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Ganoderma lucidum (Curtis) P. Karst. as a Multi-Target Anticancer Agent

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Ganoderma lucidum (Curtis) P. Karst., commonly known as reishi or lingzhi, is one of the most extensively studied medicinal mushrooms. It has been used in traditional Asian medicine for centuries and is now increasingly recognised in modern biomedical research. It contains a wide range of bioactive compounds, including polysaccharides, triterpenoids, sterols, phenolic compounds, alkaloids and immunomodulatory proteins, all of which contribute to its pharmacological properties. Of these, its anticancer activity has attracted significant attention due to its multi-target mechanisms, which involve the modulation of apoptosis, cell cycle arrest, the reduction of oxidative stress, the activation of the immune system, and the regulation of tumour-related signalling pathways, such as PI3K/Akt, MAPK, NF-κB and p53. This review summarises the latest preclinical research demonstrating the inhibitory effects of *G. lucidum* and its derivatives on various cancers, including breast, liver, lung, gallbladder, osteosarcoma and colorectal cancers. Consistent results from both *in vitro* and *in vivo* studies show that bioactive compounds from *G. lucidum* suppress tumour proliferation, induce apoptosis, modulate the tumour microenvironment, and enhance the efficacy of conventional chemotherapeutic agents. Although limited, emerging clinical data suggest potential benefits in improving immune function, quality of life, and survival outcomes in cancer patients, particularly when used as an adjuvant therapy. Importantly, toxicological and safety assessments indicate a favourable safety profile. No significant adverse effects were observed in animal models or clinical trials at commonly used doses. However, potential interactions with anticoagulant, antihypertensive, and antidiabetic drugs emphasise the importance of careful clinical supervision. Despite the promising results, there are still significant gaps in our understanding of the precise molecular mechanisms of action and in the establishment of standardised dosing regimens. Therefore, well-designed clinical trials are required to validate its therapeutic efficacy fully and facilitate its integration into evidence-based oncology.

Keywords: *Ganoderma lucidum*, reishi, lingzhi, anticancer activity, polysaccharides, medicinal mushrooms

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Introduction

Ganoderma lucidum (Curtis) P. Karst., a medicinal mushroom belonging to the *Ganoderma*taceae family, is traditionally known as lingzhi in China and reishi in Japan. It has been revered for centuries as the 'mushroom of immortality' thanks to its reputed health-promoting and longevity-enhancing properties (Wachtel-Galor et al., 2011). In traditional East Asian medical systems, it was regarded as a highly valuable tonic fungus reserved for emperors and the elite, further contributing to its symbolic status as a substance associated with vitality, spiritual balance and overall well-being. It was deeply embedded in holistic health practices, where it was used not only to treat specific ailments, but also as a general adaptogen to support the body's long-term resilience (Wachtel-Galor et al., 2011; Oke et al., 2022).

Traditionally used in Chinese medicine to restore qi, strengthen cardiac function, alleviate respiratory symptoms and calm the mind, *G. lucidum* is now recognised in both the American Herbal Pharmacopoeia and the Chinese Pharmacopoeia (Wachtel-Galor et al., 2011). These official recognitions reflect its transition from traditional ethnomedicine to evidence-based complementary medicine, where standardised extracts and preparations are being investigated more and more for their pharmacological potential. Contemporary biomedical research has confirmed that this mushroom exhibits a wide spectrum of biological activities, including anti-inflammatory, antioxidant, anti-glycaemic, anti-ulcer, immunomodulatory and anticancer effects (Ahmad, 2018; Cör Andrejč et al., 2022). Notably, these activities are not attributed to a single mechanism, but rather to the complex interplay of multiple signalling pathways, including the modulation of cytokine production, the inhibition of oxidative stress, the regulation of glucose metabolism, and the enhancement of innate and adaptive immune responses (Ahmad et al., 2024).

G. lucidum contains numerous bioactive constituents, including polysaccharides (GLP) and triterpenoids, which are considered the main contributors to its anti-cancer activity (Chen et al., 2004; Wu et al., 2013). These compounds have been shown to influence tumour cell proliferation, induce apoptosis and suppress angiogenesis, while simultaneously enhancing host immune surveillance against malignant cells. In addition to these well-characterised fractions, the mushroom contains sterols, peptides and phenolic compounds that may act synergistically to further amplify its pharmacological profile (Plosca et al., 2025). Consequently, *G. lucidum* continues to attract significant scientific interest as a promising natural source of multi-target therapeutic agents with potential applications in oncology, metabolic disorders and immune-related diseases (Liu et al., 2025; Plosca et al., 2025).

This review aims to provide an analysis of the current knowledge regarding the anticancer potential of *G. lucidum*. Particular emphasis is placed on its major bioactive compounds, the molecular mechanisms of action and the evidence derived from preclinical and clinical studies. The review also evaluates the safety profile, toxicological data and clinical considerations associated with its use, emphasising its therapeutic potential and the limitations that currently exist in oncology.

Main bioactive components of *Ganoderma lucidum*

G. lucidum is a mushroom that is both nutritionally and biochemically rich. It is composed of around 90% water and 10% bioactive constituents, including polysaccharides, triterpenoids, phenolic compounds, sterols, proteins, minerals, lipids and vitamins (Wachtel-Galor et al., 2011; Plosca et al., 2025). The dry mass contains carbohydrates, fibre, proteins, fats and ash, as well as a broad spectrum of essential minerals, such as potassium, phosphorus, magnesium, iron, zinc and selenium, which contribute to its physiological and health-promoting properties (Plosca et al., 2025). Polysaccharides are the most abundant and structurally diverse of these constituents, while triterpenoids (notably ganoderic acids) represent another major group with complex chemical structures and significant biological activity (Azi et al., 2024). Phenolic compounds, sterols, proteins and lipids further enrich its functional profile, collectively supporting its traditional medicinal use and modern pharmacological interest (Plosca et al., 2025).

