IJPSR (2021), Volume 12, Issue 11 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 16 October 2020; received in revised form, 23 March 2021; accepted, 25 May 2021; published 01 November 2021

MUSHROOM SECONDARY METABOLITES: CHEMISTRY AND THERAPEUTIC APPLICATIONS

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Keywords:

Mushroom, Bioactive fractions, Secondary metabolites, Therapeutic polysaccharides, Anti-cancer, Anti-oxidant

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ABSTRACT: Since ancient times, humans have always been captivated by nature and have explored natural products. To combat against novel emerging and reemerging diseases and tremendous side effects imposed by recent therapies, scientists have again taken an interest in natural resources. To date, plants have been the major source of natural bioactive compounds, but recently fungi have got more attention. Amongst fungi, edible and medicinal mushrooms have come out as a rich source of bioactive metabolites. Since long back, they are being consumed heavily because of their outstanding flavour, aroma, nutritional value, and medicinal properties. Both edible, as well as medicinal mushrooms, synthesize bioactive compounds known as secondary metabolites *i.e.*, polysaccharides, steroids, terpenes as well as peptides. Such metabolites possess many medicinal properties like anti-oxidant, anti-tumor, anti-diabetic, anti-cancer, anti-ageing, and also anti-obesity. Furthermore, mushroom secondary metabolites are prioritized over other natural compounds due to their non-toxic nature and low or no side effects. This review mainly covers sources and types of secondary mushroom metabolites and their therapeutic applications.

INTRODUCTION: For more than two centuries, fungi have been identified as a valuable and abundant group of organisms significant to humanity. The kingdom fungi at present is divided into four major phyla: Chytridomycota, Zygomycota, Ascomycota, and Basidiomycota. Ascomycotina (the flask fungi, cup fungi and their allies, including moulds and yeasts), Basidiomycotina (the rusts, smuts, fairy clubs, jelly fungi, stinkhorns, bracket fungi, bird's-nest fungi, earthstars and puffballs, toadstools and mushrooms) and their anamorphs (asexual fungi) are considered as representatives of higher fungi divisions, according to evidence of fungal origin, evolution, and phylogeny [1]. Mushrooms are a very large and diversified group of macro-fungi belonging to the class Basidiomycetes and Ascomycetes.

They are a widely distributed food resource on earth and have been consumed because of their nutritional value and medicinal properties for over 2000 years. In addition to their enjoyable flavor and taste, human health has improved by mushrooms due to their nutrients which include digestible proteins, carbohydrates, fiber, vitamins, minerals, and antioxidants [2, 3]. The medicinal properties of mushrooms may be because of the presence of various secondary metabolites. Secondary metabolites are bioactive low molecular

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.12(11).5677-89

The article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.12(11).5677-89

weight compounds, produced in response to stress but generally not required for the normal growth and reproduction of the fungi.

These compounds, including polysaccharides, lectins, lactones, terpenoids, alkaloids, antibiotics and metal-chelating agents, have been extensively reported for number of therapeutic properties such as anti-oxidant, anti-tumor, immunomodulaotry, anti-cancer, anti-microbial, anti-diabetic, neuro-protective, anti-HIV, hepatoprotective, anti-metastatic and anti-inflammatory activities [2, 4-6].

2. Secondary Metabolites of Mushrooms:

2.1. Polysaccharides: Polysaccharides are the major class of bioactive compounds found in mushrooms and have been reported in most of edible mushrooms. They are long chains of sugar units linked to each other by glycosidic bonds and/or combined with different branches.

They are categorized as homopolyasaccharides, which have uniform monosaccharide units, and hetero-polysaccharides which have more than one type of monosaccharide repeats. Cellulose is homo-poly-saccharides, while pectin is hetero-polysaccharides. Biological and pharmaceutical activities of both homo- and hetero-polysaccharides are closely correlated to their specific structural characteristics [7]. Several types of bioactive poly-saccharides are available in nature. Lentinan is β-glucan composed of β-(1→3)-D-glucose residues bonded to β-(1→6)-glucopyranoside by glycosidic linkages.

It is derived from *Lentinus* spp. An average molecular weight of this polysaccharide falls around 500 kDa [8, 9]. Ganoderan is extracted from *Ganoderma* spp., which contains β-(1→3)-D-glucans with β-(1→6)-D-glucopyranosyl branches [10]. Molecular weight was found to remain around 1.2×10^6 Da to 4.4×10^6 Da [9, 11].

Schizophyllan is produced by an edible mushroom called *Schizophyllum* spp. Just like lentinan, structurally, it also contains a β-(1→3)-glucan with β-glucopyranosyl group linked by β-(1→6) linkage. Molecular weight of schizophyllan is around 450 kDa [8]. Pleuran is a water-soluble and/or alkali-soluble polysaccharide extracted from *Pleurotus* spp. It may be either β-(1→3 / 1→6)-D-glucan or α-(1→3)-D-glucan by structure [12].

Another gel-forming β-(1→3)-D-glucan is Grifolan which is extracted from mushroom known as Grifola spp. Molecular weight falls in range of 770 kDa to 1650 kDa [13].

Krestin (polysaccharide-K or PSK) is protein-bound β-glucan which is derived from *Trametes* spp. It is β-(1→4)-glucan with lateral β-(1→6)-glucopyranoside chains, with molecular weight of around 94 kDa [14]. Another proteoglucan proced by *Trametes* spp. is PSPC or PSP (polysaccharide protein complex).

The *Polyporus* polysaccharide (PPS) extracted from mushroom *Polyporus* spp. consists of (1→3)-β-glucan backbone and (1→6)-β-glucopyranose side chain. Molecular weight remains around 1.6×105 Da [14].

Polysaccharides from *Agaricus* spp. display various structural varients such as: β-(1→6) / β-(1→3)-glucan, an acidic β-(1→6) / α-(1→4)-glucan and an acidic β-(1→6) / α-(1→3)-glucan and thus range of molecular weight is also very broad starting from 380 kDa to 10,000 kDa [13].

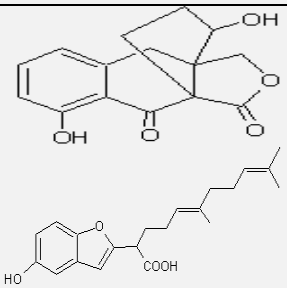
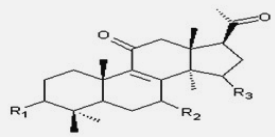
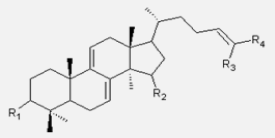
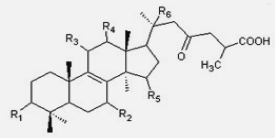
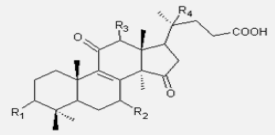
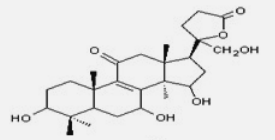
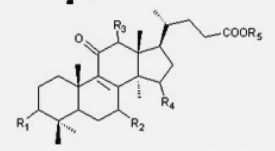
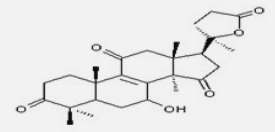
Polysaccharide from edible mushrooms *Auricularia* which are also known as jelly ears fungi was identified to have β-(1→3)-D-glucan linked with two residues of β-(1→6)-D-glucosyl for every three main chain glucose moiety.

Molecular weight was determined as 2.1×10^3 kDa [15]. *Cordyceps* extracted polysaccharides α-(1→4)-D-glucan linked with branches of α-(1→6)-D-glucan having molecular weight of about 1180 kDa [14].

Apart from this, mushrooms like *Hericium erinceus*, *Morchella esculenta*, *Flammulina velutipes*, *Inonotus obliquus*, *Phellinus rimosus*, *Astraeus hygrometricus*, *Fomes fomentarius*, *Hypsizygus marmoreusare* also good sources of polysaccharide that have been studied [13, 14].

All these polysaccharides represent therapeutic properties like anti-tumor, immunomodulaotry, anti-microbial, anti-cancer, anti-oxidant, hepato-protective, hypoglycemic, neuroprotective, anti-viral, and anti-inflammatory activities which is advantageous to the human beings.

