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Review article

Chemistry and biology of *Phellinus linteus*

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ABSTRACT

Phellinus linteus (PL) is a medicinal mushroom used to prevent or treat gastroenteric dysfunction, diarrhea, hemorrhage, allergy, diabetes, and cancer in East Asia, especially in China, Japan, and Korea. To demonstrate its pharmacological value and mechanism, and translate PL into western-accepted therapy, many researchers have investigated the effects of extracts from fruit-bodies (or mycelium) of PL by means of various *in vitro* and *in vivo* models. Subsequently, many small molecular weight pure components were isolated from extracts of PL to identify their pharmacological properties and mechanisms. These studies suggest PL and its bioactive compounds as promising candidates as anticancer, anti-inflammatory, and immunomodulating agents. This review comprehensively covers literature on these extracts, pure components, and potential therapeutic applications of PL from 1999 to June 2011. In particular, small molecular weight compounds that exhibit biological activity as well as pharmacological effects on PL's anticancer, anti-inflammatory, antidiabetic, neuro- and/or hepatic-protective, and immunomodulating activities are reviewed.

1. Introduction

Traditional remedies in Chinese, Indian, Arabic, and other indigenous medicines, are prescribed and recorded in ancient medical classics and pharmacopoeias by their traditional medical doctors; in many countries these are considered as alternative or complementary medicines [1,2]. Sources of traditional remedies are diverse: mineral substances, plants, animal species, and mushrooms. Of these, mushrooms have been used as food and traditional medicine for more than 3000 years [3]. Additionally, many mushrooms like *Phellinus linteus* (PL), *Schizophyllum commune*, *Cordyceps sinensis*, *Grifola frondosa*, *Hericium erinaceus*, *Trametes versicolor*, and *Ganoderma lucidum*, are considered not only to possess therapeutic value, but also as a source of pure biocomponents for medical usage [3–5].

PL is a species of fungus belonging to the *Hymenochaetaceae* family native mainly to tropical America, Africa, and East Asia (in particular China, Japan, and Korea); it has been used to prevent or treat gastroenteric dysfunction, diarrhea, hemorrhage, allergy, diabetes, and cancer [4]. In an attempt to translate PL

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into western-accepted therapies, many researchers have investigated the effects of the extracts from fruit-bodies (or mycelium) of PL on *in vitro* and *in vivo* activities [4].

Many earlier reviews focused on bioactive mushrooms [6–10], whereas fractionation and identification of biological active components, antitumor function, and pharmacological mechanisms of PL were reviewed in 2008 [4]. This review comprehensively covers literature from 1999 to June 2011 on the natural products purification and potential therapeutic applications of PL, in particular small molecular weight components that exhibit biological activity, as well as pharmacological effects on anticancer, immune modulating, antioxidant, anti-inflammatory, antidiabetes, and antibacterial activities of PL.

2. Bioactive small molecular weight compounds from PL

The genus *Phellinus* includes several species, of which *P. linteus, P. ribis,* and *P. igniarius*, have served as treatments for cancer, diabetes, bacterial and viral infections, and ulcer [11,12]. PL is used as an ingredient of dietary supplements in East Asia [4]. Prior studies isolated polysaccharides, proteoglycans, furan-derivatives, as well as styrylpyrones from PL and verified their bioactivity [4,11,12]. Hispidin (Compound 1; Fig. 1), a well-known styrylpyrone from mycelia culture broth of PL, is a noncompetitive β-secretase inhibitor with half maximal inhibitory concentration (IC_{50}) value of 4.9 μM and a inhibition constant (Ki) value of 8.4 μM [13]; it also acts as an antidiabetic agent by inhibiting hydrogen peroxide (H_2O_2)-induced apoptosis and increasing insulin secretion in H_2O_2-treated cells [14]. Furthermore, Compound 1 as an antioxidant could scavenge 2,2-diphenyl-1-picrylhydrazyl free radicals and 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) radical cations, as well as inhibit superoxide generation via suppressing xanthine oxidase [15]. In 2006, anticomplement furan derivatives, phellinusfurans A (Compound 2; Fig. 2) and B (Compound 3; Fig. 2), were isolated from the fruiting body of PL; both exhibited a significant inhibitory effect on the hemolytic activity of human serum against erythrocytes with IC_{50} values of 33.6 μM and 33.7 μM, respectively [16].

