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The beneficial role of edible mushrooms in human health

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Mushroom species have the potential to be developed into functional foods for their high nutritional value and because they are a source of biologically active compounds of medicinal importance. The investigation on the beneficial properties of edible mushrooms has gained attention by the scientific community during the last decades. In the light of the emerging literature, the objective of this review was to compile the more recent information about the health benefits associated to the edible mushrooms intake. It can be concluded that the consumption of mushrooms as a part of daily diet could be a natural adjuvant for the treatment and prevention of several chronic diseases.

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Introduction

Mushrooms have been consumed by many cultures for centuries. Edible mushrooms are considered a delicacy because of their sensory characteristics and their attractive culinary attributes. The most consumed mushrooms worldwide is *Agaricus bisporus* followed by *Pleurotus* spp. and *Lentinula edodes*. They are easy to cultivate and are characterized by both high nutritional value and culinary features [1]. As a demonstration of the development occurred in the world mushroom market, Table 1 depicts data of mushrooms and truffles production for years 2004, 2009 and 2014 in some of the different countries considered as major producers [2]. Excepting the cases of Belgium, France and Denmark, whose production slightly dropped during this decade, the rest of the great mushrooms producers around the world have increased their production for this period. From a nutritional point of view, mushrooms are valuable health foods since they have a significant amount of dietary fiber and are poor in calories and fat. Moreover, they have a good protein content (20–30% of dry matter) which includes most of the essential amino acids; also provide a nutritionally significant content of vitamins and trace minerals [3].

Recently, mushrooms have become increasingly attractive as functional foods for their potential beneficial effects on human health [4]. They contain bioactive compounds of high medicinal value such as lectins, polysaccharides, phenolics and polyphenolics, terpenoids, ergosterols, and volatile organic compounds, which are considered as relevant responsible agents for their healthy activities including antitumor, immunomodulating, antioxidant, radical scavenging, antihypercholesterolemia, antiviral, antibacterial, hepatoprotective, and antidiabetic effects [5]. Thus, numerous studies have revealed that different mushroom species are beneficial for the prevention and treatment of several chronic diseases, such as cancer, cardiovascular diseases, diabetes mellitus and neurodegenerative diseases [6–9]. In the light of the emerging literature, the objective of this review is to compile the more recent information about the benefits associated to the consumption of edible mushrooms on human health.

Cancer disease

Cancer is one of the main causes of death worldwide. Evidences from a large number of scientific publications show that mushrooms, and more specifically their polysaccharides, could play an important role in prevention and treatment of this disease [6,7••]. Thus, Zhang *et al.* have demonstrated that a higher dietary intake of mushrooms decreased breast cancer risk in pre- and postmenopausal Chinese women [10]. Recently, results from a meta-analysis of observational studies also suggested that a greater mushroom intake may be inversely associated with risk of breast cancer, which need to be confirmed with large-scale prospective studies further [11].

Several studies and clinical trials have evidenced that the preventive effects on cancer could be mediated by the immunomodulatory capability of mushrooms. Thus, it has been established that some of their polysaccharides would activate the innate immune system and exert antitumor activity by accelerating the host's defense mechanisms. Mushrooms polysaccharides can inhibit tumor growth by stimulating the immune system via effects on natural killer cells, macrophages and via T cells and their cytokine production [7••]. In the same line, a double-blind placebo-controlled human clinical trial

Table 1

Evolution of mushrooms and truffles production (tons) during 2004–2014 as documented by FAO (World Mushrooms & Truffles: Production, 1961–2014; United Nations, FAO, FAOStat)

Country	2004	2009	2014	Rate of increase
China	3 360 496	4 680 720	7 634 959	2.3
USA	387 601	371 844	432 100	1.1
UK	74 000	69 400	94 857	1.3
Belgium	42 380	41 792	41 754	0.9
France	165 466	113 851	108 540	0.7
Denmark	10 946	9500	10 113	0.9
Germany	50 000	52 200	59 923	1.2
Italy	94 152	720 100	600 114	6.4
Spain	138 782	131 000	149 854	1.1
Poland	150 000	204 886	254 221	1.7
Netherlands	260 000	230 000	310 000	1.2
Iran	25 000	60 000	80 239	3.2

investigated the potential of *Pleurotus cornucopiae* to up-regulate of the immune system. After consuming this mushroom extract for 8 weeks, the results clearly suggested that *P. cornucopiae* had the potential to enhance the immune system, through Th1 phenotype potentiation as the macrophage-IL-12—IFN-γ pathway, leading to the activation of the cell-mediated immune system as exemplified by up-regulation of natural killer cell activity [12]. The study by Dai *et al.* [13] has also established that a regular intake of *L. edodes* resulted in improved human immunity function, as seen by increased cell proliferation and activation and the higher levels of secretory immunoglobulin A produced.

