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# The Therapeutic Effects of *Ganoderma lucidum* on Cancer and Immune System Such as Anti-Tumor, Anti-Metastatic, Antioxidant, Anti-Angiogenic, Anti-Inflammatory, and Immuno-Modulating

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**Abstract**

*Ganoderma lucidum* is a fungus pertaining to the Ganodermataceae family, also known as Lingzhi in China and Reishi in Japan. The *G. lucidum* has been utilized to treat several illnesses, ameliorate health and longevity and it also affects the quality of life. Researches have demonstrated advantageous impacts of *G. lucidum* as an adjuvant treatment for cancer patients without toxicity. *G. lucidum* comprises different compounds, which predominantly contain, polysaccharides, triterpenoids, steroids, nucleotides, peptides, fatty acids, which augment the immune system and have effects such as anti-tumor, anti-metastatic, antioxidant, anti-angiogenic, anti-inflammatory. *G. lucidum* polysaccharides is the essential ingredient in the water dissolved extractives of this mushroom. Polysaccharides and triterpenoids are important because of their anti-cancer properties. Many research has been done on the therapeutic effects and identification of the chemical constituents of this valuable medicinal fungus in the world. In this article, we peruse the consequences of the researchers on the therapeutic effects of this fungus on cancer and introduce compounds reported from it. *G. lucidum* contains compounds, that play a significant role in the prophylaxis and treatment of cancer, activate our immune system for many defense functions**.** Research indicates that *G. lucidum* has a high capacity for acceptance as healthy dietary complement for patient cancer therapy. The reason for some lack of preparation of Ganoderma as a

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drug may be due to problems with production. Further studies are needed to further illuminate the mechanisms of the modulatory impacts of the immune system also the direct anticancer impacts.

## Introduction

Fungi have a long history of more than four thousand years of drug use in the Far East [1-5]. A relatively considerable number of fungi are utilized because of their extraordinary and life-enhancing qualities [5]. Principally in Asian countries, various kinds of fungi grow in nature and are employed as disinfectants. There is evidence of the application of different fungal extracts due to the antibacterial, anti-inflammatory, antiviral, anti-cancer, anti-diabetic, and anti-cancer features [6]. One of the most popular therapeutic fungi is *G. Lucidum* with a bright appearance [1,7]. It has been reported in Asian populations because of its unusual therapeutic properties [5]. *G. lucidum* is used by the Far East countries for pharmaceutical purposes in various ways. While this fungus is not poisonous, it's consumption is quite challenging. This fungus is so hard that it cannot be eaten raw, and its ingredients are unbelievably bitter [1, 5, 8]. It is used in powder form. *G. lucidum* is produced in several commercial goods, namely powders, supplements, and tea [5, 8]. In herbal medicine, *G. lucidum* is prescribed in various ways [1, 5]. These methods range from injecting powders to drinking soups, syrups, teas, capsules, etc. [1]. *G. lucidum* is a fungus pertaining to the Ganodermataceae family, also known as Lingzhi in China and Reishi in Japan. It is regularly referred to as "mushroom of immortality ", "mushroom of spiritual potency", and "spirit plant" [9, 10]. Having been used for almost 2,000 years in Chinese medicine, the fungus has a glossy surface, and a deep red color. Its title is originated from the word "lucidus", meaning bright [11, 12]. These fungi are usually utilized in Chinese medicine with the idea that they are useful in reinforcing energy, stimulating the immune system, and lengthening life [13]. *G. lucidum* has been accepted as a herbal Chinese drug for health promotion, Continuation of youth, and vivacity for thousands of years [14-17] due to its medicinal qualities, including improving vital energy and boosting cardio function. *G. lucidum* is indexed in American Herbal Pharmacopoeia and Chinese Pharmacopoeia. According to Chinese Pharmacopoeia, *G. lucidum* alleviates cough and asthma. Therefore, it is prescribed for the therapy of dizziness, sleeplessness, palpitations [18]. New medical studies have revealed that this fungus covers a broad scope of biological activities, namely anti-inflammatory, antioxidant, anti-ulcer, anti-cancer, and immune system support [19-24]. *G. lucidum* has been applied to cure a diversity of chronic diseases, namely hypertension, bronchitis, diabetes, and cancer [17-25]. It has been particularly recognized as an alternative adjunctive remedy to cancer and diabetes [22-26]. Ganoderma oral liquid substantially ameliorated memory and learning in a sleep deprived rat [27].

