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Medicinal Mushrooms: Potent Fungi for Diverse Human Health Benefits

Nand Lal

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Abstract

Mushrooms are a wholesome food that provide ample amount of nutrients including essential amino acids, ions, minerals and vitamins to humans and can be used to compensate for the lack of nutrition and eradicating many health related problems especially malnutrition. Mushrooms also contain secondary metabolites (bioactive compounds) having role in regulating the body's immune system. With China being the largest producer of mushroom, other countries too are coming together and mushroom production and trade are growing globally. Mushroom farming is easy, feasible, less time consuming and returns good profit margins. The agro waste left after the harvesting can be biodegraded or recycled if they can be used for mushroom cultivation thus, don't need to be burned. Mushrooms have been nutritionally beneficial to humans for ages by providing many essential nutrients and have been used as medicines by the people of China and Japan. Many other countries and folk people utilized mushrooms as local medicines to treat many diseases and wounds topically. Their value has been recognized and is being exploited in modern medicine as many studies have shown successful results upon animal models and few on human patients. Folklore studies can help rediscover properties and make advancements in molecular medicines and clinical therapies. Current studies indicate that mushroom bioactive compounds regulate the immune system by eliciting immune responses or by interacting with the gut microbiota. Mushrooms also possess properties like anti-cancer, anti-diabetic, anti-inflammatory, anti-obesity and anti-neurodegenerative. Although these properties are presently being used for clinical therapies and treatment of various diseases, still there is a dire need for more experiments on the mushrooms and their extracts. This review aims to consolidate understanding of the medicinal and nutritional benefits of mushrooms including nutritional components, bioactive components, mention in folk literature and role today in clinical therapies.

Keywords: Agro industry; Edible fungi; Ethnomycology; Malnutrition; Mushrooms; Medicinal effects; Nutritional benefits.

INTRODUCTION

With changing perceptions and beliefs, today the lifestyle is also changing. With changed life style, modern dietary patterns and physical activity patterns, the risk of chronic diseases has also increased. The changed dietary pattern and the quality of food have taken a toll on the health of people. The world today is majorly facing hunger and malnutrition problems and poor nations and needy people are mainly affected by this. According to World Health Organization (WHO), ***"Malnutrition refers to deficiencies, excesses, or imbalances in a person's intake of energy and/or nutrients".*** Chronic diseases as described by WHO are cardiovascular diseases, obesity and diabetes and are known as Non-communicable Diseases (NCDs). These have significantly increased and affected a large part of the world and become a leading cause of death around the world with approximately 46% as global burden of diseases.

Author's Affiliation: Professor, Department of Life Sciences, Chhatrapati Shahu Ji Maharaj University, Kanpur 208024, Uttar Pradesh, India.

Corresponding Author: Nand Lal, Professor, Department of Life Sciences, Chhatrapati Shahu Ji Maharaj University, Kanpur 208024, Uttar Pradesh, India.

E-mail: nl_pr@yahoo.co.in

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The mortality rate because of the chronic diseases as recorded by WHO are 38 million deaths annually. HIV/AIDS, malaria, and tuberculosis are also chronic diseases as described by WHO and they too are leading cause of death around the globe.

WHO Defines Malnutrition by Categorizing it into three Types;

- Undernutrition which is related to wasting (syndrome; unwanted weight loss, severely malnourished), stunting and underweight
- Micronutrient deficiency, which is related to lacking/excess of essential vitamins and minerals for the body.
- Overweight, obesity and diet related which includes heart diseases, stroke, diabetes and some cancers.

WHO (2020) reports 1.9 billion adults as overweight/obese, 462 million adults as underweight, 149 million children as wasted who are under the age of 5 years, and 38.3 million overweight or obese around the world. 45% of death among children is because of undernutrition, mainly in countries with low income. According to the Global Hunger Index (2019) report, Central African Republic is affected severely by hunger and malnutrition and has index of 53.6. Countries heavily affected by hunger and malnutrition are Central African Republic, Yemen, Chad, Madagascar, Zambia, Liberia, Haiti, Timor-Leste, Zimbabwe, Afghanistan, Sudan, Democratic Republic of the Congo, Djibouti, Uganda.

Malnutrition prevails even today in the many sections of Indian society because of poverty, which limits the quality and quantity of food intake. The low-quality food is deficit of the essential nutrients and vitamins required for proper healthy body growth and to avoid many diseases. To get rid of these problems and to lead a healthy life, a proper diet rich in nutrients, vitamins and anti-oxidants is necessary. WHO recommends a healthy diet to combat malnutrition altogether and to prevent non-communicable diseases and should be practiced early in life. According to WHO, energy intake should be balanced with the amount of energy being released. It is recommended that total fat consumption must be less than 30%, consumption of saturated fats be less than 10%, and trans-fat consumption must be less than 1% of the total energy consumed. Sugar intake be less than 10% or can be more beneficial if cut down to only 5% or less. Salt intake must be cut down to 5g/day or less to avoid NCDs. For adults, it is advised to include fruits, green vegetables, nuts and whole grains. Unsaturated fats such as fish, avocado, nuts, sunflower, soybean, canola, olive oil preferred over saturated fats (fatty meat, butter, palm, coconut oil, cheese and ghee, etc.) and trans-fats (baked food, pre-packaged foods snacks, foods like frozen pizza, pies, cookies and wafers etc.) for a healthy life. For Infants, the initial diet is essential as it ensures a healthy life later in life and will prevent problems of obesity, overweight, NCDs. Breastfeeding is most important for infants in the initial months, and it should be accompanied with nutrient dense food as well as salt and sugars should be strictly avoided during the 6 months of age. A single diet containing multiple nutrients is preferable over the urge to consume different food for different nutrients and to solve the problem mushrooms come to the rescue.

From compensating for body vitamin and nutritional requirements to combating and avoiding the possibility of cancer, cardiovascular diseases, and many more in the body, mushrooms can be a boon to humans especially to the ones who cannot afford variety of food materials. From the earliest times, mushrooms being treated a special food and recognized as a delicacy. Mushrooms are nature's hidden treasure that is considered as whole food and suitable for any age group. There are many culinary possibilities with mushrooms; one can choose to bake them, grill, sauté, fry, roast or even stuff them and a lot experiments could be done to soothe the taste buds. Being rich in protein, vitamins, minerals and anti-oxidants, they become ideal food for consumption on a daily basis. Different species do different medicinal and nutritional benefits in human body (Khatun *et al.*, 2012).

Just like other plants, mushrooms also produce compounds as primary metabolites and secondary metabolites. Primary metabolites include proteins, carbohydrates, vitamins, minerals etc. which are required for its growth whereas secondary metabolites terpenes, steroids, triterpenoids, phallic acid, non-ribosomal peptides confer variety of adaptations to mushrooms. Mushrooms are a source of many bioactive compounds, which are usually present in cell wall as polysaccharides, proteins or as secondary metabolites. Different species of mushrooms produce different secondary metabolites like terpenes, terpenoids, phenolic compounds, benzoic acid derivatives etc. (Sanchez, 2017; Raman *et al.*, 2018). Mushroom consumption in U.S. is very high as compared to that of India. The top producers are China, the Netherlands, Poland, the United States and Italy. Mushroom industry in India has increased over the years with cultivation mainly of button mushrooms. India majorly trades

mushrooms abroad. Mushroom consumption is less in India today as compared to other countries even though the consumption has increased over the years in India (Ma *et al*., 2018). Apart from edible mushrooms, there are various poisonous mushrooms producing compounds fatal to humans. In actual there is no specific test to distinguish between the two. The hit and trial methods in earlier times has helped people recognize edible mushrooms and poisonous mushrooms.

