IJPSR (2011), Vol. 2, Issue 8 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 08 April, 2011; received in revised form 18 May, 2011; accepted 17 July, 2011

THERAPEUTIC PROPERTIES AND CURRENT MEDICAL USAGE OF MEDICINAL MUSHROOM: *GANODERMA LUCIDUM*

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Keywords:

Ganoderma lucidum, Antioxidant, Anticancer, Anti-immunomodulatory, β-D- glucans

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ABSTRACT

Mushrooms are an important natural source of food and medicines. Traditionally medicinal properties of mushroom have been well demonstrated particularly in Eastern Asian countries. In modern clinical practices, the bioactive compounds derived from the extract of mushroom sporocarps or mycelium has been widely used for the prevention and treatment of various human diseases such as cancer, diabetes, immune system disorders and infections. Recently, considerable attention is focused on anticarcinogenic bioactive compounds particularly those derived from medicinal or wild mushrooms. The present review analyses the potential therapeutic properties of medicinal mushroom *Ganoderma lucidum* and their applications in human health care.

INTRODUCTION: In recent years, natural products have attracted extensive attention in drug discovery and development [1]. However, there is strong and consistent evidence showing that a diet rich in natural product such as fruits, vegetables, herbs, cereals, sprouts and edible mushrooms are associated with decreased risk of many diseases [2]. Such natural bioactive substances possess an enormous structural and chemical diversity, unsurpassable by any synthetic library; they are evolutionally optimized as drug-like molecules and might be considered biologically validated.

It is empirically known that mushrooms have been valued throughout the world as both food and medicine for thousands of years. They represent a major and as yet largely untapped source of potent pharmaceutical products. There is a common saying that "medicines and food have a common origin" [3]. However, dietary mushrooms provide a wide variety of medicinal properties and they are effective against certain life-threatening diseases. It is estimated that there are approximately 1.5 million species of fungi in world, of which approximately 82,000 are described [4]. About of the known species belong to macrofungi, of which about 5,000 are edible and 2,000 safe [5]. Fungi from the basidiomycota division are of great interest due to the presence of a large number of biological active compounds they contain [6].

Traditionaly, *Ganoderma* is highly regarded as a herbal treatment and is claimed to alleviate or cure virtually all diseases [5, 7, 8]. Ling Zhi encompassed several *Ganoderma* species, which are widely used for medicinal purposes eg., *Ganoderma lucidum, Ganoderma luteum* steyaert, *Ganoderma atrum* Zhao, Xu and Zhang, *Ganoderma applanatu* (pers.:Wallr) pat.,*Ganoderma australe* (Fr.) pat., *Ganoderma capense* (Lloyd) Teng, *Ganoderma tropicum* (Jungh) Bres.,*Ganoderma tenue* Zhao, Xu and Zhang and

Ganoderma sinense Zhao, Xu and Zhang. Worldwide, more than 250 *Ganoderma* species have been described [9, 10]. However, in therapeutic practices and literature citation, *Ganoderma* usually refers to the species of *Ganoderma lucidum.*

Ganoderma lucidum, is a Woody basidiomycotina mushroom belonging to the family of Ganodermaceae of polyporales, which is widely used in oriental medicine for longevity and health promotion [11]. *Ganoderma lucidum* is commonly named as "Lingzhi'' in china, "Youngzhi'' in Korea, "Reishi'' in Japan, and just "*Ganoderma*'' in USA [12]. *Ganoderma lucidum* is the annular mushroom grows in a wide variety of dead or dying trees, eg., Deciduous trees especially oak, maple, elm, willow, sweet gum, magnolia and locust and less frequently found on coniferous tree (eg., Larix, ptea, pinus) in Europe, Asia and North and South America (in temperate rather than subtropical region [13].

Current research is focused on purification and characterization of the bioactive components and determination of their clinical values [5, 7, 8]. Chemical investigations on the fruiting bodies, spores and mycelia of *Ganoderma lucidum* reveal that they contain various bioactive substances [14.] Because of its presumed health benefits and apparent absence of side effects; it has attained a reputation in the east as the ultimate herbal substance. Ling Zhi has now been added to the American Herbal Pharmacopoeia and Therapeutic compendium.