## General Characteristics of *Ganoderma lucidum*

*Ganoderma lucidum* Karst species belong to the Basidiomycota branch, Aphyllophorales category, family Ganodermataceae and Ganoderma genus [28]. This species has a bean-shaped basidiocarp, usually with a lateral base. The upper level of the basidiocarp has concentric circles and is detected in orange, red, purple, black-brown with a white or yellow to reddish-brown edge. The lower surface of the basidiocarp holds 4 to 5 round pores per mm. This class regularly grows at the bottom of trees or in their lower holes and comes in two forms: saprophyte and plant parasite [29].

## Ganoderma lucidum ingredients

The fruiting body, mycelium, and spore of *G. lucidum* include 400 active substances [30-33]. *G. lucidum* carries a broad range of compounds, such as glycoproteins, polysaccharides, triterpenoids, meroterpenoids, sesquiterpenoids, steroids, alkaloids, benzopyran derivatives, and benzoic acid derivatives, [34, 35] and some minerals, namely potassium, calcium, phosphorus, magnesium, selenium, iron, and zinc [17]. Melanin is another constituent of this fungus. Melanin has antioxidant activity, reinforces the immune system, and protects against radiation [36]. Polysaccharides and triterpenes are the chief constituents of



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this fungus. The anticancer properties of *G. lucidum* are primarily attributed to its polysaccharides and triterpenes [17, 37, 38]. *G. lucidum* polysaccharides belong to an essential group of physiologically active compounds, and they are commonly denominated biological answer regulators [39]. *G. lucidum* polysaccharides consist of (1→ 3) ,(1→6) α/β glucans, glycoproteins, and water-dissolved heteropolysaccharides [35]. *G. lucidum* polysaccharides suppress anticancer activities by restraining tumor increase and metastasis as well as strengthen the immune function of patients through different mechanisms, such as anti-metastatic, anti-angiogenic, anti-inflammatory, antioxidant and immune-modulating impacts [40-42]. The only ramified glucan consisting of (3 → 1), (4 → 1), (6 → 1) -β-D grafts have been recognized with new antitumor activity against tumor metastases [43-45]. Ganoderma β-D-glucans have been appeared to have higher antitumor activity than commercial β-D-glucans [43]. However, the antitumor activity of β-D-glucans is predominantly observed in the graft (3 → 1) of the branched chain attached to type 3 complement receptor and begins a set of molecular pathways such as NF-kB mitogen enabled protein kinase, and protein kinase C. This, in turn, activates the host immune answer to immune cell proliferation and cytokine production [46, 47]. Chitin polysaccharides detected in the cell wall of fungi possess therapeutic qualities. Such that it plays a significant role in adjusting the liver, intestine, and kidney function [36]. The triterpenoids in *G. lucidum* hold antiviral, anti-inflation, detoxifying [48], inhibiting platelet aggregation [49], inhibiting cholesterol synthesis, and its uptake [50] properties.

