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Mushrooms: Natural factory of anti-oxidant, anti-inflammatory, analgesic and nutrition

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Abstract
Mushrooms have been consumed as food items and medications since earliest history; old Greeks had a strong faith that mushrooms gave strength to warriors in fight and the Romans saw them as the "Food of the Gods". For hundreds of years, the Chinese culture has treasured mushrooms as a wellbeing nourishment, an "elixir of life." They have been a piece of the human culture for thousands of years and had been the item of considerable interest for the most essential civic establishments in history on account of their sensory attributes. Likewise, they additionally incorporate numerous bioactive metabolites which make mushrooms and truffles regular parts in medication, particularly in Africa, the Middle East, China and Japan. It is accounted for and in some cases have demonstrated that mushrooms have numerous pharmacological and remedial activity including anti-oxidant, anti-cancer, anti-inflammatory, analgesic, nutraceutical and numerous others. However, this attempt has been made to concentrate on the short reviews of anti-oxidant, anti-inflammatory, analgesic and food values of mostly used mushrooms all over the world.

Keywords: mushrooms; anti-oxidants; anti-inflammatory; analgesic; nutrient

Introduction

Mushrooms are a substantial and diversified collection of macrofungi having a place with Basidiomycetes and Ascomycetes; with a cell cycle including the arrangement of sexual spores. Mushrooms have been viewed as gourmet food over the globe since vestige for their unique taste and inconspicuous flavor. As of late, it has been found that many mushroom species are miniature pharmaceutical factories producing thousands of novel constituents with exceptionally helpful biologic properties. They have a long history of utilization in Oriental prescription, however their incredible impacts in advancement of good health and imperativeness are being upheld by contemporary reviews. Recently, mushrooms have developed as great wellspring of nutraceuticals, anti-oxidants, anticancer, prebiotic, immune modulating, anti-inflammatory, cardiovascular, anti-microbial and anti-diabetic.

Inadequate nutrition because of current way of life and the expansion of normal life span are the two key purposes behind the increased rate of ailment everywhere throughout the world. Oxidative stress created by an imbalanced digestion and an abundance of reactive oxygen species (ROS) end into a scope for disorders i.e., metabolic disease, coronary disease, severe neural disease, for example, Alzheimer's and Parkinson's, untimely aging and some cancers. ROS are created inside, in the cellular organism, as well as through different outer sources like ultra violet, ionizing radiation, chemotherapeutics, inflammatory cytokines, and environmental poisons. Breathing in poisonous chemicals from the environment has turned out to be unavoidable in current human progress. Manufactured phenolic antioxidants include butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT) and others e.g., propyl gallate, tert-butylhydroquinone (TBHQ), ethoxyquin (EQ), that all adequately hinder oxidation [6]. Nonetheless, some synthetic anti-oxidants may bring about antagonistic harmful impacts under specific conditions [7, 8]. BHA, which is all the time utilized as an additive in sustenance industry, can negatively affect the control of the movement of mitogen-activated protein kinase (MAPK) contingent upon the dose [8, 9]. A few synthetic anti-oxidants are approved for being used as additive in the European Union [10]. Lately, the confinement on the utilization of synthetic anti-oxidants, for example, BHA and BHT, has brought on a quickly expanded interest towards natural anti-oxidant substances [7, 8]. Prerequisites for natural option for anti-oxidant foods and ingradiants are derived basically from purchasers. Lately edible mushrooms have pulled in consideration as a business source of anti-oxidants [7, 8, 11]. They may be utilized straightforwardly in improvement of anti-oxidant guards through dietary supplementation to lessen the level of oxidative stress. There is an abundance of confirmation to uphold the adequacy of such a methodology in vitro.