Among the polysaccharides, β-glucans are known to be the most effective compounds to exert the anti-tumorigenic effects via enhancement of cellular immunity. Relevant effects using grifolan, a β-glucan extracted from *Grifola frondosa*, have been reported in gastrointestinal, lung, liver and breast cancers [14]. Grifolan is a macrophage activator that increases cytokine production, augments the expression of IL-6, IL-1 and tumor necrosis factor-alpha (TNF-α) of macrophages. Some authors have proposed that the induction of this proinflammatory cytokine response is the responsible for the antitumor activity [7••], since inflammation could help to isolate the tumor. However, other authors have evidenced that a grifolan containing extract increased the production of both stimulatory (IL-2) and suppressive (IL-10) cytokines in a clinical trial with 34 postmenopausal breast cancer patients, free of disease after initial treatment [15]. Therefore, the clinical effect of the balance of these cytokines and the mechanism by which it happens is still unknown. Further studies are needed to understand the role of grifolan in the activation of the immune system and in the cancer prevention.

Beside the capacity of mushrooms polysaccharides to prevent cancer by activating the immune system, it is also known that they have a direct antitumor activity against various synergetic tumors, and avoid tumor metastasis. Their activity is especially beneficial when used in conjunction with chemotherapy [5]. Thus, *L. edodes* polysaccharides have been used in clinical practice with other conventional forms of cancer treatment such as chemotherapy and surgery. Ren *et al.* [16] found that a combination of *L. edodes* polysaccharide with 5-fluorouracil, a chemotherapeutic drug, could significantly reduce the tumor weight and volume in H22-bearing mice.

On the other hand, fungal lectins have also attracted considerable attention due to their antitumor, antiproliferative and immunomodulatory activities. Lectins from mushrooms display antiproliferative potential by cross-linking cell surface glycoconjugates or through immunomodulatory effects [17••].

Metabolic syndrome

Metabolic syndrome is a medical condition characterized by central obesity, hyperglycemia, hypercholesterolemia and hypertension. Edible mushrooms, their extracts, polysaccharide fractions and isolated compounds possess hypoglycemic, cholesterol and triglyceride lowering ability, hypotensive effects, as well as weight managing activity [8]. The most active compounds are β-glucans as well as lectines and small compounds such as eritadenine, triterpenes, sterols and phenolic compounds [8].

Obesity and hyperlipidemia

Several studies have been carried out about the effect of mushrooms on hyperlipidemia and obesity. *L. edodes* has been associated with antihyperlipidemia activity and preventing body weight gain as shown in the following studies. Rats fed a high fat diet enriched with *L. edodes* significantly lowered plasma triacylglycerol (TAG) and fat deposition by −55% and −35%, respectively, compared to rats fed with high fat diet without the *L. edodes* [18]. In a later study by the same research group, where authors wanted to identify the mechanism on how high-dose *L. edodes* prevents obesity, the authors discovered an undesirable increase of TAG in the liver, rather than in adipose tissue [19]. Eritadenine, a component of *L. edodes*, is effective in lowering dyslipidaemia by decreasing the concentration of phosphatidylcholine (PC) and increasing the concentration of phosphatidylethanolamine (PE) in the liver [20]. PC is an important phospholipid for lipoprotein assembly and secretion from the liver. Adding eritadenine to the rat diet significantly decreased the level of plasma TAG but increased the concentration of TAG in the liver. However, when the eritadenine was given concurrently with choline supplementation did not significantly increase liver total fat, liver TAG and liver weight; PC deficiency could be prevented by the addition of choline chloride (8 g choline chloride/kg) [20].

