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Review

Enhancing Gastrointestinal (GI) Cancer Therapies with *Ganoderma Lucidum*: A Review of Mechanisms and Efficacy

Kaushal K. Sharma[1,*], Saksham Gupta[2], Prakash S. Bisen[3]

[1]Department of Health Science, University of the People, Pasadena, CA 91101, USA

[2]Department of Biochemistry, Bundelkhand University, Jhansi 284128, India

[3]School of Studies in Biotechnology Jiwaji University, Gwalior 474010, India

[*]Corresponding author: Kaushal K. Sharma, academicskaushal2@gmail.com

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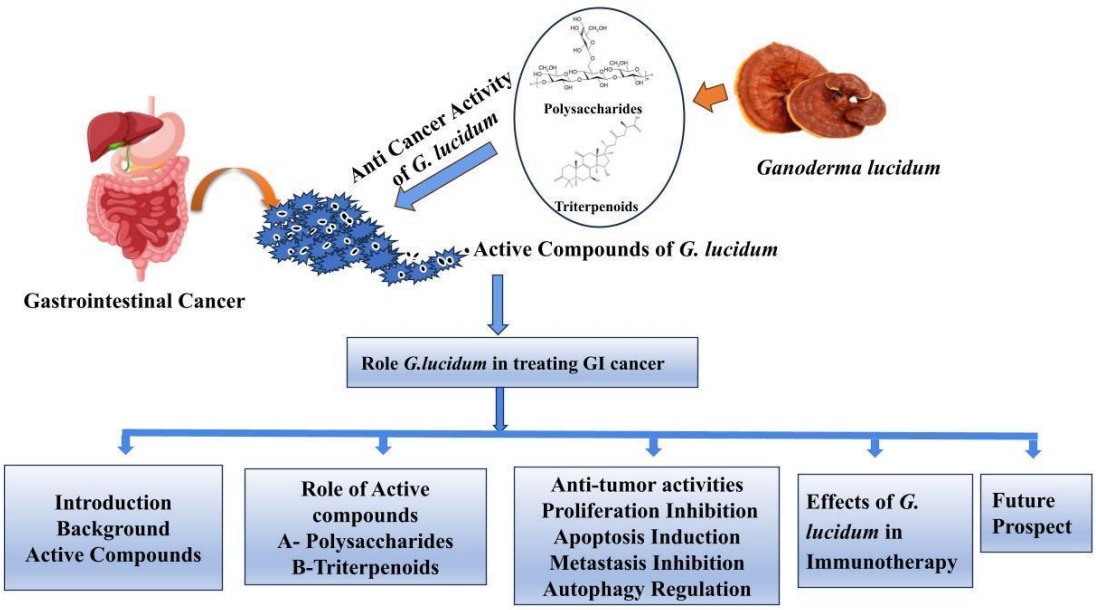
Abstract

Gastrointestinal (GI) cancer stands as a global health challenge, necessitating effective therapeutic approaches with minimal adverse effect. This review delves into the potential of *Ganoderma lucidum,* a macro fungus, commonly recognized for its medicinal properties, in traditional Chinese medicine. Macro fungus acts as a promising adjunct for treating gastrointestinal cancer. The bioactive compounds from *Ganoderma lucidum* are polysaccharides, triterpenes, and proteins demonstrating anti-tumor activities by modulating key cellular mechanisms such as proliferation, apoptosis, metastasis, and autophagy. This review elucidates the mechanisms underpinning *G. lucidum's* anti-GI cancer properties through an extensive exploration of available literature. Furthermore, it provides understanding of the clinical applications of *Ganoderma lucidum,* shedding light on its potential as a complementary therapeutic option in the realm of both traditional Chinese and western medicine. The comprehensive analysis presented herein aims to serve as a valuable guide for future studies endeavors, fostering a deeper understanding of *G. lucidum's* role in both preventing and treating GI cancer.

Graphical Abstract



1. Introduction

Gastrointestinal (GI) cancers represent a significant health issue, encompassing malignancies like gastric, esophageal, colorectal, pancreatic, and liver cancers. Frequency of GI cancers is a rapidly growing concern in Asian Countries. For example in China, GI cancers are particularly alarming, accountable for 45% of cancer-related deaths, excluding those caused by lung cancer [1].

Notably, liver cancer has become the second the primary reason for cancer-related deaths in 2020, surpassing its ranking of third in 2018 [1,2].

Hepatocellular carcinoma (HCC), constituting 85-90% of liver cancers, and cholangiocarcinoma (CCA) are the most common subtypes. While surgery remains the primary treatment for liver cancer, advancements in targeted therapy, immunotherapy, liquid biopsy, and robot-assisted surgery are increasingly being integrated into clinical practice [3]. Gastrointestinal (GI) cancers present a considerable health concern burden, encompassing a variety of malignancies. Gastric cancer (GC), ranked as the sixth most prevalent cancer worldwide. It stands as the third highest contributor to cancer-related mortalitys [1,2]. Adenocarcinomas, arising from the stomach lining, constitute the majority (around 90%) of GC cases. Surgical intervention is the primary treatment approach for initial stages and operable GC, while advanced stages often incorporate cisplatin chemotherapy [4,5]. Colorectal cancer (CRC), the fifth most common cancer globally, stands at tenth place in terms of cancer-related deaths [2]. Treatment strategies for CRC encompass local therapies like surgery, radiotherapy, and ablative interventions, alongside systemic therapies such as chemotherapy, targeted therapy, and immunotherapy [6]. Pancreatic cancer, although less frequent, carries a high mortality rate, ranking seventh among all cancers [2]. More than 90% of pancreatic cancer cases are pancreatic ductal adenocarcinomas (PDAC), with other forms including acinar carcinoma, adenosquamous carcinoma, and neuroendocrine tumors. The only potential for a cure in pancreatic cancer lies in surgical resection, although treatments such as radiotherapy, chemotherapy, interventional therapies, and best supportive care are essential for managing the disease and improving patient survival [2,7].

Gastrointestinal (GI) cancers encompass a variety of malignancies that have a substantial impact on global health. Esophageal cancer (EC), which ranks as the tenth most common cancer and the sixth leading cause of cancer-related deaths globally, is predominantly made up of squamous cell carcinoma, followed by adenocarcinoma and small cell carcinoma [8]. Surgical intervention is a cornerstone of curative treatment for EC, often complemented by a combination of postoperative therapies including radiotherapy, systemic drug therapy, and endoscopic procedures [8]. GI cancers pose a substantial challenge despite advancements in personalized therapy (Figure 1). Considerable number of patients struggle with distant spread of the cancer and resistance to drugs, underscoring the pressing requirement for new therapeutic targets and efficient strategies targeted drugs in GI oncology [1-8].

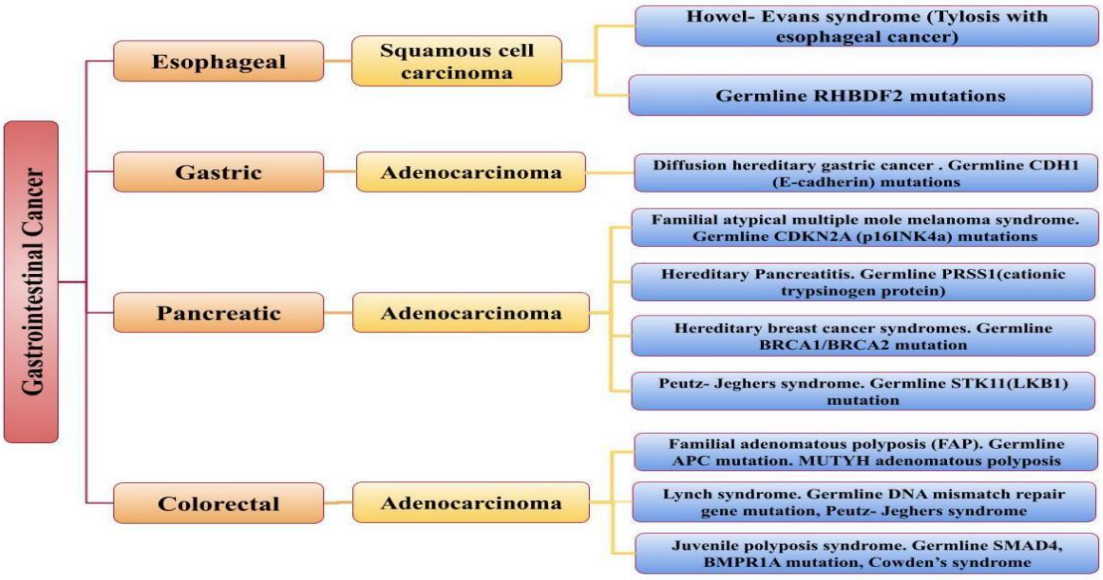


Figure 1. Types of gastrointestinal cancers and their associated genetic syndromes or germline mutations linked to diffuse hereditary gastric cancer by germline mutations in the CDH1 (E-cadherin) gene.