In the human body, inflammation is thought to be a piece of the complex organic reaction to expel damage or destructive jolts, for example, pathogens, harmed cells or disturbance. This reaction prompts numerous physical side effects, for example, fever, pain, and swelling, therefore of many related changes, for example, vasodilation, expanded vascular penetrability and plasma extravasation. Then again Pain is a physiologically applicable sensation important to identify or potentially avert harm; it is once in a while helpful to us [12, 13]. Generally, it is an immediate reaction to an untoward occasion related with tissue harm, for example, damage and inflammation, yet serious agony can emerge freely of any undeniable redisposing cause or hasten recuperating after harm for a moderately long time. It can likewise happen as a consequence of brain or nerve damage. Pain signaling to the central nervous system is started when hurtful energy and primary afferent nociceptive C and A fibres are often brought on by actuation of a few sorts of ionotropic channels and etabotropic receptors [14, 15]. Actually, transient receptor potential and corrosive detecting particle diverts take an interest in creating nociceptive flags because of different particular toxic stimuli [15-17]. Action of some of these channels and different proteins implicated in nociceptive signaling pathways can be up regulated by protein kinase C [18-20]. Subsequently, pain is produced.

The genuine nutritive estimation of mushrooms has quickly turned out to be known and perceived by mushroom specialists and farmers as well as by the general customers [21]. Notwithstanding their great flavor, mushrooms have positive chemical composition with high measures of useful proteins, low total fat level and the high extent of polyunsaturated fatty acids (PUFA), making them appropriate for low calorie diets. Palatable mushrooms give a nutritiously noteworthy substance of vitamins (B1, B2, B12, C, D, and E) [22–24]. Besides, mushrooms have a low glycemic record and high mannitol, which is particularly valuable for diabetics. Mushrooms have low sodium (Na) concentration, which is valuable for hypertensive patients and a high amount of potassium (K) and phosphorus (P), which is an imperative orthomolecular perspective [21]. In Asia, mushrooms are utilized as critical wellspring of home cures against different sicknesses inspired by oxidative stress [11].

The progressing research tasks are planned to advance mushrooms as new generation source of mostly craved drugs and help in the further research process to identify the novel compund from the mushroom species and help in human welfare.

Mushrooms with anti-oxidant properties

A whole variety of edible mushrooms were reported to possess antioxidant activity (Table 1). It is generally accepted that extracts of fungi contain many components, each of which has its own specific biological effects [25, 26]. Antioxidant compounds found in fruit bodies, mycelium and broth confirmed to be phenolics, flavonoids, glycosides, polysaccharides, tocopherols, ergothioneine, carotenoids, and ascorbic acid [24, 27, 28–105].

Table 1: Some studies of antioxidative properties of wild and cultivated mushrooms

