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A Comprehensive Review on the Cultivation and Pharmaceutical Applications of the Ganoderma lucidum

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Abstract: Traditional cultivation of Ganoderma lucidum involved growing it on logs, but recent developments have optimized production by using substrates such as sawdust, rice, and even agricultural waste. Advances in controlled indoor farming have been applied to cultivate Ganoderma lucidum, enabling better control over environmental variables such as temperature, humidity, and light, which are crucial for maximizing the growth and quality of the mushrooms. Ganoderma lucidum is renowned for its medicinal properties and is rich in a variety of bioactive compounds, including polysaccharides, triterpenoids, β-glucans, glycoproteins, steroids, amino acids, lactones, and fatty acids, all of which contribute to its therapeutic effects. Present study has revealed that bioactive compounds produced from Ganoderma lucidum has many pharmaceutical applications such as immunomodulatory, anti-aging, anti-cancer, antimicrobial, anti-diabetic, antioxidant, anti-inflammatory, and cardioprotective. To harness these beneficial compounds, several extraction techniques have been developed. This review explores various cultivation methods of Ganoderma lucidum, highlights the significance of its bioactive compounds.

Key words: Ganoderma lucidum, bioactive compounds, Pharmacological properties, Cultivation methods

1. Introduction

Ganoderma a genus of Polypore fungi belongs to family Ganodermaceae[1].The Ganoderma genus was extensively used all around the world but historically it's importance was seen in Asian countries for its medicinal properties[2].There are many species of Ganoderma such as Ganoderma atrum, G. australe, G. carnosum, G. colossus,G. curtisii, G. formosanum, G. leucocontextum, G. neo-japonicum, G. praelongum, G. pfeifferi, G. resinaceum and G. sinense but most important is

Ganoderma lucidum, also known as Reishi in Japanese or Lingzhi in Chinese because they contain many bioactive compounds that are currently used in pharmaceutical production[3].They usually grow on rotting, dead wood of deciduous and coniferous species[4]. Distributed throughout China, Japan, South Korea and other south east Asian countries. These sites have a long history of using Ganoderma lucidum, which is often used in traditional medicine. Bioactive compounds include fatty acids, steroids, triterpenoids, polysaccharides, proteins, amino acids, alkaloids, nucleosides, lactones and enzymes. These bioactive substances play an important role in strengthening immunity, fighting tumors, anti-aging, preventing liver aging and lowering blood lipids[5].[6]K. Sulkowska-Ziaja et al emphasize the importance of contemporary culture techniques for extracting medicinal components from Ganoderma species. Ganoderma species are less abundant in nature. As the global market for Ganoderma lucidum fruiting bodies and mycelial biomass expands, plant breeding becomes increasingly significant. For decades, the successful use of logs, packing wood or straw substrates in agriculture has been known for Ganoderma lucidum production, particularly in China. Biotechnological cultivation using bioreactors Solid matrix cultures, also known as submerged liquid matrix cultures, have been established and employed on a small and pilot scale[7]. This varies on location and cultivation circumstances.

Ganoderma lucidum has a long history in China, where people utilized it to increase lifespan and vitality[8]. In addition to traditional Chinese medicine and herbal medicine, Ganoderma lucidum is said to enhance energy and have anti-inflammatory and hepatoprotective pharmacological characteristics[9]. Aside from that, it was employed as a material for functional foods in everyday living, including tea, soup, yogurt, and wine.With the increasing worldwide demand for Ganoderma lucidum, products derived from fruiting bodies, mycelia, and spores are sold as tea, coffee, drinks, spore oil, and dietary supplements, as well as food and medical supplements[10]. Aside from the pharmacological benefits of G. lucidum bioactive components, it is vital to extract them utilizing proper extraction techniques. The bioactive ingredients of medicinal and culinary mushrooms can be extracted using a variety of techniques, the most commonly used being hot-water extraction, ethanol/water extraction, supercritical fluid extraction, ultrasound assisted extraction, microwave assisted extraction, and pressurized liquid extraction[11].

2. Techniques for cultivating Ganoderma lucidum

Variety of methods are utilized for the cultivation of Ganoderma lucidum. Depending upon the requirement cultivation methods were different wood log cultivation and substitute or saw dust cultivation for producing fruiting bodies whereas for the production of mycelia solid state cultivation and submerged cultivation in bioreactor were practiced.

