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Potential secondary bioactive compounds of *Ganoderma lucidum* (Reishi Mushroom) against various pathogenic activity

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Abstract

Since the dawn of time, mankind has been enchanted by nature and has extensively researched upon natural resources. Scientists have been analyzing the composition, molecular structures, and pharmacological activities using activity-guided experiments. Although green plants have been the first preference for extraction of natural drugs recently, fungi have been also drawing attention as they have been reported to be the rich source of bioactive compounds. Among them, Reishi mushroom or *Ganoderma lucidum*, has been studied greatly due to its notable potential against various diseases. Bioactive compounds derived from reishi were found to be - anti-inflammatory, anti-tumor, and anti-microbial in effect. Besides, they are also known to be immuno-modulators, antidepressant and neuro-protectants etc. Polysaccharides and triterpenoids are the groups which possess major pharmacological properties of reishi as compared to other chemical groups. Recent studies show that compounds such as: colossolactone (VIII, E, G), ergosterol, heliantiriol F and velutin can act as anti-SARS-CoV-2 agents as well. The present article explores the medicinal properties of *Ganoderma* in depth and discusses the possibilities to use this mushroom for a condition like SARS. The present review digs into the major pharmacological activities associated with reishi mushroom.

Keywords: *Ganoderma lucidum*, SARS-CoV-2, Bioactive compounds, Antagonistic effect, Protagonistic effect

1. INTRODUCTION

Due to the growing population and unpredictable change in lifestyle of an individual, every 10th person in this world is suffering from some or the other disease. To treat such diseases majorly modern medicines are used which are believed to cure the disease at much faster rate as compared to the traditional medicine but, at the same time they are found to be associated with side-effects too. Herbal medicines have many been used for humankind since ancient times as they are generally easily available, economical, work in a holistic manner and have no or less side effects. According to a WHO report of 2019, about 80% of the rural population depends upon these naturally occurring drugs for their primary treatments. About 118 natural sources are being used for crude drug extraction and around 74% drugs are derived from plants whether natural or synthetic [1].

Among the other natural sources of medicines, mushrooms are one such group of fungi which are used for both as food item and medicine. Among them, *Ganoderma lucidum* or reishi mushroom, is polypore fungus, widely used to treat various diseases in Japan, Korea, China and other Asian countries. Chinese and Japanese medicine practitioners believe that it promotes health and longevity in humans as it strengthens the body, promotes gut health, and helps in wound healing. Therefore, it's also known as "medicinal mushroom". It has 400 bioactive compounds belonging to the groups: polysaccharides, proteins. triterpenoids, nucleotides, steroids, phenolic compounds and many more having exceptionally high medicinal value. Compounds from the groups: polysaccharides and triterpenoids are commercially and pharmacologically essential due to properties such as: antimicrobial, anti-tumor, anti-inflammatory, anti-diabetic, anti-asthmatic, anti-atherosclerotic, antidepressive, cytotoxic, anti-melanogenic, and antihyperlipidemic. Apart from these properties they act as protectant for various organs, anti-oxidant, and immune-modulator [2]. This article deals with the brief working of such compounds against various pathogenic activities.

2. BIOACTIVE COMPOUNDS OF *G. lucidum* AND THEIR BIOLOGICAL FUNCTIONS

Generally, mushrooms are composed of 90% water and the remaining portion consist of other components. In *G. lucidum*, 10% residual is mainly composed of carbohydrates (26-28%), proteins (7-8%), fibers (59%), fat (3-5%), ash (1.8%) and some minerals and vitamins. In addition to that, it is also composed of a wider array of naturally active compounds as described above such as: polysaccharides, triterpenoids, nucleotides, steroids, phenolic, triterpenoids, nucleotides and their derivatives. Polysaccharides and triterpenoids are widely studied due to their high concentration, structure and functionality in fungi [3] as mentioned in Table 1.

2.1 Polysaccharides

Polysaccharide is present in high quantities in various portions of such *G.lucidum* as myċeliúm, spore, and the fruit body. Mycelium is highly rich in polysaccharide content while the fruiting body has the least. Glucose is abundant in fruiting body mycelium, spores but galactose majorly contribute to fruiting

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body [4]. Along with monosaccharides it consists of heteropolymer of mannose, galactose, xylose and fructose with various conformations of 1-3,1-4,1-6 linkage and β and α-D (or L)-substitutions [3].

The polysaccharide portion of this plant is known to have anticancer effects. Depending upon the portion used for extraction, the anti-tumor effect varies. This is due to the solubility and branching conformation. Polysaccharide extracted from the fruiting body exhibits antitumor effect due to immunomodulation while the mycelium portion exhibits antitumor effect being anti-angiogenesis. In addition, it protects cells from free radicals and peroxidation [5].

2.2 Triterpenoids

About 200 types of triterpenoids have been discovered from various sections such as the fruiting body, spores, and mycelium of reishi mushroom. Mycelium is least rich in triterpenoids content while the fruiting body has the maximum [4]. It is a subclass of terpenes which is highly rich in physiological activities such as anti-inflammatory, antitumor, and hypolipidemic [2]. Basic composition of terpenoids consists of 30 units of carbon atoms in a tetracyclic partner. 24-27 units of carbon atom structure are rarely observed [6]. All triterpenoids are tetracyclic in nature. Based on their functional groups and branching these are classified as ganoderal, ganoderiol, ganoderone, ganoderic acid and ganoactone [4].

The Ganoderic acid group has a cytotoxic effect and inhibits proliferation of tumor cells. The Ganoderiol group inhibits proliferation along with the formation of invasive, metastatic, and drug-resistant tumour cells [2]. Ganoderic acid T the most prevalent triterpenoids, reported to have anticancer action followed by Ganoderic acid A whereas,Ganoderic Acid D interacts to proteins directly, which may aid apoptosis in human epithelial cell lines. Another triterpenoids rich in *G.lucidum*, Ganoderiol F shows significant cytotoxic activity [7].