Mushroom Species	References
Agaricus bisporus, *Agaricus brasiliensis* (=*Agaricus blazei ss. Heinem.*), *Agrocybe aegerita*, *Auricularia auricular*, *Auricularia cornea*, *Auricularia polytricha*, *Auricularia mesenterica*, *Auricularia fuscosuccinea*, *Agrocybe cylindracea*, *Amanita rubescens*, *Agaricus arvensis*, *Armillariella mellea*, *Agaricus silvicola*, *Agaricus silvaticus*, *Agaricus romagnesii*, *Antrodia camphorate*	[31, 33, 37-39, 46, 47, 9, 53, 59, 60, 68, 71, 73, 77, 79, 81, 85-89, 91, 94, 96, 98, 100]
Boletus edulis, *Boletus badius*	[47, 79, 100]
Cantharellus lutescens, *Cantharellus clavatus*, *Cantharellus cibarius*, *Cordyceps sinensis*, *Calvatia gigantea*, *Cerrena unicolor*, *Coprinus comatus*	[24, 47, 49, 53, 60, 71, 90, 96, 98, 100, 103]
Dictophora indusiata	[70]
Flammulina velutipes (white), *Flammulina velutipes* (yellow)	[51,59,61,92-94]
Inonotus obliquus	[34-36]
Ganoderma lucidum, *Ganoderma tsugae*, *Grifola frondosa*, *Ganoderma applanatum*, *Geastrum arenarius*, *Geastrum saccatum*,*Ganoderma atrum*	[30-32, 42-45, 47, 49, 50, 52, 54, 55, 63, 65, 67, 70, 74, 75, 83, 98, 101, 102]
Hericium erinaceus, *Hericium coralloides*, *Hydnum repandum*, *Hygrophorus agathosmus*, *Hypsizigus marmoreus*, *Hypholoma fasciculare*, *Helvella crispa*	[47, 53, 59, 69-71, 79, 96, 103]
Lepista nuda, *Lentinus edodes*, *Lactarius sanguifluus*, *Lentinus squarrosulus*, *Lactarius deliciosus*, *Lentius sajor-caju*,*Leucopaxillus giganteus*, *Lactarius piperatus*, *Laetiporus sulphureus*, *Lycoperdon molle*, *Lycoperdon perlatum*, *Lactarius piperatus*	[29, 30, 37, 40, 47, 51, 53, 55, 59, 60, 62, 71, 76, 78, 81, 82, 84, 89, 96, 100, 101, 103]
Morchella esculenta, *Morchella conica*, *Macrolepiota procera*, *Morchella angusticeps*, *Macrolepiota procera*	[41, 47, 74, 96]
Pleurotus ostreatus, *Pleurotus eryngii*, *Pleurotus citrinopileatus*, *Pleurotus djamor*, *Pleurotus sajor-caju*, *Pleurotus cystidiosus*, *Pleurotus australis*, *Pleurotus tuber-regium*, *Phellinus linteus*, *Phellinus rimosus*, *Phellinus merrillii*, *Polyporus squamosus*, *Picoa juniperi*, *Pleurotus florida*, *Pleurotus pulmonarius*, *Paecilomyces japonica*, *Piptoporus betulinus*	[104, 31, 37, 44, 47-49, 51, 53, 58-60, 64, 71, 72, 80, 89, 97, 98, 100, 105]
Russula brevipes, *Russula cyanoxantha*, *Russula delica*, *Ramaria botrytis*, *Russula vinosa*	[47, 57, 60, 79, 96]
Sparassis crispa, *Suillus bellini*, *Suillus luteus*, *Suillus granulatus*, *Sarcodon imbricatus*, *Schizophyllum commune*	[28, 47,79,81,96,103]
Tricholoma acerbum, *Tricholoma equestre*, *Tricholoma giganteum*, *Tricholomopsis rutilans*, *Termitomyces microcarpus*, *Termitomyces schimperi*, *Termitomyces mummiformis*, *Termitomyces tylerance*, *Termitomyces heimii*, *Termitomyces albuminosus*, *Termitomyces robustus*, *Terfezia claveryi*, *Tremella fuciformis*, *Trametes (Coriolus) versicolor*, *Trametes orientalis*	[30,46,47,49,55,56,70,71,74,79,89, 96,101,103]
Verpa conica, *Volvariella volvacea*	[59,60,62,76]

The different strategies utilized to measure the anti-oxidative properties of mushroom compounds or concentrates are fit for different levels of anti-oxidative activity, for example, techniques based on the exchange of electrons and hydrogen atoms, the capacity to chelate ferrous (Fe2+) and cupric (Cu2+) particles, the electron spin resonance (ESR) strategy, erythrocyte hemolysis and the observing of the action of SOD, CAT and GPx [24, 27, 28–98,101–103].

It has been established that mushroom agents can exhibit their defensive properties at various phases of the oxidation procedure and by various mechanisms. There are two fundamental sorts of mushroom anti-oxidants, in particular, primary (chain breaking, free radical scavengers) and secondary or preventive [106, 107, 108, 24, 28–98, 101–103]. Secondary antioxidants are the result of deactivation of metals, restraint or breakdown of lipid hydroperoxides, recovery of anti-oxidants, singlet oxygen ($_1O_2$) extinguishing and so forth. Some mushroom substances that display anti-oxidant activity work as inducers and additionally cell signals, prompting changes in quality expression, which result in the enactment of catalysts that dispose of ROS [107, 64-67, 109]. Diverse logical strategies have been connected for its recognizable proof and evaluation: high performance liquid chromatography (HPLC) and gas chromatography (GC) coupled to unmistakable detection gadgets, Nuclear Magnetic Resonance (NMR), Fourier transform infrared (FT-IR), UV-VIS spectroscopy and different spectrophotometric measures [24, 27, 28–103, 105].

Fig 1: *Agaricus* species, the most cultivated mushroom worldwide

Fig 2: *Lentinus edodes* or "shiitake mushroom."

