

Review Article

GANODERMA LUCIDUM: A TRADITIONAL CHINESE MEDICINE USED FOR CURING TUMORS

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ABSTARCT

Ganoderma lucidum is generally called "Lingzhi or Reishi", and also be a Traditional Chinese medicine utilized in over 2000 y for their better therapeutic activity like antitumor, antiallergenic, antiviral, hepatoprotective, antioxidant, hypotensive, immunomodulator, hypoglycemic, anti-inflammatory, antithrombotic, antibacterial and many other health benefits. *Ganoderma lucidum* is one of the oldest herbal remedy found and grow in wide variety parts on deciduous trees (dead/dying tree) specifically in oak, pyrus, maple, elm, willow, sweetgum, magnolia, locust, acer, betula, castanea, coryolus, fagus, populus, plums and other plants species. It also be contains 400 major bioactive chemical constituents include polysaccharides, triterpenoids, polysaccharide-peptide complex, β -glucans, lectins, natural germanium (Ge), adenosine, phenols, steroids, amino acids, lignin, vitamins, nucleotides or nucleosides possesses specific curative properties and formed a wide variety of viable products from *Ganoderma* fruiting bodies, mycelia, spores i.e. coffee, powder, dietary enhancements, tea, spore items, drinks, syrups, toothpastes, cleansers or creams. Many *in vitro* or *in vivo* analyses with regards *Ganoderma lucidum* evidenced their antitumor activity but some conducted clinical studies are questionable and remains undefined for their antitumor effect. Though, we reviewed and summarized in this article about treatment and various pharmacological mechanism against tumor with respect to extract (polysaccharide and triterpenoid) of *Ganoderma lucidum*.

Keywords: *Ganoderma lucidum*, Triterpenoid, Polysaccharide, Anti-tumor, Traditional Chinese medicine

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INTRODUCTION

Medicinal mushrooms are fungal organisms that contain fruit-body of fungus and considered as traditional medicinal agents as health foods, nutritional supplements and nutraceuticals. The utilization of remedial fungal mushrooms for promotion of health, permanency and for illness since long in East Asian countries where Traditional Chinese Medicine has used as herbal preparations for a large number of years but the use is slightly increasing in Western world since the last few years [1-4]. However, Asia is also the historical site of mushroom cultivation is reported in China in 12th century. Nowadays, China is responsible for 70% of the world's mushroom production [2].

In between the cultivation and traditional system of medicine, fruiting bodies of certain mushrooms types of *Ganoderma* are utilized as conventional medication in China or another Asian nation for across 2000 y which elevates health and endurance to brings down the threat of malignant growth, increases immune activity, in treatment of frailty or faintness, sleep disorder, diabetes and other health benefits or properties. A variety of trade items are developed from *Ganoderma* fruiting bodies, mycelia, spores include powder, dietary enhancements, tea, spore items, drinks, syrups, toothpastes, cleansers and creams, which marketed as valuable crude medication supplements and effective health food for health benefits [5-7].

One of the oldest medicinal mushrooms, *Ganoderma lucidum* considered as wood-decaying fungus or phytopathogenic fungus that forming by white rot of wide variety of trees, which has longest history of use. *Ganoderma lucidum* are most desired remedial mushrooms utilized widespread medication in china or japan over 2000 y meant for wide series of diseases prevention [8, 9, 3, 6]. *Ganoderma lucidum* are derived from words "Gano (Greek) or lucidus (Latin) means shiny or brilliant" and "derma (Greek) means skin" refers to smooth appearance of the surface of mushroom. The Chinese name of *Ganoderma lucidum* refers as-"Lingzhi" and "Reishi" or in Japan called "Mannentake" [7]. As per Chinese traditional culture, the word of "Lingzhi" (*Ganoderma lucidum*) considered as the combination of spiritual potency, the essence of immortality or stared "herb of spiritual potency", sign of happiness, good wealth, symbolizing success, divine power and longevity [7, 4]. The

medicinal property or value of *Ganoderma lucidum* has been documented in gone back almost 2000 y of Chinese literature to Shen Nong Materia Medica (102-200AD). In excess of 120 *Ganoderma* types become described on earth among that 98 species occurred originate in China. But, just 2 forms of *Ganoderma* such as *Ganoderma lucidum* (Leys. ex Fr.) Karst or *Ganoderma sinense* Zhao, Xu et Zhang remain recognized into Chinese Pharmacopoeia (2010) named *Lingzhi* [4].



Fig. 1: Lingzhi mushroom (*Ganoderma lucidum*) [58]

Ganoderma species are more often disseminated in humid or temperate areas globally in a few kinds with dark, red, purple, light, yellow and white or around 250 species of this mushroom are identified mainly in tropical area of India. Ordinarily used medicinal *Ganoderma* species i.e. *Ganoderma Lucidum*, *Ganoderma tsugae* Murrill, *Ganoderma capense* Junhua or Ronglan and *Ganoderma applanatum* (Pres.) Pat. have their own characteristic's biological properties and physiological effect. Each type of *Ganoderma* species considered in unmistakable laccate or non-laccate, sessile to stipitate basidiomata, binary-walled basidiospores or interwall columns [10, 8].

Ganoderma lucidum is beneficial and popular remedy which exhibit a wide range effect of anti-cancer/anti-tumor activity via improving TNF- α , IFN- γ and IL-2 (initiated at Purdue University in the United States) or anti-aging via raising α -DNA polymerase and anti-HIV by suppression of virus proliferation. Shell broken *Ganoderma* spore extracts are also effective in combination with chemotherapy or radiation therapy for the treatment of the patient with late-stage cancer, which allows undergoing surgery, chemotherapy or radiation therapy. The other significant property of active constituent in *Ganoderma lucidum* has display a beneficial effect in treating a several diseases include persistent hepatitis, joint pain, hypertension, hyperlipidemia insomnia, neoplasia, asthma, diabetes, anti-inflammatory, antimutagenic, anticarcinogenic, antitumor, nephroprotective, cardioprotective or in other diseases conditions [11, 8].

Global production

Ganoderma lucidum is normally developed in China, Taiwan, Japan, Korea, Malaysia or North America and also common in tropical and warm temperate regions of India. The worldwide creation of *Ganoderma* around 4900-5000 tons in year of 2002, out of that 3800 tons remained to turn out in China and annually 4300 tonnes production were cultivated artificially in over 10 countries. However, approx. 2-billion-dollar estimated world trade of this mushroom or in India, about Rs 120 crores were projected annual market for *Ganoderma*-based nutraceuticals (Unspecified 2002). While USA is considered as a biggest market for medicinal mushrooms or their items. In this manner, the natural product assemblage of *Ganoderma lucidum* is retailed in market Rs 600-700/Kg [9].

The overall market estimation of remedial mushrooms estimated about US \$6.0 billion in 1999 that increased \$18.0 billion in 2014. The growth of these market product was expanded in over last 25 y that are more greatly in North America. In year of 1990, only a limited nutritional supplement companies offering mushroom products but in year of 2015 every company has offering one or more mushroom preparations in their product line [2]. Thus, mushrooms signify a chief or to a great extent, an accessible wellspring of powerful drug product about 10,000 known species of mushrooms, out of which 2000 are harmless for individuals' wellbeing and around 300 have significant therapeutic properties [8].

Biological source

Ganoderma lucidum (M. A. Curtis: Fr.) P. Karst comes under class Basidiomycetes, has a place with the family Polyporaceae or Ganodermataceae and order of Aphyllophorales. The Ganodermataceae family derived from "Gano" means shiny or bright and "derma" means skin, a varied group of saprophytic fungi sustain on wood and having a bright or shiny surface covering the fruiting body. Its fruiting bodies recognized as "Lingzhi" by Chinese, "Reishi or Mannentake" by Japanese, "Chaga" by Russian, "Lingchich" in American or "Youngzhi" in Korean that means "Herb of Spiritual Potency", representing achievement, prosperity, divine strength, and longevity [12, 4, 6, 7, 9]. *Ganoderma lucidum* similarly be utilized as a health-promoting folk remedy and turned into a "king of herbs" for longevity in Asian nations [12].

Nomenclature

Kingdom: Fungi.

Phylum: Basidiomycota.

Class: Agaricomycetes.

Order: Polyporales.

Family: Ganodermataceae/Polyporaceae.

Genus: *Ganoderma*.

Species: *lucidum*.

Common names

United States: Reishi mushroom, *Ganoderma*.

China: Lingzhi, Lingzhi Cao, Ling Chih, Hong Ling Zhi, Chi Zhi.

Japan: Reishi, Mannentake, Rokkaku Reishi.

Korea: Young ji.

Vietnam: Ling chi.

Russian: Chaga.

American: Lingchich.

Korean: Youngzhi [13, 14].

Geographical source and habitat

Ganoderma lucidum (fruiting body) are generally found and grows in densely wooded mountains of high humidity or both tropical and temperate geographical areas and far countries in Asia, China, Japan, Africa Taiwan, Korea, North and South America and Europe [15, 6]. It is mainly grown in wide variety parts of Himalayas on deciduous trees (dead/dying tree), specifically in oak, pyrus, maple, quercus, elm, willow, sweet gum, magnolia, locust, acer, alnus, betula, tilia, castanea, coryolus, fagus, fraxinus, populus, plums and less acquired in coniferous trees i.e. larix, picea, pinus. It is mostly growing on plum trees and furthermore found on bases usually close to the soil exterior or rarely rising from repressed roots [16, 6].

Ganoderma species consume an inclusive multitude variety in excess of 44 species from 34 genera of plants actuality recognized by means of probable hosts. Plant-pathogenic or wood-crumbling *Ganoderma* varieties influenced to affect extreme ailments include stem decay, butt decay and root decay in financially significant plants or recurrent harvests in tropical nations [17]. Whereas dietary mushrooms offered an extensive assortment of therapeutic properties which is compelling against convinced serious illnesses. However, around 1.5 million classes of fungi have been identified globally out of which almost 82,000 are defined and around 5,000 are palatable and 2,000 safe known species belong to macrofungi [18].