The genus *Pleurotus* have also been pointed out for its effects on preventing weight gain and hyperlipidemia. β-glucans from *Pleurotus sajor-caju* prevent the development of obesity and oxidative stress in C57BL/6J mice fed a high fat diet, due to their capacity of inducing lipolysis and inhibit adipocyte differentiation [21]. Different studies have indicated the hypolipidemic effects of *Pleurotus eryngii*, for example polysaccharides from *P. eryngii* were able to decrease the lipid level in a high-fat loaded mouse model [22]. Feeding rats with different concentrations of *P. eryngii* cellulose during six weeks resulted in an enhanced antioxidant capacity of hepatic tissue, improved hepatic lipase activity, and reduced hepatic fat deposition, thereby playing a role in hepatic protection and lowering lipid levels [23].

As a consequence of this actions, several authors have associated the intake of edible mushrooms to a reduction in the risk of suffering cardiovascular diseases [1,6]. Most of the mushrooms health activities described such as hypoglycemic, hypocholesterolemic and triglyceride lowering ability, together with the presence of antioxidant and anti-inflammatory compounds are beneficial in the management of heart and circulation health complications [24].

Hypercholesterolemia

Edible mushrooms are an ideal food for the dietetic prevention of atherosclerosis due to their high fiber and low fat content. Indeed, mushrooms and their extracts could be considered as a new source of compounds with hypocholesterolemic activity because they are rich in derivatives of ergosterol, eritadenine, β-glucans and inhibitors of the enzyme HMG-CoA reductase, the key enzyme in the endogenous cholesterol biosynthesis [6,25••]. Eritadenine could reduce cholesterol and triacylglycerol levels in rats by acting as inhibitor of the *S*-adenosylhomocysteine hydrolase (SAHH), a key enzyme in the phospholipid metabolism [16,25••]. Recent assays using *L. edodes* and eritadenine corroborate their hypocholesterolemic effects, Yang *et al.* [26] demonstrated that supplementation with eritadenine and *L. edodes* powder significantly inhibited the development of hypercholesterolemia in mice induced by a high fat diet. It was manifested a reduction of serum lipid levels, hepatic fat accumulation and aortic atherosclerotic plaque formation in these animals. Regarding the possible mechanism of this decrease, Gil-Ramirez *et al.* [25••] reported that the water extracts of *L. edodes* were capable of inhibiting the HMG-CoA reductase and modulated the transcriptional profile of some genes involved in the cholesterol metabolism in HepG2 cell cultures and in normocholesterolemic mice. The same scientific team also carried out an investigation focused on the hypocholesterolemic effects of the dietary fiber extracts obtained from *Pleurotus ostreatus*, *L. edodes* and *A. bisporus*. In an *in vitro* gene expression study they checked that *P. ostreatus* was the one that showed larger transcriptional changes and it was selected for *in vivo* study. This assay revealed the suitability of its dietary fiber fraction to reduce the hepatic triglyceride accumulation because it induced a molecular response similar to hypocholesterolemic drugs in liver [27]. Ergosterol obtained from mushrooms has also been identified as a hypocholesterolemic agent for its ability to compete with the cholesterol molecules for their incorporation in the dietary mixed micelles during *in vitro* digestion because of their structural similarity [28]. Indeed, ergosterol is able to influence the circulating cholesterol concentration via other mechanisms such as modifying the mRNA expression of cholesterol-related genes [29].

A. bisporus, the most consumed mushroom worldwide, has been also described to have beneficial effects on hypercholesterolemia. The study of Jeong *et al.* [30] found that oral administration of *A. bisporus* to rats fed a hypercholesterolemic diet resulted in a significant decrease in plasma total cholesterol, low-density lipoprotein, triglyceride concentrations and a significant increase in plasma high-density lipoprotein concentrations. In this line, de Miranda *et al.* [31] tried to investigate the underlying mechanism involved in the cholesterol-lowering effect of the *Agaricus brasiliensis* mushroom. They observed that the supplementation of a hypercholesterolemic diet with *A. brasiliensis* promoted a significant reduction in serum cholesterol levels by increasing expression of 7α-hydroxylase (CYP7A1), ATP-binding cassette subfamily G-transporters (ABCG5/G8), and low-density lipoprotein receptor (LDLR), key genes involved in hepatic cholesterol metabolism. These changes directly stimulated the rate of biliary cholesterol excretion, thus favoring the clearance of cholesterol from the body.