To identify active principles for diabetics from the fruiting body of PL, hispidin and its derivatives (Compounds 4–9; Figs. 3 and 4), along with protocatechuic acid (Compound 10; Fig. 5), protocatechualdehyde (Compound 11; Fig. 5), caffeic acid (Compound 12; Fig. 5), and ellagic acid (Compound 13; Fig. 5) were isolated and elucidated by spectroscopic methods. Among them, Compounds 5, 7, and 13 revealed potent inhibitory effects on rat lens aldose reductase and human recombinant aldose reductase with IC_{50} values of 0.33 μM, 0.82 μM, 0.63 μM, and 0.56 μM, 1.28 μM, 1.37 μM, respectively [17]. At an early stage of protein glycation, Compounds 4, 8, and 9 exhibited inhibitory activity on

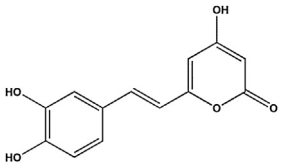

Fig. 1 – Structure of hispidin (Compound 1).

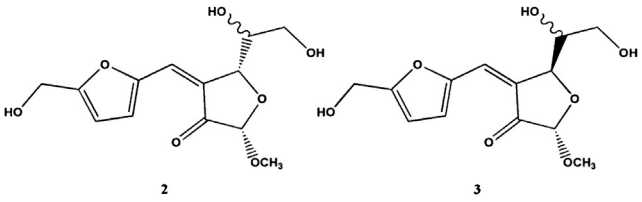

Fig. 2 – Structures of phellinusfurans A (Compound 2) and B (Compound 3).

hemoglobin A_{1C} formation; at the middle stage, Compounds 4, 8, and 11 showed a significant inhibitory effect on methylglyoxal-medicated protein modification with IC_{50} values of 144.28 μM, 213.15 μM, and 158.66 μM, respectively. Of these, Compound 8 also potently inhibited the last stage of glycation and proved more effective than positive control amnoguanidin. Hence interfungins A (Compound 8) showed the most potency in suppressing protein glycation [18].

Nagatsu et al isolated additional styrylpyrones—meshimakibnol A (Compound 14; Fig. 5), meshimakibnol B (Compound 15; Fig. 5), phellifuropyranone A (Compound 16; Fig. 5), and phelligridin G (Compound 17; Fig. 6)—from fruit bodies of wild PL, then evaluated their antiproliferation against five B16 mouse melanoma cells (wild, BL6, F1, F10, and C2M) and human lung cancer cells (A549, EBC-1, and SBC-3) [19,20]. Of these, Compounds 14–16 showed weakly antiproliferative activity against cell lines, with 50% growth inhibition concentration ranging 5.6–31.3 μM [20].

A retinolic acid derivative, (2*E*,4*E*)-γ-ionylideneacetic acid (Compound 18; Fig. 6), that reverses liver fibrosis at an early phase through downregulation of reactive oxygen species (ROS) generation and calcium influx in HSC-T16 cells, was isolated from the mycelium of PL [21]. Also, a new antimicrobial furanone derivative, phellinone (Compound 19; Fig. 6), was isolated from stem-cooked rice culture broth of PL.

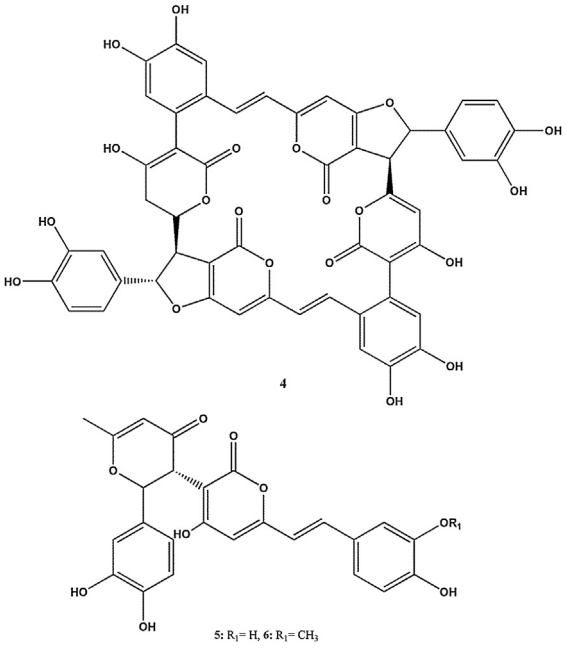

Fig. 3 – Structures of Compounds 4–6 isolated from PL.