Natural products have continuously been crucial in the exploration and advancement of anti-tumor drugs. *Ganoderma lucidum,* a versatile medicinal mushroom with a 2400-year history of safe and non-toxic use, exemplifies this approach. According to the 2020 Chinese Pharmacopoeia, *Ganoderma lucidum* refers to the dried fruiting body of either *Ganoderma lucidum* (Leyss. ex Fr.) Karst. or *Ganoderma sinense* Zhao, Xu et Zhang, which are members of the Polyporaceae family [2,9]. Modern medicine *Ganoderma lucidum* for various ailments, including asthma, fatty liver disease, sleep disorders, and even cancer [9-14]. The anti-tumor properties of *Ganoderma lucidum* have attracted considerable scientific attention. Preclinical and basic research indicates that *Ganoderma lucidum,* whether used alone or in combination with conventional therapies, can inhibit the proliferation of tumor cells and induce apoptosis (programmed cell death), suppress metastasis (cancer spread), and regulate autophagy (cellular recycling process) in tumors [15-17]. Clinical studies have shown promising results for *Ganoderma lucidum* in treating lung cancer, colorectal cancer, and other malignancies [18-20]. Traditional medicine views *Ganoderma lucidum* as a means to bolster healthy Qi

(vital energy) and eliminate pathogenic factors. This translates to stimulating the body's natural repair processes, enhancing its internal environment, and attaining a harmonious balance of Yin and Yang. For cancer patients with Qi deficiency and an excess of "evil spirits" (pathogens), *Ganoderma lucidum* offers a potential approach to address both symptoms and root causes. By strengthening deficiencies and reducing excesses, *Ganoderma lucidum* may alleviate cancer symptoms and improve patient survival, aligning with the concept of tumor pathogenesis in modern medicine [9].

2. Gastrointestinal Tract Cancer: An Overview

Gastrointestinal (GI) cancers encompass various malignancies affecting the colon, rectum, stomach, pancreas, esophagus, and other digestive organs [1]. Common in Western countries, colorectal, gastric, and pancreatic cancers are prevalent, with risk factors including smoking, alcohol, aging, infections, chronic pancreatitis, and obesity [1-4]. Despite advancements in molecular characterization, GI cancers remain a leading cause of cancer-related deaths due to late-stage diagnosis and poor survival rates following metastasis. Early detection through screening has improved outcomes, but current methods are invasive and expensive, underscoring the need for noninvasive biomarkers [2]. Symptoms like bloating and pain often appear late, and treatments include surgery, radiation, and chemotherapy [21,22].

2.1 Types of Gastrointestinal Tract Cancers

Gastrointestinal (GI) cancers, impacting various parts of the digestive system, are influenced by lifestyle changes, socio economic development, and preventative measures. Recent trends show a shift in the landscape of these cancers, with risk factors and outlooks evolving accordingly. The digestive system is divided into upper (esophagus, stomach, small intestine) and lower (colon, rectum, appendix) sections, with cancers like esophageal carcinoma, gastric carcinoma, and colorectal cancer affecting these areas (Table 1). Risk factors include hereditary conditions like hereditary nonpolyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP) [23,24].

Table 1. Classification of gastric cancer with primary locations, histological subtypes, key risk factors, trends, and challenges highlighting geographical disparities, lifestyle influences, and difficulties in early detection and effective screening.

Cancer Type	Primary Locations	Histological Subtypes	Key Risk Factors	Trends and Challenges
Esophageal Cancer	Esophagus	Adenocarcinoma (AC), Squamous Cell Carcinoma (SCC)	Tobacco use, alcohol consumption, obesity, gastroesophageal reflux disease, dietary habits, opium use, air pollution	Geographical disparities, increasing obesity rates, declining smoking levels, late diagnosis, need for more effective and accessible screening methods [25-27].
Gastric Cancer	Stomach (Cardiac and Non-cardia regions)	Cardia Gastric Cancer (CGC), Non-cardia Gastric Cancer (NCGC)	H. pylori infection, obesity, gastroesophageal reflux disease	Decreasing occurrence due to improved food preservation and socioeconomic development, recent increases in younger age groups, *H. pylori* [28,29].
Colorectal Cancer	Colon, Rectum, Anus	Mucinous adenocarcinoma, Signet ring cell adenocarcinoma, Medullary carcinoma	High-fat diet, high sugar intake, animal-source food consumption, sedentary behavior, obesity, alcohol consumption, red and processed meats, physical inactivity, smoking	Increasing incidence globally, lifestyle and dietary changes, population-level health initiatives, disparities in survival rates, projections indicating doubling of cases by 2035 [30-32].
Liver Cancer	Liver (Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma)	Hepatocellular Carcinoma (HCC), Intrahepatic Cholangiocarcinoma (ICC)	Chronic hepatitis B or C infection, aflatoxin exposure, alcohol consumption, obesity, diabetes, smoking	Declines in HBV and HCV prevalence, rising obesity and metabolic disorders, importance of HBV vaccination, early detection challenges, poor prognosis, varying survival rates across regions [33-35].
Pancreatic Cancer	Pancreas	Adenosquamous carcinoma, invasive Mucinous cystic neoplasm (MCN), Acinar cell carcinoma (ACC), Squamous cell carcinoma (SCC)	Smoking, diabetes, obesity, high consumption of red and processed meats, excessive alcohol consumption	Difficult early detection due to nonspecific symptoms, low survival rates, increasing incidence rates with improved registration, challenges in screening and targeting high-risk individuals [36,37].

2.2 Mechanism of Gastrointestinal Tract Cancer

Cancer research has identified several key mechanisms underlying the development of gastrointestinal cancers. At the core lies a genetic basis, where mutations disrupt genes that regulate normal cell growth, death, and differentiation. These genetic alterations can arise through various factors, including inherited

predispositions, exposure to carcinogens, chronic inflammation, and the accumulation of spontaneous mutations over time [38].

Cancer research has identified several mechanisms underlying neoplastic transformation in the gastrointestinal tract. At the core lies a genetic basis, where mutations disrupt genes regulating cell growth, death (apoptosis), and differentiation [39]. This disrupts normal cellular control, leading to uncontrolled proliferation. Various factors can contribute to these mutations, including:

(1) inherited predisposition [40], (2) exposure to carcinogens [41], (3) chronic inflammation [42,43] and (4) the accumulation of spontaneous mutations and epigenetic alterations throughout life [44] (Figure 2).

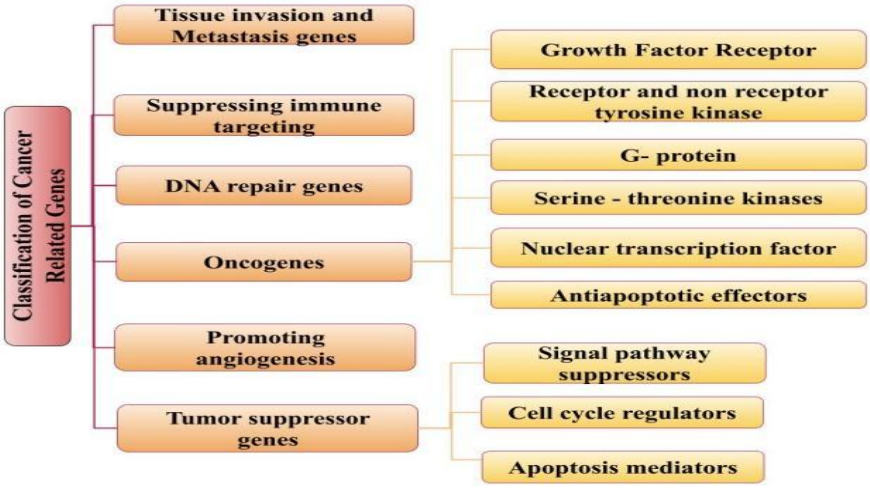


Figure 2. Classification of Cancer Related Genes.

Inherited mutations contribute to gastrointestinal (GI) tract cancers in some families, affecting organs like the esophagus, stomach, intestines, colon, and pancreas [45-47]. Familial syndromes often involve multiple tumors at a younger age without other risk factors, with significant cancer penetrance across generations. Studying these families has provided insights into cancer development, as genes mutated in familial syndromes are also found in sporadic cancers [39,40,45-47]. For example, familial colon cancer syndromes like FAP and Lynch Syndrome, which represent about 5% of cases, have helped identify key pathways in sporadic colon cancers. Advances in DNA sequencing have improved hereditary risk assessment [46], though the specific triggers for cancer in cells with inherited mutations remain unclear. Biallelic inactivation of tumor suppressor genes are crucial for tumor formation, but additional mutations are likely needed [47]. The tissue specificity and variable cancer penetrance in hereditary cancers highlight the need for further research into cancer development processes.

