"Nutraceutical Mushroom Tea": can it be considered the lost elixir of life!

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Abstract:—This review describes a novel concoction of pharmacologically active compounds from mushrooms and a special Cardio Protective Water to formulate a daily use medicinal mushroom tea which has been proved to be with cardio protective, anti-diabetic, antimicrobial, antiviral, antitumor, anti-allergic, immunomodulating, anti-inflammatory, anti-atherogenic, hypoglycemic, hepato-protective properties. The paper covers all the recent nutraceutical aspects of mushrooms including anti-oxidant, cardio-protective, hypercholesterolemia effect, antimicrobial, hepato-protective and antitumor properties. Some focus is also on the clinical trials carried out using the mushrooms and their availability of medicine in India. Overall the present review provides a deep insight on the potential of the mushrooms as dietary supplements along with its use with Cardio Protective water for formulating a mushroom tea which can increase the average human life span.

Keywords:—Mushroom, Tea, Cardio-protective-water, Nutraceutical, Anti-oxidative, Cardiovascular, Hypercholesterolemia, Antimicrobial, Antitumor

1. INTRODUCTION

A nutraceuticals can be defined as a substance that may be considered a food or part of a food that provides medical or health benefits like the prevention and treatment of disease.

Mushrooms have become attractive as a functional food and as a source for the development of drugs and nutraceuticals [85] for their antioxidant, antitumor [65], [66], [67] and antimicrobial properties. The awareness of their medicinal properties came not only from Asia but also from the folklore of central Europe, South America and Africa [52], [53]. Besides their pharmacological features, mushrooms are becoming more important in our diet due to their nutritional value, related to high protein and low fat / energy contents [1]. *Trametes versicolor* (L.) Lioyd has been considered among the 25 major medicinal macrofungi worldwide [26], mainly due to its traditional usage. Interesting polysaccharopeptides have been purified from this species, showing experimental immunomodulatory and anti-cancer effects [29], [30], [31], [32], [33], [34], [112]. In India, numbers of species of mushroom have been listed by various workers [93], [24], [124], [14], [81], [82], [106], [154], [47], [152]. Uttarakhand a hill state of India is gifted with a rich medicinal flora that includes *Ganoderma, Cordyceps* [133], [134], [135], [136] and *Auricularia* [136]. Codycepin and cordycepic acid are regarded as the most important constituents of *Cordyceps sinensis* and owe high medicinal significance [35]. In developing countries like India mushrooms are boon for progress in the fields of food, medicine and unemployment. Mushrooms in the twentieth century are well known to people all over the Asian countries as an important bio-source of novel secondary metabolites. In India, particularly the alternative systems of medicine, utilize the curative properties of mushrooms. The secondary metabolites of these mushrooms are chemically diverse and possess a wide spectrum of biological activities, which are explored in traditional medicines and in new targets of molecular biology. They have important present status and possess a potential to design future strategies for human health values.

Scientific studies in several last decades have proved that magnesium plays crucial role in proper functioning of heart and blood vessels. Low magnesium intake thus emerged as number one risk factor for cardiovascular disease. World Health Organization publication on drinking water suggests that water containing 25-30 milligrams/liter magnesium can reduce deaths due to heart disease by minimizing clogging of arteries [40]. Chromium along with magnesium is helpful for glucose metabolism and diabetes. Studies have also proved that bicarbonate alkalinity in drinking water reduces urinary loss of calcium and magnesium and hence beneficial for heart and bones. Bicarbonate alkalinity also helps to counter adverse effects arising from metabolic acidosis and minimizes accumulation of toxic elements in the body. This water can be used with mushrooms to prepare a special mushroom tea to increase the effects to many folds.

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Hence, this review paper deals with the use of a concoction of cardio protective water with medicinal mushroom to make a novel mushroom tea which can be used as antioxidants, cardiovascular, hypercholesterolemia, antimicrobial, hepato-protective, anticancer, antitumor, helps in glucose metabolism and increasing the overall life span of human population.

2. NUTRITIONAL VALUE

It is probable that from its earliest beginning man has utilized mushrooms as a food [118]. Mushroom is an excellent source of folic acid, the blood building vitamin that prevents anemia [68], [25]. Mushroom protein is comparable to muscle protein in terms of nutritive value [68]. The species that have been properly analyzed for medicinal value are *Ganoderma lucidum* (Reishi), *Lentinus edodes* (Shiitake), *Grifola frondosa* (Maitake),*Agaricus blazei* (Hime-matsutake), *Cordyceps militaris* (Caterpillar fungus), *Pleurotusostreatus* (Oyster mushroom) and *Hericium erinaceous* (Lions mane). There are many more species of cultivated, wild, edible and non-edible mushrooms that have been analyzed for both their nutritional and nutraceutical components [85]. The active constituents found in mushrooms are polysaccharides, dietary fibers, oligosaccharides, triterpenoids, peptides and proteins, amino acids, alcohols and phenols, and mineral elements such as zinc, copper, iodine, selenium and iron, vitamins, etc [112]. These have been found to boost the immune system, have anti-cancerous properties, act as anti-hypercholesterolemia and hepato-protective agents, show anti-HIV activity and anti-viral activity, and ameliorate the toxic effect of chemo- and radiotherapy. Many of the species are known to be aphrodisiacs.

