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Review

Immunomodulatory Effects of *Ganoderma lucidum* on NK Cells: From Traditional Use to Modern Immunotherapy

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ABSTRACT: The historical importance of *Ganoderma lucidum* is noteworthy within traditional Asian medical systems. This thorough investigation examines the immunomodulatory properties of *G. lucidum*, specifically its role in modulating natural killer (NK) cells, which are crucial components of the immune response against infectious pathogens and tumors. The primary constituents of *G. lucidum*, which include polysaccharides and triterpenoids, have been demonstrated to enhance the cytotoxic capabilities of NK cells and stimulate cytokine synthesis. The chemical substances enhance the activation of NK cell receptors, particularly NKG2D and natural cytotoxicity receptors, thereby commencing a chain of intracellular signaling pathways that strengthen the immune response. Furthermore, the significance of *G. lucidum* within the framework of cancer immunotherapy is examined, highlighting its potential to induce apoptosis in cancerous cells, impede angiogenesis, and improve the effectiveness of standard therapeutic modalities. The exploration of properties of *G. lucidum* reveals its multifaceted role in cancer treatment, particularly in augmenting the immune system's capacity to combat malignancies and enhance therapeutic outcomes. The analysis further highlights the antiviral and anti-inflammatory properties of *G. lucidum*, specifically its ability to modulate immune responses within the context of viral infections and chronic inflammatory conditions. A deeper understanding of the underlying molecular mechanisms is crucial for the effective integration of *G. lucidum* into contemporary therapeutic frameworks. This review provides a comprehensive examination of the existing research on the immunomodulatory properties of *G. lucidum* and its therapeutic potential in oncology, viral infections, and inflammatory conditions, while also exploring prospective avenues for further investigation and clinical application.

Keywords: Biological aspects, Health, Immune modulation, Infections, Reishi mushroom.

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1. INTRODUCTION

Since ancient times, people have sought natural immunomodulators with potent action and no adverse side effects. The market is currently crowded with various immunomodulators, as well as individual combinations that promise the Golden Fleece: activating an active immune response at a low cost. On the one hand, some, such as β-glucan, are currently the focus of numerous clinical trials and have been the subject of over 10,000 scientific studies published in peer-reviewed journals. However, many people restate assertions with little to no scientific support (Vetvicka and Vetvickova, 2014). Compounds known as immunomodulators help maximize the immune response. The immune system can weaken, even though it can self-produce cells that identify and destroy foreign invaders in the body (Han et al., 2024). An immunomodulator (immunostimulants, immunoadjuvants, or immunosuppressants) is one of their classifications (Behl et al., 2021). Immunostimulants are believed to enhance the response of body to infection and are typically nonspecific in their action. Both innate and adaptive immune responses can be used to support them. In an individual with a compromised immune response, they are intended to function as immunotherapeutic agents

(Hooda et al., 2024). Immunoadjuvants, which are believed to be specific immune stimulants, are used to enhance the effectiveness of vaccines. Immunosuppressants are primarily used to treat organ transplant rejection and autoimmune disorders. Additionally, they are administered together, similar to multidrug therapy (Kumar et al., 2012), as shown in Table 1.

Table 1. Types of Immunomodulators.

Type of Immunomodulator	Description	Medical Uses	References
Immunosuppressive	Through suppressing or decreasing the immune responses.	Rheumatoid arthritis, multiple sclerosis, lupus, etc.	Behl et al., 2021; Hooda et al., 2024; Kumar et al., 2012
Immunostimulatory	Enhancing the immune responses.	Immunotherapy (immunodeficiency).	
Mixed Immunomodulators	Modify the immune responses (inhibiting or enhancing).	Treatment of some types of cancer and autoimmune diseases.	
Topical Immunomodulators	Reducing the immune responses (at the specific site in the body).	Treatment of some skin inflammations.	

2. IMPORTANCE OF NK CELLS IN IMMUNE DEFENSE

As a subset of lymphoid cells with innate immunological activity, natural killer (NK) cells are unique (Cerwenka and Lanier, 2001). NK cells are produced in the bone marrow and circulate throughout the blood, where they are triggered by either cytokines or target cells that express NK cell receptor ligands (Lanier, 2005). Unlike Band T-cell antigen receptors, which undergo somatic recombination, NK cell receptors are encoded in the germline. Instead, a mixture of signals from activating and inhibitory receptors dictates the outcome of NK cell action. Some inhibitory receptors prevent NK cells from attacking healthy cells by recognizing MHC class I, which is present on almost all cells (Lodoen and Lanier, 2006). According to the "missing self-hypothesis" NK cell activation may result from the loss of MHC class I from cells due to infection or transformation (Ljunggren and Kärre, 1985), provided that the activating receptor is in use. The pathogen-encoded or host-derived ligands that are upregulated on "stressed" or infected cells are bound by these activating NK receptors. NK cells mediate their immune response to infection by directly lysing target cells through the exocytosis of perforin and granzymes, as well as by secreting cytokines, including tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ). By acting as main responders and warning the host of the presence of infectious pathogens, NK cells serve as crucial immune system sentinels (Lodoen and Lanier, 2006).

Many signals are integrated to determine the effector function of NK cells. NK cells perceive their surroundings by using a tightly controlled ratio of germline-encoded activating and inhibitory receptors, and signaling through these receptors is necessary to start an NK cell response. Circulating NK cells are primarily at rest under physiological settings, but they can infiltrate pathogen-infected or malignant tissues after being activated by a variety of cytokines (Sharrock, 2019).