Chemistry

Ganoderma comprises 400 different bioactive compounds, primarily situated in glossy fruiting body, mycelium or spores. *Ganoderma* mycelia contain high molecular weight bioactive ingredient polysaccharides, which found to be heteropolymers with monomer units of xylose, mannose and galactose and also be carry auxiliary metabolites included as triterpenoids, alkaloids, proteins, coumarin, flavonoid, phenols, lignocellulose debasing enzymes or nucleosides. Whereas *Ganoderma* products *Reishi* teas are rich source of water-soluble polysaccharides [4, 6]. Several triterpenoids of *Ganoderma* spores are isolated from ethyl acetate fraction, which includes as Ganoderic acid, Methyl ganoderate, Ganodermic Acid, estero sterol peroxide and have been identified with common Movalonic acid pathway. The fruiting body of *Ganoderma* has been studied for his chemical constituents and focus on spores have their biological activity against several diseases and health and inflammatory conditions [6].

Historical background

The Chinese name of *Reishi* mushroom (*lingzhi*) formerly described a "shaman crying for rain", that represents magical or heavenly assets be situated by *lingzhi* and generally considered as "Mushroom of Immortality", "Ten-thousand-year Mushroom", "Mushroom of Spiritual Potency", or "Soul Plant". *Ganoderma lucidum* (*Reishi*) mushroom was recorded between 120 prevalent stimulants (Shang pin) in many popular Chinese Materia Medicas (Shen Nung Ben Cao Jing). However, Red *Reishi* located beneficial to chest binding treatment, tonify the heart, sustain the middle, hone the mind or develop the memory [14].

Ganoderma lucidum (Curtis) P. Karst or *Lingzhi/Reishi*, a woody polypore (Basidiomycota) assume a crucial part of therapeutic mushroom in Chinese or Japanese traditions in any event of 2000 y. However, the term "*Lingzhi*" in China measured a powerful herbal medicine and signify a spiritual strength, improves wellness and longevity. The impression of "*Lingzhi*", mushroom with mystical powers was primary looked in Qin Dynasty (221-207 BCE). "*Lingzhi*" is significant folk Chinese medicine but declarations about

concept of *Lingzhi* were initiated in India with a Vedic plant called "Soma" (Soma-haoma). More than 200 *Ganoderma* species were known yet just two species i.e. *Ganoderma lucidum* (W. Curtis: Fr.) P. Karst or *G. sinense* Zhao, Xu et Zhang, remain formally documented named "*Lingzhi*" in Chinese Pharmacopoeia was inscribed in Ming Dynasty (A. D. 1590) recorded with similar or beneficial pharmacological properties [19, 17].

The fungus of *Ganoderma* was first seemed in Chinese fiction in Han Dynasty (206 B. C.–220 A. D.) and was authenticated in first book which exclusively dedicated to portrayals of herbs or their restorative qualities was "Shen Nong Ben Cao Jing" recorded in Han Dynasty (206 BCE–220 CE) or Eastern Han dynasty of China (25–220 AD). This book likewise represents "Classic of the Materia Medica" (502–536 A D) or "Shen-nong Herbal Classics" or permitted "Ben Cao Gang Mu" by Li Shin-Zhen which called an original Chinese pharmacopoeia (1590 AD, Ming dynasty). It defines botanic, zoological, or mineral substances, was collected in 2nd century beneath alias of Shen-nong ("Divine Farmer") and persistently efficient and reached with valuable impacts of a few mushrooms concerning *Ganoderma lucidum* therapeutic mushroom. An Emperor Wu has developed the growth inward Majestic Palace compartment by herb of immortality recognized basically by means of *Chih plant* or *Chih fungus*. While, "*Lingzhi*" is cited in 2000 y old poem written by Han Dynasty chronicler, Pan Ku and utilizing the expression "*ling chih*". Though, the term *ling Chih*, afterwards transformed to *Reishi* by Japanese and association among unique *Chih fungus* or *Ganoderma lucidum* evidently procure starting folklores of a prior secretive *Chih fungus* and *Chih herb* of immortality according India documentation. In early 800 y ago, "*Lingzhi*" is characterized in canvases, wood carvings, carvings of jade and deer's prongs, furniture, cover plans, balustrades, jewels, ladies' hair brushes, fragrances, crafted works or several artistic artworks by Yuan Dynasty (A. D. 1280–1368). Consequently, *Ganoderma lucidum* has assigned with therapeutic properties (State Pharmacopoeia of People's Republic of China, 2000) or medicinal remedy in Far East countries (North America and Europe) for old time in therapy of neurasthenia, sleeping disorder, anorexia, hepatopathy, nephritis, faintness, bronchitis, asthma, gastric ulcers, persistent hepatitis, hypercholesterolemia, mushroom poisoning antidote, coronary illness, hypertension, carcinoma or bronchial cough in mature age. As per Traditional Chinese Medicine (TCM), and Japanese herbalists stated various kinds of *Ganoderma lucidum* have different tastes and distinctive biological activity and also be classified six unique sorts of *Ganoderma lucidum* (Reishi mushroom) on the basis of color i.e. green, black, white, red, yellow, and purple [7, 16, 17].

Bioactive chemical constituents

Ganoderma lucidum contains 400 bioactive constituent which play vital role in various therapeutic activity. Major bioactive constituents are polysaccharides, triterpenoids, polysaccharide-peptide complex, β -glucans, lectins, natural germanium (Ge), adenosine, phenols, steroids, amino acids, lignin, nutrients, nucleotides or nucleosides with its particular therapeutic properties i.e. immune-modulators, antioxidants, chemo preventive or tumoricidal [18].

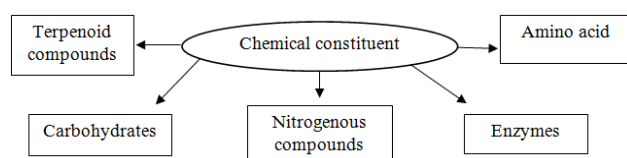


Fig. 2: Major bioactive constituents of *Ganoderma lucidum*.

Terpenoid compounds

Triterpenes

Triterpenes are subclass of terpenes which comprise 6 isoprene units. These isoprene's units by and large direct ties or overlay up or a ring-like structure. Around 140 types of triterpenes and

triterpenoids estimated in *Ganoderma lucidum* having molecular weight in between 400 to 600 kDa or complex substance structure or profoundly oxidized. The center of triterpenes structure depends upon lanostane i.e. metabolite of lanosterol are biosynthesized by squalene cyclization.

Triterpenoids also favoring with beta-glucans in immune system activation and also be responsible for bitter taste of *Reishi*, that a rapid method of defining the quality of *Reishi* product. Ganoderic acid is subtypes of triterpenes or major bioactive compound in *Ganoderma lucidum* involve four cyclic and two linear isoprenes and the carboxyl group, answerable for some natural impacts such as anti-inflammatory, against tumorigenic, anti-HIV and hypolipidemic activity. Over 150 highly oxygenated and pharmacologically active ganoderic acid (A, AM1, B, C1, C2, D, DM, F, G, H, K, Me, Mk, S, T, TR, Y), triterpenoids, ergosterol, Lanostane derivatives were extracted from other fungi of *Ganoderma* and *Ganoderma lucidum* genus (fruiting bodies, spores, and mycelia) and other include Ganoderols (A, B), Ganosporeric acid A (another triterpenoid, secluded from ether-solvent division of spores), Ganoderic acid α , Ganoderiol F, Ganoderatriol, Ganoderal A, Methyl ganoderate D, Ganoderate G or Lucidenic acid A,O, Lucidenic lactone and Cerevisterol having their significant biological activity.

Some of triterpenes were extracted more than 20 y i.e. ganoderic acids U, V, W, X or Y established cytotoxicity against hepatoma cells *in vitro* and Ganoderic acids A or C inhibited farnesyl protein transferase (enzyme in initiation of Ras oncoprotein involved in cell changes). The newly extracted ganoderic acids γ , δ , ϵ , ζ , η or θ didn't interfered in any activity against cancer cells. However, Ganoderic acid T is record significant malignant growth impacts by inhibiting MMP-9 expression (Matrix Metalloproteinase-9) in both *In vitro* or *In vivo* examines. Triterpenes with low molecular weight can mark cellular progressions include apoptosis, cell cycle regulation or angiogenesis by absolute connection among sub-atomic levels. While, Ganoderic acid D shown directly effect by binding with 14-3-3 ζ protein which improve to apoptosis in HeLa cell. Whereas, Ganoderiol F (GA-F) considered a tetracyclic triterpene demonstrated cytotoxicity *in vitro* in opposition to Lewis lung carcinoma (LLC), Meth-A, Sarcoma-180, and T-47D cell lines [20–26, 1, 2, 6, 7, 16].

Carbohydrates

Polysaccharides

About 200 different polysaccharides include glucose, xylose, mannose, galactose and fructose (β -D-glucans, α -D-glucans, α -D-mannans or polysaccharide-protein complexes) were isolated from *Ganoderma lucidum* (*Reishi*) fruitbodies, spores, mycelia having molecular weights around 4×10^5 to 1×10^6 Daltons. The basic outline of *Ganoderma lucidum* polysaccharide contain α - or β -(1 \rightarrow 3)-, (1 \rightarrow 4), (1 \rightarrow 6)-glucans linked main chain with single β -(1 \rightarrow 3)-connected D-glucopyranosyl by parts of mono-, di- or oligosaccharide side chains replacing at C-6 glucosyl deposits and other hetero-saccharides formed to glucose, mannose, Uronic acid galactose, xylose, fucose, rhamnose, arabinose remained identified in 10–50% in dry *Ganoderma lucidum*.

Although, cereal endosperm beta-glucans are rectilinear polysaccharides made out of cellotriosyl- and cellotetraosyl-units connected (1 \rightarrow 3)-beta and smaller level of cello oligosaccharides of higher-level polymerization also linked (1 \rightarrow 3)-beta-existing polysaccharides. *Ganoderma lucidum* polysaccharides (GL-PSs) exhibited in wide-range biological activities with various diverging adaptations or dissolvability influenced in various immune reactions with variable immune influences and other anti-inflammatory, hypoglycemic, antiulcer, antitumorigenic and immunostimulant effects. However, β -D-glucans involving (1-3)-, (1-4)- or (1-6)- β -D linkages showed stronger anti-tumor potency, improving absorption, host immune response and persuading cytotoxic pathways contrasted with different polysaccharides in *Ganoderma lucidum* [21, 23–26, 1, 2, 6, 7, 16].

