The Edible Mushroom *Pleurotus* spp.: II. Medicinal Values

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Abstract: Mushrooms health benefit was recognized in the Orient from several thousand years ago as globally consumption and has third largest commercially production. The genus *Pleurotus* (oyster mushroom) is an organoleptic fast growing fungus which belongs to basidiomycota group. Although 70 species is discovered until now for this genus, but only few of them are available in market such as *Pleurotus florida, P. sajor-caju* and *P. ostreatus.* They have been used in human diet throughout the world due to their rich nutrients such as protein, fiber carbohydrate, minerals, vitamins and lipid. It should be noted that low amount calories, Sodium, fat and cholesterol is reported in this genus. Many pharmaceutical companies in the Far East and China are viewing the medicinal mushrooms as a rich source of innovative biomedical molecules. These molecules can be extracted from different part of oyster mushroom such as fruiting body, mycelia and culture broth. Mainly they are biopolymers including polysaccharides, proteins and nucleic acids as they are more variable to carry biological information. The medicinal properties of *Pleurotus spp* studied by several authors, as a result antitumor, immunomodulating, antiviral, antibacterial, antigenotoxic, antioxidant, anti-inflammatory, hypocholesterolamic, antihypertensive, antiinociceptive, anti-hyperglycaemic, anti-platelet-aggregating, antihepatoma, anti poliferative and antiatherosclerotic. In this chapter, biodivertsity of genus *Pleurotus* will be discussed regarding nutritional and bioactive compounds. Furthermore the prospective of oyster mushroom for therapeutic application and concept will be highlighted.

Keywords: *Pleurotus spp.,* medicinal mushrooms, mushrooms bioactive metabolites, immunomodulatory, antimicrobial.

1. INTRODUCTION

Mushrooms have been cultivated around the world as human diet based on their high nutritional profile including wide range of essential nutrients such as protein, fiber, carbohydrate, minerals, vitamins as well as low content of cholesterol, sodium, fat [1-6]. In addition of the traditional consideration of mushrooms as excellent source of food ingredients since thousands years, mushrooms have been also considered as one of the essential components of treatment in many cultures all over the world and become important part of traditional medicine [7, 8]. This based on their wide range of bioactive compounds of high potential bioactivities for pharmaceuticals industries. This based on their wide range of bioactive metabolites from different groups: polysaccharides, proteins, phenolics, and many other low molecular weight compounds. These compounds exhibited many medicinal values as anticancer, immunomodulators, antioxidants, anti-hypocholesterolemics, anti-hyperglycemics, antimicrobials, anti-inflammatory, anti-thrombogenic, antidiabetic, hepatoprotective, and anti-osteoporotic. In addition to their medicinal uses, recent research showed also the potential applications of mushroom metabolites in cosmeceutical industries [9, 10]. Therefore, mushrooms have been considered as one of the major components of wellness industries [11, 12].

Of different types of mushrooms known worldwide, species belong to the genus *Pleurotus* (oyster mushrooms) are considered as one of the most interesting species based on many factors. Frist; their ability to grow under different environmental conditions (tropical and subtropical rainforest), ability to degrade wide range of lignocellulosic substrates due to highly diversified enzymatic activities, ease of cultivation in both solid state fermentation and submerged culture with higher growth rate compared to other types of

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mushrooms, higher nutritional value compared to other mushrooms, and production of wide variety of bioactive molecules of medicinal values. Therefore, *Pleurotus* sp. is nowadays ranked the third most cultivated mushrooms after *Agaricus* and *Lentinula* [6]. In our previous work we reviewed and highlighted the latest up to date information available about the biodiversity and nutritional value of *Pleurotus* sp. [5]. In this work, we focus on the medicinal values of the mushrooms bioactive compounds of this species as well as the recent application of this type of mushrooms in medical field when used either in crude or purified compound form.