Mushrooms are edible fungi that earlier were considered as plants. Presence of chitinous cell wall and absence of chloroplast are special features that separate them from being true plants. They are not just nutritionally valuable but also medicinally. Mushrooms are macro-fungi that belong to the group ascomycetes and basidiomycetes. These are large and diverse groups. It bears an umbrella-shaped fruiting body and pileus. Outside of pileus is lamella(s) structure, which produces spore. Mushrooms are epigeous structures. They exhibit two growth phases; one being the vegetative phase and other being the reproductive phase. The substrate after germination is followed by formation of hyphae that grows and forms a network of hyphae or mycelia. The mycelial function is increased respiration and production of enzymes. The cell wall of mushrooms is generally made up of chitin, mannoproteins and β-D-glucans (Sanchez, 2017). From ages, mushrooms are considered of a great value and are being used in medicines, therapies, analgesics etc. It was known as the 'Food of the Gods' by the Romans and Chinese culture regarded mushrooms as 'elixir of life'. Some used it to intoxicate others while some in a positive way. Some used mushrooms even to hallucinate people in religious ceremonies in the older times (Valverde *et al*., 2015).

Its medicinal use has been recognised and studied thoroughly and compounds are being extracted and used as medicine to treat various human diseases. In industry and medicine, mushrooms hold a valuable place, as they are a reservoir of several beneficial compounds. The low-fat content makes them ideal for consumption on a regular basis. Apart from proteins, they are a good source of secondary metabolites like benzoic acid derivatives, terpenes, terpenoids. Moreover, this is not just enough, as they happen to have significant amounts of vitamins such as B1, B2, B12, C, D and E. All these properties make these edible fungi anti-oxidant, anti-cancerous, anti-diabetic, anti-allergic, anti-parasitic, anti-bacterial, anti-fungal, anti-viral and immunomodulators. Many species are found to possess the property of inhibiting tumour development by inhibiting cell proliferation (Lindoquist *et al*., 2005; Valverde *et al*., 2015). *Piptoporous betulinus* has shown to be effective in the treatment of rectal and stomach cancer in Bohemia. In 16th/17th century, a complex called melanin was found in *Inonotus obliquus*, which has genoprotective effects on peroxidase-catalysed oxidation of aminodiphenyls (Lindoquist *et al*., 2005). The drugs manufactured in the modern era, works by activating immune cells like macrophages and Natural Killer cells to secrete cytokines like TNF-a, IFN-g and IL-1b. In response, they induce apoptosis and differentiation in cells. In addition, β-glucan found in the mushroom cell wall binds to membrane receptors type 3 (CD3, aMb2 integrin or CD11b/ CD18). Japan, China, Korea, and other East Asian countries (Sanchez, 2017) are mainly using these drugs.

TAXONOMY AND CLASSIFICATION OF THE FUNGI

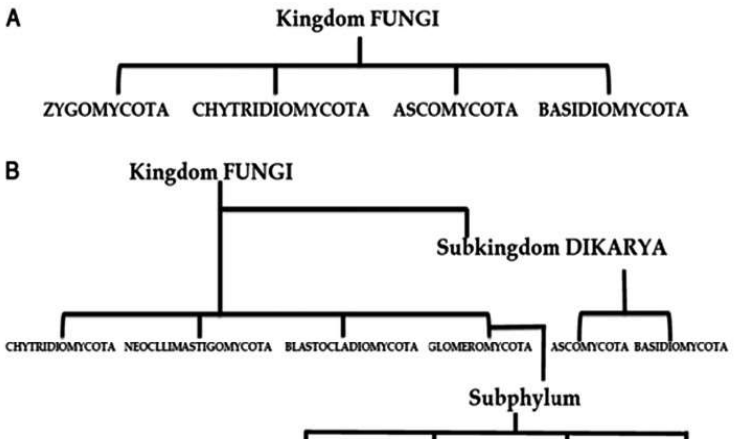

Fig. 1: Flow Chart depicting (A) Old proposed classification, which today is rejected, (B) New Classification that is accepted internationally (Qwon-Chung, 2012).

ASCOMYCOTA

They constitute as largest group of fungi producing endogenous spores by sexual reproduction; ascospores within ascus that can be parasites, pathogens, saprotrophs or symbionts. Within the fruiting bodies, the asci are present which is also known as ascomata (formed by sexual reproduction). Many asexual reproducing ascomycetes are recognized that produces conidia (asexual spores) on a stalk known as conidiophores (Fig. 2). These are known as anamorphs (Money, 2016). Around 33,000 species have been recognized within this phylum including yeast and filamentous fungi. Many are in symbiotic association with algae and cyanobacteria as well as in close associations with plant and animal pathogens, mycorrhizal species and saprotrophs. The septum cell wall contains single and centrally located pore instead of perforations like basidiomycetes. The hyphae of Ascomycetes lack dolipore septa unlike basidiomycetes. Ascomycetes are useful in many industrial applications including production and flavouring of food and the fruiting bodies can be exploited as edible source. They comprise species like *Cordyceps militaris, Tuber aestivum,* and *Urnula craterium*

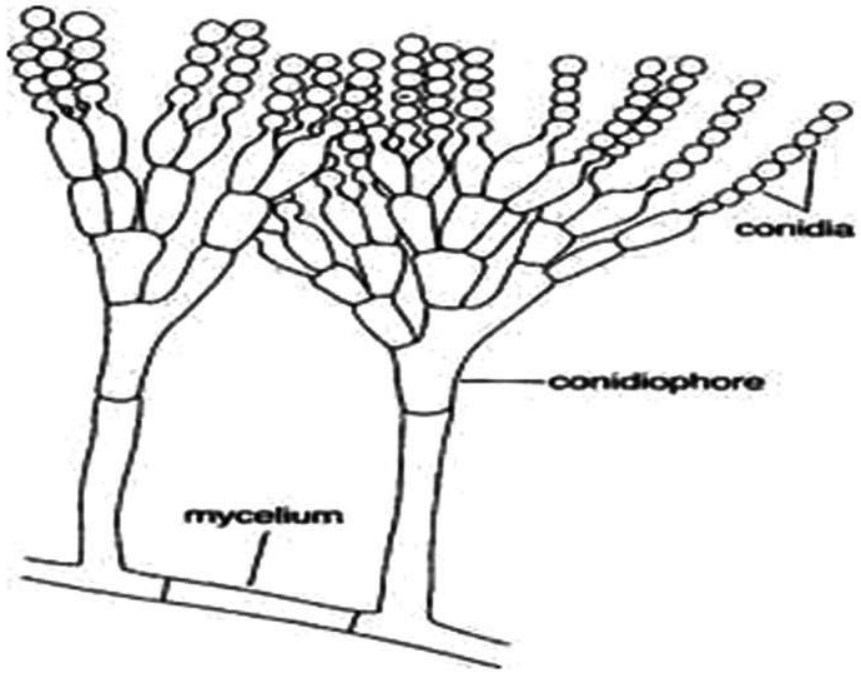

Fig. 2: Ascomycota showing chains of conidia at the ends of conidiophores.