Phenolic compounds

Phenolic compounds exhibit antioxidative and antiradical activity revealed to scavenge free radicals, contribute hydrogen, chelate metal ions, interrupted radical chain responses or extinguish singlet oxygen *in vitro* or *in vivo*. It contains backbone of glucose residues

connected via β -(1 \rightarrow 3)-glycosidic bond which often linked through side-chain. The scavenge free radical's mechanism are influenced in certain regulating pathological conditions include ageing, cancer, Alzheimer's disease, heart diseases, neurodegenerative disorders, atherosclerosis, cataracts and inflammation and also exhibited in antimicrobial properties against *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* or *Klebsiella pneumoniae* [1].

Sterols

Sterols assume an urgent part in keeping proper structure or province of all eukaryotic cells. Over 20 forms of sterols were estimated in *Ganoderma lucidum* or their skeletons separated within ergosterols (in fungi) or cholesterol. Almost 6 sterols components were found in fruiting body of *Ganoderma lucidum* exhibit antiviral activity against Epstein bar virus and several pharmacological effects include anti-HIV-1, anti-ageing properties or protective cerebral cortical neurons from hypoxia or re-oxygenation injury. However, a component of Ganodosterone (a *Ganoderma* derived sterol involve in inhibiting cholesterol synthesis) has been extract as a steroid which influenced antihepatotoxic [24, 1].

Proteins

Mycelium of *Ganoderma lucidum* contains Ling Zhi-8 (LZ-8) protein, a polypeptide having molecular mass 12 kDa and made out of 110 amino acid deposits with an acetylated amino end. LZ-8 be similar to biological activities and heavy chain of immunoglobulins then lectins with mitogenic activity and immunomodulatory effect to mouse spleen cells, human peripheral lymphocytes, agglutination of sheep red blood cells, effective suppressor of bovine serum albumin-initiated hypersensitivity in CFW mice *in vitro*. LZ-8 proteins also possessing strong antioxidant properties by inhibiting the oxidative reaction or altering the physical site of transition metals making insoluble metal complexes. While, Ganodermin isolated from *Ganoderma lucidum* display antifungal assets in contrast to *Botrytis cinerea*, *Fusarium oxysporum* and *Physalospora piricola* [16, 22, 24, 1].

Nitrogenous compounds

Nucleotides and nucleosides

Ganoderma lucidum (*Reishi*) comprises nucleosides i.e. adenosine cysteine, guanosine, inosine, thymidine, uridine just as nucleotides are adenine, guanine, hypoxanthine, thymine or uracil [16, 22, 24].

Enzymes

The major protein enzymes are extracted from *Ganoderma lucidum* included as β -N-Acetyl hexosaminidase, α -1, 2-mannosidase, endo- β -1,3-glucanase, β -1,3-glucanase or glutamic protease.

Amino acids

Almost 18 types of amino acids are identified in *Ganoderma lucidum* or extremely important amino acid are Leucine having durable hypoglycemic or antioxidant actions [24].

Other constituents

Ganoderma lucidum (*Reishi*) comprises oleic acid, cyclo-octa sulfur, ergosterol peroxide (5,8-epidioxy-ergosta-6,22E-dien-3-ol), cerebrosides (4/8E)-N-D-2-hydroxystearoyl-1-0- β -D-glucopyran-ocyl-9-methyl-4-8-sphingadienine or (4/8E)-N-D-2-hydroxypamitoyl-1-D- β -D-glucopyranosyl-9 methyl-4-8-sphingadienine, flavonoids, tannins, coumarins and anthocyanin. Moreover, some vitamins include vitamins B1, B2, B6, β -carotene, C, D, E were identified. Whereas, spores of *Ganoderma lucidum* comprise choline, tetracosanoic acid, betaine, stearic acid, palmitic acid, ergosta-7,22-dien-3-ol, nonadecanoic acid, behenic acid, tetracosane, hentriacontane, ergosterol and β -sitosterol and a pyrophosphosphatidic acid lipid. While, Alkaloids (stimulate central nervous system, antimicrobial, sympathomimetic, vasodilator, antihypertensive, antipyretic and antimalarial), vitamins, essential minerals, flavors and fatty acids (inhibit histamine) were identified [16, 18, 1].

Inorganic ions

Ganoderma lucidum contains major inorganic ions are Magnesium, Calcium, Zinc, Iron, Copper, and Geranium whereas, Ash of

Ganoderma lucidum contains minerals of potassium, sodium, phosphorus, chromium, arsenic, silicon, aluminum, cobalt, molybdenum, nickel, and lead [18, 24, 7].

Nutritional values

Nutritional value and composition may affect by several factors include changes between strains, development substrate, technique for cultivation, phase of collecting, definite segment of fruiting bodies for identification. The formation of *Ganoderma lucidum* concentrate (% of dry weight) contained Folin-positive material (68.9%), glucose (11.1%), protein (7.3%) or metals (10.2%) K, Mg, Ca, Ge (489 μ g/g). However, starch content fermented control reduced expressively (** $P \leq 0.001$) from 64.5 to 25.3% as well as content of reducing sugar enhanced expressively (** $P \leq 0.001$) 4.2 to 20.6%. Consequently, solid state fermentation (SSF) likewise expressively (** $P \leq 0.01$) expanded 11.0 to 16.5% in protein matter [18].

Cultivation and collection

Ganoderma lucidum (*Reishi*) are generally originate in living and dead wood of deciduous trees cultivates in subtropical or temperate climate areas in China and Asian countries i.e. Japan or Korea, USA, Europe or South America. In Far East countries its mostly grows in dead trees of Japanese plum (*Prunus salicina*). While, in Europe it found in dissimilar species of deciduous trees in summer and Autumn seasons. Whereas, In Poland it is found in the Świętokrzyskie mountains. Moreover, it mostly cultivated dead or dying trees include oak, alders, plum trees, maple, elm, willow, sweet gum, magnolia, locust or fewer located on coniferous tree i.e. larch, spruce, pte and pinus [27, 22, 18].

During ancient time, *Ganoderma lucidum* were extracted primarily from forest. But in the past, it is cultivated in small amounts only in wild because of very expensive. Traditional cultivation and axenic cultivation measured the most common in several yields, is faster or more practical. Although, in last 10 y it is generlly cultivated by artificial methods on media of wood meal, rice grain, wood wedges in China, Japan and United States were increased for better production. Artificial cultivation of *Ganoderma* was tried in 1937 and first efficacious cultivation of 1035 *Ganoderma* was achieved in 1969 by using spore separation cultivation method in Chinese Institute of Microbiology or Chinese Academy of Sciences (Beijing). The way toward making *Ganoderma lucidum* fruiting bodies is like more cultivated comestible mushrooms involves firstly preparing the fruiting culture, stock culture, mother spawn or planting spawn. Whereas, secondly preparing development substrates for mushroom cultivation.

Meanwhile, late 1980 a new method is remodeled the usage of short logs (15 cm or less) for their cultivation, today this technique is best for *Ganoderma* characteristic-log cultivators in China, Japan and Korea, which takes which takes a while to create the fruiting body, mycelia-based or culture broth-based items to guarantee quality control and constant creation in the year. Several environmental factors are important of cultivation of *Ganoderma lucidum* genus i.e. oxygen level and calcium ion concentration and different geographical regions. Recently, there are several other methods assumed for viable production of *Ganoderma lucidum* such as basswood cultivation, sawdust cultivation, substituted cultivation, short wood portion, tree stump, sawdust pack, and bottle methods [28, 16]. Agricultural wastes have been attained using substrates include grain, wood log, tea waste, cotton seed husk, sunflower seed hull, corn cobs, olive oil press cakes. However, sawdust and wood chips added with rice, wheat bran, finger millet or ragi as substrate (9:1 ratio) be applicable for *Ganoderma lucidum* cultivation for higher productivity, extensive or significant market value. Currently, *Ganoderma lucidum* isn't just species developed for a marketable reason in global in numerous types of crude medication, dried preparations, phytomedicines and teas yet additionally *Ganoderma applanatum*, *Ganoderma capense*, *Ganoderma sinense*, *Ganoderma tsugae* or *Ganoderma neo-japonicum* occur developed in accessible homesteads [29-33, 7, 14, 17, 19].



Fig. 3: Cultivation background of *Ganoderma lucidum* [59]

Morphological character

Macroscopic Identification

Fruiting Body-Annual, smaller with cap and stalk, intermediate, an infrequent antlered structure.

Cap-Rounded to crescent, flat, rounded, fan or kidney formed, 2-20 (35) cm wide, 30 to 250 mm in diameter, 4-8 cm thick, superior smooth surface, irregularly knobby or concentric waves, corky, rough, with or without stained emergence, shiny, red, cherry-red, reddish-brown or reddish-black in color, dark red to reddish brown or reddish black in middle, ochre/yellowish to sideline, flesh yellowish brown to dark brown, undeveloped fruitbodies are yellow-brown, yellow-red or by mature darker color, stipe is glossy, sporadically wound or 50-120x10-20 mm in size, hymenophore is trimitic, elastic, corky, fine, whitish, beige or brown color.

Pores-1 or 2 spore film creating tubes with 2-20 mm long, pores minute, thick 4-7/ μm , whitish while crisp, maturing or wounding earthy colored, surface yellowish cream, pore 6 for each mm, unpredictable, tube 3-5 mm long, unstratified, whitish brown.

Stalk-3-14 cm long, 0.5-4 cm thick, turned, amplified at base, similar shading or appearance as top surface.

Antler form-Rare antlered type of *Ganoderma lucidum* is profoundly valued remedially in China and Japan that grows normally or developed in situations with slight light and significant levels of carbon dioxide.

Aroma-moldy and fungus alike.

Taste-Depend upon strain and triterpenes may be strongly unpleasant.

Bitter fracture-Tough, sinewy, relentless, crushing into strips disclose dissimilar film of fruiting body.

Powder-Light to dark brown, lenient, flexible or gristly, pieces of Plectenchyma of cap, dark brown sections of tubes, basidiospores.

Distribution-Mostly saprophytic nonetheless might be parasitic on the bottom, roots or stumps of hardwoods, infrequently on conifers, diverse in distribution [34, 14, 22].

