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Medicinal Properties of *Pleurotus* Species (Oyster Mushroom): A Review

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Abstract: Mushrooms have been used as food supplement from times immemorial not only for their flavour, aroma and nutritive values but also for their medicinal properties as evident from ancient literature. In the present day world they are known for culinary values due to their high-quality proteins, vitamins, fibres and many medicinal properties and accordingly they are called nutraceuticals. *Pleurotus* as health promoter and environmental restorer is gaining more importance as compared to other medicinal mushrooms resulting in an upsurge in their R and D activities during the past two decades. The chemical nature of the bioactive compounds present in this mushroom includes: polysaccharides, lipopolysaccharides, proteins, peptides, glycoproteins, nucleosides, triterpenoids, lectins, lipids and their derivatives. In this review databases were extensively searched, collected and analysed with an aim to update the present status and to project future prospects of *Pleurotus* for their biomedical potentials. The presented information will give a new notion to researchers for upgrading *Pleurotus* species from functional food to holistic mushroom medicine.

Key words: Medicinal values % Oyster mushroom % *Pleurotus* species % Bio-active metabolites % Functional food

INTRODUCTION

Besides plants many fungal species are known to possess medicinal values and some are already being used for such purposes. Mushrooms are used in folk medicine throughout the world since ancient times as 'the ultimate health food' [1]. As per *Dictionary of the Fungi* [2] total 97,330 discovered species of fungi includes slime molds, chromistan fungi, chytridiaceous fungi, lichen-forming fungi, yeasts and molds including mushroom producing filamentous fungi.

Among fungi mushroom fungus is more prominent due to its distinctive fruiting body which can be hypogeous or epigeous, large enough to be seen with the naked eye and to be picked by hand [3]. Mushrooms includes 14,000 to 22,000 species while the real number may be much higher associated with the un-description of species and the non-differentiation associated with overlapping morphological characters [4]. There are over 2000 species of mushrooms that are edible; however, a dozen of them are commercially cultivated; a few of them are highly poisonous if consumed [5]. Poisonous mushrooms mainly belong to genus *Amanita*, *Inocybe*, *Panaeolus* and *Russulaceae* [6]. Toxic effects of poisonous mushroom are due to their secondary metabolites.

However, for a common man mushrooms are still considered as one of the curiosities of nature and many of them are widely consumed for their flavor and aroma. Their nutritive and medicinal values were known as early as 1500 BC based upon many ancient literatures [7, 8]. In the world of medicinal mushrooms, *Ganoderma* is number one and has been considered as king of medicinal mushrooms followed by *Lentinula* and others including *Pleurotus*, the later produces oyster mushroom. For the first time in 1986 [9] reported the hypotensive activity of *Pleurotus* mushroom in mouse model, later anti-tumor activity was shown by Nanba [10] in this mushroom; since then a number of studies have indicated their medicinal potentialities and accordingly Chang and Buswell [11] called them as 'mushroom nutriceuticals; of late they have been included in the category of functional foods. Functional foods are those foods enriched/modified and consumed as normal diet to provide health giving benefits. Rajarathnam *et al.* [12] and later Cohen *et al.* [13] thoroughly reviewed and up

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dated bio-potentialities of *Pleurotus* species that resulted in an upsurge in R and D of this mushroom fungus. Keeping in view the growing importance of mushrooms in general, the International Journal of Medicinal Mushroom (IJMM) was launched in 1999 to boost up of the new emerging field of medicinal mushrooms [14].

Commercially button mushroom ranks first followed by Shiitake and oyster mushroom occupies third position [15]. *Pleurotus* species belongs to phylum Basidiomycota that produce oyster shaped mushrooms (basidiocarps) and accordingly they have been called as oyster mushroom (*OM*). *OM* enjoys worldwide distribution from temperate to tropical regions growing saprophytically at a temperature range of 12-32°C [16]. They may be white to variously coloured, stalked or sessile, above or underground and even epiphytic but rarely parasitic comprising of about 40 species. *Pleurotus* species grows on various types of lignocellulosic un-composted agro-wastes and produce *OM* rich in high value proteins, vitamins and minerals; *OM* contains very lower amount of carbohydrates, sugars and no or very lesser amount of cholesterol [8]. Extensive work on medicinal attributes of *Pleurotus* was done by Wang, Li and their colleagues in the first decade of the new millennium [17, 18, 19]. Later Gregori *et al*. [20] updated and reviewed the nutritional and medicinal values of *Pleurotus* species. Recently Khan and Tania [21] have given a comprehensive account of nutritional with some medicinal aspects of *Pleurotus* species. The present review gives an updated comprehensive account of medicinal properties of *Pleurotus* species to help the researchers in their crusade to explore more untapped metabolites from this mushroom fungus that can be used as new life-saving drugs.