Fig 3: *Pleurotus* or "oyster mushroom"

Mushrooms with anti-inflammatory & analgesic properties

Inflammation is a complex arrangement of co-operations among soluble factors and cells that can emerge in any tissue in case of injury, diseases, or post-ischaemic, poisonous, or immune system damage [110]. In ordinary cases, the body's reaction to inflammation is self-restricting through the down-direction of pro-inflammatory protein expression, the expanded expression of anti-inflammatory proteins, and an inversion in the vascular changes that is encouraged by the initial immune cell recruitment process [111]. The procedures prompting inflammation are typically connected to the activities of the cells required in the rebuilding of tissue structure and function. At the point when cells are exposed to safe stimulants, the pro-inflammatory cells, for example, macrophages, monocytes, or other host cells, begin to create numerous molecular mediators which start the inflammation procedure. Of the different inflammatory biomarkers that are created, the most understood are interleukins (IL-1β), IL-6; IL-8; tumor necrosis factor (TNF-α); nuclear factor κB (NF-κB), intercellular adhesion molecule 1 (ICAM-1), inducible type cyclooxygenase-(COX- 2), prostaglandin E2 (PGE2); 5-lipooxygenase (5-LOX); and inducible nitric oxide synthase (iNOS), which prompts the generation of receptive nitrogen species, for example, nitric oxide (NO). Overproduction of these inflammatory mediators prompts various types of cell damage. What's more, drawn out inflammation causes numerous inflammatory disease, for example, Juvenile idiopathic arthritis (JIA), inflammatory bowel disease (IBD), multiple sclerosis, rheumatoid arthritis, gastritis, bronchitis, and atherosclerosis [112]. Subsequently, expanded attention is presently being focused around bioactive compound which can stifle the generation of inflammatory mediators.

Mushrooms are widely used for their high nutritional value and used as a functional food. Additionally, they have been highly appreciated for their medicinal and therapeutic applications [113, 114]. Many of the bioactive compounds found in mushrooms exhibit significant anti-inflammatory properties. Table 2 enlists most of the well-known mushroom species reported to be possessing anti-inflammatory, used parts and the solvent applied for extraction.

Table 2: Mushroom species with anti-inflammatory activity

Mushroom species	Plant part	Extracting solvent	references
Agaricus blazei	WM	1	115
Agaricus bisporus	WM	3	116
	FB	4	117
Agaricus subrufescens	WM	2	118
Agrocybe aegerita	FB	3	119
Agrocybe cylindracea	FB	2	120
Albatrellus caeruleoporus	FB	3	121,122
Amanita muscaria	FB	2,3,4	123
Boletus edulis	WM	3	116
Cantharellus cibarius	WM	3	116
Cantharellus tubaeformis	WM	2	124
Cordyceps militaris	SC/FB	4	125

Cordyceps pruinosa	FB	3	126
Caripia montagnei	FB	3	127
Cyathus africanus	SC	5	128
Cyathus hookeri	SC	5	129
Daldinia childiae	FB	N.M.	130
Elaphomyces granulatus	FB	4	131,132
Flammulina velutipes	WM	4	133
Fomitopsis pinicola	SC	4	134
Grifola frondosa	SC	5,6	135
	SC	3,5	136
Ganoderma lucidum	FB	4	137
	FB	4	138
Geastrum saccatum	FB	4	139
	FB	2,4,5	140
Inonotus obliquus	FB	8,5	141
	FB	3	142
	FB	4	143
Lactarius deliciosus	WM	3	116
Lactarius rufus	FB	2,4	144
Lentinus edodes	FB	2	145
Lentinus polychrous	SC	4	146
Lyophyllum decastes	FB	3	147
Phellinus linteus	FB	9	148
	FB	4,7,9	149
Pholiota nameko	WM	4,6,10	150
Pleurotus pulmonarius	FB	N.M.	151
	FB	2,4	152
Poria cococs	SC	4	153
Termitomyces albuminosus	SC/FB	4	154

WM, whole mushroom; SC, submerged culture; FB, fruiting bodies.
Solvent: N.M., not mentioned; 1, chloroform; 2, water; 3, methanol; 4, ethanol; 5, ethyl acetate; 6, acetone; 7, n-hexane; 8, petroleum ether; 9, n-butanol; 10,acetyl ether.

