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Bioactive Metabolites of Ganoderma Species: Molecular Mechanisms Underlying Their Anticancer and Cytotoxic Potential

Abstract

The fungal genus *Ganoderma* has attracted significant attention because of its extensive medicinal properties and potential applications in cancer prevention and treatment. While *G. lucidum* remains the most heavily investigated species, focusing narrowly on a single taxon risks overlooking unique bioactive variations present across the wider genus. This review provides a comprehensive evaluation of *Ganoderma* secondary metabolites, highlighting how emerging research into non-lucidum species expands our understanding of the genus's collective phytochemical diversity. Over the past decade, substantial progress has been made in characterizing the structural diversity of *Ganoderma* metabolites, including polysaccharides, triterpenoids, phenolics, sterols, and other secondary metabolites associated with anticancer activity. Modern analytical techniques such as high-performance liquid chromatography (HPLC), liquid chromatography–mass spectrometry (LC-MS), and gas chromatography–mass spectrometry (GC-MS) have enabled the separation and characterization of complex fungal extracts, while spectroscopic approaches including nuclear magnetic resonance (NMR) and tandem mass spectrometry (MS/MS) have provided insight into structure–function relationships. Mechanistic studies indicate that *Ganoderma*-derived metabolites exert anticancer effects through multiple pathways, including apoptosis induction, cell-cycle regulation, angiogenesis inhibition, immunomodulation, and oxidative stress reduction. Despite these promising findings, several challenges continue to limit clinical translation. Metabolite composition varies significantly among species, strains, cultivation conditions, and environmental factors, complicating extract standardization and reproducibility. Furthermore, many bioactive compounds exhibit poor solubility, limited stability, and low bioavailability, restricting their therapeutic evaluation in vivo. Addressing these limitations will be essential for advancing *Ganoderma*-derived compounds toward translational and clinical applications as potential anticancer therapeutics.

Research Article

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Introduction

Importance of *Ganoderma* in anticancer research

Cancer remains one of the most significant global health challenges. While advances in diagnosis and treatment have steadily improved individual survival outcomes, the absolute number of worldwide incidence and mortality continues to rise. According to the International Agency for Research on Cancer (IARC), nearly 20 million new cancer cases were reported worldwide in 2022, with lung, bronchial,

and tracheal cancers among the most frequently diagnosed malignancies [1]. Conventional therapeutic strategies, including chemotherapy, radiation therapy, and targeted treatments, often face major limitations such as toxicity to healthy tissues, development of drug resistance, and limited efficacy against metastatic tumors or cancer stem cells [2]. In addition to these biological challenges, the financial burden associated with cancer treatment remains substantial. A World Health Organization (WHO) survey reported that only 39% of surveyed countries provided coverage for basic cancer management, while only 28% covered palliative care and pain relief services [3]. These limitations have intensified the search for inexpensive, selective, and less toxic therapeutic alternatives, particularly those derived from natural products.

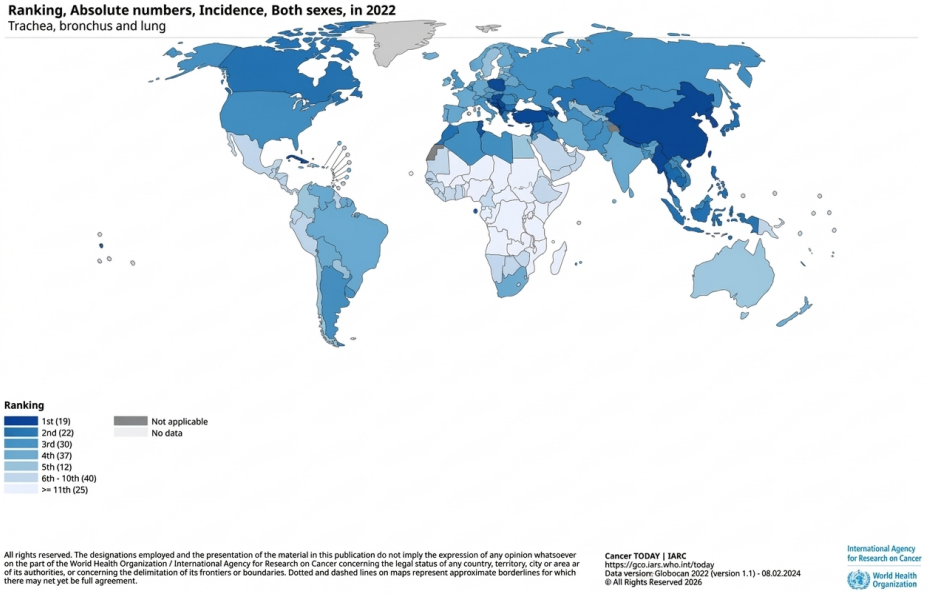

Figure 1: Global cancer incidence among both sexes in 2022. The heat map illustrates geographic variation in reported lung, brachial, and tracheal cancer cases, with higher incidence observed in East and Southeast Asia. Differences in incidence across regions may reflect variation in population size, age distribution, screening practices, and reporting systems [1].

