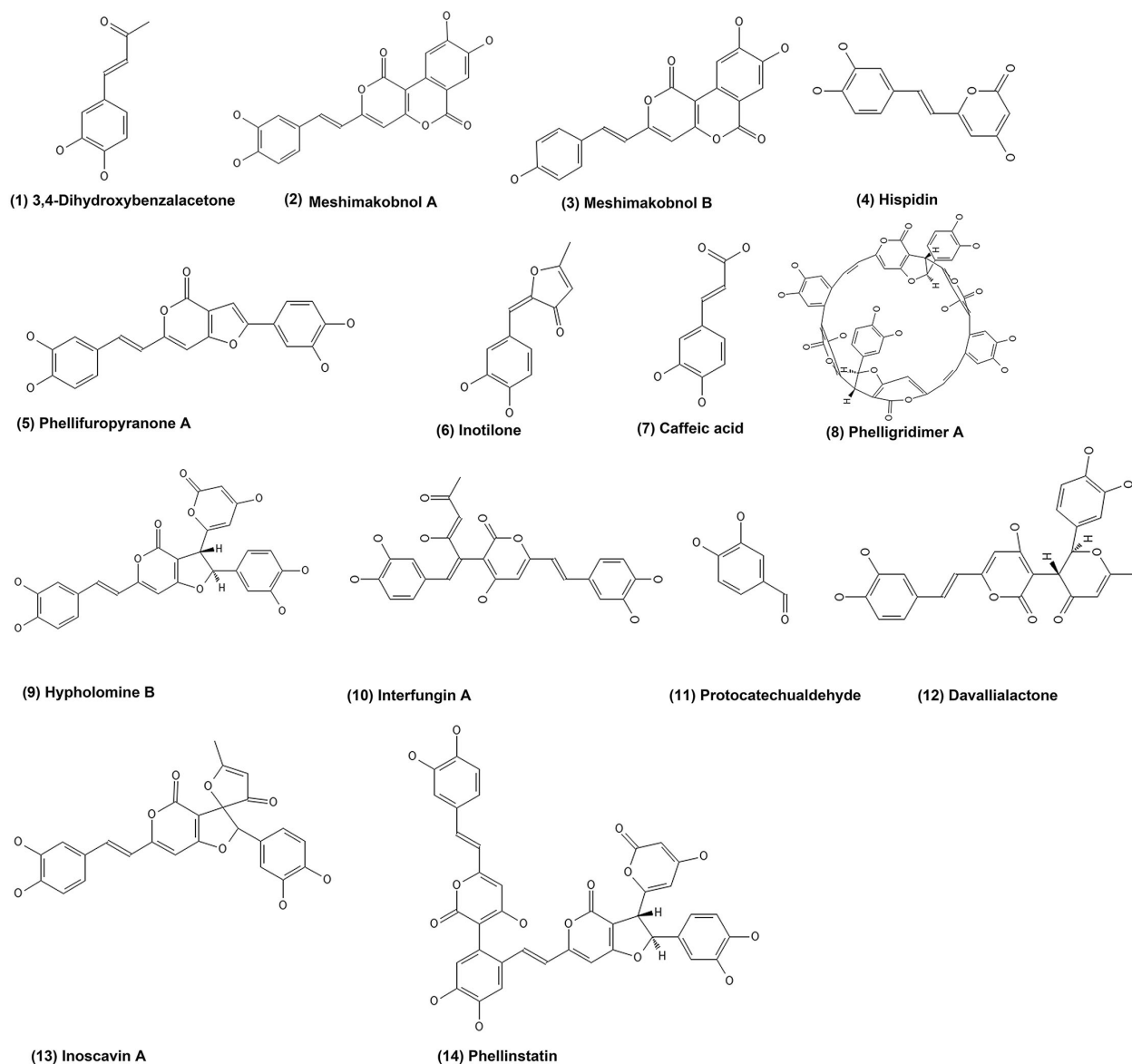


Fig. 3. Chemical structures of phenylpropanoids (1–14) isolated from *Sanghuangporus*.

3.3.3 Furans

Furan derivatives represent another bioactive class of metabolites isolated from *Sanghuangporus*. Phellinone (42), obtained from the mycelium, displays broad-spectrum antimicrobial activity [119]. From the fruiting bodies, regioisomeric phellinusfurans A and B (43, 44) inhibit the classical complement pathway without cytotoxicity to human keratinocytes [120]. Additionally, 5-Hydroxymethylfurfural (5-HMF), an active monomer of the anti-diabetic traditional Chinese medicine Prepared *Rehmannia glutinosa*, exerts anti-diabetic protective effects by enhancing autophagy and attenuating oxidative stress-induced apoptosis in pancreatic β -cells [121].

