Mechanisms Involved in Edible Mushrooms' Health Beneficial Effects



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Abstract Despite the mushrooms' long application history, only in the last century, more data regarding their nutritional qualities and beneficial effects have been available. The progress in scientific fields such as biology, chemistry, medicine, and pharmacology allowed obtaining data on the mechanisms involved in the mushrooms' beneficial effects. The main mechanisms linked to the presence of different mushrooms' biologically active compounds are antioxidant activity, antimicrobial activity, immunomodulatory effect, and anticancer and antitumor activity.

Although much data has been obtained until now, the study of mushrooms is still far from being completed because many wild mushrooms have not yet been studied, the number of biological compounds is huge, and the mechanisms involved in the beneficial effects of mushrooms are still not fully elucidated.

Keywords Anticancer · Antioxidants · Antimicrobial activity · Edible mushrooms · Immunomodulatory effect

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Abbreviations

CD	Cluster of differentiation
CDC	Centers for Disease Control and Prevention.
СТ	Clinical trial
DCs	dendritic cells
DNA	Deoxyribonucleic acid
FIPs	Fungal immunomodulatory proteins
IL	Interleukin
INF	Interferon
iNOS	Inducible nitric oxide synthase
NF-kB	Nuclear factor kappa-light-chain enhancer of activated B cells
NK	Natural killer
NO	Nitric oxide
TLR	Toll-like receptor
TNF	Tumor necrosis factor
USD	United States dollar
WHO	World Health Organization

1 Introduction

The fungi existed 750–850 million years ago (Bonneville et al. 2020), and the mushrooms, which are a part of the Fungi kingdom, were considered by the Romans "Food of the Gods" (Valverde et al. 2015). From ancient times, mushrooms have been known either for their nutritional and culinary characteristics (edible mushrooms) or for their toxic compounds (nonedible mushrooms) (Wasser 2010). The market for mushrooms has been increasing over the years. According to the 2021 Market Research report 2019, the global mushroom edible market size was 28.6 billion USD and is expected to reach 52 billion USD by 2026. Another important part of the mushroom market includes medicinal mushrooms, even if they are not edible. The study of edible mushrooms is far from being completed due to the increased interest in wild mushrooms and the need to determine the safety of their use.

The mushrooms are a group of fungi having distinctive fruiting bodies. Based on molecular biology techniques, including DNA molecule sequencing, Fungi's kingdom is divided into *Zygomycota*, *Chytridiomycota*, *Basidiomycota*, and *Ascomycota* phyla. The mushrooms are considered mainly belong to the *Ascomycota* and *Basidiomycota* phyla. *Ascomycota* phylum is considered the largest phyla of fungi and includes more than 40,000 species distributed worldwide (Zafar et al. 2020). Seven hundred mushroom species are considered safe and beneficial for consumers' health (Li et al. 2021), and 100 mushroom species of edible mushrooms are

Cantharellaceae sp. (chanterelles), *Lycoperdon* sp. and *Calvatia* sp. (puffballs), *Coprinus comatus* (shaggy mane), *Pleurotus ostreatus*, *Pleurotus cystidiosus* (oyster mushrooms), *Boletus* sp. (boletes or porcini mushrooms), *Laetiporus sulphureus* (sulfur shelf), *Agaricus bisporus* (button mushroom), *Morchella esculenta* (morels), *Hericium erinaceus* (bearded tooth), *Volvariella volvacea* (straw mushroom), *Flammulina velutipes* (Eenoki), *Lentinula edodes* (shiitake), *Hypsizygus marmoreus* (beech mushroom), *Pleurotus eryngii* (French horn mushroom), and *Grifola frondosa* (dancing mushroom) (Das et al. 2022).

The wild mushroom species are sometimes specific to different regions and are more or less studied even though some of them are superior to cultivated ones in terms of nutritive value and beneficial effect (Kalač 2013; Nakalembe et al. 2015; Barros et al. 2007; Angelini et al. 2020; Anusiya et al. 2021; Huo et al. 2020).

On an industrial scale, around 20 species are cultivated, of which the most wellknown are *Agaricus bisporus*, *Pleurotus* sp., *Lentinula edodes*, *Auricularia* spp., *Volvariella volvacea*, *Flammulina velutipes*, and *Tremella fuciformis*.