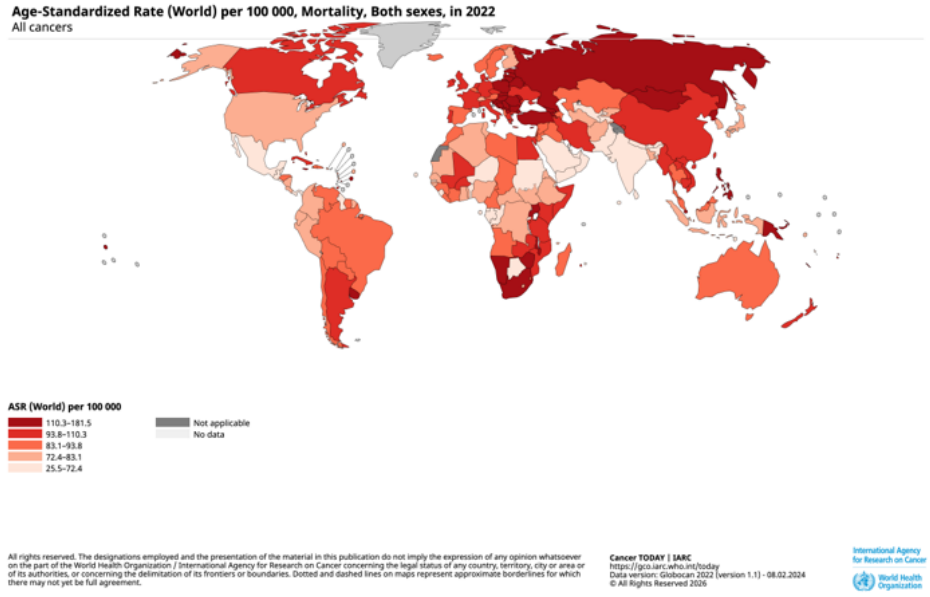

Figure 2: The heat map illustrates geographic variation in reported cancer cases (all cancer types) for age-standardized mortality rate per 100,000 in both sexes 2022 [1].

Among natural sources, fungi represent an exceptionally rich reservoir of structurally diverse secondary metabolites. Unlike primary metabolites required for growth and reproduction, secondary metabolites function primarily in environmental adaptation, defense, signaling, and interspecies competition. Fungal secondary metabolite clusters (SMCs), also referred to as biosynthetic gene clusters, encode

coordinated pathways responsible for producing chemically complex compounds with diverse biological activities [4]. Many fungal metabolites possess unique molecular scaffolds not commonly observed in plants, making fungi an important source of pharmacologically active compounds. Historically, fungal metabolites have been widely recognized for their antimicrobial properties, most notably the discovery of penicillin from Penicillium chrysogenum. More recently, fungal-derived compounds have gained increasing attention for their anticancer potential, particularly within species of the genus *Ganoderma*, which have long been used in traditional East Asian medicine. Current research reveals their diverse pharmacological properties, including immunomodulatory, antioxidant, and anticancer effects [5].

Extracts from *G. lucidum* contain numerous biologically active compounds such as triterpenoids, polysaccharide, sterols, phenolics, peptides, and other secondary metabolites, many of which are known to exhibit anticancer properties. Triterpenoids, which are synthesized from six isoprene units, have been reported to possess antiproliferative, anti-metastatic, and anti-angiogenic activities [6]. More than 300 triterpenoid compounds have been isolated from *G. lucidum*, highlighting its remarkable chemical diversity [7]. In addition, *G. lucidum* produces polysaccharides (GLPs) that demonstrate cytotoxic/apoptosis-inducing activity in cancer cells and reactive oxygen species (ROS) generation [8]. These polysaccharides, which are major structural components of the fungal cell wall [9], are also known to modulate immune responses by activating B cells, T cells, natural killer cells, dendritic cells, and macrophages [10].

While *G. lucidum* remains the most extensively investigated species, other *Ganoderma* species have also shown promising anticancer potential. For example, *G. tsuage* produces polysaccharides and triterpenoids capable of modulating oxidative stress and inducing apoptosis through activation of caspase pathways and regulation of the B-cell lymphoma 2 (Bcl-2)/Bcl-2-associated X protein (Bax) signaling axis [11]. Similarly, G. australe has attracted attention for its antioxidant polysaccharides, which may enhance immune function and suppress cancer cell proliferation [12].

There is a growing body of research supporting the anticancer potential of *Ganoderma* metabolites; however, most current evidence is derived from in vitro or preclinical models, and standardization of these fungal extracts are notoriously difficult. Metabolite composition can vary depending on species, strain, environmental conditions, and cultivation methods [13]. Furthermore, once inside a living system, many of these bioactive compounds exhibit limited bioavailability and pharmacokinetic stability, reducing their therapeutic effectiveness. Successful clinical translation will therefore require improved extraction and cultivation strategies, and deeper understanding of the molecular pathways underlying *Ganoderma*-derived anticancer activity to develop effective drug delivery systems [14].

Crucially, most literature continues to study individual compounds or single species in isolation. This leaves a major gap in our understanding of how chemical diversity across the entire genus contributes to shared anticancer mechanisms. This review aims to address this gap by evaluating the diversity of bioactive metabolites produced by *Ganoderma* species and their pathways in cancer inhibition.

Methods

A literature search was conducted using the PubMed, Scopus, and Google Scholar databases. Articles published between 2006 and 2025 were identified using combinations of the keywords "*Ganoderma*," "bioactive metabolites," "anticancer potential," "cytotoxicity," and "mechanism of action," along with targeted searches combining *Ganoderma* with specific anticancer mechanisms, including apoptosis, cell cycle arrest, angiogenesis, immunomodulation, and oxidative stress. Additional searches were performed using the names of individual *Ganoderma* species, including *G. lucidum*, G. tsugae, G. zonatum, and other reported medicinal species, to capture species-specific bioactive compounds and anticancer mechanisms. Articles were selected based on their relevance to the anticancer activity, bioactive metabolites, molecular mechanisms, and therapeutic potential of *Ganoderma* species. Priority was given to peer-reviewed studies investigating molecular pathways, in vitro and in vivo anticancer effects, pharmacological interactions with conventional cancer therapies (including chemotherapeutic agents and immunotherapies), and recent review articles to provide a comprehensive overview of the current evidence.

Taxonomic and biological background of *Ganoderma* species

The genus *Ganoderma* comprises a diverse group of wood-decaying polypore fungi widely dispersed across tropical, subtropical, and temperate ecosystems across five continents: Africa, Asia, Europe, North America, and South America [15]. They are usually

found in deciduous forests and are characterized by their woody basidiocarps, polypore hymenophores, and distinctive double-walled basidiospores with a truncated apex [16]. As white-rot fungi, *Ganoderma* species play a crucial ecological role in the decomposition of lignin-rich plant materials, thereby contributing to nutrient cycling and forest ecosystem stability [16].

