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REVIEW ARTICLE

Historical and current perspectives on therapeutic potential of higher basidiomycetes: an overview

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Abstract

Mushrooms are macroscopic fungi which can be either epigeous or hypogeous and is estimated to be 140,000 on earth, yet only 10% are known. Since ancient time, it played a diverse role in human history for mycolatry, mycophagy and as medicine in folklore and religion. Many Asian and western countries consider mushrooms as panacea for a large number of diseases and utilized for consumption as a gourmet food for its taste as well as flavor. In recent years, scientific research fraternities have confirmed that various extracts and metabolites of mushrooms used traditionally are able to treat a wide range of diseases due to their balanced modulation of multiple targets thereby providing a greater therapeutic effect or equivalent curative effect to that of modern medicine. Medicinal mushrooms especially those belonging to higher basidiomycete groups are reservoir of bioactive compounds with multiple therapeutic properties. The present review provides historical importance as well as an updated information on pharmacologically relevant higher basidiomycetes belong to the genus *Agaricus, Auricularia, Phellinus, Ganoderma, Pleurotus, Trametes* and *Lentinus* and their biologically active secondary metabolites. This will help the researchers to understand various type of secondary metabolites, their therapeutic role and related in vivo or in vitro work at a glance. The mounting evidences from several scientific community across the globe, regarding various therapeutic applications of mushroom extracts, unarguably make it an advance research area worth mass attention.

Keywords *Agaricus* · *Auricularia* · *Ganoderma* · *Lentinus* · *Phellinus* · *Pleurotus* · *Trametes*

Introduction

Mushrooms are macro-fungi which grows abundantly on the substrate with distinctive basidiocarp which can be either hypogeous or epigeous (Chang and Miles 1978).

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Significance of mushroom in religion and various cultures since immemorial times

Evidences about the use of mushroom since antiquity could be easily searched globally, especially certain ancient cave art displaying native mushrooms. Mushrooms often symbolized as an integral part of religion especially in settings of the rites of passage ceremonies (Zent 2008). Perseverance of mushrooms in folklore and fairy tales were evident from ancient Babylonian, classical Mediterranean, Germanic, Indian (Polosmak 2010) and Finnish mythological tales, while some of which have direct influence or derived from China or Persian countries (Dugan 2008).

Mushroom as food and medicine: a holistic and traditional approach

Mushrooms have gained attention as a favored and healthy food due to their flavor, high mineral, vitamin, amino acid, low fat and sodium contents, high dietary fibers, digestible proteins with near to no calories (Firenzuoli et al. 2008). Since ancient time till date, mushrooms have been cultivated and utilized in Asian countries like China, Japan, Korea (Rathee et al. 2012).

Ayurveda; an Indian traditional medicinal system believes in maintaining the balance between mind, body, soul and rectifying doshas (i.e., health issues) such as *Kapha*, *Pitta* and *Vatta*, to attain healthy life, the treatment of which lies in nature and varies with each individual. Similar are the views of traditional Chinese medicinal system. Where, mind and body are treated as a miniscule universe in which each and every individual are treated as exclusive entities and their health depends on the balance between Ying and Yang (Bonell 2001). In accordance to this, Emperors of great dynasties would drink tea, concoction made out of mushrooms especially Lingzhi or *Ganoderma* for attaining a state of perpetuity. Amongst fruits and vegetables used to treat kapha, mushrooms, though not relentlessly, are also administered (Satyavati 2008).

Mushrooms in Indian folk medicine

Consumption of wild mushrooms as food and medicine are well documented by various investigators (Kaul and Kachroo 1974; Purkayastha and Chandra 1985; Bhatt and Lakhanpal 1988, 1989; Harsh et al. 1993, 1996, 1999; Kaul 1993; Rai et al. 1993; Sharma and Doshi 1996; Sharda et al. 1997; Barua et al. 1998; Singh and Rawat 2000; Sagar et al. 2005; Karwa and Rai 2010; Semwal et al. 2014).

Several documentary evidences could be found on traditional use of mushroom in India viz. Baiga tribes in Central India used *Ganoderma lucidum* for treating asthma, *Agaricus* sp. to cure goiter and *Lycoperdon pusillum* for gum bleeding and wound care (Rai et al. 2005). Tribes in Assam such as Gaos, Adivashis, Bodos and Rajbangshis consumed wild edible mushrooms as food.

Kharia and Bhuyan tribes from Odisha uses *Volvariella* sp., *Russala* sp., *Astraeus hygrometricus*, *Geastrum* sp., *Termitomyces reticulates*, *Lactarius* sp., *Lycoperdon* sp. and *Tuber* sp. not only as food but also as medicine as prescribed by vaidus (Panda and Tayung 2015).

