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Bioactive Compounds from Mushrooms for Human Health Benefits

Nand lal*, School of Life Sciences and Biotechnology, C.S.J.M. University, Kanpur – 208024, INDIA
*Corresponding author: nl_pr@yahoo.co.in

Introduction

Mushrooms are a large and diversified group of macrofungi belonging to basidiomycetes and ascomycetes, having two phases of growth: the reproductive phase (fruit bodies) and the vegetative phase (mycelia). These organisms are epigeous (grow above the earth) in habit with the umbrella-shaped fruiting body, which produce spores (in lamellae, structures on the underside of the pileus). The fungal spores for these two groups are located in a special structure called basidium (for basidiomycetes) or ascus (for ascomycetes). In the fungal growth, after spore germination (or inoculation of in vitro-grown mycelia), the substrate is invaded by microscopic filaments called hyphae. The cells in a hypha are separated by a cross-wall called septum. Hyphae continually grow and branch to form a network of hyphae or mycelia (mycelial growth). Mycelial growth is generally coupled with increased enzyme production and respiration. Hyphae absorb digestive products, and penetrate the substrate to some extent. The fungal cell wall can be formed by mannoproteins, b-D-glucans, and chitin. Mushroom fungi can be saprotrophs, parasites, and mycorrhiza. Most of the cultivated mushrooms are saprotrophs. Mycorrhizal mushrooms have a symbiotic relationship with vegetation, mainly trees, for a relationship of mutual benefit. Saprotrophs are able to obtain nutrients from dead organic material, and parasites obtain their food from living animals and plants, causing harm to the host. Mushrooms have been eaten and appreciated for their exquisite flavor, economic and ecological values, and medicinal properties for many years. In general, mushrooms contain 90% water and 10% dry matter (Sánchez, 2010). Their nutritional value can be compared to those of eggs, milk, and meat (Oei, 2003). Mushrooms contain vitamins (thiamine, riboflavin, ascorbic acid, ergosterol, and niacin) as well as an abundance of essential amino acids. They also have proteins, fats, ash, glycosides, volatile oils, tocopherols, phenolic compounds, flavonoids, carotenoids, folates, organic acids, etc. The total energetic value of mushroom caps is between 250 and 350 cal/kg of fresh mushrooms (Sánchez, 2010). Mushrooms can be considered as functional food which provides health benefits in addition to nutritional value (Rathee et al., 2012). They have been collected in several countries for hundreds of years, and technological improvements have made possible their cultivation worldwide.

Bioactive Compounds from Mushrooms

Mushrooms being rich in various nutritional compounds are also potent as medicines. They are natural source of many bioactive compounds that serve as supplements for human health. A wide variety of compounds are comprised in just one food, making them versatile in providing health supplements and also as medicinal cure (Kumla *et al.*, 2020). Today a lot of natural products are being extracted from mushrooms and used to treat many human diseases. They work great as medicines or as an adjuvant for therapies (Lu *et al.*, 2020). Mushrooms from ancient era are being exploited for its therapeutic uses, in treatments because of its anti-inflammatory, anti-diabetic, anticancer properties and people today are acknowledging them as unexplored reservoir of many bioactive compounds that promotes health. In Taiwan, *Antrodia cinnamomea* is known as 'National Treasure of Taiwan' and 'Ruby in the Forest' as it is a rare parasitic fungus with anti-tumour, anti-fatigue, anti-inflammatory, anti-oxidant and hepatoprotective functions (Zhang *et al.*, 2019). Apart from being widely accepted for its culinary, mushrooms are being widely accepted for its organoleptic, medicinal and economic merits. They are a rich source of primary as well secondary metabolites. They contain ample amounts of Vitamins, Minerals, Protein content, carbohydrate and oxalic acid as primary metabolites and contain anthraquinones, benzoic acid derivatives, steroids, triterpenes, terpenoids, terpenes, as secondary metabolites. Mushrooms contains plentiful of proteins with essential amino acids, good amounts of vitamins like B1, B2, B12, C, D and E, significant amount of fibres and interestingly are low with fat content. Over 30 species of mushrooms are found to have anti-cancer properties and over 100 mushrooms are found to have medicinal effects on human health including anti-viral, anti-bacterial, anti-inflammatory, anti-parasitic and anti-tumour activity. Polysaccharides are considered most important constituent for medicines especially α-Glucans and β-Glucans are considered best and versatile. The fruiting bodies of mushroom bear the bioactive compounds which can be glycosides, polysaccharides, proteins, minerals, alkaloids, volatile oils, terpenoids, phenols, flavonoids, carotenoids, folates, lectins, enzymes, ascorbic acid and organic acids. They can be consumed directly in the diet or as nutraceutical medicines (Kumla *et al.*, 2020). The effectiveness and the concentration of the bioactive compounds depend upon the cultivation environment, storage conditions, cooking method, type of mushrooms and age/developmental stage (Yongabi *et al.*, 2004). Different bioactive compounds found in mushrooms and their bioactivities are summarized in table 1.

Table 1: Bioactive compounds in various mushrooms and their bioactivity.