3. ANTI-OXIDATIVE PROPERTIES OF MUSHROOM

Oxidation is essential for all living organisms for the production of energy to fuel biological processes. However, oxygen-centered free radicals and other reactive oxygen species that are continuously produced *in vivo*, result in cell death and tissue damage. Oxidative damage caused by these free radicals may be related to ageing and diseases, such as atherosclerosis, diabetes, cancer and cirrhosis. The antioxidant potential has been studied from water and methanol extracts of fruiting bodies of 23 species of mushrooms naturally grown in different geographic locations of India [107]. Three species of *Pleurotus florida, P. pulmonarius and P. citrinopileatus* can be cultivated almost throughout the year in the plains of India were examined for their antioxidant potentialities with a view to popularize medicinal mushrooms among common middle class people at low-cost instead of administering costly medicines. Reducing power, chelating activity of $Fe^{2+}$and total phenol were observed to be higher in *P. florida* than in *P.pulmonarius* and *P. citrinopileatus* respectively. Among anti-oxidative enzymes, *P. florida* exhibited highest peroxidase and superoxide dismutase (SOD) whereas catalase activity was found to be highest in *P. pulmonarius* [72].The aqueous extracts of *G. lucidum* and *C. sinensis* showed a high anti-oxidative activity by giving protection against oxidative DNA damage [65]. It is reported that the reducing power and chelating activity of $Fe^{2+}$of *G. lucidum* and *C. sinensis* aqueous extract increased with increase in concentration. The *G. lucidum* aqueous extract showed higher anti-oxidative properties than *C. sinensis*, probably due to differences in the compounds present in the fruiting bodies [136]. The antioxidant activity of *Phellinus rimosus* seems to be more effective than the *Pleurotus florida, P. sajour-caju* and *G. lucidum* [83], [84], [3], [4], [5], [6]. It was found that the mushroom may be a potential source of therapeutically useful antioxidant [64], [146], [108]. Phenols contained good antioxidant [128], [129], [72] ant mutagenic [83] and anticancer properties [2]. Fruiting bodies of medicinal mushroom (*G. lucidum*) contains polysaccharides, triterpenoids, adenosine, germanium, protein (L2-8), amino acids etc. found to have antitumor and immuno-modulating affect [133], [134], [135], [136]. The pre-dominating species are *Phellinus senex, P. rimosus, P. badius,P. fastuosus, P. adamantinus, P. caryophylli* and *P. durrissimus* [130]. About 18species are found to occur in Kerala, most of them are wood inhabiting [86]. *P. rimosus* (Berk) Pilat is found growing on jackfruit tree trunks in Kerala. In Kerala, this mushroom is commonly found on living Moraceae members. In Chinese medicine hot water extract of the fruiting bodies of *Phellinus* species have been used for an extensive range of ailments and it is believed to work as a miracle drug refreshing the human body and prolong longevity [165]. Recent studies have compared hot water extract of *Phellinus* with other anticancer mushrooms. The *Phellinus* extract showed the strongest evidence of tumor proliferation suppression [99]. Methanol extract of *P. rimosus* effectively reduced ferric ion in FRAP assay and scavenged DPPH radicals [6].Extracts from fruiting bodies and mycelia of *G. lucidum* occurring in South India were found to possess *in vitro* antioxidant activity [65], [83] and ant mutagenic activities (Lakshmi et al., 2003).The results of the antioxidant assays [6] showed that ethylacetate, methanol and aqueous extract of *G. lucidum* effectively scavenged the O_2 and OH radicals (Table 1). However the aqueous extract was not effective to inhibit the ferrous ion induced lipid peroxidation [65]. The extract showed significant reducing power and radical scavenging property as evident from FRAP assay [6] and DPPH radical

scavenging assay [84], [6]. *Pleurotus* species have high medicinal value. Compounds extracted from these mushrooms exhibit activity against various chronic diseases including hypertension, hypercholesterolemia [53], [52], [160]. The medicinal beneficial effects of *Pleurotus* species were discovered independently in different countries. The awareness of their medicinal properties came not only from Asia but from the folklore of central Europe, South America and Africa [52], [53]. Oyster mushrooms (*Pleurotus* species) are excellently edible and nutritious, rank among one of the most widely cultivated mushrooms in the world [33]. Species of *Pleurotus* are found to possess significant antioxidant, anti-inflammatory and antitumor activities [67], [66]. The methanol extract of fruiting bodies of *Pleurotus florida* was found to possess OH radical scavenging and lipid peroxidation inhibiting activities (Table 1) [67]. The extract also showed significant reducing power and radical scavenging property as evident from FRAP assay [6] and DPPH radical scavenging assay [84], [6].

Based on the results they obtained, the aqueous extract of mushrooms can be much more beneficial than their direct intake as food.

TABLE 1
IN VITRO ANTIOXIDANT ACTIVITY OF ETHYL ACETATE (ETOAC), METHANOL (MEOH) AND AQUEOUS (AQ) EXTRACTS OF P. RIMOSUS (PR), G.LUCIDUM (GI), P.FLORIDA (PF), AND P.PULMONARIUS (PP) [AJIT AND JANARDHANAN, 2007].

Extracts	IC_{50}(μg/ml)			
	Super oxide scavenging	Nitric Oxide scavenging	Hydroxyl Radical scavenging	Lipid peroxidation inhibiting
EtOAc	22.0 ± 1.0(Pr) --- (Pf)	438.0 ± 21.6 (Pr) ----(Pf)	68.0 ± 4.1 (Pr) 530.0 ± 29.4 (Pf)	162 ± 7.0 (Pr) 496.0 ± 4.7 (Pf)
MeOH	25.3 ± 1.2 (Pr) 152.5 ± 2.5 (GI) ---(Pp) ---(Pf)	126.7 ± 12.6 (Pr) --- (GI) ---(Pp) ---(Pf)	93.0 ± 10.3 (Pr) 560.0 ± 0.1 (GI) 476.7 ± 24.6 (Pp) 263.3 ± 24.9 (Pf)	282 ± 12.8 (Pr) 873.5 ± 7.2 (GI) 960.0 ± 10.0(Pp) 320.0 ± 10.0 (Pr)
AQ	126.0 ± 5.1 (Pr) 475.0 ± 25.0 (GI) ---(Pf)	31.0 ± 4.5 (Pr) --- (GI) ---(Pf)	71.0 ± 4.7 (Pr) 140.0 ± 2.0 (GI) 263.3 ± 24.9 (Pf)	318 ± 2.4 (Pr) --- (GI) --- (Pf)

Values are mean ±SD, n = 3. Names of mushrooms included in the parenthesis.

4. CARDIO PROTECTIVE DRINKING WATER AS A SOURCE OF NUTRACEUTICAL MUSHROOM TEA

Water magnesium inhibits absorption of part of dietary fat and cholesterol in body by converting into highly insoluble Mg-Fatty acid salt in digestive tract, controls synthesis of excess LDL by activating controlling enzyme, controls harmful C Reactive Protein, inhibits blood clot formation, inhibits clogging of arteries, prevents calcification of heart tissues, regulates heart beat (ECG), stops spasms of arteries, improves blood flow, reduces blood pressure, improves efficiency of heart muscle cells for oxygen utilization, increases survival time of heart muscles before death under oxygen deficient environment and enhances insulin action along with Chromium. The required amount is 25-30 milligrams magnesium per liter of drinking water. Magnesium injections are given to save patients from sudden cardiac death and during heart surgery. Magnesium deficient body cells bring about faster aging thus causing shortened life spans. Most of the people do not get adequate magnesium in diet or water. Various study reports have been published Most of them in WHO [40].