BASIDIOMYCOTA

They comprise mushroom forming fungi, jelly fungi, rust, and smuts. Many show mycorrhizal associations with trees, shrubs and others and support the ecology of forest by decomposing wood and leaf litters. Few prey upon scale insects and are in symbiotic association with termites and leaf cutter ants. Until today, 30,000 basidiomycetes are identified which are ecologically important. Few are capable of causing deathly infection in humans. They produce spores (basidiospores) in basidia (Fig. 3) by nuclear fusion and meiosis process (Somashekharan and Loganandhan, 2020).

A characteristic feature of basidiomycete group is the presence of dolipore septum, which separates the compartments along the hyphae. It is a perforated barrel shaped structure of the septum cell wall. It comprises species like *Agaricus campestris, Malassezia globosa, Puccinia sessilis* and *Tramella fuciformis.*

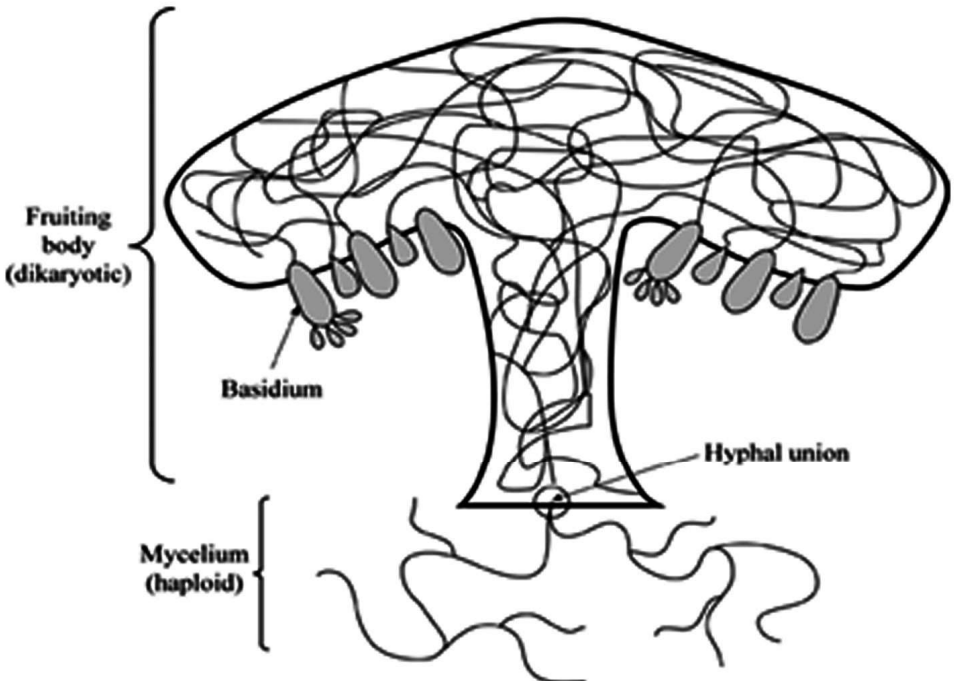

Fig. 3: Basidiomycota showing Fruit body bearing basidium.

HISTORY

The presence of mushroom dates back to the upper palaeolithic period. The Max Plank Institute for Evolutionary Anthropology in Leipzig reported the existence of mushrooms since upper palaeolithic period. The "Red Lady", was found buried from the caves of El Miron Cave in Cantabria in 2010 whose teeth upon dental calcus proved the existence of mushrooms and radiocarbon dating of the burial site reported it as 18700 years old. Other evidence found was from the examination of a hunter named Ötzi who lived around 3300 BCE, three fungal objects were found from his equipment. One material was prepared from *Fomes fomentarius* also known as 'Black Matter' and the other two were the fruiting bodies of *Fomitopsis betulina. F. fomentarius* was used to start fires and *F. betulina* was used as a medicine or remedy in old times against whipworm infection (Kotowski, 2019).

People in ancient times believed in ergotism, which is poisoning because of the alkaloid containing sclerotia in mushrooms. Gangrenous and convulsive are the two forms of ergotism. Gangrenous ergotism was believed to cause burning sensations, pain, gangrene, shredding off of the limbs leading finally to death while convulsive ergotism was believed to cause avitaminosis which begins with headache and includes symptoms like sensation of thirst, hunger, convulsions, hallucinations leading to death. According to Paracelsus, "Nothing is poison, only the doses render a substance to bet it" which means the substances i.e., alkaloids can cause ergotism, the poisoning can also be used as treatment when administered or applied in proper doses. In ancient China and by Hippocrates, these alkaloids were used in herbal medicine in labour and for stopping the bleeding post childbirth. A grass parasite, an ergot known as 'Secale Cornutum' *Claviceps purpurea* is both a medicinal and poisonous fungi that contains a good amount of alkaloids (Molitoris, 1994).

Mayan culture describes that most of psychedelic fungi which belongs to *Psilocybe* genus and fly agarics as body and food of Gods. Dancing humans holding fungal fruiting bodies shaped resembling items have been found in the caves of Tassili mountain range of south-east Algeria which dates back to 5000 BCE. God Osiris gave mushrooms to the people in the Ancient Egypt and they are known as plant of immortality. Mushrooms regarded as food of royals, commoners were not allowed to eat them, and mere touch them. Romans too had great affection for mushrooms and regarded them as the Food of Gods. They used mainly porcini mushrooms, caesar mushrooms and puffball mushrooms. In ancient Roman times, mushrooms were only available for the rulers as they were a

status of luxury, and even exploited as poisons to intoxicate the rulers. One such story is of Caesar Claudius, a Roman Empire ruler from AD 41 to 54 whose wife Agrippina intoxicated him by hiring assassin Locusta, a poison maker who served poison mushroom in a dish (Kotowski, 2019).

CULTIVATION

Cultivation of mushrooms in the world is increasing progressively with high profit returns of 50-100%, which is encouraging self employment, as it requires very low inputs for farming. It is becoming a source of income for many unemployed people or the weaker sections of the society. Increased demand for mushrooms has led to increase in mushroom farming in more than 100 countries. High nutritional and medicinal values have generated high demand for consumption of mushrooms (Huchchannanavar *et al.*, 2020; Somashekharan and Loganandhan, 2020).