2. MEDICINAL PROPERTIES OF *PLEUROTUS* SPP.

2.1. Antitumor, Antiproliferative and Antiapoptotic

Producing natural derived compounds with anticancer properties are becomes hot research topic with special consideration to apply novel compounds which provide potential bioactivity with low toxicity [13-15]. Currently mushroom-derived substances with antitumor and immunomodulating properties are used as dietary supplements or drugs [13, 16]. Several linear and branched glucans and heteroglycans isolated from higher basidiomycetes exert strong immunostimulating and anti-tumor activities [13, 16-19]. Considering that anticancer drugs should be able to distinguish between cancer and normal cells, the importance of developing immunomodulators as a novel chemotherapy agent will be realized [13, 21]. Several studies indicate that bioactive compounds from *Pleurotus* spp can be regarded as potential antitumor agent without any effect on normal cells [14, 18, 22]. However, antitumor effect of mushroom is not only limited to polysaccharides but also other bioactive compounds such as proteins of potential anticancer properties were also isolated from *Pleurotus* spp [23-25]. The antitumor properties of mushroom derived polysaccharides is in cooperation with both enhancing the immune system and direct attacking to cancer cell [13, 26-27].

The antitumor activity of polysaccharides is significantly correlated with the structure, molecular weight, solubility, monosaccharide composition and extraction method [22, 28]. It is claimed that soluble polysaccharides are stronger anti-tumor and immunomodulators compared to insoluble fractions. Hence, some efforts have been done to increase the polysaccharides solubility using some chemical modifications [29, 30]. In addition, solubilization of non water soluble polysaccharide promotes the feasibility of intravenous administration.

It is demonstrated that carboxymethylated β-glucans from *P. tuber-regium* significantly strengthen water solubility and notably promote *in vitro* anticancer activity against HL- 60 tumor cell culture as well as *in vivo* one against Sarcoma 180 tumor implanted on mice. In addition, the immunomodulatory effect of this carboxymethylated β-glucans is proven to be higher than native β-glucans as they are detected to be broadly contributed in priming effect for TNF-α production in the present of lipopolysaccharides [31]. In another approach, carboxymethylated glucan of *P. tuber-regium* performed high antitumor activity against human breast carcinoma [25]. Furthermore, the sulfated and carboxymethylated derivative of two polysaccharide-proteins from this mushroom is exposed to anti-proliferative test against Sarcoma 180 tumor cells. Although the native polysaccharide and their derivatives perform proliferation inhibitory effect, but most inhibitory ratio is reported for sulfated polysaccharides- protein complex followed by carboxymethylated one with notable distance. Besides, the polysaccharide-protein complex with higher molecular weight reflects better antitumor activity [32]. In addition water soluble polysaccharide which composed of mannose, galactose and glucose in a molar ratio of 1:2.1:7.9 proposed intense antitumor activity against Hela tumor cell line [22].

It is revealed that the hot water soluble polysaccharide(Low molecular weight α-glucan) from *P. ostreatus* up regulate the expression of pro-apoptotic proteins such as Bax and Cytochrome c, which give a raise to apoptosis and HT-29 cell death in a mitochondrion apoptotic. As a result proliferation activity of cells will be suppressed. HT-29 cancer cells are not affected by defatted alcohol-soluble fraction of same mushroom [18]. Another water soluble polysaccharide from *P. citrinopileatus* reduce number of tumor cells in mice with artificial pulmonary metastatic tumors [33]. However, water insoluble polysaccharide of this mushroom exhibit higher inhibition effect on Sarcoma 180 tumor cells in mice than the soluble ones. It may due to high β-D-glucan content of their water insoluble polysaccharides compared to soluble form [34]. Other study reported also that polysaccharide peptide from submerged fermentation of *P. eryngii* exhibited cytotoxicity activity against sarcoma 180 tumor cells in mice [35].

Polysaccharides from hot water extraction of *P. pulmonarius* show potent antitumor activity against sarcoma180 tumor cell in mice [36]. Further studies also reported that glucans from mycelis and fruiting

body extract of *P. pulmonarius* exhibited direct anti-proliferative effect on colon cancer cell line (HT-29, Caco2, HCT-116, LS174T, HM-7) through up regulation of galectin-3 expression and down regulating tumor cell adherence [27].