TABLE 1: SECONDARY METABOLITES OF *GANODERMA LUCIDUM* (ADAPTED FROM 22, 31)

S. no.	Secondary Metabolites	Examples	Chemical Structures
1	Others	Meroterpenoids (Lingzhiol); Benzofurans (Ganofuran B)	
2	C24, C25 lanostanes	Lucidone A, B, C	
3	C30 lanostanes	Aldehydes, alcohols, esters, glycosides, lactones, and ketones Ganoderal A; Lucidal; Lucialdehyde A; Lucidadiol; Lucidumol B; etc.	
		Ganoderic acid Ganoderic acid A-Z, AM1, B8, C6, Df, Me, Mf, Sz, TR1, DM, LM2, α, β, γ, δ, etc.	
4	C27 lanostanes	Lucidenic acid Lucidenic acid A, B, C, D1, D2, E1, E2, F, N, P; 20 Hydroxy lucidenic acid D2,E2,F,N;	
		Alcohols, lactones and esters Lucidenic lactone; Lucidenolactone; Methyl lucidenate A, C, F, N, P, Q, D1; Ethyl lucidenate A; Butyl lucidenate A, N, P, Q, D2, E2; Methyl 20(21)-dehydrolucidenate A	
			
			

2.2 Terpenes: Terpenes are the largest group of anti-inflammatory compounds in mushrooms. They are biologically active compounds that contribute to a vast array of medicinal and health benefits. They are a class of naturally occurring compounds where carbon skeleton are mainly composed of one or more isoprene C5 units. Terpenes are non-polar metabolites comprising of different groups like monoterpenes, diterpenes, triterpenes, and sesquiterpenes. Terpenoids from mushrooms possess numerous bioactive properties like anti-microbial, anti-viral, anti-malarial, anti-fungal, anti-cancer, anti-tumor and anti-oxidant activities [16, 17].

Terpenes can be categorized as: sesquiterpenes, diterpenes, triterpenes, and meroterpenes. Mono-terpenes generally consist of two isoprene units having molecular formula $C_{10}H_{16}$. They may be acyclic or possess cyclic rings. Monoterpenes which are having oxygen functionality or missing a methyl group are known as monoterpenoids. The most common example is menthol which is used as a flavour. Linalool is one of the monoterpene derivatives having anti-bacterial activity [18]. Sesquiterpenes are usually composed of three isoprene units, and their general molecular formula is $C_{15}H_{24}$. They are generally produced by the plant and some fungi. The most common example of

sesquiterpenes is geosmin which is produced by actinomycetes [18]. Several fungal sesquiterpenic molecules show effect against *Leishmania major*, *L. infantum*, *L. donovani*, *Trypanosoma brucei*, *T. cruzi*, *T. gondii*, *Neospora caninum*, *Eimeria tenella* and *Acanthamoeba castellanii*, and some other parasites [17]. *Lentinus* species can yield variety sesquiterpenes. The sesquiterpenes hypnophilin and panepoxydone were isolated from the ethyl acetate extracts of mushroom *Lentinus strigosus* [17, 19]. Some sesquiterpenes like panepoxydone, panepoxydione, and dihydrohypnophilin were isolated from the ethyl acetate extracts of fungus *Lentinus conatus*. Another mushroom *Phallus indusiatus* is also known to produce two novel sesquiterpenes. Diterpenes are a class of terpenes consisting four isoprene rings with molecular formula $C_{20}H_{32}$. They are also produced by some fungi, plant and animals.

Functionalized diterpenes are also called diterpenoids. Retinol and phytol are bioactive diterepenoids which are having anti-inflammatory and anti-bacterial activities [18]. Triterpenes are a class of terpenes that are composed of three terpene units *i.e.,* six isoprene units. Their common molecular formula is $C_{30}H_{48}$. Triterpenes are also produced by fungi, animals, and plants. Their molecular weight ranges from 400 to 600 kDa. Functionalized triterpenes are also popular as triterpenoids. Chemical structures of triterpenes are based mostly on lanosterol. Triterpenes are a class of naturally occurring biologically active compounds which have a vast range of medicinal applications and health benefits such as cytotoxic, hepatoprotective, hypocholesterolemic, hypo-lipidemic, anti-tumor, anti-cancer, anti-viral, anti-obesity, and neuro-trophic activities [20-22].

Mushroom species such as *Ganoderma*, *Antrodia* and Inonotus have been reported to yield triterpenes [23]. Ganoderic acids produced by *Ganoderma* spp. is one of the triterpenes composed of four cyclic and two linear isoprene units. Till date, around 140 various kinds of ganoderic acids (GAs) have been successfully isolated from fruiting bodies, mycelia, and cultures of *Ganoderma* lucidum, and most of them are lanostane type [20, 24, 25]. Chemical structures of secondary metabolites extracted from *Ganoderma lucidum* are recorded in **Table 1**.

Apart from this, another mushroom named *Antrodia cinnamomea* is more abundant in bioactive triterpenoids than that of *Ganoderma lucidum*. Recently, over 40 different types of triterpenoids have been recognized in *Antrodia cinnamomea*, which are therapeutically potent [26]. Many researchers have reported ergostane and lanostane as major components of triterpenoid skeleton in *A. cinnamomea*. In which, ergostane type occurs mainly as tetracyclic triterpenoids with a 29-carbon skeleton having a 24-exo-methylene-26-oic acid side chain and conjugated double bonds among C-7, C-8, C-9, and C-11, whereas lanostane type triterpenoids generally consist of a eubricane skeleton with 24-exo-methylene-21-oic acid side chain and a double bond system along C-7, C-8, C-9 and C-11 [27-29]. Some tritepenes like ergosterol peroxide, ergosterol, 3β-hydroxy-8,24-dien-21-al, trametenolic acid and inotodiol have also been isolated from *Inonotus obliquus*, which were identified to possess some medicinal values [23, 30].

2.3 Steroids: All organisms produce steroids as they are an important source of biologically active compounds as they are able to penetrate cell membranes and bind to nuclear and membrane receptors. Structurally steroids are composed of seventeen carbon atoms bonded in four rings arranged in specific molecular configuration. As depicted in **Fig. 1**, three rings out of four (A, B, and C) are cyclohexane rings, and the fourth (D) is cyclopentane ring. The diversity in steroids is mainly due to the presence of different functional groups attached to this four-ring structure. They are reported to possess anti-tumor, anti-cancer, anti-microbial, anti-inflammatory, and anti-viral properties [17].

Sterols are steroid alcohols. Ergosterol with anti-parasitic activity was successfully extracted from mushroom *Pleurotus salmoneostramineus* [32]. The n-hexane extract to *Trametes* versicolor yielded ergostane named 5α, 8α-epidioxy-22E-ergosta-6, 22-dien-3β-ol [17, 33]. It was reported that *Pleurotus ostreatus* also produced similar ergostane [17, 34]. In the course of time, two other sterols, ergosterol and 5α, 8α-epidioxy-(22E, 24R)-ergosta-6, 22-dien-3β-ol were isolated from fruiting bodies of an edible mushroom *Agrocybe aegerita*. Another mushroom *Paxillus panuoides* was also reported to yield two ergosteroid compounds: 5α, 8α-epidioxy-(22E,

24R)-ergosta-6, 22-dien-3β-ol and (22E, 24R)-ergosta-4, 6, 8(14), 22-tetraen-3-one. From edible truffle mushroom *Tuber indicum* four ergostane-type compounds *i.e.* brassicasterol; (22E,24R)-ergosta-7, 22-dien-3β, 5α, 6β-triol; (22E,24R)-ergosta-4, 6, 8(14), 22-tetraen-3-one and 5α,8α-epidioxy-(22E, 24R)-ergosta-6,22-dien-3β-ol as well as one novel polyhydroxy sterol glycoside named tuberoside *i.e.* identified as 3-O-β-D-glucopyranosyl-(22E, 24R)-ergosta-7, 22-dien-5α, 6β-diol were obtained. Two novel secoergosterols, tylopiols A and tylopiols B, structurally 3β-hydroxy-8α, 9α-oxido-8, 9-secoergosta-7, 9(11), 22-triene and 3β-hydroxy-8α, 9α-oxido-8, 9-secoergosta-7, 22-diene-12-one respectively were identified from the fresh fruiting bodies of *Tylopilus plumbeoviolaceus*.