Usages of Oyster Mushrooms: Mushrooms are also considered as functional foods because they elicit their positive effect on human being in several ways [22]. Functional food comprises products of microbial, plants and animals origin containing physiologically active compounds beneficial for human health and reducing the risk of chronic diseases. It includes dietary supplements, nutriceuticals, medicinal foods, vita foods, pharma foods, phytochemicals, mycochemicals and so on [23]. Many mushrooms are helpful in human ailments because they possess many typical pharmacological features like: to act as metabolic activators, prevent/control intoxication and microbial/viral infections, help in immune-balancing and immnomodulation, as antioxidants with rejuvenating and energy boosting properties [24]. Species of *Ganoderma* (commonly known as Reishi mushroom) is well known as the king of medicinal mushrooms belongs to phylum Basidiomycota. Extracts of *Ganoderma* species have been very useful in the treatment of various human ailments right from microbial infections to viral infections including HIV due to its immunopotentiation and immunomodulatory properties; treatment of malignancies such as lung cancer, cardiac failure etc. [24, 25, 26]. *Lentinula edodes*, a sub-tropical mushroom of Asian origin [27] is useful in the treatment of various human ailments such as cancer, high cholesterol level, high blood pressure, blood sugar etc. [28, 29].

Fruiting bodies as well as active mycelia of *Pleurotus* species also possesses a number of therapeutic properties like antiinflammatory, immunostimulatory and immunomodulatory [30], anticancer activity [24], ribonuclease activity [31] and many more activities detailed later. Chemical analyses have shown that many of the biologically active compounds isolated from mushrooms belongs to hemicelluloses, polysaccharides, lipopolysaccharides, peptides, proteins, glycoproteins, nucleosides, triterpenoids, complex starches, lectins and lipids or other complex compounds [32, 24, 33, 26]. Though *OM* is third important mushroom of culinary value, there has been a upsurge in *Pleurotus* mushroom research activities in the last two decades not only for its nutritive and medicinal values but many other biopotentialities of *Pleurotus* species such recycling of agricultural residues [12, 34], bioconversion of ligno-cellulosic wastes [35, 36], production or improved animal feed [37], bioremediation and degradation of xenobiotics [38, 39], industrial dye degradation [40, 41], bioremediation [42, 12], degradation of xenobiotics for bioremediation [43, 44], bioconversion of lignocellulosic wastes [45, 13], enzyme production [46, 47] etc. Medicinal value-wise detailed attributes of *Pleurotus* is given below.

Reported Therapeutic Values of *Pleurotus*

Antimicrobial: OM has been explored to combat simple and multiple drug resistant isolates of *Eschrichia coli*, *Staphylococcus epidermidis*, *S. aureus* [48] and species of *Candida* [49], *Streptococcus*, *Enterococcus* [50-53]. Methanolic extracts of *Pleurotus* species demonstrated an inhibition in growth of *Bacillus megaterium*, *S. aureus*, *E. coli*, *Klebsiella pneumoniae*, *C. albicans*, *C. glabrata*, species of *Trichophyton* and *Epidermophyton* to different degrees that was lower with respect to two antifungal agents: Streptomycin and Nystatin [48]. Antimicrobial and antifungal activity of *OM* depended upon the nature of the solvent, ether extract were more active against Gram negative bacteria as compared to acetone extract [54].

Ether and acetone extracts of *OM* was effective against *B. subtilis*, *E. coli* and *S. cerevisiae*. Later, Nithya and Ragunathan [55] using extracts of *P. sajor-caju* reported higher antibacterial activity against *Pseudomonas aeruginosa* and *E. coli* when compared with the Gram positive organism *S. aureus*.