While in West Bengal especially in Darjeeling, various tribes use *Amanita* sp., *Calocybe* sp., *Fistulina hepatica*, *Grifola frondosa*, *Hericeum* sp., *Lentinus squarrosulus*; *Meripilus giganteus*; *Pleurotus* sp., *Russala* sp., *Schizophyllum* sp., *Termitomyces* sp. and *Volvariella* sp. as food and *Daldinia concentric*, *Schizophyllum commune*, *Termitomyces clypeatus*, *Cordyceps sinensis* and *Pisolithus arhizus* as medicine to gain relief from minor skin infections, as an anti-aging, revitalizer as well as an invigorative (Panda and Tayung 2015). Hence, Mushrooms are regarded as highly sought-after group of fungi which, with ethnic knowledge, can be relished as gourmet food and medicine.

Mushroom toxicity, diagnosis and therapy

Besides edibility and health benefits, mushrooms are known to causes serious intoxication which implicated in the death of some historical figures such as Roman emperor Claudius in AD 54 (Marmion and Wiedemann 2002) and Holy Roman emperor Charles VI in 1740. Mushroom poisoning majorly occurred as forager misidentification of poisonous mushroom as edible species, for self-killing and due to the involvement of psychotropic substances (Tran and Juergens 2019).

Symptoms can be as meager as gastrointestinal upset to potentially catastrophic manifestations like organ failures, neurological sequelae and even death. Severity of symptoms depends on various factors such as the type of species, toxins and amount of mushroom ingested as well as geographical area in which the mushroom was growing.

Mushroom poisoning can be divided into nine categories based on the type of toxic and clinical symptoms: (A) Phalloides (B) Orellanus (C) Gyromitra (D) Muscarine (E) Pantherina (F) Psilocybin (G) Gastrointestinal mushroom syndrome (H) Corpinus (I) Paxillus (Ko 1993).

These syndromes target Autonomic nervous system, Central nervous system, organ like Kidney (Lheureux et al. 2005; Bronstein et al. 2009; Beuhler et al. 2009), Liver failure (Diaz 2018) as well as affects intestine (Table 1).

Diagnosis of mushroom poisoning is carried out primarily by collecting anamnestic data, expert identification of mushroom from the food ingested and finally chemical analysis. Therapeutic strategies involve primary detoxification by the induction of emesis, stomach pumping or gastric lavage and use of activated charcoal; while secondary detoxification includes symptomatic treatment and use of specific antidotes (Beer 1993).

Medicinal mushroom

Medicinal mushroom which mainly belongs to higher basidiomycetes is ecologically, physiologically and taxonomically a diverse group of a fungal kingdom (Asatiani et al. 2010). Recent decade has seen a marked increase in potential use of higher basidiomycete, especially mushrooms in biotechnology and commercial utilization, particularly in food, pharmaceutical, enzymes and cosmetics sectors (Asatiani et al. 2010).

Table 1 Classification of syndromes caused by mushrooms

S. no.	Syndrome	Organ/System	Symptoms	Latency period	References
1	Paxillus		Hemolytic Anemia		Winkelmann et al. (1982); Ko (1993)
2	Coprinus	Autonomic nervous system (indirect)	Ethanol intolerance		Haberl et al. (2011); Ko (1993)
3	Phalloides	Liver, Kidney and Intestine		6–24 hr 6–12 hr 0.5–2 hr	Santi et al. (2012); Ko (1993)
4	Gyromitra	Liver and Kidney			Horowitz and Horowitz (2019); Ko (1993)
5	Orellanus	Kidney		30hr–14 days	Gallego Domínguez et al. (2008); Ko (1993)
6	Muscarine	Autonomic nervous system (direct)		0.5–2 hr	Ko (1993)
7	Pantherina	Central nervous system		0.5–3 hr	Łukasik-Głebocka et al. (2011); Ko (1993)
8	Psilocybin	Central nervous system			Ko (1993)
9	Gastrointestinal mushroom syndrome	Intestine		0.5–2 hr	Hamzah et al. (2017); Ko (1993)

Table 2 Bioactivities of secondary metabolites of Genus *Agaricus*

S. no.	Name	Polysaccharide	Steroid/Terpenoid	Role	Cell line	Animals	References
1	*Agaricus bisporus and Agaricus brasiliensis*	Polysaccharide		Immunomodulatory effects	✓		Smiderle et al. (2011)
2	*Agaricus bisporus (brown)*	ABP-AW1		Immunomodulatory effects	✓	✓	Zhang et al. (2014)
3	*Agaricus blazei*	Polysaccharide		Immunomodulatory effects		✓	Cui et al. (2013)
		Glucan Polysaccharide		Analgesic		✓	Gonzaga et al. (2013)
		Polysaccharide		Antitumor	✓		Mizuno et al. (1999)
		Polysaccharide		Antitumor	✓		Endo et al. (2010)
			Agarol (an ergosterol derivative)	Antitumor		✓	Shimizu et al. (2016)
			Blazein (steroid)	Antitumor	✓		Itoh et al. (2008)

Nutritional importance

Higher basidiomycetes are rich in carbohydrates (accounts more than 50% bulk on dry weight basis), digestible proteins (comparable to egg protein), low fat content, vitamins (especially vitamin B complex) and minerals like organic selenium and germanium (Wani et al. 2010).