Carcinogen exposure is a major contributor to sporadic gastrointestinal cancers. These carcinogens can directly damage DNA (genotoxic) or need metabolic activation to become active forms that bind to DNA and cause mutations. Examples include aflatoxin from molds contaminating food staples, tobacco smoke with its many mutagens (Table 2), and dietary nitrates converted to genotoxic N-nitrosamines in the stomach [46-51]. These mutations, if not repaired, can lead to altered gene function and potentially cancer [50].

Table 2. Different carcinogens, their mechanisms of action, and associated gastrointestinal cancers.

Carcinogen	Mechanism of Action	Associated Gastrointestinal Cancers
Aflatoxin	Metabolized by hepatic cytochrome P450 enzymes, forms adducts with guanine nucleotides	Hepatocellular cancer [51].
Tobacco smoke	Contains over 40 chemical mutagens and carcinogens, causes damage to DNA nucleosides	Head and neck, esophageal squamous cell cancers [49].
Nitrates	Converted into genotoxic N-nitrosamines by gastric bacteria and acid	Gastric, esophageal cancers [23].

Chronic inflammation significantly increases gastrointestinal cancer risk with longer inflammation duration exacerbating this risk [23]. Causes of inflammation include infections (*H. pylori*, hepatitis viruses), chemical/enzymatic injury (GERD, pancreatitis), and autoimmune diseases (Crohn's, ulcerative colitis) [52]. Inflammation promotes cancer through DNA damage by reactive oxygen/nitrogen species from inflammatory cells, cytokines and chemokines stimulating tumor growth, and eicosanoids enhancing cell proliferation, angiogenesis, and producing genotoxic products like malondialdehyde and 4-hydroxy-2(E)-nonenal [53-56]. These processes highlight how inflammation fosters a cancer-promoting environment through multiple mechanisms (Table 3).

Table 3. Involvement of extensive genes in inflammation, their pathways and mechanisms of action.

Gene	Pathway	Mechanism of Action
TNFα	Inflammatory Response	Promotes cell proliferation, inhibits apoptosis, promotes cell migration and angiogenesis
IFNγ	Inflammatory Response	Induces cell proliferation, inhibits apoptosis, enhances new blood vessel growth
IL-6	Inflammatory Response	Induces cell proliferation, inhibits apoptosis, promotes angiogenesis
CXCL8	Inflammatory Response	Promotes cell migration, stromal degradation, angiogenesis
CXCL12	Inflammatory Response	Promotes cell migration, stromal degradation, angiogenesis
Cox-2	Eicosanoid Metabolism	Produces HPODEs, which decompose into genotoxic lipids that damage DNA and alter gene expression

Sporadic gastrointestinal cancers, the most common type, are likely to arise from a complex interplay of factors accumulating over time [24]. While random mutations throughout life are likely to contribute specific exposures like high-fat diets, obesity, or certain backgrounds can increase risk for specific cancers [57,58]. Conversely, the use of aspirin/NSAID and dietary choices may offer some protection [58]. Genetic variations may also play a role in individual susceptibility [24,58]. Overall, the mechanisms behind sporadic GI cancers are intricate and vary significantly between people.

3. *Ganoderma Lucidum*: A Promising Source of Bioactive Molecules

Ganoderma lucidum (Fr.) Karst. (Ganodermataceae), a member of basidiomycetous fungus, has been traditionally used as a medicinal remedy in China, Korea, and Japan for centuries. This macro fungus has been historically believed to enhance vitality and promote longevity due to its medicinal properties. Moreover, it has traditionally been employed to treat a wide range of conditions including allergies, hyperglycemia, hypertension, arthritis, bronchitis, gastric ulcers, chronic hepatitis, liver disorders, insomnia, nephritis, neurasthenia, scleroderma, inflammation, and cancer [59]. Various bioactive compounds have been identified from the mushroom's mycelia, fruiting bodies, or spores of *Ganoderma lucidum*, each potentially offering therapeutic benefits [60,61].

Ganoderma lucidum, also known as reishi mushroom, possesses a sweet and fatty taste and is traditionally used in China to invigorate the body's vital energy (Qi), calm the mind, and alleviate cough and asthma [62,63]. Ancient Chinese texts like Sheng Nong's herbal classic and the Compendium of *Materia Medica* document its use for various ailments [62,63]. Modern scientific studies have confirmed these applications and revealed a wider range of potential health benefits.

Ganoderma lucidum is rich in various bioactive compounds, including triterpenoids, polysaccharides, proteins, enzymes, vitamins, amino acids, flavonoids, steroids, alkaloids, and minerals (Figure 3), which are believed to be responsible for its medicinal properties [63,64]. Triterpenoids, especially ganoderic acids (GA), have garnered considerable interest because of their anti-tumor properties [65]. Several methods exist for extracting these bioactive compounds, including traditional techniques like organic solvent extraction and modern approaches like supercritical fluid extraction. Polysaccharides are another major class of bioactive molecules in *Ganoderma lucidum*. They primarily consist of alpha and beta-glucans and polysaccharide-protein complexes [66]. The most used method is hot water extraction for isolating polysaccharides, while other methods like ultrasonic and enzymatic extraction are also employed [67]. Extensive research supports the anti-tumor potential of *Ganoderma lucidum* extracts and their bioactive components. These effects include inhibiting cancer cell proliferation and metastasis, inducing apoptosis (programmed cell death), and regulating autophagy (cellular recycling process).

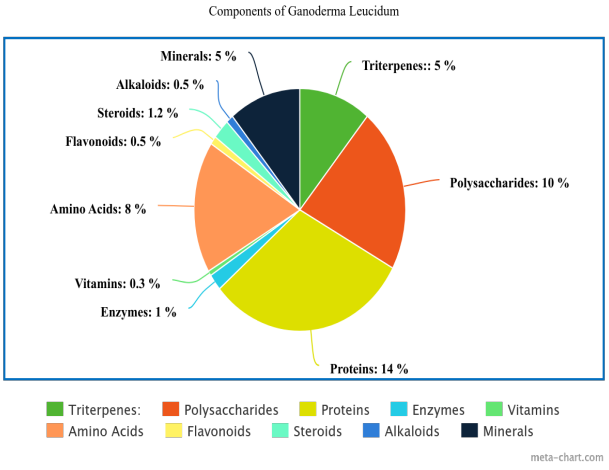


Figure 3. Approximate Percentage breakdown of the major chemical constituents of *Ganoderma lucidum*.

3.1 Triterpenoids for Cancer Prevention

Triterpenoid fractions from *Ganoderma lucidum* are typically extracted using either organic solvents or aqueous solutions. Organic solvents are effective for isolating pure triterpenoids. Meanwhile, water extraction is commonly employed to obtain crude *Ganoderma lucidum* extracts, which may also contain polysaccharide fractions. In this context, triterpenoid mixtures from *Ganoderma lucidum* are divided into two subgroups: *Ganoderma lucidum* extracts containing triterpenoids (GLCTs) and *Ganoderma lucidum* triterpenoid-enriched extracts (GLETs) [68,69].

3.1.1 GLCTs & GLETs

Extracts from *Ganoderma lucidum* containing triterpenoids (GLCTs) show anti-proliferative effects on various human cancer cell types by causing cell cycle arrest and apoptosis. The specific molecular pathways activated by GLCTs vary by cell type and treatment method. Screening 26 human cancer cell lines revealed that hematological cell lines like HL-60, U937, K562, Blin-1, Nalm-6, and RPMI8226 are highly sensitive to GLCTs, with median effective doses (ED50) ranging from 26 to 63 μg/ml. GLCTs induce G2/M phase cell cycle arrest and apoptosis [69].

GLCTs exhibit cytotoxic, anti-invasion, and anti-angiogenesis effects within a dosage range of 0.125 to 2.5 mg/ml. *In vitro* and *in vivo* studies show that GLCTs activate signaling pathways such as ERK, PI3K, JNK, AKT, and FAK, leading to the activation of transcription factors like AP-1 and NF-kB. This modulates gene expression, suppressing MMP-2, MMP-9, uPA, and reducing the secretion of VEGF, TGF-beta1, and IL-8 [70-74]. ReishiMax, a commercial *Ganoderma lucidum* extract with 13.5% polysaccharides and 6% triterpenoids, inhibits cancer cell growth by suppressing the AKT/NF-kB pathway, inducing apoptosis, and causing cell cycle arrest. It affects estrogen receptors in MCF-7 cells and inhibits angiogenesis in PC-3 cells [75-78]. ReishiMax combined with green tea extract (97% polyphenols) synergistically inhibits cell proliferation by suppressing c-Myc and reduces migration and invasion by blocking uPA secretion [79].

