Engineering in Life Sciences

WILEY-VCH

Engineering in Life Sciences

REVIEW OPEN ACCESS

Polyporus umbellatus, A Precious Rare Fungus With Good Pharmaceutical and Food Value

Sizhu Ren[1,2,3] | Hua Liu[1] | Qing Sang[1] | Yifan Sun[1] | Liyan Li[1] | Wenjie Chen[1,2,3]

[1]College of Life Sciences, Langfang Normal University, Langfang, Hebei, China | [2]Technical Innovation Center for Utilization of Edible and Medicinal Fungi in Hebei Province, Langfang, Hebei, China | [3]Edible and Medicinal Fungi Research and Development Center of Hebei Universities, Langfang, Hebei, China

Correspondence: Wenjie Chen (chenwenjieliu@163.com)

Received: 24 May 2024 | **Revised:** 27 December 2024 | **Accepted:** 2 January 2025

Funding: This study was supported by Hebei Province Modern Agricultural Industrial Technology System Innovation Team Project (Grant number: HBCT 2023090201).

Keywords: diuretic properties | medicinal ingredients | pharmacological activities | *Polyporus umbellatus*

ABSTRACT

Polyporus umbellatus is a rare porous fungus that exhibits notable pharmacological activities. Particularly, due to its diuretic properties, it is considered an important source of targeted drugs for the treatment of kidney disease. Extensive research has been conducted on this fungus, focusing not only on its challenging cultivation techniques but also on its diverse array of medicinal ingredients, including polysaccharides and steroids. These active compounds demonstrate considerable variability and exhibit a wide range of medicinal properties. As a result, extracting, separating, and purifying these active compounds has become a subject of interest. This review aims to provide a comprehensive overview of the types, structures, and physicochemical properties of these active compounds. Additionally, the medicinal effects of *P. umbellatus* are thoroughly examined, offering valuable insights into the utilization of its resources and the rational development of medical fungi.

1 | Introduction

The rise in public health awareness has sparked a new trend in the production of “drug homologous food” products and functional foods. In eastern countries, herbal medicine is gaining popularity [1]. Medicinal fungi, such as *Polyporus umbellatus*, hold a prominent position in herbal medicine owing to their antimicrobial, antiviral, and anti-inflammatory properties [2]. *P. umbellatus*, a widely distributed medicinal fungi species, can be found in Europe, North America, China, and Japan [3]. Among these countries, China is the largest producer and exporter. *P. umbellatus* is commonly used to treat various acute and chronic conditions, including diuresis, obstructed urination, and edema, and as an anticancer agent. It is also considered an ideal alternative medicine for chronic hepatitis and diabetes [4]. Consequently, the demand for *P. umbellatus* in the market is steadily increasing. At present, the wild sclerotia found in *P. umbellatus* are primarily used for medicinal purposes. However, a lack of effective resource protection measures has resulted in a considerable decline in the production of wild resources. This limitation inevitably hampers the development of related products and the wider application of pharmaceuticals [5]. Additionally, strain characteristics and degeneration, as well as the low quality and activity of wild fungal cultivation, pose challenges [6].

Morphologically, *P. umbellatus* comprises the fruiting body and subterranean sclerotia. Even though the fruiting body of *P. umbellatus* has some medicinal effects, such as improving gastrointestinal function, reducing blood sugar, and acting as an antioxidant [7], it is primarily valued for its edible mushroom, which is rich in protein, vitamins, and minerals. As for the sclerotium, it has a mild, sweet, and bland flavor [8]. However,

Summary

- The active ingredients of *Polyporus umbellatus* were full of triterpenoids, sterols, alkaloids, polypeptides, amino acids, polysaccharides, organic acids, and other compounds. This fungus has potential for the treatment and for regulation of different systems of the body. Furthermore, the extracts of mycelium and fruiting body are a collection of active compounds that are the raw materials for the synthesis of a variety of drugs. Although, the *P. umbellatus* has no or little side effect which has confirmed the safety profile of this mushroom.
- China is the main producing area of *P. umbellatus* in the world. In recent years, the extraction and processing technology of *P. umbellatus* has been maturing, combined with the nutritional and its medicinal value, a variety of deep processing products have emerged, which has greatly expanded the actual utilization range of *P. umbellatus*. Using its effective ingredients, it can be made into various functional foods and drugs, which can not only meet people's needs for nutrients, but also meet people's demands for nutrients.

the formulation of the sclerotium in nature is affected by factors such as nutrients, osmolarity, humidity, and pH [9]. Additionally, the different growth conditions can result in variations in the chemical composition and medicinal efficacy of the sclerotium. The sclerotia that grow in soil have an irregular, uneven, multi-branched, tuberous, and woody structure with a dark brown to black surface and white interior [8].

Interestingly, *P. umbellatus* cannot survive without the support of *Armillaria mellea*, and a symbiotic relationship exists between the two fungi (Figure 1). *Armillaria* thrives in the woods, and its rhizomorphs make contact with the sclerotium of *P. umbellatus*, invading its interior. The main source of nutrients for *P. umbellatus* growth is the secretion provided by *Armillaria*. Furthermore, once *Armillaria* invades the sclerotia of *P. umbellatus*, it can stimulate the sclerotia, breaking their dormancy and triggering various physiological activities and immune response mechanisms. As the hyphae cells of *P. umbellatus* become lignified, they form an isolation cavity with a structure similar to the sclerotium epidermis. *Armillaria* and a portion of *P. umbellatus* are enclosed within this isolation chamber, where *Armillaria* digests the *P. umbellatus* present in the cavity. Additionally, *P. umbellatus* can also invade or attach itself to the *Armillaria* cord to absorb its metabolites and grow new *P. umbellatus* after germination.

Once the symbiotic relationship between *P. umbellatus and A. mellea* is established, the signaling and metabolic pathways in *P. umbellatus* undergo significant changes [10]. After being infected by *A. mellea*, the sclerotium of *P. umbellatus* undergoes a significant change in its metabolic program. This shift stimulates the physiological activity of sclerotium, enabling it to absorb nutrients from *A. mellea*, the surrounding soil, and secretions from some plant roots. Additionally, the sclerotium can interact with metabolites produced by other microorganisms, allowing it to exploit various nutrient sources under natural conditions. Moreover, the growth of biological regulators involved in sclerotia formation is inhibited by *A. mellea*.

The purpose of this review is to clarify (1) the primary medicinal components of *P. umbellatus* and provide research examples, (2) recent research on the main medicinal constituents of *P. umbellatus*, and (3) its medicinal effects and applications.

2 | Medicinal Ingredients

P. umbellatus was used to improve health and promote contribute to longevity. This is mainly due to the various chemical components that have been isolated from *P. umbellatus*, including emodin [3], chrysophanol [11], and ergosterol peroxide [12] (Figure 2). Among these active ingredients, ergosterol and polysaccharides are the most important functional components [13]. Compared to other Chinese herbs, *P. umbellatus* has different active components. Even within the fruiting bodies, sclerotium and mycelium of *P. umbellatus*, there are structural, functional, and content differences in the active substances [8]. Similarly, among different from the same origin, these active compounds also vary in terms of content, activity, and effectiveness. Furthermore, there are certain differences in the composition and content of active substances at different growth stages. For example, young fruiting bodies of *P. umbellatus*, contain higher levels of protein compared to polysaccharides. However, their polysaccharide/protein ratio is lower than that of other edible mushrooms such as *G. lucidum* and *Lentinula edodes*, and so forth [14].