Major Histocompatibility Complex Class I (MHC I) molecules are expressed by healthy cells and function as ligands for NK cell inhibitory receptors, which help these cells develop "self-tolerance". The primary inhibitory receptor profile of NK cells, which binds to MHC I molecules and preserves tolerance for healthy host cells, is composed of killer cell immunoglobulin-like receptors in humans or Ly49 family members in mice (Hammer et al., 2018). However, MHC I molecules are often down-regulated during viral infection and tumor formation, which lowers the NK cell's inhibitory signaling threshold and causes cell activation (Bessoles et al., 2014). The activation of receptors on NK cells is upregulated in response to cellular stressors associated with infection or cancer progression, such as DNA damage responses and the activation of tumor suppressor genes (Sharrock, 2019).

3. *GANODERMA LUCIDUM*: A TRADITIONAL MEDICINAL MUSHROOM

One of the most widely used medicinal mushrooms in the world is *G. lucidum*. It has been used in traditional Chinese medicine to advance health. In Japan, China, India, and other Asian countries, it has traditionally been consumed to promote longevity and good health. Around the world, it is referred to by several synonyms, including lingzhi, reishi, and the "mushroom of immortality" (Ahmad et al., 2024b). The Chinese Pharmacopoeia, Therapeutic Compendium, and American Pharmacopoeia list the active ingredients and their corresponding potencies for *G. lucidum* (Kozarski et al., 2019; Swallah et al., 2023). *G. lucidum* grows in a variety of environments worldwide.

Deciduous woodlands are among its typical habitats. In deciduous woodlands, *G. lucidum* frequently grows on dead or dying trees, such as oak, maple, and elm. Pine, spruce, and fir trees are among the coniferous trees that develop

mushrooms in coniferous woods. *G. lucidum* grows on a range of trees in temperate climates, such as poplar, beech, and birch. All things considered, *G. lucidum* is a versatile fungus that can thrive in a range of global settings (Stamets, 2011; Cortina-Escribano et al., 2020; Hapurachchi et al., 2015). The majority of the more than 300 species in the genus *Ganoderma*, as identified through taxonomic investigations, are found in tropical regions (Richter et al., 2015).

3.1. Historical Use in Traditional Medicine

People are more likely to select medical products made from natural sources, such as plants and fungi, due to growing public awareness of drug safety, which is driven by their clear benefits, including fewer adverse consequences and reduced harm. Secondary metabolites obtained from living things are known as biological natural products. These sources may comprise single compounds or complex combinations derived from raw materials (Wang et al., 2020). Among the popular medicinal fungi, *Ganoderma lucidum* (Curtis) P. Karst. and other *Ganoderma* species demonstrated more benefits than other chemical medications. The word "*ganoderma*" comes from the Greek words "ganos," which means brilliance, and "derma," which means skin. In 1881, Finnish mycologist Petter Adolf Karsten gave it the name *Ganoderma* (Massee, 1904). The definition of *Ganoderma* species has evolved with the advancement of molecular biology.

For instance, *G. lucidum*, now regarded as a distinct species, namely Lingzhi, is extensively cultivated commercially in China (Cao et al., 2012). There are currently 131 species of *Ganoderma* worldwide (Richter et al., 2015; Xing et al., 2018). Modern investigations have demonstrated the medicinal value of 20 different varieties of *G. lucidum* (Lingzhi) (Cao et al., 2012). In Africa, America, Asia, and Oceania, as well as in Europe, *Ganoderma* is extensively found in tropical and subtropical climates (Wang et al., 2020).

3.2. Phytochemical Composition and Bioactive Compounds

Ganoderma was shown to contain around 380 terpenoids, including lucidenic acids, ganoderic acids (GAs), aldehydes, esters, alcohols, lactones, glycosides, and meroterpenoids, in addition to over 430 secondary metabolites (Baby et al., 2015; Sharma et al., 2019). *Ganoderma* contains terpenoids and steroids demonstrated strong biological action. The primary physiologically active components that render *G. lucidum* a promising agent are polysaccharides and triterpenoids (Kohno et al., 2017). Lanosterol is the source of triterpene chemicals, which include lucidones, ganoderic acids, lucinedic acids, ganodermic acids, and ganodermic alcohols. Although over 200 polysaccharides, such as α-D-glucans, β-glucans, and β-D-glucans spores, mycelia, and fruiting bodies, as well as polysaccharide-protein complexes (Jiang et al., 2019). According to numerous studies (Chen et al., 2017; Yin et al., 2024; Parepalli et al., 2021; Wachtel-Galor et al., 2011), other complex compounds include provitamin D2, alkaloids, glycoproteins, nucleotides, coumarins, lysozyme, flavonoids, enzymes, long-chain fatty acids, essential amino acids, phenols, sterols, germanium, and various minerals like copper, zinc, selenium, potassium, calcium, phosphorus, magnesium, and iron (Ahmad et al., 2024b).

G. lucidum is a potential health agent since it contains very high levels of leucine and lysine as well as a high proportion of polyunsaturated fatty acids relative to total fatty acids (Wachtel-Galor et al., 2011; Ahmad et al., 2023; Sanodiya et al., 2009). Reishi is used in over 100 goods available on the market. *G. lucidum*'s effectiveness has been demonstrated in Anticancer (Gündoğdu and Özenver, 2023), antioxidant(Karimi et al., 2022), antidiabetic (Shao et al., 2022), antihyperlipidemic (Jing et al., 2022), antimutagenic (Pascale et al., 2022), anti-aging (Luo et al., 2022), antimicrobial (antiviral, antibacterial, and antifungal) (Luo et al., 2022; Cör Andrejč et al., 2022), hepatoprotective (Chen et al., 2022; Ahmad et al., 2023), anti-hyperpigmentation (Kozarski et al., 2019), cardioprotective (Ahmad, 2019), anti-allergic (Das et al., 2019), and antinociceptive (De Camargo et al., 2022).