Complex studies conducted in recent decades have confirmed not only the nutritional qualities but also the existence of biologically active compounds in mushrooms that improve the health of the consumer (Lu et al. 2020; Sheng et al. 2021; Vamanu et al. 2018; Abdelshafy et al. 2022; Ache et al. 2021; Aida et al. 2009; Zhang et al. 2001; Ko et al. 1995; Końska 2006; Manzi et al. 1999; Ma et al. 2018).

2 Edible Mushrooms' Nutritional Effects

The most important characteristic of edible mushrooms is their nutritional value. Despite the concentration variation of components with nutritional impact, all edible mushrooms contain proteins, glucides, lipids (Table 1), organic acids, enzymes, vitamins, phenols, terpenoids, steroids, lectins, and minerals (Kalač 2013; Assemie and Abaya 2022). The main mushroom vitamins are thiamin (B1), biotin (B7), nicotinamide (B3), folic acid (B9), vitamin D2, vitamin C, and in small amounts, vitamins A and E (Wani et al. 2010). In terms of mineral contents, mushrooms have diverse and high amounts of potassium (K), phosphorus (P), sodium (Na), calcium (Ca), and magnesium (Mg) and lower amounts of copper (Cu), zinc (Zn), iron (Fe), molybdenum (Mo), manganese (Mn), and selenium (Se).

The amount of nutritional components depends mainly on the following:

- The mushroom species.
- The growth conditions.
- Time of harvesting.
- The soil texture.

About 30 years ago, most edible mushrooms were considered to have no medicinal value (Chang 1996). However, numerous scientific studies proved mushroom compounds' direct or indirect beneficial effects in improving the health of consumers (Table 2).

Table 1 The nutritiv	'e values o	f some edib	le mushre	oom spec	ies and 1	main microe	clements					
Components	Proteins	Glucides	Lipids	Fiber	Ash	Energy (kcal)	Ca	×	d	Na	Mg	References
Mushroom species	g/100 g d	ry matter					mg/100	g dry matt	er			Ache et al. (2021)
Termitomyces microcarpus	30.69	44.23	2.17	11.6	11.3	319.27	37.47	1112.76	898.17	12.91	39.03	
Auricularia polytricha	17.44	51.23	2.91	20.69	7.74	301.51	88.62	294	623.96	10.91	83.54	
Polyporus tenuiculus	10.89	58.84	3.22	15.48	11.57	299.49	90.95	428.41	592.25	9.70	94.48	
Volvariella speciosa	19.95	48.44	3.56	4.19	14.13	248.64	12.8	3196.4	612	16.1	7.14	Nakalembe et al. (2015)
Termitomyces tyleranus	21.77	42.99	3.00	3.08	16.87	220.75	15.5	2530.1	794.9	16.8	31.9	
Termitomyces clypeatus	18.00	49.35	3.79	7.69	11.2	250.62	14.8	1869.7	612.3	10.3	10.32	
Agaricus bisporus	33.48	46.17	3.10	20.9	5.7	499	47.0	4015.0	1350.0	5?	4.9	Manikandan (2011), Goyal
Pleurotus sajor-caju	19.23	63.40	2.70	48.60	6.32	412	73.0	3218.0	1246.0	No data	4.5	et al. (2020)
Lentinula edodes	32.93	47.60	3.73	28.8	5.2	387	No data	No data	No data	No data	No data	