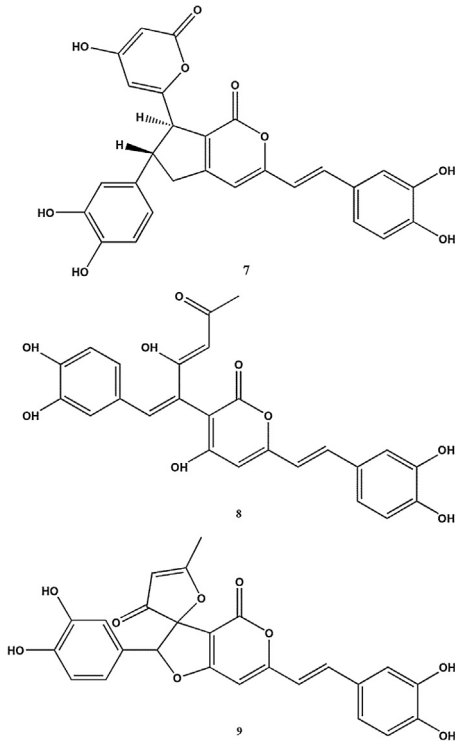

Fig. 4 – Structures of Compounds 7–9 isolated from PL.

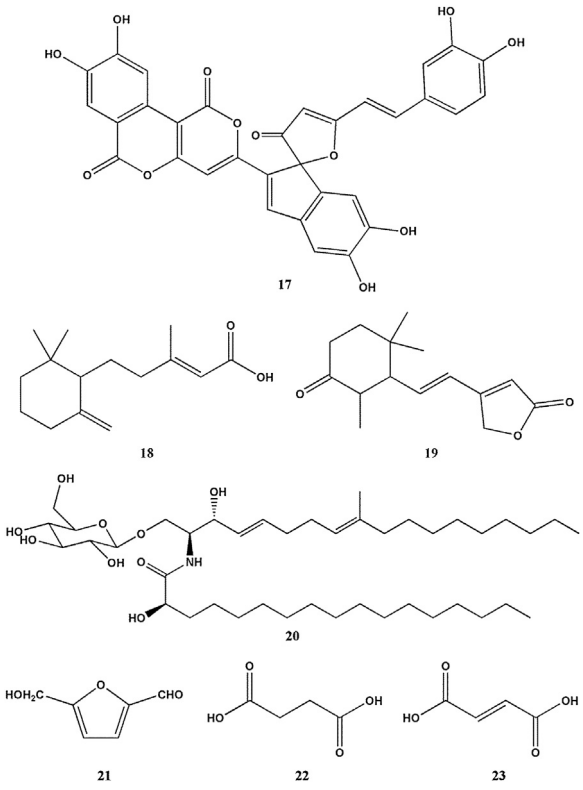

Fig. 6 – Structures of Compounds 17–23 isolated from PL.

Compound 19 showed selectively antimicrobial activity against *Bacillus subtilis* at a concentration of 10 μg/mL [22].

Cerebroside B (Compound 20; Fig. 6), protocatechualdehyde (Compound 11), 5-hydroxymethyl-2-furaldehyde (Compound 21; Fig. 6), succinic acid (Compound 22; Fig. 6), and fumaric acid (Compound 23; Fig. 6) were isolated and identified from the fruiting body of PL by Kang et al in 2004 [23]. Compounds 11 and 21 inhibited tyrosinase activity with IC_{50} values of 0.40 and 90.8 μg/mL and Ki values of 1.1 μM and 1.4 mM, respectively [23].

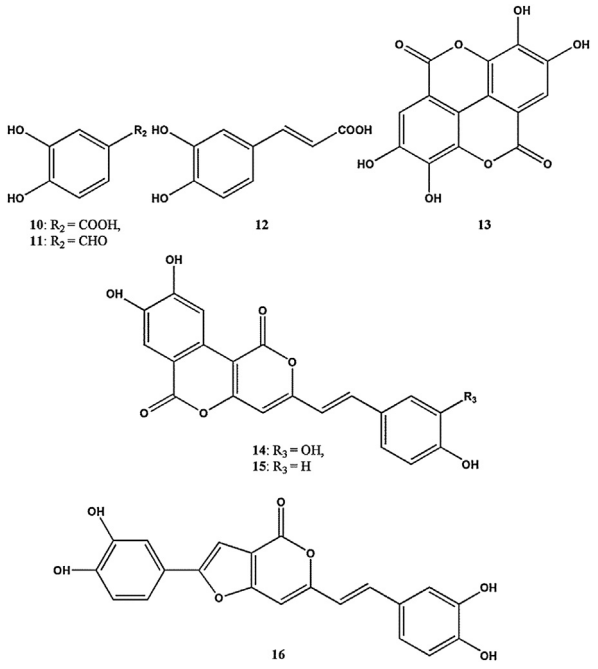

Fig. 5 – Structures of Compounds 10–16 isolated from PL.