Bioactive Constituents: The bioactive constituent of *Ganoderma lucidum* originates from its chemical composition. The mushroom contains polysaccharides, polysaccharide- peptide complex, β-glucans, lectins, organic germanium(Ge), adenosine, triterpenoids, phenols, steroids, amino acids, lignin, mycins, vitamins, nucleotides and nucleosides each having their own outstanding medicinal effects [15, 16]. Most fractions of identified polysaccharides and triterpenes have more than hundred compounds that are potent immune-modulators, antioxidants and /or chemo preventive and tumoricidal [17].

Nutritional Values: Nutritional analysis of several mushroom species of different origins had been carried out in many laboratories in the world. But nutritional values of locally cultivated mushrooms remain speculative. Moreover, nutritional composition is affected by many factors; these include differences among strains, composition of growth substrate, method of cultivation, stage of harvesting, specific portion of the fruiting bodies used for analysis [18]. The composition of *Ganoderma lucidum* extract (% of dry weight) **Table 1**, consisted of folin-positive material (68.9%), glucose (11.1%), protein (7.3%) and metals (10.2%) (K, Mg and Ca are the major components with Ge having the 5th highest metal concentration at (489µg/g). These results generally agree with those reports of other authors [13, 12, 22]. Whereas, nutritional analysis of *Ganoderma lucidum* contains mainly protein, fat, carbohydrate **Table 2** and fiber.

TABLE 1: MAIN NUTRITIONAL COMPONENT OF FERMENTED PRODUCTS OF *GANODERMA LUCIDUM* AND A NON-FERMENTED CONTROL ON A DRY BASIS [23]

Component (%)	Non Fermented	Fermented	P(t-test)
Protein	11.0±0.5	16.5±0.7	<0.01
Crude fat	10.3±0.6	8.5±0.3	<0.01
Starch	64.5±1.5	25.3±0.8	<0.001
Reducing sugar	4.2±0.2	20.6±0.8	<0.001

The starch content of the fermented control reached 64.5%, the reducing sugar content was only 4.2%. However, the starch content of the fermented product decreased significantly ($p<0.001$) from 64.5 to 25.3%; while the reducing sugar content increased significantly ($p<0.001$) from 4.2 to 20.6%. Solid state fermentation (SSF) also produced a significantly ($p<0.01$) increased from 11.0 to 16.5% in protein content. After SSF, the crude fat content decreased significantly ($p<0.01$). However, these are qualitative and quantitative differences in the chemical composition of *Ganoderma lucidum* product depending on the strain, origin, extracting process and cultivation conditions.

TABLE 2: CARBOHYDRATE COMPOSITIONS OF CRUDE *GANODERMA LUCIDUM* EXTRACT [19]

Sugar components	Percentage (%)
d-Glucose	58.0
d-Mannose	15.5
l-Fucose	9.7
d-Galactose	9.3
d-Xylose	5.4
d-GlcNAC	1.0
d-Rhamnose	0.5

Other Constituents: Reishi also contain sterols, amino acids **Table 3** Soluble proteins, oleic acid, cyclo-octa