Several scientific studies in last decade have proved that magnesium plays crucial role in proper functioning of heart and blood vessels. Low magnesium intake thus emerged as number one risk factor for cardiovascular disease. Several long term studies in US, Canada, Finland, Sweden, India, South Africa, France, Australia, Japan, etc have shown that higher intake of magnesium can reduce mortality due to cardiovascular disease and diabetes by 33,50,80,37,35,50,32,70,65 percent [60]. On conservative estimate 30-35 percent lower deaths due to CVD and diabetes is achievable. World Health Organization publication on drinking water suggests that water containing 25-30 milligrams/liter magnesium can reduce deaths due to heart disease by minimizing clogging of arteries. Chromium along with magnesium is helpful for glucose metabolism and diabetes. Studies have also proved that bicarbonate alkalinity in drinking water reduces urinary loss of calcium and magnesium and hence beneficial for heart and bones. Bicarbonate alkalinity also helps to counter adverse effects arising from metabolic acidosis and minimizes accumulation of toxic elements in the body. Several other minerals essential for healthy body can also be incorporated in drinking water which can be helpful to reduce the impact of pain from arthritis, reducing suicidal tendency, vitamin B_{12} synthesis in intestine, inducing softer stools / helpful for constipation, minimizing certain types of cancer etc [40]. With application of science

and technology it is possible to incorporate such health giving qualities in drinking water. Drinking water is a good source of essential minerals and anions as it is quickly absorbed and bioavailability is higher. Any low mineralized ordinary drinking water or hard water containing high calcium can be also processed by formulations and process developed by Indian water researcher to obtain cardio protective water. The invented method is such that by using formulated chemicals (suitable for drinking water) it is possible to obtain such water in homes or in bottling plants [60].

5. Cardiovascular and Hypercholesterolemia Effect of Mushroom

Diabetes mellitus (DM) is a major endocrine disorder affecting nearly 10% of population all over the world. The major risk factors in development of coronary artery disease (CAD) have been identified as DM, increased blood levels of total cholesterol, low density lipoprotein (LDL) cholesterol and very low density lipoprotein (VLDL) cholesterol as well as lowered levels of high density lipoprotein (HDL) cholesterol. Mushrooms in general and *Pleurotus*, *Lentinus*, *Grifola* in particular, because of their high fiber content, proteins, microelements and low caloric value, are almost ideal for diets designed to prevent cardiovascular diseases as first suggested by traditional Chinese Medicine. The therapeutic potential of *Agaricusbisporus* and its antioxidant effect in hypercholesterolemia induced albino rats has been studied [75]. The consumption of *P. florida* supplemented diet renders anti-hyperglycemic as well as anti-hypercholesterolemia effect to all oxan induced diabetic rats [19], [20]. Previous studies had shown the antihyperglycaemic effect of aqueous extracts of *P. pulmonarius* against all oxan-induced diabetic mice [16], [17]. The anti-hyperglycemic effect of medicinal mushroom may be due to its significant antioxidant activities properties [72]. *Lentinus edodes* can lower both blood pressure and free cholesterol in plasma, as well as accelerate accumulation of lipids in liver by removing from circulation.

In most developed countries, the common cause of death is coronary artery disease. The main risk factors are hypercholesteromia and dislipoproteinemia, diabetes, disturbance in blood platelet binding and high blood pressure. The initial step in the prevention and treatment of CAD and hypercholesterolemia is the modification of nutritional regime with a diet low in fats and fatty acids and rich in crude fibers. Clinical intervention studies have clearly demonstrated therapeutic importance of correcting hypercholesteromia [7]. Mevinolin is produced commercially from the filamentous fungus *Aspergillus tereus*. This is the first specific inhibitor of microzomal enzyme that occurs early in the biosynthetic pathway to cholesterol formation. The addition of 4% dried *Pleurotus* to a high cholesterol diet reduced cholesterol accumulation in the serum effectively and liver of experimental rats [92] Cholesterol lowering effect of the mushroom *Pleurotus ostreatus* in hyper cholesterolemicrats is also reported. It has been suggested that *Pleurotus* mushrooms could be recommended as natural cholesterol lowering substance within the human diet [52]. In Western countries coronary artery disease is the major cause of death, while hypercholesterolemia is a risk factor, which causes the hardening of the arteries. In humans, 50% or more of total cholesterol is derived from de novo synthesis. It has been proven that Shiitake mushroom is used to lower blood serum cholesterol (BSC) via a factor known as eritadenine, which is also called 'Lentinacin' or 'Lyntisine'. It is known that, apparently, eritadenine reduces BSC in mice, not by inhibition of cholesterol biosynthesis, but by the acceleration of excretion of ingested cholesterol and its metabolic decomposition [147], [148]. Eritadenine also lower the blood levels of cholesterol and lipids in animals [142]

6. Antimicrobial Properties

Medicinal mushrooms have been re-investigated as sources of novel antibiotics mainly as a result of increasing difficulty and the cost of isolating novel bioactive compounds from Actinomycetes and Streptomycetes. The research showed the antibiotic activity of some of the important wild mushrooms of Central India [70]. Growth of medically challenged bacteria like *S. aureus*and *B. cereus* was inhibited by five mushrooms out of six selected. Moreover the synthetic antimicrobial discs have shown a marked increase in their activity when combined with mushroom extract. The petroleum ether, chloroform, acetone and water extracts of mushroom *Osmoporus odoratus* has shown the antibacterial activity against *Staphylococcus aureus, Streptococcus pyogenes, Bacillus subtilis, E. coli* and *Pseudomonas aeruginosa*; the water extract alone showed antibacterial activity against the tested organisms and the results were comparable with that of amphicillin rather than chloramphenicol [137]. Determination of antimicrobial activity of *Lycoperdon perlatum, Cantharellus cibarius, Clavaria vermiculris, Ramaria formosa, Maramius oreades* and *P. pulmunarius* tested against the pathogenic bacteria and fungi indicated that the concentration of bioactive components directly influence the antimicrobial capability of the isolates [123]. Quershi et al. (2010) [117]

studied the antimicrobial activity of various solvent extracts (40µg/ml) of *Ganodermalucidum* against six pathogenic species of bacteria. Acetone extract exhibited maximum antibacterial activity (31.60±0.10), while the most susceptible bacterium observed was*Klebsiella pneumoniae.* The antimicrobial effect of ethanol extracts of *Pleurotus sajorcaju*, *P. florida* and*P. aureovillosus* were tested against four species of Gram-positive bacteria, five species of Gram-negative bacteria and one species of yeast.