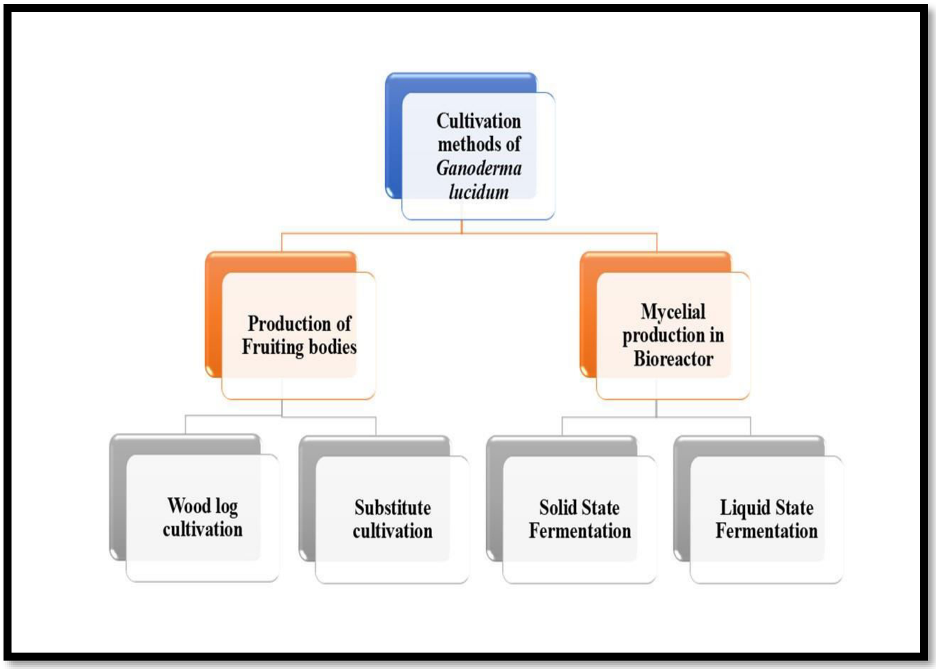

Fig 1. Cultivation methods for Ganoderma lucidum production

2.1. Artificial Cultivation

In order to restore Ganoderma lucidum habitat and permit high-quality production artificial cultivation methods are used. Wood log cultivation uses hardwoods including oak, maple, beech, and birch[12]. Other techniques that employ various substrates, such as synthetic materials or by-products in substitute cultivation and use of bioreactor in case of solid-state fermentation and liquid fermentation. Better growth control, higher yields, and the capacity to recover and reuse substrates are just a few of the benefits that alternative cultivation techniques offer over traditional techniques[13].

2.1.1. Production of fruiting bodies

Ganoderma lucidum fruiting bodies are enormous, kidney or irregular in shape depending on the variety, elongated, with thick edges, dark brown to red in colour, shiny exterior, and woody texture. The morphology of the mushrooms varies depending on the environmental conditions[14]. To date, the two most frequent ways for producing fruiting bodies have been wood-log cultivation and substitute cultivation.

Wood-log cultivation

There are two different approaches used in this: long unsterilized logs and short sterilized logs[15]. The long unsterilized log method took a lot longer to produce full fruiting bodies on the substrate, requiring two to three years of incubation where the latter is a new trend of employing shorter engines that began in the late 1980s.

Due to its higher demand producers have grown short-season crops in China, Japan, the US, and other nations. Quick financial turnaround, excellent yields, and short sowing times. Because of the brief cultivation period, it only takes four to five months for the mycelium to bloom and the fruit can be harvested in the same year.

Substitute cultivation

Another method for the production of Ganoderma lucidum is a substitute cultivation technique that uses sawdust, cotton seed husks, or agricultural byproducts as a substrate. The core components in such a cultivation method are corncobs, sawdust, husk, as well as bagasse. Substrate type and its composition play a crucial role in promoting mycelial growth, fruiting body production, and concentration of bioactive compounds in the Ganoderma species. Some additional components were also added to the substrate, like wheat bran, rice bran, corn flour and some other substrates[16]. Cultivation of Ganoderma lucidum under substitute cultivation was carried either in polypropylene bags or in bottles in which these substrates are filled. The bag cultivation method is quite more accessible than the bottle cultivation because of their easy transportation and handling[17].

2.1.2. Mycelial production

Through modern fermentation methods faster and more production of mycelial biomass can be achieved in lesser time with minor chances of contamination. This includes solid state fermentation and liquid state fermentation techniques that are run into a bioreactor through series of process[18]. Solid state fermentation is a cost-effective method than liquid state fermentation because of the usage of agricultural wastes and other solid organic waste as a substrate source for the production of various enzymes and chemicals. The optimum conditions that are required for effective production are source of carbon and nitrogen, dissolved oxygen, optimum pH, temperature, relative humidity and other additional components. But the type of substrate used in solid state fermentation and liquid state fermentation are different as per the requirements.