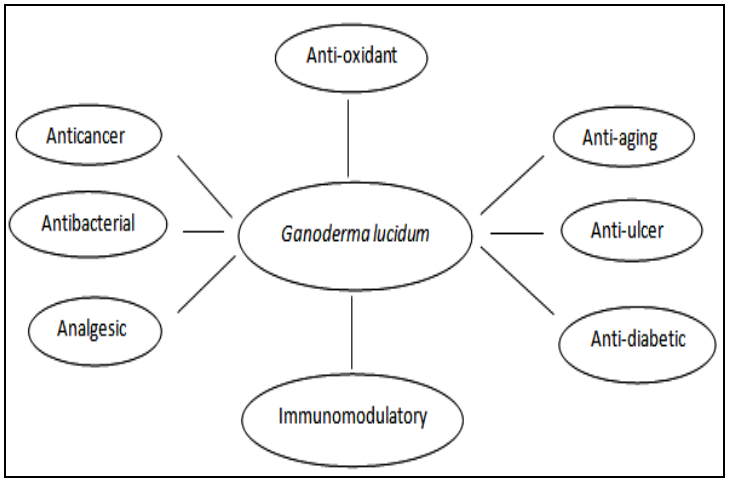
sulfur, an ergosterol peroxide (5,8-epidioxy-ergosta-6,22E-dien-3-ol) and the cerebrosides(4E',8E)-N-D-2'-hydroxystearoyl-1-0-β-D-glucapyran-ocyl-9-methyl-4-8-sphingadienine and (4E,8E)-N-D-2'-hydroxypamitoyl-1-D-β-D-glucopyranosyl-9-methyl-4-8-sphingadienine [9, 10, 17, 18,20]. Regarding the inorganic ions, the mushroom contains Mg, Ca, Zn, Mn, Fe, Cu and Ge. The spores themselves contain choline, ketain, tetra cosanoic acid, palmitic acid, ergosta-7, 22-dien-3-ol, nonadecanoicacid, behenicacid, tetracosane, hentriacontane, ergosterol and β-sitosterol. One of the lipids isolated from *Ganoderma lucidum* is pyrophosphosphatidic acid [10, 15, 17, 24].

TABLE 3: AMINO ACID ANALYSES OF *GANODERMA LUCIDUM* EXTRACT [19]

Amino acid	Relative abundance
Aspartic acid	117
Threonine	66
Serine	54
Glutamic acid	120
Proline	60
Glycine	108
Alanine	100
Valine	61
Methionine	6
Isoleucine	36
Leucine	55
Tyrosine	16
Phenylalanine	28
Histidine	12
Lysine	21
Arginine	22

Therapeutic Applications:

Preclinical and Clinical Studies:



Ganoderma lucidum has also become popular because of its promising properties that might extend life span while increasing vigor and vitality [58]. *Ganoderma lucidum* has been reported to have a number of pharmacological effect including immunomodulating, antiartherosclerotic, anti-inflammation, analgesic, chemopreventive, anti-tumor, radioprotective, sleep-promoting, antibacterial, antiviral (including anti-HIV), hypolipidemic, anti-fibrotic, hepatoprotective, diabetic, antioxidative and radical-scavenging, anti-aging, hypo-glycemic and anti-ulcer properties **Table 4** [10, 22, 24, 26, 27].

TABLE 4: THERAPEUTIC EFFECTS AND BIOACTIVE COMPOUNDS OF *GANODERMA LUCIDUM*

THERAPEUTIC EFFECTS	BIOACTIVE COMPOUNDS	REFERENCES
Immunomodulation	β-D-glucans	Zhang et al, Wang et al, Xia et al, Lei et al, Chien et al, Cao et al, Hsu *et al.*
Anti-inflammatory	Ganoic acid-A,-F, -DM,-T,-Q	Akihisa *et al*.
Anticancer, Antitumor	β-D-glucans, GA-T	Lim et al, Tang *et al.*
Antioxidant	Chloroform extract (Compound not reported)	Karaman et al, Joseph *et al.*
Anti Aging	GA-B, -C_2 & -G	Guesnet *et al.*
AntiDiabetic	Ganopoly	Goy *et al.*
Antibacterial	Neutral & Acidic proteins, bound Polysaccharide, Ganodermin	McKenna *et al.*, Wasser *et al.*

Ganoderma lucidum has now become recognized as an alternative adjuvant in the treatment of leukemia, carcinoma, hepatitis and diabetes [6-8, 17]. Since the last decades, clinical trials on the use of *Ganoderma lucidum* preparation used to treat cancer and other diseases have been reported in international peer-reviewed journals.