Despite their ecological importance, the taxonomy of *Ganoderma* remains complex and subject to ongoing debate. Morphological similarities among species, environmental influences on growth characteristics, and inconsistencies in historical classification systems have contributed to significant taxonomic confusion. Recent molecular phylogenetic studies have revealed that many specimens previously classified under broad categories, particularly *G. lucidum*, represent multiple genetically distinct lineages. Consequently, estimates of species diversity within the genus vary widely, ranging from approximately 60 to more than 140 recognized species [17]. This taxonomic instability is also reflected in species of synonymy and reclassification. For example, some phylogenetic analyses treat *G. meridithae* as a distinct species, whereas others classify it as a synonym of G. curtisii. These inconsistencies illustrate the ambiguity of species boundaries and highlight the need for integrative taxonomic approaches that incorporate both morphological and molecular evidence [18].

The medicinal importance of *Ganoderma* has been documented for centuries. In East Asian traditional medicine, *G. lucidum* is known colloquially as “Reishi” or “Lingzhi” and has long been valued for its reputed ability to promote longevity, vitality, and overall health. This historical significance has stimulated modern scientific investigations into the pharmacological properties of *Ganoderma* species and their potential applications in biotechnology and medicine. [19].

One of the most remarkable features of *Ganoderma* is its ability to synthesize a broad array of secondary metabolites that play important roles in signaling, defense, and environmental adaptation. Genomic analyses have revealed that the genome of *G. lucidum* contains an extensive repertoire of biosynthetic gene clusters responsible for the production of terpenoids, polyketides, and other bioactive compounds that have demonstrated cytotoxic and anti-cancer potential. These clusters encode enzymes such as terpene synthases, polyketide synthases, cytochrome P450 monooxygenases, and various regulatory proteins that collectively support complex metabolic pathways. Environmental factors also influence metabolite production in *Ganoderma*. Studies have shown that conditions such as nutrient availability, oxidative stress, light exposure, and cultivation parameters can significantly alter the expression of genes involved in secondary metabolism. These environmental signals interact with regulatory pathways such as calcium signaling and ROS-mediated pathways to modulate metabolite synthesis. As a result, different *Ganoderma* species, strains, or cultivation conditions can produce markedly different metabolite profiles [20]. This genomic architecture suggests that secondary metabolite diversity is not incidental but rather an evolutionary trait that supports the fungus’ ecological success, host interactions, and adaptive responses

Together, these genomic and environmental factors contribute to the extraordinary metabolic diversity observed within the genus. This diversity forms the biological basis for the wide range of pharmacologically active compounds identified in *Ganoderma*, many of which exhibit promising anticancer properties [21].

Phytochemical Diversity and Major Compound Classes

Species within the genus *Ganoderma* contain a wide range of bioactive metabolites associated with anti-inflammatory, antioxidant, immunomodulatory, and anticancer activities. Major compound classes identified in *Ganoderma* species include triterpenoids, polysaccharides, proteins and peptides, sterols, and phenolic compounds. These metabolites contribute to cytotoxic activity through diverse mechanisms involving apoptosis induction, oxidative stress regulation, immune modulation, and cell-cycle arrest. Investigating the structural and functional properties of these compounds provides insight into the molecular basis of *Ganoderma*-associated anticancer activity and highlights their potential for therapeutic development.

Triterpenoids

Triterpenoids are among the most extensively studied bioactive compounds in *G. lucidum* and are widely recognized for their antiproliferative, antimicrobial, antiviral, and anticancer activities. One researcher investigated the chemical diversity and cytotoxic potential of *G. lucidum* triterpenoids by isolating 43 compounds, including six previously unidentified metabolites, and evaluating their effects against human cervical cancer cell lines. Several compounds, including ganoderic acids, lucidadiol, and ganoderiol F, demonstrated significant cytotoxic activity [22]. Structural analyses further revealed that relatively

small modifications in oxidation state, hydroxylation patterns, or side-chain composition substantially altered biological activity. Using NMR spectroscopy, the authors linked structural variation to cytotoxic potential, establishing an important framework for understanding structure–activity relationships among *Ganoderma* triterpenoids. These findings support the idea that the structural diversity of *G. lucidum* metabolites plays a critical role in determining anticancer efficacy [23].

Additional evidence for the anticancer activity of *Ganoderma* triterpenoids was provided by [23] who identified a novel cytotoxic triterpene isolated from dried *G. lucidum* fruiting bodies. The compound was extracted using 90% ethanol and structurally characterized through NMR and mass spectrometry. Functional analyses demonstrated moderate but significant cytotoxic effects against A549 lung cancer cells and HepG2 liver cancer cells, with IC_{50} values in the low micromolar range. Mechanistic studies further showed that the compound induced apoptosis through activation of the p53/caspase-3 signaling pathway, a major tumor suppressor pathway commonly targeted in cancer therapy. Unlike earlier studies focused primarily on structural characterization, this work directly linked a newly identified triterpene to a defined apoptotic mechanism, strengthening evidence for the therapeutic relevance of *Ganoderma*-derived metabolites [23].

[24] further investigated the large-scale production and anticancer potential of triterpene acids from submerged cultures of *G. lucidum*. Because conventional fermentation methods often yield low concentrations of bioactive metabolites, the authors optimized fermentation conditions by adjusting pH, temperature, and rotation speed using response surface methodology. Under optimized conditions (pH 6.0, 161.9 rpm, and 30.1°C), triterpene acid production reached 291.0 mg/L in a 5-L bioreactor, representing a 70.8% increase compared with non-optimized cultures. The process was subsequently scaled to a 200-L bioreactor, where production rates reached 47.9 mg/L/day, the highest reported yield for large-scale *G. lucidum* fermentation at the time of the study. Cytotoxicity assays demonstrated that the extracted triterpene acids inhibited growth of SMMC-7721 liver cancer cells and SW620 colon cancer cells. Chemical analyses identified ganoderic acids T and Me as the predominant active compounds. Collectively, these findings demonstrate that optimized fermentation systems can efficiently produce bioactive triterpene acids while preserving their anticancer activity, supporting the feasibility of large-scale metabolite production for future therapeutic applications [24].