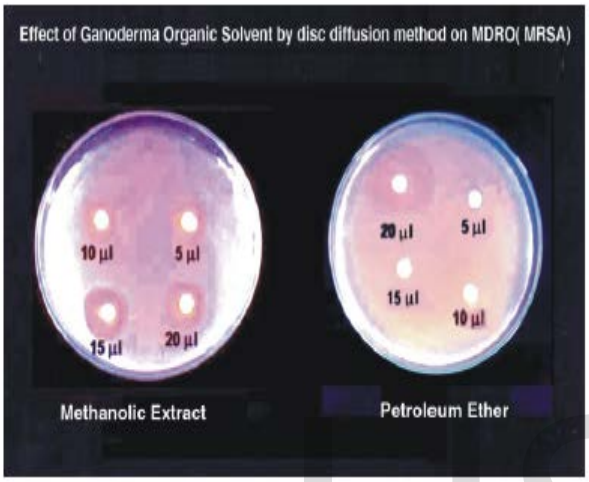

Figure 2: Effect of *Ganoderma* organic solvent by disc diffusion method on MDRO(MRSA) [116]

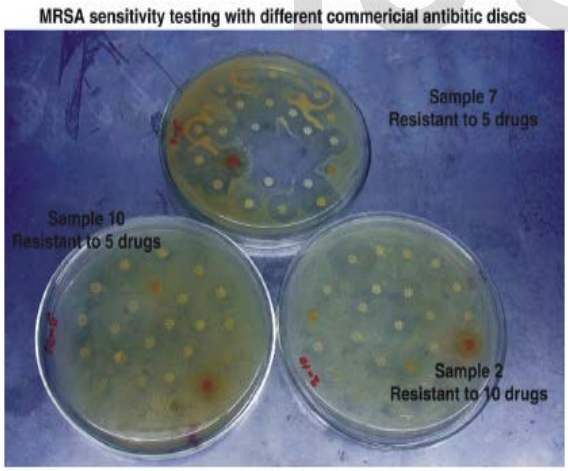

Figure 1: MRSA sensitivity testing with different commercial antibiotic disc (Prasad and Wesely, 2008)

Pleurotus species exhibited narrow antibacterial spectrum against Gram-negative bacteria and strongly inhibited the growth of the Gram-positive bacteria tested, including *Bacillus subtilis*, and *M. luteus* [90]. The antioxidant and antiviral activities against *Herpes simplex* virus 1 (HSV-1) and Human Influenza viruses of the solvent extract is obtained from an edible mushroom *Agaricus heterocystis* under *in vitro* condition [90]. Sheena et al., (2003) [131], [132] have observed that three macrofungi *Ganoderma lucidum*, *Navesporus floccose* and *Phellinus rimosus* are showing antibacterial activity that were found in South India. *G. lucidum*, which not only contained 120 different triterpenes but also polysaccharides, proteins and other bioactive compounds; the spectrum of detecting the pharmacological activities of mushrooms was very broad on Multidrug (Figure1-3) resistant *Staphylococcus aureus* [116].

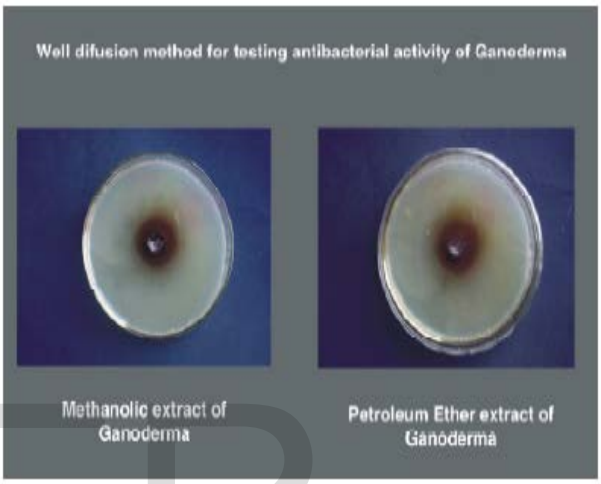

Figure 3: Well diffusion method for testing antibacterial activity of *Ganoderma*[116]

New sesquiter penoid hydroquinones, produced by the European *Ganoderma* species *Ganoderma pfeifferi* Bres., named ganomycins, inhibit the growth of methicillin-resistant *Staphylococcus aureus* and other bacteria [103]. Besides, whole extracts of this mushroom inhibit the growth of microorganisms responsible for skin problems [*Pityrosporum ovale*, *Staphylococcus epidermidis*, *Propionibacterium acnes* [50]. Steroids like 5a-ergosta-7, 22-dien-3b-ol (3) or 5,8-epidioxy-5a,8aergosta-6, 22-dien-3b-ol [139],[78], isolated from *Ganoderma applanatum* (Pers.) Pat., proved to be weakly active against a number of Grampositive and Gram-negative microorganisms [78]. Oxalic acid is an agent responsible for the antimicrobial effects of *Lentinula edodes* (Berk.) against *S. aureus*and other bacteria [15]. Ethanolic mycelial extracts from *L. edodes* possessanti-protozoal activity against *Paramecium caudatum* [15]. The antimicrobial activity of *Podaxis pistillaris* (L. Pers.), is being used in some parts of Yemen for the treatment of nappy rash of babies and in South Africa against sun burn [109], which is caused by epicorazins. These substances belong to the group of epipolythiopiperazine- 2, 5-diones, an important class of biologically active fungal metabolites [109]. Other