Extracts from *Ganoderma lucidum* containing triterpenoids (GLCTs) reduce cell growth by decreasing c-Myc levels and inhibit movement and invasion by suppressing urokinase plasminogen activator (uPA). In murine models, GLCTs prevent colon cancer by reducing inflammation and limiting abnormal cell growth [80]. Triterpenoids are more effective than polysaccharides in inhibiting cell growth and promoting apoptosis [81-84]. Among 58 mushroom types, *Ganoderma lucidum* methanol extracts were notably effective against cancer cells, outperforming other fungal species and *Ganoderma siense* [84-86].

GLCTs induce cell cycle arrest at various phases: G1 in MCF-7, MDA-MB-231, and HT-29 cells; G2/M in Huh-7 and HUCPC cells; and S phase in H69 cells. They can shift murine macrophage RAW264.7 cells from G0/G1 to G2 arrest, downregulating cyclin D1 and CDK4 while upregulating p21 and p53188. Apoptosis is induced via the mitochondrial pathway, increasing Bax expression and caspase activation, with no effect on the extrinsic pathway. GLCTs also promote autophagy through beclin-1 and LC3-II expression, inhibiting the p38 MAPK pathway in HT-29 colon cancer cells [87-91].

GLCTs induce DNA damage in cancer cells by downregulating telomerase and inhibiting topoisomerase activities. They protect normal cells from radiation-induced DNA damage and enhance apoptosis in human leukemia HL-60 cells when combined with *Duchesnea chrysantha* polysaccharides. Combining GLCTs with cisplatin or adriamycin increases oxidative stress, DNA damage, and apoptosis. GLCTs with lovastatin significantly inhibit tumor growth and exhibit cytotoxicity in mouse models against both drug-sensitive and drug-resistant small-cell lung cancer cells [92,93].

Ganoderma lucidum ethanol extracts (GLETs) exhibit antioxidative properties by activating Nrf-2, increasing superoxide dismutase (SOD), catalase, and phase II detoxification enzymes [93]. They reduce radiation-induced ROS in normal mouse splenic lymphocytes and enhance endogenous antioxidant enzymes. GLETs inhibit cell adhesion, movement, and invasion, crucial for metastasis. Ethanol extracts are more effective than water extracts in promoting actin polymerization and inhibiting cell migration in bladder cancer cells. Lucidenic acid-enriched extracts reduce invasion and metastasis in HepG2 xenografts by inhibiting ERK and AKT phosphorylation and AP-1 and NF-kB translocation, decreasing MMP-9 expression. GLETs also impede tumor vessel formation, highlighting their anti-angiogenic potential [94-96].

3.1.2 Chemical Structure and Classification of Triterpenoids in *Ganoderma Lucidum*

The triterpenoids in *Ganoderma lucidum* are mainly oxygenated lanostane structures, classified into about ten groups based on structural and functional similarities. These groups include triterpenoids like Ganoderic acid (GA), Ganosporeric acid, methyl Ganoderate, Ganodsporelactone, Ganoderenic acid, Ganolucidic acid, methyl Ganolucidate, Ganoderiol, Ganoderal, Epoxyganoderiol, Lucidenic acid (LA), Methyl Lucidenate, Lucidone, Ganolactone, lucidumol, and lucialdehyde. Over 50 triterpenoids are unique to *Ganoderma lucidum*, with many being Ganoderic acids, known for their bitter taste [97,98] (Figure 4).

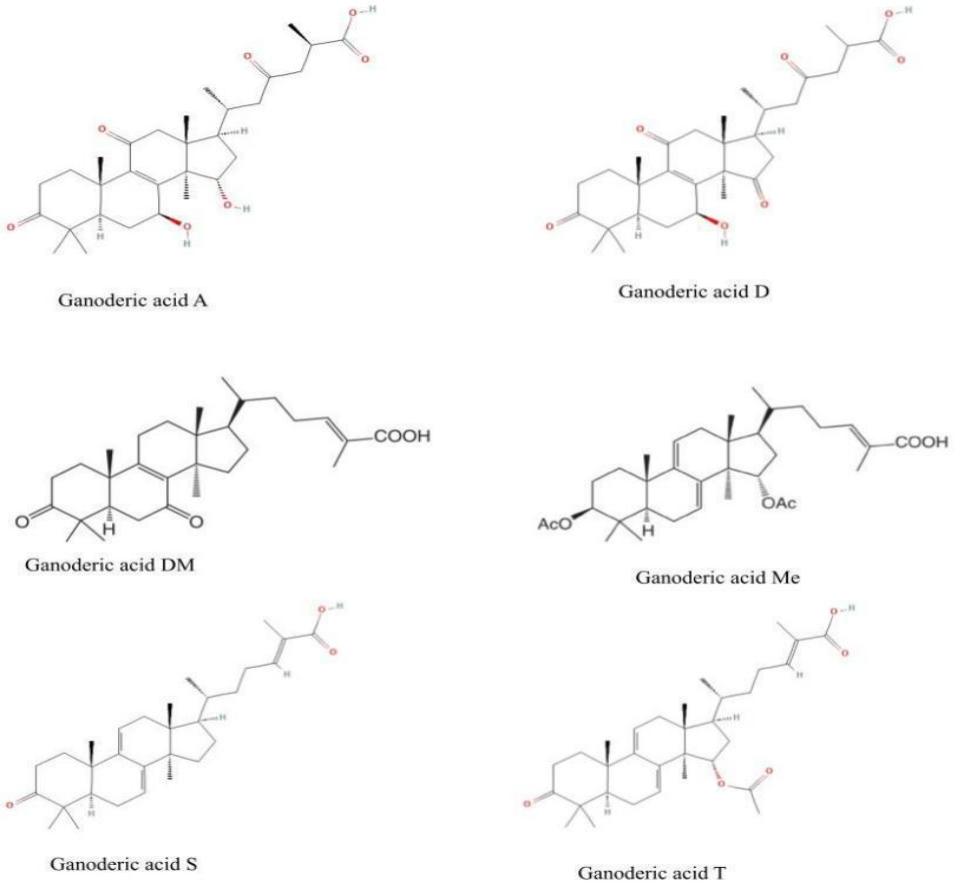


Figure 4. The chemical structure of different triterpenoids isolated from *Ganoderma lucidum.*

The first triterpenoids from *Ganoderma lucidum*, GA-A and GA-B, were isolated in 1982. Since then, over 140 triterpenoids with defined chemical structures have been discovered. Recently, ethyl lucidenate A was found in *Ganoderma lucidum*. Structure-activity relationship studies with 43 isolated triterpenoids revealed that side chain structure, C-3 carbonyl group presence, double bonds (Δ7,8, Δ9,11), and hydroxyl group number significantly influence cytotoxicity. Notably, 15α,26-dihydroxy-5α-lanosta-7,9,24(E)-trien-3-one, Lucidadiol, and Ganoderiol F show strong cytotoxic effects with IC50 values of 1, 5, and 8 μM, respectively. Ganoderic acids and Ganoderiol, known for their potent anti-cancer properties, are significant research subjects [98,99].

3.1.3 Ganoderic Acid Discussion (Ganoderic Acid DM & Ganoderic Acid T)

Ganoderic acid DM (GA-DM), a lanostane-type triterpenoid from *G. lucidum*, shows significant anti-proliferative and anti-metastatic effects against various human cancer cells. Due to its structural similarity to androgen and estrogen, GA-DM may interact with estrogen receptors (ER) or androgen receptors (AR). GA-DM induces G1 cell cycle arrest, DNA damage, and apoptosis in ER-positive MCF-7 breast cancer cells, but minimally affects ER-negative MDA-MB-231 cells [100].

GA-DM inhibits 5α-reductase, preventing the conversion of testosterone into dihydrotestosterone (DHT), which binds AR and increases anti-apoptotic proteins. GA-DM can competitively bind to AR, blocking DHT interactions and inhibiting AR-induced cell growth. It induces caspase-dependent apoptosis via the mitochondrial pathway by increasing Bax, Apaf-1, and cytochrome c, activating caspase-9 and caspase-3 in human melanoma cells. GA-DM shifts the balance between autophagy and apoptosis, peaking autophagy at 6 hours and significant apoptosis at 12 hours, reducing cell growth. In murine B16 melanoma models, GA-DM effectively reduces tumor volume [101,102].

GA-DM inhibits the maturation of bone-resorbing cells linked to prostate cancer metastasis, reducing c-Fos and NFATc1 gene activity and fusion of these cells [103]. GA-DM acts as a tubulin inhibitor in PC-3 cells, affecting prostate cancer spread by impacting the cytoskeleton and osteoclastogenesis, suggesting its potential as a treatment for advanced prostate cancer [102-105]. Structure-activity relationship studies indicate that the carbonyl group at the C-3 position is crucial for GA-DM's cytotoxic properties, while a carbonyl group at

C-7 hinders osteoclast differentiation. Methyl-GA-DM is more effective in inhibiting osteoclastogenesis than GA-DM [102-107].