## Anti-cancer effects of *G. lucidum* Cytotoxic, Anti-Tumor and Anti-Metastatic Effects

Research has revealed that various extracts of *G. lucidum* restrain tumor increase by activating the immune response and stimulating cytokine production [51]. Besides, these substances can boost interleukin-2 production and help activate the immune system [52]. Zhang & Lin [53] have attributed *G. lucidum*`s antitumor activity to the programmed death provoked by TFN-α released from macrophages and TFN-γ released by T lymphocytes. A study by Ooi et al. [54] showed that polysaccharides isolated from Ganoderma fungi by boiling water, boost the immunity system and suppress sarcoma 180 tumors in mice. The impact of *G. Lucidum* on cancer is due to its glucan and triterpenes. Beta glucans seem to activate the immune system. Besides, triterpenes are believed to have cytotoxic impacts versus different cancer cells [15, 55-57]. Triterpenes are believed to lessen tumor attacks by decreasing matrix metalloproteinases expression and restraining tumor metastasis by restricting the binding to the endothelium [58, 59]. *G. Lucidum*, which possesses an antiproliferative effect [60], shows the induction of apoptosis cytotoxicity effect by stopping the tumor cell cycle [61-64]. Chen and co-workers investigated the impact of Ganoderic Acid Me on tumor attacks. The consequences confirm the anti-metastatic impacts of ganoderic acid Me, which has been proved by inhibiting cell adhesion and cellular mobility also containing matrix metalloproteinase-2 and Matrix metallopeptidase -9 gene expression. Therefore, ganoderic acid ME has the potential of being an assuring new anti-metastatic factor [58]. Ganoderic acid DM is a lanostane-kind triterpene that isolates from *G. lucidum* and exhibits cytotoxicity in cancer cells [65, 66]. Hsu and co-workers perused the effect of lucidenic acids, A, B, C and N inhibition of cell growth and apoptosis in human leukemia cells HL-60. They noticed that lucidenic acid B reduced cell viability in some tumor cell divisions and noticeably increased apoptosis among HL-60 cells [67]. Gao and partners studied the antitumor impacts of Ganoderma alcohol in vivo, ganoderiol F, which displayed the strongest results in cytotoxicity test. ganoderiol F was injected into mice having Lewis lung carcinoma cells, which significantly repressed the tumor growth [68]. Jiang and partners revealed that ganodermanontriol, an alcohol present in Ganoderma, blocks the growth and progress of invasive ,metastatic, and therapeutic resistant human breast cancer cells [69]. *G. lucidum* polysaccharides restrain cell adhesion in MT-1 cancer cells by reducing β1 integrin expression [70]. *G. lucidum* polysaccharides inhibit 4-aminobiphenyl- arising migration by inducing actin polymerization and the creation of focal adhesion complexes in the human bladder cancer cell [71]. Microsporum Ganoderma restrains Epidermal growth factor (EGF)-arising phosphorylation and activation of epidermal growth factor receptor (EGFR) and AKT pathway kinases. Ganoderma microsporum restrained the EGF-arising depolymerization [72]. researches has demonstrated



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that polysaccharides separated from *G. lucidum* contain higher antitumor activity by composition with cyclophosphamide in sarcoma 180-bearing mice [73] and GLP could ameliorate chemotherapy-linked tiredness through regulation oxidative stress and diminution of nephrotoxicity, these consequences illustrated the synergistic impacts of GLP on antitumor impact with cisplatin [74]. A composition of *G. lucidum* polysaccharides and triterpenoids from this mushroom provided a multi-compound medicine with cytotoxic activities and modulated the immune system activities, augmenting release of cytokines and activating the immune cells [75]. Li and co-workers found that triterpenoids extracted from the broken spores with ethanol could adjust the expression of important genes and key proteins, resulting to cell cycle restrain during G0/G1 phase, stimulating programed cell death , decreasing Matrix metalloproteinase-1 and Matrix metalloproteinase-2,stimulating expression of E-cadherin, which then caused HCT116 cells to be unable of migrating and proliferating, and accordingly had a remedial influence on colon cancer [76]. after extracting triterpenoids from *G. lucidum* ,Liu and partners realized that these triterpenoids could be beneficial ingredients for a therapeutic method against benign prostatic hyperplasia via inhibition of 5a-reductase [77]. the Lingzhi-8 protein in *G. Lucidum* might be a beneficial chemotherapeutic factor for the therapy of lung cancer because due the essential role of focal adhesion kinase targets in metastasis [78]. Lin and partners demonstrate a new anticancer impact of Lingzhi-8 through targeting EFGR mutation and epidermal growth factor receptor-dependent processes in lung cancer cells [79]. GMI is a protein that modulates immune system and isolated from *G. lucidum* microsporum. Hsin and partners understood that GMI can remarkably raise the cancer cell death through autophagy via cisplatin. The composition of cisplatin and GMI considerably augmented the cytotoxic impact [80]. *G. lucidum* polysaccharides extracted from the sporoderm-broken spores of *G. lucidum* substantially restrained cell proliferation and caused colorectal and prostate cancer cells programed death [81, 82].