antimicrobial compounds from the Aphyllophorales were summarized by Zjawiony (2004) [169].Many antimicrobial compounds such as terpenes, lectins, polysaccharides etc. act on the bacterial cytoplasmic membrane [87], [164]. Various extracts of *G. lucidum* have been found to be equally effective when compared with gentamycinsulphate. Dulger and Gonuz (2004) [49] reported the antimicrobial properties of 4 different extracts of macrofungus (*Cantharellus cibarius*) against 50 important human pathogens. He observed good antimicrobial activity with ethanol and acetone extracts against most of the pathogens. Cowan (1999) [41] reported that the most active components are generally water insoluble, hence it is expected that low polarity organic solvents would yield more active extracts. In another study, the aqueous extract from *G. lucidum* exhibited moderate activity against *E. coli* and *P. aeruginosa* followed by *S. aureus* while least zone of inhibition was recorded for *Bacillus* species. Klaus and Miomir (2007) [74] have studied the influence of various extracts isolated from *G. lucidum* on *E. coli*, *Bacillus* species, *S. aureus* and *Salmonella* species. The aqueous fruiting body extract showed maximum zone of inhibition against *Bacillus* species while least zone of inhibition was reported for *E. coli* and *Salmonella* species. Yoon et al. (1994) [166] investigated the bioactivity of aqueous extracts from the fruiting body of *G. lucidum* and found that the extracts also exhibited inhibitory activity towards *Bacillus* species. Extracts from *G. applanatum* [141] and *G. pfeifferi* [103] have been shown to possess significant antibacterial activity against *E. coli*. Sheena et al. (2003) [83], [131] reported that methanol extract of *G. lucidum* showed remarkable antibacterial activity against *E. coli*, *Salmonella* species and *B. subtilis*. Keypour et al. (2008) [71] investigated the antibacterial activity of a chloroform extract of *G. lucidum* from Iran. The results of disc diffusion tests showed that the chloroform extract had growth inhibitory effects on *B. subtilis* and *S. aureus*. Smania et al. (2007) [140] observed MIC value of 2mg/ml for *E. coli* and *P. aeruginosa* while 1mg/ml in case of *S. aureus* and 0.25mg/ml for *Bacillus* species with *G. austral ate* extract. Significantly high MIC of an aqueous *Ganoderma* extract against *B. subtilis* (3.5mg/ml), *Bacillus* species (3.5mg/ml) have been reported by Yoon et al. (1994) [166]. Keypour (2008) [71] recorded MIC value of 8mg/ml for *S. aureus* and *B.subtilis* with chloroform extract of *G. lucidum*. Results with present mushroom indicate the MIC values to be lower in comparison to MIC value obtained by other investigators, indicating that the acetone extract possesses more potential as an antibacterial agent at lower concentrations. The water extract of *Lentinus edodes* demonstrated growth-enhancing effects on colon inhabiting beneficial lactic acid bacteria, *Lactobacillus brevis* and *Bifidobacteria brevis* and *Bifidobacteria brevie.* The effective factor in the extract is considered to be the disaccharide sugar, trehalose. The *L. edodes* extract can improve the beneficial intestinal flora of the gut and reduce harmful effects of certain bacterial enzymes such as β-gucosidase, β-glucorinidase and tryptophase as well as reduce colon cancer formation [18]. The heavy molecular weight cell wall polysaccharides, for example, PSP from *Trametesversicolor* inhibits growth of infection yeast, such as *Candida albicans* [153], [125], [126]. Antitumor polysaccharides inhibit bacteria such as *Bacillus subtilis, Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*. *Hericiumerinaceum* shows strong antimicrobial activity against a broad range of infectious agents.

Compounds extracted from *Agaricus bisporus*, *Lentinus edodes, Coprinus comatus* and *Oedemansiella mucida* have been reported to have antifungal and antibacterial properties.

It is clear from the above discussion that mushrooms also have antimicrobial properties. The bioactive compounds like mniopetals, oudemansin, lanostane and bioactivity of various types of mushrooms are shown in Table 2. Their dose compensation and mode of action is subject for research for new generation researchers. Clearly, the antimicrobial potential of several medicinal mushrooms from Basidiomycetes are not yet exploited must warrant extra examination.

Table 2.Compounds showing antimicrobial activity.

Mushrooms	Bioactive compounds	Bioactivity	Reference
Cheimonophyllum Candissimum	Cheimonophyllon A-E	Antibacterial, Weak antifungal	[145]
Clitocybe cyanthiformis	Cyanthiformine A	Antibacteria, Antifungal	[11]
Clitocybe diatreta	Diatretol	Antibacterial	[11]
Coprinus Atrementarius	Illudin C2, Illudin C3	Antimicrobial	[85]
Crepidotus Fulvotomentosus	Strobilurin E	Antifungal	[161]
Favolaschia sp.	Favolon	Antifungal	[9]
Flagelloscypha Pilatii	Pilatin	Antibiotic	[54]
Lentinus edodes	Lentinan	Antiviral	[99]
Mniopetalum sp.	Mniopetals	Antimicrobial	[77]
Mycena sp.	Strobilurin M, Tetrachloropyrocatechol	Antifungal, Antibacterial	[42]
Omphalotusilludens	Illudinic acid	Antibacterial	[48]
Oudermansiella radicata	Oudemansin X	Antifungal	[9]
Poria cocos	Lanostane	Phospholipase A2, inhibitor (group of anti-inflamatory agents)	[41]

Bilirubin concentration has been used to evaluate chemically induced hepatic injury. Besides various normal functions, liver excretes the breakdown product of hemoglobin namely bilirubin into bile. It is well known that necrotizing agents like paracetamol produce sufficient injury to hepatic parenchyma to cause large increases in bilirubin content [115]. *Lentinus edodes* extract prevented severity of liver damage caused by paracetamol as evidenced by the low level of bilirubin in the serum. Similar results were also reported by Jayakumar et al. (2006) [64]. They used oyster mushroom (*Pleurotus ostreatus*) extracts onCCl_4-induced liver damage in male Wistar rats. They reported that when rats with CCl_4-induced hepatotoxicity were treated with the extract of *P. ostreatus*, the serum SGOT, SGPT and SALP levels reverted to near normal.

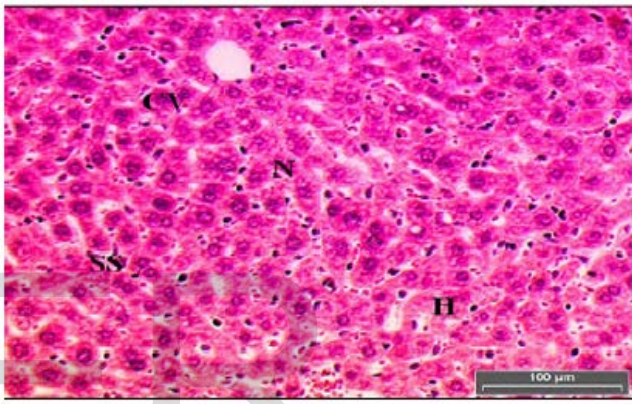

Figure 4. Light microphotographs of haematoxylin and eosin stained sections of the formalin fixed liver cell of normal mice.
Liver cells of Group 1 mice (normal) have hepatic cells with well-preserved cytoplasm, prominent nucleus and nucleolus. (H, hepatocytes; N, nucleus; SS, sinusoid; CV, central vein) [128]

Figure 4 shows [128] the liver tissue of mice which received 1 mL/kg of saline and free access to pellets. Control group showed a normal liver architecture of hepatocytes where they were well arranged without any alteration at central and portal veins.

7. Hepato-Protective and Antitumor Effect

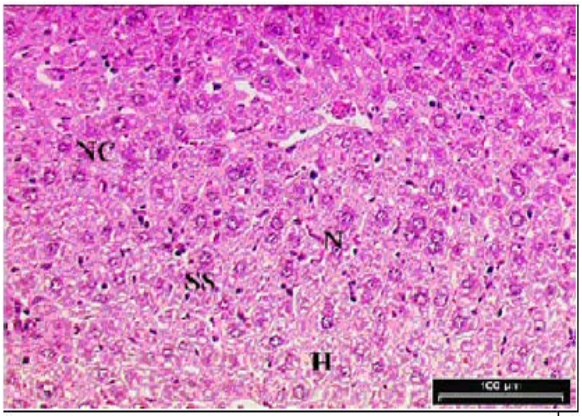

Figure 5. Light microphotographs of haematoxylin and eosin stained sections of the formalin fixed liver cell of mice exposed to paracetamol.