Pain signaling to the central nervous system is initiated when harmful excitement and primary afferent nociceptive C and A fibres are frequently caused by activation of several types of ionotropic channels and etabotropic receptors [14, 15]. In fact, transient receptor potential and acid-sensing ion channels participate in generating nociceptive signals in response to various specific noxious stimuli [16-18]. Activity of some of these channels and other proteins implicated in nociceptive signaling pathways can be up regulated by protein kinase C [19-21]. Thus, pain is generated. Mushrooms are also becoming a good source of analgesic medicine and they are being vastly used for pain amelioration as it is also a part of the inflammatory process. The list of mushrooms used as analgesic are long. But the mostly used edible mushrooms are listed in table 3 with their active compound.

Table 3: Mushroom species with analgesic activity

Mushroom species	Active compunds	References
Pleurotus pulmonarius	β-glucans	155-158
Pleurotus florida	Hydroethanolic extract	159
Pleurotus eous	Methanol and aquous extract	160
Agaricus brasiliensis	Fucogalactan	161
Agaricus bisporus var. hortensis	Fucogalactan	161
Agaricus macrospores	Agaricoglycerides	162-167
Coriolus versicolor	Polysaccharopeptides	168-172
Cordyceps sinensis	Cordymin	173-175
Termitomyces albuminosus	Crude saponin and polysaccharide extract	176
Inonotus obliqus	Methanol extract	177
Phellinus linteus	EtOH extract	178
Lactarius rufus	Soluble β-glucans	179
Grifola frondosa	Agarucoglycerides	180

Pain is natural for feelings of these diseases, for example, cancer, inflammation and wounds. Accordingly, the pain ameliorating impacts of edible mushrooms have an extensive variety of utilizations. The active components in many mushrooms with pain relieving properties are clear. Additionally these mushrooms specifically the consumable ones have far less side effects than other synthesized drugs found in the market.