Solid state fermentation (SSF)

This method involves growing microorganisms on a solid substrate's surface without the need for freely flowing water. In terms of low energy consumption, nutrient medium concentration, and achieving high volumetric conductivity in a smaller bioreactor, this technique is more successful than liquid-state fermentation[19]. In solid-state fermentation, we can generate concentrated products using less expensive substrates such agricultural wastes and agro-industrial leftovers. In the SSF technique, a number of steps are involved, including strain selection, seed preparation, substrate preparation and sterilization, aseptic inoculation, process optimization, fermentation harvesting, and final purification. The crucial elements that come into this technique are temperature, pH, moisture content, aeration and bed properties.

Liquid state fermentation (LSF)

The procedure of submerging microorganisms in a liquid state medium in which they are accompanied by nutrients and other necessary elements[20]. It is a quick and affordable substitute process for effectively producing polysaccharides and ganoderic acids from G. lucidum. Carbon sources (like glucose, sucrose, fructose, etc.) and nitrogen sources (like organic nitrogen) are crucial elements needed for submerged fermentation. The initial pH value, oxygen delivery, temperature, inoculation density management, fungal elicitors and oxygen availability are other critical parameters for its cultivation[21]. Generally, Lingzhi fermentation was carried out between 25℃- 35℃, with a majority of the fermentation occurring at 30℃[22]. The five steps of LSF are as follows: choosing the strain, preparing the culture maintenance medium for each culture phase, inoculation, cultivating the chosen strain in a fermenter or seedling tank and harvesting the mycelia or isolating the final products. To promote quicker mycelial growth, some magnesium sulphate and potassium dihydrogen phosphate are also added to the media. Any method of cultivating Ganoderma lucidum requires a number of processes which includes: Substratum production, substrate preparation, including substrate formulations, spawn preparation, inoculation, spawn running at 26±1°C in darkness, incubation; and fruiting body growth management. These are the essential elements needed to produce Ganoderma lucidum.

3. Recent Advances in Cultivation of Ganoderma lucidum

With the growing global demand for G. lucidum, cultivation methods have advanced to reach maximum yield in less time. This can be accomplished by changing, manipulating, and fusing the protoplasts of different species to produce the desired result in a shorter amount of time. The following are the sophisticated ways used to cultivate Ganoderma lucidum.

3.1. Genetic Engineering

It is the procedure by which the intended outcomes that cannot be acquired by natural mating or recombination or reproduction are produced by modifying the genetic material of plants, animals, microbes, cells, and other biological units. The first transformation was performed in 1993 on the edible basidiomycete Agaricus bisporus[23]. In general, the process of genetic engineering entails a number of steps, including the following: Choosing donor strains, separatinggenes, reconstructing genes in vitro, transferring genes into the recipient cell, reproducing and expressing recombinant DNA and choosing a new individual. Genetic and metabolic engineering improved Lingzhi production and made it useful for additional research. Protoplast-mediated transformation (PMT), Agrobacterium tumefaciens-mediated transformation (ATMT), electron transfer, biolistic transformation, restriction enzyme-mediated transformation (REMI), and lithium acetate are the six types of transformation techniques that have been used for filamentous fungi. Additionally, all of these techniques are effectively used to the breeding of Lingzhi[24].

3.2. Breeding through Mutation

In contrast, the Ganoderma species are not the subject of selective breeding or cross-breeding, which are reserved for edible mushrooms, plants, animals, and microbes. An innovative and successful application of artificial selection is mutation breeding. The following actions are necessary for this: Choosing the starting strain, preparing the liquid for spore or protoplast suspension, viable count and mutagenizing, spreading the plate for cultivation, selecting the desired strains and inoculation, first screening, slant culture, re-screening and selecting the best strains[25]. This technique is used to enhance the quality, yield, and resilience to high temperatures of the Lingzhi strains. According to previous studies done by the researchers, physical or chemical agents are typically used to cause mutations. As an example of such technique, scientists Zhang et al. have generated a high-temperature resistance spore strain of G. lucidum by inducing UV radiation mutation technology[26].