Ganoderic acid T (GA-T), a lanostane triterpenoid obtained from the methanol extracts of *G. lucidum* mycelia, has exhibited notable pharmacological impacts on cell proliferation and invasion. In 95-D lung cancer cells, GA-T's ability to hinder cell growth is connected to G1 cell cycle interruption and programmed cell death, influenced by the increase in p53 and Bax levels, along with the mobilization of cytochrome c from mitochondria to the cytoplasm. GA-T also demonstrates anti-invasive qualities by suppressing NF-κB and matrix metalloproteinases (MMPs) in HCT-116 colon cancer cells. Animal research has indicated that GA-T can diminish tumor expansion and lung spread by diminishing MMP-2 and MMP-9 mRNA expression levels. Further studies have pinpointed p53 as a pivotal focus in GA-T's anti-invasive effects. Investigations on novel GA-T variations in HeLa cells propose that the carboxyl group of GA-T is dispensable for its toxic effects [108,109].

3.2 *Ganoderma Lucidum* Polysaccharides (GLPs)

Mushrooms, long valued in traditional medicine, are being explored for their potential in gastrointestinal cancer treatment. Despite advancements in medical care, there is a growing interest in natural agents with minimal side effects. Ganoderma, a type of medicinal mushroom, shows promise in cancer treatment due to its various bioactive compounds. *Ganoderma lucidum*, commonly referred to as "Lingzhi" or "Reishi," has been utilized for centuries in Asian cultures due to its perceived health advantages [110]. Research highlights polysaccharides and triterpenoid compounds from *Ganoderma lucidum* for their potential in cancer treatment. These compounds have attracted attention for their significant pharmacological effects. Polysaccharides from *Ganoderma lucidum* are particularly intriguing due to their ability to be modified for targeted drug delivery. These modifications make them responsive to tumor microenvironments, enhancing their effectiveness in cancer treatment. Studies also explore polysaccharide-based nanocarriers as potential delivery systems for anticancer drugs. Incorporating *Ganoderma lucidum* polysaccharides into nanoparticles retains their immunomodulatory and antitumor properties, improving drug delivery and efficacy. Additionally, research aims to minimize chemotherapy-associated toxicity by using *Ganoderma lucidum* polysaccharide-based nanoparticles [110]. Moreover, this review explores the mechanisms behind the anticancer properties of *Ganoderma lucidum* polysaccharides, including their cytotoxic and antioxidative characteristics. It also explores the potential of combining *Ganoderma lucidum* polysaccharides with other therapeutic agents for more comprehensive cancer treatment.

The polysaccharides extracted from *Ganoderma lucidum* are classified based on their branching, higher structures, molecular weight, and composition. Various polysaccharides from *Ganoderma lucidum* form complexes, including homo-glucans, hetero- β -glucans, heteroglycans, and α -manno- β -glucan compositions. Homoglucans consist of linear or branched structures with glucose monomers linked α - or β -wise, such as (1→6)- β -glucans and (1→6)- α -glucans, with potential side chains. β -glucans, predominant in fungal cell walls, can have linear (1→3)- β -glucan backbones or branched ones with (1→6)- β -glucan branches [111]. Hetero-glucans incorporate various constituents like arabinose, galactose, glucuronic acid, mannose, ribose, and xylose. Glycans, another polysaccharide type from *Ganoderma lucidum*, differ in backbone composition, including fucans, galactan, mannans, and xylan [112,113].

Polysaccharides have the ability to bond covalently with proteins and peptides, creating structures such as protein-polysaccharides, peptide-polysaccharides, glycoproteins, glycopeptides, and proteoglycans. While these compounds demonstrate substantial biological promise, their wide array of chemical compositions leads to diverse effects on bioactivity [114].

Ganoderma lucidum, a widely studied medicinal mushroom, is known for its rich content of bioactive polysaccharides, commonly referred to as *Ganoderma lucidum* polysaccharides (GLP). The structural characterization of GLP has been a primary focus, as it provides insights into the diverse biological activities associated with these polysaccharides. GLP consists of a diverse blend of different monosaccharides, such as D-glucose, D-fructose, D-galactose, D-mannose, D-xylose, L-fucose, L-rhamnose, and L-arabinose. The relative amounts and total content of these monosaccharides vary within GLP contribute to the structural and biological characteristics of GLP. Notably, the monosaccharide composition can vary considerably based on the specific parts of *Ganoderma lucidum* from which it is sourced [115,116].

Recent research has underscored the possible anti-cancer properties of GLP, especially concerning gastrointestinal cancers. Polysaccharides extracted from *Ganoderma lucidum*, which are rich in glucose and mannose, have been linked to immune-boosting effects. These particular monosaccharides can be identified and interacted with by specific cell surface receptors found on effector cells, such as dectin-1, the mannose receptor (MR), toll-like receptor (TLR) 4, complement receptor type 3 (CR3), scavenger receptors, and TLR2. The interaction between these receptors and the polysaccharide extracts from *Ganoderma lucidum* has been demonstrated to be vital in starting and boosting the immune response against cancer cells. Additionally, research has shown that GLP containing elevated levels of galactose and rhamnose exhibit anti-inflammatory and antioxidant characteristics [117,118].

Polysaccharides, complex carbohydrates, are broadly classified into homopolysaccharides and heteropolysaccharides based on their monosaccharide composition. Homopolysaccharides are composed of a single type of monosaccharide, such as glucose or mannose, making them less structurally complex. In contrast, heteropolysaccharides consist of a variety of

different monosaccharides, including glucose, mannose, xylose, fucose, galactose, and arabinose, which contributes to their greater structural complexity. Both types have shown anti-tumor properties, but heteropolysaccharides exhibit remarkable immunomodulatory effects due to their diverse composition. Unlike homopolysaccharides, which do not contain covalently attached protein branches, heteropolysaccharides can exist as proteoglycans, where protein branching significantly enhances their bioactivity. Additionally, heteropolysaccharides are often acidic, rich in uronic acid, which enhances their antioxidant and immunomodulatory activities compared to the generally neutral homopolysaccharides. Both types typically contain β -(1 → 3)-glucans, known for their immune-enhancing and anti-tumor properties [119] (Table 4).

Table 4. Comparison of the key differences between homopolysaccharides and heteropolysaccharides derived from *Ganoderma lucidum* based on their structure, anti-tumor properties, impact of protein branching on their bioactivity.

Characteristic	**Homopolysaccharides**	**Heteropolysaccharides**
Monosaccharide Composition	Consists of a single type of monosaccharide (e.g., glucose, mannose)	Composed of a variety of different monosaccharides (e.g., glucose, mannose, xylose, fucose, galactose, arabinose [119].
Structural Complexity	Less structurally complex	More structurally complex due to the diverse monosaccharide composition [119].
Anti-Tumor Properties	Have demonstrated the ability to inhibit tumor cell growth by suppressing cyclin production and triggering cellular stress responses	Have shown remarkable anti-tumor and immunomodulatory properties, attributed to the diverse monosaccharide composition [120].
Protein Branching	Do not contain covalently attached protein branches	Can exist as proteoglycans, which are highly branched heteropolysaccharides covalently attached to a protein [121].
Bioactivity Enhancement	Protein branching does not significantly enhance the bioactivity	Protein branching can augment the functional impacts and bioactivity of the polysaccharides [121].
Acidic Heteropolysaccharides	Homopolysaccharides are generally neutral glucans, while most of the heteropolysaccharides are polyanionic due to the presence of uronic acid	High levels of acidic heteropolysaccharides, rich in uronic acid, can enhance antioxidant and immunomodulatory activities compared to homopolysaccharides [122].
Predominant Glycosidic Bonds	Typically contain β-(1→3)-glucans	Also contain β -(1 → 3)-glucans, which exhibit notable immune-enhancing and anti-tumor properties [123].

Ganoderma lucidum polysaccharides (GLP) have been the subject of much research attention for their anti-cancer potential to stomach cancer by mitigating the oxidative stress and inflammation linked to stomach cancer [103]. Numerous scholarly investigations have examined the methods by which GLP impacts stomach cancer cells and the surrounding tumor microenvironment (Table 5). It was observed that certain cytokines, such as IL-2 (interleukin-2), IL-4 (interleukin-4), and IL-6 were significantly increased in activated T cells in GLP administered Wistar rats in a dose dependent manner. They are essential for inducing regulatory effects on different immune systems for IgE production [103]. Furthermore, IL-10, a significant immunomodulatory cytokine, has a role in controlling inflammatory responses by affecting TNF-α production [103]. GLP significantly reduced cell viability and promoted apoptosis in stomach cancer cells with a rise in cleaved-PARP and a decrease in the expression of pro-caspase-3 and the anti-apoptotic protein Bcl-2 [124]. The potential of GLP, especially more from sporoderm removed spores GLP, act as an autophagy regulator in gastric and maybe in other cancer types [124].