Immunomodulatory Activtiy: Immunomodulatory properties alone with low cytotoxicity raise the possibility that it could be effective in the cancer patients receiving conventional chemotherapy and/or radiational treatment, to build up immune resistance and decreased toxicity. Numerous experimental and clinical investigations demonstrated that *Ganoderma lucidum* had immunomodulatory activities. A number of reports have demonstrated that *Ganoderma lucidum* polysaccharides stimulated immune function both *in vivo* and *in vitro*. Recent literature has been

found that *Ganoderma lucidum* modulate many components of the immune system such as the antigen-presenting cells, NK cells, T and B lymphocytes, macrophages, resulting in the production of cytokines, including interleukins, tumor necrosis factor-α (TNF-α) and interferon [28]. Chen W C *et al*., (1995) showed that a crude aqueous extract of *Ganoderma lucidum* probably administered was effective in enhancing the recovery of leukocytes count, splenic blastogenic responses and splenic CD4 and CD8 T cell subsets in mice subjected to γ-irradiation [29]. Choi-Lan-Ha *et al*., 2003 have demonstrated the inhibitory effect of the Chinese herb *Ganoderma lucidum* mycelium on gut immunoglobulin A responses to cholera toxin in mice [30].

Mechanisms Of *Ganoderma Lucidum* On Immunomodulatory Activity: The immunomodulating effect of *Ganoderma lucidum* were extensive, including promoting the *function* of antigen-presenting cells, mononuclear phagocytes system, humoral immunity and cellular immunity and cellular immunity and the action site of *Ganoderma lucidum* was speculated to be located in the course of proliferation and differentiation of immune precursor cells to effector cells.

Mono-Nuclear Phagocyte System: Many scientific investigations have found that one polysaccharide isolated from *Ganoderma lucidum* which were mainly composed of β-D-glucans **Fig. 1** could TNF-α Synthesis in primary culture of human peripheral blood mononuclear cells (PBMC). And exposure of human neutrophils to *Ganoderma lucidum* polysaccharides time-dependently caused increases in protein kinase C (PKC), P^{38} mitogen-activated protein kinase (MAPK), hematopoietic cell kinase (HCK), moreover tyrosine kinase Lyn activities, these may be the action that corresponded to an enhanced unspecific immune function [31].