2.3 Polypeptides

LZ-8 is a bioactive protein in *G.lucidum,* composed of 110 amino acids with acetylated amino acid at the terminal end. It possesses an immunomodulating effect thus, is also known as immunomodulatory protein when extracted from mycelium [4]. Some other proteins such as lectins are cytotoxic, hypoglycemic and help to improve innate immunity. These are generally reversally attached to mono or oligosaccharides [5]. Basic nucleosides uridine, inosine, adenosine, thymidine, cytidine and guanosine, nucleotides: uracil, hypoxanthine, thymine, guanine and adenine are also observed to be attached with each polypeptide. During the extraction process, glutamic protease was majorly derived along with β-1,3-glucanase, α-1,2-mannosidase, endo-β-1,3-glucanase, and β-N-Acetylhexosaminidase for enzymatic properties [4].

2.4 Phenolic Compounds

Gallic acid, kaempferol, hesperetin, quercetin,trans-cinnamic acid and naringenin have been identified. Quercetin, kaempferol, hesperetin, naringenin are categories as flavonoids whereas gallic acid and *trans*-cinnamic acid are phenolic compounds based on HPLC-DAD analysis. Hesperetin and naringenin were the most prevalent phenols with abundance of 1.875–3.222 g/g and 1.235–2.856 g/g, respectively. Quercetin,

myricetin, and morin in ethanolic extract from mycelia were discovered as flavonoids. The total phenol concentration in phenol extracts varied from 2.5 to 12.3 g/g, with phenolic chemicals such as p-hydroxybenzoic, p-coumaric, and cinnamic acid [8].

2.5 Minerals and Vitamins

Some essential minerals can be obtained from *G.lucidum* such as calcium, sodium, potassium, magnesium, iron, zinc, aluminum and copper in major quantities. Apart from these minerals, silicon, cobalt, phosphorus, carbon, magnesium, manganese, arsenic, nickel, lead, and chromium are obtained. Several vitamins such as Vitamin B_1, B_2, B_6, C, D, E and β-carotene were observed in *G.lucidum* [4].

2.6 Steroids

These are organic compounds with one pentagonal and three hexagonal rings with biological functions placed in a particular arrangement. About 20 types of steroids were observed in *G.lucidum* [4]. These compounds possess anti-obesity, anti-viral, anti-tumor, and anti-inflammatory properties. Thus, it mainly helps in hepatoprotection, and reduction of bad cholesterol [9]. Among which ergosterol and cholesterol containing groups were widely studied, extracted from spores and fruiting bodies mainly. Ergosta-4,7,22-triene-3,6-dione was only found in mycelium [4].

3. PHYSIOLOGICAL ACTIVITY OF BIOACTIVE COMPOUNDS OF *G. lucidum*

As mentioned earlier, medical mushrooms have many effects which are proven through *in-vitro, in-vivo* and *ex-vivo* activities. These effects may be antagonistic or protagonistic on pathogens and parasites on human and animal cell lines. Such beneficial aspect of *G.lucidum* are discussed below:

3.1 Antioxidant

According to the National Cancer Institute (2006), chemical antioxidants interact and reduce free radicals thus, preventing them from damage. Free radicals may play a vital part in cancer, heart disease, stroke, and other diseases of aging. As, antioxidants work against free radicals by neutralizing them as they give up some of their own electrons. Due to this, they act as a natural switch for free radicals. Antioxidants found in *G.lucidum* includes: lycopene, carotene, Vit. A, C, E, and other natural products [59].

In Chinese medicine,*G.lucidum* is known as the "mushroom of immortality" and polysaccharides extracted from this species are key contributors to the antioxidant activities [10]. Free radicals and ROS may harm cells as well as tissues through the oxidative activity, and the long-term buildup of such damage caused by free radicals and ROS causes ageing and a variety of age-related illnesses. ROS and free radicals in cells have the ability to damage proteins and DNA, resulting in oxidative stress, which can be mitigated by antioxidative enzymes and repair processes. Excessive oxidative stress, on the other hand, has been shown to overcome the natural protective mechanism,which can lead to a range of biological problems, including tumor [7]. According to a study conducted by Zhu et al (1999), *G. lucidum's* antioxidative activity was investigated using *in vitro* experiments. The aqueous extract was separated when the raw Ganoderma

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substance was subjected to boiling water medium. It has proven possible to get terpene and polysaccharide-rich fractions. The antioxidative properties of both fractions were investigated. The antioxidant activity of the terpene fraction was found to be the greatest. Ganoderic acids A, B, C and D, lucidenic acid B, and ganodermanontriol were the most abundant in that fraction [11]. Another study conducted by Hasnat et al., (2013), shows significant antioxidative properties when tested against various in vitro antioxidant systems. The extract used for this study was derived from GLBR. Administration of GLBR extract enhanced the enzymatic activity such as superoxide dismutase, catalase, and glutathione peroxidase in the serum, liver, and brain of mice [12].

Immune modulation, anticancer activities, and strong antioxidant effects are all given by GLPs, a primary active element in Ganoderma. *In vitro* photoaging in human fibroblasts was reduced by GLPs-associated reduction of UVB-induced photoaging [13]. After UVB exposure, GLPs reduce MMP-1 protein production, enhance C-telopeptides of type I collagen protein, and restrict the formation of ROS in fibroblasts [4]. MMPs are a family of zinc-dependent proteolytic enzymes that degrade a variety of Extracellular Matrix and non-Extracellular Matrix molecules, causing tissue change in both healthy and pathological processes. Various stimuli stimulate and activate MMPs in vascular tissues, including MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-12, and MT1-MMP [14]. Long-term exposure to free radicals and ROS increases ageing and age-related illnesses.

The antioxidant activities of fresh proteins isolated from myćeliúm and the fruit body of *G.lucidum* were investigated by Sarnthima et al.(2015). Protein content obtained from mycelium as well as the fruiting body showed antioxidative properties. In terms of 2,2′-azino-bis and DPPH radical-scavenging abilities, mycelial protein extract exceeded fruiting body protein extract [15]. The comet assay was used to assess ROS production and oxidative stress indicators. Furthermore, on comparison in the ethanolic extract, H_2O_2-induced Production of ROS was minimal [16].