Antiviral: *Pleurotus* mushroom contain substances that exert direct or indirect antiviral effects as a result of immune-stimulatory activity [56]. Ubiquitin, an anti-viral protein was isolated and identified from fruiting body of oyster mushroom [57]. Water-insoluble $-glucans isolated from sclerotia of *P. tuber-regium* and their corresponding water-soluble sulphated derivatives were active against herpes simplex virus type-1 and type-2 [6, 20]. The anti-viral activity was due to binding of sulphated $-glucans to viral particles thereby preventing them from infecting the host cells [20]. Not only intracellular proteins of *P. ostreatus* but its extracellular extract also contains polysaccharides that have immuno-modulating effects [58].

Anti-Human Immunodeficiency Virus (HIV): Ribonucleases (RNases: mol. wt. 10.7 kDa) have been isolated and characterized from the *P. ostreatus* [59] that has the potentiality to neutralize HIV through degradation of viral genetic material. On the other hand RNases (mol. wt. 14.5 kDa) was isolated and characterized from sclerotia of *P. tuber-regium*, exhibited very stable nuclease activity at 100°C for 30 min. with a higher ribonucleolytic activity toward Poly-G [60]. Another ribonuclease, pleuturegin, was also isolated from both fresh and dried sclerotia of *P. tuber-regium* [17]. Later in the fruiting bodies of *OM* they observed a novel ubiquitin-like protein having *HIV*-1 reverse transcriptase inhibitory activity [18]. Similarly hot water extracts of *P. sajor-caju* and *P. pulmonarius* inhibit *HIV*-1 reverse transcriptase activity by SU2 molecule having 4.5 kDa mol. wt. [61]. A lectin isolated from fresh fruiting bodies of P. citrinopileatus also inhibited *HIV*-1 reverse transcriptase [19]. Most recently it was reported that a hemolysin (mol. wt. 27.0 kDa), a monomeric protein isolated from *P. nebrudensis*, exhibited anti-*HIV*-1 activity in CEM cell culture [62].

Antineoplastic: In 1969, Wantanabe [63] detected antineoplastic activity of polysaccharide extracted from the fruiting body of *P. ostreatus*. Later polysaccharides extracted from mycelium of *P. sajor-caju* [64], *P. citrinopileatus* [65] and *P. ostreatus* [66] were also shown to have antineoplastic activities. These polysaccharides are components of the cell wall of *OM* [65]; polysaccharide extracted from *P. ostreatus* culture broth when injected intra-peritoneally (*i.p.*) in the female Swiss albino mice [49] caused 76% reduction in the number of neoplastic cells. Similar result was observed with extracts extracted from cell walls of *P. sajor-caju* in Ehrlich ascitic tumor in ascitic form [67]. Extracts from mushrooms including species *Pleurotus* may modulate the response of host immune system; in particular, various mushroom polysaccharides are likely to effect promotion and progression stages towards cancer as reviewed by Chatterjee *et al*. [68].

Antitumor: Hot water extract, showed a remarkable host-mediated antitumor activity against Sarcoma, S-180, extracted from the fruiting body of polyporaceae family [69] due to presence of $-D-glucan [70]. Later the antitumor properties of mushroom-derived $-glucan were reviewed by Wasser [24]. Similar activity was also observed by Choi *et al.* [71] with hot water and ethanol extracts from fruiting body of oyster mushroom that exerted positive effect on three human solid carcinomas, a lung carcinoma (A549) and two cervical carcinomas (SiHa and HeLa). Their report showed that ethanol extracts of *Pleurotus* species had higher antitumor activity towards lung cancer cells (A549). Recently a potent antioxidant activity against both *DPPH* and *ABTS* radicals was detected in the ethanolic extracts of *Pleurotus* mushroom [72]. Many more reports are available indicating that *OM* possesses antitumor activity [73, 74]. Lectin isolated from P. citrinopileatus exerted potent antitumor activity in mice bearing sarcoma S-180 [19]. In their *in vitro* studies with *P. ostreatus* extracts against cancer cell (HL-60), the cytotoxic effect was reported due to presence of higher content of flavonoids in fruiting body. Cibacron blue affinity purified protein, protein fraction extracted from *P. ostreatus*, has been shown to have potent antitumor activity against different tumors using mice model [75].