Polysaccharides

Ganoderma polysaccharides (GLPs) are among the most abundant and biologically active compounds found in *G. lucidum* (Hsu et al., 2017). These consist of complex mixtures of homopolysaccharides and heteropolysaccharides, including β-glucans, α-glucans and heteroglycans, which are composed of various monosaccharides, such as glucose, mannose and xylose (Gao and Homayoonfal, 2023). The structural diversity of GLPs, including branching patterns, molecular weight (10^3–10^6 Da) and triple-helix conformations, has a significant impact on their biological activity and determines their interaction with immune

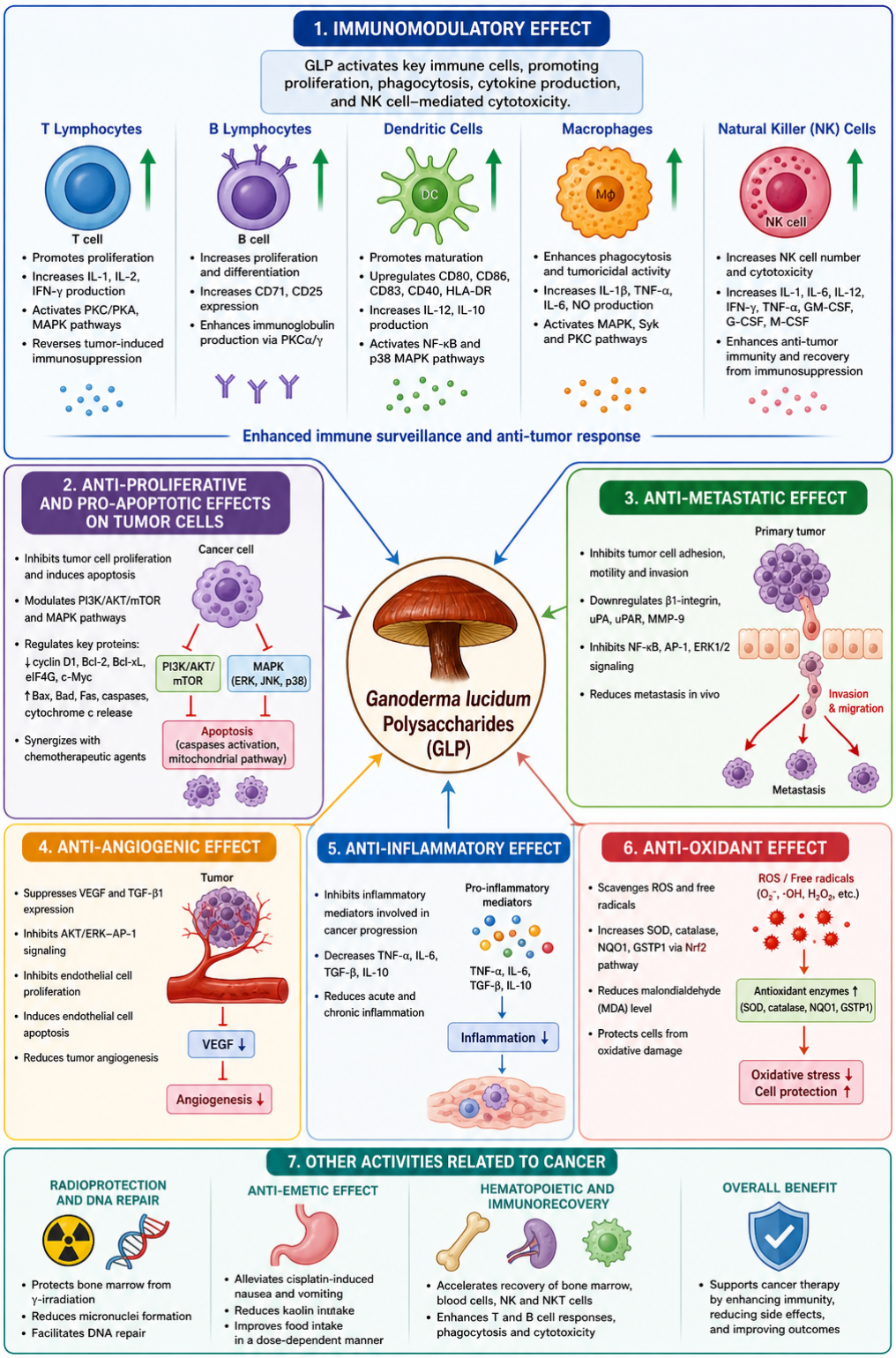

Figure 1 Immunomodulatory and anticancer mechanisms of *Ganoderma lucidum* (Curtis) P. Karst. polysaccharides (GLPs)
GLP – *Ganoderma lucidum* polysaccharides; NK – natural killer; DC – dendritic cell; Mφ – macrophage; ROS – reactive oxygen species; IFN-γ – interferon gamma; IL – interleukin; TNF-α – tumor necrosis factor alpha; TGF-β – transforming growth factor beta; G-CSF – granulocyte colony-stimulating factor; M-CSF – macrophage colony-stimulating factor; MAPK – mitogen-activated protein kinase; ERK – extracellular signal-regulated kinase; JNK – c-Jun N-terminal kinase; p38 – p38 mitogen-activated protein kinase; PI3K – phosphoinositide 3-kinase; Akt – protein kinase B; mTOR – mechanistic target of rapamycin; NF-κB – nuclear factor kappa B; AP-1 – activator protein 1; VEGF – vascular endothelial growth factor; MMP-9 – matrix metalloproteinase-9; uPA – urokinase-type plasminogen activator; uPAR – urokinase plasminogen activator receptor; Bcl-xL – B-cell lymphoma-extra large; Bcl-2 – B-cell lymphoma 2; Bax – Bcl-2-associated X protein; SOD – superoxide dismutase; NQO1 – NAD(P)H quinone dehydrogenase 1; GSTP1 – glutathione S-transferase pi 1; MDA – malondialdehyde

receptors and cellular membranes (Lu et al., 2020). Additionally, differences in the extraction source (fruiting body, mycelium, or spores) contribute to variability in composition and potency. Chemical modification of GLPs, such as sulfation or carboxymethylation, can further enhance solubility, stability, and anticancer potential, making them more suitable for pharmaceutical applications (Luo et al., 2021). These structural and functional features establish GLPs as some of the most promising natural macromolecules in modern biomedicine. Building upon this structural complexity, considerable attention has been given to improving the efficiency of GLP production and extraction processes, which directly affect yield and bioactivity.