Scientific Name	Bioactive Compound	Bioactivity	Reference
Agaricus bisporus	Pyrogallol, Hydroxybenzoic acid, Flavonoids	Anti-inflammatory, Hepatoprotective, anti-tumour by inducing apoptosis, immune stimulatory by inhibiting expression of IL-1 and COX-2	Sanchez, 2017; Ma et al. 2018
Agaricus macrosporus	Agaricoglycerides	Anti-inflammatory	Sanchez, 2017
Agrocybe cylindracea	β-glucans, Agrocybin	Anti-oxidant, Hypoglycaemic, Anti-fungal	Sanchez, 2017
Antrodia camphorata	Glycoprotein ACA, Diterpenes	Immunomodulatory, Neuroprotective	Sanchez, 2017
Auricularia auricula	Glucan	Hyperglycaemic, Immunomodulatory, Anti-tumour, Anti-inflammatory	Sanchez, 2017
Boleus edulis	Polysaccharides	Anti-inflammatory	Sanchez, 2017
Boletus spp.	2,4,6-trimethylacetophenone, imine, glutamyl tryptophan, azatadine, lithocholic acid glycine conjugate	Anti-oxidant	Sanchez, 2017
Cantharellus cibarius	Pyrogallol, Flavonoids, Polysaccharides, Caffeic acid, Catechin	Anti-microbial, Anti-oxidant	Sanchez, 2017
Calvatia gigantea	Calvacin	Anti-oxidant	Sanchez, 2017
Clitocybe maxima	Laccase	Anti-tumour	Sanchez, 2017
Coprinus comatus	β-1,3-glucan, Protein fractions and polysaccharides fractions	Immunomodulatory	Sanchez, 2017
Cordyceps sinensis	Cordycepin, Ciclosporin, Cordymin	Anti-oxidant, Immunosuppressive, Anti-inflammatory	Sanchez, 2017
Craterellus cornucopioides	Myricetin	Anti-oxidant	Sanchez, 2017
Daldinia concentrica	1-(3,4,5-trimethoxyphenyl) ethanol, caruilignan C	Neuroprotective	Sanchez, 2017
Dictyophora indusiata	Dictyophorine A and B, Dictyoquinazol A, B and C	Anti-neurodegenerative	Sanchez, 2017
Flammulina velutipes	Peptidoglycan, Polysaccharides, Flammulin	Anti-inflammatory, anti-viral, anti-inflammatory, anti-tumour, neuroprotective, anti-asthmatic	Sanchez, 2017; Ma et al., 2018

	(protein), Fungal Immunomodulatory Proteins		
Fomitopsis pinicola	Polysaccharides	Anti-inflammatory	Sanchez, 2017
Ganoderma lucidum	Ganoderic acids, ganoderiol, ganodermanontriol, Ganoderan A and B, Ganopoly, Lucidenic acid, Lanostane type triterpene acids, Ling zhi-8, Ganodermin, Se-containing proteins	Anti-tumour, anti-metastatic, anti-HIV, anti-viral, anti-inflammatory, Hepatoprotective, Immunomodulatory, Anti-fungal, Anti-neurodegenerative	Sanchez, 2017, Lindoquest et al., 2005
Ganoderma microsporum	Protein GMI	Immunomodulatory	Sanchez, 2017
Grifola frondosa	Grifolan, Polyglycan, Heteroglycan, Galactomannan, Glucoxylan, Mannogalactofucan, Fucomannogalactan, Agaricoglycerides	Immunomodulatory, Anti-tumour, Anti-viral, Hepatoprotective	Sanchez, 2017
Hericium erinaceus	Hericenons C, D, E, F, G, H, Erinacines, Resorcinols, steroids, Triterpenes, Diterpenes, Lectins, Heteroglycan peptide, Dilinoleoylphosphatidylethanolamine	Anti-oxidant, Anti-biotic, Anti-carcinogenic, Anti-diabetic, Anti-diabetic, Anti-fatigue, Hyperglycaemia, Immunomodulatory, nephroprotective, neuroprotective	Sanchez, 2017
Hypsizygus marmoreus	Ergosterol, Mannitol, Trehalose, Methionine, Marmorin, Flavonoids, Phenolic compounds, ribosome inactivating proteins	Anti-oxidant, anti-inflammatory, anti-allergic, anti-tumour, Anti-bacterial, anti-fungal,	Sanchez, 2017, Ma et al., 2018
Inonotus obliquus	β-D-glucans, Mannogalactoglucans, Sterols, Triterpenes	Anti-oxidant, anti-cancer, anti-inflammatory	Sanchez, 2017
Lentinus edodes	Lentinan, mannoglucan, glucan, fucomannogalactan, Lentin, Catechin, Phenolics, Flavonoids, KS-2	Immunomodulatory, anti-tumour, anti-bacterial, anti-fungal, anti-oxidant	Sanchez, 2017, Ma et al., 2018
Lenzites betulina	Betulinan A	Anti-oxidant	Sanchez, 2017
Phellinus linteus	Glucans, Acid Polysaccharides, Hispidin	Anti-tumour, Immunomodulatory, Anti-oxidant	Sanchez, 2017
Schizophyllum commune	Schizophyllan, Sonifilan, SPG	Anti-tumour	Sanchez, 2017
Tricholoma giganteum	Protein-Trichogin	Anti-fungal	Sanchez, 2017
Tricholoma giganteum	Laccase	Anti-viral, anti-tumour	Sanchez, 2017
Volvariella volvacea	Fip-vvo	Immunomodulatory	Sanchez, 2017