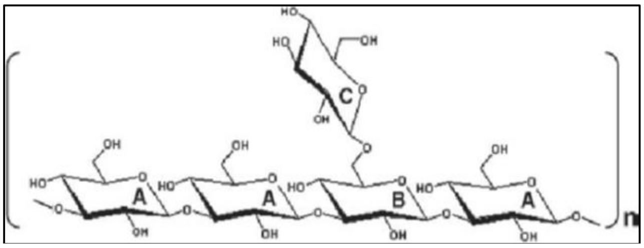

Fig 4: Chemical structure of β-glucan isolated from *Pleurotus pulmonarius*

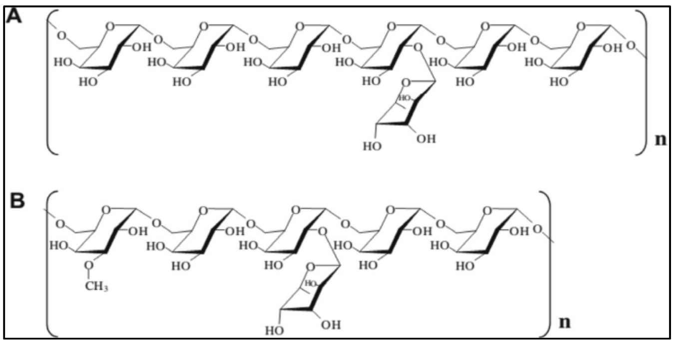

Fig 5: Structure of the fucogalactans EPF-Ab and EPF-Ah

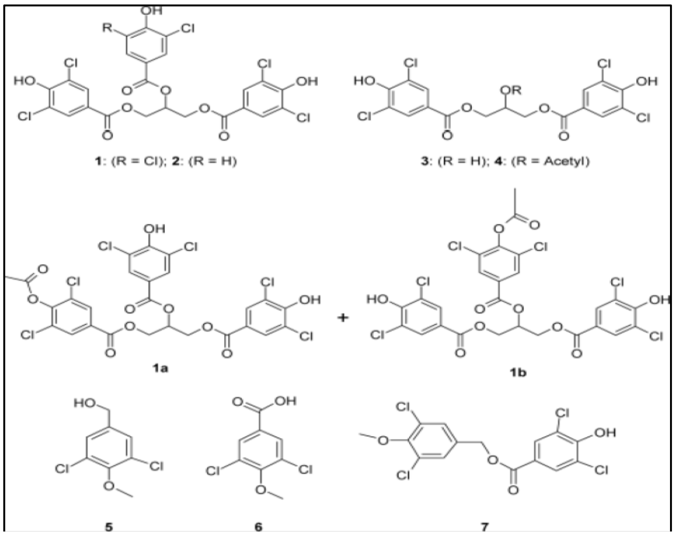

Fig 7: Chemical structures of metabolites isolated from *Agaricus macrosporus.* 1: Agaricoglyceride A; 2: Agaricoglyceride B; 1a/b: Monoacetyl-agaricoglycerides A (isolated as inseparable mixture); 3: Agaricoglyceride C; 4: Agaricoglyceride D; 5: DCMB; 6: 3, 5-Dichloro-4-anisic acid; 7: Agaricic ester.

Mushrooms as source of nutrients

Mushrooms have been considered as ingredient of gourmet cuisine across the globe; especially for their unique flavor and have been valued by humankind as a culinary wonder. More than 2,000 species of mushrooms exist in nature, but around 25 are widely accepted as foods and few are commercially cultivated. Mushrooms are considered as a delicacy with high nutritional and functional value and they are also accepted as nutraceutical foods. Compared to other conventional sources of dietary fibre, such as cereals, fruits, legumes and vegetables, mushrooms or fungi are underutilized [181, 182]. In fact, edible mushrooms or macrofungi are a rich source of some novel dietary fibers (DFs) that have various beneficial health effects to humans which are discussed below. Mushrooms are defined as fungi that have distinctive and visible fruiting bodies [183] and they include edible and medicinal ones. The fruiting bodies of edible mushrooms (*e.g. Lentinus edodes*) are mainly consumed in dried form, while medicinal mushrooms (*e.g. Ganoderma lucidum*) are non-edible fungi that have biopharmaceutical applications due to the bioactive components such as polysaccharides and triterpenoids that they contain. While plant cell walls are major sources of DF, mushroom cell walls can also be considered as DF. Mushroom cell walls contain a mixture of fibrillar and matrix components which include chitin (a straight-chain (1→4)-*β*-linked polymer of *N*-acetyl-glucosamine) and the polysaccharides such as (1→3) - *β*-*D*-glucans and mannans, respectively [184]. These mushroom cell wall components are non-digestible carbohydrates (NDCs) that are resistant to human enzymes and can be considered as source of DF. They have a great nutritional value since they are quite rich in protein, with an important content of essential amino acid, fiber and poor fat (Table 4).

Table 4: food values of different species of mushrooms

Species	Protein (%)	Fat (%)	Ash (%)	Carbohydrates (%)	Energy (kcal/kg)
Agaricus bisporus	14.1	2.2	9.7	74.0	325
Lentinus edodes	4.5	1.73	6.7	87.1	772
Pleurotus ostreatus	7.0	1.4	5.7	85.9	416
Pleurotus eryngii	11.0	1.5	6.2	81.4	421
Pleurotus sajor-caju	37.4	1.0	6.3	55.3	
Pleurotus giganteus	17.7	4.3	-	78.0	364
Agaricus blazei	31.3	1.8	7.5	59.4	379

Adapted from Carneiro *et al*. 2013 [185]; Kalaˇc 2013 [186]; Phan *et al*. 2012 [186]; Reis *et al*. 2012 [188].

It is important to remark that the growth characteristics, stage and post-harvest condition may play a great role in the chemical composition and the nutritional value of edible mushrooms. Also, a varied number of differences can occur both among and within species [29, 30]. Mushrooms contain a high moisture percentage that ranges between 80 and 95 g/100 g, approximately. As above mentioned, edible mushrooms are a good source of protein, 200–250 g/kg of dry matter; leucine, valine, glutamine, glutamic and aspartic acids are the most abundant. Mushrooms are low-calorie foods since they provide low amounts of fat, 20–30 g/kg of dry matter, being linoleic (C18:2), oleic (C18:1) and palmitic (C16:0) the main fatty acids. Edible mushrooms contain high amounts of ash, 80–120 g/kg of dry matter (mainly potassium, phosphorus, magnesium, calcium, copper, iron, and zinc). Carbohydrates are found in high amounts in edible mushrooms, including chitin, glycogen, trehalose, and mannitol; besides, they contain fiber, *β*- glucans, hemicelluloses, and pectic substances. Additionally, glucose, mannitol, and trehalose are abundant sugars in cultivated edible mushrooms, but fructose and sucrose are found in low amounts. Mushrooms are also a good source of vitamins with high levels of riboflavin (vitamin B2), niacin, folates, and traces of vitamin C, B1, B12, D and E. Mushrooms are the only non-animal food source that contains vitamin D and hence they are the only natural vitamin D ingredients for vegetarians. Wild mushrooms are generally excellent sources of vitamin D2 unlike cultivated ones; usually cultivated mushrooms are grown in darkness and UV-B light is needed to produce vitamin D2 [189, 190, 191–196].