## Antioxidant effects

Nowadays, scientists focus considerable attention on the antioxidant properties of plants. They attribute this to the discovery of the function of antioxidant compounds in the prophylaxis and handling of different illnesses, including heart disease, cancer, and activity inhibition of free radicals [33]. A study by Saltarelli et al. on antioxidant properties of this fungus revealed that polyphenols in *G. lucidum* are the cause of this activity. Scientists gather that the antioxidant properties of these substances are because of resuscitation activity and absorption of oxygen radicals [23]. More studies on the ethanolic extract of this fungus revealed that it carries low-weight molecules with notable antioxidant activity. Also, methanol extract and polyacrylamide saccharides aqueous extract can have antioxidant activity [23]. Free radicals and active species of oxygen, which are by-products of various metabolic processes, can critically damage cells via oxidation .The extended accumulation of free radicals and reactive oxygen species aggravates the aging rate and diseases related to it [5]. Some researches prove that *G. lucidum* extract enhances superoxide dismutase (SOD) activity and catalase enzymes that are vulnerable to the degradation of reactive oxygen species [83, 84]. Zhu and partners perused the antioxidant effects of *G. lucidum* in vitro tests. In these experiments, raw Ganoderma was exposured to boiling water medium, after which the aqueous extract was sequestered. Next, a rich fraction of Terpene and polysaccharide was obtained, both of which were examined for their antioxidant effect. Terpene has been reported to have the most antioxidant effects. In the terpenes, Ganoderic acids A, B, C and D, lucidenic acid B, and ganodermanontriol had the highest portion [85]. Heleno and co-workers decided that the extract collected from *G. lucidum* displayed notable antioxidant activity versus various antioxidant systems in vitro. Using *G. lucidum* extract can enhance the activity enzymes, such as SOD, catalase, and glutathione peroxidase in the serum, liver, and brain of mice [86]. Zhu et al. Displayed the immunogenic valence of the low molecular weight polysaccharides present in the water extracted from *G. lucidum* fruit bodies [87]. Polysaccharides obtained from fruit bodies of Reishi exhibited antioxidant activities [88]. A Kao and partners report, revealed that a low-molecular-weight glucan extracted from *G. lucidum* was able to notable improvement the viability of a mice leukemic monocyte-macrophage cell division with $H_2O_2$-related oxidative stress and a decrease in reactive oxygen subspecies. It also contained the activity of neutral sphingomyelinase and its acidic form



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[89]. The ample polysaccharides extracted from *G. lucidum* and *G. lucidum* polysaccharide (GLP) contains 14 amino acids. This molecule has a high capacity for increasing antioxidants, serum insulin levels, and lessen lipid peroxidation. Macrophage durability and mitochondrial protection against membrane oxidant damage [90] are also reported to have high antioxidant activity. Chen and co-workers stated that *G. lucidum* polysaccharides can notably heighten antioxidant enzyme activity [88]. Liu and partners illustrated that sulfate efficiently enhances the solution in water as well as improves the bile acids' binding capacity of a water-soluble polysaccharide from *G. lucidum* [91]. Triterpenoids extract of *G. lucidum* can defend mice versus hepatic necrosis related to chloroform and d-galactosamine. The protective impacts of the liver were probably linked to the capability to ameliorate the activity of inhibitory enzymes for hepatic free radicals in mice and accordingly enhance the capability of antioxidation in mice [92]. New yolk-shell particles have been produced by tri-needle coaxial electrospraying and are utilized for treating wounds. *G. lucidum* polysaccharides were surrounded into the outer shell of the Yolk–shell particles as essential ingredients with antioxidant activity [93]. triterpenoids extracts from *G. lucidum* fruiting bodies by ethanol under reflux can protect the liver by their Antioxidative and radical scavenging activities as well as prevention of apoptosis [94].