2.1 | Polyporus Polysaccharides

Bioactive polysaccharides have made significant progress, particularly in the fields of molecular biology and genetic engineering. As a result, the scope of prebiotics and other research has expanded from basic to applied science [15]. *Polyporus polysaccharide* (PPS) is a secondary metabolite [16]. Due to its biological activities and physicochemical properties, PPS can be used in regenerative therapies and as a nanosized drug-delivery carrier in medicine and food additives [17]. PPS is the dominant active ingredient in sclerotia or polyporus flowers [18], and it can effectively inhibit tumors, regulate immune function, and enhance radiation resistance [19]. The composition of polysaccharides is the main reason for their activity [20]. PSS mainly includes xylose–glucose, mannose, and galactose. Furthermore, the activity of PPS is also influenced by the types of sugar linkages, branch lengths, branching frequencies, molecular size, and molecular conformation [3]. However, the structural features of polysaccharides in *P. umbellatus* and their structure–activity relationship have not been fully elucidated to date. In 1980, Ueno et al. [21] isolated a soluble polysaccharide from *Grifola umbellate*, which is a homogeneous G-glucan with a molecular weight of 1,200,000. Herein, it was found that an alkali-soluble polysaccharide comprises a backbone of p-(1+3)-linked D-glucopyranosyl residues and has a single/I-D-glucopyranosyl group joined by O-6 of every third D-glucopyranosyl residue on the backbone. Two years later, Ueso et al. [22] verified the antitumor activity of the polysaccharide, which can be effectively applied against sarcoma 180. Huang et al. [23] studied

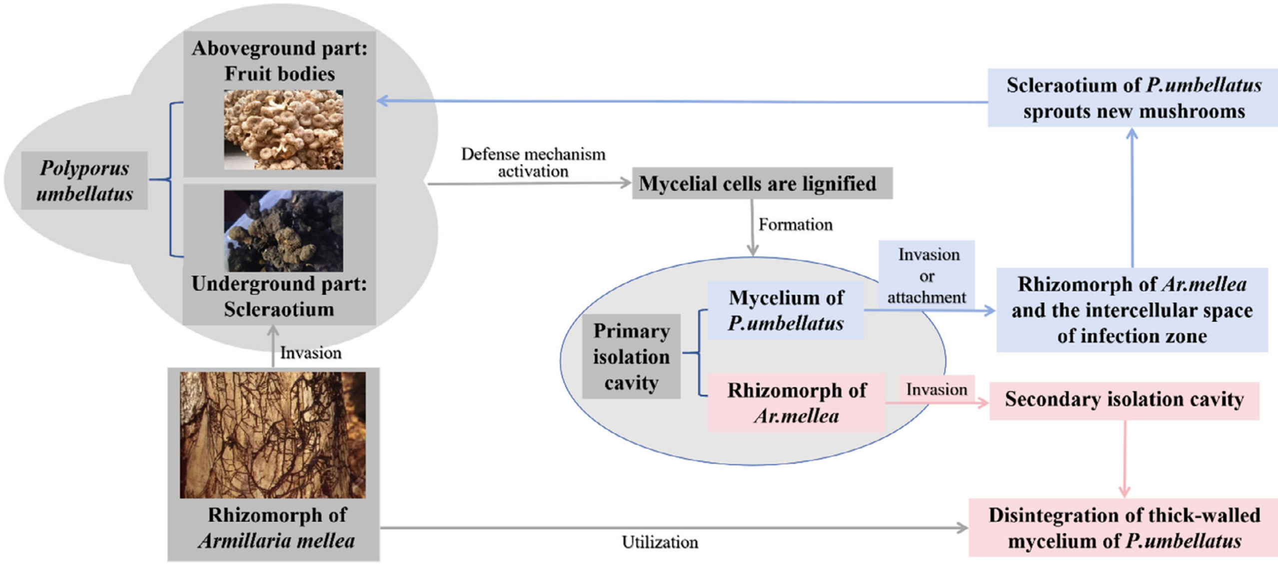

FIGURE 1 | Symbiotic relationship between *Polyporus umbellatus* and *Armillaria mellea*.

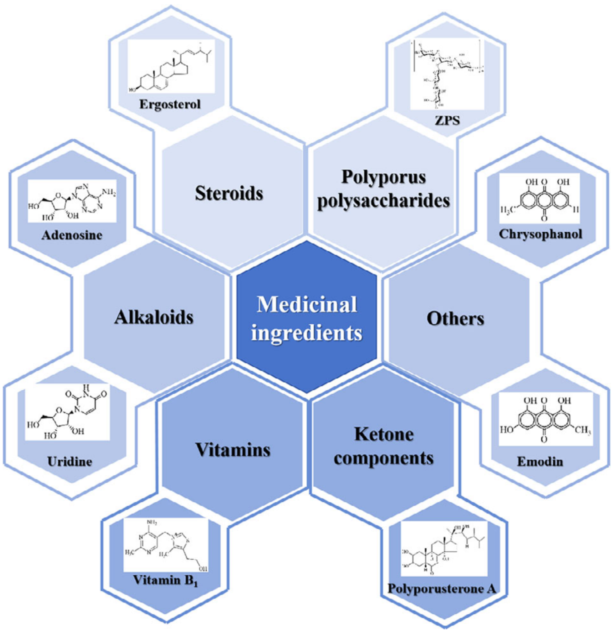

FIGURE 2 | Medicinal ingredients of *Polyporus umbellatus*.

the relationship between culture conditions, mycelial growth, and exopolysaccharide (EPS) production. The best medium constituents for production were mixtures of glucose and skim milk with some mineral salts. The highest specific EPS yield can reach 112.35 mg/g, which is critical for mushroom cultivation engineering in further industrial production and applications.

PPS exhibits strong antioxidant activity, indicating its effective scavenging effects on hydroxyl radicals and superoxide anion radicals. The scavenging ability is positively correlated with the addition of PPS [24]. Additionally, PPS restricts tumor growth, improves systemic conditions, enhances immune function, and promotes the expression of proinflammatory mediators [25]. Moreover, the majority of the studies have shown that PPS has low or no toxicity [26]. Liu et al. [27] discovered that PPS significantly enhances the antigen-presenting capability of macrophages. Specific proteins are stimulated by TLR4 signaling, resulting in the activation of NO, IL-6, and TNF-α secretion, which can activate CD86 and CD40. PPS binds to receptors on the cell surface and induces an immunomodulatory response in macrophages. The NF-κB pathway primarily determines the possible molecular mechanism regulation. Li et al. [28] conducted a study on the PPS-induced phenotypic and functional maturation of murine bone-derived dendritic cells (BMDCs). They used flow cytometric analysis as the means of detection and observed that fluorescence-labeled PPS is specifically bound to BMDCs. This binding was blocked by unlabeled PPS and anti-Toll-like receptor 4 (TLR4). PPS promotes the activation and maturation of murine BMDCs via TLR4, contributing to the understanding of fungi-mediated immunomodulatory activity. Similar studies have been conducted by Li and coworkers [29]. They explored the molecular mechanism of macrophage responses using polysaccharides prepared from *P. umbellatus*. PPS strongly upregulated macrophage functions, such as NO production and cytokine expression. PPS significantly stimulated the proliferation and production of splenocytes. Additionally, PPS can specifically bind to target cells, exerting its immunostimulatory potency via TLR-4 activation of the signaling pathway.

In the immunomodulatory treatment of cancer, Liu et al. [27] found that PPS can effectively treat bladder cancer with minimal side effects. Additionally, they elucidated the molecular mechanism through which PPS inhibits bladder cancer. PPS plays an upstream role in the activation cascade of the nuclear factor (NF)-κB signaling pathway by interfering with IκB phosphorylation. PPS regulates NF-κB (P65) signaling by interfering with Toll-like receptor-4, INOS, and cyclooxygenase (COX-2). Other studies on the evidence of PPS inhibiting cancer include Zhang et al. [30] explored whether PPS combined with *Bacille Calmette-Guerin* (BCG) can significantly reduce cancer invasiveness in model rats. Flow cytometry was used to show that costimulatory molecules, including CD86, CD40, and TLR4/CD14, were all increased in combination with PPS and BCG. This was mainly because PPS strongly reduced side effects and displayed synergistic effects during BCG instillation in rat bladder cancer. However, PPS is unstable. Thus, Gao et al. [31] developed a new type of selenium nanoparticle that can stabilize PPS. These composites can effectively inhibit the proliferation of four cancer cell lines in a dose-dependent manner while showing no significant cytotoxicity toward three normal cell lines. Furthermore, these nanoparticles exhibited excellent storage stability at 4°C under dark conditions, showing strong potential for applications in cancer chemoprevention. Sun et al. [32] analyzed the polysaccharides from *P. umbellatus*. The molecular weight of the mycelial polysaccharide was 857 kDa, consisting of glucose and galactose in a molar ratio of 1.57:1. In comparison, the molecular weight of the fruiting body polysaccharide was 679 kDa, slightly smaller, and composed of glucose and galactose in a mole ratio of 5.42:1. However, there was no significant difference in the medicinal effects of the two. Both of them could increase the killing potency of lymphokine-activated killer and lymphokine-activated killer cells in the mouse spleen. They could also promote the proliferation of mouse B cells and T cells. PPS has an obvious inhibitory effect on *Escherichia coli* and *Staphylococcus aureus*, which is beneficial for human health.