GLPs exhibit broad anticancer activity, primarily through their strong immunomodulatory effects. GLPs activate key immune cells, including T and B lymphocytes, dendritic cells, macrophages and natural killer (NK) cells. This enhances lymphocyte proliferation, phagocytosis and cytokine production (e.g. IL-1, IL-2, IL-6, IL-12, IFN-γ and TNF-α), as well as NK cell cytotoxicity (Kladar et al., 2016; Sohretoglu and Huang, 2018). These effects strengthen both cellular and humoral immune responses and improve antigen presentation. GLP acts through multiple signalling pathways, including NF-κB, MAPK (ERK, p38 and JNK), PI3K/AKT, and PKC- and PKA-dependent cascades (Cör et al., 2018; Sohretoglu and Huang, 2018). Consequently, GLP can counteract tumour-induced immunosuppression and restore effective antitumour immune surveillance (Figure 1).

In addition to immune activation, GLP exerts direct anti-cancer effects by inhibiting tumour cell proliferation, inducing apoptosis, and suppressing migration, invasion, and angiogenesis (Figure 1). These activities are associated with modulation of the cell cycle (e.g., downregulation of cyclin D1), inhibition of the PI3K/AKT/mTOR and MAPK pathways, activation of caspases and regulation of pro- and anti-apoptotic proteins such as BAX, BCL-2 and BCL-xL (Gao and Homayoonfal, 2023). GLP also reduces tumour-associated inflammation and oxidative stress, both of which contribute to carcinogenesis (Hsieh and Wu, 2011). Further *in vivo* studies demonstrate the inhibition of tumour growth and metastasis, as well as the synergistic effects of GLP with chemotherapeutic agents (Zhao et al., 2012; Pillai et al., 2014). This supports its potential as an adjuvant in cancer therapy.

Figure 1 provides a comprehensive overview of the multitarget anticancer effects of GLPs, which extend beyond immunomodulation to encompass direct actions on tumour biology.

Sterols

Sterols from *G. lucidum* (GLSs), including ergosterol derivatives, are key structural components of fungal cell membranes. There, they regulate membrane fluidity, permeability and metabolic processes (Shahzad et al., 2017; Wu et al., 2024). This species contains approximately 27 sterol types, many of which exhibit notable anticancer activity (Xu et al., 2021). Their structural diversity enables interaction with multiple molecular targets involved in cell proliferation and survival. For instance, ergosterol peroxide has been demonstrated to induce apoptosis in cancer cells by inhibiting the AKT signalling pathway and activating Foxo3-dependent transcriptional programmes, resulting in cell cycle arrest and programmed cell death (Li et al., 2016). Additionally, these sterols modulate inflammatory responses by regulating MAPK and NF-κB signalling pathways, thereby linking anti-cancer and anti-inflammatory effects (Xu et al., 2021). This dual functionality enhances their therapeutic relevance in chronic disease contexts. Beyond their molecular mechanisms, sterols also demonstrate a broad range of biological effects at the systemic level.

Triterpenoids

Alongside sterols, triterpenoids represent another major and highly diverse class of bioactive metabolites. *G. lucidum* triterpenoids (GLTs) are important bioactive compounds with diverse pharmacological properties that are attracting increasing attention in natural product chemistry and biomedical research (Lu et al., 2020; Xu et al., 2021). GLTs are highly oxidised lanostane derivatives characterised by strong lipophilicity, facilitating their interaction with biological membranes and intracellular targets. GLTs are widely distributed in fruiting bodies and mycelia, though their concentration varies depending on cultivation conditions, developmental stage and environmental factors (Xie et al., 2020). GLTs can be tetracyclic, pentacyclic or, less frequently, linear or bicyclic in structure, with tetracyclic lanosterane-type triterpenes predominant (Gao et al., 2018; Wang et al., 2020). This structural variability underpins their wide range of biological activities and contributes to their ability to interact with multiple molecular targets. Furthermore, their lipophilic nature enables them to cross cellular membranes efficiently, which is particularly relevant for their pharmacological activity in cancer and metabolic diseases. These characteristics establish triterpenoids as one of the most pharmacologically significant groups of compounds in *G. lucidum*. Selected triterpenoids exhibit diverse

biological activities, including anti-cancer, anti-viral, anti-inflammatory and enzyme-inhibitory effects, which highlight their multifunctional therapeutic potential (Galappaththi et al., 2022). Ganoderic acids A, B, C and their derivatives are among the most extensively studied, having demonstrated cytotoxic activity against a wide range of cancer cell lines (Radwan et al., 2011).

To date, over 380 triterpenoids have been identified in *G. lucidum*, including the well-known ganoderic acids and ganoderols (Zheng et al., 2023). Most of these compounds contain 27 or 30 carbon atoms, reflecting their biosynthetic origin and structural classification (Xia et al., 2014). Importantly, even minor structural modifications, such as hydroxylation or acetylation, can significantly alter their pharmacological profile. This remarkable structural diversity provides a strong foundation for the development of novel therapeutic agents derived from *G. lucidum* triterpenoids. Numerous studies have therefore focused on identifying representative compounds and evaluating their biological activities.

Alkaloids

Alkaloids are an important class of secondary metabolites in *G. lucidum*. They are characterised by their complex cyclic structures, which typically contain one or more nitrogen atoms incorporated into heterocyclic ring systems (Sharma et al., 2019; Olofinsan et al., 2023). These compounds are synthesised through various metabolic pathways, often from amino acids, and exhibit significant structural variability, which directly impacts their biological activity (Dai et al., 2018; Dey et al., 2020). This diversity enables them to interact with a wide range of molecular targets, including enzymes, receptors and nucleic acids, making them highly relevant in pharmacological research. Key alkaloids identified in *G. lucidum* include choline, betaine and γ-trimethylaminobutyric acid, as well as structurally unique compounds such as lucidimines and sinensines. These molecules have attracted considerable attention due to their diverse biological activities, including neuroprotective, antioxidant, anti-inflammatory and antiproliferative effects (Chen and Lan, 2018; Lu et al., 2019; Zhang et al., 2021).

Proteins and peptides

In addition to low-molecular-weight compounds, *G. lucidum* contains various bioactive proteins, such as fungal immunomodulatory proteins (FIPs) and glycoproteins. These proteins are crucial mediators of immune regulation and tumour suppression (Xu et al., 2023). These proteins can enhance the activity of immune cells, such as macrophages, T lymphocytes and natural killer cells, thereby strengthening the body‘s defence mechanisms. Furthermore, FIPs have been shown to modulate cytokine production and influence signalling pathways associated with inflammation and the immune response. Their antitumour effects are partly attributed to their ability to inhibit tumour cell proliferation and induce apoptosis (Drzewiecka et al., 2024). Glycoproteins, on the other hand, may contribute to cell-to-cell communication and immune recognition processes (Ekiz et al., 2023). These proteinaceous compounds represent an important component of the therapeutic potential of *G. lucidum*.