Innumerable bioactive secondary metabolites

Mushrooms contain several bioactive compounds exhibiting diverse curative activities mainly by boosting immune system. These bioactive compounds include polysaccharides, glycoproteins or polysaccharide–protein complexes, triterpenoids, sesquiterpenoids, sterols, proteins, peptides, amino acids, nucleosides, nucleotides, alkaloids, vitamins and essential minerals.

Therapeutic and curative benefits

Medicinal mushrooms exhibit multitudinous bioactivity such as tumor regressing (Hetland et al. 2011), cholesterol lowering (Im et al. 2018), antimicrobial (Knežević et al. 2018), maintain blood glucose level (Lu et al. 2018), increase glucose tolerance (Guo et al. 2010), antiviral (Krupodorova et al. 2014), improvise cognitive function and promote proliferation of Neural Progenitor (Huang et al. 2017), immunomodulatory (Staniszewska et al. 2017), anti-aging (Park et al. 2005 and Tuli et al. 2014), wound healing stimulator (Gupta et al. 2014), as probiotics (Chang et al. 2019) and in bioremediation (Pezzella et al. 2017).

Genus *Agaricus* (L.)

Agaricus blazei (Murrill) is native to Brazil and extensively cultivated in Japan for its curative properties (Firenzuoli et al. 2008). Byzantine in medical treatises from 4th Century AD and Orivasion and Apuleius in 15th Century AD described the use of *A. blazei* against various ailments (Ramoutsaki et al. 2002). Scientific evaluation has validated traditional knowledge on *A. blazei* and confirmed its medicinal properties due to secondary metabolites. Polysaccharides (especially β-glucans) were found to inhibit tumorigenesis and carcinogenesis via combination of various mechanisms (Liu et al. 2015a, b; Hetland et al. 2016 and Jiang et al. 2018), displayed potential role as immunomodulator (Chan et al. 2007; Kang et al. 2015), controls cholesterol level in blood (Kim et al. 2005; de Miranda et al. 2014) and prevention of hepatic diseases (Al-Dbass et al. 2012) due to immunologically active glucans, i.e., (1-3)-β-D linked glucose polymers. Terpenoids of *A. blazei* have been used in cosmetic industry and the formulation is US patented (Grothe et al. 2016). Various clinical studies were carried out for evaluating its potential role as analgesic in patients with Crohn's disease (Therkelsen et al. 2016), as dietary supplement in patients with multiple myeloma (Tangen et al. 2015) and type-II diabetes (Hsu et al. 2007). Though clinical trials are giving significant confirmation on its therapeutic property, perplexing concern associated with the presence of agaritine, a carcinogenic substance (Firenzuoli et al. 2008), and various heavy elements like cadmium, lead, mercury or even ability to accumulate radioactive substance posed limitations on its utility (Garcia et al. 1998).

Another species of *Agaricus* is *A. bisporus* (J.E. Lange), commonly known as white button mushroom. It is a native to grasslands in North America and Europe. Historically, in France, these mushrooms were cultivated for first time (Bhushan and Kulshreshtha 2018). The mushroom is rich in dietary fibers, protein, micronutrients, vitamins, carbohydrate and low-fat content (Anderson and Fellers 1942; Abou-Heilah et al. 1987; Beaulieu et al. 1999; Valverde et al. 2015). Secondary metabolites present in the fruiting body display various bioactivities such as in vitro and in vivo antioxidant activity (ethanolic extract) (Liu et al. 2013), Mannogalactoglucan displays cytotoxic effect against HepG2 cell lines (Pires et al. 2017), ABP-1 and ABP-2, polysaccharides showed significant antiproliferative effect on MCF-7 and reduces tumor growth in mice implanted with Sarcoma 180 cells (Jeong et al. 2012), dried *A. bisporus* mushrooms improved the intestinal microflora of broiler chicken (Kavyani et al. 2014), silver and gold nanoparticles were synthesized from *A. bisporus* elicited antimicrobial activity against a wide range of Gram-positive and Gram-negative bacteria (Dhanasekaran et al. 2013) and purified tyrosinase showed melanogenic potential against skin disorder vitiligo (Zaidi et al. 2016).