In addition, derivatization broadens the application range of polysaccharides. Liu et al. [7] discovered that PPS exhibited significant antiviral activity against various viruses, including SARS-CoV-2 and COVID-19 in vitro. This is particularly evident in polysaccharides with sulfate functional groups. Therefore, the development of sulfated polysaccharides can be utilized as adjuvants in vaccine preparation and as components in functional foods. This plays a crucial role in enhancing host immunity and antioxidant activity.

2.2 | Steroids

Twenty-five types of steroidal substances have been isolated from *P. umbellatus*, including ergosterol, ergocalciferone, polypore steroid, acetosyringone, and more. Ergosterol is widely found in nature and is a common component of fungi. It is also an important raw material for synthesizing vitamin D [33]. Ergosta-4,6,8(14),22-tetraen-3-one is the diuretic component of *P. umbellatus*. It not only alters the balance of Na^+/K^+ by antagonizing aldosterone, thus exerting a diuretic effect but also confirms the diuretic effect of ergosterol in water accumulation or the stimulation of water double absorption [34]. Ergosterol is the main sterol in *P. umbellatus*, and its content is closely related to the species and growth characteristics of the fungus [33]. It is an important component of the precursor to vitamin D2 and can be converted to vitamin D2 through thermal rearrangement [35]. Additionally, ergosterol has demonstrated antitumor effects and diuretic activities, as well as therapeutic effects on kidney disorders. Due to its strong diuretic activity, ergone was synthesized using ergosterol as a substrate [34], resulting in a 72% yield. Lee et al. [2] compared the inhibitory effects of Ergosta-4,6,8(14), and 22-tetraen-3-one on different cancer cell lines and found that ergosterol exhibited varying degrees of cytotoxicity in several cancer cell lines, including HT-29 (colon cancer), HeLa 229 (cervix cancer), Hep3B (liver cancer), and AGS (stomach cancer). Zhao and his colleagues extracted five potent cytotoxic compounds from the n-hexane and ethyl acetate extracts of *P. umbellatus* [36]. All of these compounds showed activity against HepG2

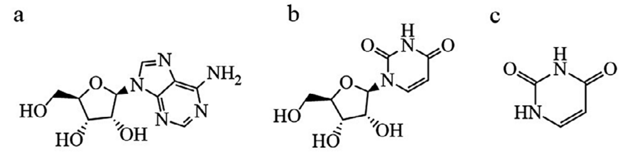

FIGURE 3 | Several alkaloids of different types in porus. (a) Adenosine; (b) Uridine; (c) Uracil [3].

cells. Furthermore, the inhibitory activities of ergone on cancer cell growth were compared with HUVEC, with HepG2, HeLa, and Hep-2 exhibiting better inhibitory activities than HUVEC. The study also found that ergone and the steroid components induced apoptosis and exhibited excellent anticancer activity. Interestingly, Zhao et al. [37] further investigated the antitumor effect of ergosterol and found that it could inhibit tumor cell growth by blocking the cell cycle, inhibiting cell division, and inducing apoptosis.

2.3 | Alkaloids

The alkaloids are typically derived from amino acids and are classified as heterocyclic compounds [38] with one or more nitrogen atoms integrated into their structures [39]. Alkaloids possess several noteworthy medicinal properties, such as anti-inflammatory, anticancer, antiangiogenic, and antispasmodic effects [40]. Various alkaloids, such as chuanbeinone, halofuginone, and tetrandrine, have been found to exhibit significant efficacy in suppressing tumor angiogenesis (Figure 3).

Fungal alkaloids widely exist in a variety of fungi, which are an important class of secondary metabolites in fungi [41]. These alkaloids include two major groups, indole alkaloids and purine alkaloids [42]. Among fungi, mushrooms, particularly those in the Psilocybe species, are the predominant producers of alkaloids [43]. Notably, harmine and harmaline are well-known mushroom alkaloids with pharmacological properties [44, 45]. However, limited research has been conducted on the alkaloids found in *P. umbellatus*. Bandara et al. [8] identified and characterized three alkaloids in the sclerotium of *P. umbellatus*. Similarly, Lee et al. [46] isolated three alkaloids from the sclerotia of *P. umbellatus* and determined their structures to be 9-β-D-ribofuranosyladenine (adenosine), 1-β-D-ribofuranosyluracil (uridine), and 2,4-pyrimidinedione (uracil). It should be noted that other studies have reported the presence of nephrotoxic alkaloids in certain species, such as Aconitum, which contains the diester alkaloid aconitine [39, 47]. However, there is currently no direct evidence indicating the toxicity of alkaloids in *P. umbellatus*. If such evidence emerges in the future, it may be necessary to implement specific processing methods to mitigate the toxicity associated with *P. umbellatus* alkaloids.

2.4 | Vitamins

Fungi produce many vitamins such as vitamin A, vitamin B [48], vitamin C, and vitamin E, but they utilize external B vitamins from soil microorganisms, particularly thiamin, during mycelial growth and nucleus formation. Furthermore, the levels of vitamins B_1, B_2, and E in *P. umbellatus* are higher than those found in cereals and legumes, while the content of vitamin B_{12} exceeds that of proteins and seafood. It has been demonstrated that the production and demand for B vitamins in fungi are closely associated with pH, and this demand varies among different species [49, 50]. Vitamins play a role in the development and morphological transformation of fungi. Liu et al. [51] conducted a single-factor study to examine the effects of eight vitamins on mycelial growth and sclerotial formation in *P. umbellatus*. The study found that the categories of vitamin have no relations with their sclerotial formation. Xing et al. [52] investigated the effects of antioxidants, including diphenyleneiodonium chloride (DPI), apocynin (Apo), and vitamin C, on the production of reactive oxygen species (ROS) and sclerotium formation in mycelium. The findings revealed that low concentrations (1 mg/mL) of vitamin C were beneficial for the production of ROS and the differentiation of sclerotium. Conversely, DPI and Apo did not yield the same effect.

2.5 | Ketone Components

Ketones possess potent properties that significantly impact skincare and health. They play a crucial role in cell tissue regeneration and melanin lightening. In addition, ketones offer nourishment to the nerves, promote mental relaxation, and exhibit sterilizing and tonifying effects on the kidneys. Polyporusterone, the primary active component found in Chinese herbal medicine derived from *P. umbellatus*, is utilized for the treatment of hair disorders and stimulation of hair growth [53]. Naturally occurring *P. umbellatus* contains a diverse range of porinones. Among these, polyporusterone A has been identified as the most abundant secondary metabolite within *P. umbellatus* sclerotia, and its concentration can be increased through the symbiotic relationship with *Amillariella* [54]. Ohsawa et al. [55] extracted seven different ketones from the crude drug in *P. umbellatus* fruiting bodies and conducted a thorough analysis of their structure and function. Their findings demonstrated that the extracted polyporusterone exhibited significant cytotoxic effects on leukemia L-1210 cells. Sun and Yasukawa [56] conducted similar research, evaluating the anti-inflammatory activity of eight different polyposterones (1–8) in comparison to the commercially available anti-inflammatory drug indomethacin. All of the tested polyposterones exhibited strong inhibitory activity, with those possessing two hydroxyl substituents on the side chain demonstrating even greater anti-inflammatory effects than the others. Liu et al. [12] found that polyporusterone A and polyporusterone B exhibit high bioaffinity for xanthine oxidase (XOD), resulting in the inhibition of XOD activity and potential antigout properties. Polyporusterone has also been shown to have an antihemolytic effect, protecting red blood cells from lysis induced by 2,2-azo-bis dihydrochloride [3]. Additionally, ketones have a renal protective effect on rat renal intestinal fibrosis induced by aristolochic acid or adenine [57].