However, polysaccharides are not the only bioactive compounds which are extracted from *Pleurotus* considering antitumor activity, but other compounds which carry the biological information is also isolated such as proteins. The half maximal inhibitory concentration (IC_{50}) of 0.22 and 0.1μM decline in tumor cells HepG2 (hepatoma) and L1210 (leukemia) survival have been recorded respectively, when they exposed to 12 kDa ribonuclease from *P. saju-caju.* It also possesses antimitogenic effect on the murin splenocytes as well [37]. Eryngeolysin (kind of hemolysin) is another functional protein which isolate from *P. eryngii* destruct leukemia (L1210) cells [38]. Another kind of hemolysin purified from *P. nebrodensis* known as nebrodeolysin give rise to cytotoxicity against Lu-04, Bre-04, HepG2, L929, and HeLa cells. Microscopic observation and DNA ladder evidence that this protein is capable of apoptosis induction against L929 and HeLa cells, respectively [25].The other hemolysin which prevent the proliferation of human fibrosarcoma HT-1080 and human breast MCF-7 cancer cell lines is successfully isolate form *P. ostreatus* [23]. In another study, nonlectin glycoprotein (PCP-3A) from *P. citrinopileatus* arrest the growth of human myeloid leukemic U937 cells in S phase in time dependent manner and induce apoptosis against them [24]. Lectin from fresh fruiting bodies of same mushroom inhibits the growth of sarcoma 180 in mice and caused murine splenocytes mitogenic response [29]. Also the growth of sarcoma S-180 and hepatoma H-22 is inhibited by a lectin from *P. ostreatus* [40]. In addition, a 66-kDa laccase purified from fresh fruiting bodies of the edible mushroom *P. cornucopiae* excreted antiproliferative activity against murine leukemia cell line L1210 and human hepatoma cell line HepG2 [41].

The antitumor properties of *P. ostreatus* extract is studied by several authors mainly focus on colon and breast cancer. It is suggested that preventive effect of *P, ostreatus* extract against colon carcinogenesis is due to modulatory mechanisms of inflammation in combination with suppression of tumor growth in mice [42]. *P. ostreatus* methanol extract detected as most potent suppresser for human breast cancer (MCF-7, MDA-MB-231) and colon cancer (HT-29, HCT-116) cell proliferation among mushroom species of *Agaricus bisporus*, *Flammulina velutipes* and *Lentinula edodes.* As it is previously mentioned, anti-proliferative and pro-apoptotic effects of hot water-soluble polysaccharides from *P. ostreatus* submerged fermentation is reported as well [18, 43, 44]. Anti-proliferation property of this species follows a time and dose dependent manner and also has influence on the cancer cell morphology. It is demonstrated that cell cycle arrest at G0/G1phase, as a result of up-regulation of p53 expression in breast cancer cell and p21 for both breast and colon cancer cell lines, is responsible for reported anti-proliferation effect. Two other report documented G0/ G1 phase cycle arrest of cancer cell lines. One of them evaluates the antiproliferative activity of chemical modified β-glucan from *P. tuber-regium* against MCF-7 breast cancer cell line. In this study, down regulation of anti-apoptotic protein along with over expression of pro-apoptotic proteins such as Bax associated with the inhibitory effect on cancer cell lines [26]. The other one recorded a decline in Sarcoma-180-bearing mouse model injected with mycelia derived proteoglycan from *P. ostreatus*. A crude fraction have less apoptotic effect on cancer cells than other purified one [13]. Moreover, the methanol extract of *P. ostreatus* have no effect on normal epithelial mammary (MCF-10A) and colon cells (FHC) [14]. Ehrlich ascites carcinoma is another cancer, which *P. ostreatus* extract perform an antitumor effect against it [21]. In addition, aqueous extract of same mushroom detected to have remarkable inhibitory effect on melanoma B16 in female mice comparing to 16 other species of higher basidiomycetes [45].