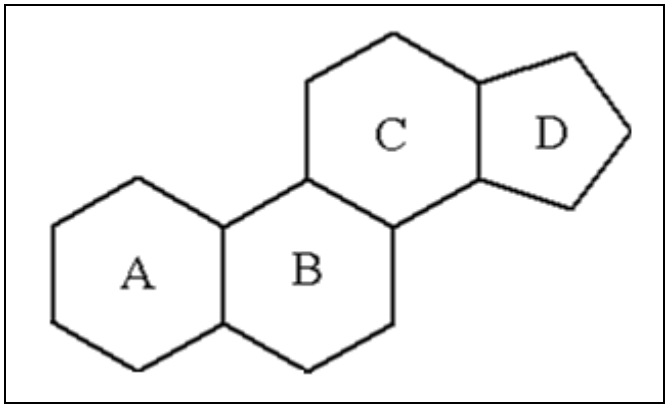


FIG. 1: COMMON STRUCTURE OF STEROIDS (DRAWN USING ACD/CHEMSKETCH FREEWARE)

2.4. Alkaloids: Alkaloids are naturally occurring organic secondary metabolites which mostly contain basic nitrogen moieties. A large variety of organisms, including bacteria, fungi, plants, and animals are able to synthesize alkaloids. From crude extracts, they can be purified either by acid-base extraction or solvent extraction methods, followed by the use of column chromatography techniques. Different alkaloids possess a wide variety of pharmacological activities such as anti-cancer, anti-asthamatic, anti-malarial, cholinomimetic, anti-arrythamic, analgesic, anti-bacterial, vasodilatary and hypoglycemic activities.

Alkaloids like cocaine, caffeine, nicotine, and theobromine have stimulant activities, whereas some alkaloids such as atropine and tubocurarine are toxic too. *Tricholoma terreum* possesses a rare 10 ring structured alkaloid that has been extracted from its fruiting bodies and is named terreumols [35]. Edible mushroom *Tricholoma matsutake* was reported to synthesize matsutakone with unprecedented polycyclic ring structure [36]. From ethyl acetate fractions of the large black fruiting body and valued flavor possessing edible mushroom *Phlebopus portentosus*, three new pyrrole alkaloids, phlebopines A, B and C, have been isolated. All of these three pyrrole alkaloids were investigated to have neuroprotective activities along with acetylcholine esterase inhibition activities [37]. The odoriferous indole and skatole were identified in extracts of genus Tricholoma. A lump of unpleasant coal- or tar-like odor possessing indole-3-carboxaldehyde was found in the volatile extract of *Tricholoma sulphureum*. The genus Tricholoma of mushrooms produces a number of indole alkaloids containing a methyl group at the C2-position *i.e.*, lascivol. 4-Methoxymethyl-5-methylindole has also been identified in *Tricholoma caligatum* [38, 39]. 6-hydroxyindole-3-carbaldehyde and 6-hydroxy-indole-3-acetamide, have been extracted from *Agrocybe cylindracea*, with both showing free radical scavenging activity [38, 40]. The mushroom *Hericium coralloides* produces the indole alkaloid corallocin C [38, 41].

2.5 Peptides and Proteins: A short chain of amino acids bonded together via peptide bonds is known as a peptide. Many peptides join together to form a polypeptide, and when such polypeptides fold into a typical confirmation, they yield a macromolecule called protein. Several biologically active peptides and proteins are synthesized by mushrooms. Such proteins or peptides may or may not possess catalytic activity. For example, lectins do not have enzymatic activity. Some of the important bioactive proteins are laccases, ribosome-inactivating proteins (RIPS), and fungal immunomodulatory proteins (FIPS). Lectins are glycoproteins or non-immune proteins which specifically bind to carbohydrates of the fungal cell wall and have cell agglutination abilities. Enzymes that inactivate ribosomes by removing adenosine from rRNA are recognized as RIPS. FIPS are novel bioactive proteins that target immune cells. Laccases are phenol oxidases which are generally employed for degradation of lignocellulosic biomass; also possess bioactive properties [23]. These peptides and proteins possess several bioactive properties like anti-microbial, anti-inflammatory, anti-mitogenic, anti-tumor as well as immunomodulatory activities.

Pleurostrin, a 7 kDa anti-fungal peptide, was extracted from *Pleurotus ostreatus* [42]. An anti-inflammatory peptide, cordymin with 10,906 kDa molecular weight was obtained from mushroom *Cordyceps sinensis* and *Cordyceps militaris* [43, 44]. Xylose-specific lectins having molecular weight of about 28.8 kDa showing anti-mitogenic and anti-tumor activities was extracted from fruiting bodies of *Xylaria hypoxylon* [45]. Laccases isolated from *Pleurotus eryngii* and *Pleurotus ostreatus* display antiviral properties [46, 47]. Various FIPS have been successfully isolated from different mushrooms such as Fip-fve from *F. velutipes*, Fip-vvo from *Volvariella volvacea* and Fip-gts from *Ganoderma tsugae* [48-50].

It was reported that Fip-fve had been successfully applied for tumor immunotherapy [51, 52]. Marmorin, a 9 kDa RIP with anti-tumor properties, was isolated from *Hypsizigus marmoreus* [53].

3. Therapeutic Applications of Mushroom Secondary Metabolites: Traditionally, mushrooms were unknowingly being consumed, which provided nutrition as well as many health benefits.

These benefits were the results of their secondary metabolites, which are nowadays well known for bioactive properties. A few of those bioactivities are summarized in **Fig. 2**.