Although most studies focus on *G. lucidum*, other *Ganoderma* species also exhibit significant anticancer potential. *G. tsuage* possesses a distinct metabolite profile enriched in lanostane-type triterpenoids, a major class of compounds frequently associated with anticancer activity. [25] demonstrated that *G. tsuage* extracts significantly inhibited colorectal cancer cell proliferation and reduced tumor growth in vivo. Mechanistic analyses showed that the extract induced G^2/M cell-cycle arrest through downregulation of cyclins A and B1, proteins required for mitotic progression, alongside upregulation of the cyclin-dependent kinase inhibitors p21 and p27. These alterations suggest that *G. tsuage* metabolites suppress tumor growth by interfering with mitotic regulatory pathways.

Additional characterization of *G. tsuage* metabolites was performed by [26] who isolated a novel lanostanoid triterpenoid, tsugaric acid F, along with several seco-lanostanoids and a palmitamide-type alkamide from *G. tsuage* fruiting bodies. Functional assays demonstrated that some of these compounds exhibited antioxidant and enzyme inhibitory activities associated with cancer chemoprevention. Specifically, one lanostanoid inhibited xanthine oxidase activity, while a seco-lanostanoid strongly suppressed superoxide anion generation in stimulated rat neutrophils, indicating inhibition of ROS production. Although only weak direct cytotoxicity was observed against PC-3 prostate cancer cells, these findings suggest that certain *G. tsuage* triterpenoids may function primarily as chemopreventive agents by regulating oxidative stress and inflammation rather than inducing direct tumor cell death [27].

A broader review by [28] further emphasized the therapeutic significance of *Ganoderma* triterpenoids, particularly lanostane-type compounds commonly referred to as ganoderic acids. These metabolites have been reported to induce apoptosis in multiple human cancer cell lines through mechanisms involving mitochondrial dysfunction, ROS accumulation, activation of caspase cascades, and modulation of pro- and anti-apoptotic proteins. Several ganoderic acids also exhibit selective cytotoxicity toward malignant cells while displaying lower toxicity toward non-cancerous cells, an important characteristic for potential chemotherapeutic agents. Collectively, the ability of *Ganoderma* triterpenoids to induce apoptosis, regulate cell-cycle progression, and modulate oxidative stress highlights their broad and multimodal

anticancer potential.

Polysaccharides

Polysaccharides derived from *G. lucidum* have attracted considerable attention because of their immunomodulatory and anticancer properties. [8] reviewed the anticancer potential of *G. lucidum* Polysaccharides (GLPs) and their emerging applications in drug delivery systems. The authors reported that GLPs inhibit cancer cell proliferation, induce apoptosis, and exhibit direct cytotoxic effects against tumor cells. In addition, GLPs were shown to increase intracellular ROS levels, thereby promoting oxidative stress and cancer cell death. These findings suggest that GLPs act through multiple complementary pathways affecting both cell survival and intracellular signaling. Because of their multifunctional biological activity, GLPs have been proposed as promising candidates for future anticancer therapies and drug delivery applications.

Ganoderma polysaccharides also contribute significantly to immune-mediated anticancer responses. [28] describe how *Ganoderma*-derived polysaccharides activate several key immune cell populations, including B cells, T cells, macrophages, and natural killer (NK) cells. These immune cells collectively contribute to adaptive and innate antitumor immunity through antigen presentation, cytokine signaling, phagocytosis, and cytotoxic activity. A water-based *G. lucidum* extract was further shown to enhance NK cell cytotoxicity against leukemia cell lines through activation of NK Group 2 member D / Natural Cytotoxicity Receptor receptors and Mitogen-Activated Protein Kinase signaling pathways [29]. In addition, *Ganoderma* polysaccharides stimulate production of pro-inflammatory cytokines including tumor necrosis factor-alpha, Interleukin-1 beta, and Interferon gamma, which may further enhance immune-mediated tumor suppression. Together, these findings demonstrate that *Ganoderma* polysaccharides possess substantial immunotherapeutic potential by strengthening host antitumor immune responses.

Proteins and Peptide

Proteins and peptides isolated from *Ganoderma* species also exhibit significant anticancer activity. Four major fungal immunomodulatory proteins (FIPs) have been identified in *Ganoderma* species: Lingzhi-8 (LZ-8), Fip-gts, GMI, and Fip-gat. These proteins regulate cancer cell survival through diverse mechanisms involving apoptosis, autophagy, and cell-cycle control [28].

Recombinant LZ-8, cloned from *G. lucidum*, induces autophagic cell death by triggering endoplasmic reticulum (ER) stress and activation of the Activating Transcription Factor 4–C/EBP Homologous Protein signaling pathway. Fip-gts, cloned from G. tsuage, inhibits telomerase activity, thereby suppressing tumor cell proliferation. GMI, cloned from G. microsporum, promotes both autophagy and apoptosis through autophagy/caspase-7-dependent pathways independent of surviving and Excision Repair Cross-Complementing 1 signaling. Fip-gat, cloned from G. atrum , induces G1/S cell-cycle arrest and enhances apoptotic activity [28].

Peptides derived from *Ganoderma* species also contribute to anticancer activity through oxidative stress regulation and apoptosis induction. [30] reported that *G. lucidum* oligopeptides promote apoptosis in cancer cells by inhibiting Thioredoxin/Thioredoxin Reductase expression while enhancing Mouse Double Minute 2 homolog (MDM2)/ p53 signaling. These changes increase ROS accumulation and trigger programmed cell death. Collectively, these findings demonstrate that *Ganoderma*-derived FIPs target multiple cellular pathways involved in tumor progression.

Sterols and Phenolics

Phenolics and sterols represent additional classes of secondary metabolites that contribute to the antioxidant and anticancer properties of *G. lucidum*. Phenolic compounds, including phenolic acids and flavonoids, possess strong antioxidant activity and can reduce ROS involved in cancer progression. By lowering oxidative stress, these compounds may inhibit tumor cell proliferation and promote apoptosis [31].