Diabetes

Many studies have been conducted on the hypoglycemic activity of whole mushrooms and their mushroom bioactive components isolated from the fruiting bodies. The genus *Pleurotus* has been associated with a strong hypoglycemic activity. The oral administration of *P. eryngii* extracts reduced the blood glycated hemoglobin and serum glucose levels in alloxan-induced hyperglycemic mice. The authors suggested that extracts from *P. eryngii* may become a new potential hypoglycemic food for hyperglycemic people [32]. In the same line, different studies using an aqueous extract of *P. pulmonarius* [33], polysaccharides from *Pleurotus citrinopileatus* [34] or an aqueous extract from *P. sajor-caju* [35] also revealed a potent antidiabetic effect by reducing glucose levels in diabetic rats.

The genus of *Agaricus* has also been linked with antiglycemic properties as demonstrated by several studies with different *Agaricus* species [30,36,37]. In the assay of

Jeong *et al.* [30], the intake of *A. bisporus* powder for 3 weeks significantly reduced plasma glucose in rats with type 2 diabetes induced by injection of streptozotocin. *Agaricus sylvaticus* [36] and *Agaricus blazei* [37] are potentially beneficial in the control of type 1 diabetes by reducing blood glucose, cholesterol and triglyceride levels and increasing HDL cholesterol in an experimental model of type I diabetes mellitus induced by streptozotocin. These authors suggest that both mushrooms have a protective effect on cells of the islets of Langerhans, responsible for insulin secretion.

On the other hand, the administration of an aqueous extract of *Hericium erinaceus* (100 and 200 mg/kg body weight) to diabetic rats for 28 days resulted in a significant decrease in the serum glucose level and a significant increase in the insulin level and attenuated serum lipid profiles as compared to control rats [38].

Hypertension

Angiotensin-converting enzyme (ACE) is a central component of the renin–angiotensin system which indirectly increases blood pressure by causing blood vessels to constrict. ACE inhibitors are widely used as pharmaceutical drugs for treatment of cardiovascular diseases. In recent years, researchers are interested on replacing synthetic antihypertensive drugs by natural sources of these compounds. Mushrooms species such as *G. frondosa*, *H. erinaceus*, *Hypsizygus marmoreus*, *A. bisporus* or genus *Pleurotus* have been considered as an excellent food alternative for treating hypertension [1,39•,40]. Hot water extract of these mushrooms contains active antihypertensive constituents such as several peptides, D-mannitol, D-glucose, D-galactose, D-mannose, triterpenes and potassium. Thus, these different components could act together to prevent and ameliorate hypertension based on various mechanisms, predominantly via inhibiting the renin angiotensin–aldosterone system by interaction at the active site of the ACE enzyme [1]. In this line, the research group of Lau *et al.* [40] identified two bioactive peptides from *A. bisporus* having the amino acid sequences Ala-His-Glu-Pro-Val-Lys and Arg-Ile-Gly-Leu-Phe, both peptides exhibited potentially high ACE inhibitory activity even after *in vitro* gastrointestinal digestion. Other studies carried out in this field with demonstrated that *P. pulmonarius* mycelium contains proteins with potential antihypertensive effect via the angiotensin-converting enzyme inhibitory activity [41]. Indeed, Kang *et al.* [42] demonstrated that the water-extract containing ACE inhibitor from *H. marmoreus* showed clear antihypertensive effect on a spontaneously hypertensive rat.

Neurodegenerative disease

Sarcodon scabrosus, *Ganoderma lucidum*, *G. frondosa* and *H. erinaceus* are reported to have activities related to nerve and brain health [9]. Among these, *H. erinaceus* has been more extensively studied for its neurohealth properties.

Jiang *et al.* [43] divided the functions of *H. erinaceus* on the nervous system into two types. On the one hand, *H. erinaceus* can regulate the growth and development of the neurons and accessory structures. It has been demonstrated that bioactive compounds isolated of *H. erinaceus*, can stimulate the nerve growth factor (NGF) synthesis mediated neurite outgrowth on PC12 cells [44]. NGF is the best characterized neurotrophic factor and it is recognized as an important regulatory substance in the nervous system. On the other, *H. erinaceus* is associated with the treatment or/and prevention of neurodegenerative disorders such as Alzheimer's disease, dementia, depression disorder and cognitive impairment which are related with a progressive function loss of the neurons [43]. This mushroom can improve sleep quality, ameliorate depression and alleviate the mild cognitive impairment [45,46]. Mori *et al.* [47] examined the effect of oral administration of *H. erinaceus* powder added to the mouse diet over a 23 day experimental period on the amyloid β(25–35) peptide-induced learning and memory deficits (cognitive dysfunctions) in mice. The results revealed that *H. erinaceus* prevented the cognitive deficits induced by amyloid β(25–35) peptide, so that, this mushroom may be a promising treatment for the prevention of cognitive dysfunction.