Cancer cells with higher extracellular signaling-regulating kinase 1/2 (ERK1/2) activity were recently more sensitive to hispolon (Compound 24; Fig. 7), with hispidin analog from PL demonstrated as being able to attenuate MDM2 expression so as to inhibit breast and bladder cancer cell growth [24]. Likewise, Compound 24 decreased expression of matrix metalloproteinases-2 and -9, and urokinase–plasminogen activator, while inhibiting phosphorylation of ERK1/2, phosphatidylinositol-3-kinase/serine/threonin protein kinase, and focal adhesion kinase in SK-Hep1 cells [25]. By contrast, treatment of male ICR (imprinting control region) mice with Compound 24 significantly inhibited not only acetic acid-induced writhing response, but also formalin-induced pain. Furthermore, Compound 24 decreased the level of malondialdehyde in the edema paw through augmenting activities of superoxide dismutase, glutathione (GSH) reductase, and GSH peroxidase in liver tissue [26]. Results indicate that hispolon acts as a lead antimetastatic and anti-inflammatory agent. A new trimeric hispidin derivative, phellinstatin (Compound 25; Fig. 7), together with known dimeric hispidin derivative hypholomine B (Compound 26; Fig. 7), were isolated from culture broth of PL. Both exhibited potently inhibitory effect on *Staphylococcus aureus* enoyl-ACP reductase with IC_{50} values of 6 μM and 15.3 μM. However, only Compound 25 showed antibacterial activity against methicillin-resistant *S. aureus* [27].

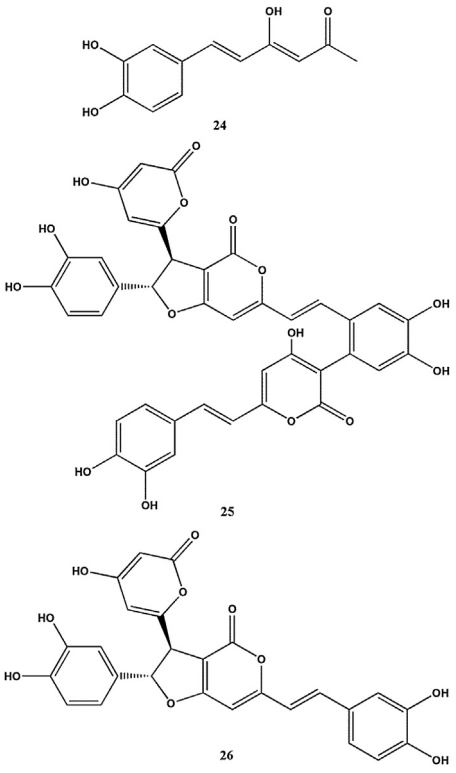

Fig. 7 – Structures of Compounds 24–26 isolated from PL.

3. Pharmacological properties of the extracts and fractions from PL

3.1. *Neurorelative activity of PL*

Thromboembolic occlusion of cerebral artery causes cerebral infarction, further inducing cerebral ischemia causes brain damage and death. Many reports indicate that free radical generation plays a vital role in brain lesions during cerebral ischemia [28]. Administering high-molecular-weight (≥12,000) fractions of PL culture filtrate results in reduction of cortical cerebral infarction in a rat permanent focal ischemia model [28]. Monocarboxylate transporter (MCT) proteins include isoforms MCT1–4. Among them, MCT1 plays a major role in the influx of lactic acid for oxidation; MCT4 modulates in efflux of lactate from muscle fibers, particularly in white muscle fibers, during intense exercise [29,30]. Levels of MCT1 and MCT4 thus modulate muscle activity and rate of lactate transport [29]. Treatment with 200 mg/kg aqueous extracts of PL not only led to a significant increase in time to fatigue in response to running on a treadmill, but also raised MCT1 and MCT4 expression in gastrocnemius muscles; both 5-hydroxytryptamine synthesis and tryptophan hydroxylase expression decreased in the dorsal raphe of rats after administering the same dosage of PL [29].