3.3. Protoplast Fusion Breeding

It is a method of breeding that modifies the fungi's genetic makeup. This technique was first used in several Asian nations for edible mushrooms, including basidiomycetes [27]. This method has evolved throughout time and is now utilized for the preparation and isolation of Lingzhi protoplasts as well as protoplast fusion. By fusing intrageneric protoplast, it has been frequently employed in breeding novel strains and protoplasts that are intergeneric[28]. A common cell fusion engineering breeding approach consists of the following steps: Selecting the parent strain then confirming its genetic markers after this detaching the protoplast from the parent strain, cultivating and renewing the protoplast then in the next step fusion of protoplast and so on[29].

4. Ganoderma lucidumbioactivecompounds and its pharmaceutical applications

Due to its widespread usage in traditional medicine to cure a variety of illnesses, including hepatitis, gastric ulcers, hypertension, bronchitis, and hypercholesterolemia, Ganoderma species are quite popular. G. lucidum also has the ability to prevent DNA strand breaks brought on by hydroxyl radicals or UV light. The majority of research on the significant fungus Ganoderma lucidum has concentrated on its advantages and application in conventional medicine[30].

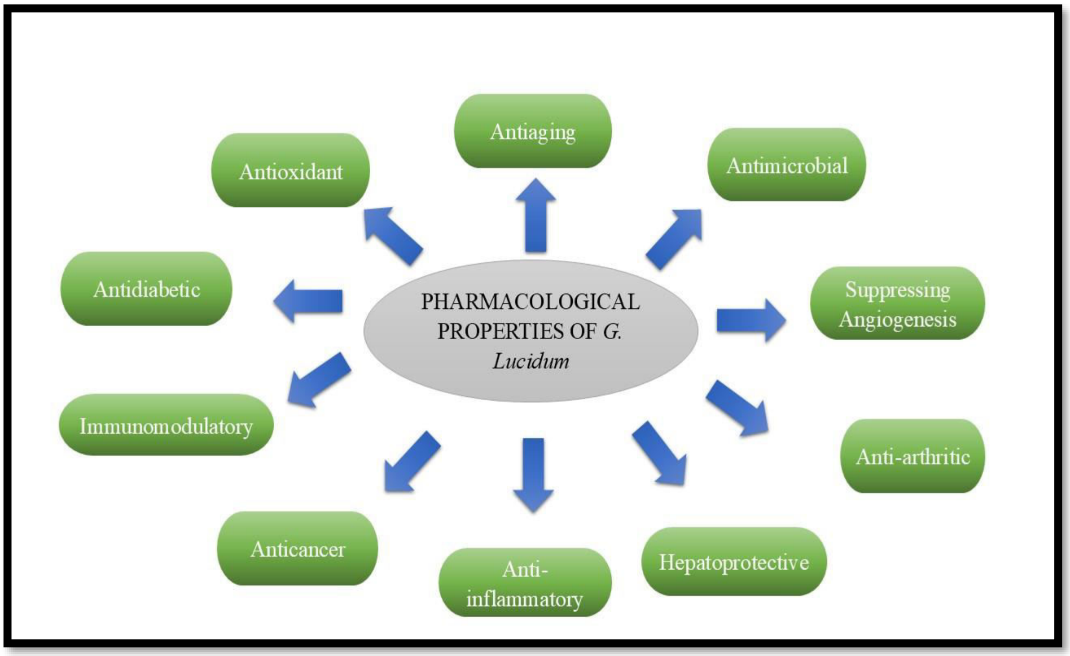

Figure2. Various pharmaceutical applications of the bioactive components found in Ganodermalucidum

4.1. Major Bioactive components found in Ganoderma lucidum

The pharmacologically active components of Ganoderma lucidum include mannitol, amino acids, polysaccharides, triterpenoids, steroids, beta-glucans, phenols, glycoproteins, flavonoids, alkaloids, oligosaccharides, and vitamins B1, B2, B6, choline, and inositol. Nucleotides and their derivatives are also present in Ganoderma lucidum. 90% of G. lucidum is made up of water, with the remaining dry matter consisting of minerals (Ca, P, K, Mg, Cu, Fe, Zn, and Se), 2%-8% fat, 3%-28% carbohydrate, 3%-32% fiber, and 10–40% proteins[31].The list of all the bioactive components of Ganoderma lucidum along with itspharmacological effects are mentioned in the Table1.

Table 1. List of key bioactive compounds along with their pharmacological effects.