Table 5: fatty acid content of different species of mushrooms (g/100g fresh weight)

Species	Palmitic	Stearic	Oleic	Linoleic	Linolenic
Agaricus bisporus	11.9	3.1	1.1	77.7	0.1
Lentinus edodes	10.3	1.6	2.3	81.1	0.1
Pleurotus ostreatus	11.2	1.6	12.3	68.9	0.1
Pleurotus eryngii	12.8	1.7	12.3	68.8	0.1
Agaricus blazei	11.38	2.8	1.85	72.42	nd

Adapted from Carneiro *et al*. 2013 [185]; Reis *et al*. 2012 [186]. Nd, not detected.

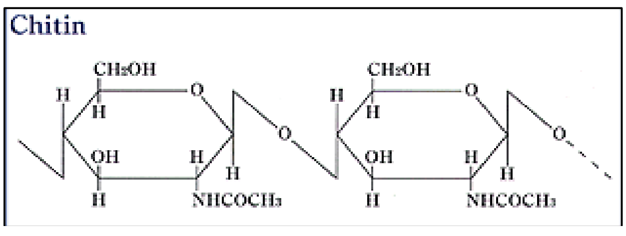

Fig 8: Structure of chitin

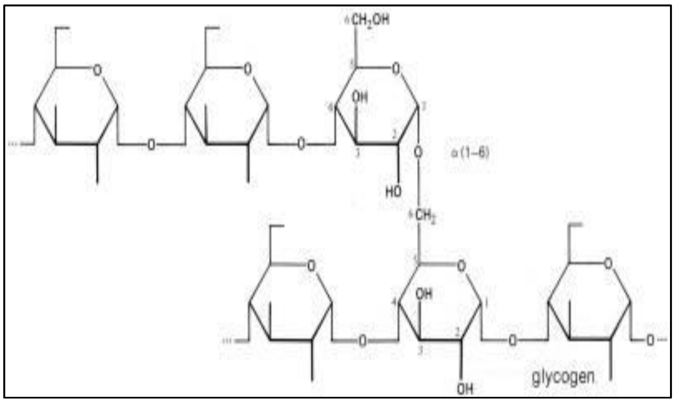

Fig 9: Structure of Glycogen

Conclusion

A few mushroom species have been brought up as source of bioactive compounds, in addition their imperative dietary esteem. The incorporation of entire mushrooms into the eating routine may have viability as potential dietary supplements. The production of these medicinal mushrooms and the extraction of bioactive metabolite should be taken care of and advanced and proficient biotechnological strategies should be obtained to get these metabolites with highest yield. It has been appeared by an extensive variety of studies that mushrooms contain parts with exceptional properties to prevent or treat distinctive types of diseases. This review has demonstrated the importance of mushrooms as potential bio-factories for the production of natural anti-oxidant, anti-inflammatory and analgesic metabolites of highly diversified chemical structure. In addition to the high potential application of anti-inflammatory metabolites from mushrooms in forms of unpurified extract and extra pure compounds in medical applications, they can also be used in cosmeceutical products as safe and natural active ingredients without undesired side effects. Conservation and cloning of therapeutic mushrooms is needed for sustainable development. Dedicated research should be undertaken to isolate, purify and structural investigation of novel anti-oxidant, anti-inflammatory, analgesic and nutraceutical compounds. Studies to date have identified a number of compounds and elucidated underlying mechanism. However, research is needed to elucidate the different roles of multiple active compounds and the pathways involved which will give us a better opportunity to make a life where we can take drugs to ameliorate human sufferings with far less side effects.

Competing Interests

The authors declare that they have no competing interests.

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