The Global mushroom and truffle production as per Food and Agriculture Organization of the United States statistics (FAOSTAT) for the period 2015-2018 the production recorded was approximately 9.0 to 8.9 million tonnes. Rise in the production in the statistics indicates towards the increased demand for mushrooms in the market. China is the leading mushroom producer worldwide followed by the United States of America and the Netherlands (FOASTAT, Molitoris, 1994). Mushroom farming is practiced today at an annual rate of 6-7% and American and European countries with high tech industry have adopted new methods for mechanized production. Mushrooms, because of its wholeness, are being widely accepted as an alternative to meat and fish. Mushrooms are vegetarian diet, which provides the benefits of a non-vegetarian diet such as vitamins, minerals, essential amino acids. This is beneficial to encounter problems like national food security and malnutrition (Huchchannanavar *et al.*, 2020). According to FOASTATS, production of mushrooms in India for the period 2015-2018 recorded is 5.1 to 6.0 thousand tonnes. Indian mushroom market mainly exports to Canada, Israel, Mexico and U.S.A. They are exported both as fresh and pressed/processed form which can be canned, dried, packed in frozen form. Indian Council of Agricultural Research (ICAR), New Delhi in 1961 started first cultivation of *Agaricus bisporus* (Button Mushroom) in Solan and thereafter established more schemes in Punjab, Bengaluru and New Delhi. Indian mushroom market focuses mainly on the production and cultivation of button mushrooms. The National Committee on the use of Plastics in Agriculture (NCPA) 1982, on the use of plastics in agriculture has recommended greenhouse technology adoption in various regions of India and created large opportunities in the rural areas (Raman *et al.*, 2018). Mushrooms can be grown on various agricultural by products rich in lignin content at 25 °C whereas other studies and experiments have shown that *Pleurotus sajor-caju* can be grown on paddy and maize stalk and black gram straw, soybean straw, sesame straw and wheat straw can also be used for the same purpose (Kotowski, 2019). *Agaricus, Agrocybe, Auracularia, Ganoderma, Lentinula, Hammulina, Lentinus, Pleurotus, Tremella* and *Volvariella* are some of the globally commercial edible mushrooms (Kumla *et al.*, 2020).

Agriculture industries produce a large amount of Agro industrial waste worldwide. Agro industrial waste generates pollution and is needed to be recycled. Burning or disposing of these wastes in landfills leads to serious environment problems and cause potent harm to the health of humans, the environment and wildlife as well. Therefore, recycling the agro industrial waste is the need of the hour. Mushroom culturing can be done on these agro industrial wastes, as it is rich in cellulose, hemi-cellulose and lignin (lignocellulosic substrates) which are suitable for mushroom cultivation. In this way, agro-wastes can be recycled and a nutritional gap can be fulfilled in India. In addition, the agro-industrial waste can be used as fertilizers, for biogas production and to feed animals (Kumla *et al.*, 2020).

Mushrooms in India are considered as cash crops that are cultivated mainly for commercial purpose more than as customary diet itself. White button mushroom, Oyster mushroom, Shiitake mushroom and other mushrooms are the main mushroom cultivated species in India with 95% of total production and export of white button mushrooms. Paddy straw, milky and reishi mushrooms are cultivated at small scale. The production of mushrooms is under guidance of India's FDI (Foreign Direct Investment) in controlled conditions. India is a country of diverse climatic conditions with a large proportion of population engaged in agriculture activities. The Research & Development sector and biotechnology laboratories are ensuring advanced mushroom

breeding in India (Raman *et al.*, 2018).

COMMON CULTIVATED MUSHROOM SPECIES

Button Mushroom

Button mushrooms are the most exploited and commercially cultivated amongst all species of mushroom, ranking first on a global level. White button mushroom include species like *Agaricus bisporus, A. bitorquis and A. blazei* (Fig. 4). *A. bisporus* is grown in temperate regions on partially decomposed organic matter under aerobic conditions as substrate while *A. bitorquis* in tropical or high temperature conditions (Gupta *et al.* 2018). Button mushrooms are rich in flavonoids, which inhibits lipid peroxidation and play a key role in controlling diabetes. *A. bisporus* contains rich amounts of tocopherol (vitamin E) and ascorbic acid (vitamin C) (Ekowati *et al.*, 2018).

Fig. 4: White Button Mushroom : (i) Agaricus bisporus (ii) Agaricus blazei.

OYSTER MUSHROOM

Oyster mushrooms generally comprise of *Pleurotus* mushrooms as known by the world and 'Dhingri' in India. *Pleurotus* adapts well to the varying agroclimatic conditions and is therefore a suited choice for cultivators. They can be grown both in temperate and sub-tropical regions. Most suitable species for temperate region with temperature range 20-30 ºC and high humidity are *Pleurotus eryngii, P. florida, P. fossulatus* and *P. ostreatus* (Fig.

Fig. 5: Oyster mushroom: (i) *Pleurotus ostreatus* (ii) *Pleurotus eryngii.*

5). Cultivation of oyster mushrooms is very easy and requires very low input with moderate profit outputs. They do not require compost for their growth (Gupta *et al.*, 2018).

MILKY MUSHROOM

Calocybe indica, generally known as milky mushrooms have Indian origin and are drawing attention of the cultivators (Fig. 6) due to their delicacy, sturdy size, alluring colour, long shelf life make them attractive mushroom for a venture. Milky mushrooms are grown in Central India,

Fig. 6: Milky Mushrooms: (i) *Calocybe indica* (ii) *Calocybe.*

South India and North India because of the tropical climatic conditions with Tamil Nadu as the largest producer in India using Paddy straw, Wheat straw and lignocellulosic residues (Gupta *et al.*, 2018).

PADDY STRAW MUSHROOM

Mushrooms grown on paddy straws like *Volvariella* sp. are known as paddy straw mushrooms (Fig. 7). They are also known as 'Chinese mushrooms' because of their cultivation in China for more than 300 years. The demand of paddy straw mushrooms is high because of its long shelf life and flavour

Fig. 7: Paddy Straw Mushroom, *Volvariella species.*

Fig. 8: Shiitake Mushroom, *Lentinus edodes.*

and is ranked as sixth most important species for cultivation in the world. Indian climatic conditions are suitable for its cultivation and Orissa province is the leading producer of paddy straw mushrooms (Gupta *et al.*, 2018).

SHIITAKE MUSHROOM

Shiitake mushrooms like *Lentinus edodes* (Fig. 8) are rich in nutrients as well as contains lentinan as bioactive compound which makes it medicinally important too. They are anti-carcinogenic and therefore are the world's most popularly cultivated mushroom (Gupta *et al.*, 2018). The aqueous extracts of *L. edodes* are found to reduce tumour activity by decreasing cell proliferation. Shiitake

mushrooms are rich in b-glucans and Lentinan. In clinical assays, lentinan is used as adjuvant therapy (Lindoquest *et al.,* 2005).

ETHNOMEDICINAL LITERATURE OF MUSHROOMS

Ethnomycology refers to the study of macro-fungi, their relevance to the pre historic times and acknowledging its uses and value then with morphometric identification by collecting information/data from different tribal groups regarding their medicinal and nutritional properties. India is a country full of diversities and hence a lot of tribal communities and ethnic groups acknowledge nature better and acquire better and deep understanding of the uses of natural resources. In India, 34 macrofungal species are used by tribal people found in West Bengal; out of which 31 are edible and 5 are traditional medicines. In Uttar Pradesh, Gorakhpur forest division, it was found that *Termitomyces species* were exploited by forest dwellers for food and as medicinal purposes. In earlier times, people recognized the healing properties of mushrooms and the nutritional benefits as source of supplements (Ekowati et al., 2018). *Daldinia concentrica* is recognized as a cure for upset stomach, *Auricularia auricular-judae* and *Lentinus squarrosulus* as a medication for infertility and to treat anaemia, and *Trichobatrachus robustus* for anaemia and high blood pressure (Okigbo and Nwatu, 2015). The knowledge is transmitted vertically from one generation to the other. The less knowledge about ethnomycology and despite sparse knowledge exploitation of mushrooms can lead to some serious health problems like damage to liver and kidneys and these damages are irreversible. Therefore, proper documentation of the acquired knowledge becomes important for future generations (Rexhepi and Reka, 2020). Peoples' knowledge about mushrooms varies from one community to another. These non-timber forest products (NTFPs) were a great source of nutrition and rich diet for the local people. Therefore, passing ethnobotanical knowledge from one generation to another was a feasible and reliable idea to preserve the core knowledge of mushrooms (Zeleke *et al.*, 2020). This would help in maintaining the bio-heritage of the world and conservation

Table 1: Ethnomedicinal uses of mushroom in different forms reported from various geographical regions.