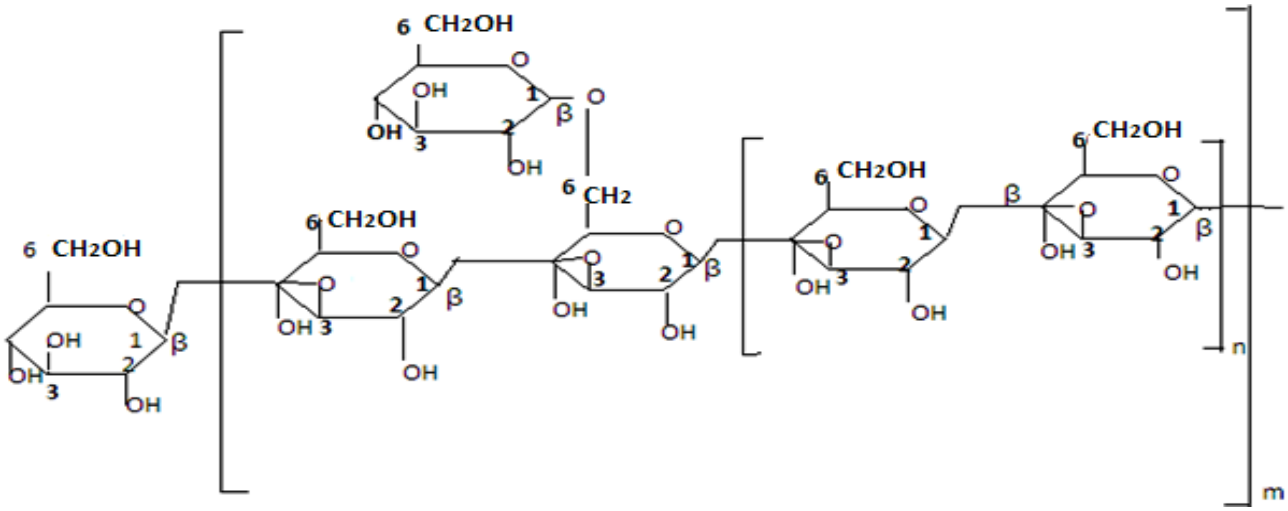


FIG. 1: POSSIBLE REPEATING UNIT OF *GANODERMA LUCIDUM* GLUCANS [32]

Antigen-Presenting Cells: Dendritic cells (DC), a kind of professional antigen- presenting cells, are pivotal for initiation of primary immune response. Cao LZ et al., reported that *Ganoderma lucidum* promote not only the maturation of cultivated murine bone marrow derived DC *in vitro* but also the immune response initiation induced by DC [33].

Natural Killer (Nk) Cells: Recent report suggested that treatment with the water soluble extract of *Ganoderma lucidum* (F3) F3-Polysaccharide fraction could increase the presence of natural killer cells (CD56 (+) marker) significantly from 1.1% to 3.2% in mononuclear cells, indicating that F3 quantitatively influenced NK cells activities [34].

T-Lymphocytes: The cell–mediated immune function was also enhanced by Ganoderma *lucidum,* as suggested by the observation that *Ganoderma lucidum* promoted the mixed lymphocyte reaction (MLC) [35]. It also exerted an increasing effect on the induction of delayed hypersensitivity to protein antigen. *Ganoderma lucidum* polysaccharides like BN3A, BN3B and BN3C are three kinds of polysaccharides significantly increased the lymphocyte proliferation induced by Con A and IL-2 production in the normal

mice, as well as in the aged mice *in vitro*. BN3A and BN3C also could antagonize the suppressive effect of hydrocortisone on the proliferation of mouse spleen cells [36]. Moreover, *Ganoderma lucidum* increased the production of IFN-γ and significantly increase IFN-γ mRNA expression in the T-Lymphocytes [37].

B-Lymphocytes: A bioactive fraction (GLIS), isolated from the fruiting body of *Ganoderma lucidum* could stimulate the activation, proliferation and differentiation of B-Lymphocytes. The B-Lymphocytes were to enlarged, expressed CD71 and CD25 on the cell surface, and showed an increase in the secretion of immunoglobulin. However, the activation of B-Lymphocytes by GLIS did not depend on the activation of T-Lymphocytes. It was associated with stimulation of the expression of protein kinase C α and protein kinase C γ in B-Lymphocytes by GLIS directly [38].

Macrophages: Macrophages are responsible for killing pathogen in the body. The substances from *Ganoderma lucidum* activation of macrophages which result in the release of cytokines and other mediators. Whereas, polysaccharides from *Ganoderma lucidum* in particular β-D-glucans are potent stimulators of murine and human macrophages *in vitro* and *in vivo* [39]. Crude water- extracted polysaccharides isolated from fresh fruiting bodies of *Ganoderma lucidum* potentiated the production of cytokines, including IL-1β, IL-6, IFN-γ and TNF-α by human macrophages, which were anti-proliferative, differentiation and apoptosis inductive to the HL-60 and the U937 leukemic cells.

Anti-inflammatory Effects: Anti-inflammatory drug make up about half of analgesics, remedying pain by reducing inflammation as opposed to opioids which affect the brain. Joseph et al., showed the anti-inflammatory activity of chloroform extract of *Ganoderma lucidum* in dose dependent carrageenan induced acute and format induced chronic inflammatory models in mice [40]. In addition Akihisa et al., also investigated the anti-inflammatory activity of GA-A, -F, -DM and -T-Q in 1-O-tetradecanoylphorbol 13 –acetate- induced inflammation in mice [41].