3.2 Immuno-modulation

According to the National Cancer Institute, immunomodulation is defined as any change in the body's immune system through agents which can either suppress or activate the response and function of the system. Such agents are known as immunomodulators [59]. This is achieved through multiple mechanisms such as activating cytotoxic effects of B lymphocytes, dendritic cells, T-cells, macrophages, NK cells, interleukins and other immune cells or by alternating TLR-4 pathway [5].

Aqueous extract of *G.lucidum* polysaccharides induces immunomodulating effect through Interleukin-1 gene expression by modulating PK-mediated signal transduction. Protein tyrosine kinase-mediated phosphorylation is also found to be stimulated, which is followed by initiation of PKs and finally activation of MAPKs, ERK, JNK, and p38 [17].

PD-1 is a surface protein present on immune cells (B and T cells) interacting with ligand PD-L1, which inhibits T-cell proliferation as well as its inflammatory activities, and prevents autoimmune diseases. *G.lucidum* extract from the

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spores has a great impact on PD-1 as it increases transcription of PD-1 gene and shows reduced PD-1 concentration in B lymphocytes. This could be accomplished by increasing PD-1 protein membrane internalisation and subsequent ubiquitination. It also increases expression of the Chemokine Ligand 5 [18].

3.3 Anti-melanogenic Effect

Tyrosinase enzyme is known to modulate melanin synthesis by decreasing the activities of tyrosinase and tyrosine-related proteins, G.lucidum reduces hyperpigmentation.The tyrosinase inhibitory activity of methyl lucidenate F obtained from G.lucidum was an addiction, with an IC50 of 32.23M. G.lucidum provides the active ingredient Ganodermanondiol. Ganodermanondiol's inhibition of CREB phosphorylation resulted in a decrease in MITF expression and melanin production. ERK and JNK phosphorylation suppressed melanin formation, except p38 phosphorylation stimulated melanin synthesis and MITF expression. The phosphorylation of ERK was elevated by Ganodermanondiol, while the phosphorylation of p38 was reduced by JNK. GLPs directly affect melanogenesis [58].

Ganodermanondiol, a triterpenoids derived from G.lucidum, reduces melanin formation by inhibiting the activity and cellular tyrosinase, tyrosinase-related protein, and MITF expression. Melanogenesis of B16F10 melanoma cells is also impacted by ganodermanodiol as it alters the MAPK cascade and cAMP-dependent signalling pathway [20].

On exposure to UV radiation, a critical enzyme in skin called tyrosinase is activated, which leads to an increase in melanin production as well as DNA damage, inflammation, and other skin ailments. Skin pigmentation is caused by an abnormal buildup of melanin [19].

UV exposure is a major contributor to skin ageing, causing coarse wrinkling, dryness, and laxity. UVB irradiation increases MMP-1 secretion while decreasing collagen fibers synthesis, thus accelerating skin ageing. By inhibiting ERK pathways, the extract of G.lucidum can decrease UVB-induced MMP-1 expression and enhanced pro-collagen expression.UVB-induced skin pigmentation can be counteracted by GLP. GLP can reduce melanogenesis in melanocytes by inhibiting most of the paracrine effects of keratinocytes and fibroblasts via the Fibroblast Growth Factor or MAPK pathway. G. lucidum can be used to treat solar lentigo, chloasma, freckles, and senile plaques [4].

3.4 Anti-inflammatory Effect

Inflammation is the body's most common form of infection or injury and anti-inflammatory drugs work by inhibiting or reducing the effects of various chemicals such as: cytokines, in the body that can cause inflammation [59]. It is a natural reflex action to an illness or injury that helps the body defend itself and repair itself. Increased amounts of TNF-α, IFN-γ, and IL-4 in the body's inflammatory environment can speed up inflammation in the dermis causes harm to the epidermal barrier function.Sulfated polysaccharide(GLPss58) derived from G.*lucidum*'s fruiting body, inhibits L-selectin binding to receptors, activates complement mechanisms, and prevents TNF-α and INF-binding to antibodies. All L-selectin, complement, and cytokine-mediated inflammatory pathways are inhibited by GLPss58. Furthermore, GLPs decrease TNF-α, IL-1β, IL-6, and IL-4

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secretions in mice, preventing inflammation, regulating intestinal immune barrier activity and sustaining intestinal homeostasis.GLPs' anti-inflammatory qualities are beneficial in the treatment of sensitive skin in clinics [4].

The antiinflammatory activity of an ethanolic extract of *G.lucidum* was investigated by Yoon et al in 2013 as well. In the BV2 cell line, induced with LPS, quantity of nitric oxide, prostaglandin E2, and cytokines (IL-1β and TNF-α) it was found that the culture supernatants, after treatment of cell lines with extract up to 1 g/ml, iNOS mRNA protein expression was significantly inhibited. [21].

Similarly, *G.lucidum* was used as a (GAC1) triterpene ganodermic acid , was isolated and evaluated on RAW 264.7 macrophages. When Crohn's disease patients were given GAC1, TNF production by macrophages and PBMCs was reduced. Inflamed colonic biopsies from Crohn's disease patients produced substantially less TNF-α, IFN-γ, and IL-17A when given GAC1. The NF-B signalling pathway was downregulated, which resulted in these findings [22].