Both whole mushroom extract and putative purified compound of species is investigated regarding their therapeutic application and health benefit, however the difference between them in exerting therapeutic properties such antitumor, anti-proliferation and anti-apoptotic still unclear. In addition more accurate data should be obtained regarding how to take advantage of nutraceutical properties of mushrooms [18].

2.2. Immunomodulators

Polysaccharides are referred as strong immune enhancing compounds. The activation of immune cells such as macrophages, cytokines, natural killers and T-helpers as a consequence of mushrooms polysaccharides administration is indicated by several authors [46, 47]. It have been also reported that mushroom and it derivatives compounds possess antitumor activity through activation of these immune compounds, natural killers cells in particular [13, 21,

48-50]. Macrophage activation as well as splenocytes, and thymocytes proliferation is observed by Roy *et al*. as a result of applying homopolysaccharides with D-glucose constituent from *P. florida* are indicators of immunoenhancing activity of this polysaccharide [49]. Another polysaccharide isolated from fruit bodies of this taxon (consist of D-glucose and D-galactose in a molar ratio of 5:1) exhibit same immunomodulator activity in mouse cell culture medium [51]. Numerous studies have been conducted with the aim of immunoenhancing properties of natural derived polysaccharides from *Pleurotus* species. A branched heteropolysaccharide, constitute of D-glucose and D-galactose in a molar ratio of 7:1, from *P. ostreatus* activate macrophages and proliferate splenocytes and thymocytes of mice cells [16, 29]. Another heteropolysaccharide from this mushroom (D-galactose and D-glucose in a molar ration of 2:1) is capable of lymphocytes proliferation enhancement on murine, while a crude polysachharide extract has no effect on them. This suggest an existence of immunosuppressive compounds in the crude polysaccharide extracts which should be clarify in further research [19].

Three mycelia derived proteoglycan from *P. ostreatus* significantly enhance macrophage and natural killer cells and considered as splenocyte proliferators [13]. Furthermore, intraperitoneal administration of *P. eryngii* polysaccharide-peptide complex enhances the activity of natural killers and macrophage phosphatase [35]. Also aqueous extract of *P. ostreatus* as well as *P. cornucopiae* efficiently stimulate the immune compounds [45]. An increase in T cells along with $CD4^+$ and $CD8^+$ is observed in mice feed by polysaccharide from *P. citrinopileatus* [33]. In addition, It is proposed that stimulation of human mononuclear cells as a result of applying glycoprotein (PCP-3A) from same mushroom into human myeloid leukemic U937 cells lead to secretion of cytokines TNF-R, IL-2, and IFN-γ and inhibition of U937 cells growth subsequently [52]. A clinical trial study using Immunoglukan P4H® syrup (A β-glucan of *P. ostreatus* and vitamin C) showed the significant decreasing effect of flu and flu like disease for children suffering from recurrent respiratory tract infections [53].