3.3.4 Other Bioactive Constituents

Sanghuangporus also produces other distinct bioactive compounds, such as ellagic acid (46), the hispidin derivative hispolon (47), and ergothioneine (48). These exhibit anti-hyperglycemic [104], anti-inflammatory/antitumor [122,123,124], and antidiabetic [103] effects, respectively, further enriching the fungus's pharmacopeia.

4. Pharmacological Activities and Mechanisms

Sanghuangporus extracts and purified compounds exhibit a broad spectrum of biological activities, which are known to involve complex interactions with multiple cellular pathways. To elucidate these multifaceted mechanisms,

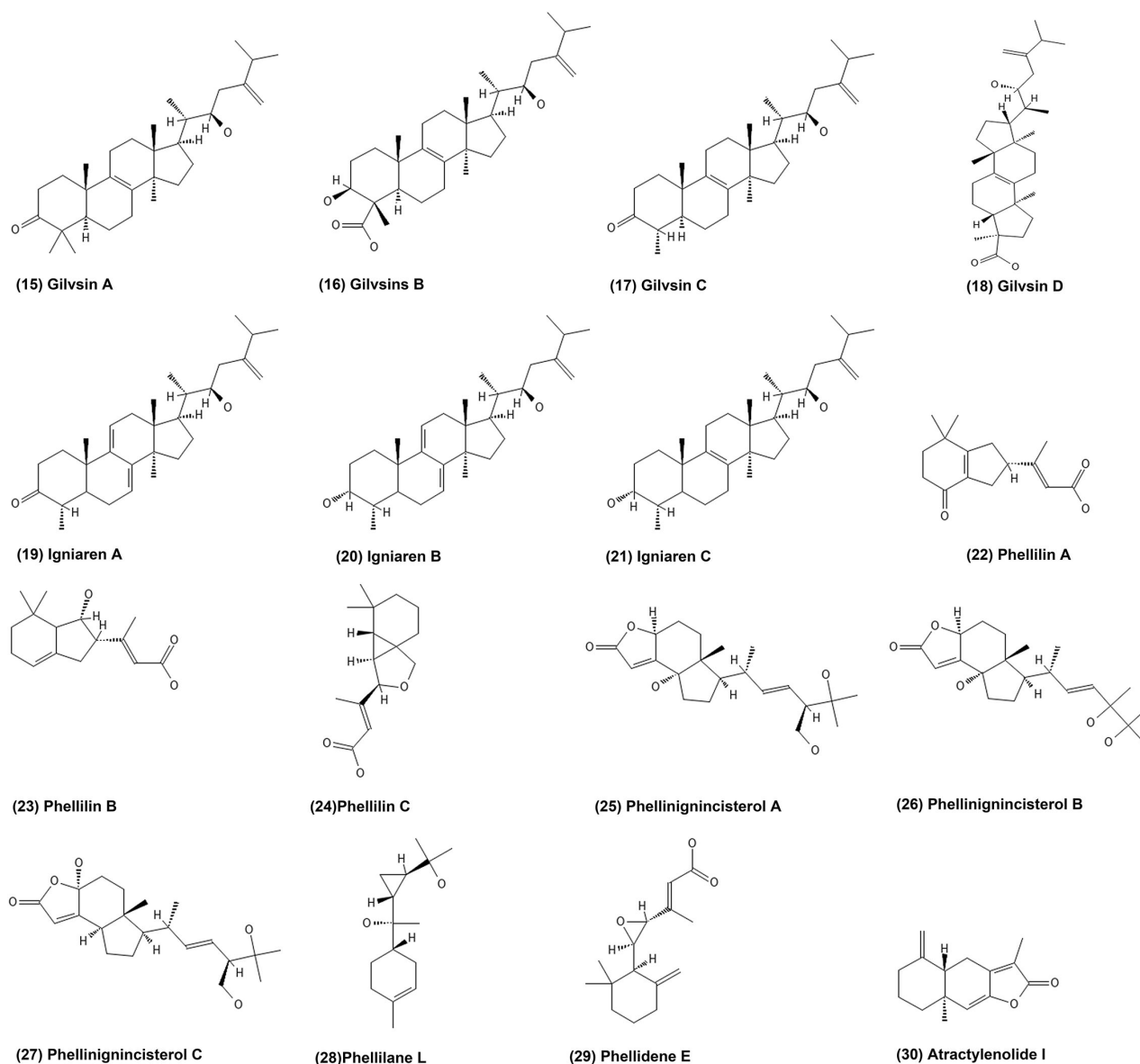


Fig. 4. Chemical structures of terpenoids (16–25, 29–31), and steroids (26–28) isolated from *Sanghuangporus*.