Jiao et.al (2020), investigated the effect of GLSO on skin burn wound healing and the underlying mechanisms. The skin wound healing assay was carried out on mice. Photography, hematoxylin/eosin staining, Masson's Trichrome staining, and immunohistochemical analysis were used to examine the wounds. The 16s rRNA sequence and quantitative data were used to examine the microbiota on the wounds.The level of LPS in skin wounds and serum was determined using an enzyme-linked immunosorbent assay, quantitative polymerase chain reaction and immunofluorescence assays were used to evaluate TLR4 expression and the relative amounts of inflammatory cytokines.The researcher applied an antibiotic-treated pseudo-germless mouse model to see if skin burn wound healing was speed up by GLSO through skin microbiota. It was observed that GLSO significantly accelerated skin wound healing and controlled the amounts of gram-negative and positive bacteria. GLSO lowered the levels of TLR4, also some inflammatory cytokines. In comparison to antibiotic treatment, GLSO exhibited a considerable acceleration in skin wound healing in the pseudo-germ-free mice model. Thus, GLSO slowed skin wound healing by reducing inflammation via controlling the skin microbiota.These results provided scientific support for the use of GLSO as a therapeutic cure in skin burn injuries [23].

According to the experiment conducted by Xu, Xiao et al. (2021), GLS reduces inflammation in macrophages by reducing LPS-induced cell polarisation, as well as the inhibiting the secretion and mRNA expression of pro-inflammatory mediators iNOs, TNF-α, IL-1β, and IL-6. Furthermore, MAPK pathways is inhibited by GLS through suppressing phosphorylation of p38 only whereas ERK or JNK are effected much.Polysaccharides and triterpenes, which inhibit the expression of JNK and ERK, may have a synergistic anti-inflammatory response with GLS.NF-κB pathway is also inhibited by GLS through preventing IκB-α phosphorylation and degradation, as well as blocking NF-κB p65 phosphorylation.GLS was found to be directly linked to the active sites of p38 and p65, preventing them from being activated, according to molecular docking. As a result of their findings, GLS as a natural and safe anti-inflammatory drug, it can be used to treat and prevent inflammatory disorders. (**Fig. 1)** [24].

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3.5 Anti-obesity Effect

WHO defines obesity as excessive fat accumulation which causes health disorders in 2017, over 4 million people died due to obesity worldwide every year. Thus, it has become one of the major causes for other health issues [60]. Treatment of adipocytes with the oligopeptide derived from *G.lucidum* reduced the expression of adipogenic transcription factors (PPAR-γ) as well as, other components like as SREBP-1c, C/EBP-α, FAS, ACS1, FABP4, FATP1, and perilipin, which regulate synthesis of glucose, fatty acid, and lipid as well as, their transportation. Furthermore, it activates AMPK signalling pathways, indicating that the polysaccharide might be useful as an antiobesity and anti-diabetic drug [25]

In addition to this, ergosterol peroxide is one of the steroidal compounds extracted from *G.lucidum* and reported to have anti-obesity properties. It inhibits triglyceride synthesis at mRNA level along with 3T3-L1 adipocyte differentiation. This is achieved by inhibiting lipid droplet synthesis or expression of PPARγ and C/EBP-α. SREBP-1c expression is responsible for the positive feedback mechanism for PPARγ activity **(Fig.2)**.

Ergosterol peroxide inhibits SREBP-1c expression which results in inhibition of PPARγ, which further inhibits FAS, ACC and FAT which act as lipogenic factors. In addition, MAPKs activity is also inhibited which is responsible for cell proliferation [9]. As a result of inhibiting PPARγ, SREBP-1c, and C/EBP-α in the early/intermediate stages of adipocyte differentiation suppresses expression of adipocyte-specific genes, and lipid synthesis is decreased at the ultimate stage of adipocyte development [25].

3.6 Neuro-protectant

According to Bartels et al Neuroprotective substances are substances that can alter the course of physiological activities following the onset of ischemia, potentially decreasing stroke damage. Calcium channel blockers, naloxone, gangliosides, glutamate antagonists, and free-radical scavengers are of these substances [26].

Oxidative stress is a factor in many neurological diseases, including Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Alzheimer's disease.Inhibiting acetylcholinesterase, which regulates the action of the neurotransmitter acetylcholine in the brain, is one of the therapies for Alzheimer's disease. Triterpenoid chemical reaction in *G.lucidum* enhances neuronal lifespan and lowers weariness.The potential use of *G.lucidum* in the treatment of neurological disorders has been taught, and it has been proven that following a *G.lucidum* diet can reduce the growth of Alzheimer's disease.[2].

Polysaccharides obtained from reshi show anti-apoptotic properties in neurons suffering from ischemia/reperfusion injury, and although mechanisms remain unknown. The processes through which *G.lucidum* polysaccharides protect neurons from oxidative stress-induced apoptosis. In larger cerebellar granule cells, H_2O_2 has been utilised to cause apoptosis. *G.lucidum* polysaccharides significantly reduced H_2O_2 subscript-induced indopoposis, reduced caspase-3, Bax, and Bim expression, and enhanced Bcl-2 expression in these cells. These findings imply that polysaccharides from *G.lucidum* inhibits oxidative-induced

neuronal death by regulating the expression of apoptosis-related abilities[27].

3.7 Nephro-protectant

According to Gaikwad et al. (2009), nephroprotective compounds have the ability to reduce the effects of nephrotoxicity. Medicinal plants offer therapeutic powers due to the existence of numerous chemical compounds [28]

According to the experiment conducted by Sheena et al.(2003), methanolic extract of *G.lucidum* reduces nephrotoxicity caused by cisplatin treatment as it restores antioxidant defence systems in the kidneys [29]. Whereas, based on other experimental results Zhong et al. (2015), suggests that GLPP protects the kidneys from RIRI. GLPP therapy decreased IR-induced myeloperoxidase activity in the kidney. The production and accumulation of ROS in renal tissue as a result of RIRI exceeds the capacity of endogenous antioxidases to scavenge them [30]. Another researcher found that in human PTEC produced by HSA, LZ-8 substantially decreases oxidative damage and apoptosis. Various components of the LZ-8 reduced the amount of IL-8 or sICAM-1 produced from HAS-activated PTEC in varying ways, suggesting that Ganoderma components with diverse molecular weights may have different roles and methods in preventing HSA-induced PTEC damage [31].