S.No.	Pharmaceutical Applications	Key Bioactive compounds found in G. lucidum	References
1.	Anti-cancer	Polysaccharides, Ganoderic acids, Triterpenoids, Peptidoglycans, LZ-8 protein	32
2.	Anti-oxidant	Polysaccharides, Triterpenes, Phenolic component, polysaccharide-peptide complex and polysaccharide extracts	33 34
3.	Anti-diabetic	Triterpenoids, polysaccharides and proteoglycans	35
4.	Anti-angiogenic	Glycopeptides, peptidoglycans, polysaccharides, triterpenoids, polysaccharides	36
5.	Anti-inflammatory	Ganoderic acids T-Q and lucideinic acids A, D2, E2 and P	37
6.	Anti-tumor	LZ-8 protein, Triterpenoids, polysaccharides, peptidoglycans	38 39
7.	Anti-microbial	Polysaccharides, triterpenoids (ganoderic acids, Ganoderic acid A and Ganoderic acid B, lucidumol B), triterpenes, ganomycein and methanolic extracts	40 41
8.	Anti-viral	Ganoderiol F, ganoderma nontriol against HIV-1, Ganoderic acid derivatives against H5N1 and H1N1 influenza, Triterpenoids against Enterovirus 71	42 43
9.	Immunomodulatory	LZ-8 protein, ganodermin A, glycoproteins, peptidoglycans, ribonucleases, lectin	44

10.	Cardiovascular problems	Polysaccharides (Ganopoly)	45

4.2. Pharmaceutical Applications of the Bioactive Components

Ganoderma species are commonly utilized as functional foods to treat a variety of immunological illnesses. The bioactive components of this mushroom have a wide range of health benefits and can be used to treat a variety of conditions such as hepatopathy, nephritis, hypertension, hyperlipidemia, arthritis, neurasthenia, insomnia, bronchitis, asthma, gastric ulcers, atherosclerosis, leukopenia, diabetes, anorexia and cancer[46]. G. lucidum's secondary metabolites are predominantly triterpenoids. This mushroom's fruiting bodies, spores, and mycelia contain triterpenoids, which account for many of its therapeutic advantages.

4.2.1 Antimicrobial properties

The antibacterial qualities of G. lucidum are mostly attributed to its polysaccharides[47]. G. lucidum has antibiotic components that can stop both gram-positive and gram-negative bacteria from growing. When combined with the four antibiotics—cefazolin, ampicillin, oxytetracyline, and chloramphenicol—it exhibits some synergistic effects[48].

4.2.2 Antioxidant properties

G. lucidum, which has antioxidant qualities and is composed of polysaccharides, triterpenes, and phenolic components[49]. Following consumption, these antioxidants are rapidly absorbed and increase the activity in human plasma. In addition to increasing interferon production in human blood cells, the glucans found in G. lucidum exhibit the ability to scavenge free radicals and inhibit lipid peroxidation[50].

4.2.3 Anticancer properties

Beta-glucans, a group of polysaccharides, have anticancer properties. G. lucidum polysaccharide, which is thought to be the primary mechanism of antitumor action, mediates the activation of immune function[51]. The polysaccharides of G. lucidum also promoted dendritic cell maturation and activity, cytokine generation, cytotoxic T lymphocyte, and cytokine-induced killer cell (CIK) function[52]. According to new research, G. lucidum also inhibits the expression of urokinase-type plasminogen activator (uPA) and urokinase-type plasminogen activator receptor (uPAR) in cancer cells, induces the immune response in host cells, induces Phase 2 metabolizing enzymes, induces cell differentiation, and inhibits angiogenesis and direct cytotoxicity[53].

4.2.4 Effects on B lymphocytes and T lymphocytes

G. lucidum, which contains many pharmaceutical ingredients and is crucial to the growth and maturation of NK cells, splenic mononuclear cells, dendritic cells, and B and T lymphocytes[54]. The fruiting body of G. lucidum contains bioactive chemicals that have been found to induce B lymphocyte activation, proliferation, and differentiation. G. lucidum extracts effectively activate T cells by triggering the release of a variety of cytokines. The crude water extract of G. lucidum was found to support the induction of cytokine expression, including interleukin-10, in an in-vitro research. In human peripheral blood mononuclear (PBM) cells, an in vitro study revealed that the crude water extract of G. lucidum stimulates the induction of expression of cytokines, such as interleukin-10 (IL-10), interleukin-1b, interleukin-6 (IL-6), tumour necrosis factor (TNF)-a, and interleukin-2 (IL-2)[55].