Antimutagenic: Filipic *et al.* [76] tested extracts of 89 different mushrooms species for their antigenotoxic and bio-antimutagenic activities on *S. typhimurium* and *E. coli* amongst them *P. cornucopiae* was found to be most effective. Methanolic extracts of *P. ostreatus var. florida* showed significant inhibition of mutagenicity elicited through mutagens requiring activation [77]. Dried *P. ostreatus*, in diet, reduced pathological changes in dimethylhydrazine-induced colon cancer, in rats. Furthermore, extracts of *P. cornucopiae* significantly reduced H_2O_2-induced *DNA* damage in Chinese hamster

lung cells [78] and *P. ostreatus* extract mitigated genotoxicity through suppression of *DNA* damage induced by different mutagens in the *Drosophila DNA* repair test [79]. *P. citrinopileatus* fruiting body extracts have shown antioxidant activities *in vitro* and in hyperlipidemic hamster rats [80]. Of late Li *et al.* [81] observed up-regulated gene expression of antioxidant enzymes and consequently their activities were increased. However, a water extract of *P. sajor-caju* fruiting bodies had no such activity since it did not prevent H_2O_2-induced oxidative damage to cellular *DNA* [82].

Antioxidant: Fruiting bodies of *Pleurotus* possessed higher concentration of antioxidants than other commercial mushrooms [83, 84, 85]. This activity was mainly due to presence of polysaccharide pleuran ($-glucan) that has been isolated from *P. ostreatus* showing a positive effect on rat colon with pre-cancerous lesions [86]. *P. ostreatus* increased the activities of important antioxidant enzymes (*viz.* superoxide dismutase, catalase and peroxidase) thereby reducing oxidative damage in humans [84, 87]. Oyster mushrooms are now widely used as ingredients in dietary supplements in the hope of maintaining health and preventing diseases [88] due to their higher free radical scavenging activities [89]. These free radical scavenging activities of oyster mushrooms depend upon the colour of fruiting bodies as per Yang *et al.* [84]. Fruiting bodies of *OM* have higher phenol concentration when compared with mycelium and fermentation broth filtrate of *P. citrinopileatus* [90-93]. And these phenolic compounds have free radical scavenging property that reduces inhibitory effects of mutagens and carcinogens [94]. Recently a very surprising result was shown by Shaha *et al*. [95] that juvenile bud stage (one day stage) contained highest amount of phenols (2.79 mg/g) and antioxidants that gradually decreased (1.27 mg/g), but upon maturity (four day stage), the total concentration of total phenol was again increased (2.08 mg/g). Similar result was found earlier by Iwalokun *et al.* [54], when they compare the *in vitro* antioxidant capacity of acetone extracts and petroleum ether extract. Recently, Venkatakrishnan *et al.* [72] have shown that extract from *P. ostreatus* inhibited the growth of HL-60 cells by cell cycle arrest i.e. by the induction of apoptosis by their experiments due to the presence of flavonoid (quercetin equivalent) and phenolics components (catechin equivalent) in fruiting bodies. Methanolic extract of *P. eous* significantly enhanced the activity of antioxidant enzymes [96].

Antilipidemic: Hyperlipidemia is the leading risk factor for atherosclerosis. Feeding of mushroom powder increases the excretion of total lipids and cholesterol through faecal matter. Mevinolin (a statin: polysaccharide), present in fruiting bodies of *P. ostreatus* and *P. citrinopileatus* exhibited anti-hypocholesterolemic activities [97, 98]. *P. pulmonarius* exhibited potent synergistic antihyperglycemic effect when used in combination with glyburide [99]. Recent report produced by Alam *et al.* [100] states that when hypercholesterolemic rat feeding of diet containing 5% fruiting bodies of *P. ferulae* reduced the total cholesterol in plasma, triglyceride, low-density lipoprotein, total lipid, phospholipids etc. Whereas 5% mushroom powder of *P. salmoneostramineus* reduced total lipid, phospholipids and LDL/HDL ratio by 29.67, 16.61 and 65.31 %, respectively [101].