the following sections synthesize the observed effects according to major disease areas and physiological systems, thereby shifting from a compound-centric classification to a more integrated, mechanism-based perspective.

4.1 Anticancer and Immunomodulatory Activities

The extensively documented anticancer potential of *Sanghuangporus* involves both direct cytotoxicity and immunomodulation, with high-molecular-weight β -glucan polysaccharides playing a central role.

Their direct antitumor effects include inhibiting the proliferation, migration, and invasion of various cancers (e.g., lung, liver, cervical, colorectal, and breast). These effects are mediated by inducing apoptosis and cell cycle arrest (primarily in S and G0/G1 phases) through modulation of key pathways, including STAT3, p53, and

VDR/Wnt [126,127,128,129,130]. Apoptosis is specifically triggered via regulation of the Bcl-2/Bax ratio, caspase activation, and disruption of mitochondrial membrane potential [64,130].

Beyond these direct cytotoxic effects, the polysaccharides exert immunostimulatory actions. They activate dendritic cells and macrophages through MAPK/NF- κ B pathways, thereby enhancing the secretion of IL-12, IFN- γ , and NO and promoting phagocytosis [131,132,133]. In immunosuppressed models, they aid in restoring thymic and splenic tissues [133] and modulate the gut-immune axis by influencing processes such as L-arginine biosynthesis and T-cell activation [134]. Furthermore, a specific polysaccharide fraction, SVPS2, enhances the efficacy of conventional chemotherapeutics while reducing their toxicity [65,135,136]. Notably, polysaccharides derived from fruit-