2.6 | Others

P. umbellatus also contains many other active compounds. Among them, emodin is a natural anthraquinone derivative that is found in *P. umbellatus*. Some studies have found that emodin (Figure 4a) has a wide range of pharmacological properties, including antimicrobial activities [58], constipation relief [59], treatment of pulmonary fibrosis [60], and ascites [61], kidney disease treatment [62, 63], anti-inflammatory effects [64], and anticancer properties [65]. However, long-term and high-dose usage of emodin may cause hepatotoxicity and kidney toxicity. To further explore its biomedical applications, strict dosage control is needed, along with proper processing of medicinal herbs and the addition of other compatible medicines to minimize the harm of these compounds on normal human cells.

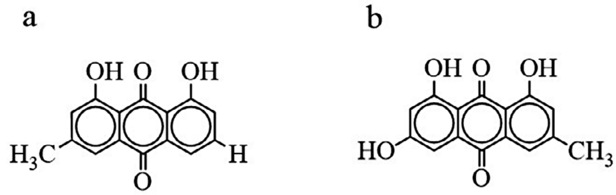

FIGURE 4 | Structure of emodin and chrysophanol, (a) Chrysophanol; (b) Emodin. Referred to [3] with some modifications.

Chrysophanol (Figure 4b), which was also called 1,8-dihydroxy-3-methyl-an-thraquinone and chrysophanic acid [66], is another important medicinal component in *P. umbellatus*. Chrysophanol was originally discovered in *Rheum rhabarbarum*, an herbaceous perennial plant [67]. Zhou et al. [11] were the first to use petroleum ether and dichloromethane for extracting chrysophanol from *P. umbellatus*'s sclerotia. Numerous scientific studies have confirmed its beneficial biological activities, including anticancer, antidiabetic, anti-inflammatory, antiseptic, hypolipidemic, liver protection, nerve protection, antiulcer, and antiobesity effects [67]. However, little is known about the toxicology and pharmacology of chrysophanol in *P. umbellatus*.

The chemical components of *P. umbellatus* also include some long-chain fatty acids, anthraquinones, nucleosides [3], amino acids [68], and so forth.

3 | Medicinal Effects

P. umbellatus is a species of mushroom that possesses a wide range of bioactive compounds including polysaccharides, terpenes, nucleosides, sterols, alkaloids, and several others. These chemical components contribute to the diverse pharmacological properties exhibited by *P. umbellatus*, such as diuretic activity, antitumor effects, liver protection, immune modulation, antiaging properties, protection against DNA damage, antimutagenic effects, improvement of renal function, and amelioration of renal collagen deposition and subsequent fibrosis (Figure 5). In addition, *P. umbellatus* demonstrates antiallergic effects and enhances microcirculation, making it not only a medicinal agent but also an ideal green healthcare product.

3.1 | Diuretic Effect

P. umbellatus kernels have diuretic effects. Ergaster-4,6,8,22-tetraen-3-one, the main source of diuretic effects, relies on the regulation of Na^+/K^+ ion balance in the body to exert diuretic effects [34]. Ergosterol and D-mannitol contained in *P. umbellatus could* expedite the diuretic process. As the strongest diuretic in all

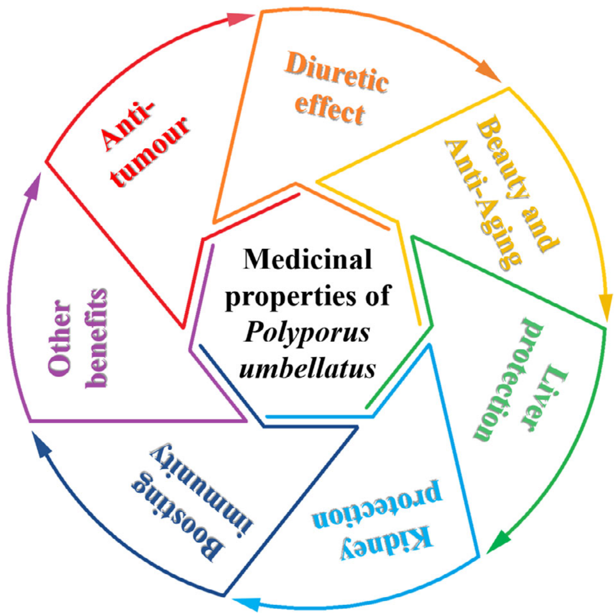

FIGURE 5 | Medicinal properties of *Polyporus umbellatus*.

the active compounds, ergone can influence the variation of the urinary Na^+/K^+ ratio, which is mainly because of two possible mechanisms including aldosterone-blocking activity and a direct effect on Na^+/K^+ ion channels. Also, it can increase urinary volume in the states of water accumulation or the stimulated states of water reabsorption caused by mineralocorticoids [3]. Zhang et al. [69] found that the diuretic mechanism of *P. umbellatus* may be related to the reabsorption effect of renal tubules. In a comparison experiment with furosemide, which is a diuretic widely used in clinical practice, an 8-day dose of *P. umbellatus* extract produced a diuretic effect like that of furosemide, while excretion of the electrolytes Na^+, K^+, and Cl^- was significantly greater than that of furosemide.

3.2 | Antitumor Efficacy

PPS can regulate the activity of glycogen isomerase in the organism, which in turn regulates gluconeogenesis to improve overall body function [7]. Bladder cancer is a malignant tumor closely associated with immune dysfunction in macrophages, and *P. umbellatus* polysaccharide has been used as an antitumor drug for bladder cancer [27]. A water-soluble polysaccharide called Haishen polysaccharide peptide (HPP), found in *P. umbellatus*, was discovered to have a strong immunomodulatory effect. It significantly increased the secretion of immune factors, such as nitric oxide (NO), interleukin-6 (IL-6), interleukin-1β (IL-1β), and interleukin-23 (IL-23), by macrophages stimulated with γ-interferon-γ (IFN-γ). It also enhanced the expression of the cell membrane molecule CD80. HPP was recognized by Toll-like receptor 2 (TLR2) and activated the nuclear factor-κB (NF-κB) and NLRP3 signaling pathways in a bladder cancer microenvironment model, indicating that HPP enhanced the function of the organism's immune system. These findings suggest that HPP may be a potential immunomodulatory agent for the treatment of immune disorders or bladder cancer [70]. Breast cancer has a high mortality rate among women worldwide. AKT is considered an important signaling pathway that regulates cell proliferation and apoptosis, acting through the Mdm2/p53 and Caspase-3 signaling pathways, respectively. The ability of *P. umbellatus* to inhibit breast cancer cell proliferation is associated with the activation of AKT, which downregulates the proliferative activity of breast cancer cells [71]. Kim et al. [72] isolated mycelial fusions of *G. lucidum* and *P. umbellatus*. These fusions increased the intracellular calcium concentration in MCF-7 breast cancer cells and induced the production of ROS, ultimately resulting in the elimination of cancer cells, as determined by flow cytometry. Additionally, polyporusterone A-G exerts cytotoxic effects on leukemia 1210 cells, and polyporusterone A and B can act as active substances to promote hair regrowth [73].