According to the study conducted by Mahran et.al. (2020), *G.lucidum* inhibits EGFR signaling and autophagy-mediated apoptosis to prevent cisplatin-induced nephrotoxicity. Cisplatin CDDP is a chemotherapeutic agent with a broad spectrum of activity. The drug's nephrotoxicity, the most serious side effect, has been blamed on CDDP.The medicinal mushroom *G.lucidum* possesses antioxidant and anti-inflammatory properties.As a result, it showed potential nephroprotection in rats when exposed to CDDP-induced nephrotoxicity, as well as, potential molecular mechanisms such as EGFR downstream signalling, apoptosis, and autophagy. Nephrotoxicity is indicated by a significant rise in renal markers and oxidative stress. Also, CDDP obtained plenty of inflammatory and apoptotic responses, resulting in increased expressions of HMGB-1, NF-κB, and caspase-3, while GL considerably improved all of these indices. It also suggests the stimulation of the autophagy protein LC3 II is responsible for the suppression of apoptotic pathways, caspase-3, and (TDT) renal expressions in GL-mediated nephroprotection. These findings demonstrate that GL reduced CDDP-induced nephrotoxicity is mediated through antioxidant, anti-inflammatory, and related genes cytotoxicity, as well as that EGFR signalling inhibition may be involved in nephroprotection [32].

3.8 Osteo-protectant

According to Che et al. (2016), osteoporosis is an inherent bone disease that causes loss of bone density and microstructure, resulting in decreased bone strength and an increased risk of fracture. In cell-based and/or animal models, Chinese medicinal herbs have been shown to exhibit osteo protective and associated effects [33].

Ganomycin I(GMI), a meroterpenoid derived from the Vietnamese fungus *G.lucidum*, provides a wide range of health benefits. The influence of GMI on the progress of RANKL-induced osteoclasts in BMM mice using RAW264.7 cells were

analyzed ref. BMMs or RAW264.7 GMI-treated cells are followed by cell function tests, RANKL classification caused by osteoclast, actin-ring formation, and reconstruction function. Western blot analysis is used to assess the impact of GMI on MAPK phosphorylation caused by RANKL and the expression levels of NFATc1 and c-Fos. Western blot analysis and transcript retrieval of quantitative polymerase chain reaction are used to determine the gene expression levels of the osteoclast marker. GMI reduced phosphorylation of ERK, JNK, and p38 MAPKs produced by RANKL, alongwith the coding levels of c-Fos and NFATc1, two key transcription factors for osteoclast formation, at the cellular level. GMI's anti-osteoclastogenic action may enhance our comprehension of the molecular processes underlying the biological and pharmacological activities of *G.lucidum* is a classic anti-osteoporotic medication that suppresses RANKL-mediated MAPKs and NFATc1 signalling pathways [34].

According to a study conducted by Yang et al. (2019), LZ-8 isolated from *G.lucidum* inhibited osteoclast bone resorption through the RANKL pathway or downstream signalling transduction involving ERK, JNK, and p38 MAPKs, leading to the reduction of the levels of c-Fos and NFATc1, two important target genes for osteoclastogenesis [35].

3.9 Cancer Treatment

Cancer, one of the major causes of death across the globe with new chemotherapeutic and chemopreventive agents. Galor et al. (2011) briefly explained the anticancer effect of *G.lucidum* and its bioactive compounds. It can cure breast, lung, liver, and prostate cancer by arresting cell growth at different phases of cell cycle. Breast cancer cell line at G_0/G_1 phase while lung tumor cell at G_1 phase and liver cell at G_1/G_2 phase followed by apoptosis [3]. This is achieved by increasing CD3, CD4, CD8, and NK cells percentage in the body through various extracts of *G.lucidum* [36]. GLPP extracts tend to increase the expression of pro-apoptotic protein Bax and inhibit antiapoptotic protein Bcl-2 in Human Umbilical Cord Vascular Endothelial Cells. Later it suppresses cell cycle at G1 phase followed by apoptosis which was confirmed by Terminal deoxynucleotidyl transferase dUTP Nick End Labeling. While triterpenoids extract induced apoptosis by increasing the annexin-V (apoptosis maker) which downregulates telomeric phase expression in Human Urothelial cells [3]. GLPs from mycelium greatly suppress growth of tumor cells in the liver by increasing Teffs/Tregs ratio and eliminating Treg-induced suppression; Teff proliferation through increasing Interleukin-2 secretion [37]. Lz-8 protein in its recombinant form induces apoptosis by forming clusters of endoplasmic reticula and inducing endoplasmic reticulum stress which leads to increased levels of activate transcription factor 4 and C/EBP homologous protein expression in human gastric cancer cells [38].

3.10 Liver and Gastric Injury

Ganoderic acid, extracted from the fruiting body was reported to have hepatoprotective effect by inhibiting β-glucuronidase effect. Maintaining hepatic Phase I and II enzymes, hepatocellular calcium level, and immunomodulation are other mechanisms involved[39]. A lucidenic acid–rich *G.lucidum* extract inhibits phosphorylation of ERK and protein kinase B signalling in human liver cancer cell line, promoting death via

downregulating down cascade of NF-κB and proto-oncoproteins(c-Jun and c-Fos) activity[40]. Polysaccharides and triterpenoids are active substances that work on the immune system to provide hepatoprotective effects and cure liver damage. By reducing peroxidation of lipids, increasing antioxidant enzymatic activity, and lowering cell death and the immunological inflammatory response, GLPs can protect hepatocytes from Carbon Tetrachloride-induced damage [4].

Ethanol extract from *G.lucidum*(EGL) affects the gastric carcinoma cell line. This is achieved by inhibiting adenocarcinoma gastric cells (AGS) growth by modulating expression of pro-apoptotic protein (BAX and BAD) and activation of caspase which leads to inhibition of PI3K/Akt pathway initiating cytotoxic apoptosis. Entire mechanism can either be an extrinsic or intrinsic pathway. Mitochondrial pathway is activated leading to the release of Smac/Diablo, removing the IAP barrier of caspase activation. In AGS cells, EGL raised the Bax/Bcl-2 ratio and caused mitochondrial malfunction, resulting in apoptosis. Another pathway involves FasL binding to Fas receptor leading to oligomerization and induction of death signaling followed by caspase 8 activation and then translocation of cleaved Bid in mitochondria. Leading to conformational change in BAX and caspase 9 activation, followed by caspase 3 activation leading to apoptosis [41].