Anticancer mechanisms of *Ganoderma lucidum* bioactive compounds

G. lucidum anti-cancer effects are primarily mediated by the inhibition of tumour cell proliferation, migration and survival, as well as the induction of apoptosis via multiple signalling pathways. For instance, *G. lucidum* spore oil has been shown to suppress breast cancer cell growth by activating the mitochondrial apoptotic pathway, thereby upregulating Bax and caspase-3 and reducing tumour progression *in vivo* (Jiao et al., 2020). Similarly, *G. lucidum* extracts have been shown to inhibit the proliferation and migration of glioblastoma and hepatocellular carcinoma cells by inducing cell cycle arrest and modulating Wnt/β-catenin signalling and the downregulation of cyclin-related proteins (Zhang, 2017; Cheng et al., 2020; Ding et al., 2023). These effects collectively result in reduced tumour growth, enhanced apoptosis, and impaired metastatic potential (Figure 2).

A central mechanism of *G. lucidum* action is immunoregulation, whereby GLPs enhance the polarisation of macrophages, activate natural killer (NK) cells, T cells and dendritic cells, and increase the production of cytokines (e.g. TNF-α, IL-6 and IL-1β), thereby strengthening antitumour immunity (Lin, 2005; Zhang et al., 2002). GLPs also modulate key pathways, such as MAPK/NF-κB and PI3K/AKT, thereby promoting immune-mediated tumour suppression (Song et al., 2021; Li et al., 2023). Furthermore, GLPs inhibit immune checkpoint molecules such as PD-1 and CTLA-4, thereby enhancing T-cell-mediated responses (Su et al., 2018). Beyond its effects on the immune system, *G. lucidum* also targets tumour metabolism and survival by inducing mitochondrial dysfunction, inhibiting telomerase activity, suppressing angiogenesis via VEGF downregulation and reversing multidrug resistance by inhibiting P-glycoprotein

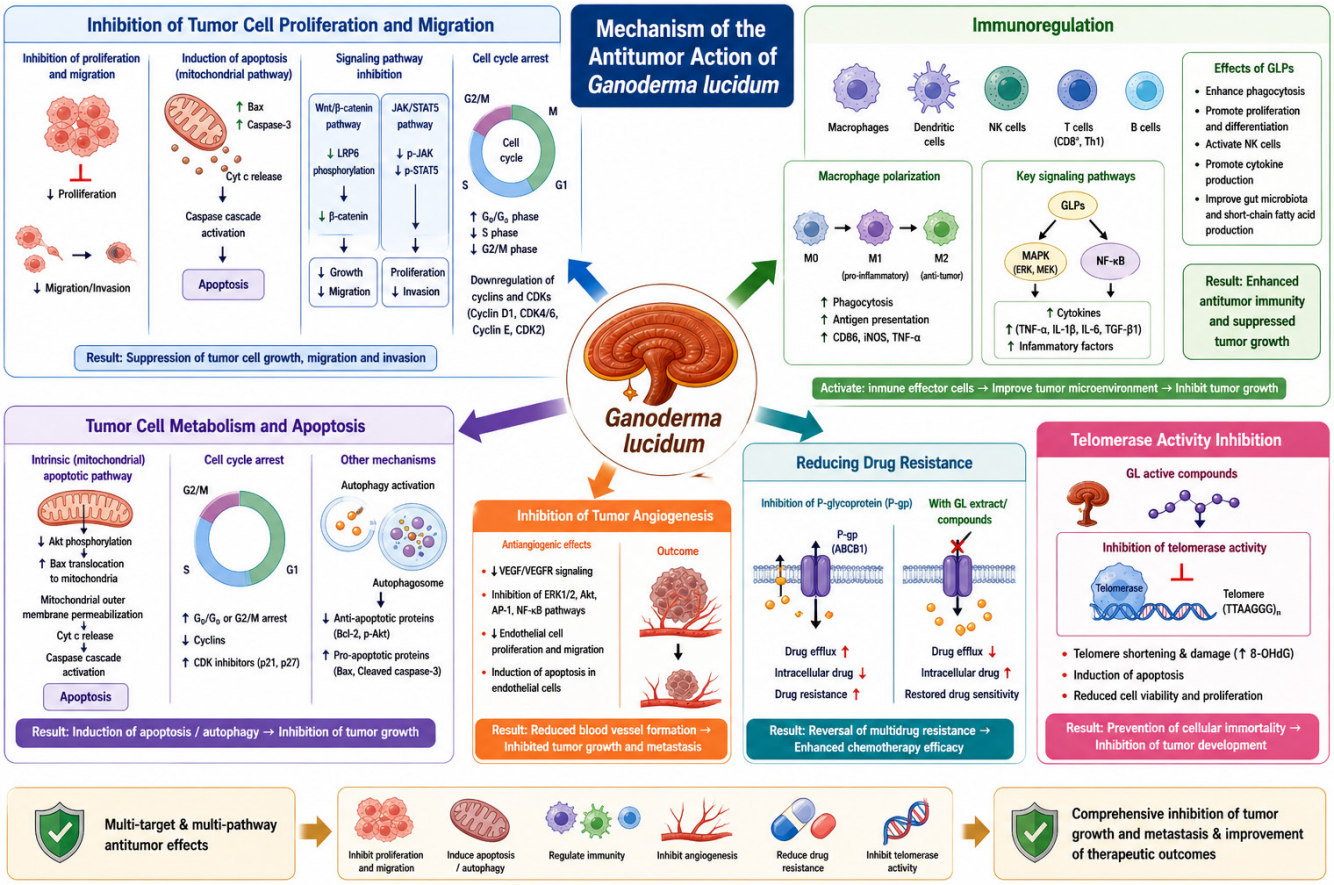

Figure 2 Anticancer mechanisms of *Ganoderma lucidum* (Curtis) P. Karst.
GL – *Ganoderma lucidum*; GLPs – *Ganoderma lucidum* polysaccharides; ROS – reactive oxygen species; NK – natural killer; Th1 – T helper type 1; MAPK – mitogen-activated protein kinase; ERK – extracellular signal-regulated kinase; NF-κB – nuclear factor kappa B; AP-1 – activator protein 1; PI3K – phosphoinositide 3-kinase; Akt – protein kinase B; JAK – Janus kinase; STAT5 – signal transducer and activator of transcription 5; Wnt – wingless/integrated signaling pathway; β-catenin – beta-catenin; LRP6 – low-density lipoprotein receptor-related protein 6; P-gp (ABCB1) – P-glycoprotein (ATP-binding cassette subfamily B member 1); VEGF – vascular endothelial growth factor; VEGFR – vascular endothelial growth factor receptor; TNF-α – tumor necrosis factor alpha; IL – interleukin; TGF-β1 – transforming growth factor beta 1; iNOS – inducible nitric oxide synthase; CD86 – cluster of differentiation 86; Bcl-2 – B-cell lymphoma 2; Bax – Bcl-2-associated X protein; CDK – cyclin-dependent kinase; Nrf2 – nuclear factor erythroid 2–related factor 2; 8-OHdG – 8-hydroxy-2′-deoxyguanosine