In adult patients with type-II diabetes, oral administration of *A. bisporus* resulted in reduction of inflammatory markers and increase in the antioxidant status of the diabetic individuals (Calvo et al. 2016); whereas in Phase I trials, mushroom powder decreased immunosuppressive factors in patients with recurrent prostate cancer (Twardowski et al. 2015). In certain cases, results from clinical trials do not prove high therapeutic efficacy of *A. bisporus* when reaches at human trial. Hence, not all data obtained after experiments in animal model systems could be applied to real clinical practice, and thus, various diseases including cancer therapies need to be chosen very carefully to produce the anticipated effects (Volman et al. 2010). Bioactivities of few secondary metabolites of this mushroom are mentioned in Table 2.

Genus *Auricularia* (Bull. ex Juss.)

Ear-shaped fruiting bodies of *Auricularia* grow particularly on shrubs and on the woods of broad-leaved deciduous trees. *Auricularia* are commonly known as wood ear fungus, cloud ear fungus, black ear fungus or Jews ear fungus; while in countries like China, they are known as heimùěr (wood ear) and kikurage in Japanese (Sekara et al. 2015). *Auricularia* has been credited as the first mushroom to be cultivated by man as documented in Tang Ben Cao around 600 A.D. (Chang and Miles 1978).

Table 3 Bioactivities of secondary metabolites of Genus *Auricularia*

S. no.	Name	Polysaccharide	Role	Cell line	Animals	References
1	*Auricularia auricula*	Polysaccharide	Cholesterol lowering effect		✓	Cheng et al. (2008)
			Prevention against LPS induced acute liver injury		✓	Zhuan-Yun et al. (2015)
2	*Auricularia polytricha*	Polysaccharide	Anti-hypercholesterolemic effect		✓	Zhao et al. (2015a, b)
			Apoptotic induced cytotoxicity	✓		Yu et al. 2014)

As stated in 'Doctrine of signatures', fungi and plants which are similar in structure and shape to any parts of human body could be employed to treat disease associated with that part (Boehme 1651). Hence, in traditional Asian medicine (Roupas et al. 2012), *Auricularia* was used in treating ear infection (Ardigò 2017); similarly, it resembles the folds of throat and hence used in treating throat infection and it is also used to treat eye-related ailments by blending with eye medicine due to its gelatinous consistencies (Chauhan 2009). A significant validation of documented traditional knowledge on *Auricularia* is confirmed by modern science.

More scientifically explored species of *Auricularia* are *Auricularia auricula-judae*, *Auricularia polytricha* and *Auricularia fuscosuccinea*. *Auricularia* species are rich in carbohydrate, protein, vitamins, minerals and less fat (Mau et al. 1998). The preliminary screening by Ikekawa et al. (1969) initially demonstrated a lesser antitumor potential of *Auricularia auricula-judae* but later on with improved extraction techniques; it was revealed that tumor regressing capacity of the mushroom completely depends upon covalently linked polysaccharides. Whereas, an alkali-soluble (1→3)-β-D-glucan had no potential antitumor effect (Misaki and Kakuta 1995). Recent studies revealed that fruiting bodies extracted with various solvents induce cytotoxicity against tumor cells via apoptosis (Reza et al. 2014). Oral administration of *Auricularia* in patients with gastrointestinal cancer exhibited increased efficiency of chemotherapeutical drugs (Oxiplatin, Cisplatin and adriamycin) and long survival rate with no adverse side effects (Ma et al. 2018). Besides polysaccharides, other secondary metabolites—polyphenols, exhibit cholesterol lowering effect (Chen et al. 2011). Crude extract of *Auricularia* exhibited antimicrobial activity against *E. coli* and *S. aureus* and antioxidant activity by exhibiting its promising potential when used as dietary supplement (Cai et al. 2015). Not only *Auricularia auricula-judae* but also other species such as *Auricularia polytricha* is a potent source of pharmacologically important compounds. *Auricularia polytricha* exhibits free radical scavenging effect, antitumor and immunomodulating effect (Puttaraju et al. 2006; Mau et al. 2001; Sheu et al. 2009). It also elicited anti-inflammatory activity in animals with fatty liver (Chiu et al. 2014). Mycology Research Laboratories (United Kingdom) have manufactured and commercialized *Auricularia auricula-judae* in the form of *Auricularia*-MRL™—a dietary supplement which supports immune system and maintains homeostasis. Bioactivities of few secondary metabolites are given in Table 3.

Genus *Trametes* (Fr.)

It is commonly known as turkey tail, 'Kawaratake' in Japan and 'yun-zhi' in Chinese (Yang et al. 1993). It is a highly adaptive fungus with cosmopolitan nature. This mushroom displays an immunomodulating effect in patients treated for breast cancer (Standish et al. 2008), exhibited antibacterial effect (Matijašević et al. 2016), cytotoxic effects against cancer cell lines, anti-fungal effect and anti-neurodegenerative effect (Knežević et al. 2018).