## Anti-Angiogenic effects

Angiogenesis refers to the formation of new blood vessels from pre-existing ones, which has a pivotal role in elevating tumor growth and metastasis [95]. Several investigations have confirmed that *G. lucidum* polysaccharides can restrain angiogenesis. It has been confirmed that *G. lucidum* polysaccharides contain VEGF overexpression. Tumor angiogenesis is in vitro in metastatic melanoma cells of mice [96, 97]. In two studies on mice, *G. Lucidum* also had an anti-angiogenic activity [98, 99]. In a different study, it seems that in the prostate cancer cell lines, *G. Lucidum* inhibits VEGF and TGF-β1, which both are angiogenic agents [100]. equivalent findings have been perceived in research on lung cancer cell lines [101]. *G. lucidum* essence contains prostate cancer-associated angiogenesis by repressing VEGF and TGF-β1 secretion. This is achieved by restraining AP-1 activity by AKT / ERK [100]. The *G. lucidum* polysaccharides peptide represses angiogenesis by directly restraining the duplication of human cord vascular endothelial cells [98]. The *G. lucidum* polysaccharides peptide can also directly induce the death of human cord endothelial cells by decreasing the expression of the anti-apoptotic Bcl-2 protein and augmenting the expression of the pro-apoptotic Bax protein. Therapy with *G. lucidum* polysaccharide peptide decreases VEGF secretion in human lung cancer cells under hypoxic conditions [101].

## Anti-Inflammatory effects

Chronic inflammation provokes cellular events that can end in malignant transformation of cells and carcinogenesis [102, 103]. various inflammatory Intermediaries, like TNF-α, IL-6, TGF-β, and IL-10, have been revealed to contribute to the start and progress of cancer [104]. *G. lucidum* polysaccharides have an anti-inflammatory effect in a dose-dependent method. prescription of *G. lucidum* polysaccharides can restrain inflammation [105]. *G. lucidum* represses proinflammatory cytokines TNF-α and IL-17 [106, 107]. *G. lucidum* polysaccharides promote the inhibition of indomethacin-induced small intestinal injury GM-CSF ,by promoting peritoneal macrophages activity which creates an anti-inflammatory effect [108]. Barbieri and partners illustrated that the release of IL-8, IL-6, matrix metalloproteinase-2 and Matrix metallopeptidase 9 was considerably inhibited by ethanolic extracts from *G.lucidum* in cancer cells under pro-inflammatory situations [109]. Triterpenoids are the major anti-cancer ingredients extracted from *G. lucidum.* These combinations present cancer prophylaxis activity. In food-borne carcinogen and inflammation induced colon cancer mice models, *G. lucidum* triterpenoid-enriched extracts inhibit colon carcinogenesis by barricading inflammation and suppressing focal hyperplasis and aberrant crypt foci formation, thereby preventing colitis affiliated cancer in vivo [110].

## In vitro studies on *G. Lucidum* effects on cancer

Studies in recent years have revealed that *G. lucidum* is efficient in the therapy and prophylaxis of cancer. These allegations are mainly based on laboratory and animal examinations. There have been some in vitro and animal