Table 5. Various studies on the effects of GLP (*Ganoderma lucidum* polysaccharides) across different cancer types. For colon and colorectal cancers, GLP consistently reduced cell viability, induced apoptosis, and inhibited tumor growth in both *in vitro* and *in vivo* models, including cell lines like HCT-116, HT-29, and xenograft mice. Studies on gastric cancer also showed reduced cell viability and enhanced apoptosis, with additional anti-inflammatory and antioxidant effects.

Cancer type	GLP dose	Study model/cell line	Result
Colon and Colorectal	*In vitro*: 0.625–5 mg/mL, 0–72 h	*In vitro*: HCT-116 cell lines	Decreased cell viability inhibited cell migration and altered cell morphology [125,126].
Colon and Colorectal	*In vitro*: 0–10 mg/mL, 0–72 h	*In vitro*: HCT-116 cell lines	Decreased cell viability led to cell cycle arrest in the S phase, induced apoptosis, and triggered DNA fragmentation [125,126].
Colon and Colorectal	*In vitro*: 0–10 mg/mL, 0–72 h	*In vitro*: LoVo cell lines	Decreased cell viability inhibited cell migration, triggered apoptosis, and caused DNA fragmentation [127].
Colon and Colorectal	*In vitro*: 200 μg/mL, 24 h	*In vitro*: HT29 (p53R273H) and SW480 (p53 R273H&P309S)	Promoted apoptosis, recovered p53 [128].
Colon and Colorectal	*In vitro*: 0–7.5 mg/mL, 0–48 h *In vivo*: 0–300 mg/kg/day, six weeks	*In vitro*: HCT116 cell lines *In vivo*: Xenograft mice	Decreased cell viability slowed cell cycle progression, promoted apoptosis, and reduced tumor growth [129].
Colon and Colorectal	*In vivo*: 393.75 g/kg/day	*In vivo*: xenograft mice	Prevented colon shortening, reduced the mortality rate, and decreased the abundance of faecal *Oscillospira* and related genes [130].
Colon and Colorectal	*In vitro*: 0–10 mg/mL, 0–72 h *In vivo*: 0–300 mg/kg/day, 14 days	*In vitro*: HT-29 and HCT-116 cell lines *In vivo*: xenograft mice	Decreased cell viability triggered autophagy and reduced both tumor growth and volume [131].
Colon and Colorectal	*In vitro*: 0–0.32 mg/mL, 24 h *In vivo*: 0–300 mg/kg/day, 14 days	*In vitro*: HT-29 cell lines *In vivo*: xenograft mice	Reduced inflammation [132].
Colon and Colorectal	*In vitro*: GLPs: 3 μg/mL, 72 h Paclitaxel: 0.5 μM, 72 h *In vivo*: 2 mg/kg/day, 30 days	*In vitro*: CT26 and HCT-15 cell lines *In vivo*: xenograft mice	Reduced cell growth and viability, suppressed tumor growth, and induced apoptosis [133,134].
Gastric	*In vivo*: 400 and 800 mg/kg/every two days, four weeks	*In vivo*: Wistar rats bearing gastric cancer	Reduced inflammation and increased antioxidant activity [135].
Gastric	*In vitro*: 0–15 mg/mL	*In vitro*: AGS cell lines	Reduced cell viability, promoted apoptosis and autophagy [136].

4. Other Bioactive Components of *G. Lucidum*

Cultivated *Ganoderma lucidum* fruit bodies contain phosphorus, silica, sulfur, potassium, calcium, and magnesium as predominant minerals, with lower level of iron, sodium, zinc, copper, manganese, strontium and heavy metals like lead, cadmium, and mercury in traces [9,111,137]. In contrast, *Ganoderma lucidum* collected from the wild and freeze-dried showed a mineral content

of 10.2%, with potassium, calcium, and magnesium being the primary constituents with no detectable cadmium or mercury. *G. lucidum* is reported to contain up to 72 μg/g dry weight of selenium (Se) with the capability to biotransform a notable portion (20–30%) of inorganic selenium from the growth substrate into selenium-rich proteins [138,139]. Germanium was the fifth most abundant mineral found in *Ganoderma lucidum* fruit bodies collected from natural environments, with a concentration of 489 μg/g. Germanium is also present in trace amounts in various plant-derived foods such as ginseng, aloe, and garlic, typically measurable in parts per billion. Germanium has been reported to be associated with immune-boosting, anti-tumor, antioxidant, and antimutagenic effects when administered at low level. However, there is no definitive evidence establishing a direct correlation between this element and the health benefits commonly attributed to the mushroom [139]. *Ganoderma lucidum* contains various proteins and lectins that may enhance its supposed medicinal benefits. Lectins were extracted from both the fruiting body and the mycelium of the mushroom *viz.* 114-kDa hexameric lectin. This lectin was characterized as a glycoprotein containing 9.3% neutral sugar and demonstrating hemagglutinating activity on pronase-treated human erythrocytes. The protein content in dried *Ganoderma lucidum* is lower compared to edible mushrooms (7–8%) playing a pivotal bioactive role for its medicinal qualities *viz.* LZ-8, an immunosuppressive protein and ganodermin, a 15-kDa antifungal protein extracted from mycelia and fruiting bodies, respectively [1,140,141]. Dehydrated *G. lucidum* contains carbohydrate and crude fiber levels of about 26–28% and 59%, respectively [9]. Metalloprotease, known for its ability to prolong clotting time, as well as ergosterol (provitamin D2), nucleosides, and nucleotides (including adenosine and guanosine) are additionally extracted from *Ganoderma lucidum*. SKG-3, a highly selective and efficacious reversible inhibitor of α-glucosidase was isolated and physiochemically characterized from *Ganoderma lucidum* fruit bodies with the mixture of various long-chain fatty acids potentially combating tumor development [1,141,142].

5. Recent Advancements on the Effect of *G. Lucidum* in the Anti-Gastrointestinal Cancer

Studies have revealed that the anti-cancer effects of *Ganoderma lucidum* primarily stem from its polysaccharides and triterpenes. *Ganoderma lucidum* polysaccharides (GLP) comprise (1→3), (1→6)- α / β - glucans, glycoproteins, and water-soluble heteropolysaccharides. GLP fights against cancer by impeding tumor growth and spread, while also bolstering immune function through diverse mechanisms such as inhibiting cell proliferation, promoting cell death, hindering metastasis, and preventing angiogenesis.

5.1 *Ganoderma Lucidum* in Cell Proliferation

Ganoderma lucidum exerts its effect on cancer through the modulation of cell proliferation in various gastrointestinal cancer cell lines, a vital process that is often dysregulated in the development and progression of gastrointestinal cancers such as colorectal cancer (CRC) and esophageal squamous cell carcinoma (ESCC) [143-151] (Figure 5). The cancer-fighting capabilities of *Ganoderma lucidum* are credited largely due to abundance of triterpenes based bioactive compounds *viz.* a lanostane triterpene known as GA, has shown the ability to hinder the proliferation of the human hepatoma cell line BEL7402 by halting the cell cycle in the G2/M phase, leaving normal liver cells unaffected. A lanostane triterpenoid derived from methanol extracts of *Ganoderma lucidum* mycelia, GA-T, has been demonstrated to exert pharmacological effect on suppression of cell proliferation and invasion, induce apoptosis, and disrupt cell cycle progression in colorectal cancer cells. GA-Me has also exhibited promising anti-invasive and anti-metastatic properties [149]. Cell proliferation is a tightly regulated process governed by an intricate interplay of various proteins, genes, enzymes, and signaling pathways. The orchestration of cell division occurs through the cell cycle having four distinct phases *viz.* G1, S (synthesis), G2, and M (mitosis). Progression activities through this cycle are precisely controlled by cyclins and cyclin-dependent kinases (CDKs) modulated by CDK inhibitors. The control and initiation of cell proliferation are mainly coordinated by external signaling molecules, such as growth factors and cytokines. These signals are transduced into the cell through cell surface receptors, notably receptor tyrosine kinases (RTKs). Upon ligand binding, RTKs undergo conformational changes, leading to their dimerization and autophosphorylation. This event triggers a cascade of intracellular signaling pathways, including the Ras/Raf/MEK/ERK (mitogen-activated protein kinase) pathway and the phosphoinositide 3-kinase (PI3K)/Akt pathway. The Ras/Raf/MEK/ERK pathway is a central signaling cascade that regulates cell proliferation. Activated RTKs recruit adapter proteins like Grb2, which facilitates the activation of the small GTPase Ras. Activated Ras then binds to and activates the serine/threonine kinase Raf, which subsequently phosphorylates and activates MEK (MAPK kinase). MEK, in turn, phosphorylates and activates ERK, a MAPK that translocates to the nucleus and activates transcription factors involved in cell cycle progression, such as c-Myc, c-Fos, and c-Jun. Another vital signaling pathway that enhances cell survival and proliferation is the PI3K/Akt pathway. Upon RTK activation, PI3K is recruited to the plasma membrane, where it generates phosphatidylinositol-3,4,5-trisphosphate (PIP3). PIP3 serves as a docking site for the serine/threonine kinase Akt (also known as protein kinase B), which is activated upon recruitment. Activated Akt phosphorylates and inhibits various pro-apoptotic proteins, thereby promoting cell survival, and also activates downstream targets that stimulate cell cycle progression. In addition to growth factors and cytokines, cell proliferation is also regulated by proto-oncogenes and tumor suppressor genes. Mutations in proto-oncogenes, such as Ras, Myc, and Src, can lead to their constitutive activation, motivating uncontrolled cell proliferation. On the other hand, mutations that deactivate tumor suppressor genes like p53 and Rb, can disrupt cell cycle checkpoints and