3.11 Diabetes Mellitus

Various bioactive compounds of *G.lucidum* possess hypoglycemic properties and help to cure diabetes through various mechanisms. GLP decreases plasma sugar level and increases insulin level resulting in inhibition of glycogenolysis and gluconeogenesis. Fudan-Yueyang-G. lucidum (FYGL) is proteoglycan which inhibits Protein Tyrosine Phosphatase 1B(PTP1B) activity in skeletal muscle cells, resulting in increased blood insulin level [45]. Polypeptides extracted inhibits PTP1B expression reesulting in downregulation of glucose transporter 2 and 4 activity. Triterpenoids show inhibitory enzymatic activity of aldose reductase and α-glucosidase while LZ-8 reduces lymphocytes infiltration by modulating Treffs and increases insulin detecting antibody activity [42]. Triterpenoids have inhibitory effects for aldose reductase and glucosidase, which are linked to glucose metabolism and diabetes consequences. Another mechanism involves scavenging of free radicals, which helps to "neutralise" the detrimental impact of oxidative stress on pancreatic -cells, which is one of the etiological causes of diabetes [43]. F31 is GLP, composed of β-heteropolysaccharide which decreases Fasting Serum Glucose (FSG), Fasting Serum Insulin (FSI) and epididymal fat/BW ratio in the body. F31 in the liver, downregulates mRNA expression of hepatic glucose regulatory enzymes and upregulates p-AMPK/AMPK ratio weheras, in epididymal fat tissues F31 increases mRNA expression of GLUT4 and inhibits FAS, ACC and resistin activity. Thus, it increases GLUT4 protein level and decreases resitin in the body **(Fig.3)** [44]. LZ-8 decreases plasma glucose and reduces lymphocyte infiltration thus, improving insulin detection by insulin in beta cells. Therefore, LZ-8 controls diabetics by immunomodulatory effect [42].

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3.12 Asthma and Chronic Bronchitis

Asthma is a diverse airway disease characterised mostly by allergic inflammation triggered by Th2 cytokines. Excessive synthesis of TNF-α and increased NF-κB expression are linked to steroid-resistant asthma [46]. TNF-α production is inhibited by LPS by the activity of GAC1 compound isolated from *G. lucidum*. LPS activates many intracellular signalling pathways, including NF-κB, activator protein 1, and MAPK while GAC1 causes suppressed the NF-κB signalling pathway by lowering p-IκB levels in total cell protein and p-p65 levels in nuclear protein. It also inhibited the activator protein 1 family, by downregulating c-Jun expression, and the MAPK pathway by suppressing p-ERK and p-JNK expression. As a result, GAC1 regulation of TNF-α and NF-κB is due to reduction of MAPK and activator protein 1 [47]. Another reason for asthma is neutrophilic inflammation which can be cured by glucocorticoids by decreasing the expression of Histone Deacetylase-2, resulting in downregulation of proinflammatory genes via modulating glucocorticoid receptor complex. Enhanced HAT activity and reduced Histone Deacetylase-2 protein levels in lung tissue results in increased activity of NF-κB, and mRNA expression of TNF-α and Granulocyte-macrophage colony-stimulating factor [46].

According to Hifas da Terra, chronic bronchitis is a condition marked by a decrease in expiratory flow during forced expiration, as well as a phlegmy cough and mucus that is generally greenish yellow [61]. Lucidone D(LUC), a ethanol extracted triterpenoid from the fruiting body of G.*lucidum* possesses an anti-inflammatory response which is crucial for the regulation of inflammatory reactions and prevents chronification. LUC decreases the expression of iNOS and Cyclooxygenase-2 proteins by inhibiting the synthesis of inflammatory mediators. Resulting in inhibition of TNF-α and IL-6 production. Thus, it helps in prevention of chronic bronchitis and enormous mucus production [51].

3.13 Cardiovascular Disease

According to the WHO, cardiovascular diseases are heart and blood vessel abnormalities such as coronary heart disease, cerebrovascular disease, rheumatic heart disease, and other ailments that are leading causes of morbidity and death across the globe [60]. *G.lucidum* has antioxidant properties via boosting antioxidant enzymes and suppressing oxidative stress-related enzymes. It also boosts superoxide dismutase, glutathione-S-transferase, glutathione peroxidase, catalase, mitochondrial succinate dehydrogenase, and manganese superoxide dismutase activity while lowering glutathione levels. Thus, it protects cardiovascular diseases through its antioxidant properties via oxidative stress modulation [48]. GLPs inhibits Carbon Tetrachloride--induced free radical lipid peroxidation to lower iNOS and CYP2E1 enzyme activity. In liver tissues, NOS and CYP2E1 activities are inhibited, as well as MDA and IL-1 levels, while serum levels of interleukin-1, IL-18, IL-6, and tumour necrosis factors were depleted [49]. Triterpenoids defend against disrupted flow-induced oxidative stress, by closing the carotid arteries, which causes persistent oxidative stress along with inflammation by inhibiting neointimal thickening and and restore endothelium's thermoresistant by suppressing endothelin-I induction, von

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Willebrand factor, and monocyte chemoattractant protein-I [50]. Lastly, by activating adenosine receptors on the cell surface, nucleotides and nucleosides have cytoprotective effects on the cardiovascular and neurological systems. Antioxidant enzymes are activated when these receptors are activated. This is accomplished by PK-C by phosphorylating substrates or precursors enzymes or intermediates involved in their initiation [43].