Scientific Name	Vernacular Name	Preparation	Medicinal Uses	Reported from	Reference
Agaricus campestris	Livadski, Palski, Shampinjon, Kikul cocombiyako	Garlic, onion and milk added to flour and cooked; consumed as food, soup or tonic	Relieved burning, itching, heals minor skin infections, helps with ulcers, diabetes and an immune-booster	Osogovo Mountain, North Macedonia; Cameroon, Central Africa	Rexhepi and Reka, 2020, Yongabi et al., 2004
Agaricus macrosporous	Golem Shampinjon	Thin sliced garlic/ onion with chopped mushrooms added in water with butter	Immune-booster, Diabetes, Provides strength	Osogovo Mountain, North Macedonia	Rexhepi and Reka, 2020
Amanita rubescens	Biserka	Fresh mushrooms soup along with onions, salt, tomato, flour and butter	Skin Problems, Immune system, Strengthening	Osogovo Mountain, North Macedonia	Rexhepi and Reka, 2020
Agrocybe cylindreaca	Bela topolka	Fresh mushrooms soup along with onions, salt, tomato, flour and butter	Improves Digestion, Heart burns, Liver, Rheumatoid Arthritis	Osogovo Mountain, North Macedonia	Rexhepi and Reka, 2020
Auricularia auricula-judae	Judova pecurka	Fried and consumed as food, salad, tonic and applied directly	Immune system, stops bleeding, relieve throat inflammation, eye irritation, Strengthening	Osogovo Mountain, North Macedonia	Rexhepi and Reka, 2020
Boletus edulis	Vrganj	Fruit body cooked with oils and spices	Anti-inflammatory, Boosts Immune System, Antioxidant, Strengthening	Osogovo Mountain, North Macedonia	Rexhepi and Reka, 2020
Boletus aestivalis	Mrzhestonog vrganj	Fruit body cooked with oils and spices	Anti-inflammatory	Osogovo Mountain, North Macedonia	Rexhepi and Reka, 2020

Cantharellus cibarius	Lisicarka	Mushroom mixed with flour, onion and butter	Antioxidant, Immunity Booster, Insecticidal	Osogovo Mountain, North Macedonia	Rexhepi and Reka, 2020
Hericium spp.	Iglicarka	Mushroom mixed with flour, onion and butter	Helps with Stress and Depression	Osogovo Mountain, North Macedonia	Rexhepi and Reka, 2020
Rozites caperata	Cigance	Mushroom mixed with flour, onion and butter	Cures Respiratory Problems	Osogovo Mountain, North Macedonia	Rexhepi and Reka, 2020
Ganoderma lucidum	Kep	-	Skin Infections, Abssesses, Tumours, Asthma	Cameroon, Central Africa	Yongabi et al., 2004, Malik et al., 2017
Daldinia concentrica	King Alfred's Cake	Dried powder and applied topically on wounds	Treats skin irritation, wound healing	Tamil Nadu, India	Debnath et al., 2019
Schizophyllum commune	Pakha chhatu	Tonic is prepared with mushroom fruitbody and water	Wound healing	West Bengal, India	Debnath et al., 2019
Termitomyces clypeatus	Bali chhatu, Kalunge	Tonic is prepared with mushroom fruitbody and water	Treatment of pox	West Bengal, India	Debnath et al., 2019
Cordyceps sinensis	Yarsa gumba	One piece with a cup of milk/ alcohol (chang)/hot water, Root decoction	Cures diabetes, cancer and sexual potency	North Sikkim, India	Debnath et al., 2019
Pisolithus arhizus	Tumbe Onth, Sonajhuri chhatu, Bomb chhatu	Powder of fruitbody mixed with coconut oil and applied topically, Yellow coloured spores used as medicine	Relieved burning, itching, heals minor skin infections, wound treatment	Eastern Lateritic Part of India	Debnath et al., 2019
Calvatia gigantean	-	-	Cure stomach upset, treat menstrual pain, treat male infertility and male visceral organ infections	Tamil Nadu, India	Debnath et al., 2019
Termitomyces microcarpus	Bhoroan Pihiri, Doda	Sundried crushed fruit bodies mixed with leaves of Ocimum spp., black pepper and salt consumed with cow milk or boil this mushroom	Treatment of partial paralysis and for weakness	Jabalpur, M.P., India	Debnath et al., 2019
Podaxis pistillaris	Put-puta, Roogda	Spores used directly	treat burns	Dehradun, India	Debnath et al., 2019
Geastrum triplex	Phut phuta	Spores applied with stored rain water	treat burns	Dehradun, India	Debnath et al., 2019
Astraeus hygrometricus	Savan Putpura	Ointment: spores mixed with mustard seed oil (1:1)	treats burn	Jabalpur, M.P., India	Debnath et al., 2019
Lycoperdon perlatum	Nilnass, Shale saes	-	Dressing wounds	Kashmir, Himalayas, India	Malik et al., 2017
Lycoperdon pyriforme	Nilnass, Shale saes	-	treat frost bites`	Kashmir, Himalayas, India	Malik et al., 2017
Stereum sp.	-	Paste of dried and crushed fruitbodies	wound healing	Dehradun, India	Malik et al., 2017
Phallus rubicundus	Jhiri Pihiri	Mixed with old sugar-cake	Treats typhoid and relieves labour pain	Jabalpur, M.P., India	Debnath et al., 2019

Xylaria polymorpha	Phoot Doot	Mushroom dried and finely crushed then mixed with sugar-cake with cow's milk	Induces lactation	Jabalpur, M.P., India	Debnath et al., 2019
Termitomyces reticulates	Parabana, Ada Chatu	-	Helps with Rheumatism, lowers high blood pressure	Northern Odisha	Debnath et al., 2019
Agaricus bisporus	Maazh hadur	Powder mixed with butter	treats leukoderma, cardiovascular disease	Kashmir Himalayas	Debnath et al., 2019
Flammulina velutipes	Heand, Drubdi	-	Immunomodulator, diabetes	Kashmir Himalayas	Debnath et al., 2019
Fomes fomentarius	Frassi lashe, Heand	Ash mixed with oil	Against skin ailments, disinfectant for wounds, inti-inflammatory, against arthritis	Kashmir Himalayas	Debnath et al., 2019
Bovista plumbea	Mwikhun daudwi	Powdered fruiting body	Treat sores, skin infections and ulcers	Chirang District of Assam, North-East India	Debnath et al., 2019
Coprinus comatus	Ajjio	Cap of the fruiting body is opened and spores bearing gills used	Skin related diseases like bruises, lesions, wounds	Gujrat, India	Debnath et al., 2019
Lactarius deliciosus	Kater	Powder of dried fruiting body	Immune booster, treats frostbite	Kashmir Himalayas	Debnath et al., 2019
Lentinus trigrinus	Vire haddur	-	anti-diabetic	Kashmir Himalayas	Debnath et al., 2019
Lentinus edodes	Vansarta	-	Anti-cancer, anti-oxidant, immuno-booster	Assam and Gujrat, India	Debnath et al., 2019, Lu et al., 2020
Termitomyces sp.	-	-	Treats rheumatism, diarrhoea, lowers blood pressure	Simphal biosphere reserve, Odisha, India	Debnath et al., 2019
Lentinus sajor-caju	-	-	Treats cold and cough	Simphal biosphere reserve, Odisha, India	Debnath et al., 2019
Pleurotus sp.	-	Finely grind powder of fresh fruiting bodies added to water to make a paste	Treats pneumonia, constipation, eczema, asthma	Gujrat, India	Debnath et al., 2019
Fomitopsis pinicola	Yaade lashe	Crushed dried fruitbody	Treats rheumatoid arthritis, stops minor external injury bleeding	Kashmir Himalayas	Debnath et al., 2019
Inonotus hispidus	Chunth lashe	Fruiting body extract	Disinfectant, treats boils	Kashmir Himalayas	Debnath et al., 2019