allow abnormal cell division [152]. Furthermore, telomere length and telomerase activity play crucial roles in regulating cellular proliferative capacity. Telomeres act as protective caps at the tips of chromosomes, progressively shortening with each round of cell division [152].

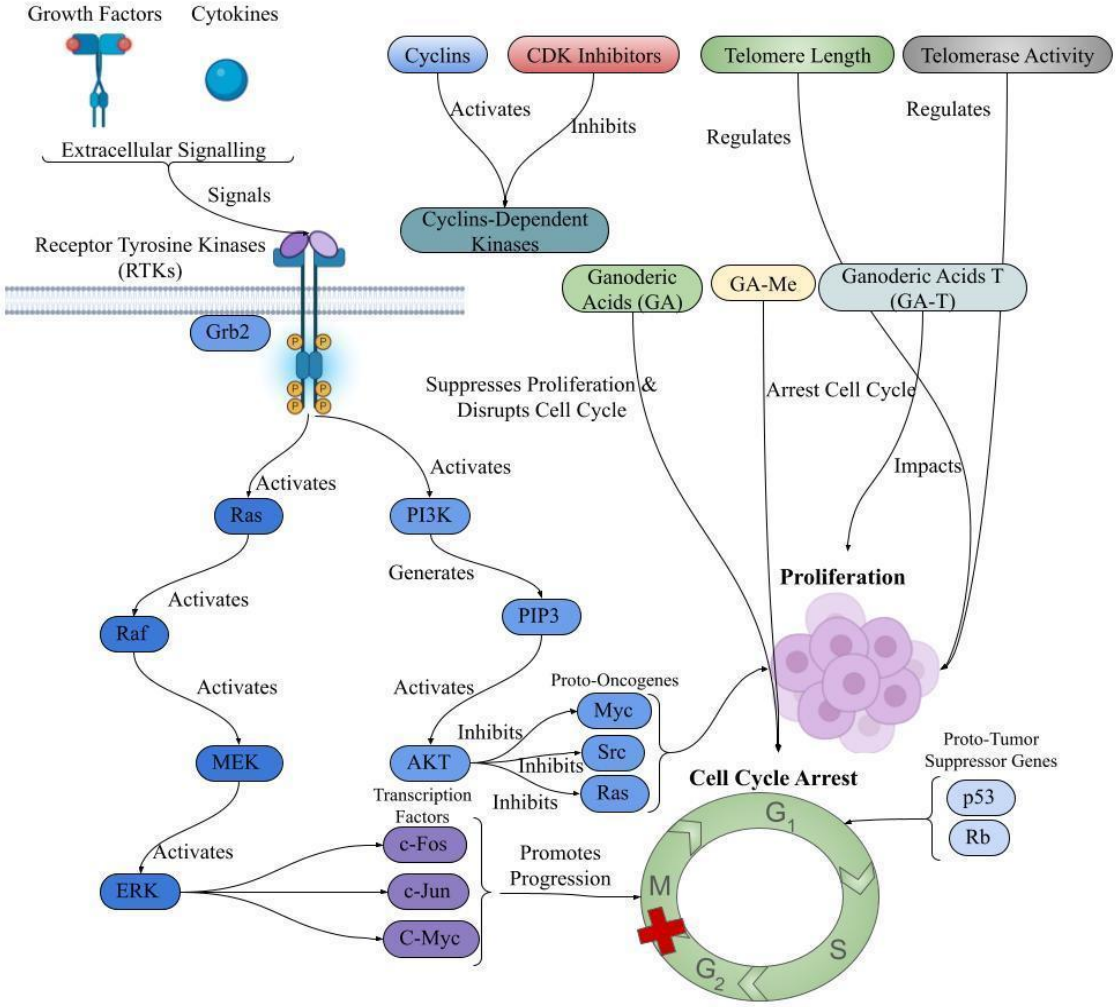


Figure 5. Signaling pathway network: molecules, and processes regulating cell proliferation, cell cycle progression, and tumorigenesis.

Once telomeres reach a critical length, cells either enter a phase of replicative senescence or undergo programmed cell death known as apoptosis. Telomerase, an enzyme that can elongate telomeres, is often upregulated in cancer cells, conferring them with an unlimited proliferative potential. This intricate network of proteins, genes, enzymes, and signaling pathways precisely orchestrates cell proliferation, ensuring that it occurs in a controlled and regulated manner (Figure 5). Dysregulation of these mechanisms can lead to various pathological conditions, including cancer, making a thorough understanding of these processes essential for developing effective therapeutic interventions [142,144]. The antioxidant properties of triterpenoid fraction of *Ganoderma lucidum* extract inhibits colorectal cancer cell proliferation possibly through DNA synthesis [145].

Ganoderma lucidum polysaccharide (GLP) exhibited significant cytotoxic effect on HSC-3 cell line of oral squamous cell carcinoma (OSCC) by inhibiting their proliferation and migration in a dose-dependent manner, with an IC50 of 0.91 mg/mL. Mechanistic analysis revealed that GLP treatment upregulated miR-188 expression, which in turn suppressed BCL9, a component of the Wnt/β-catenin signaling pathway. This suppression led to reduced β-catenin signaling and downregulation of genes involved in cell cycle progression and metastasis suggesting further research to validate its clinical relevance [146].

5.2 *Ganoderma Lucidum* in Cell Apoptosis

Cell Apoptosis, an intricately regulated process of programmed cell death, is fundamental to various physiological phenomena in multicellular organisms. This coordinated cellular death is regulated by two main pathways: the extrinsic pathway, triggered by external signals binding to death receptors on the cell surface, and the intrinsic pathway which involves mitochondria-mediated events triggered by internal cellular stressors. Endoplasmic reticulum (ER) has emerged as an additional crucial player in apoptosis, responding to perturbations in cellular homeostasis. Central to the execution of apoptosis are caspases, a family of cysteine proteases, and the B-cell lymphoma-2 (Bcl-2) family of proteins, collectively regulating the fate of cell [2,38,147,148] (Figure 6).