4.2.5 Anti-inflammatory properties

According to the previous studies, phenolic compounds and triterpenes have anti-inflammatory qualities that can trigger the expression of different inflammatory genes, including TNF-α, iNOS, COX-2, and IL-6[56].The immunomodulatory polysaccharide beta-glucan of G. lucidum interacts with the receptor dectin-1. According to the scientists, this c-type lectin can work with TLR2 to stimulate innate immune responses in antigen-presenting cells.

4.2.6 Antidiabetic properties

By controlling the expression of several important enzymes in the glucose metabolism pathway, including hepatic glucokinase, phosphofructokinase (PFK), glucose-6-phosphate dehydrogenase, fructose-1, 6-bisphosphatase, phosphoenolpyruvate carboxykinase (PEPCK), and glucose-6-phosphatase (G6Pase), respectively, polysaccharides found in G. lucidum have the ability to inhibit hyperglycemia, which is found to be higher in individuals with diabetes and obesity[57].

4.2.7 Hepatoprotective properties

The extensive hepatoprotective capabilities of G. lucidum are demonstrated by the fruiting bodies, which have been used to treat liver problems[58]. According to previous studies, G. lucidum consisting oftriterpenoids show a protective effect against acute hepatitis caused by carbon tetrachloride. Research conducted both in vitro and in vivo has revealed that G. lucidum having strong antioxidant and radical scavenging properties offer hepatoprotection[59]. Triterpenes in G. lucidum are responsible for its hepatoprotective effects; they can inhibit the activation of hepatic stellate cells, hepatoprotective factor β-receptor activation, and the proliferation event in hepatic fibrosis[60].

4.2.8 Cardioprotective properties

Certain research studies have indicated that during clinical trials G. lucidum extracts lower blood cholesterol levels and stop rats from developing atherosclerosis.G. lucidum significantly affects the cardiovascular system, lowering blood pressure, triglyceride levels, and cholesterol levels. According to previous studies, polysaccharides and peptide complexes have a protective effect on human blood vessel endothelial cells. Additionally, there is a tendency for the G. lucidum treatment to increase glutathione (GSH), a cofactor for antioxidant enzymes like catalase (CAT), superoxide dismutase (SOD), Glutathione peroxidase (GPx), and Glutathione stransferase (GST). This suggests that antioxidant defense plays a significant role in cardio protection[61].

4.2.9 Anti-arthritic properties

It has been demonstrated that G. lucidum inhibits the synthesis of monocyte chemoattractant protein (MCP)-1, IL-1β or lipopolysaccharides-induced IL-8, and rheumatoid arthritis synovial fibroblasts (RASF). G. lucidum having immunomodulatory and anti-inflammatory properties may be used to treat autoimmune diseases including rheumatoid arthritis[62].

4.2.10 Suppressing the angiogenesis

Angiogenesis is the physiological process that creates and enhances preexisting blood vessels to develop new ones. It has been discovered that G. lucidum possesses anti-angiogenic qualities, inhibits the synthesis of nitric oxide (NO), and stimulates angiogenesis mediators that are overexpressed in malignancies[63]. Human umbilical cord vascular endothelial cells' (HUVEC) ability to proliferate is inhibited by G. lucidum polysaccharide peptide (Gl-PP) in a dose-dependent manner. When a high dose of Gl-PP is administered for 18 hours under hypoxic conditions, the amount of released vascular endothelial growth factor led to a decrease in lung cancer cells in humans according to previous research and trials[64].

Conclusion

Recent advancements in the cultivation of Ganoderma lucidum have significantly improved both the efficiency and scale of production, making this medicinal mushroom more accessible for pharmaceutical applications. The medicinal mushroom Ganoderma lucidum has a number of bioactive ingredients that have positive pharmacological effects on humans. It has been utilized for a longer period of time to prolong life and preserve youthful energy and vitality. Many dietary supplements have been made from Ganoderma. Additionally, because of its numerous pharmacological properties such as anti-inflammatory, anti-cancer, antdiabetic, antioxidative, antibacterial, and so forth it has been utilized in Asian nations since ancient times. According to current study, G. lucidum is a common constituent in many goods and is also utilized to make nutraceuticals. We are able to extract the bioactive compounds from both edible and medicinal mushrooms using various extraction procedures. The ongoing research into the extraction and purification of these bioactive compounds promises to further elevate the therapeutic potential of Ganoderma lucidum in treating a wide range of health conditions, from cancer and liver disease to chronic inflammation and metabolic disorders. Further after reviewing previous findings, we have found that India is least growing Ganoderma, we suggest researchers to focus of growing Ganoderma at large scale in India as it has numerous applications.

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