Pleurotus ostreatus	Lectins, Pleurans, Proteoglycans, Laccase, Pleurostrin	Anti-diabetic, Anti-neurodegenerative, Anti-tumour, Immunomodulatory, Anti-fungal, Anti-oxidant	Sanchez, 2017, Ma et al., 2018
Pleurotus eryngii	Laccase	Anti-viral, anti-tumour	Sanchez, 2017
Pleurotus pulmonarius	Polysaccharides β (1,3)-D-glucopyranosyl	Anti-inflammatory	Sanchez, 2017
Psilocybe spp.	Psilocybin	Anti-depressant	Sanchez, 2017
Termitomyces albuminosus	Termitomycesphins, Termitomycamides	Anti-neurodegenerative	Sanchez, 2017
Trametes versicolor	Krestin, Coriolan	Anti-metastatic, Anti-diabetic	Sanchez, 2017

Proteins

Protein content in mushrooms is high but varies from species to species. In general, the protein content varies from 150-255 g/kg of dry matter which is much higher than available in any other protein sources. Amino acids like isoleucine, leucine, glutamine, valine, glutamic acid and aspartic acid are found in profuse amount. Apart from nutritional supplement, the protein content found in mushrooms is medicinally valuable too. Mushroom proteins and peptides are models to the nutraceutical as well as pharmaceuticals from benefiting the digestion and better absorption of food to help immune system fight against pathogen. Pharmaceutical prospects include fungal immunomodulatory proteins (FIPs), ribosome-inactivating proteins (RIPs), lectins, ribonucleases, laccases (Valverde *et al.*, 2015; Sanchez 2017, Ma *et al.*, 2018).

Lectins are glycoproteins that bind to cell surface carbohydrates and exhibit properties like immunomodulator, anti-tumour, anti-viral, anti-bacterial and anti-fungal. Lectins are nonimmune proteins and have been discovered in recent studies (Valverde *et al.*, 2015; Sanchez, 2017; Ma *et al.*, 2018). Xylose specific lectin isolated from *Xyleria hypoxylon* has compelling anti-tumor and anti-mitogenic properties (Sanchez, 2017). They show polypeptide conjugated to specific carbohydrates and stimulates nitrites production, increases the production of tumour necrosis factor (TNF)-α and interleukins. They activate lymphocytes and increase the production of macrophage activating factor (Zhao *et al.*, 2020).

Fungal immunomodulatory proteins (FIPs) are bioactive proteins that have shown potent effects against tumour as adjuvants in tumour immunotherapy. FIPs contain high contents of valine and aspargine but low histidine, cysteine, methionine and have functions similar to hemaglutinin and immunoglobulins. More 30 FIPs have been isolated and identified which have ~13kDa molecular weight (Dudekula *et al.*, 2020). FIPs inhibit the invasion and metastasis of the tumour (Ma *et al.*, 2018). Ling zhi-8 (LZ-8) isolated from *G. lucidum* shows immunomodulatory effects (Kino *et al.*, 1989). Many FIPs induce apoptosis, cause cell growth inhibition and induce autophagy (Dudekula et al. 2020). Fip-fve isolated from *F. velutipes* has been used for tumour immunotherapy (Ding *et al.*, 2009).

Ribosome inhibiting proteins (RIPs) removes adenosine residues from rRNA thereby inactivating ribosomes. RIPs can inhibit the HIV-1 reverse transcriptase activity (Ma et al. 2018). Marmorin extracted from *Hypisizigus marmoreus* is a 9 kDa RIP that exhibits anti-tumour activity (Wong *et al.*, 2008).

Laccases are phenol oxidases that show anti-viral and anti-tumour effects. *Pleurotus ostreatus* shows anti-viral activities as well as uses laccases to degrade lignocellulosic materials (Sanchez, 2017). Laccases belong to the blue multicopper oxidase family and function by oxidizing one electron of phenolic compound and producing water as a by-product by the reduction of oxygen. Phenoxy-free radicals are produced by the oxidation of both phenolic compounds like methylated phenol, aromatic amine and non-phenolic compounds like veratryl alcohol of lignin using laccases. This helps in lignin degradation and conversions. White rot fungi of basidiomycetes like *Pycnoporous cinnabarinus, Phlebia radiate, P. ostreatus and T. versicolor* are the major Laccase producers (Kumla *et al.*, 2020).

Vitamins

Mushroms are a great source of vitamins especially riboflavins (vitamin B12), niacin, folates and traces of vitamin C, B1, B12, D and E can be found in edible mushrooms. Edible mushrooms are the only food source of vitamin D for the vegetarian people. Vitamin D2 can be produced in cultivated mushrooms by growing them under darkness and exposing them to UV-B light (Cardwell *et al.*, 2018).

Lipids/Fatty acids

Studies show that fatty acids are low in mushrooms but contains all the important lipid fatty acids at the same time which helps to reduce serum cholesterol. Sterols and linoleic acid rich diet helps prevent cardio-vascular diseases. Also, linoleic acid regulates triglyceride levels and blood pressure.Tocopherols acts as anti-oxidants and are free-radical peroxyl scavangers; prevents cancer and cadiovascular diseases (Sanchez, 2017).