Sterols such as ergosterol and ergosterol peroxide have also been identified as important bioactive metabolites in *Ganoderma* species. These compounds exhibit cytotoxic activity by inducing apoptosis and disrupting cancer cell survival pathways [32]. Additional studies suggest that ergosterol derivatives, such as ergosterol peroxide, trigger apoptosis in breast cancer by disrupting mitochondrial membrane potential and causing excessive (ROS) generation [33]. Variability in phenolic and sterol composition among *Ganoderma* species may therefore influence differences in antioxidant capacity and cytotoxic potential [33].

Further evidence supporting the anticancer role of these metabolites was reported by [4], who demonstrated that a polyphenol-rich extract of G. neo-japonicum exhibited strong antioxidant activity

and inhibitory effects against human colon cancer cells. The phenol-rich butanol fraction displayed the highest biological activity. Sterol-rich fractions also demonstrated anticancer potential, as compounds including stellasterol and vitamin D_3 derivatives promoted cancer cell death through interactions with anti-apoptotic proteins such as Bcl-2 [4]. Collectively, these findings indicate that phenolics and sterols contribute to *Ganoderma*-associated anticancer activity through antioxidant regulation, apoptosis induction, and inhibition of tumor cell proliferation.

Comparative Anticancer Activity in *Ganoderma* Species

Species	Compound/ Class	Target Cancer Type	Mechanism	Reference
G. lucidum	Polysaccharides	Hepatocellular carcinoma	Hepatic gene regulation, proliferation inhibition	[34]
G. lucidum	Ganoderic acid B	Hepatocellular carcinoma	ATP-binding cassette subfamily B member 1 (ABCB1)-mediated multidrug resistance reversal, enhanced chemotherapy cytotoxicity	[35]
G. lucidum	6.8 Polysaccharide and triterpenoids	Human Breast Cancer, human laryngeal epidermoid carcinoma, cervical cancer, and human lung denocarcinoma	Microtubule disruption, apoptosis induction	[36]
G. lucidum	LZ-8 Peptide	Hepatocellular carcinoma	c-Met–dependent/independent pathway inhibition, tumor progression suppression	[37]
G. lucidum	triterpenes	Not specified (cancer-related targets/pathways)	Multi-target modulation (cancer/ metabolic pathways)	[38]
G. lucidum	Intracellular *G. lucidum* Polysaccharide	Mouse macrophage cell line (RAW264.7)	Proliferation inhibition	[39]
G. lucidum	Polysaccharides	Hepatocellular carcinoma	Protein Kinase B (Akt) pathway modulation, radiosensitization enhancement	[40]
G. lucidum	Ganoderic acid A	Hepatocellular carcinoma	G0/G1 arrest, apoptosis induction, migration/invasion suppression	[23]
G. lucidum	LZ-8 Peptide	Human lung adenocarcinoma (A549, CL1-5 and H226 cells)	Epidermal growth factor receptor (EGFR) targeting, oncogenic signaling inhibition	[41]
G. lucidum	Polysaccharides	Hepatocellular carcinoma	Apoptosis induction	[42]
G. lucidum	Ganoderic acid A	Insulinoma	Dose dependent proliferation inhibition, ROS reduction	[43]
G. lucidum	*G. lucidum* polysaccharides	Colorectal carcinoma	Tumor growth inhibition, autophagy flux suppression	[44]
G. lucidum	Ergosterol peroxide/ Sterol	Ductal carcinoma and human breast adenocarcinoma	G1 arrest, caspase-3/7 activation, poly(ADP-ribose) polymerase cleavage, apoptosis induction	[31]
G. lucidum	Ganoderic acid A	Human glioblastoma	Phosphatidylinositol 3-kinase/ protein kinase B (PI3K/Akt) pathway inhibition, apoptosis induction, autophagy activation, migration/invasion suppression	[45]
G. lucidum	*G. lucidum* Polysaccharides	Lewis lung carcinoma	Proliferation inhibition, migration/ invasion suppression	[46]

G. lucidum	LingZhi oligopeptides/ Peptide	Human lung adenocarcinoma	Mitochondrial dysregulation, apoptosis induction	[47]
G. lucidum	Lucidadiol triterpene	Mouse melanoma	Apoptosis induction, migration/ invasion suppression	[48]
G. lucidum	Polysaccharides	Hepatocellular carcinoma	Macrophage polarization modulation, tumor microenvironment remodeling	[49]
G. lucidum	Polysaccharides	Oral squamous cell carcinoma	Morphological alteration, migration inhibition, colony/sphere formation suppression, reduced proliferation	[50]
G. lucidum	Lucidumol A triterpene	Mouse melanoma	Proliferation inhibition, migration suppression, apoptosis induction	[34]
G. lucidum	Polysaccharide	Polysaccharide	Drug sensitivity enhancement	[50]
G. lucidum	Ganoderic acid A	Human colorectal adenocarcinoma	Chemotherapy sensitization (Oxaliplatin), potential T cell cytotoxicity enhancement	[36]
G. lucidum	Polysaccharides	Sarcoma, Lewis lung cancer, hepatocellular carcinoma, and colorectal adenocarcinoma	Tumor growth inhibition	[51]
G. lucidum	Polysaccharide	Colorectal adenocarcinoma	T cell activation, anti- Programmed cell death protein 1 immunotherapy enhancement	[52]
G. lucidum	Ganoderic acid D	Triple negative breast cancer	Hypoxia-inducible factor 1-alpha–dependent glycolysis inhibition, chemotherapy sensitization (gemcitabine)	[53]
G. lucidum	Polysaccharides	Colon adenocarcinoma and prostatic adenocarcinoma	Proliferation inhibition	[54]
G. tsuage	A fucogalactan of *G. tsuage* (GTP-a2)	Human colon adenocarcinoma	Cancer associated metabolic modulation, ophiobolin A upregulation	[55]
G. lucidum	Ganoderic acid A & Ganoderec acid B	Hepatocellular carcinoma	lncRNA FR121302 suppression, tumor growth inhibition	[56]
G. leucocontextum	Ganoderic acid (unspecified) and polyphenols	A549 cells, PC12 cells, B16 cells, HeLa cells.	Proposed downregulation of anti-apoptotic factors, upregulation of pro-apoptotic factors, apoptosis induction	[57]
G. leucocontextum	GL22 polysaccharide	Human hepatoma cell line	Mitochondrial membrane potential disruption, apoptosis induction	[51]
G. resinaceum	Polysaccharides (GRP I and GRP II)	Hepatocellular carcinoma	Oxidative stress modulation, proliferation inhibition	[48]