function (Ding et al., 2023; Liu et al., 2020; Wu et al., 2022). Thus, *G. lucidum* acts through a multi-target network that includes the induction of apoptosis, immune activation, the inhibition of angiogenesis, and metabolic disruption, making it a promising multifunctional anti-cancer agent.

GLPs exhibit strong anti-cancer properties and act synergistically with chemotherapeutic agents, such as doxorubicin and 5-fluorouracil, to enhance therapeutic efficacy whilst reducing systemic toxicity and adverse effects (Liang et al., 2014; Opattova et al., 2019; Gao and Homayoonfal, 2023). This is particularly important in combination therapies, where GLPs can increase the sensitivity of tumour cells to drugs and mitigate chemotherapy-induced immunosuppression. At the cellular level, GLPs primarily induce apoptosis in cancer cells via mitochondrial pathways, leading to loss of membrane potential, cytochrome c release, and activation of caspase cascades. GLPs also regulate the expression of key apoptotic proteins, such as Bax and Bcl-2, thereby modulating the intrinsic apoptotic balance. Additionally, GLPs exhibit immunomodulatory activity by enhancing macrophage activation, promoting cytokine secretion and stimulating natural killer cell function. Their antioxidant properties further contribute to anti-cancer effects by reducing oxidative stress and protecting normal cells from DNA damage (Raj and Sa, 2015; Fang et al., 2022). Together, these mechanisms highlight their multifunctional role in cancer prevention and therapy. Despite the well-documented biological activities of GLPs, the precise molecular mechanisms underlying their function remain an active area of investigation, highlighting existing knowledge gaps.

Although GLP activity has been well documented in numerous *in vitro* and *in vivo* studies, its receptor interactions and downstream signalling pathways remain poorly characterised. Current evidence suggests their involvement in complex regulatory networks that include Toll-like receptors (TLRs), Dectin-1 and other pattern recognition receptors, which initiate immune-related signalling cascades (Wang et al., 2012; Bentharavithana et al., 2026). However, the specificity and hierarchy of these interactions are not yet fully understood. Furthermore, intracellular signalling pathways such as MAPK, PI3K/Akt and NF-κB appear to be modulated by GLPs. However, the detailed mechanistic links between the structural features of polysaccharides and specific molecular responses require further clarification. Consequently, more advanced omics-based approaches, including transcriptomics, proteomics, and metabolomics, are needed to elucidate their comprehensive biological effects (Yang et al., 2016; Lu et al., 2020). Addressing these gaps will be crucial for translating GLP research into clinically applicable therapies.

In addition to polysaccharides, other metabolite groups, such as sterols, significantly contribute to the pharmacological profile of *G. lucidum*. GLSs exhibit a variety of pharmacological activities, including anti-inflammatory, hepatoprotective and antitumour effects, which contribute to their overall therapeutic potential. At the cellular level, they induce apoptosis through mitochondrial dysfunction, cytochrome c release and caspase activation, in a manner similar to polysaccharide-mediated mechanisms, albeit via distinct molecular targets (Ahmad et al., 2023; Pozzobon et al., 2026). Furthermore, sterols exhibit cytotoxic effects against multiple cancer cell lines, including models of liver, breast and lung cancer, indicating broad-spectrum anti-cancer activity (Lee et al., 2009; Zheng et al., 2018). *In vivo* studies also suggest potential benefits in tumour growth inhibition and metastasis suppression (Lee et al., 2011). These findings strongly support the potential of GLSs as chemopreventive and adjuvant therapeutic agents, particularly when combined with other bioactive compounds from *G. lucidum*.

GLTs exhibit a wide variety of pharmacological activities, including antihypertensive, hepatoprotective, cholesterol-lowering and potent antitumour effects (Wang et al., 2020). In the context of cancer, triterpenoids have been shown to inhibit cell proliferation and induce apoptosis in various tumour models, including HT-29 colon cancer cells, in a dose-dependent manner (Thyagarajan et al., 2010). They also interfere with angiogenesis and metastasis, thereby limiting tumour progression. Furthermore, their anti-inflammatory activity contributes to the suppression of tumour-promoting microenvironments (Ding et al., 2023). These multifunctional effects highlight the therapeutic versatility of GLTs and their potential application in treating complex, multifactorial diseases. Further studies have revealed that triterpenes isolated from *G. lucidum* can inhibit the growth of liver cancer cells induced by oxidative stress and can regulate key signalling pathways involved in cell survival and apoptosis. These effects are exerted by modulating mitochondrial function, reducing reactive oxygen species production and activating intrinsic apoptotic pathways (Ding et al., 2023; Zhao et al., 2025). Ganoderterpene A, for example, has been shown to regulate MAPK and NF-κB signalling pathways, which are critical for cell proliferation, inflammation and apoptosis (Kou et al., 2021; Zhang et al., 2022). By suppressing NF-κB activation, these compounds reduce inflammatory responses and tumour cell survival. Simultaneously, modulation of MAPK pathways influences cell cycle regulation and apoptotic signalling (Dudhgaonkar et al., 2009). Furthermore, improvements in mitochondrial function contribute to enhanced cellular homeostasis and reduced oxidative damage (Cancemi et al., 2024). These findings emphasise the multi-target mechanisms through which triterpenoids exert their anti-cancer effects.