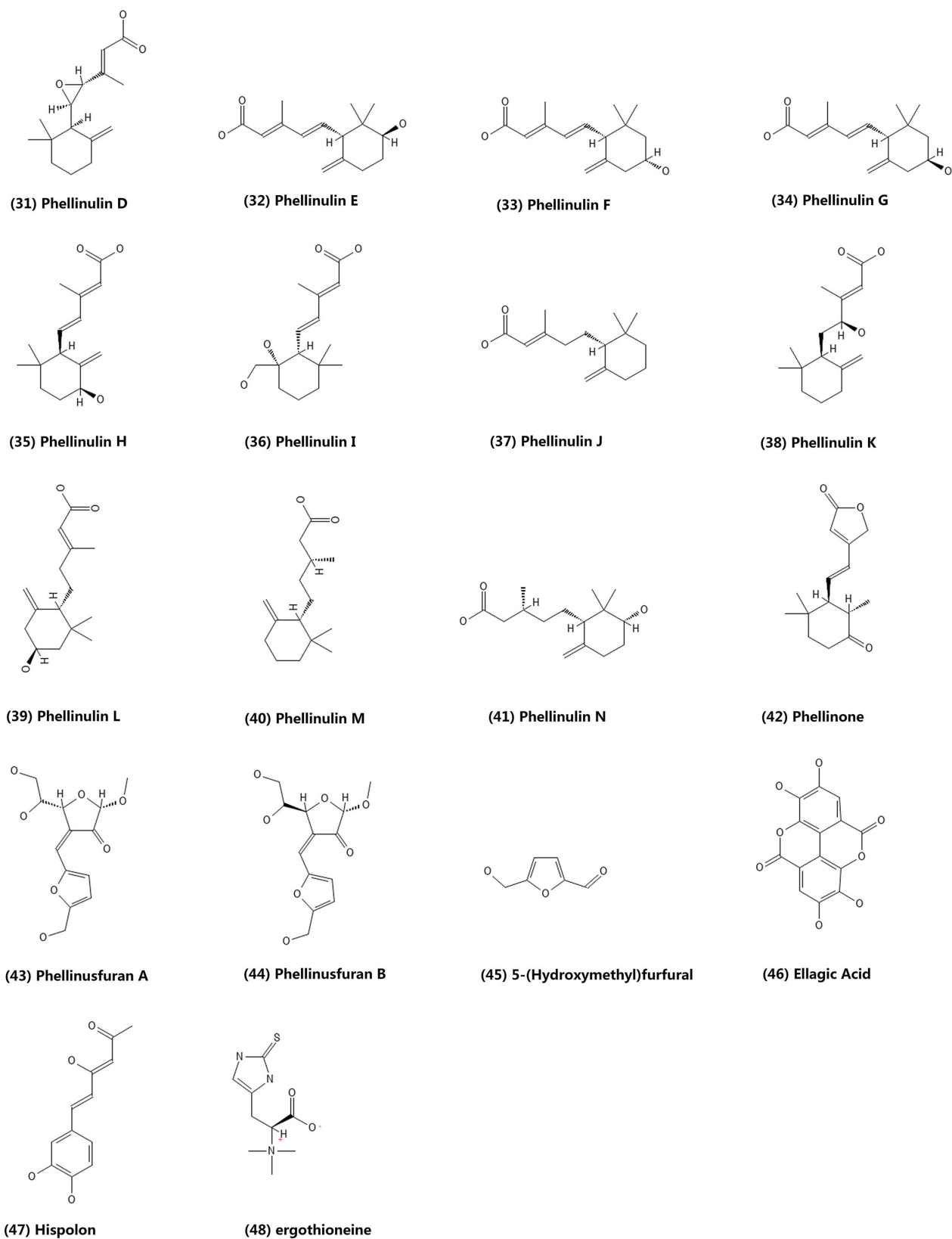


Fig. 5. Chemical structure of bioactive components isolated from *Sanghuangporus*. Terpenoids (31–41), Furans (42–45) and others (46–48).

ing bodies generally exhibit stronger antitumor activity than those from mycelia [66].

Complementing the polysaccharides, polyphenolic compounds such as hispidin and hispolon significantly contribute to anticancer activity. For instance, hispolon suppresses LPS-induced inflammatory responses, oxidative stress, and apoptosis [137]. In colon cancer models, polyphenols induce mitochondrial-mediated apoptosis and S-phase cell cycle arrest [138], whereas in lung cancer models, polyphenols promote apoptosis by increasing ROS and reducing mitochondrial membrane potential [122,139]. *S.sanghuang* total triterpenoid extracts (STTE) also demonstrate notable antitumor and antibacterial activities [51,140].

In summary, the anticancer mechanism of *Sanghuangporus* is multifaceted, integrating immune activation, apoptosis induction, anti-proliferative effects, and the suppression of metastasis and angiogenesis.

4.2 Antioxidant and Anti-Inflammatory Activities

The antioxidant and anti-inflammatory properties of *Sanghuangporus* underpin many of its therapeutic effects, resulting from the synergistic action of polyphenols, flavonoids, triterpenoids, and polysaccharides. These components scavenge free radicals (e.g., DPPH, ABTS, hydroxyl, superoxide anions) and bolster endogenous antioxidant defenses by upregulating enzymes such as SOD, CAT, and GSH-Px [51,141,142,143,144]. Composition-activity analyses suggest that flavonoids and ascorbic acid are the primary contributors, with polyphenols and triterpenoids playing secondary roles, while polysaccharides contribute to a lesser extent [142].

Closely linked to its antioxidant action, the anti-inflammatory activity involves suppressing key pro-inflammatory signaling pathways. For instance, polysaccharides inhibit the MyD88/TRAF6/NF- κ B/p38 axis, thereby reducing the production of ROS and pro-inflammatory cytokines like TNF- α and IL-1 β [145,146,147]. Meanwhile, phenolics such as hispolon attenuate inflammation by modulating the TLR4/PI3K/Akt/mTOR, NF- κ B, and MAPK cascades [115,137]. These combined mechanisms explain the efficacy of *Sanghuangporus* extracts in mitigating inflammatory conditions, including acute lung injury (ALI), idiopathic pulmonary fibrosis (IPF) [148,149,150], and ulcerative colitis [35], where they reduce inflammatory cell infiltration and levels of MPO, HMGB1, TGF- β , and IL-6.

4.3 Metabolic Regulation (Antidiabetic, Hypolipidemic, and Anti-Gout Effects)

Sanghuangporus shows significant promise in managing metabolic disorders through multi-target mechanisms.