Polysaccharides

Many *in vivo* and *in vitro* studies have reported the presence of cell wall polysaccharide and polysaccharide-protein complexes like Lentinan from *Lentinus edodes*, β-glucan fraction D from *Grifola frondosa*, Krestin (PSK) polysaccharide peptides from *Trametes versicolor*, Schizophyllan from *Schizophyllum commune*, Pleuran from *Pleurotus* species, Calocyban from *Calocybe indica* and Ganoderan from *Ganoderma lucidium*. Over hundreds of mushrooms have been examined and reported to contain rich amounts of carbohydrates that are immunomodulating, anti-tumour, and anti-oxidants (Gupta *et al.*, 2018; Ma *et al.*, 2018). Carbohydrates like Xylose, Mannose, Rhamnose, Fucose, Fructose, Glucose, Galactose, Mannitol, Sucrose, Trehalose and Maltose have been quantified from various mushrooms with their quantity varying from species to species. These polysaccharides pose strong anti-tumour effects, elicits the activation of dendritic cells, monocytes, neutrophils, NK cells, cytotoxic macrophages and cytokines. These are acidic or neutral in nature and vary in chemical structures (Ma *et al.*, 2018). Glucans extending from homopolymers to complex heteropolymers are main and important polysaccharides found in mushrooms.and inflict anti-tumour activities (Valverde *et al.*, 2015).

Glucans constitutes majorly to the fungal cell wall mass, bind to the membrane receptors elucidating biological responses. They are recognized as non-self-molecules by the human immune system and induce both innate and adaptive immune responses and therefore are potent immunological stimulators (Valverde *et al.*, 2015). β-glucans have many surface receptors like dectin-1 as its main receptor, complement-3 (CR3) and toll-like receptor-2/6 which elicits immune response against microbial attack in the human body and hence elevates health (Sanchez, 2017).

β-glucans work by elevating the response of macrophages in the body. Upon the invasion of any foreign pathogen, monocytes as macrophages are released from the blood stream and they reach to the site of pathogenesis i.e., the target site. β-glucans binds to the monocytes, activate and convert them into mature macrophages. This results in elevated response against pathogen i.e. phagocytosis and also results in the activation of cytokines (Interleukins, interferons, lymphokines) (Sanchez, 2017).

Ganopoly, a preparation of *Ganoderma lucidum* made with polysaccharide is found to have hepatoprotective effects against chronic hepatitis B; also possesses properties like immunomodulation, enhanced antibody production and lymphocytic proliferation. Antioxidative, free-scavenging effects along with anti-tumour and anti-genotoxic properties of *G. lucidum* have also been reported. *P. ostreatus* shows anti-tumourigenic effects against tumour cells directly by cytotoxic activity or indirectly by immunomodulatory effects. Monosaccharides found in *Flammulina velutipes* i.e., glucose, mannose, xylose shows anti-inflammatory activities; *Auricularia auricula*, *Boletus edulis*, *Cantharellus tubaeformis*, *Fomitopsis pinicola*, and *Geastrum decastes* too are found to show anti-inflammatory properties (Sanchez, 2017).

Phenolic Compounds

Phenolic compounds, aromatic hydroxylated compounds with one or more aromatic rings and one or more hydroxyl groups, are the plant secondary metabolites showing properties like anti-oxidant activity, free radical scavenging, peroxide decomposition and metal inhibitors. These mainly include flavonoids, phenolic acids, tannins, ligands, stilbenes, hydroxybenzoic acid and hydroxycinnamic acids (Ma *et al.*, 2018). They work as anti-oxidants by reacting with free radicals; protects against brain dysfunction, aging and cardiovascular diseases. The phenolic contents in *A. bisporus, Boletus edulis, Calocybe gambosa, Cantherellus cibarius, Craterellus cornucopioides, P. ostreatus, Hygrophorous marzuolus*, *Lactarius deliciosus* are found to inhibit lipid oxidation (Palacio *et al.*, 2011). Phenolic content of *F. velutipes* shows neuroprotective effects alongside anti-oxidation. Mushrooms are found to potentially decrease the oxidative stress in the neural system thereby reducing the neurodegenerative diseases. Hispidin which is a polyphenol, extracted from *Phellinus* spp. is found to be a good ROS scavenger (Sanchez, 2017).

Terpenes

Terpenes are volatile unsaturated hydrocarbons and non-volatile metabolites that constitute the largest anti-inflammatory group. They are classified into volatile mono and sesquiterpene oils, less volatile diterpenes, involatile tri-terpenoids and sterols and the carotenoid pigments (Ma *et al.*, 2018). Terpenes exhibit activities like anti-oxidant, anti-viral, anti-cancer, anti-inflammatory, anti-malarial and anti-cholinesterase (Ma *et al.*, 2018). Despite the fact that all terpenes exhibit anti-inflammatory properties, some terpenes like ganoderic acid C and derivatives found in *G. lucidum* are capable of inhibiting cholesterol biosynthesis while some others provide protection from atherosclerosis. Triterpenes isolated from *Antrodia camphorate* exhibits neuroprotective activity while neosarcodonin and cyathariol diterpenes extracted from *Cyathus africans* are potent anti-inflammatory metabolites (Sanchez, 2017).

The mushrooms have paved its way into the medical world because of its potent medicinal values. The bioactive compounds found in mushrooms can be exploited in medical treatments and therapies to combat various diseases. A variety of mushrooms' bioactive compounds are beneficial for the target treatment of cancer. Also, the effectiveness and the efficacy of mushrooms' bioactive components have been suggested by performing preclinical and clinical trials. Apart from cancer, many other problems could be looked upon to and with expanding understanding of mushrooms, a lot of diseases could be cured. It is in similar manner as of in ancient times, only the preparations have been replaced by therapies, treatments and medicines.