becomes easier when a detailed knowledge of plants is available. The studies show that there was involvement of at least two generations in the collection activity as it was a family activity (Cervantes *et al.*, 2019).

The tribal groups identified different mushrooms available around the world according to the geographic conditions and associated vernacular names to different species to differentiate between species. The uses and techniques of preparations using mushrooms varied from one tribal group to another. Some cooked mushrooms, some made soups and teas out of it and some liked to roast it. Similarly, the uses of mushrooms for medicinal treatments were as per convenience and depended upon the efficacy. Some mushrooms were used as

decoctions. Powdered form of some mushrooms was applied or even the spores were used on bruises (Zeleke *et al.*, 2020). Table 1 enlists botanical names, their preparations and ethnomedicinal uses of various mushrooms from different countries.

ACTIVE COMPOUNDS AND THEIR NUTRITIONAL AND MEDICINAL EFFECTS

Mushrooms being rich in various nutritional compounds are also potent as medicines. They are natural source of many bioactive compounds that serve as supplements for human health. A wide variety of compounds are comprised in just one food, making them versatile in providing health supplements and also as medicinal cure (Kumla *et al.*, 2020). They work great as medicines or as an adjuvant for therapies (Lu *et al.*, 2020). Mushrooms from ancient era are being exploited for its therapeutic uses, in treatments because of its anti-inflammatory, anti-diabetic, anticancer properties and people today are acknowledging them as unexplored reservoir of many bioactive compounds that promotes health. In Taiwan, *Antrodia cinnamomea* is known as 'National Treasure of Taiwan' and 'Ruby in the Forest' as it is a rare parasitic fungus with anti-tumour, anti-fatigue, anti-inflammatory, anti-oxidant and hepatoprotective functions (Zhang *et al.*, 2019). Apart from being widely accepted for its culinary, mushrooms are being widely accepted for its organoleptic, medicinal and economic merits. They contain ample amounts of Vitamins, Minerals, Protein content, carbohydrate and oxalic acid as primary metabolites and contain anthraquinones, benzoic acid derivatives, steroids, triterpenes, terpenoids, terpenes, as secondary metabolites. Mushrooms contains plentiful of proteins with essential amino acids, good amounts of vitamins like B1, B2, B12, C, D and E, significant amount of fibres and interestingly are low with fat content. Over 30 species of mushrooms are found to have anti-cancer properties and over 100 mushrooms are found to have medicinal effects on human health including

Table 2: Bioactive compounds in various mushrooms and their bioactivity.

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

Fomitopsis pinicola	Polysaccharides	Anti-inflammatory	Sanchez, 2017
Ganoderma lucidum	Ganoderic acids, ganoderiol, ganodermanontriol, Ganoderan A and B, Ganopoly, Lucidenic acid, Lanostane type triterpene acids, Ling zhi-8, Ganodermin, Se-containing proteins	Anti-tumour, anti-metastatic, anti-HIV, anti-viral, anti-inflammatory, Hepatoprotective, Immunomodulatory, Anti-fungal, Anti-neurodegenerative	Sanchez, 2017, Lindoquest et al., 2005
Ganoderma microsporum	Protein GMI	Immunomodulatory	Sanchez, 2017
Grifola frondosa	Grifolan, Polyglycan, Heteroglycan, Galactomannan, Glucoxylan, Mannogalactofucan, Fucomannogalactan, Agaricoglycerides	Immunomodulatory, Anti-tumour, Anti-viral, Hepatoprotective	Sanchez, 2017
Hericium erinaceus	Hericenons C, D, E, F, G, H, Erinacines, Resorcinols, steroids, Triterpenes, Diterpenes, Lectins, Heteroglycan peptide, Dilinoleoylphosphatidyletha nolamine	Anti-oxidant, Anti-biotic, Anti-carcinogenic, Anti-diabetic, Anti-fatigue, Hyperglycaemia, Immunomodulatory, nephroprotective, neuroprotective	Sanchez, 2017
Hypsizygus marmoreus	Ergosterol, Mannitol, Trehalose, Methionine, Marmorin, Flavonoids, Phenolic compounds, ribosome inactivating proteins	Anti-oxidant, anti-inflammatory, anti-allergic, anti-tumour, Anti-bacterial, anti-fungal,	Sanchez, 2017, Ma et al., 2018
Inonotus obliquus	β-D-glucans, Mannogalactoglucans, Sterols, Triterpenes	Anti-oxidant, anti-cancer, anti-inflammatory	Sanchez, 2017
Lentinus edodes	Lentinan, mannoglucan, glucan, fucomannogalactan, Lentin, Catechin, Phenolics, Flavonoids, KS-2	Immunomodulatory, anti-tumour, anti-bacterial, anti-fungal, anti-oxidant	Sanchez, 2017, Ma et al., 2018
Lenzites betulina	Betulinan A	Anti-oxidant	Sanchez, 2017
Phellinus linteus	Glucans, Acid Polysaccharides, Hispidin	Anti-tumour, Immunomodulatory, Anti-oxidant	Sanchez, 2017
Schizophyllum commune	Schizophyllan, Sonifilan, SPG	Anti-tumour	Sanchez, 2017
Tricholoma giganteum	Protein-Trichogin	Anti-fungal	Sanchez, 2017
Tricholoma giganteum	Laccase	Anti-viral, anti-tumour	Sanchez, 2017
Volvariella volvacea	Fip-vvo	Immunomodulatory	Sanchez, 2017
Pleurotus ostreatus	Lectins, Pleurans, Proteoglycans, Laccase, Pleurostrin	Anti-diabetic, Anti-neurodegenerative, Anti-tumour, Immunomodulatory, Anti-fungal, Anti-oxidant	Sanchez, 2017, Ma et al., 2018
Pleurotus eryngii	Laccase	Anti-viral, anti-tumour	Sanchez, 2017
Pleurotus pulmonarius	Polysaccharides β (1,3) D-glucopyranosyl	Anti-inflammatory	Sanchez, 2017
Psilocybe spp.	Psilocybin	Anti-depressant	Sanchez, 2017
Termitomyces albuminosus	Termitomycesphins, Termitomycamides	Anti-neurodegenerative	Sanchez, 2017
Trametes versicolor	Krestin, Coriolan	Anti-metastatic, Anti-diabetic	Sanchez, 2017