4.3.1 Antidiabetic and Hypolipidemic Effects

Polysaccharides are central to these effects. They improve insulin sensitivity and glucose metabolism by activating the PI3K/Akt pathway, inhibiting carbohydrate-digesting enzymes (α -glucosidase, α -amylase), and promoting glycogen synthesis [15,32]. In H22 tumor-bearing mice, *S. mongolicus* ethyl acetate extract (EAE) exhibited the highest tumor inhibition rate without toxicity and suppressed tumor growth via multi-target regulation involving immune responses, amino acid biosynthesis, and mitochondrial apoptosis pathways [151]. These metabolic benefits are also mediated through gut microbiota modulation. For example, intervention with an *S. vaninii* mixture (SVM) in diabetic mice altered gut microbial composition—increasing Bacteroidetes and Akkermansia while decreasing Firmicutes and *Lactobacillus*—and regulated functional modules involved in fatty acid and glycerolipid metabolism. These changes correlated with improved glucose/lipid parameters and reduced inflammation [152]. Polysaccharide-protein complexes also exhibit direct lipid-lowering properties [153]. Beyond polysaccharides, polyphenols contribute by ameliorating obesity-associated insulin resistance through inhibition of macrophage-adipocyte crosstalk and activation of the IRS1/PI3K/Akt pathway [28,124].

4.3.2 Anti-Gout Effects

Extracts, particularly from *S. vaninii*, alleviate hyperuricemia and gouty arthritis. They reduce serum uric acid levels by downregulating xanthine oxidoreductase (XOR) and upregulating hypoxanthine-guanine phosphoribosyltransferase [154,155]. Their inherent anti-inflammatory and antioxidant properties further suppress synovial swelling and oxidative stress in gout models [154,156]. This positions *Sanghuang* as a potential natural alternative to conventional XOR inhibitors such as allopurinol.

4.4 Organoprotective Effects (Hepatic, Pulmonary, and Neuroprotective)

4.4.1 Hepatoprotection

Sanghuangporus extracts protect against chemical-induced liver injury (e.g., from CCl₄, paracetamol, chlorpyrifos). The protective mechanisms involve potent free radical scavenging, inhibition of tyrosinase activity [143,144], mitigation of ferroptosis, suppression of hepatic stellate cell activation, and restoration of gut-liver axis homeostasis [157,158]. Additionally, they modulate the TLR4/NF- κ B pathway and influence key metabolic processes such as amino acid and linoleic acid metabolism [8,159].

4.4.2 Pulmonary Protection

The fungus alleviates acute lung injury (ALI) and idiopathic pulmonary fibrosis (IPF) through its potent anti-

inflammatory and antioxidant properties. These effects are mediated by the modulation of multiple pathways, including TLR4/PI3K/Akt/mTOR, NF- κ B, MAPK, TGF- β /SMAD3, and Nrf2/HO-1, leading to a reduction in profibrotic mediators and an enhancement of antioxidant defenses [43,148,149,150].

4.4.3 Neuroprotection

Bioactive components show promise against neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD). The ethyl acetate fraction (EAF) of *Inonotus sanghuang*, rich in phenolic compounds, exerts protective effects by enhancing antioxidant enzyme activities (e.g., GSH-Px, SOD), reducing levels of NO, MDA, A β , and pro-inflammatory cytokines (IL-1 β , IFN- γ , IL-6, TNF- α), and modulating the Bax/Bcl-2 ratio and caspase activation [160]. Specifically, hispolon confers neuroprotection through acetylcholinesterase inhibition and anti-amyloid- β aggregation [161]. Polysaccharide fractions also demonstrate protective effects in AD-modeled cell lines [162]. Collectively, these benefits are largely attributed to the mitigation of oxidative stress and neuroinflammation, which are key drivers of neurodegeneration [10,160,163].

4.5 Other Health-Promoting Activities

4.5.1 Anti-Aging Effects

Extracts extend lifespan in *C. elegans* models by up-regulating longevity-related genes (e.g., *daf-16*, *sir-2.1*) and reducing aging biomarkers such as lipofuscin and ROS [7,141]. Furthermore, phenolic and flavonoid constituents inhibit key skin-aging enzymes (tyrosinase, elastase, collagenase), contributing to observed anti-wrinkle activity *in vitro* [12,164,165].

4.5.2 Sleep Improvement

STTE show potential as safe sleep aids, acting through multi-target mechanisms. They enhance GABAergic and serotonergic neurotransmission, modulate REM sleep, downregulate pro-inflammatory cytokines like IL-6, and activate the Nrf2/ARE antioxidant pathway [166,167,168,169,170]. The presence of hispidin is implicated in mediating these effects [166].