In 1977, Health ministry of Japan gave approval to a polysaccharide (PSK-Polysaccharide Krestin) isolated from *Trametes Versicolor* to be used as an anticancer agent in human (Hobbs 2004). In a study carried in 2008, *Trametes versicolor* was orally administered in women with breast cancer as part of Phase I trial and a promising observation was made. The mushroom improved the immune status of immune-compromised patients (Torkelson et al. 2012).

Trametes versicolor has an ability to degrade endocrine disrupting chemicals (EDCs); hence, it is considered as natural cleanser and can be used in bioremediation (Pezzella et al. 2017). Bioactivities of few secondary metabolites are given in Table 4.

Genus *Pleurotus* ((Fr.) P. Kumm)

Pleurotus ostearus is commonly known as oyster mushrooms. It was first cultivated during World War I (Kaufer 1936). It has high nutritional value and palatability. *Pleurotus ostearus* is extensively studied for its tumor inhibiting property (Jedinak and Sliva 2008), antibacterial activity (Younis et al. 2015) and cholesterol lowering effect (Schneider et al. 2011).

Oral administration to hypertensive male with Type-II diabetes, along with anti-diabetic drug significantly reduced

Table 4 Bioactivities of secondary metabolites of Genus *Trametes*

S. no.	Name	Polysaccharide	Role	Cell line	Animals	Clinical trial	References
1	*Trametes robiniophila*		Cytotoxic/apoptosis/antitumor		✓		Zhao et al. (2015a, b)
2	*Trametes versicolor*	Polysaccharide Krestin (PSK)	Immunochemotherapy agent	✓	✓	✓	Abascal and Yarnell (2007)
			Immunomodulator in gastric cancer patients			✓	Akagi and Baba (2010)
		Tramesan	Antileukemia activity	✓			Ricciardi et al. (2017)

Table 5 Bioactivities of secondary metabolites of Genus *Pleurotus*

S. no.	Name	Polysaccharide	Steroid/Terpenoid	Role	Cell line	Animals	Clinical trial	References
1	*Pleurotus ostreatus*	Polysaccharide-FII		Antitumor	✓			Wisbeck et al. (2017)
		pleuran (β-glucan)		Antioxidant		✓		Bobek and Galbavy (2001)
				Nutritional supplement			✓	Bergendiova et al. (2011)
				Immunomodulotor			✓	Jesenak et al. (2014)
2	*Pleurotus tuber-regium*	1P, 2P and 3P		Anti Hyperglycemic and reduce oxidative stress		✓		Huang et al. (2012)
3	*Pleurotus eryngii*		Eryngiolide A	Cytotoxic/Antitumor	✓			Wang et al. (2012)
4	*Pleurotus cystidiosus*		Pleuroton A and B; Clitocybulol D, E and F	Cytotoxic/Antitumor	✓			
			Pleuroton B	Apoptotic induced cytotoxicity	✓			Zheng et al. (2015)

hyperglycemic state as well as controlled blood pressure (Jesenak et al. 2013). A formulation named Imunoglukan P4H®, containing pleuran (a beta glucan), syrup was given to Kindergarten children which resulted in significant decrease in the respiratory tract infection with no serious adverse effects (Choudhury et al. 2013).

Another well-studied species is *Pleurotus eryngii*. It contains various bioactive compounds like polysaccharides, eryngiolide A, ubiquinone-9, and triterpenoid which makes this mushroom potent and displays various bioactivities like antioxidant, antimicrobial, anticancer, antiviral, cholesterol lowering and estrogen-like activity by boosting host immune system (Fu et al. 2016). Various studies have been carried out with *P. ostearus* and *P. eryngii* in combination with other mushroom extracts for human trials. Bioactivities of few secondary metabolites are given in Table 5.

Genus *Phellinus* (Quél)

Another important genus is *Phellinus* Quél. *Phellinus* species are used in traditional medicine for centuries in various parts of the world, for example: *Phellinus rimosus* is reported to be used against mumps in Kerala (Huang et al. 2011a, b), tribes of Northern India use it to treat gastrointestinal disorders (Vaidya and Rabba 1993). While, in Chinese and Japanese dynasties, *Phellinus linteus* was taken in the form of tea and concoctions by emperor of Tang government and Shi-Zhen Li in the Ming Dynasty, for longevity and vitality. Such use of the mushroom could be found in old medicinal books or Pharmacopeia such as “New compendium of Materia Medica” (Su and Cao 1981) and “Chinese Compendium of Materia Medica” (Li and Mu 2004).