Hyperglycemic: Guanide, a compound related to the bi-guanide class of oral anti-diabetic drugs was isolated from the *Pleurotus* species that exerted anti-hypoglycemic effect [102]. Endo-polymer from submerged mycelial cultures of *P. ostreatus* possesses hypoglycemic effects [103]. High fibre and proteins content and low fat content of edible mushrooms make it ideal food for diabetic patient [104]. Aqueous extracts of *P. pulmonarius* upon oral administration decreased serum glucose level in alloxan-treated diabetic mice [105]. Polysaccharides extracted from fruiting body of *P. citrinopileatus* alleviated anti-hyperglycemic effect by the elevation of the activity of glutathion peroxidase [80].

Hypotensive: The level of antihypertensive property varies with mushroom species and their combinations while *OM* possesses blood pressure lowering activity [106]. Hot aqueous extract and dried fine particles of fruiting bodies of *P. nebrodensis* have been accounted in prevention of hypertension [107]. Hagiwara *et al.* [108] indicated that *P. cornucopiae* might bring forth the same effect associated partly with D-mannitol which inhibits angiotensin-I converting enzyme. Recently Ching *et al.* [109] have shown that protein fractions from *P. cystidiosus* possessed the highest *ACE* (angiotensin-I converting enzyme) inhibitory activity that cause the contraction of blood vessels thereby raising the blood pressure; however effect was lower compared to captopril, an *ACE* inhibitor used for the treatment of hypertension and some other types of congestive heart failure.

Anti-Inflammatory: Pleuran, isolated from fruiting bodies of *OM* possesses antiinflammatory activity [86, 110]. Extracts of many of them e.g. *P. florida, P. pulmonarius* etc. give a lowering response in both acute as well as in chronic inflammation [91, 92] and when oral or percutaneous administration of extract of *P. eryngii* was done, it suppress the inflammation in delayed type (type IV hypersensitive) allergy response in mice [111]. Nozaki *et al*. [112] reported the mechanism and reported that glycosphingolipid isolated from *P. eryngii*, induced secretion of IFN-g and IL-4 from T-cells, whereas (163), (166)-linked $-glucan isolated from *P. ostreatus* inhibited leukocyte migration to acetic acid-injured tissues [113]. Recently a nonlectin glycoprotein (PCP 3-A) isolated by Chen *et al.* [114] from fresh fruiting body of *P. citrinopileatus* down-regulated the pro-inflammatory mediators, like iNOS and NF-kB in RAW 264.7 cells (Mouse leukaemic monocyte macrophage cell line). Jedinak *et al*. [115] in their experiments also observed that anti-inflammatory activity of *OM* that was mediated through the inhibition of NF-kB and AP-1 signalling. Another potent anti-inflammatory agent, a polysaccharide has been extracted from the *P. pulmonarius* that acted against carrageenan and formalin-induced paw edema in rats [116].

Hepatoprotective: Liver damage by hepatotoxic agents is of vital consequence because chronic liver injury leads to fibrosis, end stage cirrhosis and hepato-carcinoma. Hence, there is an increasing need to search of an agent which could protect the liver from such damages. Many species of *Pleurotus* contains some active compounds like $-glucan, phenol and vitamin C that increase the activity of antioxidant-enzymes *viz.* catalase, superoxide dismutase; these enzymes are responsible for reduction of hepatic cell necrosis [117, 118]. Hepatoprotective activity of this mushroom is exerted through increased levels of serum aminotransferase enzymes in animals [90, 119]. However, hepatoprotective activity was due to the lipid peroxidation inhibition activity of this fungus [120]. It can suppress toxin induced increased level of serum bilirubin in animals, indicating the hepatoprotective effect of mushroom [121, 122]. Recently, Refaie *et al.* [123] reported the hepatopreventive and therapeutic activity of hot-water extract of *P. ostreatus* by mechanism of inhibition through preventive regimen caused less leakage of alkaline phosphatase, less pronounced increase in hepatic malondialdehyde concentration, less notable reduction in hepatic total protein, *RNA* and *DNA* contents and in contrast increased hepatic superoxide dismutase, glutathione peroxidase and glutathione reductase activities. Polysaccharopeptides extracted from fruiting body of *P. ostreatus* alleviated the thioacetamide-induced alterations, inflammation, steatosis, necrosis and fibrosis, especially in the therapeutic regimen (a systemic plan for therapy) as reported by Refaie *et al.* [123, 124]. Very recently Chen *et al.* [125] observed that water-soluble polysaccharides extracted from *P. eryngii* removes the free radicals and also increase the activities of antioxidant enzymes in liver injury mouse model.