3.2. *Antidiabetic activity of PL*

Type I insulin-dependent diabetes mellitus is a serious disorder causing progressive loss of insulin-producing pancreatic β cells [31]. Type II diabetes mellitus is not only due to pancreatic β cell defects, but also includes insulin resistance [32]. Treatment of polysaccharide fraction from PL inhibited development of autoimmune diabetes via attenuating expression of inflammatory cytokines (e.g., interferon (IFN)-γ, interleukin (IL)-2, tumor necrosis factor (TNF)-α) by T helper type 1 (Th1) cells or macrophages, while upregulating IL-4 expression by Th2 cells in nonobese diabetic mice [31].

3.3. *Anti-inflammatory activity of PL*

Kim et al reported that ethanolic extracts of PL showed a dose-dependent inhibitory effect on mouse ear edema induced by croton oil, as well as reducing writhing induced by acetic acid. Additionally, the butanolic subfraction fractionated from the ethanolic extracts of PL revealed highest inhibitory activity on chick embryo chorioallantoic membrane angiogenesis [33]. Meanwhile, this butanolic subfraction also diminished lipopolysaccharide (LPS)-stimulated nitric oxide (NO) production, ROS generation, c-Jun induction, and c-Jun N-terminal kinase activation via upregulation of heme oxygenase-1 in RAW264.7 macrophages [34]. PL increased heme oxygenase-1 expression through the PKCδ/Nrf2/ARE pathway [35]. The butanolic subfraction fractionated from the ethanolic extracts of PL also suppressed production of NO and prostaglandin E2 through downregulation of iNOS and COX-2 gene expression via nuclear factor-κB and mitogen-activated protein kinase activation in RAW264.7 macrophages [36].

Oral administration of derivative PL proteoglycan inhibits collagen-induced arthritis in mice due to a decrease in anti-type II collagen IgG and IgG2a antibody, as well as modulating cytokines IL-12, TNF-α, and IFN-γ [37], whose release induced by LPS stimulation can be manipulated via administration of acidic polysaccharide from PL in septic shock mice. Moreover, anti-inflammatory PL may associate with augmented apoptosis of a portion of the activated macrophages and lymphocytes [38].

Intraperitoneal infection, due mainly to previous surgery and abdominal inflammation, is accompanied by fibrin deposition in the abdominal cavity. This fibrin deposition may become a nidus for abscesses and, in turn, adhesion formation. Degradation of fibrin is a target in preventing adhesion formation [39–41]. Polysaccharides isolated from PL significantly attenuate adhesion formation via augmenting expression of urokinase-type plasminogen activator, urokinase-type plasminogen activator cellular receptor, tissue-type plasminogen activator, and TNF-α [39,41]. Additionally, a combination of carboxymethylcellulose and polysaccharide proved more potent than single treatment with either [40].

3.4. *Antitumor activities*

Many studies demonstrate PL as immunostimulator or immunoregulator through activating immune cells [e.g., T cells, B cells, dendritic cells (DC), and macrophages] thereby acting against tumors [4]. Park et al indicated acidic polysaccharides from PL treatment not only forming morphologically mature DC but also inducing predominant migration to lymphoid tissues. Furthermore, PL induced protein kinase C activity and phosphorylated protein tyrosine kinase in DC

[42]. Further study suggested the tumoricidal activity of peritoneal macrophages cultured with acidic polysaccharides from PL against B16 melanoma and Yac-1 cells via increasing NO and TNF-α production, and enhanced phagocytic ability. These results indicated that PL acts as an immunomodulator and enhances antitumor activity of peritoneal macrophages [43]. By contrast, proteoglycan from the fruiting body of PL targets B cells and enhances expression of CD80 and CD86 by regulating the protein tyrosine kinase and protein kinase C signaling pathways [44]. Proteoglycan also inhibits growth of MCA-102 tumor cells *in vivo* via induced production of IL-12 and IFN-γ leading to a Th1 dominant state. These effects stimulated substantial $CD11c^+$ and $CD8^+$ DC expression [45], whereas proteoglycan could induce phenotypic and functional maturation of DC through Toll-like receptors 2 and 4, further mediating nuclear factor-κB, ERK, and p38 mitogen-activated protein kinase pathways [46]. Recently, orally administrated mycelia culture of PL (250 mg/kg) to hepatoma 3B-bearing mice significantly suppressed hepatocellular carcinoma growth and improved survival rate by increasing natural killer cell activity and IL-12, IFN-γ, and TNF-α secretion [47]. Meanwhile, after administration of proteoglycan (100 mg/kg) in BALB/c-nu/nu mice, proteoglycan not only modulated immune response by protecting T cells from prostaglandin E2 attack and enhancing the mucosal IgA response, but also suppress the Reg IV/EGFR/Akt signaling pathway [48].