3.3 | Improving Immunity

Phagocytosis by macrophages is an important aspect of the immune system of organisms [74]. *P. umbellatus* acts as a signaling molecule to activate various pathways and enhance macrophage activity in destroying foreign pathogens. This activity change is independent of the microenvironment. The hot water extract of *P. umbellatus* (PRW)-treated macrophages resulted in accelerated production of inflammatory mediators (NO), activation of TLR, and expression of nitric oxide synthase (iNOS) in RAW264.7 cells and primary peritoneal macrophages. The expression of iNOS was accelerated to varying degrees. Furthermore, PPS effectively upregulated the nitric oxide production and cytokine expression in macrophages, significantly stimulating the proliferation of splenocytes and the production of TNF-α, interleukin-1β, and nitric oxide in peritoneal macrophages. Function-blocking antibodies notably suppressed PUP-mediated TNF-α and interleukin-1β, production [29]. Additionally, research has shown that the immunomodulatory activity of polysaccharides could significantly increase the secretion of immune factors by IFN-γ-stimulated macrophages, such as NO, IL-6, and ILs, as well as the expression of the cell membrane molecule CD80. PPS was recognized by Toll-like receptor 2 (TLR2) and activated signaling pathways of NF-κB and NLRP3 in various cancers, thereby improving immunity [70].

Macrophage functions are associated with surface receptors such as CR3, TLR4, TLR2, mannose receptors, and Dectin. TLR activation can induce immune factors that interfere with immune responses by promoting the release of NO from macrophages. Li et al. [29] demonstrated that *P. umbellatus* extract mimics pMs in producing inflammatory mediators and IL-1 through a pathway involving TLR4 and NF-B activation, suggesting that TLR-4 is a receptor for PPS-mediated macrophage activation. TLR activation induces immune factors that interfere with the immune response by directly promoting NO release from macrophages, characterized by a decrease in antigen processing capacity and indirectly by an increase in MHC class II molecules and costimulatory molecules on the surface of stimulated intermediate cells and secretion of IL-12 to promote the growth and differentiation of T lymphocytes. *P. umbellatus* polysaccharides induced DC maturation and stimulated interleukin IL-12 secretion. Liu et al. [75] extracted and isolated extracellular polysaccharides from *P. umbellatus* liquid fermentation broth and investigated their antioxidant activity as well as other related biological activities. The extracellular polysaccharides showed a significant scavenging effect on free radicals and were dose-dependent. Polysaccharides stimulated nitric oxide production and phagocytic activity in RAW 264.7 macrophages, suggesting that polysaccharides significantly enhanced the immune function of macrophages.

In clinical applications, *P. umbellatus* polysaccharide is often used in combination with other fungal polysaccharides, due to the varying minimum dose required to produce regulatory effects on different cells. This combination helps such as *G. lucidum* polysaccharide, to improve immune cell activity [72]. According to Li et al. [76] PPS can improve the activity of macrophagocytes and NK cells, as well as regulate the immune function in healthy and colitis mouse models. Ingesting *G. lucidum* polysaccharide and *P. umbellatus* polysaccharide in daily life has been shown to reduce colon injury induced by DSS protect splenic lymphocyte proliferation and improve serum hemolysin synthesis.

3.4 | Protection of Kidney Function

As a valuable edible and medicinal fungus, *P. umbellatus* has long been used in Chinese medicine to treat urinary systems and related kidney diseases. Chronic renal failure results in significant dyslipidemia and alterations in lipid metabolism [77]. *P. umbellatus* may prevent renal injury and subsequent renal fibrosis. However, there is a lack of data on this research. Therefore, Li et al. [78] actively investigated the therapeutic effect of *P. umbellatus* polysaccharides on renal fibrosis. The Helicteres polysaccharides could improve renal function and the degree of renal collagen deposition and further fibrosis, and the underlying mechanism was related to the reduction of inflammation, inhibition of epithelial–mesenchymal transition, re-establishment of metalloproteinase homeostasis, tissue inhibitors of metalloproteinases, profibrotic, and antifibrotic factors, and so forth. These studies provide valuable information for future kidney protection. Liu et al. [79] analyzed the nephroprotective activity of diabetic nephropathy rats. They developed a medicine containing *P. umbellatus* that can lower the high plasma glucose level in diabetic rats. Not only that, the medicine regulated diabetic-dependent alterations in urinary albumin, urinary albumin excretion rate, creatinine clearance, and glomerular mesangial matrix expansion. In addition, some research has been done on the molecular mechanism of *P. umbellatus*. Lee et al. [80] found that the MeOH extract in sclerotia of *P. umbellatus* had PTP1B inhibitory activity, which is the most important negative modulator in the insulin signaling pathway. PTP1B is considered a good target for curing type 2 diabetes.

The renoprotective effect and interlocking mechanism of *P. umbellatus* mainly result from the PPS, which enhances renal function, improves the degree of renal collagen deposition, and prevents further fibrosis. Furthermore, PPS has been found to decrease inflammation, suppress epithelial–mesenchymal transition, restore homeostasis between metalloproteinases and their inhibitors, and rebalance fibrotic/antifibrotic factors [78].

3.5 | Liver-Protective Effect

P. umbellatus polysaccharides can be used to treat hepatitis. He et al. [25] confirmed that the polysaccharides in *P. umbellatus* can repair pathological damage, greatly accelerating liver repair and hepatocyte regeneration. Additionally, the hepatitis B virus can be effectively ignited and serum transaminase levels can be efficiently decreased. Gao et al. [81] also made a breakthrough in the study of polysaccharides in nonalcoholic steatohepatitis (NASH). They discovered (1,3)(1,6)-β-D-glucan in *P. umbellatus* sclerotia, which can protect against hepatic inflammation, steatosis, and fibrotic activity induced by a methionine choline-deficient (MCD) diet. Moreover, *P. umbellatus* polysaccharides significantly improved the cellular immunity of mice with liver lesions and had a significant protective effect on acute liver toxicity induced by carbon tetrachloride and D-Gal-N in mice. In the treatment of chronic hepatitis B, the combination of salvia miltiorrhiza (SM) and PUPs may be more effective than treatment with SM or PUPs alone [7].

3.6 | Antiaging and Beauty Benefits

As organisms age, they accumulate large amounts of free radicals (FR) [82], which cause DNA damage and can lead to various malignant tumors [83]. The activities of superoxide dismutase (SOD) and hepatic peroxidase were increased in the blood erythrocytes of mice treated with *P. umbellatus* polysaccharides for weakness disorders. What is even more surprising in the study of the medicinal value of *P. umbellatus* is the presence of piconone A, piconone B, and acetylbutyrone, which are beneficial for hair growth [53]. Therefore, *P. umbellatus* plays an important role in addressing the issue of hair loss, which is a major concern in today's society.

3.7 | Others

Proteoglycan obtained from the sclerotia of *P. umbellatus* has an antimutagenic effect. The protein polysaccharides in *P. umbellatus* sclerotia have antimutagenic effects. Salmonella typhimurium can be effectively inhibited by the protein polysaccharides from *P. umbellatus* at a concentration of 2.5%–10.0% [7]. Many other studies have found similar results. Currently, most of the research focuses on analyzing the active ingredients and medicinal effects of *P. umbellatus*. However, few studies have mentioned its toxicity. The long-term safety and correct evaluation of its toxicity are crucial for future application. Zhao et al. [36] isolated five ergone steroids from *P. umbellatus*, which effectively combat HepG2 cells, in a dose-dependent manner. These compounds also exhibit selective cytotoxic activity against cancer cells compared to normal cells. Additionally, the cytotoxicity of the five ergones on different cell lines was studied, showing dose dependency and varying sensitivity among cells. Similarly, Lee et al. [2] isolated and identified ergone from *P. umbellatus*'s sclerotia and analyzed its cytotoxic activity on various human cancer cell lines. Unfortunately, the study did not mention whether ergone was harmful to normal cells. Based on these examples, it can be concluded that the active compounds from *P. umbellatus* have a significant inhibitory effect on cancer cells, while their toxicity to normal human cells is relatively weak. Therefore, in future biomedical applications, strict dosage control, processing of medicinal herbs, and the addition of other medications for drug compatibility are necessary to minimize the harm of these compounds to normal human cells.