Anticancer Activities: *Ganoderma lucidum*, an oriental medical mushroom has been used widely in Asian countries for centuries to prevent or treat different diseases including cancer. Dried powder of *Ganoderma lucidum*, which was recommended as a cancer chemotherapy agent, is currently used popularly worldwide in the form of dietary supplements [42].

Ganoderma lucidum extracts were reported to possess cytotoxic activity against various cancer cell lines including leukemia, lymphoma, multiple myeloma [43, 44] and human breast cancer MCF-7 [45]. The cytotoxic effect of *Ganoderma lucidum* as demonstrated by the studies of Jiang *et al*., and Zhu *et al*., in a concentration dependent manner [46, 47]. This activity of *Ganoderma lucidum* can be attributed directly to specific compounds from experiments employing isolated and purified molecules.

Wang S. Y. *et al*., showed that the anti-tumor effect of *Ganoderma lucidum* was mediated by cytokines released from activated T-Lymphocytes and macrophages [39]. *Ganoderma lucidum* could potentiate the production of cytokine including interleukin-1, interleukin-6, tumor necrosis factor, and interferon in which two antitumor cytokines, tumor necrosis factor and interferon, acted synergistically on the inhibition of leukemic-cell growth and markedly induced leukemic - cell apoptosis. The organic Germanium in *Ganoderma lucidum* may also contribute to its anti-tumor activity [49]. W. Tang *et al*., (2006) proposed that GA-T may be a natural potential apoptosis-inducing agent for highly metastatic lung tumor and it may be also applied to treat other tumor cell lines **Fig. 2**.

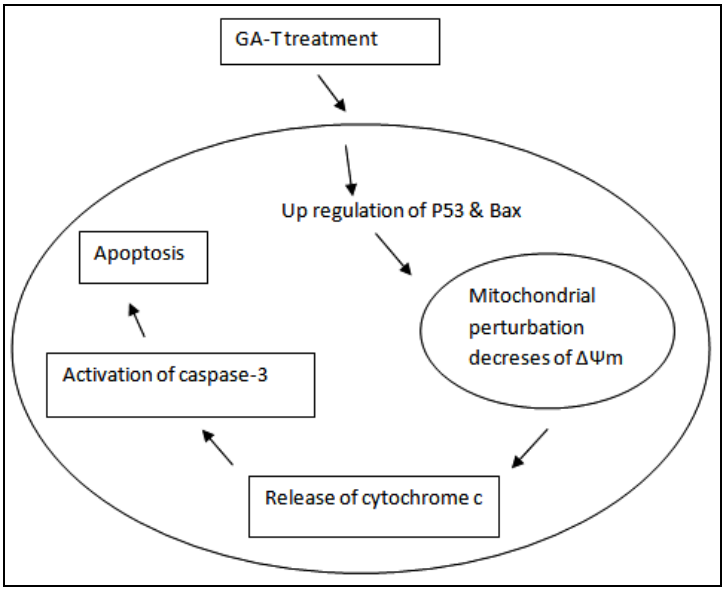


FIG. 2: PROPOSED PATHWAY INVOLVED IN APOPTOSIS INDUCED BY GA-T [50]

Antioxidant Activities: An anti-oxidant may be defined as "any substance that when present at low concentrations, compared with those of the oxidizable substrate significantly delays or inhibits oxidation of that substrate" [51]. Antioxidative effect of sporocarp extracts have not been examined so far. In as much as antioxidative activities have significant therapeutic effects; the fungal species could be used in therapy for a variety of disease states and in health nutrition as a source of naturally derived antioxidants.

These are easily noticed, collected and recognized in field and their secondary metabolites can be easily identified and extracted [52]. Many literatures have demonstrated that chloroform extract of *Ganoderma lucidum* possesses significant capacity to inhibit free radical formation and scavenging activity. The chloroform extract showed significant superoxide scavenging activity (IC_{50}: 144.6±1.5 µg / ml) and is of potential interest as source of strong natural antioxidant in the food and cosmetics industries. GA-A, -B, -C and -D also showed antioxidative effect against pyrogallol-induced erythrocyte membrane oxidation and Fe (II) ascorbic acid –induced lipid peroxidation [53].