anti-viral, anti-bacterial, anti-inflammatory, anti-parasitic and anti-tumour activity. Polysaccharides are considered most important constituent for medicines especially α-Glucans and β-Glucans are considered best and versatile. The fruiting bodies of mushroom bear the bioactive compounds which can be glycosides, polysaccharides, proteins, minerals, alkaloids, volatile oils, terpenoids, phenols, flavonoids, carotenoids, folates, lectins, enzymes, ascorbic acid and organic acids. They can be consumed directly in the diet or as nutraceutical medicines (Kumla *et al.*, 2020). The effectiveness and the concentration of the bioactive compounds depend upon the cultivation environment, storage conditions, cooking method, type of mushrooms and age/developmental stage (Yongabi *et al.*, 2004). Different bioactive compounds found in mushrooms and their bioactivities are summarized in table 2.

PROTEINS

Protein content in mushrooms is high but varies from species to species. In general, the protein content varies from 150-255 g/kg of dry matter which is much higher than available in any other protein sources. Amino acids like isoleucine, leucine, glutamine, valine, glutamic acid and

aspartic acid are found in profuse amount. Apart from nutritional supplement, the protein content found in mushrooms is medicinally valuable too. Mushroom proteins and peptides are models to the nutraceutical as well as pharmaceuticals from benefiting the digestion and better absorption of food to help immune system fight against pathogen. Pharmaceutical prospects include fungal immunomodulatory proteins (FIPs), ribosome-inactivating proteins (RIPs), lectins, ribonucleases, laccases (Valverde *et al.*, 2015; Sanchez 2017, Ma *et al.*, 2018).

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

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

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

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

VITAMINS

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

LIPIDS/FATTY ACIDS

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

POLYSACCHARIDES

Many in vivo and in vitro studies have reported the presence of cell wall polysaccharide and polysaccharide-protein complexes like Lentinan from *Lentinus edodes*, β-glucan fraction D from *Grifola frondosa*, Krestin (PSK) polysaccharide peptides from *Trametes versicolor*, Schizophyllan from *Schizophyllum commune*, Pleuran from *Pleurotus* species, Calocyban from *Calocybe indica* and Ganoderan from *Ganoderma lucidium*. Over hundreds of mushrooms have been examined and reported to contain rich amounts of carbohydrates that are immunomodulating, anti-tumour, and anti-oxidants (Gupta *et al.*, 2018; Ma *et al.*, 2018). Carbohydrates like Xylose, Mannose, Rhamnose,

Fucose, Fructose, Glucose, Galactose, Mannitol, Sucrose, Trehalose and Maltose have been quantified from various mushrooms with their quantity varying from species to species. These polysaccharides pose strong anti-tumour effects, elicits the activation of dendritic cells, monocytes, neutrophils, NK cells, cytotoxic macrophages and cytokines. These are acidic or neutral in nature and vary in chemical structures (Ma *et al.*, 2018). Glucans extending from homopolymers to complex heteropolymers are main and important polysaccharides found in mushrooms.and inflict anti-tumour activities (Valverde *et al.*, 2015).

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

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

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

PHENOLIC COMPOUNDS

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

TERPENES

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

The mushrooms have paved its way into the medical world because of its potent medicinal values. The bioactive compounds found in mushrooms can be exploited in medical treatments and therapies to combat various diseases. A variety of mushrooms' bioactive compounds are beneficial for the target treatment of cancer. Also, the effectiveness and

the efficacy of mushrooms' bioactive components have been suggested by performing preclinical and clinical trials. Apart from cancer, many other problems could be looked upon to and with expanding understanding of mushrooms, a lot of diseases could be cured. It is in similar manner as of in ancient times, only the preparations have been replaced by therapies, treatments and medicines.

WEIGHT MANAGEMENT

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

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

COGNITION

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

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

ORAL HEALTH

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

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

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

et al., 2016).

CANCER

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

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

Table 3: Mechanism of action of bioactive components of different mushrooms.

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

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

commune, Sparassia crispa, P. tuberregium, L. edodes, G. frondosa and *F. ventipules* and can be used against breast, lung, prostate, colorectal and lung cancer etc. (Ayeka, 2018).

MECHANISM OF ACTION

A therapeutic drug including the medicinal mushrooms works by interaction with the gut microbiota and immune system. The food that cannot be digested in stomach and intestine is digested in the gut by microbiome there. It therefore acts as first barrier against pathogens and elicits immune responses. The immune system then functions by initiating the innate and adaptive immunity (Jayachandran *et al.*, 2017). Various bioactive molecules of mushrooms and their targets/mechanism of action are listed in table 3.

GUT MICROBIOTA

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

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

IMMUNE FUNCTION

Any substance, that fights against any disease, acts by initiating the responses by immune system which regulates by activating innate and adaptive immunity. Mushroom bioactive compounds are no different and they initiate the innate and adaptive immunity (Fig. 9). The invasion of foreign substances leads to activation of monocytes and granulocytes. The innate immunity is regulated by secreted lipid messengers such as prostaglandins and the cytokines which are cell synthesized

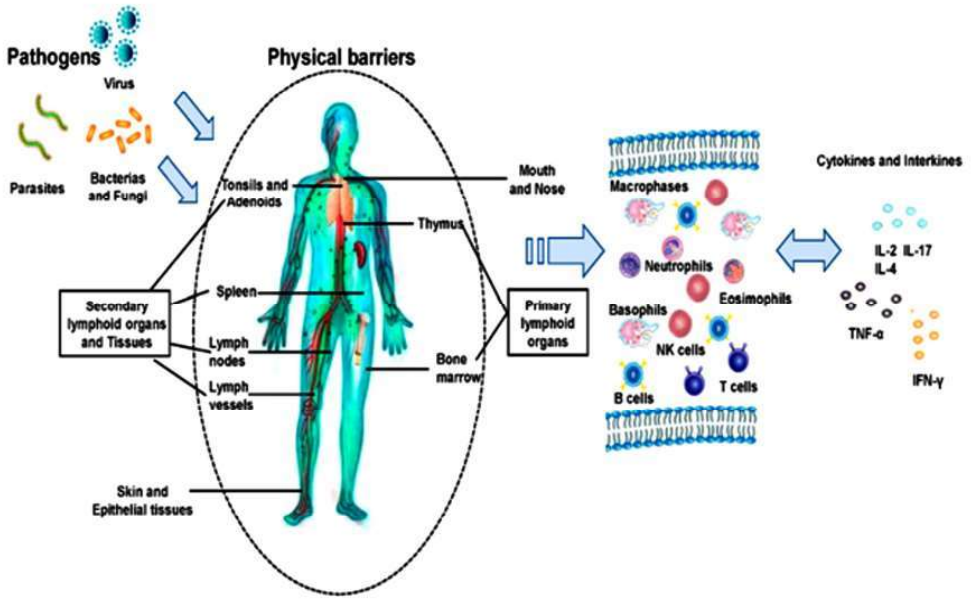

Fig. 9: A representation of immune system activation and secretion of different cells involved in neutralization of a pathogen/ killing of an abnormal cell.

molecules and triggers the adaptive immunity. Macrophages are secreted and mediated towards the target site for phagocytosis. Also, abnormal cells such as cancer cells are recognized by the NK cells and impel cancer cells towards apoptosis (Zhao et al., 2020). The tumour growth can be stopped at many levels like tumour specific pro-proliferation cell signalling, regulation of apoptosis, cancer-specific metabolism, angiogenesis, metastasis, and finally by immune modulation and hence cancer fungi-therapy is gaining recognition in the scientific field (Blagodatski et al., 2018). Some promising mushrooms species having anticancer properties are mentioned hereunder.