Microscopic Identification

Mushroom naturally breaks into little strips slightly than framing a characteristic powder. Whereas, powder is made up 3 types hyphae i.e. generative, binding or skeletal with rare basidia or basidiospores (spores). Reproductive hyphae consist of shrill-walled, colorless, clamps or concise branching. While, binding hyphae (horizontally or vertically) also consist colorless, thicker walls or immensely extended with slim tightening closes. Moreover, skeletal or basic hyphae primarily fruiting body consist of thick-walled, yellowish-earthly colored or somewhat extended, cap are more obscure in shading or palisade appearance or adjusted closures.

Cross segment of *Ganoderma* species formed external portion of cap is coriaceous with distended yellow-shaded hyphae (closely packed

with very thin plectenchyma) as well as inward portion of cap displays a grid of gray colored hyphae about 2-7 μm in width. Vertical tubes at inferior segment of cap are dark brown in color with width 200 μm and internal face is enclosed with light hymenial stroke with dark brown basidiospores. Basidia are ellipsoidal or spatulate, inconsistent, meager-walled or frequent. Spores are ovoid or curved among sprinkled surface with 8 μm long and spore edges are multiplied along more obscure inward film over external hyaline layer forming sparkling appearance. Starch and calcium oxalate are missing [14].

Medicinal uses

Ganoderma lucidum has been effective for treatment of several disease with most significant Pharmacological or Physiological results such as immunomodulatory, immunodeficiency, anti-cancer, anti-oxidant (radical scavenging properties), antiallergic, anti-inflammatory, antiparasitic properties, anti-viral (AIDS, HIV infections), anti-bacterial, anti-atherosclerosis, anti-androgenic, anti-diabetic (hypoglycemic), anti-fungal, anti-aging, stroke, anti-fibrotic, antiherpetic property, prevention of obesity, hypolipidemic, kidney tonic, heart diseases (hypertension), stimulation of probiotics, stomach ulcers, effects on nervous system (sleep-promoting, stress, mental fatigue, migraine), liver diseases (liver detoxification, hepatitis), arthritis, reduction of lower urinary tract symptoms, nephritis, bronchitis, asthma [35-40, 28-31, 18-22, 26, 33].

Therapeutic effect and antitumor activity of *Ganoderma lucidum*

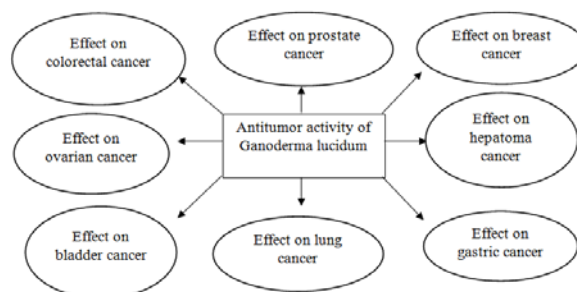


Fig. 4: Anti-tumor activities of *Ganoderma lucidum*

Effect on colorectal cancer

Colorectal cancer is major health problem in few nations or one of the upper three malignant growths analyzed in United States. A study in 2008 and 2009, the extracts of *Ganoderma lucidum* displayed to obstruct colon cancer by inhibiting cell expansion or persuaded programmed cell death in human colon cancer cells by *in vivo* and *in vitro* models. However, a report verified that Ganoderic acid T extract by *Ganoderma lucidum* inhibits development of HCT-116 and HT-29 colon cancer cell line in rodents via affecting cell cycle (G₀/G₁ stage) or induced autophagy through increasing autophagic vacuoles growth or also be raised Beclin-1 or LC-3 expression. Additionally, an aqueous concentrate of *Sporoderm (spores) Ganoderma lucidum polysaccharides (GLPS)* inhibited feasibility of HCT-116 colorectal malignant growth cells and functions of RTKs i.e. PS-F2 in dose dependent manner as well as assuming a significant part in adjustment of MAPKs, JNK, p38, ERK or NF- κ B that is influenced TNF- α in cancer signaling stimulation. In Lewis Lung Carcinoma (LLC) model *Ganoderma lucidum* decreased tumor expansion, expression of matrix metalloproteinase (MMP-2 or-9) mRNA or reduced progression in metastatic disease. In HT-29 xenograph model, *Ganoderma lucidum* triterpene include Ganodermanontriol (GNDT) inhibits development of HCT-116 or HT-29 (expanded the degrees of E-cadherin or β -catenin proteins) colon cancer cells by affecting cell cycle to decrease cyclin D1 expression (Cdk-4 and PCNA expression) in the tumor [41, 19].

Moreover, a study reported *Ganoderma lucidum polysaccharide (GLP)* decreased cell feasibility on HCT-116 cells. The western blot analysis of *Ganoderma lucidum* polysaccharide inclined the Bax/Bcl-

2, caspase-3 or-9, poly (ADP-ribose) polymerase (PARP) appearance and informed inducing GLP apoptosis in human colorectal cancer cells influenced in DNA division, reducing mitochondrial membrane potential, raising in S stage population, mitogen-activated protein kinase (MAK) pathways stimulation or inhibition in c-Jun N-terminal kinase (JNK) by SP600125 in dose dependent manner [4].

Effect on prostate cancer

Anti-tumor activity by *Ganoderma lucidum* on PC-3 prostate cancer cells in molecular component STAT-3 molecule or Jak-1 are concurrently defined the fundamental apoptotic properties to kept or censored transcriptional oncogenic STAT-3 target genes that inhibit growth of PC-3 cells in dose-dependently and confines growth and raises apoptosis by depending status of STAT-3 or Jak-1 pathway in the cells. Moreover, *Ganoderma lucidum* particularly effective and disabled STAT-3 (translocation) signaling pathway or proliferative marker articulation, serious cytotoxicity, ROS deposit, offend increasing cyclin-D1, Bcl-2 articulation, dense Bax, caspase-9 and 3 articulations or apoptosis in PC-3 cells by time dependent manner [42].

Additionally, a study revealed the ethanol or ethyl acetate concentrates of *Coprinus comatus* or *Ganoderma lucidum* prevent dihydrotestosterone instigated LNCaP cell feasibility via. arrest G1 phase in LNCaP or defeat degrees of discharged prostate precise antigen in dose-dependent manner. However, the *C. comatus* or *Ganoderma lucidum* combination also reduced androgen receptors protein level in LNCaP and glucocorticoid receptors transcriptional movement in MDA-kb2 breast cancer cells in dose-dependent manner [4].

Effect on breast cancer

Anti-cancer action of *Ganoderma lucidum* suppress breast cancer cells enlargement via preventing Akt/NF-Kappa B signaling. A current research study stated that gold nanoparticles (Au-NPs) produced from *Ganoderma lucidum* or conjugated with drug doxorubicin displayed strong anticancer or cytotoxic activity against MCF-7-doxbreast cancer cell line (97%) by Au-NPs at higher concentration was 400µM/ml that is beneficial for treatment of breast cancers. While, mRNA expression of ABCB1 gene and CDNA made from human breast cancer cell line (MCF-7) confirmed reduced expression [20].

Additionally, an examination directed in mice involving exceptionally invasive human breast cancer cells are embedded among mice breast tissues or administered *Ganoderma lucidum* once daily, noticed terminate breast-to-lung metastasis by pro-invasive genes inhibition. Then, an investigation issued in Journal of Cancer Research in April 2015 described the combination of *Ganoderma Lucidum* with Lapatinib in HER2+inflammatory breast cancer cells produced strong effect in SUM190 or KPL-4 cell lines or decreased the cell feasibility. Moreover, a study published in PLoS (2012) or directed of utilizing Ginseng and *Ganoderma lucidum* after finding of breast cancer in 4,149 patient's results 14.2 or 58.8% displayed a noteworthy impact on quality of life. Another examination displayed *Ganoderma lucidum* concentrate decreasing the tumor development by decreasing E-cadherin and eIF4G1 expression in inflammatory breast cancers [27].

In a study, *Ganoderma lucidum* produced anti-tumor effects in human ovarian OVCAR-3 cancer cells via suppressing/restrains cell development or interruption of cell cycle development by suppressing cyclin D1. Though, chemo preventive actions produced by *Ganoderma lucidum* were established in initiation of antioxidant SOD, catalase, phase-II detoxification enzyme NAD(P)H: Quinone oxidoreductase 1 (NQO1) or glutathione S-transferase P1 (GSTP1) through Nrf2 intervened signaling pathway [43].

Another study displayed the treatment of *Ganoderma lucidum* inhibit propagation of human ovarian cancer cells (HOCC) via decrease in VEGF appearance or rise in Cx43 expression in cancer cells. However, *Ganoderma lucidum* concentration was associated with level of immune-reactivity of Cx43 and VEGF (helping ovarian tumor genesis or growth) by cancer cells. Although, decreased expression of Cx43 in human ovarian cancer cells (HOCC) terminate impact of

Ganoderma lucidum on cell multiplication or lacking change in reduction of VEGF articulation in dose dependent manner that lessened cell proliferation in HOCC [44, 4].

Effect on hepatoma cancer

A study described, Ganoderic acid A (GA-A) produced significant effect by suppression of proliferation and blocked phosphorylation/activation of transcription factor STAT3, bringing about improved affectability of hepatoma cells to cisplatin. However, it should be demonstrated in 69-year old male patient with persistent hepatitis B infection created hepatoma cancer cells (HCC) was administered *Ganoderma lucidum* and *Gan Fu Le* (Chinese herbal medicine in treatment of hepatocarcinoma) after the analysis, results in following 3 mo the liver mass as well as tumor size was intensely decreased and in first several 10 y observed significant decrease in HCC and no changes in raising degree of α -fetoprotein (AFP) in serum (a tumor factor for distinguishing patients with HCC) were detected.

Alternative effect demonstrated in 72-year-old female patient with elevated level of AFP (alpha fetoprotein) and several malignant liver abrasions or single metastatic injury administered *Ganoderma lucidum* or *Pian zhi Huang* (utilized in hepatitis) repeatedly, after 12 mo diagnosis the lesion was reduced with decline AFP levels. But, in third instance of 78-year-old male patient with metastatic HCC and AFP level consistent increment after *Ganoderma lucidum* treatment till discontinuing doxorubicin treatment (chemotherapeutic agent) [26].