Hypocholesterolemic: Preliminary reports indicated that diet containing 4-10 % dried fruiting body of *Pleurotus* species show more reduction in the arterial pressure and blood cholesterol level when compared to normal diet in rabbits and rats [126, 127, 128]. Lovastatin, a drug, used in the lowering blood cholesterol level, produced by *P. ostreatus* was approved by *FDA* in 1987. When dried mushroom mixed in the diet of experimental animal acted as accelerator of *HDL* (high density lipoprotein), reduced production of *VLDL* (very low density lipoprotein), *LDL* (low density lipoprotein), cholesterol, reduced cholesterol absorption and reduced HMG-CoA reductase activity in the liver [129, 98].

Immunomodulatory: $-D-glucan, having (1?6)-$-D-glucosyl branched (1?3)-$-D-glucopyran chemical bond ranging from mol. wt. 500- 2000 kDa [130], are the most potent mushroom-derived substances stimulating immunomodulating activity [24]. It was reported that extracts from fruiting body of *P. ostreatus* possess antitumor activity against Ehrlich ascites carcinoma [33]. Later the polysaccharides distilled from *P. ostreatus* showed immunomodulatory activity against infectious bursal disease (*IBD*) when four weeks post-hatching broilers were used [58]. Whereas, *DNA* isolated from *P. ostreatus* also possesses immunomodulatory activity and bio-therapeutic potential that could be due to the presence of unmethylated CpG motifs. Oncoprotective and immunomodulatory effects of substances from *P. ostreatus* have also been demonstrated [131, 132, 133]; *P. ostreatus* diminishes the toxicity of cyclophosphamide in mice was later shown by Gerasimenya *et al.* [134]. Similar immunomodulatory properties were reported from *DNA* of *P. ostreatus* in same manner as bacterial *DNA* or *DNA* from certain viruses, yeast, nematodes, mollusks and insects; *DNA* of vertebrates like mammals, fish and frogs as well as plants (e.g. corn) lacked immunomodulatory activities as they do not possess immunogenic activity [135, 136, 137]. Inhibition of platelet aggregation was observed with methanolic extract extracted from the fruiting bodies of *P. florida*. The antiplatelet-aggregating

activity, along with the anti-inflammatory activities, suggests its potential therapeutic use against vascular disorders [92].

Anti-Ageing: Extracts of *P. abalonus* elevated levels of vitamin C and E, increased activities of catalase, superoxide dismutase and glutathione peroxidase in aged rats [138]. Similar results were obtained with the extracts of *P. ostreatus* [120]. These enzymes are known potent antioxidant enzymes [86, 87]. The levels of malondialdehyde, a polyunsaturated lipid and an electrophilic mutagen, was lowered on administration of mushroom extract to aged rats [139], that reacted with deoxyadenosine and deoxyguanosine in *DNA*, forming a *DNA* adduct. Different extracts (methanol, ethanol, acetone or water extract) of *Pleurotus* can improve the antioxidant status during ageing leading reducing the occurrence of age-associated disorders like stroke, Parkinson's disease, atherosclerosis, diabetes, cancer and cirrhosis.

CONCLUSIONS

The up dated comprehensive information made available in this review shows that oyster mushroom possesses many promising therapeutic properties that requires more high-tech approaches for deeper exploration. As such, the mushroom fruiting body, its mycelium and their extracts or concentrates have been considered a functional food as it has the potentiality to control many human ailments. Though in most cases biological activity is better understood but in many cases there is need to identify the active principle to understand the exact mechanism(s) for its exploration in right perspective. Availability of high-tech methods should allow the researchers to explore novel metabolites from *OM*, standardize their *in vitro* pharmacological effectiveness and go for clinical trial with a goal to meet international standards. In the era of 'nomics' it would be much easier to study mechanism of action with a biomarker-based approach for up-grading *Pleurotus* from functional food to holistic medicine.

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