Two important secondary metabolites, i.e., polysaccharides and polyphenols are responsible for the therapeutic potential. An array of pharmacologically relevant activities is displayed by the mycelia, submerged culture and fruiting bodies of *Phellinus* species, which includes: antioxidant (Zhang et al. 2015), anti-inflammatory (Song and Park 2014), anti-diabetic (Wang et al. 2015), reduction in triglyceride absorption and obesity (Noh et al. 2011), system protection (Suabjakyong et al. 2015), on dermatological conditions like Eczema (Hwang et al. 2012), antimicrobial

Table 6 Bioactivities of secondary metabolites of Genus *Phellinus*

S. no.	Name	Polysaccharide	Phenolics	Role	Cell line	Clinical trial	References
1	*Phellinus linteus*		Hispolon	Cytotoxic/apoptosis/antitumor	✓		Kim et al. (2016)
		Polysaccharide		Antidiabetic		✓	Kim et al. (2010)
2	*Phellinus igniarius*		Hispolon	Cytotoxic/Antitumor	✓		Hsin et al. (2017)
				Cytotoxic/Cell cycle arrest/Antitumor	✓		Huang et al. (2011b)
3	*Phellinus baumii*	Polysaccharide		Antidiabetic	✓		Hwang et al. (2005)

(Kodiyalmath and Krishnappa 2017) and anticancer activity (Konno et al. 2015).

Extensive studies were carried out on cell lines and animal models, whereas only few human studies were reported so far, which include anti-metastatic effect of *Phellinus linteus* against patient with terminal bone cancer (Shibata et al. 2004), Intake of *P. linteus* by a 65-year-old Korean man together with radiotherapy caused increased inhibition of hepatocellular carcinoma (HCC) and rapidly proliferating bone mass at front lobe (Nam et al. 2005); while, complete regression of tumor was observed in a 79-year-old man with HCC (with multiple lung metastases) who was solely depending on *P. linteus* mycelium intake without any other treatment for 1 month (Kojima et al. 2006). Bioactivities of few secondary metabolites are given in Table 6.

Genus *Ganoderma* (P.Karst)

Genus *Ganoderma* was first established by Karsten (1881). It constitutes of around 300 species of white rot wood decaying fungi with an elementary purpose of lignocellulose degradation. *Ganoderma* is derived from Greek word Ganos—"brightness" and derma—"skin". The medicinal properties of mushrooms under this genus dated back to 100 B.C.

Recordings from history

Description about shining mushroom was first documented in a *Fu* (rhapsody; prose poem), while early recordings of its medicinal properties were recorded in *Shennong bencao jing,* a pharmaceutical book dated back to 200–250 CE which categorizes the mushroom into six colors each referring to each body part (Yang 1998) and they are as follows:

Green mushroom: liver
Red mushroom: heart
Yellow mushroom: spleen
White mushroom: lungs
Black mushroom: kidney
Purple mushroom: provides essence

From the Chinese gods to earliest Chinese emperors to long-lived legendary figures named shining *Ganoderma*/*G. lucidum* as 'Herbs of deathlessness', 'the elixir of immortality', 'Herb of spiritual potency' and 'Soup of emperor with thousand mistresses' (Arora 1986; Knechtges 1996). Though such varied description was given to "Lingzhi", which refers to *Ganoderma lucidum*, researcher like Russell M. Peterson, believes that throughout the historical era, Lingzhi might be symbolizing the same species or different species of *Ganoderma* (Paterson 2006).

Most commonly and scientifically investigated species are *G. lucidum*, *G. atrum*, *G. curtisii*, *G. tsugae*, *G. microsporum*, *G. cochlear*, *G. sinense* and *G. applanatum.*

Metabolite profiling of Genus *Ganoderma*

Genus *Ganoderma* is rich in secondary metabolites exhibiting various bioactivities. Some of the unique constituents of *Ganoderma* include triterpenoids such as ganoderic acids, ganoderic alcohols. Other bioactive compounds include steroids, flavonoids, alkaloids, amino acids, modified carbohydrate moieties, nucleosides, protein and fatty acids. Bioactivities of few secondary metabolites are given in Table 7.

Pharmacological activities

Antioxidant and Immunomodulatory effects Dietary supplements improvise, provide and restore a balance between pro-oxidant and antioxidant status of a living system, thereby improving the immunity by reducing the risk associated with age-related bodily variations (Meydani 1999; Valverde et al. 2015).

Aqueous extract of *G. curtisii* exhibits antioxidant activity (Ivone et al. 2016), while polysaccharides isolated from *G. atrum* and *G. lucidum* attenuated D-galactose-induced oxidative stress in rats and exhibited immunomodulatory activities in vitro and in vivo models, respectively (Li et al. 2011; Lai et al. 2010). Furthermore, an immunomodulatory protein isolated from *G. microsporum* (GMI) inhibited the inflammatory mediators and neuronal cell death in lipopolysaccharide (LPS)/interferon-γ (IFN-γ)-treated primary neuron/glial culture (Chen et al. 2018). Furthermore, in small-scale clinical trials, it was observed that *G. lucidum* supplementation improvised the antioxidant profile in healthy volunteers without causing any significant adverse effects (Wachtel-Galor 2004a, b).