Table 1. Comparative anticancer activities of bioactive metabolites isolated from *Ganoderma* species. Table 1 summarizes major *Ganoderma*-derived bioactive compounds, their associated target cancer types, proposed molecular mechanisms, and representative studies. Compounds include polysaccharides, triterpenoids, peptides, sterols, and phenolic metabolites reported to exhibit antiproliferative, pro-apoptotic, immunomodulatory, antioxidant, and chemotherapy-sensitizing activities across multiple cancer models. Adapted from [13]

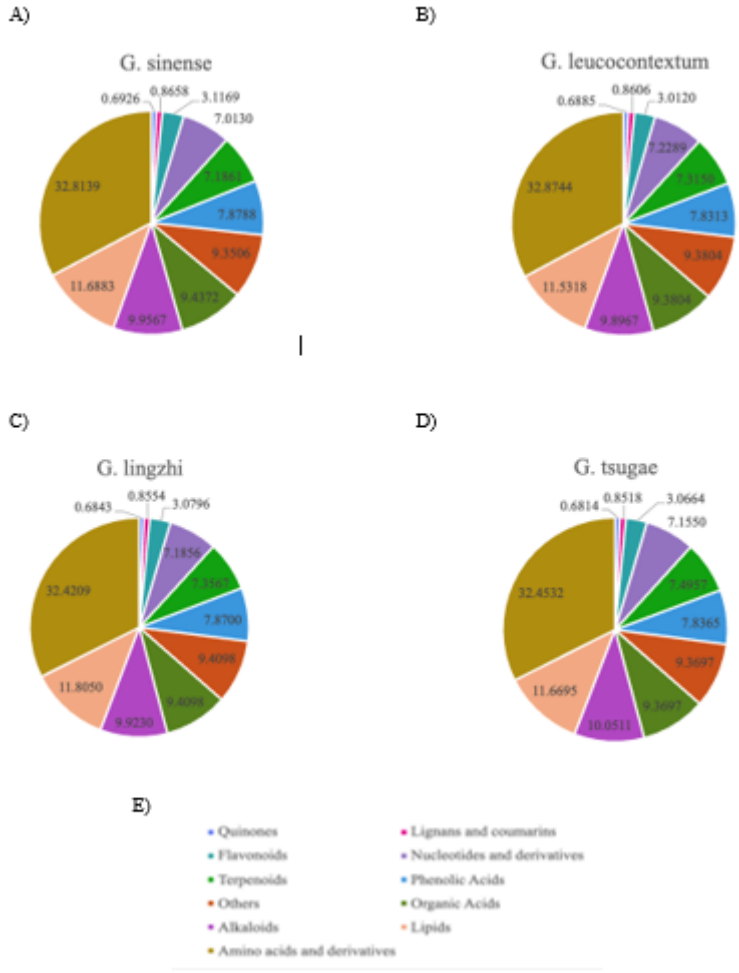

Figure 3: Comparative metabolite composition profiles of four *Ganoderma* species based on percentage abundance of major phytochemical classes. The pie charts display the distribution of metabolites in four species of *Ganoderma*, A) G. sinense, B) *G. leucocontextum*, C) G. lingzhi, and D) G. tsuage. Across all four species, amino acids and their derivatives were most prominent (~32–33%), followed by lipids, alkaloids, and organic acids, which show moderate variability between species. Smaller metabolite classes including terpenoids, phenolic acids, flavonoids, and lignans, compose a smaller fraction of the composition. All biochemical compounds are functionally important due to their bioactive roles as antioxidants and anticancer compounds. The data in the figure is adapted from [58].

Across all four *Ganoderma* species, the largest metabolite class by composition is amino acids and their derivatives, comprising roughly one-third of the total profile in each species (32–33%) (Figure 3). This similarity suggests that all four species share a similar basic structure and function, likely for the production of proteins and overall growth. Lipids form the second-largest group (11.5–11.8%), followed by alkaloids (9.8–10.0%) and organic acids (9.3–9.4%) (Figure 3). These categories show very little variation between species, indicating overall biochemical stability in their metabolism and structure.

More meaningful differences emerge in the smaller percentage groups such as terpenoids, phenolic acids, flavonoids, and lignans and coumarins. Among the four species, *G. tsuage* shows the highest alkaloid percentage (10.05%) and slightly elevated terpenoid levels (7.50%) compared with G. lingzhi (7.36%) and G. sinense (7.19%), which is consistent with its reported lanostane-type triterpenoid and the presence of unusual seco-lanostanoids. *G. leucocontextum* demonstrates higher nucleotide derivatives (7.23%) and flavonoids (3.01%), which may reflect species specific adaptations in oxidative stress defense (Lin et al., 2015). Though the percentage of these metabolites are small, they are important to the function of the species, contributing to antioxidant, immunomodulatory, and potential anticancer effects. This uniformity suggests that most *Ganoderma* species share a similar metabolic framework and mainly differ in their specialized bioactive metabolites

which contribute to the unique anticancer properties of each *Ganoderma* species.