4 | Prospect and Outlook

The medicinal properties of *P. umbellatus* have become a widely researched topic, with a solid theoretical basis for its clinical application. The increasing demand for *P. umbellatus* has resulted in the depletion of natural populations, making it crucial to develop methods for high-yield cultivation. The issue of empty *P. umbellatus* nests is widespread, and the symbiotic relationship between *P. umbellatus* and *Amillariella* has not been fully explored. Additionally, identifying *P. umbellatus* and *Amillariella* strains with beneficial symbiotic relationships remains a challenging research problem.

Due to the wide range of bioactive substances found in *P. umbellatus* and its numerous identified beneficial effects, it has garnered significant attention. The fungi demonstrate great potential for further development in pharmaceuticals, functional foods, and cosmetics. As a result, it is an ideal candidate for modern medical treatments, particularly in light of the COVID-19 pandemic and increasing sensitivity among individuals. There is a promising outlook for *P. umbellatus* to have a substantial market presence in major medical and functional food applications in the future.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated during the current study.

References

1. T. Ghosh and M. K. Biswas, "*Ganoderma lucidum*: Production, Nutritional and Medicinal Value in Comparison With Other Edible Mushrooms–A Review," *Journal of Mycopathological Research* 60, no. 3 (2022): 307–312.

2. W. Y. Lee, Y. K. Park, J. K. Ahn, S. Y. Park, and H. J. Lee, "Cytotoxic Activity of Ergosta-4, 6, 8 (14), 22-Tetraen-3-One From the Sclerotia of *Polyporus umbellatus*," *Bulletin of the Korean Chemical Society* 26, no. 9 (2005): 1464–1466.

3. Y. Y. Zhao, "Traditional Uses, Phytochemistry, Pharmacology, Pharmacokinetics and Quality Control of *Polyporus umbellatus* (Pers.) Fries: A Review," *Journal of Ethnopharmacology* 149, no. 1 (2013): 35–48.

4. J. Jiang and D. Sliva, "Novel Medicinal Mushroom Blend Suppresses Growth and Invasiveness of Human Breast Cancer Cells," *International Journal of Oncology* 37, no. 6 (2010): 1529–1536.

5. X. Xing, X. Ma, M. M. Hart, A. Wang, and S. Guo, "Genetic Diversity and Evolution of Chinese Traditional Medicinal Fungus *Polyporus umbellatus* (Polyporales, Basidiomycota)," *PLOS ONE* 8, no. 3 (2013): e58807.

6. W. J. Guo, Y. M. Xing, J. Chen, and S. X. Guo, "Growth Promoting Effects of Water Extract of *Armillaria mellea* Rhizomorph on Mycelia of *Polyporus umbellatus*," *Cryptogamie, Mycologie* 32, no. 2 (2011): 171–176.

7. G. K. Liu, T. X. Yang, and J. R. Wang, "Polysaccharides From *Polyporus umbellatus*: A Review on Their Extraction, Modification, Structure, and Bioactivities," *International Journal of Biological Macromolecules* 189 (2021): 124–134.

8. A. R. Bandara, S. Rapior, D. J. Bhat, P. Kakumyan, et al., "*Polyporus umbellatus*, an Edible-Medicinal Cultivated Mushroom With Multiple Developed Health-Care Products as Food, Medicine and Cosmetics: A Review," *Cryptogamie, Mycologie* 36, no. 1 (2015): 3–42.

9. W. Q. Yin, S. X. Guo, Y. M. Xing, and X. K. Xing, "A New Method to Induce Sclerotial Differentiation in *Polyporus umbellatus* by Split-Plate Culture," *Mycological Progress* 11, no. 4 (2012): 957–960.

10. M. M. Liu, Y. M. Xing, D. W. Zhang, and S. X. Guo, "Transcriptome Analysis of Genes Involved in Defence Response in *Polyporus umbellatus* With *Armillaria mellea* Infection," *Scientific Reports* 5, no. 1 (2015): 16075.

11. W. Zhou and S. Guo, "Components of the Sclerotia of *Polyporus umbellatus*," *Chemistry of Natural Compounds* 45, no. 1 (2009): 124–125.

12. Q. Liu, S. Zhuang, S. Li, Y. Nong, et al., "Rapid Screening, Isolation, and Activity Evaluation of Potential Xanthine Oxidase Inhibitors in *Polyporus umbellatus* and Mechanism of Action in the Treatment of Gout," *Phytochemical Analysis* 35, no. 1 (2024): 116–134.

13. G. K. Liu, N. Li, Y. J. Zhang, and J. R. Wang, "LC/MS Fingerprint and Simultaneous Quantification of Main Bioactive Compounds in *Polyporus umbellatus* (Pers.) Fr. From Different Regions and Developmental Stages," *Microchemical Journal* 144 (2019): 351–360.

14. F. Liu, V. E. C. Ooi, and S. T. Chang, "Free Radical Scavenging Activities of Mushroom Polysaccharide Extracts," *Life Sciences* 60, no. 10 (1997): 763–771.

15. N. Benkeblia, "*Ganoderma lucidum* Polysaccharides and Terpenoids: Profile and Health Benefits," *Journal of Food, Nutrition and Dietetics* 1 (2016): 1–6.

16. N. Guo, Z. Bai, W. Jia, J. Sun, et al., "Quantitative Analysis of Polysaccharide Composition in *Polyporus umbellatus* by HPLC–ESI–TOF–MS," *Molecules (Basel, Switzerland)* 24, no. 14 (2019): 2526.

17. P. He, A. Zhang, F. Zhang, R. J. Linhardt, and P. Sun, "Structure and Bioactivity of a Polysaccharide Containing Uronic Acid From Polyporus Umbellatus Sclerotia," *Carbohydrate Polymers* 152 (2016): 222–230.

18. C. Liu, D. He, S. Zhang, H. Chen, et al., "Homogeneous Polyporus Polysaccharide Inhibit Bladder Cancer by Resetting Tumor-Associated Macrophages Toward M1 Through NF-κB/NLRP3 Signaling," *Frontiers in Immunology* 13 (2022): 839460.

19. H. Wu, J. Liang, Y. Cheng, H. Huang, et al., "Radio- and Chemoprotective Effects of Zhu-Ling Mushroom (*Polyporus umbellatus*) in Human Cultured Cells and in Mice," *Toxicology Letters* 205 (2011): S37.

20. M. Zhang, S. W. Cui, P. C. K. Cheung, and Q. Wang, "Antitumor Polysaccharides From Mushrooms: A Review on Their Isolation Process, Structural Characteristics and Antitumor Activity," *Trends in Food Science & Technology* 18, no. 1 (2007): 4–19.

21. Y. Ueno, M. Abe, R. Yamauchi, and K. Kato, "Structural Analysis of the Alkali-Soluble Polysaccharide From the Sclerotia of *Grifora umbellata* (Fr.) Pilát," *Carbohydrate Research* 87, no. 2 (1980): 257–264.

22. Y. Ueno, Y. Okamoto, R. Yamauchi, and K. Kato, "An Antitumor Activity of the Alkali-Soluble Polysaccharide (and its Derivatives) Obtained From the Sclerotia of *Grifora umbellata* (Fr.) Pilát," *Carbohydrate Research* 101, no. 1 (1982): 160–167.

23. H. C. Huang and Y. C. Liu, "Enhancement of Polysaccharide Production by Optimization of Culture Conditions in Shake Flask Submerged Cultivation of *Grifola umbellata*," *Journal of the Chinese Institute of Chemical Engineers* 39, no. 4 (2008): 307–311.

24. P. F. He, A. Q. Zhang, X. L. Wang, L. Qu, et al., "Structure Elucidation and Antioxidant Activity of a Novel Polysaccharide From *Polyporus umbellatus* Sclerotia," *International Journal of Biological Macromolecules* 82 (2016): 411–417.

25. D. He, Y. Ren, X. Hua, J. Zhang, et al., "Phytochemistry and Bioactivities of the Main Constituents of *Polyporus umbellatus* (Pers.) Fries," *Phytomedicine* 103 (2022): 154196.