Anti-aging Effect: Relatively recent research on anti-ageing effect from natural products are of the highest importance for medical stakes (Oncology and immunology) and industrial development (Pharmacy and Cosmetics), it also opens prospects to scientific screening of antioxidizing natural agents among higher fungi [54].

The oxidative damage caused by these free radicals may be related to ageing and diseases, such as atherosclerosis, diabetes, cancer and cirrhosis [55]. However, antioxidant supplements or food containing antioxidants may be used to reduce oxidative damage, by not only providing essential vitamins and minerals, but include important chemo-protective agent capable of protecting against some forms of cancer[57]. Guesnet et al, 2003 stated that GA-B,-C2 and –G have anti-aging effect and can be used as cosmetic agents in various forms [56].

Antidiabetic Effect: The polysaccharide factions of *Ganoderma lucidum* have potential hypoglycemic and hypolipidemic activities have been demonstrated by animal studies. However to evaluate the anti-diabetic efficacy and safety, a clinical study were carried out on polysaccharide fractions extraction from *Ganoderma lucidum* (Ganopoly) by a patented technique in 71 patients with confirmed type II diabetes mellitus(DM) was carried out [60]. This study demonstrated that Ganopoly was well tolerated, efficacious and safe in lowering blood glucose concentrations.

Antibacterial Effects: Several studies have been demonstrated that *Ganoderma lucidum* contained antibacterial constituents that are able to inhibit gram-positive and gram-negative bacterias [61, 62]. The Aqueous extract of the carpophores of *Ganoderma lucidum* inhibited 15 types of gram-positive and gram-negative bacteria. However, further studies indicated that combination of *Ganoderma lucidum* extract with four antibiotics like ampicillin, cefazolin, oxytetracyline and chloramphenicol resulted in additive effects. Whereas, synergism in two instances where combined with cefazolin against *Bacillus subtilis* and *Klebsiella oxytoca* and antagonism in two instances [63].

Commercialization: *Ganoderma lucidum* is usually prescribed in various forms. It may be injected as a solution of powdered spore. Under the name of LingZhi or Reishi, a number of *Ganoderma lucidum* products are sold as over the counter products in the forms of health drinks, soup, syrup, tea, tablets, capsules, tincture or bolus (powdered medicine in honey) [61, 60]. In 2008, the worldwide production of *Ganoderma lucidum* was approximately 9500 tones, of which china contributed 6000 tones. *Ganoderma lucidum* is mainly used as a tonic and a remedy for the treatment of a variety of diseases. Hence, it may be noted that Ganoderma *lucidum* is an excellent source of medicine which is enabling the present need of human mankind in every aspect [58].

CONCLUSION: As seen through the review, *Ganoderma lucidum* present several mechanism of action to develop its large number of therapeutical function. Over all evidence show that *Ganoderma lucidum* a mushroom of biomedical importance, contains a number of bioactive components, many of the biological response modifiers which activate our immune system for a multitude of defensive functions. However, immune-modulating effects of *Ganoderma lucidum* are associated with its anti-tumor activity.

Likewise, the multiple mechanisms in chemoprevention activity of *Ganoderma lucidum*, as superoxide scavenging, lipid peroxidation is inhibiting and nitric oxide scavenging and anti-oxidation may be one of the important mechanism by which *Ganoderma lucidum* exerts its tumor inhibitory effect.

Even though, *Ganoderm*a *lucidum* is an immortal golden medicinal fungus are still to be exploited commercially. The reason that some of the *Ganoderma lucidum* preparations are not available as medicines may be due to difficulties related to mass production. And, the majority of research programs had been focused on extracts from the fruiting body and there have been fewer studies on extracts from the cultivated fungi. Therefore, further research may be oriented in that direction. Since, most of the therapeutic effects of *Ganoderma lucidum* are based on *in vivo* and *in vitro* studies, clinical trials are needed to fully realize its potential.

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