Liver cells of Group II mice (exposed to paracetamol) revealed extensive fatty changes, characterized by the disruption of the lattice nature of the hepatocyte, damaged hepatic sinusoids and necrosis. Presences of reticular sides are visible and nucleuses of two to three are joined together. (H.hepatocytes; N, nucleus; SS, sinusoid; NC, necrosis) [128]

Figure 5 shows mice liver tissue damage induced with paracetamol (1.0 g/kg paracetamol orally × 7 days). Toxic effect such as liver damage, haemolytic anaemia, oxidative damage to the red blood cells and bleeding tendencies due to over dosage of paracetamol was noted.

Figure 6 shows the mice liver tissue induced with paracetamol and treated with *L. edodes* extract. *L. edodes* is highly known for its medicinal value as an antioxidant agent that prevents free radicals produced by paracetamol toxicity. In this study, mice were given oral paracetamol 1 g/kg to induce hepatotoxicity and this was challenged by 200 mg/kg of mushroom extract 3 h after the administration of paracetamol. The treatment was continued for seven days. Only minimal disruption of the structure of hepatocytes was noted in liver tissue of mice exposed to paracetamol and *L. edodes* extract.

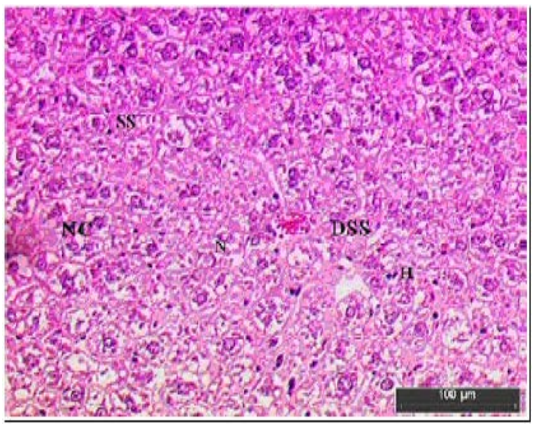

Figure 6. Light microphotographs of haematoxylin and eosin stained sections of the formalin fixed liver cells of mice treated with mushroom extract.

Liver cells of Group III mice (exposed to paracetamol and mushroom extract), only minimal disruption of the hepatic cellular structure was observed. Nucleases are at recovery stages and absence of joined nuclease. Sinusoids are slowly recovering and their presence of dilated sinusoid filled with red blood cells. (H, hepatocytes; N, nucleus; SS, sinusoid; NC, necrosis; DSS, dilated sinusoid filled with red blood cells) [128]

The liver tissue of mice treated with *Lentinus edodes* extract displayed cell recovery compared to the mice induced with paracetamol alone (Figure 6). Hepatocytes were being transformed to normal polyhedral shape with some cell lining observed. Nuclei are slowly improving and clumping of nucleus is not seen.

Lentinus edodes is a very popular food in Asia and the raw materials can be stably supplied by cultivation of the mycelia, the extract is a promising candidate for use as an antioxidant and hepatoprotective agent [84], [128].

Another Indian mushroom, *Phellinus rimosus* shows anti-hepatotoxic activities [4]. Hepatoprotective activity also has been studied from *Trianthema portulacastrum* L.against paracetamol and thioacetamide intoxication in albino rats [76].Scientists have discovered that the polysaccharide compound lentinan, found in shitake mushrooms, possess immunostimulant and anti-tumor properties. Lentinan can also prevent platelet adhesion, which causes the clots responsible for coronary artery disease and stroke. All the three extracts like ethyl acetate, methanol and aqueous extracts of the *P.rimosus* when tested for antitumor activity were found to inhibit the Dalton's Lymphoma Ascites (DLA) cell line induced solid tumor in mice and Ehrlich's Ascites Carcinoma (EAC)cell line induced ascites tumor in mice (Ajith and Janardhanan, 2003). Medicinal mushrooms occurring in India namely *Ganoderma lucidum, Phellinus rimosus, Pleurotus florida* and *Pleurotus pulmonarius* possessed profound antioxidant and antitumor activities [66], [6]. Laganathan et al. (2009) [79], [80] have studied the anticancer property of *Agaricus bisporus.* Research shows that reishi mushroom [65], [21] combat tumours, inhibit the body's production of cholesterol and stimulates the immune benefits. Polysaccharides or peptideglycan, pharmaceutically active mushroom compounds, continue to be the subject of most researches, including isolation, chemical structures and experiments*in vitro* or *in vivo*. Ten years ago the research was concentrated on the four mushrooms, *Lentinus* (*Lentinula*) *edodes*, *Schizophyllum commune*, *Grifola frondosa*, and *Sclerotinia sclerotiorum*, particularly their respective b-glucans, lentinan, schizophyllan (also called SPG, sonifilan, or sizofiran), grifolan, and SSG. Most of them, b-(1-6)-branched b-(1-3)-linked glucans, were found to exhibit significant antitumor activity [27]. In recent years, additional research has been conducted with these four mushrooms, but a host of other species and a variety of species has been explored and

investigated [110], [88]. At least 651 species representing 182 genera of hetero- and homobasidiomycetes mushrooms contain antitumor or immunostimulating polysaccharides [111], [66], [5], [23], [50]. There are also several reports of mushrooms containing more than one polysaccharide with antitumor activity [28]. An interesting example is *A. blazei*. It contains an antitumor glucan with a b-1, 6 backbone [59], [95], [100], which differs from the b-1, 3 backbone with b-1, 6 branches shared by many other antitumor glucans. In addition, a glucomannan with the main chain of b-1, 2-linked D-mannopyranosyl residues has been isolated from this mushroom and found to inhibit tumor genesis [95], [100]. The lipid fraction of *A. blazei* was found to contain a compound with antitumor activity, subsequently identified as ergo sterol [149]. The lipid fraction of *Grifola frondosa* exhibited antioxidant activity and inhibited the cyclooxygenase enzymes, COX-1 and COX-2 [141], [149], [58]. Ergosterol was again identified as one of the most active constituents. Oxidative damage is strongly implicated in the development of many chronic diseases, including cancer. The inducible form of COX, COX-2, also appears to play an important role in certain cancers. Its inhibition can result in the inhibition of tumor development, and it appears to be beneficial even in some established tumors [22]. Other mushroom constituents may inhibit promotion or progression by exerting direct cytotoxicity against tumor cells [31], [32] interfering with tumor angiogenesis, or up-regulating other non-immune tumor-suppressive mechanisms.