	Biologically		
Mushrooms	compounds	Beneficial effects	References
Cantharellus tubaeformis, Cantharellus cibarius, Boletus edulis	Vitamin D2	Antioxidant, Ca ²⁺ ion homeostasis, immuno- modulatory effect	Cardwell et al. (2008)
Lentinula edodes	b-1,3-D-glucan, Lentinan	Cancer treatment Immunomodulatory effect	Venturella et al. (2021)
Tremella fuciformis	Polysaccharides	Gut microbiota modulation	Wu et al. (2021)
Pleurotus ostreatus	Fractions of proteoglycan	Reduction of tumor and immunomodulatory effect	Sarangi et al. (2006), Jedinak and Sliva (2008)
Grifola frondosa	β-Glucan fraction	Immunomodulatory effect and antitumor effect	Venturella et al. (2021)
Flammulina velutipes	Small mole- cules enokipodins	Antimicrobial activity	Zeb and Lee (2021)
Albatrellus flettii	Grifolin, neogrifolin, and confluentin	Antimicrobial activity	Zeb and Lee (2021)
Pleurotus eryngii	Polysaccharide	Gut microbiota modulation	Ma et al. (2022)
Auricularia polytricha	Polysaccharide	Anti-inflammatory and gut modulation	Nguepi and Song (2020)
Helvella leucopus	Polysaccharide	Reducing the colonic lesion and gut modulation	Abdureyim et al. (2022)
Lentinus squarrosulus	Carbohydrate and protein fractions	Gut modulation	Ayimbila et al. (2022)
Sparassis crispa	Polysaccharides	Gut modulation, antitumor activity, and immunomodulatory effect	Zhang et al. (2022a, b)
Agaricus bisporus, Agaricus bitorquis, Agaricus campestris, Boletus edulis, Boletus satanas, Flammulina velutipes, Hericium erinaceus	Lectins	Immunomodulatory effect and anticancer effect	Chowdhury et al. (2015)
Calvatia gigantea	2- Pyrrolidinone, 1-dodecene, Ergosterol, Hexadecane, Benzene acetic Acid	Antidiabetic, antioxi- dant, anti-inflammatory	Ogbole et al. (2019)

 Table 2 Example of edible mushrooms and their beneficial effects

The edible mushrooms are a source of valuable biologically active substances, including phenolic and indolic compounds, carotenoids, flavonoids, sesquiterpenoids, glucans, glycoproteins, triterpenoids, sterols, tocopherols, antibiotics, vitamins, and elements, which are present in them in significant quantities and often act synergistically (Kała et al. 2020).

3 Mechanisms Involved in the Beneficial Effects

3.1 Antimicrobial Activity

The studies regarding the beneficial effects of edible mushrooms proved that some compounds found in edible mushrooms have antimicrobial activity against Grampositive and Gram-negative bacterial strains, yeast, and fungal strains (Table 3). The antimicrobial activity was correlated with the presence of different compounds which are present in different edible mushroom species (Ahmad et al. 2014; De Andrade et al. 2021; Ayodele and Idoko 2011; Contato et al. 2021; Özcan and Ertan 2018; Al-Mazaideh and Al-Swailmi 2021).

The data proved that the edible mushrooms could be a source of a new compound with antimicrobial activity that can be an alternative to antibiotic therapy.

In recent years accumulated data proved the antiviral activity of some biologically active compounds of edible mushrooms like lectins, polysaccharides, and terpenoids (El-Maradny et al. 2021; He et al. 2020; Elhusseiny et al. 2021a, b; Friedman 2016).

3.2 Antioxidant Activity

Molecular biology studies proved the involvement of oxidative stress in some disorders like heart disease, cancer, metabolic diseases, neuronal disorders, and even premature aging (Kozarski et al. 2015). The most frequently involved in oxidative stress are reactive oxygen and nitrogen species generated by endogenous processes or by exogenous factors like pollution, drugs, and radiation. The free radicals could interact with DNA, protein, and lipids and alter them. The free radicals could affect cells and tissues by damaging macromolecules and altering metabolic processes and homeostasis (Mwangi et al. 2022). The human organism possesses a complex antioxidative system to eliminate or minimize reactive species' negative effects and involves enzymatic (catalase, glutathione peroxidases, superoxide dismutase) and nonenzymatic systems (vitamins, carotenoids, polyphenols, uric acid, trace elements, albumin, ceruloplasmin, transferrin, ferritin) (Kozarski et al. 2015). The imbalance between reactive species and the detoxification process leads to oxidative stress. Dietary supplements rich in antioxidants are recommended to help the organism's defense mechanisms and prevent or cure some disorders.