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studies showing the immunity system, anti-inflammatory and liver-protective impacts of *G. Lucidum* extract [37, 105, 111-114]. In vitro studies have described that *G. Lucidum*, which owns Anti-proliferative property [60], shows anti-cellular activity by inhibiting apoptosis-induced tumor cell cycle [61-64] as well as induces cytotoxicity of natural killer (NK) cells against different cancer cells [115]. In an investigation concerning a mixed test of *G. Lucidum* on endometrial cancer cell lines, the livability of the cells, perhaps via autophagy induction and inhibition of their proliferation, was applied [116]. In a different study on mice, it was published that a *G. Lucidum* constituent, known as polysaccharide, helps cancer immunotherapy by repressing melanoma cells in macrophages [117]. Also, other studies are proving that *G. Lucidum* enhances radiotherapy efficiency, decreases chemotherapy-arising nausea, and enhances the sensibility of ovarian cancer cells to cisplatin [118-120]. In vitro studies trying to identify *G. Lucidum* impacts on cancer obtained the best consequences for breast cancer cell lines. In a study of mice, disseminated in 2014, extremely invasive human cancer cells were embedded in the mice's breast tissue and *G. Lucidum* was injected into them daily. As a result, *G. Lucidum* was seen to contain breast metastasis to the lung by repressing invasive genes [121]. pursuant to another study disseminated in 2015, when G. Lucidum is utilized in HER2 + breast cancer inflammatory cells with Lapatinib, it affects the SUM190 and KPL-4 cell lines and decreases the cell viability [122]. *G. Lucidum* extract reduces tumor growth by diminishing E-cadherin and eIF4GI expression in breast cancers [123, 124].

## Clinical researches in relation to *G. lucidum* effects on cancer

Clinical researches include G. Lucidum examination on cancer patients. Some experiments in China have produced positive consequences. However, these investigations were unreliable in terms of patient choice and the ways of extract employed because they were not adequately standard and accurate [125]. One of these cases was using extracts of G. Lucidum polysaccharides to increase levels of IL -2, IL-6, IFN-γ, in plasma which indicate NK cell activity [126, 127]. In a different study, a more positive response was achieved for those utilizing G. Lucidum together with chemotherapy, in comparison to those applying chemotherapy only. This increment was observed in CD3, CD4, and CD8 immunological indicators to an extent [125]. Another study discovered that G. Lucidum contains the growth of colon adenomas [128]. In a study printed in 2012, the impact of applying ginseng and G. lucidum for patients diagnosed with breast tumor, on quality of life was measured. In a study on breast cancer patients, of whom 14.2% and 58.8% utilized ginseng and G. lucidum, respectively, using ginseng proved to have a notable impact on life quality. Although Lucidum has provided a positive social impact. [129]. In a different collection of studies examining the anticancer attributes of triterpenes, which are active ingredients of G. Lucidum, it has been implied that some conclusions infer that triterpenes have anticancer attributes, including arresting cell cycle in cancer cells, apoptosis induction, suppression of metastasis and angiogenesis. These conclusions require more clinical investigations and molecular mechanisms [38]. Some modest advantage was discovered when the mushroom was prescribed with standard chemotherapy [130]. The NCT04162314 trial (phase 2,3) registered 20 patients and examined Beta-1,3/1,6-D-Glucan G. lucidum, compared to Placebos in patients with Non-infectious and Idiopathic Uveitis, the results of which included alteration of serum TNF-alpha level and alteration in anterior chamber inflammatory cells grading. NCT03589781 also registered 50 patients and examined Supplement Mikei Red Reishi Essence, compared to Supplement Placebo in patients with Prostate Cancer, the outcomes of which included a change in the function of the immune system of patients with prostate cancer and the relationship between the function of the immune system in the state of IgG in the blood and the state of the disease. NCT04319874 (Phase 2) registered 80 patients and examined G. lucidum in patients with Osteosarcoma. NCT00575926 (Phase 3) studied effects LingZhi capsule in patients with Pediatric Cancers (Cancer Children). A phase II trial employed 20 patients to study Rheumatoid Arthritis (NCT00432484) and tested Lingzhi and Sen Miao San. NCT04029649 also registered 204 patients and examined Beta-1,3/1,6-D-Glucan, compared to Placebo in patients with Ulcerative Colitis. NCT00224263 also registered 360 patients and examined Lingzhi (Ganoderma) in patients with Parkinson's Disease. (Table 2,3,4). The NCT02844114 trial registered 60 patients and examined G. lucidum spore, compared to chemotherapy and Placebo in patients with