8. Clinical Trials of Medicinal Mushrooms and Availability of their Products as Medicine in India

The National Cancer Institute (NCI), United States has recently intensified its emphasis for new drug discovery and began screening of plant extracts for anticancer activity in 1956. Ikekawa et al. (1969) [57] published one of the first scientific reports on antitumor activity of extracts of mushrooms against implanted Sarcoma 180 in animals. Soon after, three major anticancer drugs, Krestin from cultured mycelium of *Trametes* (*Coriolus versicolor*), Lentinan from fruiting bodies of *Lentinus edodus* and Scizophyllan from Schizophyllum commune, were developed [157],[95],[100],[56]. While much attention has been drawn to various immunological and anticancer properties of these mushrooms they offer other potentially important therapeutic properties including antioxidant, antihypertensive, anti-diabetic, anti-inflammatory, hepato-protective etc. Several mushroom derived compounds are now increasingly used as adjuvant to standard radio- and hemotherapy. The most encouraging effect is the ability of these mushroom derived compounds when administered prior to or during radio- or chemotherapy significantly reduced the side effects from these treatments. Their reactive oxygen and nitrogen species are implicated in the pathophysiology of several diseases. Mushrooms as dietary chemotherapeutic agents may serve as potent agents for enhancing therapeutic effect of chemotherapy, radiotherapy and offer standard therapies for the treatment of human cancer [127]. The safety criteria of these compounds have been exhaustively studied with little evidence of toxicity. *Ganoderma lucidum* and related species have the longest historical usage for medicinal properties dating back at least four thousand years [167]. In Japan it is called Reishi and in China and Korea it is variously called Ling Chu and Ling Zhi (Mushroom of immortality). Traditionally it has been used widely in the treatment of hepatopathy, chronic hepatitis, nephritis, hypertension, arthritis, insomnia, bronchitis, asthma and gastric ulcer. Scientific studies have confirmed that the substances extracted from the mushrooms can reduce blood pressure, blood cholesterol and blood sugar level as well as inhibition of platelet aggregation. *Ganoderma* species are famous tonic in Chinese medicines. They are widely distributed in India on tree trunks. *Ganoderma* belongs to the polyporaceae family of Basidiomycota. Generally *Ganoderma* species are described as beneficial to all viscera and non-toxic [89]. For 4000 years *G. lucidum* has been used as a part of Chinese and Japanese medicine especially for the treatment of most of the human ailments including chronic hepatitis, nephritis, hepatopathy, neurasthenia, arthritis, bronchitis, asthma, gastriculcer etc. *G. lucidum* [120] and other mushrooms like *G. applanatum, L. edodes, Flamulinavelutipes, Grifola frondosa* from China, Korea, Japan and India have been used in many clinical studies with animals and humans, reporting the beneficial results [119].There are several companies marketing their produce in India. These companies import the medicine into India in tablet/the capsule form and sell it as a high value medicine for cure of chronic/terminal diseases like cancers/AIDS. *G. lucidum* capsules are available in packs of100 capsules, alone and in combination with other medicinal mushrooms like caterpillar mushroom, shitake and other mushroom. The company's marketing these are: Fungi Perfecti, USA; Mycology Research Laboratory, UK; Nammex (North American Medicinal Mushroom Extra), USA; Core nutritional Products, USA and others [44]. *Cordyceps sinensis* medicine is available in freeze-dried mycelia form in capsules, alone and in combination with freeze-dried caterpillar mushroom. These medicines are available as "over the counter" products in Indian in all big cities. Its consumption is conspicuous in areas in north (Delhi-Chandigarh) and Southern India, in the state of Kerala. The consumption is high due to more per capita income of the people in these areas. Moreover, the consumption is confined to well-to-do families only [44].Clinical trials were

conducted on 56 cancer patients, 30 were chosen to receive the medicinal mushroom extract mix and another 26 comparable patients receiving the accepted pharmaceutical drug Polyactin-A as a control group. All patients were in the middle-latestages (Stage 3 and 4) of cancer. The experiment concludes that the tablets of mixed polysaccharides, made up of the six species of medicinal mushrooms, can become a new health product to improve immunity with high effectiveness and no toxicity. However, further trials are needed. The polysaccharides extracted from *Agaricus brasiliensis*, *Grifola frondosa, Lentinusedodes, Ganoderma lucidum, Trametes versicolor* and *Cordyceps sinensis* are used to produce tablets for inhibiting the growth of tumours and improving the immunity. The products of *Ganoderma lucidum* are prescribed in various forms, it can be injected as a solution of powdered spores or given as syrup. It can be taken as tea, soup, capsules, tinctures, or bolus. In tincture form, the dose given is 10 ml thrice daily. In case of syrup the dose is 4-6 ml/day. The dried mushroom (200-300 g) is prepared in water and given as a drink, the recommended dose is 3-5 times daily [165], [168].In Japan, *Ganoderma lucidum* is used for the treatment of the cancer [162]. The results obtained after application shows that the patient sleeps well with a healthier feeling and has an increased appetite; Reishi also provides relief from angina pectoris. Injection of spore powder is effective in curing progressive deterioration, atrophy and muscles stiffness. The effect of elevation changes has been prevented and cured by tablets of mushroom spores. In a experimental study for therapeutic application of *G. lucidum*, 143 patients with advanced previously treated cancer were given an oral *G. lucidum* polysaccharide extract of 1800 mg three times daily for 12 weeks. Twenty seven patients were not assessable for responsible and toxicity, because they were unable to track for follow-up or refused further therapy before the 12 weeks of treatment were up. Of the 100 fully assessable patients, 46 (32.2%) had progressive disease before or at the six weeks evaluation point (range: 5 days-6weeks). There was no significant change in the Functional Assessment of Cancer Therapy-General (FACT-G) scores in 85 assessable patients. In the group with stable disease, FACT-G scores improved in 23 patients, remained unchanged in five, and declined in one. Within this group, the median change from the baseline score to the 6 and 12 weeks was+7.6 and +10.3, both statistically significant ($P< 0.05$). For the 38 patients with SD, the median change from the baseline score was 28.1±10.2 weeks. This indicates that Ganopolymay have an adjunct role in the treatment of patients with advanced cancer although objective responses were not observed in the study [155].*G. lucidum* and other mushrooms like *G. applanatum, Lentinus edodes, Flammulinavelutipes, Grifola frondosa* from China, Korea, Japan and India have been used in many clinical studies with animals and humans, reporting the beneficial results. The high molecular-weight polysaccharides from the cell wall of *G. lucidum* are physiologically active. They are used against various diseases like diabetes, Alzheimer's disease, retinal pigmentary degeneration, atrophic myotonous hepatodymia, rhinitis, leucopoenia, insomnia,
dyspnea, neurasthemia and duodenal ulcers. The water extract from fruit body had inhibitory activity on histamine release from rat peritoneal mast cells, induced by compounds 48/80 or antigen-antibody reaction and on passive cutaneous anaphylaxis reaction in guinea pigs and the rats. The activity is due to the Ganoderic acid C and D, which are also responsible forth treatment of asthma and allergy. The polysaccharides and triterpenoids have also shown the anti-HIV activity. They also show protective effects on liver in animal and human studies [156]. Ganopoly is well-tolerated and appears to be active against HBV patients with chronic hepatitis-B. The mechanism for hepatoprotective effects of *G. lucidum* has been largely undefined. However, accumulating evidence suggests several possible mechanisms, which include antioxidants and radical scavenging activity, modulation of hepatic Phase I and II enzymes inhibition of β-glucuronidase, antifibrotic and antiviral activity, modulation of NO production, maintenance of hepatocellular calcium homeostasis and immuno modulating effects. *G. lucidum* also cures lung and heart dysfunction. Clinical studies on this were conducted in China in which 200 patients with chronic bronchitis were given *G. lucidum* in tablet form and 60-90% patients showed marked improvement with increased appetite. It also reduced blood and plasma viscosity in hypertensive patients with hyperlipidaemia. The extracts of this mushroom were reported to reduce blood cholesterol and blood pressure and also treat arrhythmia [46], [36]. *G. lucidum* has also shows hypoglycaemic and hypolipidemic activities. In a study, 71 patients with confirmed type II diabetes mellitus were cured and had best results. This study demonstrated that Ganopoly is efficacious and safe in lowering blood glucose concentration.