2.3. Antioxidant

From the time that therapeutic properties of *Pleurotus* mushrooms considered as an untapped source of novel pharmaceutical active compound. Apart from immunomodulatory and antitumor properly of *Pleurotus,* numerous studies focused on the antioxidant activity of many this group of mushrooms [54, 55]. Inordinate release of highly reactive oxygen species (ROS) including superoxide anion, hydroxyl radicals and hydrogen peroxide lead to oxidative stress in the animal tissue which cause various diseases such as Alzheimer's disease, multiple sclerosis, diabetes mellitus, and liver cirrhosis. The destructive effect of ROS on lipid, DNA and proteins will be alleviated by antioxidants. High proportion of vitamins A, C and β-carotene in mushrooms lead to consumption of them in a human diet with the aim of coping with these diseases from long time ago. Therefore, attempts have been done to develop products to take the advantage of antioxidant property of mushrooms [56, 57]. Future research should focus on oral nutraceutical dietary which contain active antioxidant agents from *Pleurotus* spp. considering the practical relevance [58]. The protective effect of *P. ostreatus* extract is proven as they elevated the antioxidant enzymes including catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (Gpx) and glutathione-*S*-transferase (GST) in CCL_4 induced oxidative stress kidneys, heart and brain of Wistar rats. Also a reduction in malondialdehyde (MDA) and increase in glutathione (GSH), vitamins C and E is reported [56]. The same extract enhance the activity of CAT, SOD and Gpx in liver of rats under cholesterol diet while reduce CAT activity in erythrocytes [59]. However, the same boost trend observed in expression of these antioxidant enzymes and reduction of MDA content in liver, brain and kidney of senescence-accelerated mice through oral administration of polysaccharide-peptide purified from *P. abalonus* [60]. Further studies proved the concentration-depending antioxidant activity of *P. ostreatus* ethanolic extract *in vitro*. Inhibition of lipid proxidation, ROS scavenging and chelating ferrous are indicated as causes of antioxidant activity [57]. In another approach, antioxidant activity of *P. ostreatus* extract is assayed on hepatotoxic liver of male rats. The administration of *P. ostreatus* extract notably alleviates hepatotoxicity elements and raise the antioxidant enzyme and antioxidants concentration [61]. The inhibitory of lipids and scavenging of hydroxyl radical by the ethyl acetate and methanol extracts of *P. florida* indicate the antioxidant activity of this taxon as well [62]. Interestingly, a diet of β-glucan from *P. ostreatus* did not influence antioxidant enzymes activity of rats [59]. However, a water soluble glycolprotein with 33 kDa molecular weight purified from *P. ostreatus* regarded as potent antioxidant [63]. In another approach, the antioxidant enzymes expression

unregulated through administration of polysaccharide-peptide complex from *P. abalones* in aged mice [60]. The intracellular polysaccharides of *P. corncopiae, P. nebrodensis* and *P. eryngii* have been introduced as a noble intense antioxidant as they particularly scavenged hydroxyl radicals, and superoxide anion [64]. Hydroxyl radicals and its precursors, superoxide anion, coxidative initiate the lipid peroxidation as well as producing other oxidative agents and free radical [64]. Phenols are other compounds of mushrooms which break up the peroxy radicals and assist the antioxidant activity of mushrooms [57]. It is found that water extract of *P. ostreatus* and *P. sajor-caju* which contain higher total phenol content than ethanol extract propose better antioxidant activity. Moreover, *P. ostreatus* possess stronger antioxidant activity than *P. sajor-caju* [65]. In another approach the antioxidant activity of ethanolic, cold and hot water extracts of *P. citrinopileatus* is evaluated. Obviously phenol content in fruiting body extract was higher as well as antioxidant activity and ethanol extraction method proposed better antioxidant properties [66]. However, recent research showed that the thermal treatment of mushrooms fruiting body through water boiling or microwave can increase the antioxidant properties of mushroom bioactives of different Pleurotus species [67].

2.4. Anti Hypocholesterolemic and Anti-Hyperglycemic

Higher fungi such as population of *Pleurotus* spp play prominent role in prevention as well as treatment of hypocholesterolemia as a consequence of high dietary fibers, protein and microelements concentration along with low energy content [68-69]. The degradation of cholesterol by *P. ostreatus* and *P. cornucopiae* is proven from many years ago [70]. A cholesterol lowering drug called levostatin, consider as of the best therapeutic agent which ameliorate hypercholesterolemia [57, 61]. Furthermore, the production of another anti-cholesteremic metabolite known as mevinolin is reported in the *Pleurotus* species especially *P. sapidus, P. saca* and *P. ostreatus*. Mevinolin act as inhibitor of a rate-limiting enzyme in cholesterol biosynthesis (3-hydroxy-3-methylglutaryl coenzyme A) [71-72]. It also stimulates the production of low-density lipoprotein receptors in the liver. The presence of *P. ostreatus* in a daily diet leads to decline of hepatocellular enzymes in human serum such as alanine aminotransferase and aspatate aminotransferase [69]. The present of dried *P. osteratus* in a rat diet reduced the serum and liver cholesterol content while the concentration of triacylglycerols serum in is not affected by the mushroom extract, However, it is significantly reduced in the liver [68, 73-74]. The decrease in cholesterol level of very low density lipoprotein and low density lipoprotein cause reduction of serum cholesterol concentration [70]. The enhanced activity of cholesterol 7α-hydroxylase and lecithin is reported in rat which is fed by oyster mushroom. The first enzyme is responsible for limiting the rate of cholesterol catabolism while the former one is a cholesterol acyltransferase. Neutral sterols and bile acid is also observed in fecal excrement in rats [74]. Furthermore a reduction of conjugated diene content which are produced from lipid peroxidation in erythrocytes and an induction of antioxidant enzymes activity as a result of oxidative stress is reported when oyster mushroom diet is applied to rats [68]. In contrast, insoluble β-Glucan from *P. ostreatus* did not engaged in anti-lipoperoxidation [59].