Weight Management

Mushrooms are high in vitamins, nutrients, protein, carbohydrates but amazingly has very low amounts of fat. This makes mushrooms an ideal food for daily consumption. It has been suggested for reducing obesity risk total calorie intake be cut down which can be done by substituting low calorie foods with high calorie foods. Not all foods that contains high calorie are bad as they contain plethora of beneficial nutrients which makes them rich in calories (Feeney *et al.*, 2014). Mushrooms contain polysaturated lipids with sparse fat content, high quality protein, vitamins, fibres which are congruous to weight loss.

Mushrooms are found to increase the rate of cholesterol metabolism by decreasing the VLDL levels and also by reducing the HMG-CoA reductase catalytic activity in the body. They are also effective in decreasing the plasma glucose level and triglycerides. Eating mushrooms can work as anti-obesity prebiotics as the variation of 3T3-L1 adipocytes is prevented by the decreased expression of mRNA by polysaccharide derived from the *Tremella fuciformis.* Studies suggest the reduction of adipogenic transcription factors activating transportation, storage of glucose and lipids by treatment with *G. lucidum* which also activate the AMPK signalling pathway which suggests the anti-obesity properties of mushrooms (Ganeshan and Xu, 2018).

Cognition

Mild cognitive diseases and impairments can be cured with the help of mushrooms. Many clinical experiments suggest that -amyloid peptide toxicity can be prevented by the bioactive component present in the mushroom i.e., ergocalciferol. Diseases like Dementia and Alzheimer can be prevented with the use of mushrooms (Feeney *et al.*, 2014).

A six-year study (2011-2017) conducted by the Department of Psychological Medicine, National University of Singapore (NUS) along with the Department of Life Sciences and the Mind Centre at the NUS and the Singapore Ministry of Health's National Medical Research Council (2019), has found an intriguing and encouraging correlation between the consumption of mushrooms and decline in cognitive diseases. Even the slighter amounts of consumption resulted in delayed rate but promising decline in the mild cognitive impairment. Researchers believe this decline due to a bioactive compound i.e., the ergothioneine which possesses properties like anti-oxidation and anti-inflammation and naturally ergothioneine is not produced in the body rather have to be consumed from outside in diet (Feng *et al.*, 2019).

Oral Health

The changing dietary patterns and busy life style are pushing people more towards consuming stored food or the canned food products. This in turn is disturbing not only the metabolic health but also the oral health. Problems of mouth are rising and so is the demand for the dentist. This is resulting in the shooting prices of dental clinics and not every day can a person visit a dentist and get oral treatments. Therefore, keeping a check on overall diet is one option. Foods that promote oral health are coffee, mushrooms, green tea, cranberries, garlic extract, nutmegs, red grape seeds, coffee, cocoa extracts and propolis (Avinash *et al.*, 2016).

Dental caries is one such problem that is elevating in population and known to soften the hard tissues of teeth thereby forming cavity. *Lentinus edodes* also known as shiitake mushroom is found to contain many bioactive compounds other than lentinan like Erythritol, Adenosine, Copalic acid and Carvacrol. Hence, shiitake possesses properties like anti-microbial, anti-caries and anti-carcinogenic activity. Sesquiterpenes, steroids, anthraquinone, benzoic acid derivatives and quinolones can be found in the low molecular mass fraction of shiitake mushroom (Avinash *et al.*, 2016).

Oral biofilm is caused by glucans deposition on the teeth surface by *Streptococcus mutans* and *S. sobrinus* by cell-cell interactions; adheres to the enamel of the tooth and creates a biofilm. Biofilm formation can be prevented using shiitake mushroom in presence of dextranase. Dextranase is used to reduce dental plaque and improves oral health. Adenosine causes the detachment of micro-organisms from the teeth resulting in the destruction of biofilms. The sesquiterpenes, benzoic acid derivatives and quinolones inhibits the growth of *S. mutans* by inhibiting the DNA synthesis machinery (Avinash *et al.*, 2016).

Cancer

According to the National Cancer Institute (NIH), the Asian countries have been using mushrooms since ages to treat various diseases and infections and today, they are being used to treat various diseases like pulmonary diseases and cancer as medicinal mushrooms have been proven supplements for cancer. China and Japan have been using these adjuncts from as long as 30 years. No side-effect has been reported by either single component or when combined with radiotherapy or the chemotherapy [National Cancer Institute, NIH].

Cancer is a defect of cells to act abnormal by proliferating at an uncontrolled rate by altering many molecular pathways and hence considered as a complex group of diseases. It alters pathways and therapeutic targets like p53, nuclear factor-kappa □ (NF- k□), Akt, Wnt, Mitogen activated protein kinase pathway (MAPK), Notch etc. (Jakopovic *et al.*, 2020). Both *in vivo* and *in vitro* experiments prove the therapeutic benefits of mushrooms and demonstrate the immunomodulatory function against tumours and other diseases. The bioactive compounds evoke the apoptosis process and block the angiogenesis by the elevated production of cytokines, which are triggered by the release of lymphocytes, NK cells and macrophages. Bioactive compounds responsible for this cytotoxicity are lectins, Schizophyllan, Polysaccharide K, Polysaccharide P, Active-hexose correlated compounds (AHCC) and Mitake D fractions which can be procured from *G. lucidum, G. tsugae, S. commune, Sparassia crispa, P. tuberregium, L. edodes, G. frondosa* and

F. ventipules and can be used against breast, lung, prostate, colorectal and lung cancer etc. (Ayeka, 2018).

Mechanism of Action

A therapeutic drug including the medicinal mushrooms works is by interaction with the gut microbiota and immune system. The food that cannot be digested in stomach and intestine is digested in the gut by microbiome there. It therefore acts as first barrier against pathogens and elicits immune responses. The immune system then functions by initiating the innate and adaptive immunity (Jayachandran *et al.*, 2017). Various bioactive molecules of mushrooms and their targets/mechanism of action are listed in table 2.