About 90% of the weight of *G. lucidum* is made up of water, with the remaining 10% being made up of several bioactive and nutritious substances such as proteins, phenolic compounds, sterols, polysaccharides, and triterpenoids. According to studies, the dried form of the mushroom contains 1.8% ash, 3–5% crude fat, 59% fiber, 7–8% protein, and 26–28% carbohydrates. *G. lucidum*'s health-promoting qualities are also attributed to its abundance in vital minerals, including potassium, phosphorus, calcium, magnesium, selenium, zinc, and iron (Wachtel-Galor et al., 2011; Sharma et al., 2019). The most prevalent of its bioactive constituents are polysaccharides, whose biological activity is influenced by structural changes. Another well-known class of compounds known for their structural complexity and variety of functions is triterpenoids, which include ganoderic acids.

Numerous studies have been conducted on the mushroom because of its phenolic compounds, sterols, and other nutrients, which enhance its bioactive profile. This special combination demonstrates its promise in contemporary medical and nutritional applications while bolstering traditional uses (Azi et al., 2024).

3.3. Pharmacological Relevance

Many are aware of the true pharmacological properties of *Ganoderma*, a well-liked traditional Chinese remedy. Numerous recent comprehensive studies have demonstrated the therapeutic potential of *Ganoderma* as an antiviral, antioxidant, immunomodulatory, hepatoprotective, antitumor, and anti-inflammatory agent (Sanodiya et al., 2009).

3.3.1. Antitumor action

Researchers have been gradually drawn to the antitumor properties of *Ganoderma*. The antitumor effect is linked to the induction of tumor cell death and the enhancement of the host cell's ability to regulate its immune response. In both *in vitro* and *in vivo* experiments, *Ganoderma* extract (GEs) and *Ganoderma* spore oil (GSO) demonstrated strong antitumor properties. Human leukaemia cells (K562 and HL60) and human gastric cancer cells (SGC7901) were both reduced in their development by GEs and GSO. GEs and GSO activities may target topoisomerases I and II. Triterpenoids are crucial to the anticancer properties of *Ganoderma* (Chen et al., 2017).

3.3.2. Hepatoprotective action

Although alcohol is broken down by the liver in the human body, excessive and frequent drinking can harm the liver. The primary constituents of triterpenoids are the ethanol extract of *G. lucidum*, which can upregulate alcohol dehydrogenase 1 of tautomerism between aldehydes and alcohols or ketones in humans, and regulate the conversion of CYP2E1 to regulate the conversion of ethanol into acetaldehyde/acetate (Peng et al., 2005). Discovered that fornicatin A, D, and F (392, 394, 398) can successfully reduce the levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in HepG2 cells treated with H_2O_2. 82 ALT, AST, and lactate dehydrogenase are indicators of liver damage that can be detected, indicating that *Ganoderma* may have liver-protective properties *in vivo* (Wang et al., 2020).

3.3.3. Anti-inflammatory and antimicrobial properties

When applied to the mouse macrophage line (RAW264.7), GTs have anti-inflammatory action against inflammation brought on by lipopolysaccharide. Six triterpenoids were extracted from *G. lucidum* (Wang et al., 2020). Among these, methyl lucidenate L (198) has a potent inhibitory effect on NO production by LPS and reduces the production of pro-inflammatory cytokines in RAW264.7 cells, such as IL-6 and IL-1β. Meanwhile, in LPS-induced macrophages, it successfully decreased the expression levels of iNOS, COX-2, and NF-κB, as well as the phosphorylation of IκBα and IKKβ.

3.3.4. Immunomodulatory action

NKs are immune cells that can directly eliminate infections. It can serve as one of the markers for assessing the body's ability to fight off viral and tumor infections. The quantity of it and the body's resistance to illness are closely linked to the intensity of its exercise. Zhong et al. (2021) demonstrated that after intragastric administration of GLPs for 7–9 days, the cytotoxic activities of NKs and lymphokine-activated killer (LAK) were increased. NKs can increase DCs' expression of the domain (CD86), which is crucial for tumor response (Nouroz et al., 2016; Demaria et al., 2019).

3.3.5. Activity of antioxidants

Lipid peroxidation, triggered by free radicals, can damage cell membranes and tissue cells, leading to cell death and ultimately resulting in significant bodily injury. According to studies, *Ganoderma* is an extremely promising fungus that exhibits antioxidant potential. *G. cochlear* yielded seven novel compounds. The most recognized of them, ganocochlearins A (627), B (628), C (629), and D (630) exhibit the most scavenging effects on hydroxyl, DPPH, and ABTS+ radicals. Nitrogen and other DPPH radicals are strongly scavenged by the volatile oil component separated from *G. pfeifferi* and the alkaloid component isolated from *G. lucidum*. These heterocycles, which include nitrogen, may be very important. GTs in chicken liver were resistant to peroxidation damage brought on by cadmium. The contents of superoxide dismutase and glutathione peroxidase in chicken liver treated with GTs exhibited superior antioxidant activ-

ity, which was significantly greater than that in the control group (Wang et al., 2020). DPPH free radicals can be efficiently scavenged by the meroterpenoid compounds fornicin E (590), ganocapensin A (711), B (712), and ganomycin F (723), which were isolated from *G. capense*. Their respective IC50 values are 6.00 ~ 0.09, 7.79 ~ 0.15, 8.20 ~ 0.13, and 7.44 ~ 0.13 mg/ml. Furthermore, by scavenging reactive oxygen species in mice, *Ganoderma* polysaccharides demonstrated antioxidant qualities and decreased the oxidation of low-density lipoproteins (Paterson, 2006).