TEAMMATES VESICULAR

T. vesicular shows cytotoxic, apoptotic actions on various cancer cell lines. Extractions like water ethanol extract exhibits proliferation in human breast cancer cell lines (T-47D, ZR75-30 and MCF-7), human cervical cancer cell lines Bcap37, human B-lymphoma, human promyelocytic leukemia (HL-60, NB-4) and human liver cancer cell line 7730 (Lau *et al.,* 2004; Zhou *et al.,* 2007). The isolated ethanol extracts of *T. versicolor* contains polysaccharide fractions, carbohydrates and Polyglycans which pose complex immunomodulatory effects and this becomes a base for anti-cancer treatment.

Xenograft sarcoma growth in mouse is seen to be inhibited by the glucan fractions isolated from the hot water extractions and chromatogenic purification of *T. versicolor* (Awadasseid *et al.,* 2017). This mushroom contains PSP (Polysaccharide peptide fraction) and also krestin. Japan and China are practicing PSP based immunotherapy since 1977 and 1987, respectively. PSP based immunotherapy stimulates the cytokines, chemokines like TNF-α, IL-1β, IL-6, histamine and prostaglandin E. They also activate dendritic cells and T-Cell penetration into the tumors thereby reducing painful side effects of chemotherapy. The cytokine expression by PSP is through the activation of TLR-4-TIRAP/ MAL-MyD88 signaling pathway. Combination of PSP along with acacia resin as adjuvant when administered orally leads to the increment of hapten-induced specific T-Cell dependent B-cell response in mice. In vitro experiment on krestin (PSK) shows to activate the dendritic cells through TLR-2 receptor; and through TLR-4 pathway stimulates murine macrophages by inducing TNF-α and IL-6 secretion (Blagodatski *et al.,* 2018).

YZP is another protein isolated from *T. versicolor* that triggers the differentiation of CD1d+B cells into IL-10 producing regulatory B-cells which promotes the anti-inflammatory effect (Kuan *et al.,* 2013). *T. versicolor* today is one of the most widely

used medicinal mushrooms as the Phase 1 clinical trials has proved promising results against breast cancer by boosting immune system (Torkelson *et al.*, 2012).

INONOTUS OBLIQUUS

I. obliquus is recognized for its anti-parasitic, anti-tuberculosis, anti-inflammatory and gastrointestinal properties in folk literature and even used in the treatment of liver and heart diseases (Saar, 1991). China, Japan, Korea, Russia and the Baltic countries recognized its true potential against bacterial, inflammation, cancer activity and also its effects on plasma lipid system and heart functions (Shashkina *et al.*, 2006). The antioxidant property of *I. obliquus* prevents atherosclerosis, cancer, diabetes, accelerated aging and neural degenerative diseases caused by free-radicals. HIV and Hepatitis C can be encountered by the extracts of *I. obliquus* (Park *et al.*, 2005). In medicine, young fresh sclerotia part is harvested and kept free from pollution, bacterial or viral infection conditions under cool climate and high fluctuation of season temperature (Sczychoowski *et al.*, 2020).

In present scenario, *in vivo* and *in vitro* clinical trials have shown an increase in TNF-α production with an increase in concentration of polysaccharide by mouse macrophages (Sczychoowski *et al.*, 2020). Secretion of cytokines like IL-2, IL-6, IL-12 and TNF-α was found to increase and also the phagocytic activity (Javed *et al.*, 2019). Despite limited knowledge of the bioactivity of *I. obliquus* extracts, the anti-viral activity of the aqueous (aq.) fraction is comprehended. The aquous fraction is found to contain polysaccharides which hinders with the entry of virions into cells by inhibiting protease from HIV type 1 (HIV-1) (Sczychoowski *et al.*, 2020).

GANODERMA LUCIDUM

Apart from anti-tumor, anti-viral, anti-hepatoprotective function; anti-diabetic and anti-neurodegenerative function is also evident with the use of *G. lucidum*. *G. lucidum* polysaccharide (GLPS) is well known and major bioactive compound used in medicine (Zeng *et al.*, 2019). Long-term Diabetes Mellitus (DM) can cause myocardial fibrosis (stiffness in the myocardial developments) and therefore can cause serious health problems. The polysaccharide found in G. lucidum decreases the advanced glycation end products (AGE) levels which relaxes the stiffness thereby loosening of myocardial collagen cross-linking as has been demonstrated in diabetic rat model and hence an effective therapy. The Polysaccharide fraction combined with metformin works more efficiently than administered separately as they increase and boosts the anti-oxidant activity, decreases myocardial CTGF thereby decreasing process of myocardial fibrosis (Qiao *et al.*, 2017).

An injection **"Ji 731"** was developed in China back in 1973 and later its name was changed to **"Polysaccharidium of G. lucidum karst injection"** by the Chinese State Food and Drug Administration (SFDA) in 2000. Neurosis, polymyositis, dermatomyositis, atrophic myotonia, muscle dystrophy and many other diseases is encountered with the inter-muscularly administration of this injection (Jiang *et al.*, 2020).

The polysaccharide protects the middle cerebral artery occlusion (MCAO), improving neurological deficits, cerebral infract volume and brain edema rate in rat models. Increase in angiogenesis after cerebral ischemia and also in the cerebral vascular density in the ischemic area was reported by Ke *et al.* (2017). He further proposed that increased activation of AMP- activated protein (AMP) kinase (AMPK) and eNOS (via their phosphorylation) as the mechanism for the increase of the above mentioned. This in turn results in activation of angiogenesis and neuron regeneration. In neuron ischemia (reperfusion injury) caused by hydrogen peroxide treatment with *G. lucidum* polysaccharide decreases the level of H_2O_2 by destroying the expression of Caspase-3, Bax, Bim and Bcl-2 thus initiating apoptosis (Bhardwaj *et al.*, 2018).

CONCLUSIONS AND FUTURE PERSPECTIVES

It evident from literature mushrooms contain a plethora of novel compounds and can be edible and as well as medicinal serving humans with significant health benefits. Their medicinal value has long been recognized by ancestors and cited in folk literatures. They were topically applied, orally consumed and concoctions were made out of them to fight against various diseases. There are several mushrooms for each and every type of health-related problems ranging from skin diseases to cancer. A large part of the world is engaged in mushroom farming and new sets of tools and

techniques are developed over years. Consumption and demand for mushrooms is very high across the world with China being the largest producer. India is flourishing in terms of business across the world as it is one of the major contributors but still consumption of mushrooms in India itself is low. Mushroom farming requires very low inputs as compared to yield/return, and hence it is being opted as an employment source.

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

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

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