Anticancer: antiangiogenic, antimetastatic, antiproliferative and tumor regressing activity *Ganoderma* species are plethora of bioactive compounds with anticancer properties. Numerous anticancer compounds isolated from various parts of a fruiting body/mycelium/submerged culture exhibited cytotoxic, metastatic and antiproliferative activity. Some of the activities are briefed as follows: Methanolic fraction of *G. tsugae* induced cytotoxicity towards colorectal cancer and inhibited tumorigenesis in nude mice (Hsu et al. 2008), while ethanolic extract of *G. lucidum* showed regression of neo-vasculature formation in chick embryo and dose-dependent regression of nitric oxide production in LPS-treated RAW 264.7 cell lines macrophages (Song et al. 2004). Additionally, extract of various parts of *G. lucidum*, *G. sinense* and *G. tsugae* showed potential anti proliferative

Table 7 Bioactivities of secondary metabolites of Genus *Ganoderma*

S. no.	Name	Polysaccharide	Steroid/terpenoid	Protein	Role	Cell line	Animals	References
1	*Ganoderma lucidum*	Polysaccharide			Anti Hyperglycemic		✓	Xiao et al. (2012); Zhang and Lin (2004); Li et al. (2011)
		F31			Anti Hyperglycemic		✓	Xiao et al. (2017)
		Polysaccharide			Immunomodulatory		✓	Shi et al. (2012)
			Ganoderic acid		Antitumor	✓		Gill and Kumar (2016)
			Ganoderic acid DM		Antitumor	✓		Liu et al. (2009)
			Ganoderic acid A		Antitumor	✓		Yang et al. (2018)
					Antitumor	✓		Wang et al. (2017)
			Ganoderic acid DM		Antitumor	✓		Wu et al. (2012)
			Ganoderic acid X		Antitumor	✓		Li et al. (2005)
			Ganoderic acid T		Antitumor	✓		Tang et al. (2006)
			Ganoderic acid T			✓		Liu et al. (2012)
			Ganoderic acid T			✓	✓	Chen et al. (2010)
			Ganoderic acid Me		Antitumor	✓	✓	Wang et al. (2007)
			Ganoderic acid Me			✓		Chen and Zhong (2009)
			Ganoderic acid Mf and S		Antitumor	✓		Liu and Zhong (2011)
			Ganoderic acid DM		Antitumor	✓		Wu et al. (2012)
			Ganoderic acid X		Antitumor	✓		Li et al. (2005)
			Ganoderic acid C1		Anti-inflammatory	✓		Liu et al. (2015a)
2	*Ganoderma applanatum*	Polysaccharide			cytotoxic and immunomodulatory	✓		Osińska-Jaroszuk et al. (2014)
3	*Ganoderma microsporum*			GMI (fungal immune-modulatory protein)	Antitumor	✓		Hsin et al. (2018)
4	*Ganoderma sinense*	GSP-2 (Polysaccharide)			Anti-inflammatory	✓		Han et al. (2014)

activity against MCF-7 and MDA-MB-23 cell line without exhibiting any cytotoxicity towards mouse splenic lymphocytes (Yue et al. 2006).

Secondary metabolites from *G. atrum* like polysaccharide PSG-1 exhibited antitumor activity by activating macrophage through TLR-4-dependent pathways (Zhang et al. 2013); while immunomodulatory fungal protein—FIP-gat (Xu et al. 2016), induces cytotoxicity against breast cancer cell lines.

Reports of few clinical trials could be found such as: Ganopoly®, a polysaccharide from *G. lucidum,* improved immune response in advanced stage cancer patients (Gao et al. 2003) while no studies claim *G. lucidum* or any *Ganoderma* species to be the first line of treatment for cancer therapy. But all species acts as an adjunct to existing therapies by inhibiting tumorigenesis and enhancing host immunity (Jin et al. 2012).

Organ system protective ability *Ganoderma* is known to prevent vital organs from various drug-induced toxicities and also acts as an adjuvant to various cancer therapies without interfering with their fundamental properties.

Polycyclic meroterpenoids, Cochlearols A and B isolated from *G. cochlear* provide hepato- and nephro-protection under in vitro condition, respectively (Dou et al. 2014; Peng et al. 2014). In another study, co-administration of fruit body extracts of *G. lucidum* together with *Auricularia polytricha* mitigated carbofuran-induced liver toxicity. While, sole administration of *G. lucidum* provides a better ameliorating affect as compared to its counterpart. In a combined treatment, polysaccharide from *G. atrum* enhances the tumor inhibitory efficacy of cyclophosphamide by ameliorating adverse side effects of chemotherapeutic drug (Hossen et al. 2018). Xiao et al. (2003) reported the oral administration of a spore powder 99 of *G. lucidum* provided hepatoprotection to patients poisoned with *Russula subnigricans*.