4. IMMUNE SURVEILLANCE

Conventional NK cells were previously thought to be transient innate lymphocytes with no antigen specificity. However, this notion has been contested in recent years. Studies on mice demonstrated that NK cells can develop selective memory. Hapten-induced touch hypersensitivity and recall responses in mice lacking mature T and B cells, following challenge, served as evidence for this phenomenon. Previously, this characteristic was commonly recognized as a T-cell effect. Additionally, this NK cell response was able to distinguish between several haptens and persisted for several weeks. This combines acquired activity, antigen specificity, and long-lived memory cells, the three defining features of adaptive immunity (Spits et al., 2013). Paust et al. (2010) further described the hapten-specific response. They evaluated the establishment of NK cell memory in response to several viruses, as well as the potential impact of the host's genetic background.

4.1 Cytotoxicity and Cytokine Production

There are four main steps in the NK cell cytotoxic response. The actin cytoskeleton is reorganized once the target cell and NK cell form an immunological synapse. Secretory lysosome and microtubule-organizing center (MTOC) polarization toward the lytic synapse. Secretory lysosome docking with NK cell plasma membrane. Secretory lysosome fusion with the target cell plasma membrane. Degranulation is the term for the complete process that results in the release of cytotoxic chemicals, such as granzyme and perforin. Indirect measurements of NK cell cytotoxic activity are frequently made using the degranulation of NK cells (Topham and Hewitt, 2009). Lysosomal-associated membrane proteins-1 (LAMP-1 or CD107a) and -2 (LAMP-2 or CD107b) temporarily disappear after NK cell degranulation occurs on the NK cells' surface. One indirect indicator of NK cells' cytolytic activity is the expression of LAMP-1 on their surface (Alter et al., 2004). Granzymes can enter the target cell more easily when perforin is released and polymerizes, creating holes. Granzymes are serine proteases that induce target cells to undergo apoptosis by activating caspase molecules (Martínez-Lostao et al., 2015; Topham and Hewitt, 2009; Pardo et al., 2002). For NK cells to suppress various malignancies, perforin-dependent cytotoxicity is crucial. Target cell apoptosis triggered by death receptors is another mechanism by which NK cells mediate the death of target cells. TNF receptor ligand Fas ligand (FasL), TNF, and TRAIL are all expressed by NK cells. This attaches itself to the target cell's matching receptor (Sonar and Lal, 2015). Target cell apoptosis results from the death receptor's conformation changing when it interacts with its cognate ligand, which also attracts adaptor proteins (Thorburn, 2004). It has been demonstrated that NK cell-mediated regulation of methylcholanthrene (MCA) metastasis is TRAIL dependent (Takeda et al., 2002). The antimetastatic capability of NK cells treated with IL-18 is facilitated by the Fas-FasL pathway (Hashimoto et al., 1999).

Based on these empirical observations, natural killer (NK) cells utilize an array of bioactive substances to initiate the cytotoxic response against cells subjected to physiological stress. It has been established that exosomes secreted by immune cells can augment antitumor immune responses. In contrast, exosomes derived from tumor cells within the tumor microenvironment can inhibit the activation of immune effector responses (Shoae-Hassani et al., 2017). Recent investigations have revealed that human NK cells, regardless of their activation state, release exosomes that express the NK cell-specific marker CD56, along with various other molecules associated with NK cells, including NKG2D, NKp30, NKp44, and NKp46. Additionally, these exosomes contain FasL and perforin, which exert cytotoxic effects on diverse types of human carcinoma cells (Lugini et al., 2012).

According to another study, exosomes generated by NK cells that have previously come into contact with NB cells (Nx-ANKs) exhibit increased expression of many activating receptors. When contrasted with untreated NK cells, NKp30, NKp44, NKp46, and NKG2D also exhibit increased cytotoxicity (Shoae-Hassani et al., 2017). These results suggest that NK cells exposed to exosomes generated from NB cells beforehand have undergone education, resulting in effective cytotoxicity against NB tumors (Paul and Lal, 2017).

4.2 NK Cells in Cancer and Infection Control

In addition to collaborating with other adoptive immune cells to promote antitumor immunity, natural killer cells play a crucial role in cancer immunosurveillance (Paul et al., 2016; Sconocchia et al., 2014). It has been demonstrated that NK cell removal increases the incidence of MCA-induced sarcoma, indicating that NK cells play a role in the removal of tumor cells (Smyth et al., 2001). O'Sullivan et al. (2012) offered more proof of the function of NK cells in immunosurveillance. NKG2D, IFN-γ, and perforin are among the chemicals that NK cells use to eradicate MCA-induced sarcomas (Smyth et al., 2001). It has been observed that perforin-dependent NK cell activity regulates the development of mammary cancer and B cell lymphomas (Smyth et al., 2000). It was found that NK cell-mediated destruction of senescent tumor cells is facilitated by the restoration of endogenous p53 in tumor cells in a mouse model of liver cancer (Iannello et al., 2013). Many cancers, nevertheless, develop gradually and evade NK cell attack. Immunosuppressive substances that suppress antitumor immune responses are secreted by tumor cells and include TGF-β, VEGF, prostaglandin E2 (PGE2), adenosine, and indoleamine 2,3-dioxygenase (IDO) (Baginska et al., 2013). IDO and PGE2 generated by melanoma cells have been shown by Pietra et al. (2012) to suppress the cytolytic activity of NK cells *in vitro*.