3.14 Microbial Infection

Staphylococcus aureus, *Klebsiella pneumoniae*, *Bacillus cereus*, and *Pseudomonas aeruginosa* were all found to be inhibited by ethanol-water extracts of the fruiting body. Terpenes, lectins, polysaccharides, and other antimicrobial substances act on the bacterial cytoplasmic membrane [52]. Gram-negative bacteria have an outer membrane that wraps around their peptidoglycan and restricts diffusion via their lipopolysaccharide coating, resulting in different sensitivities between gramme positive and gramme negative bacteria strains. The LPS layer is critical for selective permeability and serves as an effective barrier against fast entry of different substances [53]. Furthermore, Gram-negative bacteria have enzymes (such as hydrolytic and detoxifying) in their periplasmic region that can inhibit the activity of foreign compounds brought from the surrounding area. Permeability of Gram-positive bacteria is due to the thick, hydrophilic, porous structure which Gram-negative bacteria lack [54].

Recents *in silico* studies show that it even has aspirant molecules for SARS-CoV-2 which includes: colossolactone G, ergosterol, heliantriol F, and velutin with non-toxicity, non-carcinogenicity and non-mutagenicity properties. At HIS41, ASN142, GLN189, and HIS172, colossolactone G interacts with the active site of the SARS-CoV-2 major protease. At the ASP187 residue, ergosterol forms a hydrogen bond with viral protease. Heliantriol F interacts with the active site of SARS-CoV-2 main protease at THR190 and GLN189 whereas velutin interacts with THR190 and MET49 active sites. Colossolactone VIII interacts with the viral protease's active site at HIS41 and GLN189, whereas colossolactone E interacts at residue HIS41. Semicochliodinol A interacts with SER144, MET165, GLY143, CYS145, GLU166 and GLU166 resides. Colonossolactone G and velutin have a GLN189, whereas heliantriol F and velutin have a THR190 residue in common when observed under X-ray structure of 6LU7-N3 [55].

Naturally active polysaccharide extract such as glucans and galactomannan have been shown to increase the synthesis of antiviral lymphokine, monokine, chemokine, interleukin through immunomodulatory effects. Thus, they are suggested to exhibit antiprotease properties against the SARSCoV2 papain-like protease [56]. In in-vitro anti–SARS–CoV-2 assay, numerous constituents of L-fucose–containing polysaccharides isolated and distinguished from G.lucidum were assessed, and among them the researchers ended up finding L-fucose–containing polysaccharides fraction 3 as the best antiviral constituent with no cytotoxicity. Although initial findings from this research cannot be immediately transferred into therapeutic outcomes, they are promising. Whereas, L-fucose–containing polysaccharides fraction 3 is a potential compound that can be further investigated as an anti–SARS–CoV-2 drug [57].

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4. CONCLUSION

Natural substance pharmacotherapy is presently viewed as an alternative uprising future to conventional therapy for a variety of illnesses, particularly chronic disease. Nearly two thousand years ago, the medicinal use of mushrooms was known. They are nature's little pharmaceutical factories, packed with a diverse range of unique ingredients and ripe for discovery. The reishi mushroom, often known as "the mushroom of immortality," or *Ganoderma lucidum* has remarkable health advantages and contains more than 400 bioactive components with a variety of therapeutic properties. In context of the present scenario, bioactive components in edible domesticated and wild mushrooms are still being researched having a list of potential features and qualities, both ancient and new, that give nutraceutical and health advantages. It is a popular medicinal fungus all over the world. Many medical and cosmetic products containing this fungus are available on the market, however they come at a premium cost. Because the cultivation and production of this mushroom is restricted to a few nations, its market value has risen. To identify mode of action and characterise the bioactive components of *G.lucidum*, strategies for improving quality control and preparations are needed. Future research should focus on Ganoderma-based combination treatments with clinical chemotherapeutic medicines to reduce the hostile influence of these substances. In addition, the beneficial aspect and virulency of the product need to be properly investigated.

5. LIST OF ABBREVIATIONS

1. ROS: Reactive oxygen species
2. HPLC-DAD: High-Performance Liquid Chromatography with Diode-Array Detection
3. GLBR: *G.lucidum* grown on germinated Brown Rice
4. GLPs: *Ganoderma lucidum* Polysaccharides
5. GLP: *Ganoderma lucidum* Polypeptide
6. MMPs: Matrix MetalloProteinases
7. DPPH: 2,2-diphenylpicrylhydrazyl radical
8. H_2O_2: Hydrogen Peroxide
9. NK cells: Natural Killer cells
10. TLR-4: Toll-Like Receptor 4
11. PK: Protein Kinase
12. MAPKs: Mitogen Activation Protein Kinase
13. ERK: Extracellular signal Regulated Kinase
14. JNK: c-Jun N-terminal Kinase
15. p38: Mitogen-activated protein kinase
16. PD-1: Programmed cell death Protein 1
17. PDL-1: Programmed death Ligand
18. IC50: Half-maximal inhibitory concentration
19. CREB: cAMP-response element binding protein
20. MITF: Microphthalmia-associated Transcription Factor
21. cAMP: Cyclic Adenosine Monophosphate
22. TNF-α: Tumour Necrosis Factor alpha
23. IFN-γ: Interferon gamma
24. IL-4, IL-1β, IL-6,IL-8: Interleukin-4, Interleukin-1Beta, Interleukin-6, Interleukin-8
25. GAC1: Ganoderic Acid C1
26. GLSO: *Ganoderma lucidum* Spore Oil