Additionally, a study displayed inhibitory impacts of *Ganoderma lucidum* stagnant spores, developing spores, sporoderm-broken germinating spores (SBGS) or isolated lipids germinating spores on development of mouse hepatoma, sarcoma S-180 or reticulocyte sarcoma L-II cells results sporoderm-broken spores produced a lot of advanced bioactivities and effect on tumor size compared with whole spores. Consequently, *Ganoderma lucidum* lipids extract from developing spores or sporoderm-broken germinating spores repressed 80-90% of three tumors in dose dependent manner [4].

Effect on bladder cancer

A study demonstrated the ethanol concentrate of *Ganoderma lucidum* was estimated with cooperation of BCG in premalignant human uroepithelial cells (HUC-PC) model, resulted *Ganoderma lucidum* shows the direct cytotoxic effects whereas BCG exhibited delayed response by initiating the discharge of interleukin (IL)-6, IL-8 or monocyte chemotactic protein-1 (MCP-1). Moreover, the synergistic cytotoxic impacts detected after cancer cells remained incubated with the two medication and either be pretreated with *Ganoderma lucidum* (increased IL-6, IL-8, MCP-1). Consequently, *Ganoderma lucidum* or BCG be confirmed to attain total cytostatic effect in 24 h or impacts remained developed within 5 d. Yet, certain frequent proinflammatory cytokines are allied with high adverse reaction of BCG, marks the *Ganoderma lucidum* proposed to enhance with BCG immunotherapy in bladder malignancy meant for improved efficacy and diminishing the adverse reaction [45].

Another study exhibited chemo-preventative impacts of *Ganoderma lucidum* via *in vitro* human urothelial cell (HUC) model with HUC-PC or MTC-11 cells. They demonstrate the ethanol or water concentrates of *Ganoderma lucidum* (fruiting bodies or spores) utilized observe the progression inhibition, actin polymerization activity, effect on actin remodeling on cell migration or adhesion. In outcome's ethanol extracts of *Ganoderma lucidum* displayed powerful growth inhibition impact by cell cycle study to G2/M arrest compared with water extracts. While, these extracts of non-cytotoxic concentrations are 40-80 mg/ml persuaded actin polymerization that repressed carcinogen 4-aminobiphenyl produced passage in equally cell lines. However, enhanced actin polymerization is allied by amplified stress filaments or focal adhesion complex development but articulation of matrix metalloproteinase-2 or focal adhesion kinase remained unaffected that proposes to involved with different process of chemo preventive effect [46, 4].

Effect on lung cancer

Active constituent of Ganoderic acids found significant absolute cancer cell cytotoxicity on extensive assortment of cancer cell lines include

murine Lewis lung carcinoma (LLC), Meth-A or a large number of different angiogenesis and metastasis. While, the effect of Ganoderic acid T incites apoptosis of metastatic cellular breakdown in the lungs by inherent pathway associated with mitochondrial dysfunction produced more effective anti-cancer activity [47]. The *in vitro* analysis of triterpene aldehydes, lucialdehydes A-C isolated with *Ganoderma lucidum* fruiting bodies exhibited cytotoxicity against murine or human tumor cells. Whereas, blazein steroid extracted with *Agaricus blazei* stated to provoke cell demise or morphological variation suggestive of apoptotic chromatin reduction in human lung cancer cells [48].

In a study of plasma-incited lymphocytes inhibition in lung cancer patients are received *Ganoderma lucidum polysaccharides (GLPS)* produced significant effect by antagonizes immune inhibition toward enable tumor control in animal model or certain immunosuppressive mediators include PGE2, TGF- β , IL-10 or VEGF are delivered from cancer cells. Thus, treatment of GI-PS is effective for suppress propagation, CD69 articulation, perforin or granzyme B formation via lymphocytes by Phytohemagglutinin (PHA) stimulation in lung cancer patient's plasma [4].

A study assessed inhibitory impact of *Ganoderma lucidum* triterpenes on cell multiplication or tumor development with IC50 24.63 μ g/ml upon A549 cells produced significant effect by inhibition of tumor development in Lewis tumor-bearing mice with dose 30, 60, 120 mg/kg or marker of immune organs such as spleen or thymus remained strangely expanded via triterpenes treatment. Additionally, *in vitro* study estimated that L-fucose (Fuc)-enriched Reishi polysaccharide fraction (FMS) have been effective in inhibition of development of malignant growth cells by increment in antibody-mediated cytotoxicity or decrease in formation of tumor-related inflammatory mediators mainly monocyte chemoattractant protein-1 (MCP-1). While, *in vivo* examines displayed remarkable rise in peritoneal B1 B-cell populace signifying FMS-mediated anti-glycan IgM formation. Another, current study exhibited that plasma of patients with lung cancer obstruct propagation, CD69 appearance, perforin and granzyme B production in lymphocytes through

polyhydroxyalkanoates (PHA). Although, an alternative study described Ganoderic acid Me (lanostane triterpene give to indoleamine 2,3-dioxygenase) of *Ganoderma lucidum* facilitated in production of a tolerogenic element in lung tumors via. Initiating T cell apoptosis influenced in repressing CD8+T cell activation or increasing Treg-mediated immunosuppression [49].

Effect on gastric cancer

A research study described effect of gastric adenocarcinoma cell line (AGS) by mushroom concentrate results improved development of autophagosomes and cell levels of LC3-II but decreased p62 level that confirming with influences cellular autophagy. Moreover, treating cells via mushroom concentrate in conjugation through lysosomal protease inhibitors displays cellular degrees of LC3-II or p62 were raised. So, conclusions acquired demonstrated AGS cells treated with *Ganoderma lucidum* methanolic concentrate affects autophagy initiation more relatively decrease over autophagic transition [50, 4].

Moreover, a study conducted in 2015 described six triterpenoids include ganolucidic acid E, lucidumol A, ganodermanontriol, 7-oxo-ganoderic acid Z, 15-hydroxy-ganoderic acid S or ganoderic acid (GA) extracted in *Ganoderma lucidum* displayed inhibition growth of cell lines i.e. Caco-2, HepG2, HeLa cells via apoptosis via different concentration with IC50s 20.87–84.36 mmol [19].

Another research study examines the polysaccharide effect (expansion or apoptosis) on cultured human gastric cancer SGC7901 cells that display the growth of refined cells remained controlled through higher concentration polysaccharide treatment for longer period. The refined cells achieved distinctive apoptosis, equally morphological characters or DNA fragmentation later 10 mg/ml polysaccharide treatment intended for 48 h, resulted the 40% refined cells existing via. apoptosis yet the outflow of BCL-2 protein was down-regulated as well as concentration of BAX protein was up-regulated. Consequently, this study showed that polysaccharide actuate human gastric cancer cells apoptosis or detain cells growth that help to use for human gastric cancer active therapy [51].

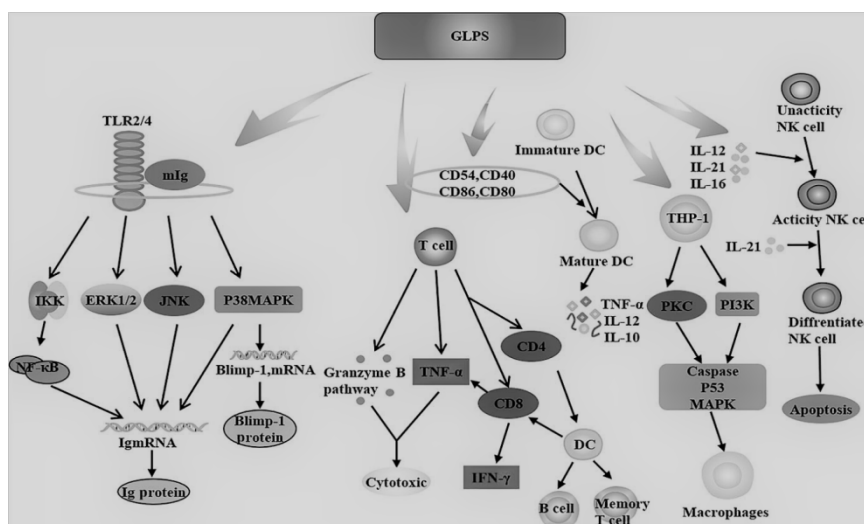


Fig. 5: Anti-cancer or Immunomodulatory actions of *Ganoderma lucidum polysaccharides (GLPS)* [28]

Other effects of *Ganoderma lucidum*

Immunomodulation

A number of different components from *Ganoderma lucidum* are used as immunomodulating agents proved to improvement of immunological effector, induction of cytokines, build up the expansion and T or B lymphocytes development, splenic mononuclear cells, NK cells or dendritic cells are demonstrated *in vitro* or *in vivo* animal reports [7].

Consequently, *in vitro* or *in vivo* studies in mice showed that water concentrate of *Ganoderma lucidum* stimulates IL-2 (presence of

hydrocortisone) production by splenocytes, T cells activators, or bringing cytokines production. *In vitro* water concentrate of *Ganoderma lucidum* in human peripheral blood mononuclear cell (PBMC) exhibit the induction via cytokines appearance i.e. TNF- α , IL-10, IL-1b, IL-6 or L-2 as well as *Ganoderma lucidum* water-extracted polysaccharide element improved splenic NK cells cytotoxicity in tumor-bearing mice and activation of macrophages by cytokines liberation, NO or different mediators exhibited anti-tumor, anti-microbial anti-inflammatory effect, antiproliferative, separated or apoptosis inducing to HL-60 or U937 leukemic cells. However, the antibody-neutralization studies revealed that IFN-g or TNF- α delivered by macrophages interfered synergistically obstruct

development of leukemic cells. additionally, the methanol extract of *Ganoderma lucidum* (Ganoderic acids C or D) inhibit histamine discharge from rat mast cells are actuated via composite 48/80 or concanavalin A results, ganoderic acids C or D showed strongly effect in inhibition of histamine liberate from rat mast cells through screening test. Moreover, triterpenoid compounds namely cyclo-octa sulfur produced positive effect in prevented histamine discharge in rat peritoneal mast cells by reacting membrane proteins near prevent Ca uptake producing a histamine activation obstruction [16].