Additionally, we have demonstrated that NK cells invading melanoma tumors exhibit poor degranulation, upregulate inhibitory receptors, and downregulate several activating receptors compared to those found in secondary lymphoid tissues containing NK cells (Paul et al., 2016). It is also known that intratumoral NK cells produce fewer cytokine receptors and pro-inflammatory cytokines, which may impair their ability to fight tumors within the tumor microenvironment. It has been documented that melanoma-associated fibroblasts inhibit the cytotoxic function of NK cells, both contact-dependently and contact-independently (Balsamo et al., 2009).

By preventing tumor-specific effector T cells from functioning, several additional suppressive cell types, including regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), can weaken the immune response to tumors. Tregs, by producing IL-10 and TGF-β, also prevent intratumoral NK cells from performing their cytolytic role, as do MDSCs and M2 Macrophages (Trzonkowski et al., 2004).

5. IMMUNOMODULATORY EFFECTS OF *GANODERMA LUCIDUM* ON NK CELLS

Numerous investigations have demonstrated that *G. lucidum* affects immunological cells in both stimulatory and suppressive ways. In immunosuppressed mice, for example, it increases the function of immune effector cells (Chang et al., 2014). Nevertheless, by triggering MAPK signaling pathways, this fungus also inhibits macrophage cell proliferation and LPS-stimulated inflammatory responses (Dudhgaonkar et al., 2009), while stimulating human polymorphonuclear neutrophil phagocytic activity and mouse splenocyte cytokine expression.

Additionally, *G. lucidum* causes leukemic cells to differentiate into mature monocytes or macrophages while suppressing their proliferation (Chan et al., 2008). It stimulates cytokine-induced killer cell proliferation and antitumor activity, and inhibits the growth of breast cancer cells, bladder cancer cells, hepatoma cells, and oral cancer cells in mice (Jiang et al., 2019). *G. lucidum* causes activated T cells and macrophages to release cytokines, which have antitumor properties. Additionally, the closely related *Ganoderma tsugae* boosts splenic NK cytotoxic activity in C3H/HeN mice in a dose-dependent manner when administered intraperitoneally. Notably, early data suggest that *G. lucidum* may be beneficial in treating human tumors when combined with traditional therapy (Sliva, 2003; Jin et al., 2020).

The molecular processes underlying the effects of *G. lucidum* on NK cells have not yet been investigated, despite extensive research on how this fungus affects animals and cultured cells. An essential component of the innate immune system, NK cells play a crucial role in the host's early defence against infections and cancers (Elhaik-Goldman et al., 2011; Yokoyama et al., 2004). Previous research by us and others has demonstrated that the cytotoxicity of NK cells is caused by the production of cytolytic proteins, such as granulysin, granzymes, and perforin, towards the target cell (Trapani and Smyth, 2002). Activated NK cells exocytose these cytolytic proteins, which then cause target cells to undergo apoptosis, thereby mediating the cell-killing action. Signals that bind to activating and inhibitory receptors on the cell surface control the cytotoxic activity of NK cells (de Saint Basile et al., 2010). Natural cytotoxicity receptors (NCRs), which include the constitutively expressed receptors NKp46 (Elboim et al., 2010) and NKp30 (Li et al., 2011), as well as the inducible receptor NKp44, are the primary activating receptors.

Furthermore, NK cell cytotoxicity is also triggered by the natural killer group 2D receptor (NKG2D), which is present on both human NK cells and T cells (Barber and Sentman, 2011). When ligands bind to activating receptors, a series of intracellular signals is triggered, causing granules to polarize and exocytose, thereby lysing target cells (Maghazachi, 2005). Important mediators of the MAPK signaling pathways that regulate the reorientation of the microtu-

bule-organizing center and trigger granule polarization and secretion in NK cells are ERK, JNK, and p38 (Lu and Chen, 2010).

5.1 Evidence from *In Vitro* Studies

Anticancer effects: Triterpenes (ganoderic acids) and *Ganoderma* polysaccharides (GLPs) inhibit migration, induce apoptosis/ROS, suppress proliferation, and enhance the sensitivity of tumor cells to treatments in various cancer cell lines. Immune-related signaling, including MAPK/JNK/p38 and PI3K/AKT regulation, as well as interference with the DNA damage response, are some of the mechanisms (Wang and Yu, 2022). Immunomodulation: GLPs stimulate dendritic cells and macrophages, enhancing phagocytosis through the NF-κB/MAPK pathways and increasing the production of TNF-α, IL-1β, IL-6, and nitric oxide. GLP fractions have anti-inflammatory and vascular effects via inhibiting IL-1β and associated inflammatory signals in cultured human vascular cells (Chan et al., 2008).

5.2 *In Vivo* Experimental Models

Tumor and immune models: In mice (usually BALB/c and C57BL/6 strains, 6–8 weeks, 18–22 g), polysaccharide extracts from *Ganoderma lucidum* (GLPs) are given orally or intraperitoneally between 50 and 200 mg/kg/day. This reduces tumor size, increases tumor-associated immunocompetent cells, and activates macrophages and antitumor cytokines. Some studies also report changes in gut microbiota, which are linked to anticancer activity (Zhang et al., 2025).

Inflammation and infection models: In Sprague Dawley rat models, which are infected or inflamed systemically, GLPs are given orally between 50 and 150 mg/kg/day. These result in a lowered pathogen load, protection of organ damage, and reduced inflammation, mainly through the inhibition of the NF-κB pathway. Cardio-metabolic and hepatic protection: *In vivo* GLPs in mice and rat models show both hepatoprotective and vascular protective effects. GLPs, when administered orally at 100-200 mg/kg/day, demonstrate their vascular protective and hepatic protective effects, which are attributed to their anti-inflammatory and antioxidant actions (Chan et al., 2008).