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27. LPS: Lipopolysaccharide
28. GLS: *G.lucidum* Sterols
29. iNOS: Inducible Nitric Oxide Synthase
30. NF-κB: Nuclear factor kappa B
31. TDT - Terminal deoxynucleotidyl transferase
32. IκB-α: Inhibitor of NF-κB
33. PPAR-γ: Peroxisome Proliferator Activated Receptor Gamma
34. SREBP-1c: Sterol Regulatory Building Protein 1
35. C/EBP-α: CCAAT/Enhancer-Binding Protein Alpha
36. FAS: Fatty Acid Synthase
37. ACS1: Acyl-CoA Synthetase-1
38. FABP4: Fatty Acid Binding Protein-4
39. FATP1: Fatty Acid Transport Protein-1
40. AMPK: AMP-activated protein kinase
41. ACC: Acetyl-CoA Carboxylase
42. GLPP: *G.lucidum* Polysaccharide Protein
43. RIRI: Renal Ischemia Reperfusion Damage
44. LZ-8: Ling Zhi-8
45. HSA: Human Serum Albumin
46. PTEC: Proximal Tubular Epithelial Cells
47. sICAM-1: Soluble Intercellular Adhesion Molecule 1
48. CDDP: Cis-Diaminedichloroplatinum
49. RANKL: Receptor Activator of Nuclear Factor kappa beta
50. EGFR - Epidermal Growth Factor Receptor
51. c-Fos: Fos proto-oncogene
52. NFATc1: Nuclear factor of activated T-cells
53. Tregs: Regulatory T-cell
54. Teffs: Effector T-cell
55. BAX: BCL2 Associated X
56. BAD:BCL2 associated agonist of cell death
57. GLUT4: Glucose transporter type 4
58. CYP2E1: Cytochrome P450 2E1
59. WHO: World Health Organization
60. SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2

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Table 1: *G. lucidum* major bioactive compound and their common bioactivities

Bioactive Compounds	Bioactivity
Polysaccharides	Anti-tumor, anti-diabetic, cardio-vasular, antioxidant, antimicrobial, anti-angiogenesis
Triterpenoids	Anti-tumor, cytotoxic, inhibits proliferation, antimicrobial, anti-diabetic, anti-inflammatory, anti-oxidant
Proteins/Polyp-eptides	Immunomodulatory, antitumour
Steroids	Hepatoprotectant, anti-tumor, anti-viral, anti-inflammatory, neuroprotectant and balance cholesterol level
Phenols	Antioxidant, antiproliferative

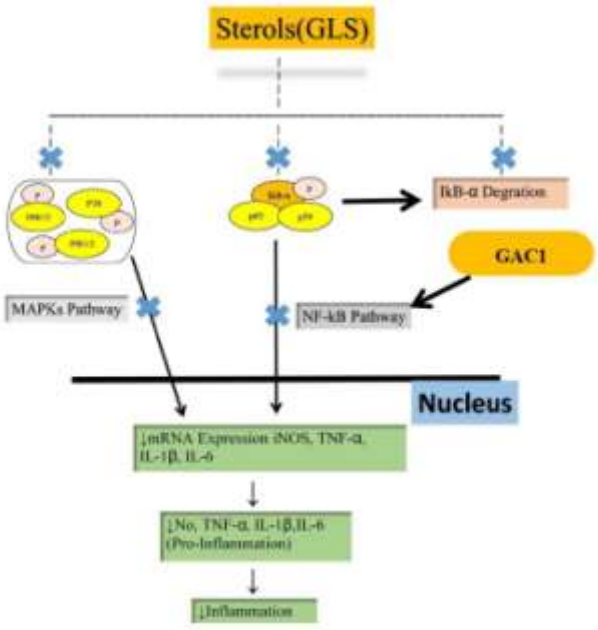

Fig.1. Anti-Inflammatory Effect of *G. lucidum*

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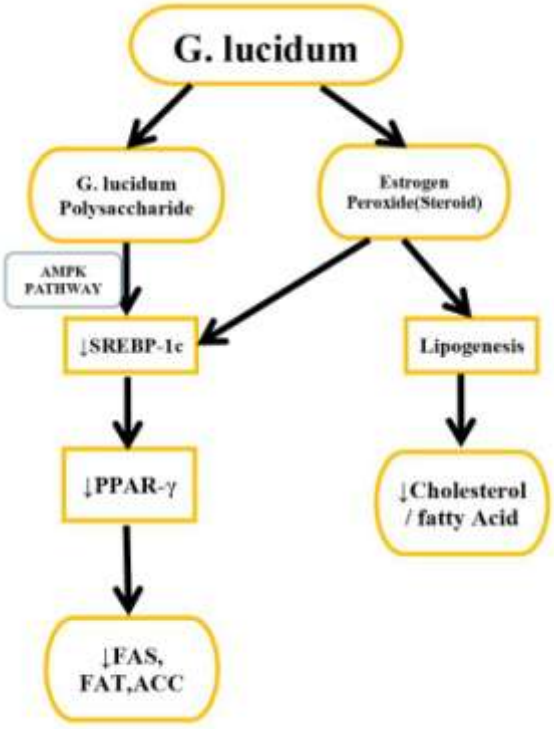

Fig.2. Anti-Obesity Effect of *G.lucidum*

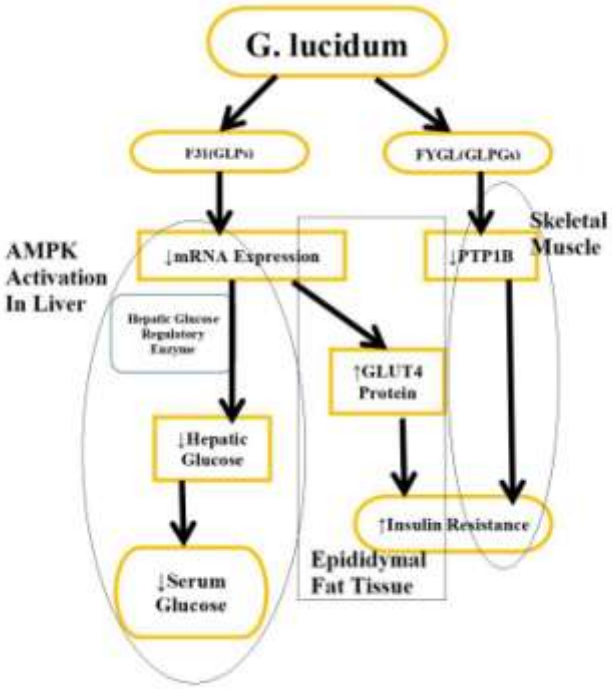

Fig.3 Anti-Diabetic Effect of *G.lucidum*

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