26. W. Tang, D. Liu, J. Y. Yin, and S. P. Nie, "Consecutive and Progressive Purification of Food-Derived Natural Polysaccharide: Based on Material,

Extraction Process and Crude Polysaccharide," *Trends in Food Science & Technology* 99 (2020): 76–87.

27. C. P. Liu, X. Zhang, Q. L. Tan, W. X. Xu, et al., "NF-κB Pathways Are Involved in M1 Polarization of RAW 264.7 Macrophage by Polyporus Polysaccharide in the Tumor Microenvironment," *PLOS ONE* 12, no. 11 (2017): e0188317.

28. X. Li, W. Xu, and J. Chen, "Polysaccharide Purified From *Polyporus umbellatus* (Per) Fr Induces the Activation and Maturation of Murine Bone-Derived Dendritic Cells via Toll-Like Receptor 4," *Cellular Immunology* 265, no. 1 (2010): 50–56.

29. X. Li and W. Xu, "TLR4-Mediated Activation of Macrophages by the Polysaccharide Fraction From *Polyporus Umbellatus(pers.) Fries*," *Journal of Ethnopharmacology* 135, no. 1 (2011): 1–6.

30. G. W. Zhang, G. F. Qin, B. Han, C. X. Li, et al., "Efficacy of Zhuling Polyporus Polysaccharide With BCG to Inhibit Bladder Carcinoma," *Carbohydrate Polymers* 118 (2015): 30–35.

31. X. Gao, X. Li, J. Mu, C. T. Ho, et al., "Preparation, Physicochemical Characterization, and Anti-Proliferation of Selenium Nanoparticles Stabilized by *Polyporus umbellatus* Polysaccharide," *International Journal of Biological Macromolecules* 152 (2020): 605–615.

32. Y. Sun and X. Zhou, "Purification, Initial Characterization and Immune Activities of Polysaccharides From the Fungus, *Polyporus umbellatus*," *Food Science and Human Wellness* 3, no. 2 (2014): 73–78.

33. J. C. M. Barreira, M. B. P. P. Oliveira, and I. C. F. R. Ferreira, "Development of a Novel Methodology for the Analysis of Ergosterol in Mushrooms," *Food Analytical Methods* 7 (2014): 217–223.

34. Y. Y. Zhao, R. M. Xie, X. Chao, Y. Zhang, et al., "Bioactivity-Directed Isolation, Identification of Diuretic Compounds From *Polyporus umbellatus*," *Journal of Ethnopharmacology* 126, no. 1 (2009): 184–187.

35. A. Villares, A. García-Lafuente, E. Guillamón, and Á. Ramos, "Identification and Quantification of Ergosterol and Phenolic Compounds Occurring in *Tuber* Spp. Truffles," *Journal of Food Composition and Analysis* 26, no. 1-2 (2012): 177–182.

36. Y. Y. Zhao, X. Chao, Y. Zhang, R. C. Lin, and W. J. Sun, "Cytotoxic Steroids From *Polyporus umbellatus*," *Planta Medica* 76, no. 15 (2010): 1755–1758.

37. Y. Y. Zhao, X. Shen, X. Chao, C. C. Ho, et al., "Ergosta-4,6,8(14),22-Tetraen-3-One Induces G2/M Cell Cycle Arrest and Apoptosis in Human Hepatocellular Carcinoma HepG2 Cells," *Biochimica Et Biophysica Acta (BBA)—General Subjects* 1810, no. 4 (2011): 384–390.

38. P. F. Rosales, G. S. Bordin, A. E. Gower, and S. Moura, "Indole Alkaloids: 2012 Until Now, Highlighting the New Chemical Structures and Biological Activities," *Fitoterapia* 143 (2020): 104558.

39. Y. Rui, S. Li, F. Luan, D. Li, et al., "Several Alkaloids in Chinese Herbal Medicine Exert Protection in Acute Kidney Injury: Focus on Mechanism and Target Analysis," *Oxidative Medicine and Cellular Longevity* 2022, no. 1 (2022): 2427802.

40. R. Li, X. Song, Y. Guo, P. Song, et al., "Natural Products: A Promising Therapeutics for Targeting Tumor Angiogenesis," *Frontiers in Oncology* 11 (2021): 772915.

41. Y. Zhang, T. Han, Q. Ming, L. Wu, et al., "Alkaloids Produced by Endophytic Fungi: A Review," *Natural Product Communications* 7, no. 7 (2012): 963–968. 1934578×1200700742.

42. P. Dey, A. Kundu, A. Kumar, et al., *Recent Advances in Natural Products Analysis* (Weinheim: Elsevier, 2020), 505–567.

43. F. Blei, S. Dörner, J. Fricke, F. Baldeweg, et al., "Simultaneous Production of Psilocybin and a Cocktail of β-Carboline Monoamine Oxidase Inhibitors in "Magic" Mushrooms," *Chemistry—A European Journal* 26, no. 3 (2020): 729–734.

44. R. Benzekri, L. Bouslama, A. Papetti, M. Hammami, et al., "Anti HSV-2 Activity of *Peganum harmala* (L.) and Isolation of the Active Compound," *Microbial Pathogenesis* 114 (2018): 291–298.

45. F. A. Khan, A. Maalik, Z. Iqbal, and I. Malik, "Recent Pharmacological Developments in β-Carboline Alkaloid "Harmaline"," *European Journal of Pharmacology* 721, no. 1-3 (2013): 391–394.

46. H. Lee, K. Lee, Y. Park, and M. W. Lee, "Chemical Constituents of the Sclerotia of *Grifola umbellata*," *Journal of Korea Forestry Energy* 21 (2002): 16–24.

47. B. Yang, Y. Xie, M. Guo, M. H. Rosner, et al., "Nephrotoxicity and Chinese Herbal Medicine," *Clinical Journal of the American Society of Nephrology* 13, no. 10 (2018): 1605–1611.

48. D. Moore and S. Chiu, "Fungal Products as Food," *Bio-Exploitation of Filamentous Fungi* (Hong Kong, Weinheim: Fungal Diversity Press, 2001), 223–251.

49. E. Strzelczyk, H. Dahm, and R. Pachlewski, "B-Group Vitamins Production by Mycorrhizal Fungi in Response to pH (In Vitro Studies)," *Plant and Soil* 137, no. 2 (1991): 237–241.

50. W. J. Robbins and V. Kavanagh, "Vitamin Deficiencies of the Filamentous Fungi," *Botanical Review* 8, no. 7 (1942): 411.

51. Y. Y. Liu and S. X. Guo, "Nutritional Factors Determining Sclerotial Formation of *Polyporus umbellatus*," *Letters in Applied Microbiology* 49, no. 2 (2009): 283–288.

52. Y. M. Xing, L. C. Zhang, H. Q. Liang, J. Lv, et al., "Sclerotial Formation of *Polyporus umbellatus* by Low Temperature Treatment Under Artificial Conditions," *PLOS ONE* 8, no. 2 (2013): e56190.

53. H. Ishida, Y. Inaoka, J. I. Shibatani, M. Fukushima, and K. Tsuji, "Studies of the Active Substances in Herbs Used for Hair Treatment. II. Isolation of Hair Regrowth Substances, Acetosyringone and Polyporusterone A and B, From *Polyporus umbellatus* Fries," *Biological & Pharmaceutical Bulletin* 22, no. 11 (1999): 1189–1192.

54. Y. M. Xing, B. Li, L. Liu, Y. Li, et al., "*Armillaria mellea* Symbiosis Drives Metabolomic and Transcriptomic Changes in *Polyporus umbellatus* Sclerotia.," *Frontiers in Microbiology* 12 (2022): 792530.

55. T. Ohsawa, M. Yukawa, C. Takao, M. Murayama, and H. Bando, "Studies on Constituents of Fruit Body of *Polyporus umbellatus* and Their Cytotoxic Activity," *Chemical & Pharmaceutical Bulletin* 40, no. 1 (1992): 143–147.