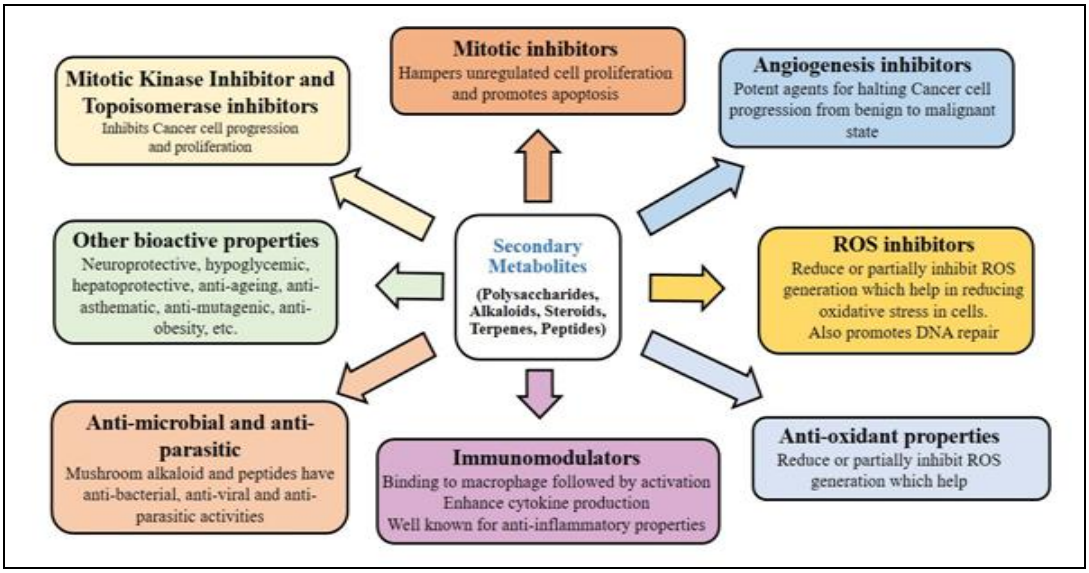


FIG. 2: VARIOUS BIOACTIVE PROPERTIES OF MUSHROOM SECONDARY METABOLITES

3.1. Anti-tumor and Anti-cancer Activities: Cancer is one of the leading causes of the death around the globe. Surgery and chemotherapy are usually the remedy for its treatment. Chemotherapy is the widely used treatment of cancer which has mostly relied on cytotoxic drugs, which act by inhibiting tumor cell proliferation and in turn, cause cell death. But major disadvantage of chemo-therapy is its harsh side effects on the human body. Thus it became compulsory to discover novel chemotherapeutic and chemopreventive agents. Luckily, mushrooms have got those bioactive secondary metabolites which have anti-tumor and anti-cancerous properties. Tumors formed in cancer are due to unrestricted growth of cells. Generally, tumors are classified as: benign and malignant tumors. Former one is less harmful as it grows and stays at a single place inside the body, but the later one is more dangerous as it can travel inside the body along with the body fluids. Anti-tumor compounds are those which can restrict the growth of tumor cells. Many biologically active secondary metabolites with anti-tumor activities have been investigated from mushrooms. The growth of several types of tumors like Sarcoma [37], Sarcoma 180 solid tumor, Ehrlich solid tumor, Lewis lung carcinoma and Yoshida sarcoma were inhibited by polysaccharides produced by mushrooms [54, 55]. For the very first time in 1960s, anti-tumor activity of mushroom polysaccharide lentinan was reported [56]. *Cordyceps militaris* polysaccharide has shown promising in vitro anti-tumor activity against HeLa and HepG-2 cells and significantly inhibited the growth of K562 and HT-29 cells [21]. *Pluerotus ostreatus* extracted polysaccharides are compounds of β-glucan family.

They have ability to boost cellular immunity because of anti-tumorogenic properties. They exerted anti-tumor activities against HeLa cells [23, 57]. Triterpenoids extracted from *Ganoderma lucidum* inhibited the growth of hepatoma cells was inhibited by suppressing protein kinase C and activating nitrogen-activated protein kinases [31, 58]. A triterpenoid Ganoderic acid T isolated from *Ganoderma lucidum* leads to apoptosis and prevent growth of lung tumor cell via an intrinsic pathway and by causing mitochondrial dysfunction [58, 59].

Among various types of cancer, colorectal cancer is the second most leading cause of death occurring due to cancer. A biologically active low molecular weight α-glucan extracted from mycelia of an edible mushroom *Pleurotus ostreatus* displayed anti-apoptotic activity [4]. Bioactive fractions of *Cerrena unicolor* and *Pycnoporus sanguineus* in habited the growth of colon cancer cells [60]. The medicinal mushroom *Sarcodona spratus* produced sterol 9, 11-dehydroergosterol peroxide 9(11)-DHEP which was reported to suppress the growth of human colon adenocarcinoma HT-29 cells [4].

Breast cancer occurs due to the proliferation of cell growth and DNA damage caused by the presence of estrogen in the breast of postmenopausal women. Triterpenes of *Ganoderma lucidum*, the medicinal mushroom, suppress the growth of MDA-MB breast cancer cell lines by inhibiting cell proliferation [62]. Researchers have reported the inhibition of the transcription factors AF-1 and NF-κB which in turn downregulate the expression of Cdk4 and suppress the uPA secretion [4].

Leukemia, the cancer of the blood, occurs at high rates of about 3-5% with 4-5% of mortality rate. *Ganoderma tsugae* extracts strobfly inhibited growth of human chronic myeloid leukemia cells [4, 61]. The triterpenes obtained from mycelia of *Ganoderma lucidum* arrest cell cycle of HT-29 human leukemia cancer cell lines between G2-M phases [4, 63].

Factors such as cigarette smoking, tobacco chewing, deficiency of niacin and iron are responsible for oral cancer. Increased intake of vitamins A and C reduces the risk of oral cancer. In patients with oral leucoplakia, the incidence of oral malignancy can be reduced by retinoids. Polysaccharides obtained from mushroom *Lentinus edodes* (LEP) increased serum, and oral mucosa IL-1b and TNF-α levels healed oral ulcers effectively in rats [4, 64].

An uncommon gastric cancer may occur because of risk factors like environmental, genetic, and infection. Inflammation of gastric mucosa is caused due to bacterial infection from *Helicobacter pylori*. Endogenous nitrosamines, smoked meat, high-salt, high-carbohydrate, and high-fat diet are also accountable for the occurrence for gastric cancer. The consumption of high dietary fiber, fruits, and dairy products reduces the risk of gastric cancer [4, 65]. The methanolic extracts of *Ganoderma lucidum* enhance autophagy and formation of autophagosomes in the treatment of a gastric adenocarcinoma cell line (AGS) [4, 66].

Pleurotus pulmonarious extracted polysaccharide-protein complex inhibits the proliferation of hepatocellular carcinoma by suppressing PI3K / AKT signaling pathway and overexpressing the constitutively active form Myr-AKT in liver cancer cells [4, 67]. It was reported that the cell cycle of HuH-7 hepatocarcinoma cells was arrested due to the treatment of triterpenes [20, 68].

3.2. Anti-oxidant Activities: Antioxidants assist in guarding the cellular components from oxidative damage, thereby reducing the risk of mutation and carcinogenesis. They are also important in the protection of the immune cells, allowing them to sustain immune surveillance and response. Oxidative stress is known to be one of the risk factors for the cause of cancer. Free radicals and reactive oxygen species (ROS) are by-products of metabolic processes. ROS and free radicals damage cells and tissues that may lead to age-associated diseases.

An anti-oxidative enzyme such as superoxide dismutase, catalase, and peroxidase has potential to repair the damage caused due to oxidative stress up to some extent. Polysaccharide extracted from *Pleurotus eryngii* by ultrasonic extraction method showed best DPPH and superoxide radical scavenging activities [69]. Polysaccharides of *Amanita strobiliformis* displayed hydroxyl radical scavenging activities [70]. Some researchers have reported that the triterpenes of *Ganoderma lucidum*

have ability to decrease oxidative damage directly by scavenging free radicals [71]. Triterpenes isolated from *Ganoderma lucidum* displayed anti-oxidant activity in mice that may be because of elevated activity of anti-oxidant enzymes. It was also observed that total terpenes could prevent radiation-induced DNA damage in mice under *in-vivo* conditions [20, 72]. Furthermore, when total triterpenes were administrated in Swiss albino mice under in vivo conditions, they were found to be very much efficient in decreasing the levels of protein oxidation and lipid peroxidation. Total triterpenes have also successfully repaired the DNA strand breaks and restored the activities of antioxidant enzymes as well as glutathione level in both liver and brain of irradiated mice [20, 73]. A lanostane triterpene glycoside, fomitoside-K, extracted from the fruiting bodies of *Fomitopsis nigra* induce apoptosis of human oral squamous cell carcinomas *via* the ROS-dependent mitochondrial apoptosis pathway [58, 74, 75].

3.3. Anti-microbial Activities: Antibiotic resistance is one of the major obstacles in curing infections now days. Besides, strains are also getting more pathogenic as well as virulent due to some environmental factors and mutation. Thus researchers are now developing more interest in discovering novel compounds with anti-microbial properties such as anti-bacterial, anti-fungal, and anti-viral properties [1]. Secondary metabolites produced by mushrooms possess strong anti-microbial properties.

Coprinol, a cuparane-type terpenoid which has been isolated from mushroom *Coprinus* spp. showed remarkable anti-bacterial activity against multi-drug-resistant Gram-positive bacteria [58, 76]. Most of the polypore fungi exhibit strong anti-microbial activities [1, 77]. *Clitopilus passeckerianus* mushroom synthesizes a tricyclic diterpenoid, pleuromutilin, which was later identified as retapamulin antibiotic [58, 78, 79].

Terpenoids nambione A-D and 1-epi-nambinone B yielded by a bioluminescent mushroom *Neonothopanus nambi* were reported to exhibit antitubercular activity [16, 58]. Antimycobacterial activity was also observed in lanostane type triterpenoids ganorbiformins A-G extracted from *Ganoderma orbiforme* [58, 80].

Extracts of *Ganoderma lucidum* showed better anti-bacterial against *Staphylococcus aureus* and *Bacillus cereus* than ampicillin and streptomycin antibiotics [22, 81]. Some fungi such *Candida albicans*, *Aspergillus* spp., *Cryptococcus neoformans*, *Pneumocystis carinii*, *Fusarium oxysporum*, *Botrytis cinera* and few others are associated with life-threatening diseases. But for treatment of such diseases, only a few numbers of agents with anti-fungal activities are available.