Diabetes patients control their blood glucose level by virtues of diets, physical exercise and medication. As there is feasibility of side effect for medications, there is trend in developing drug with natural active compound basis. Of different groups of bioactives to regulate blood sugar, polysaccharides in general have been used in many studies in the treatment of type 2 diabetes [10]. It is reveal that water-soluble polysaccharides (SPPC) from *P. citrinopileatus* have anti-hyperglycemia in rats with streptozotocin (STZ)-induced diabetes. Lower fasting glucose level recorded for diabetic rats with SPPC diet comparing to negative control group. Also, higher dosage of SPPC leads to decrease in damage of the islets of Langerhans [75]. In addition, *P. eryngii* diet in db/db mice proved its anti-hyperglycemic and anti-hyperlipidemic activity and assist in promoting insulin sensitivity. A remarkable decline in homeostasis model assessment for insulin resistance (HOMA-IR), cholesterol and triglyceride is observed while HDL-cholesterol is increases after *P. eryngii* administration. The risk of cardiovascular disease as a consequence of type 2 diabetes can be alleviated by regulating hyperglycemia and dyslipidemia, as result *P. eryngii* diet can take the edge of type 2 diabetes and cardiovascular disease sympthons [76]. Before this, blood glucose lowering effect of *P. eryngii* fruiting body extract is identified in streptozotocin (STZ)-treated rats [77]. Also, the preventive effect of *P. eryngii on* the development of atherosclerosis is elicited in mice [78].

2.5. Antimicrobial

Mushrooms have been reported as potential source for antimicrobial compounds against different classes

of microbes. These based on their rich content of highly diversified groups of bioactive compounds [79-81]. For example, mushroom contains high protein content and many of these proteins exhibited antifungal and antibacterial activity. A eryngeolysin (kind of hemolysin) isolated from *P. eryngii* inhibit the growth of *Bacillus* sp. but didn't show any effect on other microbial species [37]. Also a fungal peptide designed as eryngin is active against *Fusarium oxysporum* and *Mycosphaerella arachidicola* [82]. *P. sajor-caju* mycelia growth is triggered by ribonuclease inhibitory effect in the fungi *F. oxysporum* and *M. arachidicola*. Moreover bacterial growth of *Pseudomonas aeruginosa* and *Staphylococcus aureus* was inhibited as well. However, No inhibitory effect exhibited against 10 other bacteria (*P. fluorescens*, *Proteus vulgaris*, *Bacillus subtilis*, *B. cereus*, *B. megaterium*, *B. subtilis*, *Escherichia coli*, *Enterobacter aerogenes*, *Micrococcus luteus* and *Mycobacterium pheli)* [37]. In addition, other compound such as Pleurostrin, a 7 kDa peptide compound isolated from fresh fruiting bodies of *P. ostreatus*, exhibited also potent antifungal peptide against *F. oxysporum, M. arachidicola,* and *Physalospora piricola* [80]. Other antimicrobial compounds such as Glucosylceramide was also isolated from the fresh fruiting bodies of golden oyster mushroom *Pleurotus citrinopileatus* and exhibited activity against *E. coli* and *Staphylococcus aureus* [84].