Table 2: Mechanism of action of bioactive components of different mushrooms.

Scientific Name	Bioactive molecule	Target/ Mechanism of action	Cancer/ Gut microbiota	Reference
Agaricus bisporus	Lectin, Polysaccharide, Pyrogallol	Induces apoptosis, inhibit angiogenesis, stimulate TNF-α	Breast, colorectal cancer	Ayeka, 2018
	Polysaccharides	Increases antimicrobial activity	Gut microbiota	Jayachandran et al., 2017
Agaricus blazei	Heteroglycan, Glycoprotein, β-D-glucan	Stimulates NK cells, macrophages, dendritic cells and granulocytes, Induces TNF, IL-8, Interferons, suppress tumour growth and inhibits angiogenesis	Leukemia, haematological, stomach and lung	Ayeka, 2018, Zhao et al., 2020
Ganoderma lucidum	Ganoderan, Heteroglycan, mannoglucan, glycopeptide	Stimulates TNF-α, IL-1, IFN-γ production, activate NK-kB	Breast, cervical, colorectal, prostate, liver, lung cancer	Ayeka, 2018, Zhao et al., 2020
	Ganopoly, Ganoderan	Reduces endotoxin-bearing Proteobacteria levels, maintains intestinal barrier integrity and reduces metabolic endotoxemia	Gut microbiota	Jayachandran et al., 2017
Trametes versicolor	Polysaccharide-peptide Krestin (PSK)	Increases the expression of cytokines, stimulates the macrophage phagocytosis	Breast, Colorectal and Skin	Ayeka, 2018, Zhao et al., 2020
	Krestin, PSK	Prevents diarrhoea in host, clostridium infection and inflammatory bowel infection	Gut microbiota	Jayachandran et al., 2017
Lentinus edodes	Lentinan	Increases secretion of IL-1, IL-2, IL-6, IL-8, TNF-□, inhibits proliferation of cancer cells and DNA synthesis	Cervical, ovarian, gastric and skin cancer	Ayeka, 2018
	KS-2, Lentinan	rejuvenates immune responses	Gut microbiota	Jayachandran et al., 2017
Grifola frondosa	Grifolan, Mitake D fraction	Inhibits proliferation of HeLa, activates macrophages, increases production of IL-1, IL-6 and IL-8	Breast and bladder cancer	Ayeka, 2018
Flammulina velutipes	Flammulin	Stimulate mice splenocytes mitogenicity and inhibits the proliferation of L1210 cells	Skin cancer	Ayeka, 2018, Zhao et al., 2020
Pleurotus tuberregium	Pleuran	Stimulates maturation and proliferation of T-cells, NK cells, macrophages	Liver cancer	Ayeka, 2018

	Polysaccharides	anti-hyperglycaemic; attenuated oxidative stress in high fat diet diabetic rat	Gut microbiota	Jayachandran et al., 2017
Schizophyllum commune	Schizophyllum commune lectin	Stimulates mitogenicity of mice splenocytes, inhibits the proliferation of kB, HepG2 and S180	Cervical cancer	Ayeka, 2018, Zhao et al., 2020
	Schizophyllan, Sonifilan, SPG	Immune modulator	Gut microbiota	Jayachandran et al., 2017
Hericium erinaceus	*Hericium erinaceus* agglutinin (HEA)	Inhibits proliferation of HepG2 and breast cancer MCF7 cells	Breast, Liver cancer	Zhao et al., 2020
	Galactoxyloglucan protein complex	Changes gastrointestinal tract microbiota thereby promoting health	Gut microbiota	Jayachandran et al., 2017

Gut microbiota

The gut of humans is home to plethora of micro-organisms, mainly from two major phyla- Bacteroidetes and Firmicutes. They digest food that are not digested in the stomach or the intestine and hence plays an important role in the immune system. It acts as a barrier and does protection of the gut from harmful substances. The gut microbiome mainly digests carbohydrates derived from diet and they flourish (Jayachandran *et al.*, 2017). Study reveals the regulation of gut microbiota is through prebiotics in non-alcoholic fatty liver diseases (NAFLD) (Clarke *et al.*, 2012). The gut microbiota results in the activation of immune system upon the foreign substance invasion. Co-evolution suggests that evolution of bacteria and its host is relative to host-immune system in a way that host bacteria interaction surveillance is done by host-immune system (Jayachandran *et al.*, 2017).

Prebiotics help flourish micro-organisms like bacteria and fungi and promotes their action for the overall health of the host. Prebiotic food sources include: raw chicory root, raw Jerusalem artichoke, raw dandelion greens, raw garlic and raw onion. Mushroom too makes up good prebiotics' food source especially the mushroom polysaccharides like chitin mannans, hemi-cellulose, α- and β-glucans, galactans etc. (Hutkins *et al.*, 2016). The white button mushrooms are found to generate inflammatory responses locally, catecholamine production and the gut flora composition for the improvement and protection of GI from any infection or injury and elicit innate and adaptive immunity. *G. lucidum* reverses gut-dysbiosis and proteobacteria levels that contain endotoxins. *L. edodes* derived polysaccharide is found to change the microbiome of gut in mice and promotes healthy colon and caecum (Jayachandran *et al.*, 2017).