4.5.3 Muscle Strengthening

Hispidin-enriched mycelial extract (SS-MN4) ameliorates disuse muscle atrophy and improves physical endurance in rodent models. It restores muscle mass, enhances running performance, increases hepatic and muscle glycogen reserves, and reduces blood urea nitrogen. These benefits are likely mediated through the activation of pathways such as SIRT1/PGC-1 α [20,171].

In summary, the broad therapeutic profile of *Sanghuangporus* stems from the concerted, multi-target action of its diverse bioactive compounds on interconnected physiological pathways, thus underpin-

ning its significant potential against complex chronic diseases. The detailed pharmacological activities and mechanisms are summarized in Table 3 (Ref. [7,8,10,12,15,28,32,43,51,64,65,66,115,122,124,126,127,128,129,130,131,132,133,134,135,136,137,138,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172]).

5. Clinical Applications and Trials

While *Sanghuangporus* has a millennia-long history in traditional medicine and abundant preclinical data, its translation into evidence-based clinical practice remains in the early stages. Current clinical evidence is sparse, derived from a limited number of small-scale studies, and often lacks the methodological rigor needed for definitive conclusions.

5.1 Existing Clinical Evidence: A Summary

The few clinical studies to date have primarily explored the effects of *Sanghuangporus* extracts on immune function, vascular health, and osteoarthritis.

5.1.1 Immune Function in Healthy Smokers

A randomized, double-blind, placebo-controlled trial investigated the impact of oral *Sanghuangporus* extract (1000 mg/day) in healthy smokers. The study reported a significant enhancement of natural killer (NK) cell activity and a reduction in systolic blood pressure in the intervention group compared to placebo, suggesting potential benefits for immune enhancement and vascular health in this population [173].

5.1.2 Vascular and Metabolic Parameters

Further analysis from the same cohort, employing an integrative omics approach, indicated that the extract improved arterial stiffness. This effect was linked to enhanced nitric oxide (NO) bioavailability via endothelial nitric oxide synthase (eNOS) activation and modulation of metabolic pathways such as the tricarboxylic acid (TCA) cycle and arginine/proline metabolism [174].

5.1.3 Knee Osteoarthritis

A pilot randomized controlled trial (RCT) evaluated *Sanghuangporus* Extract (1500 mg/day) for managing knee osteoarthritis [175]. While the primary outcome measures (e.g., Western Ontario and McMaster Universities Osteoarthritis Index scores) did not show statistically significant improvement, trends toward pain reduction and enhanced quality of life were observed. This finding is consistent with the anti-inflammatory properties reported in patients with osteoarthritis [176].

Table 3. Summary of the pharmacological activities and mechanisms of *Sanghuangporus*.