Edible mushrooms	Compounds	Species of sensitive strains	References
Agaricus bisporus, Lentinula edodes, Agaricus brasiliensis	Phenolic com- pounds, Gallic acid, p-hydroxybenzoic	Staphylococcus aureus, Bacillus cereus, Escherichia coli, Salmonella enteritidis	Bach et al. (2019)
Armillaria mellea, Calvatia excipuliformis, Clavulina cinerea, Clitocybe gibba, Coprinus micaceus, Craterellus cornucopioides, Laccaria amethystina, Laccaria laccata, Lactarius rufus, Laetiporus sulphureus, Leccinum scabrum, Lycoperdon perlatum, Macrolepiota procera, Marasmius oreades, Pholiota mutabilis, Psilocybe capnoides, Rozites caperata, Sparassis crispa, Xerocomus badius	Phenolic compounds	Micrococcus luteus, Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa	Nowacka et al. (2014)
Termitomyces striatus	Mushroom extract with dichloromethane	Pseudomonas aeruginosa, Escherichia coli, Staphylo- coccus aureus, Bacillus subtilis, Candida albicans	Sitati et al. (2021)
Boletus edulis, Cantharellus cibarius, Craterellus cornucopioides, Hydnum repandum, Agaricus bisporus	Methanol and acetone mush- rooms extract	Pseudomonas aeruginosa, Escherichia coli, Enterococ- cus faecalis, Staphylococcus aureus, Klebsiella pneumoniae, Serratia marcescens, Candida albicans	Özcan and Ertan (2018)
Pleurotus eryngii	Mushroom sub- merged cultivated	Escherichia coli, Staphylo- coccus aureus, Pseudomo- nas aeruginosa, Candida albicans, Candida parapsilosis, Candida tropicalis	De Andrade et al. (2021)
Volvopluteus gloiocephalus, Clitocybe subconnexa	Phenolic acids	Escherichia coli, Pseudo- monas aeruginosa, Salmo- nella typhimurium, Enterobacter cloacae, Staphylococcus aureus, Bacillus cereus, Micrococ- cus flavus, Listeria monocytogenes Aspergillus fumigatus, Aspergillus ochraceus, Aspergillus versicolor, Aspergillus niger.	Heleno et al. (2015)

 Table 3
 Antimicrobial activity of edible mushrooms

(continued)

Edible mushrooms	Compounds	Species of sensitive strains	References
		Penicillium funiculosum, Penicillium ochrochloron, Trichoderma viride, Penicil- lium verrucosum var. cyclopium	
Termitomyces robustus, Lentinus squarrosulus	Aquatic and alco- holic mushroom extract	Staphylococcus aureus, Pseudomonas aeruginosa, Salmonella typhi, Trichoderma rubrum, Aspergillus fumigatus	Borokini et al. (2016)
Tricholosporum goniospermum	Mushrooms extract – Phenolic compounds	Pseudomonas aeruginosa, Staphylococcus aureus, Bacillus cereus, Bacillus subtilis, Candida albicans, Candida tropicalis, Candida parapsilosis	Angelini et al. (2020)
Pleurotus ostreatus, Lentinula edodes, Hypsizygus tessulatus	Methanolic extract	Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Klebsiella pneumonia, Pseudomonas aeruginosa, salmonella typhi, Candida albicans, Saccharomyces cerevisiae	Chowdhury et al. (2015)

Table 3 (continued)

The edible mushrooms have a high range of natural antioxidant compounds, potential substitutes for synthetic antioxidants, which sometimes have side effects. The antioxidants are found in fruit bodies, mycelium, and even in broth and include phenolic compounds, ascorbic acid, flavonoids, ergothioneine, polysaccharides, glycosides, tocopherols including vitamin E, carotenoids, vitamin A, vitamin D, and minerals (Chun et al. 2021; Angelini et al. 2020; Elhusseiny et al. 2021b; Mahmoud and Abdel-Hadi 2022).

The antioxidants sometimes are specific to the mushroom's family, like in the case of polysaccharides. For example, the chitin-mannan- β -glucans could be found in mushrooms from the *Ascomycete* family, while the *Basidiomycete* family contains chitin- β -glucans (Martinez-Medina et al. 2021). The main phenolic compounds in edible mushrooms are hydroxycinnamic acids (caffeic, ferulic, p-coumaric, and sinapic) and benzoic acids (p-hydroxybenzoic, gallic, gentisic, vanillic, syringic, protocatechuic, s.o.). Trace elements accumulated in edible mushrooms (Zn, Cu, Mn, and Fe) are cofactors of antioxidant enzymes (Kozarski et al. 2015).