Immune Function

Any substance, that fights against any disease, acts by initiating the responses by immune system which regulates by activating innate and adaptive immunity. Mushroom bioactive compounds are no different and they initiate the innate and adaptive immunity (Fig. 1). The invasion of foreign substances leads to activation of monocytes and granulocytes. The innate immunity is regulated by secreted lipid messengers such as prostaglandins and the cytokines which are cell synthesized molecules and triggers the adaptive immunity. Macrophages are secreted and mediated towards the target site for phagocytosis. Also, abnormal cells such as cancer cells are recognized by the NK cells and impel cancer cells towards apoptosis (Zhao *et al.*, 2020). The tumour growth can be stopped at many levels like tumour specific pro-proliferation cell signalling, regulation of apoptosis, cancer-specific metabolism, angiogenesis, metastasis, and finally by immune modulation and hence cancer fungi-therapy is gaining recognition in the scientific field (Blagodatski *et al.*, 2018). Some promising mushrooms species having anticancer properties are mentioned hereunder.

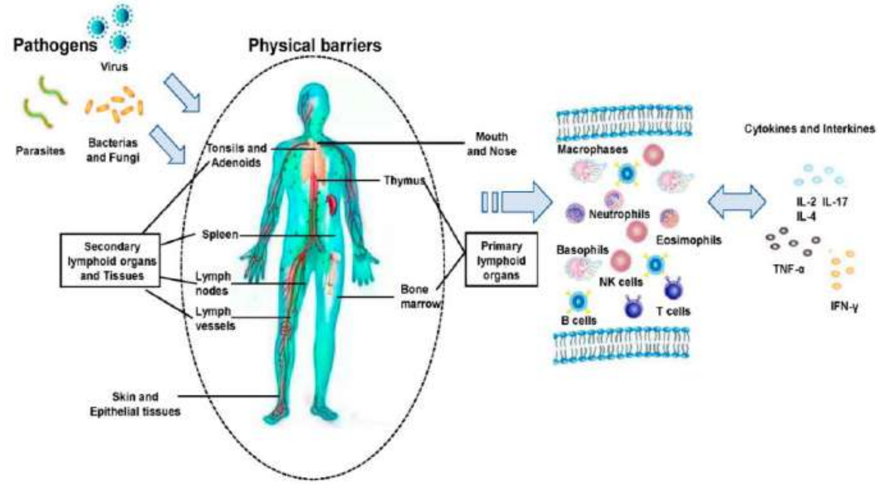

Fig. 1 - A representation of immune system activation and secretion of different cells involved in neutralization of a pathogen/ killing of an abnormal cell.

Conclusions and Future Perspectives

It evident from literature that mushrooms contain a plethora of novel compounds and can be edible and as well as medicinal serving humans with significant health benefits. Their medicinal value has long been recognized by ancestors and cited in folk literatures. They were topically applied, orally consumed and concoctions were made out of them to fight against various diseases. There are several mushrooms for each and every type of health-related problems ranging from skin diseases to cancer. A large part of the world is engaged in mushroom farming and new sets of tools and techniques are developed over years. Consumption and demand for mushrooms is very high across the world with China being the largest producer. India is flourishing in terms of business across the world as it is one of the major contributors but still consumption of mushrooms in India itself is low. Mushroom farming requires very low inputs as compared to yield/return, and hence it is being opted as an employment source.

Economically weaker nations can opt mushrooms in their diets as supplements to compensate for the nutrients they remain deficit of. The nutrients and bioactive molecules in mushrooms are beneficial against various diseases like cardiovascular diseases, cancer, hormonal imbalances, obesity, overall metabolism. These molecules impart their action through gut microbiota and immune system. The immune system combats infections or injury by releasing many immune cells like macrophages, NK cells, Cytokines. thrugh a signalling cascade. Clinical trials done till today confirm the application of mushrooms and their bioactive extracts in medicines.

A lot has been studied and experimented, still there are many gaps in the development effective drugs. The structure and mechanism of action of many bioactive compounds still needs to be identified and pharmacokinetics and pharmacodynamics of bioactive compounds needs to be studied. On the other side, metabolic pathways and genes involved therein and their mechanism of regulation needs attention to harness the benefits of mushrooms.

References

Avinash, J., Vinay, S., Jha, K., Das, D. et al. The Unexplored Anticaries Potential of Shiitake Mushroom. *Pharmacognosy Review*, 2016; 10, 100-104.

Ayeka, P.A. Potential of Mushroom Compounds as Immunomodulators in Cancer Therapy: A Review. *Evidence-Based Complementary and Alternative Medicine*, 2018, Article ID 7271509.

Blagodatski, A., Yatsunskaya, M., Mikhailova, V., Tiasto, V. et al. Medical Mushrooms as an attractive new source of natural compounds for future cancer therapy. *Oncotarget*, 2018; 9, 29259-29274.

Cardwell, G., Bornman, J.F., James, A.P., Black, L.J. A Review of Mushrooms as Potential Source of Dietary Vitamin D. *Nutrients*, 2018; 10, 1-11.

Clarke, S.F., Murphy, E.F., Neelaweera, K., Ross, P.R. et al. The gut microbiota and its relationship to diet and obesity: new insights. *Gut Microbes*, 2012; 3, 186-202.

Ding, Y., Seow, S.V., Huang, C.H., Liew, L.M. et al. Coadministration of the fungal immunomodulatory protein FIP-Fve and a tumour-associated antigen enhanced antitumour activity. *Immunology*, 2009; 128, 881-894.