Pharmacological Activity	Key Mechanisms of Action	Major Bioactive Components Involved	References
1. Anticancer & Immunomodulatory			
Direct Cytotoxicity	Induces apoptosis & cell cycle arrest via STAT3, p53, VDR/Wnt pathways; regulates Bcl-2/Bax, caspases, MMP.	High-MW β -glucan polysaccharides, Polyphenols (e.g., hispidin, hispolon), Triterpenoids.	[64,65,66,122,126,127,128,129,130,135,136,137,138,140,172]
Immunostimulation	Activates DCs/Macrophages via MAPK/NF- κ B; enhances IL-12, IFN- γ , NO secretion, phagocytosis; restores immune organs; modulates gut-immune axis.	Polysaccharides.	[65,131,132,133,134,135,136]
Chemo-adjuvant & Anti-metastasis	Enhances chemo-efficacy while reducing toxicity; inhibits cancer cell proliferation, migration, invasion, and angiogenesis.	Polysaccharides (SVPS2).	[65,126,127,128,129,130,135,136]
2. Antioxidant & Anti-inflammatory			
Antioxidant	Scavenges free radicals (DPPH, ABTS, $\bullet$ OH $O_2^{\bullet-}$); upregulates endogenous enzymes (SOD, CAT, GSH-Px).	Flavonoids, Ascorbic acid, Polyphenols, Triterpenoids, Polysaccharides.	[51,141,142,143,144]
Anti-inflammatory	Inhibits MyD88/TRAF6/NF- κ B/p38 & TLR4/PI3K/Akt/mTOR pathways; reduces ROS, TNF- α , IL-1 β , IL-6, HMGB1, TGF- β ; attenuates inflammatory cell infiltration.	Polysaccharides, Phenolics (e.g., hispolon).	[115,137,145,146,147,148,149,150]
3. Metabolic Regulation			
Antidiabetic	Activates PI3K/Akt/IRS1 pathway; inhibits α -glucosidase/ α -amylase; promotes glycogen synthesis; modulates gut microbiota ($\uparrow$ Bacteroidetes, Akkermansia).	Polysaccharides, Polyphenols.	[15,28,32,124,151,152,153]
Hypolipidemic	Modulates lipid metabolism; inhibits macrophage-adipocyte crosstalk.	Polysaccharides, Polysaccharide-protein complexes.	[15,28,124,152,153]
Anti-gout	Downregulates xanthine oxidoreductase (XOR); upregulates HGPRT; reduces serum uric acid; alleviates synovial inflammation & oxidative stress.	Extracts (esp. from <i>S. vaninii</i>).	[154,155,156]
4. Organoprotective			
Hepatoprotection	Scavenges free radicals; inhibits tyrosinase; mitigates ferroptosis; suppresses HSC activation; restores gut-liver axis; modulates TLR4/NF- κ B & metabolism.	Extracts.	[8,143,157,158,159]
Pulmonary Protection	Modulates TLR4/PI3K/Akt/mTOR, NF- κ B, MAPK, TGF- β /SMAD3, Nrf2/HO-1 pathways; reduces profibrotic mediators.	Extracts, Bioactive components.	[43,148,149,150]
Neuroprotection	Enhances antioxidant enzymes (GSH-Px, SOD); reduces NO, MDA, A β , pro-inflammatory cytokines; modulates Bax/Bcl-2 & caspases; inhibits AChE & A β aggregation.	Rich Ethyl-acetate fraction (EAF), Hispolon, Polysaccharides.	[10,160,161,162,163]
5. Other Activities			
Anti-aging	Upregulates longevity genes (<i>daf-16</i> , <i>sir-2.1</i>); reduces lipofuscin & ROS; inhibits skin-aging enzymes (tyrosinase, elastase, collagenase).	Extracts, Phenolics, Flavonoids.	[7,12,141,164,165]
Sleep Improvement	Enhances GABAergic/serotonergic transmission; modulates REM sleep; down-regulates IL-6; activates Nrf2/ARE pathway.	STTE, Hispidin.	[166,167,168,169,170]
Muscle Strengthening	Activates SIRT1/PGC-1 α pathway; restores muscle mass & glycogen reserves; improves endurance; reduces blood urea nitrogen.	Hispidin-enriched extract (SS-MN4).	[171]

Footnote: This table synthesizes the major pharmacological effects of *Sanghuangporus* extracts and compounds, organizing them by therapeutic category, underlying biological mechanisms, and key constituent classes. The referenced mechanisms are primarily derived from *in vitro* and preclinical *in vivo* studies as cited.

5.1.4 Type 2 Diabetes Management

Although direct human trial data within this review is limited for diabetes, one referenced study indicates that polysaccharides from *Sanghuangporus* ameliorated insulin resistance in diabetic models by upregulating glucose transporters and inhibiting hepatic gluconeogenic enzymes [177], providing a mechanistic basis for clinical investigation.

5.2 Critical Analysis of Trial Scale, Quality, and Conclusions

A critical evaluation of the existing clinical landscape reveals significant limitations that constrain the interpretability and generalizability of the findings.

Limited Scale and Pilot Nature: The majority of the reported studies, including the osteoarthritis trial [175], are explicitly pilot studies. They are characterized by small sample sizes, which increase the risk of type II errors (failing to detect a true effect) and limit the statistical power to draw firm conclusions. The findings, while indicative, require validation in larger, adequately powered cohorts.

Variable Methodological Rigor: The immune function trial in smokers employed a randomized, double-blind, placebo-controlled design, which is the gold standard for clinical intervention studies, enhancing the reliability of its positive findings [173]. However, details on randomization procedures, allocation concealment, and handling of dropouts are not fully elaborated in the summary provided. The reliance on surrogate markers (e.g., NK cell activity, blood pressure) rather than hard clinical endpoints (e.g., incidence of infection or cardiovascular events) also necessitates cautious interpretation, as biomarker changes do not always translate to tangible health benefits.