However, a new research showed that the methanol extract of different *P. sajor-caju* strains exhibited also antibiotic properties against *Staphylococcus aureus* in addition to *E. coli and B. subtilis.* The antibacterial activity was attributed to the presence of different secondary metabolites including flavonols, saponins, and tannins [85]. However, it was reported also that the antimicrobial variability of *Pleurotus* sp. is based on the differences in genetic variations, physical and chemical analaysis, and extraction method used [86]. Other study showed also that, methanol and ethanol extract of *P. ostreatus EVFB1 and EVFB4* performed light antibacterial effect against both gram positive and gram negative species of *Escherichia coli* CBAB 2*, Bacillus cereus* CMGB 215 and *Listeria innocua* CMGB 218 strains [54]. Other study reported also that *P. ostreatus* extract, contains p-anisaldehyde, is active against *Bacillus subtilis, Pseudomonas aeruginosa, Aspergillus niger* and *Fusarium oxysporum* [87]. However, other recent research showed also the potential antimicrobial properties of fruiting bodies extract of *P. ostreaturs* against different yeast strains such as *Candida albicans, Cryptococcus humicola,* and *Trichsporon cutaneum*, and G+ve bacteria (*Staphylococcus aureus*) and G-ve bacteria (*E. coli*). The bioactive compound was purified, characterized, and fully identified using column chromatography, IR, NMR and mass spectroscopy. The identified compound was 3-(2-aminophenylthio)-3-hydroxypropanoic acid [88]. The antimicrobial activity of *P. ostreatus* water extract can be improved when applied together with herbs such as *Mentha piperita* L. and showed antibacterial activity against *Staphylococcus epidermidis* similar to known antibiotics such as azithromycin and cephalexin [84]. Mushroom-herb synergistic antimicrobial effect have been also reported to increase the antimicrobial properties of *Pleurotus* sp. applied together with *Psychotria microphylla.* [90].

2.6. Antiviral

Sulfated β-glucan from sclerotia of *P. tuber-regium* identified as a vigorous natural anti-viral agents against herpes simplex virus type 1 (HSV-1) and herpes simplex virus type 2 (HSV-2) in contrast to native β-glucan. The antiviral activity of the sulfated β-glucan is explained by ionic binding between the biopolymer and surface glycol protein of HSV. Hence, interaction between virus and host cells will be restricted [31]. Anti-HIV-1 activity of nebrodeolysin (monomeric protein) from *P. nebrodensis* is proven in T-lymphocyte cell culture [25]. Also lectin and laccase from *P. citrinopileatus* and *P. cornucopiae* inhibit HIV-1 reverse transcriptase, respectively [39, 41]. However, the method of bioactive compound extraction influence the antiviral activity. The polysaccharide methanol extract of *P. ostreatus* exhibited more potent activity than the water extract against HSV-1 which was attributed to the higher β-glucan content [91]. Recent research reported also on the antiviral activity of some *Pleurotus* species such as *P. ostreatus* and *P. eryngii* against HSV-2 strain BH and against influenze type A (serotype H1N1) [92].

2.7. Anti-Inflammatory

Recently, mushrooms of different groups have been considered as the important natural sources of anti-inflammatory compounds [93, 94]. A (1→3)-linked glucan from *P. pulmonarius* exhibited anti-inflammatory activity similar to non-steroidal anti-inflammatory and glucocorticoid drugs. A pro-inflammatory inhibition of cytokines (such as Interleukin-1β and Tumor Necrosis Factor-α) excreted by the injurious injection is suggested as the main anti-inflammatory activity causes. In the acetic acid-induced writhing mice

migration of leukocyte to the injured site is inhibited in a dose-dependent manner through administration of this glucan. In addition, formalin test present the influence of this glucan in inhibition of both neurogenic (early stage) and inflammatory pain (late stage pain) [95]. Further studies prove the contribution of ionotropic glutam as well as pro-inflammatory cytokines in antinociceptive activity of this glucan in acute and neuropathic pain [96]. However, many researches have been also reported on the potent anti-inflammatory activities of different Pleurotus strains such as *P. tuber-regium* [97], *P. giganteus* [98], *P. ostreatus* [93], *P. florida* [99], *P. eryngii* [100].