Proteomic studies have identified anticancer peptides (ACPs) derived from *Ganoderma* species that may exert cytotoxic effects on cancer cells while sparing normal tissues (Zheng et al., 2020; Zhao et al., 2023). These peptides can interfere with membrane integrity, induce apoptosis, or modulate intracellular signalling pathways. However, their isolation, structural characterisation and mechanism of action require further investigation. Advances in this area of research could lead to the development of novel peptide-based therapeutics. Alongside proteins and peptides, the amino acids present in *G. lucidum* also contribute to its biological activity. The amino acids present in *G. lucidum* play an important role in metabolic regulation and may contribute to its anti-cancer properties. Compounds such as arginine and glutamine influence tumour growth by modulating nutrient availability and metabolic pathways (Bojarska et al., 2019; Byun et al., 2020). In particular, leucine has been shown to induce apoptosis via caspase-dependent mechanisms, highlighting its potential role in regulating cancer cells (Sheen et al., 2011). Furthermore, hydrophobic amino acids may enhance

antioxidant capacity by improving cells' ability to scavenge free radicals and reduce oxidative stress (Girjal et al., 2012). These effects support the idea that even basic metabolic components can contribute to the overall pharmacological activity of *G. lucidum*.

Phenolic compounds are an additional group of bioactive molecules found in *G. lucidum*, which contribute significantly to its antioxidant and anticancer properties. Although they are present in lower concentrations than polysaccharides or triterpenoids, their high reactivity and ability to donate hydrogen atoms make them effective scavengers of reactive oxygen species (Thapa et al., 2025). Polyphenols identified in *G. lucidum* have demonstrated strong antiproliferative effects against various cancer cell lines and have been shown to mitigate oxidative stress by protecting cellular components from damage (Kolniak-Ostek et al., 2022). Furthermore, they may modulate signalling pathways related to inflammation, apoptosis, and cell cycle regulation. The interaction between phenolic compounds and other bioactive constituents is synergistic, enhancing the overall therapeutic potential of *G. lucidum* (Plosca et al., 2025). These findings emphasise the complex, multi-component nature of this medicinal mushroom and its potential as a source of novel bioactive agents.

Preclinical and clinical evidence of *Ganoderma lucidum* in anticancer therapy

Numerous experimental studies (Garmanchuk et al., 2022; Xie et al., 2025; Zhang et al., 2026; Wang et al., 2026) have demonstrated that *G. lucidum* exhibits inhibitory effects against a wide range of malignant tumours, including liver, breast, lung and colon cancers. The available evidence can be categorised as either preclinical studies, which comprise both *in vitro* and *in vivo* models, or the more limited but emerging clinical observations. This classification provides a clearer understanding of the current state of research and the potential of *G. lucidum* in oncology.

Preclinical *in vitro* studies provide fundamental insights into the cellular and molecular mechanisms underlying the anti-cancer activity of *G. lucidum*. For instance, Jiao et al. (2020) showed that *G. lucidum* spore oil (GLSO) significantly reduced the proliferation of MDA-MB-231 breast cancer cells by triggering apoptosis via the mitochondrial pathway. This effect was associated with increased expression of pro-apoptotic proteins such as Bax and caspase-3, with no significant changes observed in caspase-8 expression, indicating activation of the intrinsic apoptotic pathway. Similarly, Kim et al. (2016) reported that a combination of *G. lucidum* and *P. umbellatus* extracts inhibited proliferation and induced apoptosis in MCF-7 breast cancer cells by increasing intracellular calcium levels and reactive oxygen species (ROS) production.

Further *in vitro* investigations have highlighted *G. lucidum*'s ability to regulate tumour cell proliferation and migration. Triterpenoids have been shown to inhibit the growth of hepatocellular carcinoma cells by suppressing proliferation and inducing apoptosis (Ding et al., 2023). Additionally, *G. lucidum* extracts were found to interfere with key oncogenic pathways such as the Wnt/β-catenin signalling pathway, thereby reducing breast cancer cell growth and migration by inhibiting LRP6 phosphorylation (Zhang, 2017). These findings confirm that *G. lucidum* targets multiple signalling pathways involved in tumour progression.

Cell cycle regulation is another important mechanism observed in *in vitro* models. For example, Cheng et al. (2020) demonstrated that *G. lucidum* extracts reduced glioblastoma cell viability in a dose- and time-dependent manner, suggesting mitochondrial dysfunction and apoptosis induction. Similarly, ganoderiol F was shown to arrest the cell cycle in the G0/G1 phase and downregulate cyclin-related proteins, thereby inhibiting the proliferation of MDA-MB-231 cells (Li et al., 2019). These results highlight the ability of *G. lucidum* compounds to disrupt the progression of the cancer cell cycle.

In addition to their direct cytotoxic effects, *in vitro* studies have revealed the strong immunomodulatory properties of *G. lucidum*. Polysaccharides (GLPs) enhance macrophage activity, stimulate cytokine production and promote the proliferation of immune cells, including lymphocytes and dendritic cells (Zhang et al., 2002; Lin, 2005). These effects contribute to improved immune-mediated tumour suppression and highlight the role of *G. lucidum* as an immunological regulator.

Moving beyond cell-based models, *in vivo* studies provide important evidence of *G. lucidum*'s systemic anti-cancer effects. In animal models, GLSO was found to significantly reduce tumour growth, confirming the efficacy observed in *in vitro* experiments (Jiao et al., 2020). Similarly, triterpenoids have been shown to inhibit tumour development in hepatocellular carcinoma models without causing significant toxicity to normal tissues (Ding et al., 2023), indicating a favourable safety profile.

Animal studies have also demonstrated that *G. lucidum* modulates the tumour microenvironment and immune system. GLPs promote the polarization of macrophages

and the secretion of cytokines, including TNF-α, IL-1β, IL-6 and TGF-β1. This enhances antitumour immunity and induces apoptosis via the PI3K/AKT signalling pathway (Song et al., 2021). Furthermore, activation of MAPK/NF-κB signalling contributes to tumour growth inhibition through immune regulation (Li et al., 2023).

In vivo studies have also shown that *G. lucidum* can regulate adaptive immunity. GLPs have been shown to increase the proportion of cytotoxic $CD8^+$ T cells and Th1 cells, while reducing regulatory T cells. This enhances antitumour immune responses (Li et al., 2024). Additionally, modulation of the gut microbiota and metabolic pathways has been shown to contribute to improved immune function and tumour suppression.