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Carcinoma, Non-Small-Cell Lung. NCT02533635 studied effects Dietary Supplement, a Master Ganoderma Detox Tea in patients with Eczema. NCT01718548 registered 100 patients and examined Cordyceps Sinensis (CS) and Lingzhi in patients with Cardiovascular Fitness and Cognitive Function. NCT02785523 registered 60 patients and examined Ganoderma Spore Lipids, compared to chemotherapy and Placebo in patients with Gastrointestinal Neoplasms. NCT02238587 studied effects of Ganoderma Spores Powder Capsules in patients with Head-and-neck Cancer.

## Effects on the immune system

## Effect on T lymphocytes

Researches reveal that *G. lucidum* polysaccharides are an activator of T lymphocytes. *G. lucidum* polysaccharides therapy significantly improves the proliferation of concanavalin A-induced mouse lymphocytes and IL-2 generation [131]. *G. lucidum* polysaccharides can also heighten DNA synthesis in mouse spleen cells in a mixed lymphocyte reaction by inducing DNA polymerase expression [132]. *G. lucidum* polysaccharides enhance IFN-γ expression in T lymphocytes [133] and IL-1, IL-2, and IFN-γ in mice splenic cells [134]. *G lucidum* was efficient in restoring spleen subset T cell damage in gamma-irradiated mice [135]. Li and co-workers illustrated that *G. lucidum* polysaccharides considerably restrained the tumor growth in hepatoma-bearing mice. This impact was affiliated with an increment in the ratio of the effector T cells to regulatory T cells [136].

## Effect on macrophages

*Ganoderma lucidum* polysaccharides stimulate bone marrow- isolated macrophages from mice holding sarcoma, ending in the manufacture of immune materials, including IL-1β, Tumor necrosis factor alpha and nitric oxide [137]. *G. lucidum* polysaccharides substantially improve phagocytosis of macrophages and macrophage-interceded tumor cytotoxicity. *G. lucidum* polysaccharides stimulate macrophages in vitro and enhance the levels of different cytokines, among others IL-1β, TNF-α, IFN-γ, and IL-6 in the culture medium [138]. Kove et al. pointed out that the mycelia of *G. lucidum* activated NF-κB in RAW264.7 murine macrophages. This indicates that NF-κB activation was one of the most important signaling pathways [139]. Ganoderan segregated from *G. lucidum*, augmented the manufacture of NO in the RAW 264.7 macrophages [140]. The cell proliferation of Raw 264.7 cell lines treated with Ganoderan was restrained. These consequences demonstrate that polysaccharides of fungus actuate macrophage and liberate NO, which is a substantial chemical messenger for inducing many biological answers [141]. The bioactive nano extract polysaccharides and triterpenes from *G. lucidum* concentrate have been demonstrated to restrain the secretion of Tumour Necrosis Factor alpha, Interleukin 6, Prostaglandin E2 and NO manufacture by inhibiting cyclooxygenase-2 and Inducible nitric oxide synthase expression in RAW 264.7 macrophages [142-145].

## Effect on B lymphocytes

*G. lucidum* polysaccharides can activate B cells by enhancing their proliferation and differentiation [15]. In vitro, *G. lucidum* polysaccharides considerably boosted the proliferation of LPS-induced lymphocytes [146, 147]. It has been proved that *G. lucidum* polysaccharides can connect to lymphocyte surfaces via particular receptors or proteins and result in the alterations in the activities of macrophages, T-helper, NK cells and other effective cells [138]. *G. lucidum* polysaccharides can stimulate CD71 and CD25 expression on B cell surface and stimulate the expression of immunoglobulins by B cells by directly stimulating PKCα and PKCγ expression in B cells [148].