Dudekula, U.T., Doriya, K., Devarai, S.K. A critical review on submerged production of mushroom and their bioactive metabolites. *3 Biotech*, 2020; 10, 1-12.

Feeney, M.J., Dwyer, J., Hasler-Lewis, C., Milner, J.A. et al. Mushrooms and Health Summit Proceedings. *Journal of Nutrition*, 2014; 144, 1128S-1136S.

Feng, L., Cheah, I.K.M., Ng, M.M.X., Li, J. et al. The Association between mushroom Consumption and Mild Cognitive Impairment: A Community-Based Cross-Sectional Study in Singapore. *Journal of Alzheimer Disease*, 2019; 68, 197-203.

Gupta, S., Summuna, B., Gupta, M., Annepu, S.K. Edible Mushrooms: Cultivation, Bioactive Molecules, and Health Benefits. *In: Merillon JM., Ramawat K. (eds), Bioactive Molecules in Food.* 2018; 1-33, Berlin: Springer.

Hutkins, R.W., Krumbeck, J.A., Bindels, L.B., Cani, P.D. et al. Prebiotics: why definitions matter. *Current Opinion in Biotechnology*, 2016; 37, 1-7.

Jakopovic, B., Horvatić, A., Klobučar, M., Gelemanović, A. et al. Treatment with Medicinal Mushroom Extract Mixture Inhibits Translation and Reprograms Metabolism in Advanced Colorectal Cancer Animal Model as Evidenced by Tandem Mass Tags Proteomics Analysis. *Front. Pharmacology*, 2020; 11, 1202.

Jayachandran, M., Xiao, J., Xu, B. A Critical Review on Health Promoting Benefits of Edible Mushrooms through Gut Microbiota. *International Journal of Molecular Sciences*, 2017; 18, 1-12.

Ke, Y., Chen, Y., Duan, J., Shao, Y. *Ganoderma lucidum* polysaccharides improve cerebral infarctions by regulating AMPK/eNOS signalling. *International Journal of Clinical and Experimental Medicine*, 2017; 10, 15286-15293.

Kino, K., Yamashita, A., Yamaoka, K., Watanabe, J. et al. Isolation and characterization of a new immunomodulatory protein, ling zhi-8 (LZ-8), from *Ganoderma lucidium*. *The Journal of Biological Chemistry*, 1989; 264, 472–478.

Kumla, J., Suwannarach, N/., Sujarit, K., Penkhrue, W. et al. Cultivation of Mushrooms and Their Lignocellulolytic Enzyme Production through the Utilization of Agro-Industrial Waste. *Molecules*, 2020; 25, 2811.

Lu, H., Lou, H., Hu, J., Liu, Z. et al. Macrofungi: A review of cultivation stratergies, bioactivity, and application of mushrooms. *Comprehensive Reviews in Food Science and Security*, 2020; 19, 2333-2356.

Lindequist, U., Niedermeyer, T., Julich, W. The Pharmacological Potential of Mushrooms. *Evidence-Based Complementary and Alternative Medicine*, 2005; 2, 286-299.

Ma, G., Yang, W., Zhao, L., Pei, F. et al. A critical review on the health promoting effects of mushrooms nutraceuticals. *Food Science and Human Wellness*, 2018; 7, 125-133.

Oei, P. Manual on mushroom cultivation: techniques species and opportunities for commercial application in developing countries. 2003; TOOL Publications, Amsterdam.

Palacio, I., Lozano, M., Moro, C., D'Arrigo. Antioxidant properties of phenolic compounds occurring in edible mushrooms. *Food Chemistry*, 2011; 128, 674-678.

Rathee, S., Rathee, D., Rathee, D. et al. Mushrooms as therapeutic agents. *Brazilian Journal of Pharmacognosy*, 2012; 22 (2), 459–474.

Sánchez, C. Cultivation of *Pleurotus ostreatus* and other edible mushrooms. *Applied Microbiology and Biotechnology*, 2010; 85(5), 1321–1337.

Sánchez, C. Bioactives from Mushroom and Their Application. In: Puri, M. (eds) Food Bioactives. 2017, Springer, Cham. https://doi.org/10.1007/978-3-319-51639-4_2

Valverde, M., Hernández-Pérez, T., Paredes-Lopez, O. Review Article Edible Mushrooms: Improving Human Health and Promoting Quality Life. *International Journal of Microbiology*, 2015, Article ID 376385.

Wong, J.H., Wang, H.X., Ng, T.B. Marmorin, a new ribosome inactivating protein with antiproliferative and HIV-1 reverse transcriptase inhibitory activities from the mushroom *Hypsizygus marmoreus*. *Applied Microbiology and Biotechnology*, 2008; 81, 669–674.

Yongabi, K., Agho, M., Martinez-Carrera, D. Ethnomycological studies on Wild Mushrooms in Cameroon, Central Africa. *Micologia Aplicada International*, 2004; 16, 34-36.

Zhang, B.B., Guan, Y.Y., Hu, P.F., Chen, L. et al. Production of bioactive metabolites by submerged fermentation of the medicinal mushroom *Antrodia cinnamomea*: recent advances and future development. *Critical Reviews in Biotechnology*, 2019; 39, 541-554.

Zhao, S., Gao, Q., Rong, C., Wang, S. et al. Immunomodulatory Effects of Edible and Medicinal Mushrooms and Their Bioactive Immunoregulatory Products. *Journal of Fungi*, 2020; 6, 1-37.