An anti-fungal protein ganodermin with 15 kDa of molecular weight inhibited the growth of *Fusarium oxysporum*, *Botrytis cinera*, and *Physalospora piricola* [22, 47]. *Ganoderma lucidum* extract also showed activity against *Trichoderma viride* fungus with higher activities than that of standards, bifonazole and ketoconazole [22, 81].

Viruses are found to be very disastrous for the last two decades, as very few anti-viral agents exist. Therefore it is now mandatory to discover new natural anti-viral agents. Researchers have studied and reported that there are some mushrooms that synthesize secondary metabolites with anti-viral properties. The triterpenoids like lucidiadol, applanoxidic, and *ganoderma*diol from *Ganoderma pfeifferi* and other species of *Ganoderma* mushrooms depicted activity against type A *influenza* virus under laboratory conditions. Alongside, *ganoderma*diol also displays anti-viral properties against type 1 herpes simplex virus [58].

Apart from *Ganoderma*, other mushrooms like *Trametes versicolor*, *Trametes gibbosa*, *Datronia mollis*, *Ischnoderma benzoinum*, *Lenzites betulina*, *Laricifomes officinalis* have been recognized to generate anti-viral compounds [58, 82, 83]. HIV-I (human immunodeficiency virus type 1) is causative agent of AIDS (acquired immune-deficiency syndrome), the deadliest viral disease. Colossolactones extracted from *Ganoderma colossum* mushroom are the lanostane type triterpenes. Varients like colossolactone V and colossolactone G were identified to be effective against HIV-I [58, 84]. *Ganoderma sinensis* extracted triterpenes *i.e.* ganoderic acid GS-2, and gaoderiol F, 20-hydroxylucidenic acid N and 20(21)-dehydrolucideinc acid N are found to have anti-HIV protease activity [58, 85].

Neuro-protective Activities: Neurodegenerative Diseases are those which result in nerve cells degeneration and/or death, which either cause ataxias or cause dementias. Parkinson's disease, Alzheimer's disease, and Huntington's disease are the most common neurodegenerative diseases.

Treatments available today can't completely cure but can somehow hinder their progression [22, 86]. Thus lack of treatment forces researchers to come out with novel compounds. Polysaccharide derived from *Ganoderma lucidum* altered the expression of MCP-1 as well as Clq and displayed neuro-protective properties in LPS and amyloid β-induced BV2 microglia cells [22, 87].

Lanostane triterpenes are promising inhibitors of acetylcholine esterase and may be regarded as better drug candidates. The triterpenoids from *Ganoderma* spp. such as methyl ganoderate A acetamide and n-butyl ganoderate H were reported to elicit specific acetlycholinesterase inhibitory activity. Other triterpenes like *ganoderma*nondiol, lucidadiol were also recognized to show moderate antiacetylcholinesterase activity. Labdane diterpenes obtained from fruiting bodies of Antrodia camphorate restricted apoptosis of serum deprivation-induced PC12 cells *in-vitro* [29, 58, 88].

Other Activities: The bioactive secondary metabolites from mushrooms have been recognized to have anti-parasitic activities. Six lanostane triterpenes from *Ganoderma lucidum* have been identified to possess *in-vitro* antiplasmodial activity [58, 89]. Aurisin A and aurisin K from poisonous mushroom *Neonothopanus nimbi* were found to be effective against *Plasmodium falciparum* and *Mycobacterium tuberculosis* [58, 90]. Apart from these, several mushroom secondary metabolites have been studied for their anti-parasitic activities.

One of the major health problems today is obesity, which in turn can result in various diseases such as diabetes, atherosclerosis, and hyperlipidemia. Pleurotus sajor-caju extracted β-glucan reduced obesity in obese mice consuming high-fat diet [4, 91]. Administration of *Pleurotus florida* extracts restrained weight gain in high-cholesterol diet rats, minimized fat deposition and total cholesterol level, triglycerides as well as LDL [4, 92]. Like this, several metabolites display anti-obesity activities.

Today, millions of people are suffering from diabetes worldwide. Diabetes is a metabolic disorder resulting due to insulin imbalances which in turn raises blood glucose levels. Polysaccharides extracted from the medicinal mushroom *Phellinus badius* displayed hypoglycemic activity in streptozotocin-induced diabetic mice [4, 93]. Compounds such as polysaccharides, triterpenoids, proteins and glycoproteins from *Ganoderma lucidum* acquire hypoglycemic properties [22, 94].

A high ratio of total cholesterol to HDL cholesterol is a sign of cardiovascular diseases. Cardio-vascular diseases may result in a heart attack or stroke. When atherosclerosis-susceptible mice were orally administrated with 30% dried *Pleurotus florida* mushroom, total cholesterol level was reduced in comparison to the control mice [4, 95]. Angiotensin II, the potent vasopressor octapeptide, is responsible for hypertensive effects. An edible mushroom *Pleurotus cornucopiae* extracted D-glucopyranose mannitol inhibited angiotensin I-converting enzyme (ACE) which is responsible for conversion of angiotensin I to angiotensin II. Thus it shows hypotensive effects [4, 96].

Moreover, mushroom secondary metabolites are also reported to possess anti-asthamatic, anti-mutagenic, anti-ageing as well as anti-mutagenic properties4.

CONCLUSION: Mushrooms are abundant sources of a vast variety of natural products with numerous therapeutic applications. Mushroom bioactive secondary metabolites can aid resources as well as modern therapeutics. Recently, mushrooms have emerged with lot of biologically active constituents such as polysaccharides, alkaloids, terpenes, *etc*. The administration of extracts containing such mushroom metabolites can help the patients to recover and people to protect them from various diseases. Though mushroom cultivation is a challenging task, mycelia can also serve as a promising source for such compounds. We hope that this review may help scientists for conducting research in edible and medicinal mushrooms.

FUTURE PROSPECTS: Unlike today's available drugs, mushrooms and their bioactive metabolites have very limited or no side effects as they are natural compounds.

Thus they serve as a promising resource to pharmaceutical industries for drug designing with minimum toxicity. Mushrooms can be used as nutraceuticals in order to protect people from life-threatening diseases. Besides, on larger scales, genomic, proteomic as well as metabolomic studies should be carried out for significant development and advanced bioprocessing platform for industrial production of mushroom secondary metabolites.

ACKNOWLEDGEMENT: The author feels grateful to acknowledge UGC for granting National Fellowship for OBCs (NFOBC).

CONFLICTS OF INTEREST: The authors have no conflicts of interest in the present review.

REFERENCES:

1. Wijayawardene NN, Hyde KD, Al-Ani LK, Tedersoo L, Haelewaters D, Rajeshkumar KC, Zhao RL, Aptroot A, Leontyev D, Saxena RK and Tokarev YS: Outline of Fungi and fungus-like taxa. Mycosphere 2020; 11(1): 1060-56.
2. He X, Wang X, Fang J, Chang Y, Ning N, Guo H, Huang L, Huang X and Zhao Z: Polysaccharides in *Grifola frondosa* mushroom and their health promoting properties: A review. International Journal of Biological Macro-molecules 2017; 101: 910-21.
3. Gong P, Wang S, Liu M, Chen F, Yang W, Chang X, Liu N, Zhao Y, Wang J and Chen X: Extraction methods, chemical characterizations and biological activities of mushroom polysaccharides: A mini-review. Carbohydrate Research 2020; 494: 108037.
4. Chaturvedi VK, Agarwal S, Gupta KK, Ramteke PW and Singh MP: Medicinal mushroom: boon for therapeutic applications. 3 Biotech 2018; 8(8): 334.
5. Ferreira IC, Heleno SA, Reis FS, Stojkovic D, Queiroz MJ, Vasconcelos MH and Sokovic M: Chemical features of *Ganoderma* polysaccharides with antioxidant, antitumor and antimicrobial activities. Phytochemistry 2015; 114: 38-55.
6. Dubey SK, Chaturvedi VK, Mishra D, Bajpeyee A, Tiwari A and Singh MP: Role of edible mushroom as a potent therapeutics for the diabetes and obesity. 3 Biotech 2019; 9(12): 1-2.
7. Wang Q, Wang F, Xu Z and Ding Z: Bioactive mushroom polysaccharides: a review on monosaccharide composition, biosynthesis and regulation. Molecules 2017; 22(6): 955.
8. Pandya U, Dhuldhaj U and Sahay NS: Bioactive mushroom polysaccharides as antitumor: an overview. Natural product research 2019; 33(18): 2668-80.
9. Ziaja-Sołtys M, Radzki W, Nowak J, Topolska J, Jabłońska-Ryś E, Sławińska A, Skrzypczak K, Kuczumow A and Bogucka-Kocka A: Processed Fruiting Bodies of *Lentinus edodes* as a Source of Biologically Active Polysaccharides. Applied Sciences 2020; 10(2): 470-81.
10. Zhang L, Li CG, Liang HL and Reddy N: Bioactive mushroom polysaccharides: immunoceuticals to anticancer agents. Journal of Nutraceuticals and Food Science 2017; 2(2): 6-10
11. Üstün NŞ, Bulam S and Pekşen A: The use of mushrooms and their extracts and compounds in functional foods and nutraceuticals. Türkmen A.(ed.). 2018; 1: 1205-22.
12. Baeva E, Bleha R, Lavrova E, Sushytskyi L, Čopíková J, Jablonsky I, Klouček P and Synytsya A: Polysaccharides from basidiocarps of cultivating mushroom *Pleurotus ostreatus*: isolation and structural characterization. Molecules 2019; 24(15): 2740.
13. GIaVaSIS I: Polysaccharides from medicinal mushrooms for potential use as nutraceuticals. Polysaccharides: Natural Fibers in Food and Nutrition 2014; 1: 171-06.
14. Zong A, Cao H and Wang F: Anticancer polysaccharides from natural resources: A review of recent research. Carbohydrate polymers 2012; 90(4): 1395-10.
15. Miao J, Regenstein JM, Qiu J, Zhang J, Zhang X, Li H, Zhang H and Wang Z: Isolation, structural characterization and bioactivities of polysaccharides and its derivatives from *Auricularia*-A review. International Journal of Biological Macromolecules 2020; 150: 102-13.
16. Duru ME and Çayan GT: Biologically active terpenoids from mushroom origin: a review. Records of Natural Products 2015; 9(4):456-483.
17. Lenzi J, Costa TM, Alberton MD, Goulart JA and Tavares LB: Medicinal fungi: a source of antiparasitic secondary metabolites. Applied Microbiology and Biotechnology 2018; 102(14): 5791-10.
18. Breitmaier E: Terpenes: flavors, fragrances, pharmaca, pheromones. John Wiley & Sons 2006
19. Kumari P, Choudhary SK and Kumar A: *In-vitro* study of antifungal activity of *Lentinus edodes* mushroom extract against *Alternaria triticina*. In Biotechnology and Biological Sciences: Proceedings of the 3rd International Conference of Biotechnology and Biological Sciences (BIOSPECTRUM 2019), August 8-10, 2019, Kolkata, India. CRC Press 2019; 392.
20. Bhat ZA, Wani AH, Bhat MY and Malik AR: Major bioactive triterpenoids from *Ganoderma* species and their therapeutic activity: a review. Asian Journal of Pharmaceutical and Clinical Research 2019; 12(4): 22-30.
21. Zhang J, Wen C, Chen M, Gu J, Zhou J, Duan Y, Zhang H and Ma H: Antioxidant activities of *Sagittaria sagittifolia* L. polysaccharides with subcritical water extraction. International Journal of Biological Macromolecules 2019; 134:172-179.
22. Sharma C, Bhardwaj N, Sharma A, Tuli HS, Batra P, Beniwal V, Gupta GK and Sharma AK: Bioactive metabolites of *Ganoderma lucidum*: Factors, mechanism and broad spectrum therapeutic potential. Journal of Herbal Medicine 2019; 17: 100268.
23. Sánchez C: Bioactives from mushroom and their application. Food bioactives, Springer, Cham 2017: 23-57.
24. Liang C, Tian D, Liu Y, Li H, Zhu J, Li M, Xin M and Xia J: Review of the molecular mechanisms of *Ganoderma lucidum* triterpenoids: Ganoderic acids A, C2, D, F, DM, X and Y. European Journal of Medicinal Chemistry 2019; 174: 130-41.
25. Gupte A, Palande A, Venkata S and Pol R: Docking studies of *Ganoderma lucidum*. International Journal of Pharmaceutical Sciences and Research 2018; 9(3).
26. Kumar KS and Wang SY: Medicinal Plants and Fungi: Recent Advances in Research and Development, Springer, Singapore 2017: 135-64.
27. Zhang BB, Guan YY, Hu PF, Chen L, Xu GR, Liu L and Cheung PC: Production of bioactive metabolites by submerged fermentation of the medicinal mushroom *Antrodia cinnamomea*: recent advances and future

development. Critical Reviews in Biotechnology 2019; 39(4): 541-54.