In addition to activating immune cells against tumors, PL can also control growth and metastasis of tumors through other pharmacological mechanisms (e.g., apoptosis, anti-adhesion, and antiangiogenesis) [4]. In 2006, a combination treatment with low doses of PL and doxorubicin was found to result in synergistic effect on induction of apoptosis in prostate cancer LNCap cells via activated c-Jun N-terminal kinases and caspases [49]. Furthermore, it was demonstrated that high doses of PL not only activate the androgen receptor-dependent pathway via caspase 2, a specific intracellular switch for regulating susceptibility of prostate cancer LNCap cells, but also induce apoptosis in prostate cancer LNCap, and PC3 cells activate the androgen receptor-independent pathway [50]. A subsequent *in vivo* study indicated growth of prostate cancer DU145 and PC3 cells is dramatically attenuated after administration of PL (30 mg/kg in PBS) every 2 days for 12 days. Additionally, histochemistry of immunochemistry analysis also revealed that PL induces tumor apoptosis by activation of caspase 3 [51]. In addition to prostate cancer cells, PL induces cell cycle arrest and apoptosis in different cancer cells including human colon carcinoma cells, melanoma cells, epidermoid cells, and lung cancer cells by regulating signaling pathways [52–56].

Cancer metastasis consists of several processes including abnormal cell proliferation, invasion, migration, and adhesion. Furthermore, angiogenesis also play an important role in tumor growth and metastasis [57]. PL inhibits cancer cell adhesion to and invasion through interaction with cell-to-extracellular matrix *in vitro* and *in vivo* tests in B16F10 cancer cells and in mice, respectively [58]. In addition, PL can suppress growth, angiogenesis, and invasive behavior by inhibition of phosphorylation of protein kinase B at Thr^{308} and Ser^{473} in breast cancer MDA-MB-231 cancer cells [57].

Chemopreventive agents are a major topic in anticancer drug development. These agents involve diverse pharmacological mechanisms, such as antioxidation and the induction of Phase II detoxification enzymes [59]. Butanol and water extracts of PL elevate quinine reductase and GSH S-transferase activity, and GSH levels, thereby catalyzing the metabolism of xenobiotics and carcinogens (e.g., 4-nitro-*O*-phenylenediamine, sodium azide, and 2-aminofluorene) and reducing toxicity [59]. Moreover, the 70% ethanol extracts of PL showed scavenging of free radical activity, as well as inhibiting lipid peroxidation [60].

On the basis of these investigations, PL shows diverse mechanisms including antimetastatic, antioxidant, apoptosis, cell cycle arrest, and immunomodulation, inhibiting the growth, proliferation, and metastases of tumor cells. These establish PL as a promising source for developing new generation anticancer drugs.

3.5. *Antiallergic and immunomodulating activities of PL*

Allergic disease caused by activation of Th2 cells, further induces IgE-dependent mast cell degranulation and eosinophil accumulation [61]. Extracts from PL grown on germinated brown rice and PL alone were administered orally (2 mg/kg/day) for 4 weeks in mice. The results showed that both dramatically decrease IgE; however, the INF-γ level and the proportion of $CD4^+$ were increased [61]. INF-γ is a representative Th1 cytokine, attenuating the development and activation of Th2 cells [61,62]. In addition, extracts from PL grown on germinated brown rice also exhibited modulation of intestinal Th1/Th2 balance [62].