56. Y. Sun and K. Yasukawa, "New Anti-Inflammatory Ergostane-Type Ecdysteroids From the Sclerotium of *Polyporus umbellatus*," *Bioorganic & Medicinal Chemistry Letters* 18, no. 11 (2008): 3417–3420.

57. Y. M. Xing, B. Li, X. Zeng, L. S. Zhou, et al., "Use of Transcriptomic Profiling to Identify Candidate Genes Involved in Polyporus Umbellatus Sclerotial Formation Affected by Oxalic Acid", *Scientific Reports* 11 (2021):17326.

58. X. Dong, J. Fu, X. Yin, S. Cao, et al., "Emodin: A Review of Its Pharmacology, Toxicity and Pharmacokinetics," *Phytotherapy Research* 30, no. 8 (2016): 1207–1218.

59. C. Cirillo and R. Capasso, "Constipation and Botanical Medicines: An Overview," *Phytotherapy Research* 29, no. 10 (2015): 1488–1493.

60. Y. L. Feng, D. Q. Chen, N. D. Vaziri, Y. Guo, and Y. Y. Zhao, "Small Molecule Inhibitors of Epithelial-Mesenchymal Transition for the Treatment of Cancer and Fibrosis," *Medicinal Research Reviews* 40, no. 1 (2020): 54–78.

61. Y. Mou, X. Wang, T. Wang, Y. Wang, et al., "Clinical Application and Pharmacological Mechanism of Wuling Powder in the Treatment of Ascites: A Systematic Review and Network Pharmacological Analysis," *Biomedicine & Pharmacotherapy* 146 (2022): 112506.

62. J. Chen, K. W. K. Tsim, and Y. Y. Zhao, "Editorial: Applications of Herbal Medicine to Control Chronic Kidney Disease," *Frontiers in Pharmacology* 12 (2021): 742407.

63. Y. N. Wang, H. J. Liu, L. L. Ren, P. Suo, et al., "Shenkang Injection Improves Chronic Kidney Disease by Inhibiting Multiple Renin-Angiotensin System Genes by Blocking the Wnt/β-Catenin Signalling Pathway," *Frontiers in Pharmacology* 13 (2022): 964370.

64. J. Sharifi-Rad, J. Herrera-Bravo, S. Kamiloglu, K. Petroni, et al., "Recent Advances in the Therapeutic Potential of Emodin for Human Health," *Biomedicine & Pharmacotherapy* 154 (2022): 113555.

65. Q. Zhang, W. W. Chen, X. Sun, D. Qian, et al., "The Versatile Emodin: A Natural Easily Acquired Anthraquinone Possesses Promising Anticancer Properties Against a Variety of Cancers," *International Journal of Biological Science* 18 (2022): 3498–3527.

66. L. Xie, H. Tang, J. Song, J. Long, et al., "A Review of Its Pharmacology, Toxicity and Pharmacokinetics," *Journal of Pharmacy and Pharmacology* 71, no. 10 (2019): 1475–1487.

67. Y. M. A. Prateeksha, B. N. Singh, S. Sudheer, et al., "Chrysophanol: A Natural Anthraquinone With Multifaceted Biotherapeutic Potential," *Biomolecules* 9, no. 2 (2019): 68.

68. H. Kopylchuk, O. Voloshchuk, and M. Pasailiuk, "Comparison of Total Amino Acid Compositions, Total Phenolic Compounds, Total Flavonoid Content, β-Carotene Content and Hydroxyl Radical Scavenging Activity in Four Wild Edible Mushrooms," *Italian Journal of Mycology* 52, no. 1 (2023): 112–125.

69. G. Zhang, X. Zeng, L. Han, J. A. Wei, and H. Huang, "Diuretic Activity and Kidney Medulla AQP1, AQP2, AQP3, V2R Expression of the Aqueous Extract of Sclerotia of *Polyporus umbellatus* FRIES in Normal Rats," *Journal of Ethnopharmacology* 128, no. 2 (2010): 433–437.

70. C. P. Liu, X. Li, G. N. Lai, J. H. Li, et al., "Mechanisms of Macrophage Immunomodulatory Activity Induced by a New Polysaccharide Isolated From *Polyporus umbellatus* (Pers.) Fries," *Frontiers in Chemistry* Weinheim 8 (2020): 581.

71. X. L. Tan, L. Guo, and G. H. Wang, "*Polyporus umbellatus* Inhibited Tumor Cell Proliferation and Promoted Tumor Cell Apoptosis by Down-Regulating AKT in Breast Cancer," *Biomedicine & Pharmacotherapy* 83 (2016): 526–535.

72. T. H. Kim, J. S. Kim, Z. H. Kim, R. B. Huang, et al., "Induction of Apoptosis in MCF7 Human Breast Cancer Cells by Khz (Fusion of *Ganoderma lucidum* and *Polyporus umbellatus* Mycelium)," *Molecular Medicine Reports* 13, no. 2 (2016): 1243–1249.

73. W. W. Zhou, W. H. Lin, and S. X. Guo, "Two New Polyporusterones Isolated From the Sclerotia of *Polyporus umbellatus*," *Chemical & Pharmaceutical Bulletin* 55, no. 8 (2007): 1148–1150.

74. Q. Huang, L. Li, H. Chen, Q. Liu, and Z. Wang, "GPP (Composition of *Ganoderma lucidum* Poly-Saccharides and *Polyporus umbellatus* Poly-Saccharides) Enhances Innate Immune Function in Mice," *Nutrients* 11, no. 7 (2019): 1480.

75. G. K. Liu, N. Li, S. Y. Song, Y. J. Zhang, and J. R. Wang, "Three Exopolysaccharides From the Liquid Fermentation of *Polyporus umbellatus* and Their Bioactivities," *International Journal of Biological Macromolecules* 132 (2019): 629–640.

76. L. Li, Y. Guo, Q. Huang, X. Shi, et al., "GPP (Composition of *Ganoderma lucidum* Polysaccharides and *Polyporus umbellatus* Polysaccharides) Protects Against DSS-Induced Murine Colitis by Enhancing Immune Function and Regulating Intestinal Flora," *Food Science and Human Wellness* 11, no. 4 (2022): 795–805.

77. Y. N. Wang, X. Q. Wu, D. D. Zhang, H. H. Hu, et al., "*Polyporus umbellatus* Protects Against Renal Fibrosis by Regulating Intrarenal Fatty Acyl Metabolites," *Frontiers in Pharmacology* 12 (2021): 633566.

78. H. Li, Z. Yan, Q. Xiong, X. Chen, et al., "Renoprotective Effect and Mechanism of Polysaccharide From *Polyporus umbellatus* Sclerotia on Renal Fibrosis," *Carbohydrate Polymers* 212 (2019): 1–10.

79. I. M. Liu, T. F. Tzeng, S. S. Liou, and C. J. Chang, "The Amelioration of Streptozotocin Diabetes-Induced Renal Damage by Wu-Ling-San (Hoelen Five Herb Formula), a Traditional Chinese Prescription," *Journal of Ethnopharmacology* 124, no. 2 (2009): 211–218.

80. H. S. Lee, I. H. Hwang, J. A. Kim, J. Y. Choi, et al., "Isolation of Protein Tyrosine Phosphatase 1B Inhibitory Constituents From the Sclerotia of *Polyporus umbellatus Fries*," *Bulletin of the Korean Chemical Society* 32, no. 2 (2011): 697–700.

81. W. Gao, L. Zhang, J. Wu, Y. Xu, et al., "Extraction, Characterization, and Anti-Nonalcoholic Steatohepatitis Activity of a (1,3) (1,6)-β-D-Glucan From the *Polyporus umbellatus* (Pers.) Fries," *International Journal of Biological Macromolecules* 230 (2023): 123252.

82. D. HARMAN, "Free Radical Theory of Aging: An Update," *Annals of the New York Academy of Sciences* 1067, no. 1 (2006): 10–21.

83. F. Okada, "Inflammation and Free Radicals in Tumor Development and Progression," *Redox Report* 7, no. 6 (2002): 357–368.