The mechanism involved in the edible mushrooms' antioxidant activity are as follows:

- · Chain breaking
- · Free radical scavengers
- Increasing activity of the liver's oxidative enzymes and glutathione and malondialdehyde levels

- · Inhibition or breakdown of lipid peroxides
- · Enhancing the synthesis of endogenous antioxidants
- Deactivation of metals
- Hydrogen atom transfer
- Fe²⁺ chelators
- Protectors of mitochondrial components (Chun et al. 2021; Kozarski et al. 2015; Friedman 2016)

In vitro obtained data regarding the edible mushrooms' antioxidant activity support the need to elucidate the mechanisms involved in beneficial effects and the necessity of complex pharmacological and biological studies.

3.3 Immunomodulatory Effect

The immune system's function and homeostasis are essential for good health and survival. During the last decades, clinical practice has used immunomodulators, and the market for these products has increased. The immunomodulator products include immunostimulants, immunosuppressors, and immunoadjuvants and are sometimes used to prevent diseases as prophylactic therapy. Like in the case of antioxidants, synthetic compounds used as immunomodulators could be replaced by natural compounds without or with minimal toxicity. The edible and medicinal mushrooms could be a source of immunomodulators due to their bioactive compounds (El Enshasy and Hatti-Kaul 2013; Elhusseiny et al. 2022; Patra et al. 2021).

The studies regarding edible mushroom immunomodulators started more than 25 years ago (Ko et al. 1995; Ohkuma et al. 1983). However, these are far from being completed due to the large number of mushrooms and the broad spectrum of compounds.

The immunomodulatory effect of the edible mushrooms is either direct (Wu et al. 2021; Zhao et al. 2020) or indirect after interaction with gut microbiota (Vlassopoulou et al. 2022; Zhang et al. 2022a, b; Vamanu et al. 2021; Steve and Hui 2020; Ma et al. 2021).

The mechanism involved in immunomodulation depends on the type of mushroom, and the main mechanisms and biologically active compounds are summarized in Fig. 1.

The data obtained from in vitro and in vivo studies have highlighted the ability of either total edible mushroom extract or purified compounds to influence the immune system. Some new evidences of edible mushrooms' immunomodulation effects are summarized in Table 4.

Immunotherapy based on natural bioactive compounds could be a less expensive and efficient alternative to allopathic medicine, including vaccines. The edible and medicinal mushrooms represent a great and promising source of immunomodulatory compounds.



Fig. 1 The mechanisms involved in immunomodulatory effect and main classes of compounds

Mushroom	Model	Effects	Component	References
Lentinula edodes, Agaricus bisporus, Pleurotus ostreatus, Pleurotus columbinus, Pleurotus sajor-caju	Wistar albino rats	Increase the number of white blood cells, increase the level of TNF- α , IFN- γ , and IL-1 β , and increase the nitric oxide and the lysozyme concentration	Total extract	Elhusseiny et al. (2021a, b)
Polyporus grammocephalus	In vitro studies	Stimulation of macro- phage, splenocytes, and thymocytes	Polysaccharides	Patra et al. (2021)
Lentinula edodes	In vitro studies	Inhibition of CD 3, downregulation of TNF-α, reduction of the NK cytotoxic activity	Selenium- enriched polysaccharide	Kaleta et al. (2021)
Coriolus versicolor	In vitro studies of rat cell line	Increasing the expres- sion of iNOS, activation of macrophages by pro- moting transcription of TNF- α	Polysaccharides	Zhang et al. (2021)
Volvariella volvacea	Mice C57BL/ 6 mice	Induces secretion of TNF- α , IL-2, IL-6, and IL-12, p70, promotes the action and function of DCs	Proteins	Li et al. (2021)

Table 4 Examples of edible mushrooms' immunomodulatory effects

3.4 Anticancer and Antitumor Effects

According to the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC), cancer is the second cause of death in the United States. Despite progress in the medical and pharmaceutical fields, the morbidity rate is still very high. That way, solutions are being sought to prevent and/or treat this disease. There are ongoing clinical trials (phases I and II) in which mushrooms are tested for treating breast, colorectal, and prostate cancer (Panda et al. 2022).