Mechanisms of cytotoxic activity of *Ganoderma* species

Apoptosis Induction

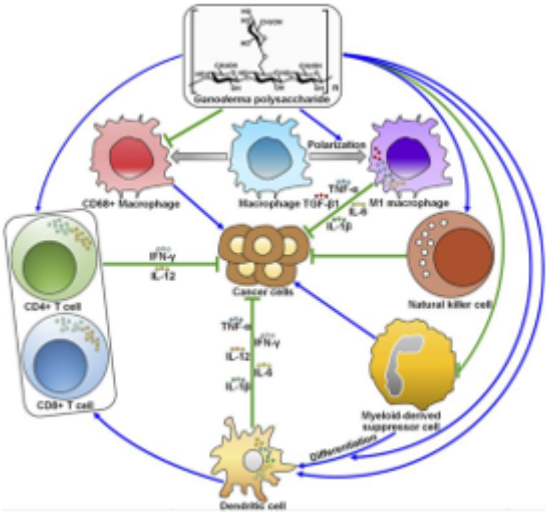

Figure 4: Apoptosis-inducing mechanisms of *Ganoderma* polysaccharides in cancer cells. *Ganoderma* polysaccharides induce apoptosis by modulating multiple signaling pathways that converge on the intrinsic mitochondrial apoptotic pathway. They activate the stress-responsive c-Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (MAPK) pathways while inhibiting the pro-survival Janus kinase/signal transducer and activator of transcription 5 (JAK/STAT5) and PI3K/Akt signaling pathways. These changes shift the balance of Bcl-2 family proteins by increasing Bax expression and decreasing Bcl-2 and Bcl-xL levels, leading to mitochondrial outer membrane permeabilization, cytochrome c release, activation of caspase-9 and caspase-3, PARP cleavage, and ultimately apoptotic cell death. Additionally, *Ganoderma* polysaccharides may enhance apoptosis through Beclin-1- and LC3-mediated autophagy and by reducing ABCB1-mediated drug efflux, thereby increasing the efficacy of anticancer drugs. Adapted from [59].

Cell-cycle regulation

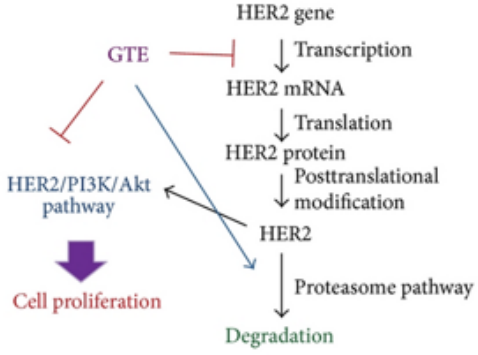

Figure 5: Cell-cycle regulation mechanism underlying suppression of breast cancer cell proliferation by G. tsugae extract (GTE). GTE suppresses cell proliferation in human epidermal growth factor receptor 2 (HER2)-overexpressing breast cancer cells. GTE interferes with the activation of the HER2 receptor, leading to reduced signaling through the PI3K/Akt pathway. When Akt activity is diminished, downstream expression of Cyclin D1 decreases, limiting the cell's ability to progress from G1 to S phase. Since Cyclin D1 is a critical regulator of early cell-cycle progression, its reduction effectively halts the cell cycle at the G1 checkpoint. Through this coordinated inhibition of HER2, PI3K/Akt, and Cyclin D1, GTE imposes a G1 phase arrest that restricts tumor cell growth and contributes to reduced proliferation in HER2-driven breast cancer models. Adapted from [59].

Angiogenesis Inhibition

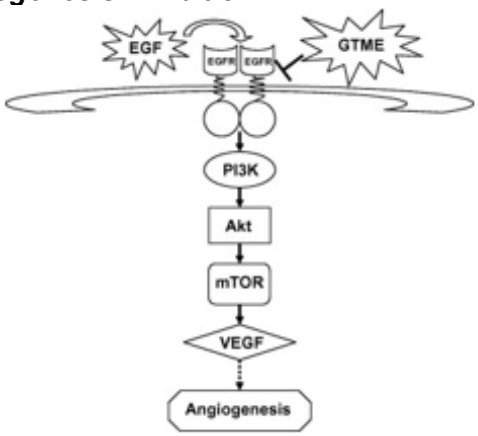

Figure 6: Anti-angiogenic mechanism of G. tsugae methanol extract (GTME) in human epidermoid carcinoma A-431 cells. GTME suppresses angiogenesis by inhibiting epidermal growth factor receptor (EGFR) signaling and reducing vascular endothelial growth factor (VEGF) expression. VEGF is the primary activator of angiogenesis, or the formation of new blood vessels from preexisting ones. Inhibition of EGFR prevents the downstream activation of VEGF and was shown to cease activity of human epidermoid carcinoma in-vitro A-431 cells and in-vivo mouse models. Adapted from [60].

Immunomodulation

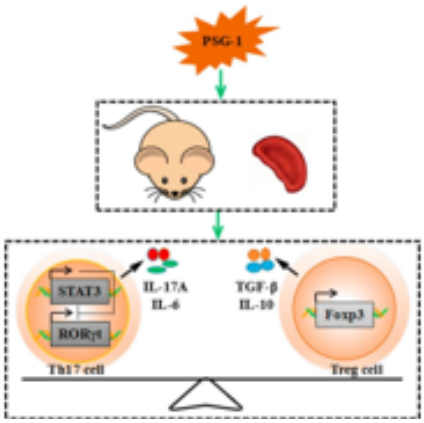

Figure 7: Immunomodulatory effects of G. atrum polysaccharide (PSG-1) through regulation of the Th17/Treg pathway. PSG-1 regulates immune function by acting on the T helper 17 lymphocytes and regulatory T lymphocytes (Th17/Treg) pathway, which is vital in maintaining immune homeostasis. In vivo, PSG-1 increases Th-17 associated cytokines (IL-7A, IL-6) and upregulates transcription factors STAT3 and RORγt, which drives Th17 development. Simultaneously, PSG-1 boosts Treg associated cytokines (TGF-β1, IL-1) and elevates Foxp3, indicating support of the Treg function. PSG-1 is able to regulate Th17/Treg balance. Knochelmann et al., (2018) demonstrate that the balance between these two cells has emerged as a prominent factor in regulating cancer by modulating antitumor events and mediating cancer regression. Adapted from [61].