5.3 Clinical Studies and Human Trials

G. lucidum, also known as "lingzhi" or "reishi," has been valued in Asian medicine for over 2,000 years and has recently drawn interest in Western medicine. With qualities that may promote health maintenance, increase longevity, and treat various systemic conditions, this fungus holds a unique position as a nutritional and therapeutic agent (Willard, 1990). Because *G. lucidum* has been shown to safely affect several CVD risk variables, research interest in this mushroom has increased. Standardized extracts in pill and capsule form are gaining popularity in Western markets, while traditional preparation methods, such as decoctions, teas, and coffee, continue to be available.

The fruiting body (basidiocarp), mycelium (thread-like structure), and reproductive spores are the three primary parts of the organism. Polysaccharides (particularly beta-D-glucans, heteropolysaccharides, and glycoproteins), triterpenes, germanium, essential and non-essential amino acids, sterols, lipids, antioxidants, B-complex vitamins (B1, B2, and B6), and minerals (iron, calcium, and zinc) are among its bioactive constituents. Its bioactive substances, such as triterpenes and polysaccharides (such as beta-D-glucans), are thought to have medicinal effects. By increasing the activity of antioxidant enzymes, such as glutathione peroxidase (GPx), and modifying inflammation through interactions with Toll-like receptors (TLRs), polysaccharides may help mitigate oxidative stress (Huie and Di, 2004). By inhibiting the angiotensin-converting enzyme (ACE), triterpenes may reduce blood pressure (BP) and improve lipid profiles by upregulating antioxidant enzymes (Huie and Di, 2004; McKenna et al., 2012).

These substances are believed to enhance the therapeutic potential of *G. lucidum*, particularly in relation to metabolic and cardiovascular health. By interacting with TLRs and inhibiting pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which are crucial in the pathophysiology of atherosclerosis and insulin resistance, beta-D-glucans, a major polysaccharide class, have been shown to modulate immune responses and reduce systemic inflammation (Klupp et al., 2015). Another important component, triterpenes, has the potential to lower blood pressure by inhibiting ACE activity and reducing oxidative stress by upregulating antioxidant enzymes, such as catalase and superoxide dismutase (SOD). This can lead to better vascular function and lipid profiles (Abdullah, 2018).

6. THERAPEUTIC EFFECTS OF *GANODERMA LUCIDUM*

Ganoderma lucidum exerts its therapeutic effects through a multifaceted network of bioactive compounds—primarily polysaccharides (including β-glucans), triterpenoids (notably ganoderic acids), proteins or peptides, and phenolics—that work synergistically to modulate immune responses, suppress inflammation, combat microbial and viral pathogens, and influence metabolic and neurogenic pathways. Polysaccharides trigger immune activation through pattern-recognition receptor pathways, including Dectin-1, MAPKs, and NF-κB, thereby enhancing cytokine production and the activity of NK cells and macrophages (Sohretoglu and Huang, 2018).

However, by blocking NF-κB and MAPK signaling, triterpenoids reduce inflammatory mediators (such as iNOS, COX-2, IL-6, and IL-1β). To strengthen antimicrobial and antiviral defenses, these two classes work in concert. Polysaccharides promote neurogenesis by activating the fibroblast growth factor receptor-1 and downstream ERK/AKT cascades, in addition to their roles in inflammation and immunology. Both of which improve glucose metabolism, preserve pancreatic β-cells, and suppress the NF-κB and MAPK pathways, among other metabolic benefits (Ahmad et al., 2024a).

Polysaccharides enhance antitumor immunity and inhibit DNA repair kinases (ATM, DNA-PK) in cancerous environments, thereby promoting apoptosis. All things considered, *G. lucidum* functions through complementary, multi-targeted molecular pathways that encompass metabolism, anticancer action, neuroprotection, anti-inflammatory effects, and immunological activation (Sohretoglu and Huang, 2018).

6.1 Activation of NK Cell Receptors

Through a unique mechanism that begins with the increased expression of activating receptors, specifically NKG2D and natural cytotoxicity receptors (NCRs), on NK cells, *Ganoderma lucidum* enhances NK cell–mediated cytotoxicity. Increased phosphorylation of kinases, such as ERK and JNK, results from the activation of downstream intracellular signaling through the MAPK (mitogen-activated protein kinase) pathway following the upregulation of this receptor. For NK cells to eliminate cancer cell targets, the activated MAPK cascade leads to the exocytosis of cytolytic effector molecules, specifically perforin and granulysin (Chang et al., 2014).

It has been demonstrated that *Ganoderma lucidum* polysaccharides and triterpenoids increase NK cell cytotoxicity primarily by modifying the expression and activity of key activating receptors, including NKG2D, NKp30, NKp44, and NKp46. The transcription and surface expression of these receptors are increased by NK cells in response to stimulation with *Ganoderma* extract (Chang et al., 2014). These receptors attach to stress-induced ligands (such as MICA/B and ULBPs) on tumor or virus-infected cells. By recruiting adaptor molecules like DAP10, NKG2D engagement sets off PI3K and Grb2-Vav1 signaling, which in turn activates the NF-κB and MAPK (ERK1/2, p38, JNK) pathways (Lu and Chen, 2010).

This cascade directly induces apoptosis in target cells by promoting cytoskeletal remodeling, immunological synapse formation, and the polarized release of cytotoxic granules containing granulysin, perforin, and granzymes. Furthermore, by stimulating macrophages and cytotoxic T cells, *Ganoderma* polysaccharides increase the production of IFN-γ by NK cells, thereby enhancing antitumor and antiviral responses (Lehrnbecher et al., 2020).