28. Qiao X, Wang Q, Ji S, Huang Y, Zhang ZX, Bo T, Tzeng YM, Guo DA and Ye M: Metabolites identification and multi-component pharmacokinetics of ergostane and lanostane triterpenoids in the anticancer mushroom *Antrodia cinnamomea*. Journal of Pharmaceutical and Biomedical Analysis 2015; 111: 266-76.
29. Chatterjee D, Das S and Halder D: Therapeutic applications of mushrooms and its compositional analysis by high throughput screening techniques. International J of Pharmaceutical Sci and Research 2019; 10(8): 3508-18.
30. Sagayama K, Tanaka N, Fukumoto T and Kashiwada Y: Lanostane-type triterpenes from the sclerotium of *Inonotus obliquus* (Chaga mushrooms) as proproliferative agents on human follicle dermal papilla cells. Journal of Natural Medicines 2019; 73(3): 597-01.
31. Lin SB, Li CH, Lee SS and Kan LS: Triterpene-enriched extracts from *Ganoderma lucidum* inhibit growth of hepatoma cells via suppressing protein kinase C, activating mitogen-activated protein kinases and G2-phase cell cycle arrest. Life Sciences 2003; 72(21): 2381-90.
32. Alexandre TR, Lima ML, Galuppo MK, Mesquita JT, do Nascimento MA, dos Santos AL, Sartorelli P, Pimenta DC and Tempone AG: Ergosterol isolated from the basidiomycete *Pleurotus salmoneostramineus* affects *Trypanosoma cruzi* plasma membrane and mitochondria. Journal of Venomous Animals and Toxins including Tropical Diseases 2017; 23(1): 30-39.
33. Leliebre-Lara V, Monzote Fidalgo L, Pferschy-Wenzig EM, Kunert O, Nogueiras Lima C and Bauer R: *In-vitro* anti-leishmanial activity of sterols from *Trametes versicolor* (Bres. Rivarden). Molecules 2016; 21(8): 1045-54.
34. Meza-Menchaca T, Ramos-Ligonio A, López-Monteon A, Vidal Limón A, Kaluzhskiy LA, Shkel VT, Strushkevich VN, Jiménez-García LF, Agredano Moreno LT, Gallegos-García V and Suárez-Medellín J: Insights into ergosterol peroxide's trypanocidal activity. Bio-molecules 2019; 9(9): 484.
35. Nandi S, Sikder R and Acharya K: Secondary Metabolites of Mushrooms: A potential source for anticancer therapeutics with translational opportunities. In Advancing Frontiers in Mycology & Mycotechnology, Springer, Singapore 2019; 563-98.
36. Zhao ZZ, Chen HP, Wu B, Zhang L, Li ZH, Feng T and Liu JK: Matsutakone and matsutoic acid, two (nor) steroids with unusual skeletons from the edible mushroom *Tricholoma matsutake*. The Journal of Organic Chemistry 2017; 82(15):7974-7949.
37. Sun Z, Hu M, Sun Z, Zhu N, Yang J, Ma Ga and Xu X: Pyrrole alkaloids from the edible mushroom *Phlebopus portentosus* with their bioactive activities. Molecules 2018; 23(5):1198-1204.
38. Homer JA and Sperry J: Mushroom-derived indole alkaloids. Journal of Natural Products 2017; 80(7):2178-2187.
39. Arnold N, Palfner G, Schmidt J, Kuhnt C and Becerra J: Chemistry of the aroma bouquet of the edible mushroom" lebre"(cortinarius lebre, basdiomycota, agaricales) from chile. Journal of the Chilean Chemical Society 2012; 57(3): 1333-35.
40. Kim SE, Hwang BS, Song JG, Lee SW, Lee IK and Yun BS: New bioactive compounds from Korean native mushrooms. Mycobiology 2013; 41(4): 171-76.
41. Wittstein K, Rascher M, Rupcic Z, Löwen E, Winter B, Köster RW and Stadler M: Corallocins A–C, nerve growth and brain-derived neurotrophic factor inducing metabolites from the mushroom *Hericium coralloides*. Journal of natural products 2016; 79(9): 2264-69.
42. Dahima V, Doshi A and Singh H: Screening of Antifungal Activity of *Pleurotus pulmonarius*, *Pleurotus florida* and *Shizophyllum commune*. International Journal of Current Microbiololgy and Applied Sciences 2020; 9(4): 997-04.
43. Elkhateeb WA, Daba GM, Thomas PW and Wen TC: Medicinal mushrooms as a new source of natural therapeutic bioactive compounds. Egyptian Pharmaceutical Journal 2019; 18(2): 88-101.
44. Ashraf SA, Abd Elmoneim OE, Siddiqui AJ, Patel M, Awadelkareem AM, Snoussi M, Ashraf MS, Adnan M and Hadi S: Cordycepin for Health and Wellbeing: A Potent Bioactive Metabolite of an Entomopathogenic Medicinal Fungus *Cordyceps* with Its Nutraceutical and Therapeutic Potential. Molecules 2020; 25(12).
45. Büttner E, Liers C, Hofrichter M, Gebauer AM and Kellner H: Draft Genome Sequence of Xylaria hypoxylon DSM 108379, a Ubiquitous Fungus on Hardwood. Microbiology resource announcements 2019; 8(44).
46. Ilyicheva TN, Teplyakova TV, Svyatchenko SV, Asbaganov SV, Zmitrovich IV and Vlasenko AV: Antiviral activity of total polysaccharide fraction of water and ethanol extracts of *Pleurotus pulmonarius* against the *influenza* A virus. Current Research in Environmental & Applied Mycology (Journal of Fungal Biology) 2020; 10(1): 224-35.
47. Wang H and Ng TB: Ganodermin, an antifungal protein from fruiting bodies of the medicinal mushroom *Ganoderma lucidum*. Peptides 2006; 27(1): 27-30.
48. Ko JL, Hsu CI, Lin RH, Kao CL and Lin JY: A new fungal immunomodulatory protein, FIP-fve isolated from the edible mushroom, *Flammulina velutipes* and its complete amino acid sequence. European Journal of Biochemistry 1995; 228(2): 244-49.
49. Hsu HC, Hsu CI, Lin RH, Kao CL and Lin JY: Fip-vvo, a new fungal immunomodulatory protein isolated from *Volvariella volvacea*. Biochemical Journal 1997; 323(2): 557-65.
50. Lynn V: Mass Spectrometry for the Detection of Endogenous Steroids and Steroid Abuse in (Race) Horses and Human Athletes. Mass Spectrometry 2017; 7: 229-52.
51. Zhao S, Gao Q, Rong C, Wang S, Zhao Z, Liu Y and Xu J: Immunomodulatory Effects of Edible and Medicinal Mushrooms and Their Bioactive Immunoregulatory Products. Journal of Fungi 2020; 6(4): 269.
52. Chang HH, Hsieh KY, Yeh CH, Tu YP and Sheu F: Oral administration of an Enoki mushroom protein FVE activates innate and adaptive immunity and induces anti-tumor activity against murine hepatocellular carcinoma. International immunopharmacology 2010; 10(2): 239-46.
53. Wong JH, Sze SC, Ng TB, Cheung RC, Tam C, Zhang KY, Dan X, Chan YS, Shing Cho WC, Ng CC and Waye MM: Apoptosis and anti-cancer drug discovery: the power of medicinal fungi and plants. Current Medicinal Chemistry 2018; 25(40): 5613-30.
54. Cheong PC, Tan CS and Fung SY: Application of wild macro-fungi as anticancer therapeutics. InBiology of Macro-fungi, Springer, Cham 2018; 243-74.
55. Lal UR, Joshi D and Banerjee S: Anticancer Agents: Plants Used in Ayurveda. Cancer Therapy 2019; 3: 181.
56. Xu H, Zou S, Xu X and Zhang L: Anti-tumor effect of β-glucan from *Lentinus edodes* and the underlying mechanism. Scientific reports 2016; 6(1): 1-3.
57. Piska KT, Sułkowska-Ziaja K and Muszyńska B: Edible mushroom *Pleurotus ostreatus* (oyster mushroom)-its