Table 3. Current biomedical applications of *Ganoderma lucidum*

Applications	References
A. Immunomodulating effects 1. Anticancer 2. Antiviral (e.g., anti-HIV) 3. Antibacterial 4.Therapyof auto-immuno disorders	Chang, 1994 [30] Mizuno, 1995a [96], 1995b [97], 1995c [98] Kim et al., 1994 [73] Yoon et al., 1994 [166]
B. Cardiovascular disorders 1. Coronary dilation and increasing coronary circulation 2. Anti-hyperlipidemic, and antiplatelet hypoglycaemic aggregation (blood clots)	Chang, 1993 [29], 1994 [30], 1996 [31] Soo, 1994 [144], 1996 [143] Chang and But, 1986 [34]
C. Cancer therapy 1. Maintain leucocyte count 2. Enhance the immune system	Chang, 1994 [30]; Soo, 1994 [144] Soo, 1996 [143]
3. Reduction of chemotherapy toxicity and elimination of induced leucopenia (low blood leucocytes) by chemotherapy 4. Remission to prevent relapses	Chang and But, 1986[34]; Hu and But, 1987 [55]; Chen and Yu, 1993[38]; Mizuno, 1995a [96], 1995b [97], 1995c [98].
D. Remission of cancer and hepatitis Treatment	Chang, 1994 [30] Ventura and Messerl, 1987 [153b]; Chang,1993 [29];
E. Enhancing oxygen utilization 1. Relief of discomfort of high altitude stress, headaches dizziness, nausea and insomnia	Mizuno, 1995a [96], 1995b [97], 1995c [98].
2. Relief of oxygen deprivation caused by coronary arteries blocked by atheromas, spasms or colts	Dharmananda, 1988 [45]
F. Anti-ageing, anti-oxidant free radical Scavengers	
G. Ant diabetic	Mizuno, 1995c[98]
H. Other examples usage in combination with other medicine 1. Physical exercise 2. Improving work capacity 3. Rapid recovery of normal physiology	Mizuno, 1995a [96], 1995b [97], 1995c [98]. Gunde-Cimerman, 1999 [52] Alexeev and Kupin, 1993 [8] Mizuno, 1995a [96], 1995b [97], 1995c [98]. Mizuno, 1995a [96], 1995b [97], 1995c [98].

Ref: [162], [38], [158], [159], [119].

The practitioner experiences along with preliminary clinical reports indicate that immunostimulating polysaccharides, inducing HIV and Epstein Barr Virus (EBV), are the cause of mononucleosis. The *G. lucidum* is one of the ingredients in skin lotions produced for protection against UV radiation [165].

9. CONCLUSION

Asia especially China has a long tradition of 5000 years for using Mushroom and Tea as Medicines and as consumable edibles. Regarding production and technologies for production of medicines from mushroom and tea, China is the first among the countries for production, research and marketing, China has a cutting edge than other countries and India is far behind in respect of this ground. Diabetes is a major endocrine disorder causing morbidity and mortality worldwide. The problem of diabetes is particularly relevant to India, as several studies have clearly documented an increased ethnic susceptibility to diabetes in-migrant Asian Indians. Recent epidemiological studies have pointed to the growing epidemic of diabetes in India. Indeed, according to the recent Diabetes Atlas produced by the International Diabetes Federation (IDF), India is home to the largest number of people with diabetes in the world, 40.9 million diabetic subjects in 2007, and these numbers are predicted to increase to 69.9 million by 2025. In country like India most of the people live below the subsistence level or poverty line and suffer from protein deficiency or protein hungriness. To combat this situation extensive research and cultivation of edible mushrooms in our country is imperative. The mushroom industry is gradually taking route in India but the pace is rather slow because of insufficient scientific support and inadequate training programs. The Indian mushroom Industry needs very badly modern technology for their survival in competitive International market. The research reports summarized in this article have highlighted that water containing Magnesium, Chromium and Bicarbonate(Cardio Protective Drinking Water) can reduce deaths due to heart Diseases and help in glucose metabolism and diabetes and clearly bring about the fact that Mushrooms are an important natural source of foods and medicines. The above two (Cardio Protective Drinking Water and Medicinal Mushroom) can be mixed into a concoction to produce a tea which is considered can be used as daily routine as a medicinal drink; it may prove to be a Novel Nutraceutical Tea which can increase the average human life span and prove against various diseases yet regarded either fatal or incurable. The medicinal importance as nutraceuticals, anti-oxidative, cardiovascular, hypercholesterolemia, antimicrobial, hepatoprotective, anticancer, clinical trials and availability of mushroom medicines in India. However, the mechanism of action of various secondary metabolites isolated from medicinal and wild edible mushroom is yet to be elucidated. Government Organizations spread over our country have already taken extensive initiative to aware the common people to practice mushroom cultivation as well as research. Non-

Government Organizations too, are actively taking initiative in this respect but enough scope is still lacking to disseminate the knowledge to each and every one of a vast country like ours.

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