The effects of *G. lucidum* on tumour metabolism and apoptosis have also been confirmed in animal studies. Compounds such as LZO-3 and lucialdehyde B have been shown to induce mitochondrial dysfunction and disrupt membrane potential, thereby triggering apoptosis through intrinsic pathways (Liu et al., 2020; Liu et al., 2023). These findings emphasise the pivotal role of mitochondrial pathways in *G. lucidum*-mediated anti-cancer activity.

Another important finding of *in vivo* studies is the inhibition of tumour angiogenesis. *G. lucidum* compounds have been shown to reduce the expression of vascular endothelial growth factor (VEGF) and suppress endothelial cell proliferation. This limits tumour vascularisation and growth (Hsu et al., 2009; Liu et al., 2020). This anti-angiogenic effect is crucial in preventing tumour expansion and metastasis.

Preclinical evidence also supports the role of *G. lucidum* in overcoming drug resistance. Extracts and triterpenoids have been shown to inhibit P-glycoprotein (P-gp) function, reduce drug efflux and increase the intracellular accumulation of chemotherapeutic agents, thus reversing multidrug resistance in cancer cells (Wu et al., 2022; Li et al., 2023). These findings suggest potential applications as adjuvant therapies in chemotherapy.

While a substantial body of preclinical evidence supports the anticancer potential of *G. lucidum*, clinical data remains comparatively limited, though generally positive. Since 1997, several clinical studies have examined its potential as an adjunct to cancer treatment, particularly when used alongside chemotherapy or radiotherapy (Wu et al., 2024). These studies suggest that *G. lucidum* preparations, such as Lingzhi capsules, extracts and spore powder, may enhance immune function, as indicated by increased NK cell activity and improved CD4/CD8 ratios. This suggests that cellular immunity is being stimulated in cancer patients (Górska-Jakubowska et al., 2025). Furthermore, clinical observations suggest that *G. lucidum* extract supplementation can enhance the quality of life for lung cancer patients and that oral spore powder can improve physical well-being and reduce fatigue in breast cancer patients undergoing endocrine therapy (Zhao et al., 2012; Liu et al., 2020). Despite these promising findings, the current evidence is insufficient to support the use of *G. lucidum* as a primary treatment for cancer. Therefore, further large-scale, well-designed clinical trials are necessary to confirm its therapeutic efficacy, determine optimal dosing strategies and establish its long-term safety profile.

Thus, the current evidence strongly supports the anticancer activity of *G. lucidum*, as demonstrated by preclinical studies *in vitro* and *in vivo*, which show its ability to target multiple pathways involved in tumour development and progression. While clinical data are still emerging, the multifunctional nature of its bioactive compounds highlights its potential as a complementary agent in cancer therapy, warranting further clinical investigation.

Safety profile, toxicological evaluation, and clinical considerations of *Ganoderma lucidum*

Preclinical and toxicological studies consistently indicate that *G. lucidum* has a high safety profile. For instance, the oral administration of a hot water extract at a dose of 5,000 $mg \cdot kg^{-1}$ over 30 days had no effect on body weight, organ mass or haematological parameters in mice (Upton, 2006). Another study demonstrated that even extremely high doses (equivalent to 220 $g \cdot kg^{-1}$) had no genotoxic or cytotoxic effects on mouse lymphocytes (Chiu et al., 2000). Further confirmation of these findings comes from acute and chronic toxicity studies, which show that the maximum tolerated dose exceeds 20 $g \cdot kg^{-1}$ body weight in animal models and that long-term administration does not adversely affect organ function, blood chemistry or histological structure (Lin et al., 2017; Xu and Li, 2019). These results strongly support the conclusion that *G. lucidum* extracts and polysaccharides (GLPs) are generally safe under experimental conditions. This safety profile is also reflected in regulatory frameworks: *G. lucidum* is classified as a Class 1 substance by the American Herbal Products Association (Liu et al., 2024), β-glucans derived from its mycelium have received GRAS status in the United States (U.S. FDA, 2012), and its fruiting body is accepted in the European Union based on

Table 1 Summary of recent studies evaluating anticancer activity of *Ganoderma lucidum* (Curtis) P. Karst. and its bioactive compounds

Model/cancer type	Experimental approach	Key findings	Mechanism of action (pathway)	References
MCF-7 breast cancer cells	ethanol and methanol extracts; MTT, RT-qPCR, flow cytometry	strong cytotoxicity (IC_{50} = 62.37 μg·mL^{-1}), G_0/G_1 arrest, apoptosis induction	energy metabolism disruption; downregulation of ACAT1/ADCY3/NME2; apoptosis induction via gene regulation	Gülüm et al. (2025)
HepG2, HCT116, MCF-7, A549	solvent extracts; UHPLC-MS, docking, DPPH assay	strong anticancer activity of ethyl acetate extract; low toxicity to normal cells	AKT1/CDK2/ERK1/TNFα inhibition via depsidone binding; apoptosis and proliferation suppression	Mohamed et al. (2025)
HeLa cells	multi-solvent extraction; GC-MS	dose-dependent cytotoxicity (>65% inhibition); strong antioxidant activity	ROS modulation; polyphenol-driven oxidative stress-mediated apoptosis	Thapa et al. (2025)
Osteosarcoma (S-180)	*in vitro*/*in vivo*; multi-omics	inhibited proliferation and induced apoptosis	glycerophospholipid and fatty acid metabolism disruption; energy depletion via β-oxidation inhibition	Pan et al. (2025)
MCF-7 cells	progesterone–GL composite; docking, cytotoxicity	enhanced cytotoxicity (IC_{50} = 81.11 μg·mL^{-1}) vs progesterone	PI3K/PR/ERα signaling modulation; synergistic hormone-triterpenoid anticancer action	Mahgoub et al. (2025)
Gallbladder cancer cells	cisplatin combination; comet assay	increased cisplatin efficacy (IC_{50} ↓ 8.98 → 4.07 μM)	DNA damage response activation (γH2AX, p-ATM/p-ATR/p53); stemness inhibition (SOX2, Oct4, NANOG)	Zhang et al. (2025)
Ovarian cancer (ES-2 model)	humanized mouse model; proteomics	tumor suppression; enhanced immunotherapy response	tumor microenvironment remodeling; Gal-1 downregulation; TILs activation	Chen et al. (2024)
Cancer cell models	nanozyme GL-CDs(Fe) system	ROS-mediated tumor cell elimination; diagnostic platform	H_2O_2 conversion to ·OH radicals; oxidative stress-induced apoptosis	Wang et al. (2024)
Triple-negative breast cancer	clinical cohort (388 patients)	improved OS and DFS in GLSP users	immune modulation (NK cells, CD4/CD8 balance); systemic anticancer immune activation	Jiang et al. (2025)
Hepatocellular carcinoma	16S rRNA sequencing; network pharmacology	tumor suppression via microbiota regulation	apoptosis and p53 pathway activation; CASP3 upregulation; gut-liver axis modulation	Xiong et al. (2023)
Lung carcinogenesis model	*in vitro*/*in vivo* chemoprevention	reduced tumor formation and inflammation	NF-κB inhibition; anti-inflammatory, antiangiogenic and apoptosis modulation	Shahid et al. (2023)
Functional food model	food fortification; digestion simulation	increased antioxidant and antiproliferative properties	polyphenol-mediated antioxidant activity; LOX inhibition; mild antiproliferative effects	Szydłowska-Tutaj et al. (2023)