Oxidative stress reduction

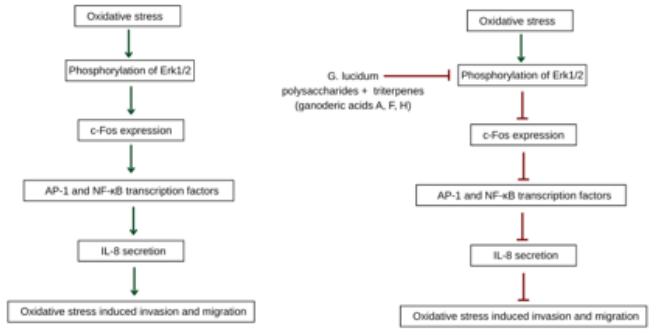

Figure 8: Oxidative stress reduction by *G. lucidum*-derived compounds in breast cancer cells. In oxidative stress conditions, elevated ROS levels activate the Extracellular Signal-Regulated Kinase 1 and 2 (Erk1/2) signaling pathway, leading to phosphorylation of Erk1/2, upregulation of c-Fos, activation of AP-1 and NF- κB, and IL-8 secretion that drives breast cancer migration and invasion. *G. lucidum* interrupts this pathway by suppressing ROS-induced Erk1/2 phosphorylation, which downregulates c-Fos and inhibits AP-1 and NF- κB activity. This leads to reduced IL-8 secretion and decreases ROS-mediated invasive behaviour. Adapted from [62].

Discussion

The studies reviewed in this paper indicate that *Ganoderma* species represent a promising source of anticancer compounds due to the broad range of bioactive metabolites they produce and the diversity of mechanisms through which these metabolites act. *Ganoderma*-derived metabolites such as triterpenoids, polysaccharides, peptides, sterols, and phenolic compounds influence multiple hallmarks of cancer simultaneously, involving apoptosis induction, oxidative stress regulation, immune modulation, angiogenesis inhibition, and cell-cycle arrest [63]. This multi-targeted may provide advantages in overcoming tumor heterogeneity and therapeutic resistance compared to conventional treatments that target one pathway. [2].

A notable trend across the literature is the contribution of chemical diversity to biological activity. Triterpenoid-focused studies demonstrate that even small structural modifications can substantially alter cytotoxic potency, highlighting the functional importance of chemical diversity within *Ganoderma* [22]. While this diversity represents a key adaptive strength, it also introduces a significant challenge for standardization. Variability in metabolite composition, driven by environmental conditions and genetic differences, complicates reproducibility and raises concerns regarding consistency across studies and potential therapeutic applications.

This has led to researchers optimizing metabolite production through controlled fermentation and biotechnological approaches. For example, controlled fermentation approaches have demonstrated that triterpene acids can be produced efficiently while retaining strong cytotoxic activity against liver and colon cancer cell lines [24]. While these strategies have successfully increased yields of specific compounds, it may not fully reproduce the complex chemical composition of natural extracts. Consequently, isolating individual metabolites could potentially reduce biological activity if interactions among compounds contribute significantly to anticancer effects. This possibility highlights the need for future studies to distinguish between the activities of purified compounds and those of whole-extract formulations to identify any synergistic interactions between *Ganoderma* metabolites.

In addition to direct cytotoxic effects, several studies indicate that *Ganoderma*-derived compounds may enhance the efficacy of existing therapies. Table 1 shows ganoderic acid A has been shown to synergistically improve the tumor-suppressive effects of the chemotherapeutic agent oxaliplatin, potentially through increased T cell-mediated cytotoxicity [64]. This suggests that *Ganoderma* compounds may be more effective as adjuncts to conventional treatments rather than as standalone therapies, although further investigation is required to confirm this role in clinical settings.

Polysaccharides derived from *Ganoderma* species also demonstrate consistent anticancer activity, including the ability to slow cancer cell growth, induce apoptosis, and increase ROS production. In addition

to these direct effects, their role in modulating immune pathways suggests a broader contribution to tumor suppression through enhancement of host immune responses. Similarly, immunoregulatory peptides activate key signaling pathways involved in immune function, further supporting the role of *Ganoderma* in immune-mediated anticancer activity [65].

Despite these promising findings, several challenges limit the clinical translation of *Ganoderma*-derived compounds. In addition to issues of standardization, many bioactive metabolites exhibit low solubility and limited stability, which may reduce their bioavailability and therapeutic effectiveness in vivo. Furthermore, much of the current evidence is derived from in vitro or preclinical models, and there remains a lack of well-controlled clinical studies evaluating safety, pharmacokinetics, and efficacy in humans.

Emerging approaches, including metabolomics, genome mining, and synthetic biology, offer potential strategies for addressing these limitations. These technologies may enable more precise identification of bioactive compounds, improved understanding of biosynthetic pathways, and controlled production of specific metabolites. However, an important unresolved question is whether these approaches can replicate the synergistic effects observed in whole extracts, which may contribute significantly to the overall biological activity of *Ganoderma*.

The literature supports the conclusion that *Ganoderma* species are a valuable source of anticancer metabolites with diverse mechanisms of action and potential therapeutic application. However, the gap identified in this review remains only partially resolved. While substantial progress has been made in characterizing individual compounds and their biological activities, further research is needed to establish standardized production methods, improve bioavailability, clarify synergistic interactions, and validate efficacy through rigorous clinical studies. Addressing these challenges will be essential for translating the anticancer potential of *Ganoderma*-derived metabolites into clinically applicable therapies.

Conclusion

Although evidence supports the anticancer potential of *Ganoderma*-derived compounds, major challenges remain in extract standardization, bioavailability, pharmacokinetics, and clinical validation. Future studies integrating genomics, metabolomics, transcriptomics, and synthetic biology approaches may improve understanding of biosynthetic pathways and facilitate the development of reproducible therapeutic formulations. Among the species reviewed, *G. lucidum* represents the most extensively studied candidate, with triterpenoids and polysaccharides demonstrating promising anticancer properties across multiple cancer models, as summarized in Table 1. Continued investigation into synergistic interactions among *Ganoderma* metabolites, as well as combination therapies with conventional chemotherapeutics, may further expand their translational potential. Collectively, these advances could help transition *Ganoderma*-derived compounds from experimental systems toward clinically relevant anticancer therapeutics.

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Conflict of Interest

None to report.

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