dietary significance and biological activity. Acta Scientiarum Polonorum Hortorum Cultus 2017; 16(1).
58. Dasgupta A and Acharya K: Mushrooms: an emerging resource for therapeutic terpenoids. 3 Biotech 2019; 9(10):369.
59. Zolj S, Smith MP, Goines JC, T'Shura SA, Huff MO, Robinson DL and Lau JM: Antiproliferative effects of a triterpene-enriched extract from lingzhi or reishi medicinal mushroom, *Ganoderma lucidum* (Agaricomycetes), on human lung cancer cells. International journal of medicinal mushrooms 2018; 20(12).
60. Pięt M, Zając A, Paduch R, Jaszek M, Frant M, Stefaniuk D, Matuszewska A and Grzywnowicz K: Chemo-preventive activity of bioactive fungal fractions isolated from milk-supplemented cultures of Cerrena unicolor and *Pycnoporus sanguineus* on colon cancer cells. 3 Biotech 2021; 11(1): 1-3.
61. Hseu YC, Shen YC, Kao MC, Mathew DC, Karuppaiya P, Li ML and Yang HL: *Ganoderma tsugae* induced ROS-independent apoptosis and cytoprotective autophagy in human chronic myeloid leukemia cells. Food and Chemical Toxicology 2019; 124: 30-44.
62. El-Sherif NF, Ahmed SA, Ibrahim AK, Habib ES, El-Fallal AA, El-Sayed AK and Wahba AE: Ergosterol peroxide from the Egyptian red lingzhi or reishi mushroom, *Ganoderma resinaceum* (Agaricomycetes), showed preferred inhibition of mcf-7 over mda-mb-231 breast cancer cell lines. International journal of medicinal mushrooms 2020; 22(4).
63. Unlu A, Nayir E, Kirca O and Ozdogan M: *Ganoderma lucidum* (reishi mushroom) and cancer. Journal of the Balkan Union of Oncology 2016; 21: 792-8.
64. Yu Z, LiHua Y, Qian Y and Yan L: Effect of *Lentinus edodes* polysaccharide on oxidative stress, immunity activity and oral ulceration of rats stimulated by phenol. Carbohydrate Polymers 2009; 75(1): 115-8.
65. Kim JH, Lee J, Choi IJ, Kim YI and Kim J: Dietary patterns and gastric cancer risk in a Korean population: a case control study. European Journal of Nutrition 2021; 60(1): 389-97.
66. Chan KM, Yue GG, Li P, Wong EC, Lee JK, Kennelly EJ and Bik-San Lau C: Screening and analysis of potential anti-tumor components from the stipe of *Ganoderma sinense* using high-performance liquid chromatography / time-of-flight mass spectrometry with multivariate statistical tool. Journal of Chromatography A 2017; 1487: 162-7.
67. Sun G, Hou YB, Jia HY, Bi XH, Yu L and Chen DJ: MiR-370 promotes cell death of liver cancer cells by Akt/FoxO3a signalling pathway. Eur Rev Med Pharmacol Sci 2016; 20(10): 2011-9.
68. Maurya SK, Shadab GG and Siddique HR: Chem-osensitization of therapy resistant tumors: targeting multiple cell signaling pathways by lupeol, a pentacyclic triterpene. Current Pharmaceutical Design. 2020; 26(4): 455-65.
69. Zhang B, Li Y, Zhang F, Linhardt RJ, Zeng G, Zhang A. Extraction, structure and bioactivities of the poly-saccharides from *Pleurotus eryngii*: a review. International journal of biological macromolecules 2020; 150: 1342-7.
70. Karaman M, Janjušević L, Jakovljević D, Šibul F and Pejin B: Anti-hydroxyl radical activity, redox potential and anti-AChE activity of *Amanita strobiliformis* poly-saccharide extract. Natural Product Research 2019; 33(10): 1522-6.
71. Wang C, Liu X, Lian C, Ke J and Liu J: Triterpenes and aromatic meroterpenoids with antioxidant activity and neuroprotective effects from *Ganoderma lucidum*. Molecules 2019; 24(23): 4353.
72. Smina TP, De S, Devasagayam TP, Adhikari S and Janardhanan KK: *Ganoderma lucidum* total triterpenes prevent radiation-induced DNA damage and apoptosis in splenic lymphocytes *in-vitro*. Mutation Research/Genetic Toxicology and Enviro Mutagenesis 2011; 726(2): 188-94.
73. Smina TP, Joseph J and Janardhanan KK: *Ganoderma lucidum* total triterpenes prevent γ-radiation induced oxidative stress in Swiss albino mice *in-vivo*. Redox Report 2016; 21(6): 254-61.
74. Bhattarai G, Lee YH, Lee NH, Lee IK, Yun BS, Hwang PH and Yi HK: Fomitoside-K from *Fomitopsis nigra* induces apoptosis of human oral squamous cell carcinomas (YD-10B) *via* mitochondrial signaling pathway. Biological and Pharmaceutical Bulletin 2012; 35(10): 1711-19.
75. Dasgupta A and Acharya K: Bioactive terpenoids from mushrooms. InNew and Future Developments in Microbial Biotechnology and Bioengineering, Elsevier 2021; 145-54.
76. Badalyan SM. Medicinal coprinoid mushrooms (Agaricomycetes) distributed in Armenia. International Journal of Medicinal Mushrooms 2020; 22(3).
77. Sharma D, Singh VP and Singh NK: A review on phyto-chemistry and pharmacology of medicinal as well as poisonous mushrooms. Mini Reviews in Medicinal Chemistry 2018; 18(13): 1095-09.
78. Paukner S and Riedl R: Pleuromutilins: potent drugs for resistant bugs—mode of action and resistance. Cold Spring Harbor perspectives in medicine 2017; 7(1): a027110.
79. Fu Y, Yi Y, Fan Y and Shang R: Cytochrome P450 inhibition potential and initial genotoxic evaluation of 14-O-[(4, 6-diaminopyrimidine-2-yl) thioacetyl] mutilin. Scientific Reports 2020; 10(1): 1-10.
80. Li W, Chinthanom P, Rachtawee P, Intereya K, Feng T, Liu JK and Isaka M: Isolation of 3, 4-seco-27-norlanostane triterpenoids from cultivated fruiting bodies of *Ganoderma orbiforme*. Phytochemistry Letters 2018; 28: 104-9.
81. Heleno SA, Ferreira IC, Esteves AP, Ćirić A, Glamočlija J, Martins A, Soković M and Queiroz MJ: Antimicrobial and demelanizing activity of *Ganoderma lucidum* extract, p-hydroxybenzoic and cinnamic acids and their synthetic acetylated glucuronide methyl esters. Food and chemical toxicology 2013; 58: 95-00.
82. Teplyakova TV, Psurtseva NV, Kosogova TA, Mazurkova NA, Khanin VA and Vlasenko VA: Antiviral activity of polyporoid mushrooms (higher Basidiomycetes) from Altai Mountains (Russia). International Journal of Medicinal Mushrooms 2012; 14(1): 37-45.
83. Kabanov AS, Kosogova TA, Shishkina LN, Tepliakova TV, Skarnovich MO, Mazurkova NA, Puchkova LI, Malkova EM, Stavskiĭ EA and Drozdov IG: Study of antiviral activity of extracts obtained from basidial fungi against *influenza* viruses of different subtypes in experiments *in-vitro* and *in-vivo*. *Zhurnal mikrobiologii*, epidemiologii, i immunobiologii 2011(1): 40-43.
84. El Dine RS, El Halawany AM, Ma CM and Hattori M: Anti-HIV-1 protease activity of lanostane triterpenes from the vietnamese mushroom *Ganoderma colossum*. Journal of natural products 2008; 71(6):1022-1026.
85. Venturella G, Saporita P and Gargano ML: The potential role of medicinal mushrooms in the prevention and treatment of gynecological cancers: a review. International Journal of Medicinal Mushrooms 2019; 21(3).
86. Mohd Sairazi NS and Sirajudeen KN: Natural products and their bioactive compounds: neuroprotective potentials against neurodegenerative diseases. Evidence-Based Complementary and Alternative Medicine 2020.

87. Cai Q, Li Y and Pei G: Polysaccharides from *Ganoderma lucidum* attenuate microglia-mediated neuroinflammation and modulate microglial phagocytosis and behavioural response. Journal of Neuroinflamm 2017; 14(1): 63-75.
88. Huang NK, Cheng JJ, Lai WL and Lu MK: *Antrodia camphorata* prevents rat pheochromocytoma cells from serum deprivation-induced apoptosis. FEMS Microbiology Letters 2005; 244(1): 213-19.
89. Adams M, Christen M, Plitzko I, Zimmermann S, Brun R, Kaiser M and Hamburger M: *Antiplasmodial lanostanes* from the *Ganoderma lucidum* mushroom. Journal of natural products 2010; 73(5): 897-00.
90. Azeem U, Hakeem KR and Ali M: Bioactive Constituents and Pharmacological Activities. In Fungi for Human Health Springer, Cham 2020; 59-95.
91. Maheshwari G, Gessner DK, Neuhaus K, Most E, Zorn H, Eder K and Ringseis R: Influence of a biotechnologically produced oyster mushroom (Pleurotus sajor-caju) on the gut microbiota and microbial metabolites in obese zucker rats. J of Agri and Food Chemistry 2021; 69(5): 1524-35.
92. Iuchi T, Hosaka T, Shiroishi M, Ono H, Inukai K, Sumita T, Sakai G, Katayama S and Awata T: Influence of treatment with extracts of *Hypsyzigus marmoreus* mushroom on body composition during obesity development in kk-ay mice. Journal of Nutritional Science and Vitaminology 2015; 61(1): 96-00.
93. Sonawane H, Arya S, Ghole V, Apte K, Shelke D and Chaskar M: Hypoglycemic and anti-cataract activity of crude exopolysaccharides of medicinal mushroom *Phellinus badius* on streptozotocin-induced diabetic rats and goat eye lenses respectively. Bioactive Carbohydrates and Dietary Fibre 2020; 24: 100241.
94. Li J, Gu F, Cai C, Hu M, Fan L, Hao J and Yu G: Purification, structural characterization, and immuno-modulatory activity of the polysaccharides from *Ganoderma lucidum*. International Journal of Biological Macromolecules 2020; 143: 806-13.
95. Fombang EN, Lobe EE and Mbofung CMF: *Pleurotus florida* aqueous extracts and powder influence lipid profile and suppress weight gain in rats fed high cholesterol diet. Journal of Nutrition & Food Sciences 2016; 6: 473-79.
96. Hagiwara SY, Takahashi M, Shen Y, Kaihou S, Tomiyama T, Yazawa M, Tamai Y, Sin Y, Kazusaka A and Terazawa M: A phytochemical in the edible Tamogi-take mushroom (*Pleurotus cornucopiae*), D-mannitol, inhibits ACE activity and lowers the blood pressure of spontaneously hypertensive rats. Bioscience, Biotechnology, and Biochemistry 2005; 69(8): 1603-05.

How to cite this article:
Prajapati D, Bhatt A, Gupte S and Gupte A: Mushroom secondary metabolites: chemistry and therapeutic applications. Int J Pharm Sci & Res 2021; 12(11): 5677-89. doi: 10.13040/IJPSR.0975-8232.12(11).5677-89.