Antioxidant Activity

Triterpenes or polysaccharide extract of *Ganoderma lucidum* exhibited antioxidative properties in mice splenocytes by means of expanding movement of antioxidant enzymes, reducing radiation-induced oxidative DNA impairment and oxidative damage induced by ROS [1]. The antioxidant and chelating property of phytoconstituents of *Ganoderma* capably scavenged O₂, OH radicals produced experimentally during *in vitro* studies. The effect of *Ganoderma lucidum* antioxidant property, scavenging, gathering capacities and absolute phenol component has been showed in a study by ethanol or water concentrate from *Ganoderma lucidum* exhibited maximum scavenging action in contrast to DPPH radicals with 50% inhibitory concentration by 0.055±0.001 mg/ml. An alternative study observed the endogenous mitochondrial DNA damaged via free radicals significant scavenging and related aspect to aging and also found effects of extract of vital antifatigue and rejuvenating activity [3].

Additionally, many investigations have been completed to assessed antioxidant property with respect to several fragments of *Ganoderma lucidum* i.e. fruiting body and mycelia. Meanwhile, the methanolic or aqueous extract have shown great free radical scavenging activity of superoxide free radicals, hydroxyl radicals and inhibit the lipid peroxidation. Thus, a number of different models of antioxidant activity assay have been performed with the extracts of *Ganoderma* species include alcoholic, aqueous alcoholic, petroleum ether and chloroform exhibited maximum antioxidant activity in hot water followed by aqueous alcoholic extract. While, petroleum ether extract produced minimum effect in scavenging the free radicals in any of models of antioxidant assays include DPPH and ABTS radical, superoxide radical scavenging assay [6].

Antidiabetic activity

Ganoderma lucidum exhibit the antidiabetic effect by interfering in multiple pathways including insulin-releasing activity via enabling of Ca²⁺-inflow to pancreatic β cells and diminution in fasting serum glucose levels with reduced mRNA expression levels involved in gluconeogenesis and glycogenolysis. In a study of china examined hypoglycemic impact of *Ganoderma lucidum* polysaccharides by utilizing I. P infusion by single doses (25, 50 or 100 mg/kg) extract in fasted mice, resulted the polysaccharides decreased serum glucose levels at 3 to 6 h. afterwards administration of extract in dose dependent manner and also be increased circulating insulin levels or intensity of [Ca²⁺] at 1 h after administration [52].

Moreover, *Ganoderma lucidum* (Ganoderans B or D) isolated polysaccharide displayed probable hypoglycemic and hypolipidemic activities confirmed by preclinical studies in rat involving administration of *Reishi* (*Ganoderma lucidum*) protected against diabetic nephropathy or enhanced injury palliate in streptozotocin-induced diabetic rats. However, clinical studies with 71 patients caused type II diabetes mellitus (DM) estimate the anti-diabetic efficacy and safety technique was carried out. Consequently, these studies reported *Ganoderma lucidum* (*Ganopoly*) was well tolerated, efficacious and safe for use comparable to oral hypoglycemic drugs or insulin [18, 1].

Additionally, a study evaluated the effect of aqueous extract on blood glucose levels in alloxan induced diabetic rats (Wistar) via intraperitoneally administered of 3 doses extract of (250, 500 or 1000 mg/Kg) *Ganoderma lucidum*. Antidiabetic impact showed at doses 500 or 1000 mg/Kg of concentrate by decrease (**P<0.05) blood glucose levels of alloxan induced diabetic rats (Wistar) by 4, 8 or 24 h. time period but not fundamentally vary blood glucose levels

with 250 mg/Kg doses. therefore, dosage 1000 mg/Kg of concentrate demonstrated together critical (**P<0.05) hypoglycemic or anti-hyperglycemic impacts [53].

Another study confirmed the petroleum ether extract (PEE) or methanol extract (ME) of *Ganoderma lucidum* mushroom decreased plasma glucose levels in alloxan or steroid initiated fasting diabetic rats in dose dependent manner with maximum reduction 55.57% detected by PEE at dose 800 mg/kg or 36.01% ME at dose 800 mg/kg in alloxan prompted or 51.41% PEE or in steroid-induced diabetic rats by 32.02% ME. Moreover, in treatment with metformin (150 mg/kg) shows decrease of fasting blood glucose levels via 60.02 or 51.12% in alloxan or steroid induced diabetic rats. Whereas, equally PEE (800 mg/kg, **P<0.001) or ME (800 mg/kg, **P<0.01) increased plasma insulin levels and decreased HbA1c (**P<0.01 or *P<0.05) in alloxan or steroid induced diabetic rats [54].

Anti-inflammatory activity

The extract *Ganoderma lucidum* (*Reishi*) presented an effective anti-inflammatory property in human keratinocytes reported in preclinical studies of animals inhibited the inflammatory damage in carrageenan induced inflammation or produced a beneficial effect against arthritis [1]. An alternative Indian study established that the extract of *Ganoderma lucidum* (β-1,3- or β-1,6-D-glucans) produced significant effect by decrease inflammation in dose or time-dependent manner. They found that dose of *Ganoderma lucidum* (100 mg/kg B. W) exhibited anti-inflammatory activities equivalent toward diclofenac dose (10 mg/kg B. W) by 50% decrease in inflammation in mouse models. While, several bioactive constituents involve in *Ganoderma lucidum* i.e. Polysaccharide or water insoluble β-1,3-D revealed the inhibition of LPS-activated nitric oxide formation via macrophages or reduces pro-inflammatory cytokines by mRNA gene expressions such as iNOS, IL-1, or TNF-α in dosage dependently by patent incentive IL-10 and pointedly increased in anti-inflammatory cytokine IL-10 via treatment of Selenium nanoparticles. Additionally, anti-inflammatory impact of *Ganoderma lucidum* reports displayed adjuvant impacts include enhancing the maturation of dendritic cell (DC) by upregulating CD40, CD80, CD54 and CD86 markers on peripheral blood monocytes [55, 41].

Another report suggests around 20% of the cancers are measured by the effect of inflammation due to the chronic overexpression of inflammatory cytokines include IL-6, VEGF or TNF-α leads to promote carcinogenesis. However, administration of triterpene concentrates of *Ganoderma lucidum* fundamentally suppress inflammatory cytokine discharge by macrophage cells that reducing degree of inflammation [20].

Antimicrobial activity

The antimicrobial property of *Ganoderma lucidum* and their bioactive constituent remain largely undefined or not clearly understood but, given with broad spectrum antimicrobial agents, the extracts might be inhibited Gram-positive or Gram-negative bacteria. An examination reported that fruit body aqueous or organic solvent (hexane, dichloromethane, ethyl acetate) of *Ganoderma lucidum* concentrate be situated similarly prohibition in opposition to all assessed strains include *Pseudomonas aeruginosa*, *Proteus vulgaris* or *Enterococcus faecalis* excepting *Listeria monocytogenes* and minor inhibitory impact reported in contrast to *Salmonella typhimurium*, *Klebsiella pneumoniae*, *Streptococcus mutans* or minimum impact against *Bacillus subtilis* but, organic solvent extract displayed low solvation ability for antimicrobial agents separation. Additionally, several studies revealed the methanolic extract exhibited complex inhibitory property compared to *S. aureus* or *B. cereus* as well as *Enterobacter aerogenes*, *Escherichia coli* or *Pseudomonas aeruginosa* comparable toward ampicillin and streptomycin antibiotics with minimal inhibitory concentrations about 0.0125–0.75 mg/ml or bactericidal concentration are 0.035–1.5 mg/ml [21].

Another study displayed the *Ganoderma lucidum* extract (*Reishi*) also inhibit development of *Helicobacter pylori* (bacteria cause gastric ulcers or gastric cancer). Whereas, isolated compound from *Ganoderma lucidum* showing antifungal action by interfered mycelial

development of *Botrytis cinerea*, *Trichoderma viride*, *Fusarium oxysporum* or *Physalospora piricola* than that of antifungal agents such as bifonazole and ketoconazole [22].

Antiaging activity

Ganoderma lucidum isolated polysaccharide compound produced significant effect by inhibit ROS production in fibroblasts and UVB induced MMP-1 protein expression, improved procollagen expression as well as stimulate C-telopeptides of type I collagen protein by inhibiting ERK pathways. Therefore, various research studies demonstrated in long-term on scavenging free radical and ROS accelerates aging and many age-related illnesses [22].

In a study reported various extractions include ethanol extract, aqueous extract, mycelia extract or water-soluble extract from *Ganoderma lucidum mycelia*, Ganodermasides A, B, C, D or medicinal constituents-polysaccharides I, II, III, IV, Ganoderma peptide, Ganoderma polysaccharide peptide, triterpenes or Ganoderic acid C1 might utilize in life expectancy extension or correlated activities. Whereas, studies revealed that *Ganoderma lucidum* as a preparation utilized many thousands of years and exposed its impact on life expectancy expansion and being confirmed to anti-aging remain also rare associated with *Ganoderma lucidum* extractions and constituent's actuality revealed [56].

Antiviral activity

Antiviral activity of Ganoderma displayed by the constituents of Ganomycin I (farnesyl hydroquinone) and Ganomycin B isolated from Vietnamese *G. colossum* produced strong effect by inhibited HIV-1 protease through IC50 value 7.5 or 1.01 µg/ml. however, constituent of Ganomycin B competitively equally blocked enzyme active site to docking beside HIV-1 protease crystal structure [48].

Additionally, the various research demonstrated impacts of *Ganoderma lucidum* on HIV with strong inhibitory properties. While, a study analyzed more than thirteen compounds extracted from *Ganoderma lucidum* exhibited anti-HIV-1 property via inhibiting HIV-1 proteases including triterpenoids (major compound has strong anti-HIV effects) and Ganoderic acid (GA-A). Whereas, *Ganoderma lucidum* comprises laccases that might inhibit HIV-1 reverse transcriptase [25].