Other biological/health activities

In addition to the above mentioned bioactivities, mushrooms and mushroom components exhibit other health benefits for instance antioxidant, anti-inflammatory, hepatoprotective, antiallergic, antimicrobial and antiviral properties [24].

A whole range of antioxidant compounds have been found in edible mushrooms such as phenolics, polysaccharides, tocopherols, ergothioneine, carotenoids, and ascorbic acid. Thus, the intake of mushrooms might enhance the antioxidant defenses reducing the level of oxidative stress. Their antioxidant activity is attributed to the ability of radical scavenging [48], lipid peroxidation inhibition and the increase of antioxidant enzymes activities, among others [49•]. It is noteworthy that although flavonoids have been included traditionally among the phytochemicals responsible for the antioxidant actions, recent studies have evidenced that edible mushrooms cannot synthesize flavonoids because they do not have the main enzymes involved in their metabolic pathway [50].

Several aqueous extracts of mushrooms have been characterized as hepatoprotectors and it seems that their potential against liver damage is due to its antioxidant activity [51,52]. Soares *et al.* [51] demonstrated that an aqueous extract of *A. blazei* is able to provide a reasonable

degree of protection against injury in hepatic tissue induced by paracetamol. Parallel, endo-polysaccharides extracted from *H. erinaceus* also seem to exert an effect in the prevention of hepatic diseases [52].

Mushrooms and their isolated compounds could be of interest for the treatment of allergic diseases via stimulating the immune system. Ethanolic extracts of the edible mushrooms *H. marmoreus*, *Flammulina velutipes*, *Pholiota nameko* and *P. eryngii* showed significant antiallergic effects in mice (oxazolone-induced type IV allergy) [53]. Jesenak *et al.* [54] have demonstrated the antiallergic effect of Pleuran (β-glucan from *P. ostreatus*) in children with recurrent respiratory tract infections by reducing the peripheral blood eosinophilia and stabilized the levels of total IgE in serum.

Various mushrooms have demonstrated potential antibacterial, antifungal and antiviral activities [17••,24]. The anti-viral effects of mushrooms do not seem to be related to viral adsorption or virucidal effects (*i.e.*, they do not kill the virus), however a number of studies have reported inhibitory effects at the initial stage of virus replication [55]. Therefore, bioactive compounds from mushrooms can be in the next future a suitable tool as adjuvants to antiretroviral treatment. Proteins, peptides and polysaccharopeptides have been reported to inhibit human immunodeficiency virus type 1 (HIV-1) reverse transcriptase and protease, the most important enzymes in the life cycle of HIV [17••]. In the same line, mushroom lectins have been found to have potent anti-HIV-1 reverse transcriptase activity, for example, lectins from *P. citrinopileatus* [56]. The exact mechanism by which lectins in general exert their anti-HIV-1 reverse transcriptase activity is yet to be fully resolved but probably involves protein–protein interaction as demonstrated for the HIV-1 protease that also inhibits HIV-1 reverse transcriptase activity [4].

Inhibitory effects on hepatitis B and herpes simplex virus type 1 have also been reported. D-fraction extracted from *G. frondosa*, in combination with human interferon alpha-2b, might provide a potentially effective therapy against chronic hepatitis B virus infections [57].

In addition, some studies have also indicated a prospective activity of mushroom on the treatment of leukemia, DNA damage, wound healing, rheumatoid arthritis and eye health [4].

Conclusion

Mushroom species have the potential to be developed into functional foods for their high nutritional value and because they are a source of biologically active compounds of medicinal importance. This review summarizes the use of mushrooms and their isolated compounds for the prevention and treatment of several chronic diseases, such as cancer, diabetes mellitus, cardiovascular and neurodegenerative diseases. It can be concluded that the consumption of mushrooms as a part of the daily diet could be a natural adjuvant in the treatment and prevention of several chronic diseases. Furthermore, their isolated bioactive compounds could also be potential nutraceuticals for different disorders, although the detailed mechanism of the various health benefits of mushrooms to humans still requires further investigation.

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