2.8. Antithrombotic

Synthetically sulfation of manogalactan from *P. ostreatoroseus* can be applied as antithrombotic agent. Also anticoagulant and antiplatelet agent can administrate for thrombotic disorders medication as blood coagulation regulation is highly correlated with thrombin. Developing novel antithrombotic drugs derived from non-animal source is crucial as there is high concern in animal source drugs regarding pathogen contaminations. The anticoagulant, antithrombotic activities, bleeding tendency and platelet aggregation of above-mentioned glucan is evaluated in rats using a venous thrombosis model [101].

2.9. Antiosteoporotic

In the aging process, the vast decrease of bone mass lead to osteoporosis. Efforts have been done to introducing new drugs with natural antiosteoporotic agent. In-vitro studies recognized *P. eryngii* extract as inhibitors of bone resorbing osteoclasts and bone forming osteoblasts stimulators. Further *in vivo* studies on ovariectomy induced osteoporosisrats proven its antiosteoporotic activity by the virtue of trabecular bond mineral density reduction [102]. Other research showed also that, β-glucan water extract of *P. citrinopileatus* inhibit the osteoclast differentiation activity especially for fractions of higher than 50 kDa could be used as anti-osteoporotic agent [103].

2.10. Other Therapeutic Applications

β-glucan from *P. ostreatus* (b-glucan-PO) lead to reduction in hind paws swelling and arthritic score of arthritic rats. The administration of methotrexate along with β-glucan, resulted in notable rise in body mass of rats and significantly potentiated the application of methotrexate. Methotrexate contribute in medication of rheumatic disorders and malignant tumors as it is an antifolate [104]. Based on the phenolic and flavonoid compounds content of *P. porrigens*, it was successfully used to chelate excessive iron when used in mice model and showed high potentiality as natural alternative in the treatment of iron overload patients [105]. Research proved also the hepatoprotective effect of ethanolic extract of *P. comucopiae* against sodium arsenite hepatic toxicity in rat model when applied in dose of 400 mg/kg. Other study showed also that mushroom glucans modulate skin wound-healing processes. The contribution of pleuran (an alkali-inslouble polysachharide from *P. ostreatus*) in the stimulation of human keratinocyte have been confirmed using in-vitro study [106]. In addition, crude or purified extracts of different Pleurotus strains are widely used nowadays in skin care, cosmetic, and cosmeceutical industries as natural source of antiaging compounds which function as inhibitor for tyrosinase, elastase, and Hyaluronidase enzymes [107,108].

3. CONCLUSION

Pleurotus spp are among one of the most diverse mushroom genus regarding morphology, geographical distribution, nutritional value and medicinal properties. In addition to food value, wide range of potential medicinal applications of genus *Pleurotus* has been reported by many authors. Numerous *in vitro* and *in vivo* studies proved the antitumor, immunomodulating, antiviral, antibacterial, antioxidant, anti-inflammatory, antihypocholesterolamic, antihypertensive, antiinociceptive, antihyperglycaemic, anti-platelet-aggregating, antihepatoma, anti poliferative and antiatherosclerotic activities of this genus. However the accurate mechanism of these activity, in most of the current studies, are not fully clarified yet and required further research. Besides, both mushroom extracts and bioactive compounds are studied for medicinal properties, but less research triggered the practical aspect for taking step toward clinical studies to develop mushroom based drug for therapeutic application. In addition to high potential medicinal applications, many research highlighted also the high potential application of Pleurotus metabolites in cosmetic and cosmeceutical industries which for sure will increase the researcher interest to investigate more about the bioactive metabolites of this genus.

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