## Effect on dendritic cells(DCs) and NK cells

*G. lucidum* polysaccharides can provoke maturation of normal human monocyte-derived DCs and leukemic monocyte-derived DCs [16, 19, 149]. *G. lucidum* polysaccharides increase cell surface expression of CD80, CD86, CD83, CD40, CD54 and human leukocyte antigens [150]. Further information demonstrated that GLPs were able to promote the toxicity of DC-induced Cytotoxic T lymphocytes at the phase of antigen presentation, chiefly via the IFN-γ and Granzyme B pathways [151]. Chien et al stated that the water-soluble extract of *G. lucidum* (F3) could extensively enhance the presence of natural killer cells in UCB mononuclear cells, implying that F3 somewhat alters the



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activity of NK cells [152]. *G. lucidum* polysaccharides improve the expression of IL-12 p40 cytokine mRNA in dendritic cell and enhance IL-12 p40 protein production. *G. lucidum* polysaccharides also improve the proliferation of mature DC-related mixed lymphocyte culture [149]. *G. lucidum* polysaccharide augmented the cytotoxicity of splenic NK cells in tumor-containing mice [153, 154].

## Nanotechnology and *G. lucidum*

gold nanoparticles (AuNP) comprising immunoactive GLP (GLP-Au), *G. lucidum* polysaccharide-gold illustrated a further diminution in Intracellular acidic phosphatase activity than *G. lucidum* polysaccharide, corroborating the strong immunostimulation of *G. lucidum* polysaccharide-gold in DCs maturation [155]. *G. lucidum* polysaccharide-gold decreased IL-12, IL-6, IL-1β, TNF-α and IFNγ mRNA levels considerably [155]. catalase, Superoxide dismutase, glutathione peroxidase and Glutathione were lessened in D-galactosamine induced hepatotoxicity [156, 157]. the animals cured with ganoderic Acid-Solid lipid nanoparticle and silymarin normalized the levels of catalase, Superoxide dismutase, glutathione peroxidase and Glutathione enzymes [158, 159]. Liu and partners [160] utilized soybean phosphatide, tween 80 and cholesterol to surround *G. lucidum* polysaccharides in liposomes, eventuating in improved incitement of splenic lymphocyte proliferation. These Studies surrounded *G. lucidum* polysaccharides and ovalbumin in liposomes [161] and this *G. lucidum* polysaccharides/ovalbumin enhanced both cellular and humoral immunity by activation and maturation of Dendritic cells in draining lymph nodes. *G. lucidum* polysaccharides have been uploaded into sodium alginate via an electrospray process and these micro-particles could protect stored *G. lucidum* polysaccharides from oxidative degradation [162]. *G. lucidum* polysaccharides nanoparticles have cytotoxic attributes against tumor cells [63].

## CONCLUSION

Conforming to the published consequences of clinical and animal models, the effect of *G. lucidum* in cancer treatment can be understood by mechanisms such as anti-tumor, anti-metastatic, Anti-Inflammatory and anti-angiogenic. Regardless of the nutritional value of fungi, their use as medicines by humans has a long history. many research in different countries on this fungus has led to the identification of the mechanism of action of different purified substances. *G. lucidum* contains compounds, many of which play a significant role in the prophylaxis and treatment of cancer and activate our immune system for many defense functions. The impacts that modulate the immune system of *G. lucidum* are affiliated with its anti-tumor activity. One of the main points that can be done more research is the use of Nanotechnology in the combination of *G. lucidum*, the use of this technology with *G. lucidum* can have considerable effects in the treatment of cancer. Researchers' data indicate that *G. lucidum* has a high capacity for acceptance as a healthy dietary complement for patient cancer therapy. In other words, the use of *G. lucidum* in the treatment of cancer can be likened to a two-edged sword. The reason for some lack of preparation of Ganoderma as a drug may be due to problems with mass production. further studies are needed to further illuminate the mechanisms of the modulatory impacts of the immune system also the direct anticancer impacts of Ganoderma.

## Ethics approval and consent to participate

Not applicable

## Consent for publication

Not applicable.

## Availability of data and materials

All data generated or analyzed during this study are included in this published article.

## Competing interests

The authors declare that they have no competing interests.

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