The edible mushrooms' mechanisms involved in anticancer and antitumor effect are exercised in all stages of the appearance, and evolution of the carcinogenic process and includes the following:

- Inactivation of cancerogenic free radicals due to the presence of antioxidants
- DNA repair
- Inducing apoptosis
- Tumor proliferation inhibition due to immune system modulation

The mushrooms' anticancer and antitumor activities include the mechanisms presented before (antioxidant and immunomodulatory activity). Still, some compounds, like lectins, have a direct effect (Końska 2006).

Lectins are carbohydrate-binding proteins with a high degree of selectivity and stereospecificity, which have immunomodulatory, anticancer, and antitumor effects. Edible mushrooms are a natural source of lectins with different chemical structures, molecular masses, and biochemical properties. Lectins have been isolated from different parts of the mushrooms: mycelia, stalk, and caps. The lectin concentration depends on the species, season, location, age, and mycelia growth (Chowdhury et al. 2015).

Other compounds from edible mushrooms with anticancer and antitumor activity are polysaccharides, peptides, and phenols.

In vitro and in vivo animal model studies proved that *Grifola frondosa* (maitake mushroom) polysaccharide (D-fraction) is involved in the anticancer effect by stimulation of apoptosis and blocking of tumor growth in breast cancer (Alonso et al. 2017, 2018). The X – fraction isolated from *Grifola frondosa* fruiting body had antidiabetic activity (Wu et al. 2021).

Some examples of anticancer compounds isolated from the mushrooms are lentinan, krestin, shizophyllan, hispolon, theanine, psilocybin, ganoderic acid, grifolin, cordycepin, antroquinonol, 5-(hydroxymethyl) furan-2-carbaldehyde, 3-isobutyl-1-methoxy-4-(4'-(3-methylbut-2-enyloxy)phenyl)-1H-pyrrole-2,

5-dione, ribonuclease, polysaccharide-peptide complex LB-1b, and polyphenol oxidase (Patel and Goyal 2012; Zhang et al. 2021; Sarangi et al. 2006).

Until now, edible mushrooms' total extracts or purified compounds have been tested to prevent and cure different types of cancer: colorectal, endometrial, gastric, liver, lung, breast, cervical, bladder, miscellaneous tumors, cachexia, pancreatic, prostate, testicular, myeloma, and nasopharyngeal (Panda et al. 2022).

3.5 Other Mechanisms

Some examples of other mechanisms involved in the beneficial effects of edible mushrooms are represented by the following:

- Reduction of total cholesterol, creatinine, aspartate aminotransferase, alanine aminotransferase, plasma glucose, and systolic and diastolic blood pressure clinical trial (CT) using *Agaricus sylvaticus* (Fortes and Novaes 2011).
- Decreasing the triglyceride and cholesterol levels CT *Pleurotus ostreatus* (González-Bonilla et al. 2022).
- Modulation of gut microbiota and prevention or curing of obesity by upregulating lipid metabolism, carbohydrate metabolism, bile acid biosynthesis, and downregulation of adipocytokine signaling pathway and steroid hormone biosynthesis animal model study using *Pleurotus ostreatus* (Hu et al. 2022).
- Improving levels of aminotransferase levels and histopathological features (steatosis, inflammatory foci, pericellular fibrosis) in nonalcoholic steatohepatitis animal model study using *Ceraceomyces tessulatus* (Suzuki et al. 2022).
- Hypoglycemic and antidiabetic effect animal model using *Lentinus edodes* polysaccharides (Gong et al. 2022).
- Reduces the neuroinflammation, regulation of neurotrophin synthesis, and modulation of acetylcholinesterase activity in the animal study using *Agaricus bisporus* (Solano-Aguilar et al. 2021).

4 Conclusion

Mushrooms have a long history of being used as healthy food due to their culinary attributes and beneficial effects. Numerous studies have proved that mushrooms could be considered the "elixir of life," as Chinese culture mentions them, due to their application in the prevention and cure of various diseases like cancer, diabetes, hypertension, metabolic diseases, infectious diseases, etc. The data from the in vitro and in vivo studies, including clinical trials, suggest mushrooms' high applicability potential due to their vast reservoir of biologically active compounds.

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