Notes: AKT1 – Protein kinase B; ADCY3 – Adenylate cyclase 3; A549 – human lung adenocarcinoma cell line; ATM – ataxia telangiectasia mutated kinase; Bax – pro-apoptotic BCL2-associated X protein; CDK2 – cyclin-dependent kinase 2; CASP3 – caspase-3; CD8+ T – cytotoxic T lymphocytes; CD4/CD8 – immune cell ratio; CCK-8 – cell viability assay; DDP – cisplatin; DOX – doxorubicin; ERK1/2 – extracellular signal-regulated kinases; FAK – focal adhesion kinase; Gal-1 – galectin-1; GC-MS – gas chromatography–mass spectrometry; G_0/G_1 – cell cycle phase; G2/M – cell cycle phase; GL – *Ganoderma lucidum*; GL-CDs(Fe) – iron-doped carbon dots from *G. lucidum*; GLSP – *G. lucidum* spore powder; GLT – *G. lucidum* triterpenes; GLPs – *G. lucidum* polysaccharides; H_2O_2 – hydrogen peroxide; HCC – hepatocellular carcinoma; HeLa – cervical cancer cell line; HepG2 – hepatocellular carcinoma cell line; HGBEC – human gallbladder epithelial cells; IC_{50} – half maximal inhibitory concentration; IL-1β/IL-6/TNF-α/TGF-β1 – cytokines; iNOS – inducible nitric oxide synthase; JAK/STAT5 – signaling pathway; LDH – lactate dehydrogenase; LOX – lipoxygenase; MAPK – mitogen-activated protein kinase pathway; MCF-7 – breast cancer cell line; MIC – minimum inhibitory concentration; MTT – cell viability assay; NF-κB – nuclear factor kappa B; NK cells – natural killer cells; NME2 – nucleoside diphosphate kinase B; Oct4 – stemness marker; OS – osteosarcoma; PI3K – phosphoinositide 3-kinase; PR – progesterone receptor; ROS – reactive oxygen species; RT-qPCR – reverse transcription quantitative PCR; SOX2 – stemness transcription factor; TILs – tumor-infiltrating lymphocytes; TNF-α – tumor necrosis factor alpha; TGFβR – transforming growth factor beta receptor; TME – tumor microenvironment; VEGF – vascular endothelial growth factor; Vero – normal monkey kidney cell line

traditional use. Meanwhile, mycelial products are regulated under novel food legislation to ensure safety (EC, 2025).

Although more limited, clinical data further support its favourable safety and tolerability profile in humans. A randomised, double-blind, placebo-controlled trial demonstrated that administering *G. lucidum* at a dose of 3 g per day for 16 weeks to patients with type 2 diabetes and metabolic syndrome did not result in any significant adverse effects or changes to biochemical or haematological markers (Klupp et al., 2016). In practice, the commonly recommended doses – ranging from 1.5 to 6 g per day for powdered forms, 150–300 mg per day for extracts, and 1–3 ml per day for liquid preparations – are generally well tolerated. Only mild and transient side effects, such as gastrointestinal discomfort or dry mouth, have been reported in some cases (Ahmad et al., 2021). Additionally, processing methods such as drying, boiling or fermentation significantly reduce antinutritional compounds (e.g. phytates, tannins and oxalates), thereby improving bioavailability and enhancing the nutritional and functional properties of *G. lucidum* (Arsov et al., 2024; Zhang et al., 2024; Guo et al., 2025).

Although *G. lucidum* is generally considered safe, certain precautions should be taken, particularly when treating specific patient populations. Due to its hypoglycaemic, anticoagulant and antihypertensive properties, *G. lucidum* may enhance the effects of antidiabetic, anticoagulant and antihypertensive medications, necessitating careful monitoring and medical consultation (Lee and Rhee, 1990; Ulbricht et al., 2010; Tran et al., 2014). It may also enhance the activity of certain antibiotics, such as tetracycline and cefazolin (Yoon et al., 1994; Karwa et al., 2011). Individuals with gastric ulcers or active bleeding, or who are preparing for surgery, should exercise caution. Special consideration is also advised for pregnant or lactating women, children, and patients with autoimmune diseases, due to limited safety data and potential immunomodulatory interactions (Paterson, 2006; Sohretoglu and Huang, 2018; Xu and Li, 2019; Ahmad et al., 2021; Plosca et al., 2025). While allergic reactions to *G. lucidum* are uncommon and poorly documented, its immunomodulatory properties indicate both therapeutic potential and the necessity of individualised assessment (Sohretoglu and Huang, 2018; Plosca et al., 2025).

Conclusions

Ganoderma lucidum is a promising natural agent with multiple targets and significant anti-cancer potential. Extensive preclinical evidence demonstrates its ability to regulate key cellular processes involved in tumour development and progression. Its bioactive compounds act through various molecular pathways, such as inducing apoptosis, arresting the cell cycle, modulating the immune system, and reprogramming the metabolism of cancer cells. While early clinical findings suggest beneficial effects when used alongside conventional cancer therapies, the current clinical evidence is insufficient to support its use as a standalone treatment. Nevertheless, its favourable safety profile, combined with regulatory acceptance and broad biological activity, highlights its potential for integration into future complementary oncology strategies. Further large-scale, well-controlled clinical studies are essential to confirm its efficacy and optimise dosage, as well as to elucidate its long-term safety and bridge the gap between experimental research and clinical application.

Conflicts of interest

The authors have no competing interests to declare.

Ethical statement

This article does not include any studies that would require an ethical statement.

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