Anti-diabetic activity: anti-hyperglycemic, cholesterol lowering, anti-obesity and diabetic wound healing effect Extensive epidemiological studies reported that risk factor associated with diabetes and its complication includes hyperglycemia and hypercholesterolemia. Type-2 diabetes is rapidly increasing among middle-aged-group people, teenage and adolescents with obesity and inactivity (Rosenbloom et al. 1999; Norris et al. 2002; Pozzilli and Guglielmi 2009). Another major clinical challenge associated with diabetes is impaired wound healing and diabetic ulcers (Monnier et al. 2004).

For centuries together, genus *Ganoderma* has been valued and used against diabetes and associated complications. Gl-PS (*Ganoderma lucidum* polysaccharide) inhibited the delay in wound healing by suppressing the oxidative stress in STZ (Streptozotocin)-induced diabetic mice (Tie et al. 2012). While in another study, polysaccharides from *G. atrum* ameliorated hyperglycemic and hyperlipidemic states in high-fat-diet- or overfed STZ-induced type-II diabetes in murine model (Zhu et al. 2013). Various extracts of *G. lucidum* fruit body are known to mitigate hyperglycemic state, exhibit cholesterol lowering effect, increase glucose tolerance by decreasing insulin resistance with and without in combination with diabetogenic drugs (Seto et al. 2009; Li et al. 2011; Qiao et al. 2014; Chang et al. 2015; Lee et al. 2016; Bach et al. 2018).

In a few clinical trials, *Ganoderma* has shown its potency as anti-hyperglycemic agent. Administration of Ganopoly® to seventy-one type-II diabetic patients for 3 months resulted in decrease in fasting blood glucose and post prandial glucose level (Gao et al. 2004). In certain other scarce cases, Dr. Jagjeet Singh Parwana from Punjab, India treated diabetic patients by orally administrating and topically applying *G. lucidum*, which seems to alleviate blood glucose level and enhance wound closure.

Application of *Ganoderma* in tissue engineering and drug delivery In tissue engineering applications, a mixture of polysaccharides isolated from *G. lucidum* and porous yolk–shell particles was developed to target oxidative stress and seems to have had great potential to be used against pulmonary and respiratory diseases. Whereas, green synthesis of nanoparticles using *G. neo-japonicum*, *G. lucidum* and *G. applanatum* has been used in cosmetic industry, pollutant clearance, agrochemical utility and targeted drug delivery (Karwa and Rai 2010; Gurunathan et al. 2013; Jogaiah et al. 2017).

Limitations: pharmaco-toxicological problems

a. Perplexing concerns on the relative content of Agaritine (aromatic hydrazines), from *Agaricus blazei* have been known to cause toxicity in experimental animals (Back et al. 1978; Toth et al. 1997).
b. Ingestion of *Lentinula edodes* causes flagellate mushroom dermatitis in people working at cultivation site of this mushroom (Boels et al. 2014; Corazza et al. 2015).
c. In a scarce report, a soft tissue infection by *Phellinus undulates* was reported in a 57-year-old diabetic female patient (Williamson et al. 2011).
d. In a very rare case, spores from *Lentinula edodes* and *Pleurotus ostearus* cause asthmatic attack and hypersensitivity (Mori et al. 1998; Senti et al. 2000).

Future perspectives

Higher basidomycetes is enriched with bioactive secondary metabolites with therapeutic potential as proven from pre-clinical as well as clinical studies. Moreover, additional information needed to gathered by solving some of the basic and crucial issues associated with mushrooms and its metabolites like apprehension or comprehension of the pharmacodynamics of mushroom metabolites, standardization of dosage and mechanisms to carry out a probable as well as reliable pharmacokinetic studies. Extensive isolation, characterization, quantification and curative properties of various bioactive compounds have been carried out using high throughput technologies over the years. Bioactivities, yield and production of secondary metabolites from mushrooms grown or cultivated varies from area to area, hence a clear evaluation is required before commercializing. Most of the mushrooms and their bioactive agents exhibit immunomodulatory action which presently and in future also enhances quality of life.

Author contributions RV and YBD wrote the manuscript. YBD did the final editing and acceptance of the paper. PYL, BPS and CKKN provided a structure, idea and proof reading for the paper.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Ethical statement I testify on behalf of all co-authors that our article ''Historical and current perspectives on therapeutic potential of Higher Basidiomycetes: An overview'' submitted to 3 biotech has not been published in whole or in part elsewhere. The manuscript is not currently being considered for publication in another journal. All authors have been personally and actively involved in substantive work leading to the manuscript, and will hold themselves jointly and individually responsible for its content.

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