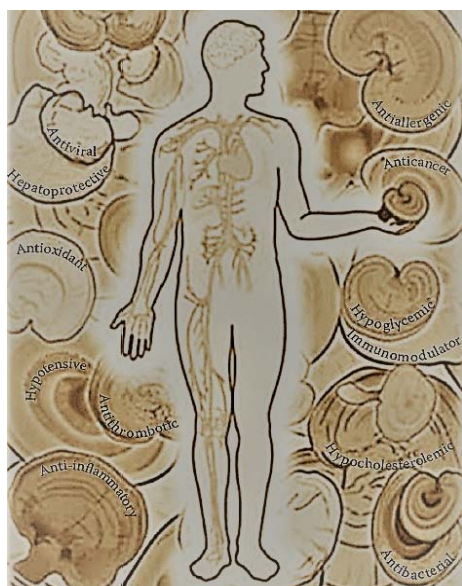


Fig. 6: Health benefits of *Ganoderma lucidum* (Lingzhi) [7]

Effect on cardiovascular function

Ganoderma lucidum (Reishi) exhibited a positive effect on cardiovascular system by reducing in blood cholesterol levels, triglyceride levels or normalize blood pressure. A clinical study

described the patients with starting phase of hypertension showing maintained blood pressure were detected following 2 mo by *Ganoderma lucidum* extract treatment. Moreover, the examinations displayed the *Ganoderma lucidum* extract (polysaccharide and peptide complexes) decreased blood lipid level or prohibited growth of atherosclerosis in rats and furthermore indicated a preventive activity with respect endothelial cells of blood vessels in peoples [22].

Another clinical study carried out in Japan with 53 hypertensive individualized subjects involving 240 mg of 6 tablets of Ganoderma extract were administered daily for 6 mo treatment to the active group results, showed that extract forming tablet of *Ganoderma lucidum* produced strong effect on lowering of blood pressure and hypertension and also showed no side effects relating to Ganoderma treatment [6].

Hepatoprotective activity

Hepatoprotective property of *Ganoderma lucidum* (Polysaccharides and Triterpenoids) against liver damage actuated via harmful synthetic compounds (CCl₄), *Bacillus Calmette-Guerin* (BCG) in addition to lipopolysaccharide (LPS) given orally and intraperitoneally to estimate markers i.e. aspartate, alanine transaminases (AST or ALT) or lactate dehydrogenase (LDH) have been demonstrated by various *in vitro* studies on animals. A present randomized placebo-controlled clinical study presented 12 w *Ganoderma lucidum* polysaccharides treatment showed significant decrease hepatitis B e-antigen (HBeAg) or HBV DNA via 25% (13/52) patients per Hepatitis B virus infection. However, 90 persistent hepatitis B patients, hepatitis B viral (HBV) DNA positive or aminotransferase remained increase in multicenter probable randomized Phase I or II analyses [16].

A study reported that Ganoderic acid's hot water extract offered mice orally for 30 min. prior ethanol administration identified a strong inhibitory impact on β-glucuronidase or malondialdehyde (MDA) development in mice liver or renal homogenate and also be reported that pretreatment by *Ganoderma lucidum* kept up ordinary estimations of AST, ALT, SOD or GSH. Whereas, a study suggest the MDA effect reported after concentrate was offered mice orally with dose 60, 120 or 180 mg/kg daily for 2 w before D-galactosamine therapy to prompted hepatic injury.

Additionally, the alcohol and CCl₄ toxicity may influenced in increasing oxidative stress or free-radical-related liver injury hence, hepatoprotective activity of hot water *Ganoderma lucidum* extract exhibited substantial radical-scavenging property compared to equally superoxide or hydroxyl radicals. Furthermore, the *Ganoderma lucidum* methanolic concentrate administered orally for rats with dose 500 mg/kg daily at 30 d prior hepatic injury induced via benzo(a)pyrene exhibited preventive in rise serum AST, ALT, alkaline phosphatase (ALP) or also GSH, SOD, GpX, CAT, glutathione S-transferase (GST). Another study observed hepatoprotective activity against liver injury persuaded through CCl₄ in mice with Ganoderic acid (10 or 30 mg/kg daily) administered in I. V infusion for 7 d. Moreover, the oral administered *Ganoderma lucidum* mycelia exhibit valuable impacts via lower serum AST or ALT actions at 96 h. post liver injury and no change in decrease transaminase activities at 24 h in control animal studies. However, a study reported an extracellular peptidoglycan formed through mycelium fermentation remained given to rats orally for 4 d earlier CCl₄ intoxication that displayed rising serum ALT levels remained expressively reduced in 70% at 24 h postinjury equated to untreated or intoxicated rats and also decreased AST levels in 27% [7].

Clinical studies

Human studies

Clinical studies are carried out in cancer patients for testing of *Ganoderma Lucidum* conducted some in China with observed significant positive results. A clinical study through *Ganoderma lucidum* polysaccharide concentrate detected to expansion in plasma levels immune markers, IL-2, IL-6, interferon γ (IFN-γ) or in NK cell activities and other study exhibit more positive responses with using *Ganoderma lucidum* in mixture with chemotherapy/ radiotherapy results an increase certain level of immunological

markers are CD3, CD4, CD8 were observed. however, a compiling database for randomized controlled trials (RCTs) made by Cochrane Collaboration in 2012 suggested that hardly 5 RCTs of 257 investigations could fulfill standards for presence all groups of patients belong to Asian nations and not more suitable data and proof supporting the ease of use *Ganoderma lucidum* in tumor patients. Whereas, *Ganoderma lucidum* utilized as alternate assistant to animate host immunity was established in a study involve 5 of 15 gynecologic tumor patients attained constant disease later utilizing *Ganoderma lucidum* (fruiting body or spore) concentrate [27, 26].

Safety Evaluation of *Ganoderma* supplementation described in double-blind placebo controlled cross over clinical trial relating the collected a month fasting blood or urine earlier or later 4 w of *Ganoderma lucidum* administered in healthy volunteers' conclusions exhibit that there is no significant change in any of biochemical parameters or any sign of liver or renal toxicity seen in patients but lower lipid levels or antioxidant capacity in urine samples were increased in the end of trial [6].

A study carried out in 34 patients with advanced-stage malignancy observed impacts of Ganopoly on immune activity found that an increase immune feedback in progressive phase tumor patients by rise in quantity of CD3+cells. Another study found in enhanced mitogen-induced lympho-proliferative immune responses by 6 mo treatment of *Ganoderma lucidum* in children with tumor. While a trial study in 2012 proposed that *Ganoderma lucidum* spore powder delivered beneficial outcomes on cancer-associated fatigue or eminence of lifespan in 48 breast cancer patients receiving endocrine therapy with no unfavorable effect [49].

Additionally, *Ganoderma lucidum* produced positive effect in inhibited platelet aggregation in immunologically cooperated subjects and rises T lymphocyte or T helper cells, reductions in T suppressor cells, recovers immune capability afterwards chemo or radiation treatments. Moreover, hepatoprotective effect of *Ganoderma lucidum* (Reishi) stated by a minor uncontrolled study involving 4 hepatitis B patients or higher bilirubin or SGPT/SGOT levels remained receive 6 gm Reishi concentrate for 3 mo, following 1-month time period investigate the bilirubin, SGPT or SGOT levels expressively decreased ($*P \leq 0.01$) just as following 90 d all ideals got back to in typical extents [13].

A study employed in 134 patients by progressive tumors of various destinations or 12 w *Ganoderma lucidum* capsules treatment at dose 1800 mg daily exhibit enhanced 80% the cellular immunity in relations of higher plasma IL-2, IL-6, interferon γ (IFN- γ) levels or natural killer (NK) cell movement. While similar procedure should be followed in 68 patients with lung cancer displayed increased immune constraints such as T cells, NK cells or CD4/CD8 proportion by treated group of *Ganoderma lucidum* with improving eminence of lifespan as far as "Karnofsky score" around 65% [7]. Another Polysaccharide property of *Ganoderma lucidum* infusion produced remedial impact on depression in adjuvant therapy of glucocorticoids as well as active in treating facial paralysis in children [28].

Animal studies

Rodent animal studies of *Ganoderma lucidum* with probable antitumorogenic effects should be carried out initial 1980s. In a trial for 10 d intraperitoneal (I. P) polysaccharide extract infusions (GL-1) from fruit body of *Ganoderma lucidum* (Lingzhi or Reishi) observe to 95-98% inhibit transplanted sarcoma 180 tumor cells progression in mice. While, in study described a compound of polysaccharides and protein from mushroom display significant antitumor activity by reported 88% inhibition rate of whole relapse of tumor in third of test animals as well as similar procedure used in a study exhibit inhibition rate about 52-81%. Moreover, hot water extract receives I. P with 2 mg/mouse for 3 d lead a typical 74% restrain tumor development in mice by 3/10 animals display comprehensive deterioration or 45-63% inhibition in oral administration for 5 w daily. Another, dry powder formulation of *Ganoderma lucidum* (antlered form) produce effect in inhibited tumor development or lengthen life expectancy equally allogeneic sarcoma-180-bearing ddY mice or synergetic MM-46 mammary

tumor-bearing C3H/He mice. A traditional herbal formulation i.e. TBS-101 proved to restrain tumor development or aggression in PC-3-implanted mice. In a study found that oral administration of mycelial extract for 9 w showed lung adenoma development prevention in mice. While 18 d orally administered triterpenoid extract repressed Matrigel-actuated angiogenesis by decreased tumor mass or quantity of tumor cell provinces in metastasized liver of C57BL/6J strain female mice by intra splenic embedding of Lewis lung cancer cells. whereas, male ICR-nu/nu nude mice infused hepatoma HepG2 cells, received 68 d orally lucidenic acid-rich concentrate with 800 mg/kg daily dose exhibit equally reduced amount or extent of cancers (99%) in liver or lung [7].

Another activity of GLPS by I. V 80 mg/kg injected to rats shown delay sleeping time or recover sleeping superiority. Various studies established, GLPS can build the degree of SOD or certain quantities of leucocytes. While in 3 autonomous studies examined the antibacterial activity of GLPS as well as another study detected the anti-skin ageing purpose of GLPS via rises mutually hydroxyproline or SOD substance in concentration-dependent manner. More studies exhibit GLPS is hepatoprotective in metabolic aberrations of diabetic mice, avoids or interruptions development of diabetic renal difficulties as well as GLPS helps blood circulation and eliminates blood stasis [28].

Ganoderma lucidum are also stimulating anti-androgenic activity with testosterone induced hyperplasia model in rats via week by week urine yield, testosterone levels or prostatic explicit antigen levels. The petroleum ether concentrate of *Ganoderma lucidum* is an effective inhibitor of prostatic hyperplasia incited via testosterone that confirmed in histological examinations on prostate segments and furthermore found a potent 5 α -reductase inhibitor produced a symptomatic mechanism against benign prostatic hyperplasia [13].