Inconsistent and Preliminary Conclusions: The clinical conclusions are preliminary and non-uniform. For immune and vascular health, results are promising but derived from a specific sub-population (smokers). For osteoarthritis, the results are negative or inconclusive on primary endpoints, highlighting that efficacy may be condition-specific and dose-dependent. There is a complete absence of large-scale, multi-center Phase III RCTs for any major disease indication, such as cancer adjuvant therapy, diabetes management, or neurodegenerative diseases, where preclinical data is most compelling.

Lack of Standardization and Pharmacokinetic Data: None of the summarized trials addresses the fundamental challenge of product standardization. The extracts used likely vary in their profiles of polysaccharides, polyphenols, and other bioactive compounds, affecting reproducibility. Furthermore, critical pharmacokinetic data—including absorption, distribution, metabolism, and excretion (ADME) of key constituents like hispidin or specific polysaccharides—are missing from human studies. This gap obscures understanding of optimal dosing regimens and bioavailability.

Safety Reporting in Long-Term Use: While the reviewed trials report no major adverse events in their short durations, systematic long-term safety data and comprehensive assessments of potential herb-drug interactions are lacking. This is particularly important for chronic conditions requiring prolonged supplementation and for patients on concomitant pharmaceutical therapies.

5.3 Conclusion and Future Directions for Clinical Research

In conclusion, the clinical application of *Sanghuangporus* is currently supported by limited evidence from small-scale trials, suggesting potential in specific areas. The field is significantly constrained by the absence of large definitive trials, standardized formulations, and human pharmacokinetic data. To bridge this gap, future research must prioritize:

1. Conducting large-scale, rigorous RCTs with chemically characterized extracts for priority indications.
2. Incorporating pharmacokinetic-pharmacodynamic studies to establish dosing rationale and confirm mechanisms in humans.
3. Implementing robust, long-term safety surveillance in clinical trials.
4. Exploring innovative, biomarker-driven trial designs for this complex natural product.

Until these steps are taken, the full transition of Sanghuang from a traditional remedy to a globally recognized, evidence-based therapeutic agent cannot be achieved.

6. Conclusions and Future Perspectives

Sanghuangporus is a revered traditional medicinal fungus historically used for hemostasis, analgesia, and treating diarrhea [178]. Modern research has significantly expanded its pharmacological profile, revealing broad therapeutic potential. This is most prominent in oncology, where polysaccharides and polyphenols like hispolon have emerged as promising candidates, although their precise molecular mechanisms require further elucidation.

Beyond its anticancer properties, Sanghuang exhibits a wide spectrum of bioactivities, including anti-inflammatory, immunomodulatory, antioxidant, antimicrobial, antiviral, hypoglycemic, hepatoprotective, and neuroprotective effects. These diverse functions are attributed to a range of bioactive components—primarily polysaccharides, flavonoids, triterpenoids, and polyphenols—which collectively modulate inflammation, oxidative stress, immunity, and tumorigenesis, while also benefiting metabolic, neurological, and musculoskeletal health. *In vivo* studies generally support its safety profile, highlighting its potential as a functional food ingredient.

The bioactivity of its extracts is highly dependent on the extraction method (e.g., hot water, ethanol, deep eutectic solvents, alkaline solutions), as well as on the fungal species and geographic origin. For instance, polysac-

charides, which are often acidic or neutral with flexible chain structures, are linked to specific immunomodulatory roles, whereas flavonoids demonstrate pronounced antitumor effects. However, the precise structural details of many key compounds remain unclear, necessitating more targeted isolation and characterization strategies.

A major historical challenge for coherent research has been inconsistent phylogenetic classification, with species frequently misassigned to genera like *Inonotus* or *Phellinus*. Recent advances in genomic and mitochondrial sequencing are helping to clarify the taxonomy and evolution of the *Sanghuangporus* genus, a development expected to unify future research efforts and accelerate its translation into standardized medicinal and functional food products.

Author Contributions

Conceptualization, YQ and GM; methodology and design of the study, XC and XZ; investigation, RR, WQ, and SW; writing—original draft preparation, YQ; writing—review and editing, XC, XZ, and GM; supervision, GM; project administration, GM. All authors have read and agreed to the published version of the manuscript. All authors contributed to editorial changes in the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

The authors thank the editing assistance of Dr. Jaime A. Teixeira da Silva (Independent researcher, Japan).

Funding

This work was financially supported by the Shandong Xiehe University High level Talent Start up Fund (SDX-HQD2024030), Guangdong Key Areas Biosafety Project (2022B1111040003).

Conflicts of Interest

The authors declare no conflicts of interest.

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