Inagaki et al orally administered (100 mg/kg) five fractions, including chloroform-soluble, ethyl acetate-soluble, methanol-soluble, water-soluble, and boiling water-soluble (BW) fractions, from mycelium of PL to determine their inhibitory effects on IgE-dependent mouse triphasic cutaneous reaction, which was induced in the ear of BALB/c mice passively sensitized with anti-dinitrophenol IgE by painting with 2,4-dinitrofluorobenzene 24 hours later. Of these, BW was more potent than other fractions [63]. In addition, BW not only exhibited inhibitory effect on the vascular permeability increase induced by passive cutaneous anaphylaxis and histamine, but also on ear swelling caused by TNF-α. BW also potentiated the production of IL-4 and IFN-γ from anti-CD3-stimulated mouse splenocytes [63]. Similarly, oral administration of water extract from PL inhibited the compound 48/80-induced systemic anaphylaxis-like reaction and ear swelling. In addition, this water extract not only decreased the compound 48/80-induced calcium uptake into rat peritoneal mast cells, but also augmented and reversed the reduction of intracellular cAMP level caused by compound 48/80 in rat peritoneal mast cells [64].

Orally administrated, the BW extracts of PL (4 g/kg/day) also augment the immune response of the spleen and concentrations of IL-4 and INF-γ in mitomycin C-induced immunodeficient mice [65]. By contrast, fish (*Epinephelus bruneus*) fed a diet enriched with extracts of PL showed dramatically augmented resistance against bacterial diseases through increases in alternative complement activity and lysosyme activity [66].

3.6. *Hepatoprotective activity of PL*

Polysaccharides from the mycelia of PL with mulberry extract showed inhibitory effect on cytochrome P450 (CYP) 1A1, CYP 1A2, CYP 2B1, and CYP 2E1 activities *in vitro* [67]. Additionally, oral administration of PB at a dose of 200 mg/kg protected the liver injury induced by carbon tetrachloride (CCl_4) via decreasing peroxidation production, catalase and superoxide dismutase activity, as well as expression of CYP 2E1 protein [68].

The methanolic extract of PL was further fractionated into *n*-hexane, ethyl acetate, *n*-butanol, and water fractions by Kim et al. Among them, the ethyl acetate fraction reversed the decrease in hepatic glutathione level induced by treatment with H_2O_2 or galactosamine. This fraction also protects hepatocytes from H_2O_2- or galactosamine-induced liver injury by restoring RNA synthesis [69]. By contrast, treatment of hepatocytes with ethanolic extracts of PL reversed ferric nitrilotriacetate (FeNTA)-induced cell viability loss, lactate dehydrogenase leakage, lipid peroxidation, and protein carbonyl formation, as well as recovery of GSH content, and GSH reductase and GSH peroxidase activity. Furthermore, the ethanolic extracts of PL revealed inhibitory effect on intracellular ROS formation induced by FeNTA. These results suggest that the extract of PL has cytoprotective activity against FeTNA-induced hepatotoxicity [70].

3.7. *Other pharmacological activity of PL*

The *n*-butanol fraction fractionated from the methanolic extracts of PL showed a good antibacterial activity against methicillin-resistant *S. aureus* strains with minimum inhibitory concentration values ranging 63–125 μg/mL [71]. Extracts of PL also exhibited potent antioxidant against oxidative stress-induced bacterial DNA strand break. In addition, cotreating with extract of PL and ginseng extracts synergistically increased the effect on the damage incurred by eukaryotic nuclear DNA exposed to oxidative stress [72]. PL also potently suppressed activation of aryl hydrocarbon receptor (AhR) and AhR-dependent gene expression triggered by cigarette smoke, dioxin, and polycyclic aromatic hydrocarbon, indicating that PL might be useful for prevention of pathologies associated with aberrant activation of AhR [73].

Recently, Ichinohe et al found that intranasal administration of NIBRD14 vaccine in combination with an extract of PL showed cross-protection against heterologous influenza A virus challenge in a nasal infection model by augmenting mucosal secretory IgA. Furthermore, PL-adjuvanted vaccine also increased postinfection survival days. These results propose PL-adjuvanted vaccine as a new mucosal adjuvant for use against influenza virus infection [74].

4. Conclusion and perspectives

In summary, extracts and fractions from PL show diverse pharmacological mechanisms, including anticancer, anti-inflammatory, neuro- and hepatic-protective, antidiabetic, immunomodulating, antibacterial, and antioxidation in multiple *in vitro* and *in vivo* tests. Bioactive components of PL extracts were also identified, suggesting PL and its bioactive compounds as promising candidates for drug discovery. To apply PL to clinical usage, further study of its pharcokinetic and pharmacodynamic profile, and other preclinical studies of PL are necessary. By contrast, bioactive components may be created by chemical modification to generate more potent agents.

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