Anticancer effect of *Ganoderma lucidum* have been demonstrated via one study involving polysaccharides remained regulated ICR/S1c mice by embedded Sarcoma 180 tumor cells produced a strong inhibitory activity against tumor cells lines. According to an *in vitro* study of immune-modulating property of hot water or ethanol concentrate of *Ganoderma lucidum* were examined in murine macrophage cultures resulted that the two concentrates improved formation of IL-6 or NO mixture in dose dependent manner and both I. P administration extracts displayed thriving ICR mice from lethal I. P contamination of Escherichia coliform or also substantial anti-tumor action opposed to strong type Sarcoma 180 in mice. Moreover, the β -glucan fraction of Ganoderan (GDN) produced similar effect in improved 4-fold NO production and 19-fold TNF- α production associated to controls group in rats. Alternative, direct *in vitro* tumoricidal action were identified to two steroidal complexes such as Ganoderic aldehyde A or ergosta-7,22-diene-2 β ,3 α ,9 α -triol extracted from Reishi fruiting bodies (*Ganoderma lucidum*) displayed a critical inhibitory effect against human hepatoma PLC/PRF/5 via ED50 2.54 or 1.17 μ g/ml and KB cells by ED50 1.25 or 0.89 μ g/ml. additionally, Ganoderic acids A or C display inhibit farnesyl protein transferase (FPT) *in vitro* by restrain reticular-activating system (RAS) dependent cell alteration can signify probable beneficial approach for tumor development. Whereas, immune-modulating or antitumor impacts informed oral intake of Reishi displayed secure against many grades of Adriamycin incited cellular toxicity in rats resulted reductions in leukocytes, platelets or furthermore cloudy swelling or vacuolar deterioration in heart, liver or kidney cells. However, there is no data and evidence with respect to reishi signify that anticancer activity in humans. Thus, direct tumoricidal activity has just demonstrated *in vitro* or immunological system of antitumor activity [14].

Therapeutic profile

Pharmacokinetics

Pharmacokinetic profile of *Ganoderma lucidum* and their bio constituent i.e. Ganoderic acid-C2, B, K or-H identified in rat plasma afterwards orally receive of concentrate utilizing high-performance liquid chromatography and Ganoderiol F detected after oral or intravenous administration utilizing Liquid chromatography and mass spectrometry. While, Ganoderic acid-A or-F are well absorbed orally in plasma and bio-transformed by reduction, oxidation,

deacetylation, desaturation, hydroxylation, sulfation, or glucuronidation. Another major constituent of Ganoderic acid-D or-B are further metabolized which is distinguished in rat kidney or stomach. In case of triterpenes it is rapidly absorbed in plasma within minutes and metabolized by phases I or II biotransformation in rats earlier excreted into bile and eliminated in more than 2 h. The polarity of Ganoderic acids is low polar in nature that changed into polar metabolites help to easily excreted. Whereas, Ganoderiol F metabolized into Ganoderadiol in anaerobic growth via bacterial culture and was detected in rat feces [26, 14].

Pharmacodynamics

The pharmacodynamics profile of *Ganoderma lucidum* are not clearly defined due to absence of specific database regarding with *Ganoderma lucidum*. However, *Ganoderma lucidum* (Reishi) are most widely researched remedial mushroom in Asia. Several pharmacological studies and scientific legislatures carried out to focused on chemistry and medical applications with specific therapeutic activity include immune enhancing, cardiovascular-regulating, hypoglycemic, and hepatoprotectant with polysaccharide and triterpene fractions and most of them conducted in China and Japan [14].

Dosage

The effective dosage of *Ganoderma lucidum* for people has not entrenched but an analysis (1994b) stated Reishi mushroom recipe about 22-108 mg every day of crude herb in Ben Cao Gang Mu of Li Shi-Zhen. While, use of dose 0.05 mg/kg of β -glucan can produce *in vivo* white blood cell microbial killing action by acting β -glucan receptor on human WBC and based on relative effective dose concentration of Reishi mushroom estimated 300 mg and maximal effective dose is around 35 g daily. However, a research (1994) mentioned dosage range of 3-15g [14].

Additionally, the *Ganoderma lucidum* are present and mainly given in different formulae that may infused like powdered spore liquid formulation or might consumed like soup, syrup, tea, tablets, capsules, tincture and bolus. However, 20% dose in tincture formula taken 10 ml for 3 times daily, tablet 1g three times daily or syrup 4-6 ml/day and if there should be an occurrence of ingestion of toxic mushrooms, dried 120-200g of *Ganoderma lucidum* is decocted in water or given as 3-5 times daily [16].

According to Pharmacopoeia of People's Republic of China enclose newly added monograph in favor of Reishi referring with dose 6-12 g everyday include as:

Powder

6-12 g daily.

Decoction

Around 375 ml two time every day.

Tincture (1:5)

10 ml for thrice every day.

Rice wine extract

30 ml for two times every day [14].

Side effects

Clinicians have informed slight digestive distressed or skin rashes in sensitive persons and risk factor of cardiovascular disease (by inhibition HMG-CoA reductase and coenzyme Q10 deficiency) [14]. Another side effect develops by oral doses (1.5-9 g/day) of powder extract of Reishi reported lethargy, thirst, rashes, swelling, incessant urination, irregular sweating or bulky oral doses of vitamin C of 6-12 g/day taken in combination with Reishi powder extract of 2-10 g/day reported countered diarrhea. Furthermore, restraint of platelet accretion produced additive effect via *Ganoderma lucidum* with taking blood thinning medicines (aspirin or warfarin) [16].

Contraindications

Due to Immune-modulating activity of reishi mushroom should be keep away from organ transplanted patients using immune-

suppressive agents or autoimmune diseases caused patients. Moreover, Reishi mushroom extracts contain a complex mixture of allergens that should be withdrawn before surgery by reason of vasodilatory activity or platelet inhibitory activity. Moreover, consult the doctor/health professional for using of Reishi (due to hypoglycemic activity) for those patients using hypoglycemic medications and also consult the doctor for using of Reishi mushrooms (due to platelet aggregation-inhibitory activity) for those patient using anticoagulants [14].

Interactions

Reishi (*Ganoderma lucidum*) enhance the tranquillizing activity of reserpine or chlorpromazine as well as provoke central stimulating action of amphetamines. Alternative, *Ganoderma lucidum* (Reishi) enhance the action of lovastatin and other lipid lowering drugs as a result of its inhibitory activity on HMG-CoA and also shown to potentiate the antioxidant effects of glutathione. Moreover, *Ganoderma lucidum* reported immune-enhancing activity that should be contraindicated in combination of post organ transplant immunosuppressive agent and also be polysaccharides of *Ganoderma lucidum* antagonize immunosuppressive impacts of morphine *in vitro* or *in vivo* [14, 16].

Toxicity

The several animal trials or toxicology studies displayed a very low toxicity with wide variety of fruiting body preparations. Whereas, a toxicology investigation of Reishi mushroom carried out in Hunan Medical College, China described 30 d Intra gastric administration of *Ganoderma lucidum* ethanol concentrate (1.2 or 12 g/kg i. g. daily) displayed no impact or toxicity indications in rats on development or improvement or slightly aberrations in liver situation, ECG or detected in significant organs. Moreover, no harmful responses identified in 15 d dogs administered cold ethanol concentrate 12 gm/kg i. g daily or 13 d administered hot ethanol concentrate 24 gm/kg i. g every day display sleepiness. In a review (1994) reported 30 d administered orally 5000 mg/kg hot water concentrate to mice resulted not any fluctuations seen in body or organ weight, hematological variables or polysaccharide segment equal dose formed no toxic or genuine impacts. Additionally, LD50 of I. P infusion of unclear Reishi formulation in mice informed as 38.3±1.048 g/kg i. g and not any noxiousness establish 10 d receiving Reishi mushroom syrup as 2-4 ml/kg p. o. every day in dogs and 10 d intra gastric administration of 4 ml/kg p. o. every day in rabbits [14]. Another activity of mushroom at dosage 10 gm/kg p. o. displayed not any variations of estrus cycles in ovariectomized mice or no rise in corpus cavernosa or testicles weight in male mice with equal dose. Another trial of toxicity of wild fruit bodies of Reishi analyzing intense toxicity by administered concentrate mixture (0.9259/kg) to male mice with equally one dose usually proposed with extract concentration resulted to cause acute toxicity, not any changes in uric acid, GOT and GPT as well as not any changes obtain in histological assessments of livers, kidneys, heart, lung, spleen and organ weights ratios compared to controls [16].

Novel approaches of mushroom in treatment of cancer therapy

Vaccinotherapy

The novel approaches of vaccine preparations were newly established in Belgium and USA with preventive possessions against liver, cervical cancer, related with hepatitis B and human papillomatosis infections. Though, addition of immunomodulating constituents from natural and synthetic source to vaccines can necessarily improve their anticancer properties. However, at the same time up to date there is no vaccine on commercial scale were developed to cure present tumors, metastases or relapses. Consequently, an isolated *Ganoderma lucidum* (mycelia) immunomodulating Ling Zhi-8 protein has been attained in patented yeast system exhibit stimulatory activity on dendritic cells and also expressively increases the effectiveness of cancer DNA vaccine in a preclinical tumor model was newly recognized [57].

Nanotechnology

The advancement of nanotechnology (nanoparticles) is an extremely focused new approaches using "green" chemistry and bioprocess

method involve in delivery and controls the release of drug in site of action to provide effective and less toxic treatment. These characteristic of living organisms play vital role for potential production of nanoparticles that involving the synthesis of unequal shaped gold nanoparticles with the help of photo-irradiation technique using reductant namely "Pleurotus florida". The factor of flavins (flavoproteins) in mushroom extract cause decrease of ions into nanoparticles through contact to sunlight via absorb photons of energy or act in reduction-oxidation reactions. However, acquired nanoparticles presented cytotoxicity against A-549, K-562, HeLa, and MDA-MB cancer cells but no produced effect against Vero normal cells [57].

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CONFLICT OF INTERESTS

Declared none

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