6.2 Modulation of Cytokine Networks

By rebalancing pro- and anti-inflammatory signaling and enhancing immunological coordination, the bioactive substances of *Ganoderma lucidum*, particularly polysaccharides and triterpenoids, modulate cytokine networks. By activating the NF-κB and MAPK pathways, which increase the transcription of Th1-type cytokines, including IL-2, IFN-γ, and TNF-α, polysaccharides stimulate macrophages, dendritic cells, and NK cells through pattern recognition receptors (e.g., dectin-1, TLR4), thereby enhancing cell-mediated immunity (Lehrnbecher et al., 2020). At the same time, *Ganoderma* triterpenoids can limit tissue damage and support regulatory T cell activity by upregulating IL-10 and TGF-β, and downregulating IL-6, IL-1β, and TNF-α through the inhibition of NF-κB translocation (Huang et al., 2017). Because of its ability to regulate immunological responses in both directions, *G. lucidum* can enhance defense against infections and malignancies while reducing chronic inflammation and autoimmune diseases.

6.3 Synergistic Effects with Other Immunotherapies

There is evidence suggesting that bioactive compounds in *Ganoderma lucidum*, specifically, polysaccharides and triterpenoids, can modulate immune responses and work synergistically with some immunotherapy treatments. In

murine tumor models, including those using BALB/c or C57BL/6 mice aged 6-8 weeks, polysaccharide extracts are administered at dosages ranging from 50 to 200 mg/kg/day, given either orally or intraperitoneally, while triterpenoid-rich extracts are administered at dosages of 25-100 mg/kg/day. *G. lucidum* polysaccharides administered with the checkpoint inhibitors, anti-PD-1 or anti-CTLA-4, elicit an immune response by producing then activating Th1 cytokines (IL-2, IFN-γ, TNF-α) and NK cells, while also enhancing dendritic cell maturation (Lehrnbecher et al., 2020), priming the immune system for anticancer efforts. Triterpenoids are also noted to suppress certain immunosuppressive cytokines, such as TGF-β and IL-10, and to enhance regulatory T cell responses, while also promoting CTL and T cell responses (Huang et al., 2017).

7. CLINICAL IMPLICATIONS

7.1 Cancer Immunotherapy

One of the most thoroughly researched benefits of *G. lucidum* is its anticancer effects. Its bioactive substances spare healthy cells while targeting cancer cells through various mechanisms. The promotion of programmed cell death, also known as apoptosis, is a primary mechanism of cell death. *G. lucidum* accomplishes this via interfering with mitochondrial activity and activating caspases. Furthermore, it prevents the formation of new blood vessels that nourish tumors by inhibiting angiogenesis, which limits the growth and metastasis of cancers (Gao and Homayoonfal, 2023). By altering the immune system, the mushroom strengthens the body's defenses against cancer. By enhancing T-cell-mediated responses and NK cell activity, *G. lucidum* improves the immune system's ability to identify and destroy cancer cells (Wang et al., 2024; Luo et al., 2024).

G. lucidum polysaccharides have been examined in many studies and have demonstrated anticancer benefits through cytotoxicity, antioxidative qualities, and induction of apoptosis. Using GLP at doses ranging from 0 to 15 mg/mL, Zhong et al. (2021) conducted an *in vitro* study to investigate the anticancer activities and cytotoxicity mechanisms of GLP. To investigate the antioxidant effects of GLP, YouGuo et al. (2009) administered to rats with ovarian cancer dosages of 200–600 mg/kg/day. Jin et al. (2020) investigated the effects of GLP on cervical cancer cells *in vitro*, focusing on its ability to induce apoptosis. GLP was applied to cancer cells for 72 hours at doses ranging from 0 to 500 μg/mL.

In rats with ovarian cancer, YouGuo et al. (2009) demonstrated that *G. lucidum* polysaccharides reduce oxidative stress by enhancing the activity of antioxidant enzymes and lowering malondialdehyde levels. According to Jin et al. (2020), these polysaccharides induce apoptosis, inhibit the migration and invasion of cervical cancer cells (C-33A and HeLa), and block the JAK/STAT5 and EMT signaling pathways. The extensive therapeutic potential of *G. lucidum* polysaccharides in oncology was confirmed by Zhong et al. (2021), who demonstrated their capacity to decrease tumor malignancy and disrupt autophagic flux in various *in vitro* and *in vivo* models.

7.2 Antiviral and Anti-inflammatory Prospects

G. lucidum has long been known to boost immunity, and new studies have shown that it may also be useful in treating viral infections. The polysaccharides and triterpenoids found in mushrooms are primarily responsible for their antiviral properties, as they stimulate immune cells and obstruct virus reproduction (Ahmad et al., 2021). Stimulating NK cells and increasing the body's production of IFN-γ are among the primary ways that *G. lucidum* fights viral infections. The identification and destruction of virus-infected cells depend on these immune reactions. *G. lucidum*'s capacity to stimulate NK cell activity strengthens the immune system's defenses against viruses such as hepatitis B, influenza, and the herpes simplex virus (HSV) (Arunachalam et al., 2022).

Furthermore, by preventing virus replication, *G. lucidum* has shown direct antiviral benefits. For instance, research has demonstrated that *G. lucidum* extract can prevent HIV from attaching to immune cells, thereby inhibiting the virus's ability to replicate (Cör Andrejč et al., 2022). Likewise, it has been demonstrated to prevent influenza virus replication by disrupting the production of viral proteins, thereby offering a natural alternative to traditional antiviral therapies (Gao et al., 2005). Due to these results, *G. lucidum* is a viable option for enhancing immune protection against various viral illnesses, particularly in individuals with compromised immune systems or those at a high risk of viral exposure.

Numerous contemporary illnesses, such as diabetes, neurological diseases, and cardiovascular ailments, are characterized by chronic inflammation. Triterpenoids, a class of potent bioactive substances found in G. lucidum, are effective anti-inflammatory agents due to their ability to block key inflammatory pathways (Ma et al., 2024). Suppres-

sion of the nuclear factor-kappa B (NF-κB) signaling pathway is a primary method. One element that controls the synthesis of pro-inflammatory cytokines is NF-κB. *G. lucidum* alleviates chronic inflammation by blocking this route, which lowers the synthesis of cytokines such as TNF-α, IL-1β, and IL-6 (Meng et al., 2023). *G. lucidum* inhibits the production of inflammatory mediators made from arachidonic acid, such as prostaglandins and leukotrienes.

In diseases like arthritis, where these molecules cause joint pain and inflammation, this impact is especially advantageous (Rowaiye et al., 2022). After taking *G. lucidum* supplements for three months, rheumatoid arthritis patients in clinical settings reported notable decreases in pain and swelling. It also has anti-inflammatory effects on the nervous system. *G. lucidum* may offer protection against diseases like multiple sclerosis and Alzheimer's disease, where persistent inflammation accelerates the course of the illness, by modifying neuroinflammatory pathways (Hapurachchi et al., 2016).

7.3 Challenges in Translating Traditional Use into Modern Therapy

The variable and frequently incorrect identification of *Ganoderma* species is one of the main obstacles. Although "*Ganoderma lucidum*" is mentioned in traditional writings, contemporary phylogenetic analyses show that many specimens with this name, particularly in Chinese traditional medicine, are actually different species, such as *Ganoderma lucidum* or *G. sichuanense*. Because the biochemical profile and effectiveness of one species may differ from another, misidentification compromises reproducibility and comparability across investigations (Antonelli et al., 2020).

In addition to taxonomy, the quality and consistency of *Ganoderma* products vary greatly. The procedures used for cultivation, harvesting, extraction, and processing are not sufficiently standardized. Unpredictable pharmacological effects and safety issues may arise from heavy metal trace contamination, inadequate spore disruption, or inadequate control of active chemical concentrations. It remains challenging to transform *Ganoderma* into trustworthy medicinal agents in the absence of stringent quality requirements (Karunarathna et al., 2025).

There remains a dearth of high-quality human clinical data to support medicinal claims of *Ganoderma*, despite its conventional acclaim and substantial *in vitro* and animal research. Small sample sizes, irregular dosage schedules, and methodological flaws are common problems in clinical trials. According to systematic reviews, there is no solid evidence to support the effectiveness of this approach for diseases such as cardiovascular disease or type 2 diabetes (Sullivan et al., 2006). There are both practical and conceptual difficulties in converting conventional medical ideas into a contemporary biomedical paradigm. While modern medicine requires precise objectives, dosage-response correlations, and well-defined mechanisms of action, traditional *Ganoderma* treatments are frequently described in holistic, systemic terms. It is challenging to reconcile conventional wisdom with evidence-based medicine in the absence of a shared conceptual vocabulary, especially considering the intricacy of *Ganoderma*'s numerous bioactive ingredients (Hapurachchi et al., 2016).

8. FUTURE TRENDS IN MUSHROOM-BASED IMMUNOTHERAPY

The use of *Ganoderma lucidum*, in particular, in mushroom-based immunotherapy is expected to grow as it is integrated with cutting-edge biomedical technologies and precision medicine methodologies. Future developments include the creation of defined bioactive compounds and the production of standardized, high-purity extracts to ensure repeatable immune modulation. Additionally, combination therapies are being explored, in which polysaccharides and triterpenoids derived from mushrooms work in concert with checkpoint inhibitors, CAR-T cells, or cancer vaccines to enhance antitumor immunity **(**Jiang et al., 2019).

While omics technologies (genomics, proteomics, and metabolomics) are used to determine precise mechanisms of action and predictive biomarkers of response, nanotechnology and targeted delivery systems are being investigated to enhance bioavailability and tissue-specific delivery of active compounds (Zhang et al., 2016; Paterson, 2006) Furthermore, the ability of mushroom polysaccharides to modify the gut microbiota is becoming recognized as a crucial mechanism for influencing systemic immunity, which may lead to customized immunotherapy. Standardization initiatives and rigorous clinical trials that transform traditional medicinal fungi into approved immunotherapeutic adjuvants are likely to enhance the integration of mushroom-based medicines into mainstream clinical protocols as regulatory frameworks evolve**.**

9. CONCLUSION

Ganoderma lucidum is regarded as a key immunomodulatory substance, exhibiting various therapeutic properties, particularly through its influence on natural killer (NK) cells, which play a vital role in immune defense processes. Polysaccharides and triterpenoids in *G. lucidum* significantly contribute to the enhancement of natural killer cell activity, the facilitation of cytokine release, and the overall strengthening of the immune response. The features described suggest that *G. lucidum* exhibits substantial potential as an ideal candidate for the development of additional therapeutic frameworks targeting neoplastic diseases, viral infections, and chronic inflammatory conditions. Nonetheless, in light of its historical and current applications in traditional medicine, formidable challenges remain in standardizing its bioactive elements, ensuring uniform quality across diverse formulations, and substantiating its clinical efficacy through rigorous trials. Moreover, it is necessary to conduct further examinations to accurately clarify the molecular mechanisms that regulate the immune-augmenting properties of *G. lucidum*, as well as its potential interactions with multiple immunotherapeutic compounds. As the domain of mushroom-based immunotherapy evolves, the integration of *G. lucidum* into current clinical methodologies reveals substantial prospects for enhancing immunotherapeutic interventions and improving patient prognoses in various pathological conditions.

Ethical Statement

Not Applicable.

Conflicts of Interest

The authors declare no competing interests.

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