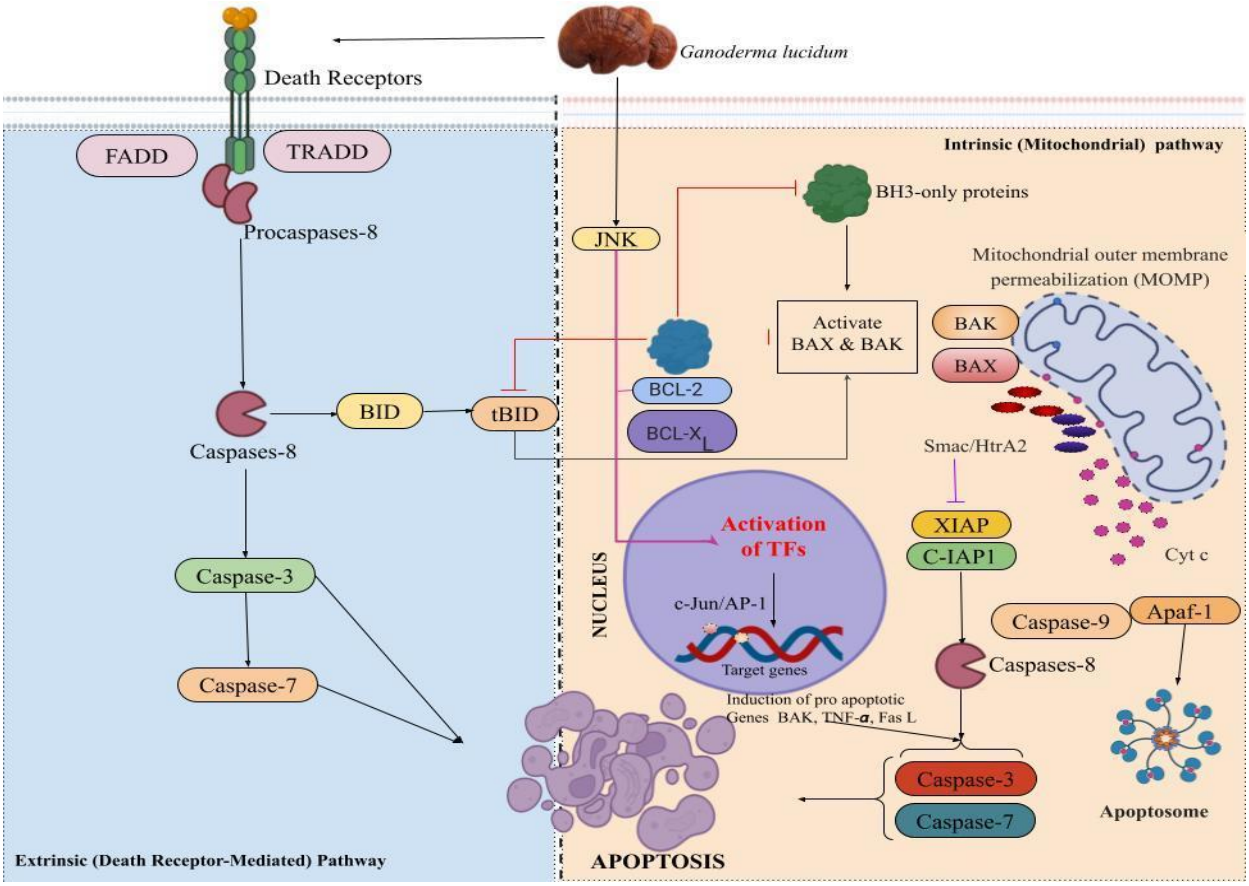


Figure 6. The dual apoptosis pathways: the extrinsic (death receptor-mediated) pathway, initiated by death receptors and leading to the activation of caspase-3 and caspase-7, and the intrinsic (mitochondrial) pathway, involving mitochondrial membrane permeabilization, activation of BAX and BAK, and the release of cytochrome c, culminating in apoptosis. *Ganoderma lucidum* is shown to influence these pathways by affecting proteins like JNK, BCL-2, and caspases.

5.2.1 Intrinsic (Mitochondrial) Pathway

The signaling pathways triggered by *Ganoderma lucidum* compounds are illustrated in Figure 6. Mitochondria play a key role in regulating *Ganoderma lucidum* compound-induced apoptotic cell death in cancer cells. In the intrinsic pathway, an increase in mitochondrial outer membrane permeability (MOMP) leads to the release of molecules like cytochrome c (Cyt c), Smac/DIABLO, and Omi/HtrA2 from the inner mitochondrial space, initiating a caspase cascade through the activation of proapoptotic proteins Bax/Bak [153-157]. Cyt c, in the presence of deoxy-ATP or ATP, forms apoptosomes with apoptotic peptidase activating factor 1 (Apaf-1) and procaspase 9, activating caspase 9/3. Smac/DIABLO and Omi/HtrA2 promote caspase activation by inhibiting inhibitors of apoptosis proteins (IAP), leading to cell death [154-158].

The tumor suppressor protein p53 regulates the transcription of proapoptotic genes such as Bax, Noxa, Puma, and Fas. It also binds to antiapoptotic proteins like Bcl-2 and Bcl-xL, increasing BH3-only proteins like Bid and Bim, and thus regulates the Bax/Bad-mediated apoptotic pathway [159]. Bcl-xS blocks Bcl-xL, further enhancing the Bax/Bak-mediated pathway [160-162].

JNK (c-Jun N-terminal kinase) is necessary for the release of Cyt c from mitochondria during apoptosis [161]. Activated JNK promotes Bax translocation from the cytosol to the mitochondria by phosphorylating 14-3-3, which anchors Bax in the cytoplasm [162]. Studies on mouse embryonic fibroblasts (MEFs) from JNK1 − / − JNK2−/− mice suggest that JNK is essential for apoptotic signaling in response to various genotoxic and cytotoxic stresses [163-165]. JNK activation in response to growth factors is quick and short-lived, while γ -ray-induced proapoptotic JNK activation is delayed. In cancer cells sensitive to *Ganoderma lucidum* compounds, JNK activation is sustained over time, whereas in resistant cells, it is brief [163,164]. Transfection with a dominant-negative JNK allele inhibited JNK activity and blocked *Ganoderma lucidum* compound-induced apoptosis in sensitive cells [165].

JNK also phosphorylates p53 family proteins in the apoptosis pathway, likely contributing to the p53-mediated upregulation of proapoptotic genes like Bax and Puma [166,167]. Additionally, JNK activation caused by DNA damage stabilizes and activates p73, another p53 family member that induces proapoptotic genes like Bax and Puma [168,169]. Apoptosis mediated by p73 in response to *Ganoderma lucidum* compounds depends on JNK, which phosphorylates p73. Mutations at the JNK phosphorylation site of p53 reduce p73 stabilization and transcriptional activity, diminishing compound-induced apoptosis [168]. JNK regulates the expression of proapoptotic and prosurvival genes through various transcription factors in a cell-specific and stimulus-specific manner.

5.2.2 Extrinsic (Death Receptor-Mediated) Pathway

MOMP (mitochondrial outer membrane permeability) induced by Bax/Bak activation promotes apoptotic cell death, and Bid activates Bax/Bak after being activated by caspase-8 that are illustrated in Figure 6. Caspase-8 is triggered when Fas and DR4/5 bind to the death factor receptor FasL and the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). This interaction recruits proteins such as TRADD (tumor necrosis factor receptor 1 death domain protein), FADD (Fas-associated death domain protein), and procaspase-8, forming a death-induced signaling complex (DISC) that activates procaspase-8 [170].

Following TRAIL activation, FADD is recruited after TRADD dissociates, forming complexes with receptor-interacting protein (RIP) and tumor necrosis factor receptor–associated factor 2 (TRAF2). These proteins mediate both cell survival and death through pathways like nuclear factor–kappa B (NF-κB) and JNK1, respectively. Caspase-8 cleaves Bid into tBid, which activates the Bax/Bak-mediated mitochondrial pathway [171]. TNF-α (tumor necrosis factor-alpha) also activates caspase-8, which triggers JNK to activate Bid (jBid) through phosphorylation-mediated cleavage, promoting the release of Smac and Omi [172]. Smac inhibits cellular IAP 1 and X-linked inhibitor of apoptosis protein (XIAP), leading to the activation of caspases-3 and -7, which drive apoptosis [173]. Caspase-8 directly activates caspase-3 without requiring the amplification of the mitochondrial pathway, and it also induces non-apoptotic cancer cell death through lysosome-associated mechanisms [174].

In some cases, the duration of JNK activation plays a crucial role in determining apoptotic cell death. For example, TNF-α induces apoptosis in cells via JNK activation, and inhibiting JNK can suppress this process [175]. Sustained JNK activation may be necessary for the induction of apoptotic cell death in certain types of cancer cells, particularly in response to *Ganoderma lucidum* compounds.

5.2.3 Anti-apoptotic Pathway

The release of apoptotic small molecules via mitochondrial outer membrane permeability (MOMP) through Bax/Bak activation is crucial for both caspase-dependent and caspase-independent apoptotic pathways. This process is blocked by antiapoptotic proteins like Bcl-2 and Bcl-xL [176]. These proteins inhibit the movement and oligomerization of Bax before it integrates into the mitochondrial outer membrane. Bcl-xL also inhibits DISC formation and Bid activation by caspase-8, implying its regulatory role in both the mitochondrial and receptor-dependent pathways [177]. Bcl-2 partially inhibits death receptor-dependent pathways. MOMP leads to the loss of mitochondrial membrane potential, which varies based on the trigger and results in the production of reactive oxygen species (ROS) that activate lysosomal enzymes responsible for non-apoptotic cell death [178]. Bcl-2 and Bcl-xL prevent the loss of mitochondrial membrane potential and reduce ROS production, partly due to Bcl-2's antioxidant properties [177].

The antiapoptotic PI3K/Akt pathway plays a critical role in tumor development and progression [179]. Akt, a serine-threonine kinase, is activated by hormones and growth factors and regulates pro-apoptotic proteins such as Bax and Bad. Phosphorylation of Bax promotes its interaction with antiapoptotic proteins like MCL1 and Bcl-xL, preventing Bax from relocating to mitochondria. Bad is dephosphorylated, allowing it to bind and inactivate 14-3-3 proteins, further inhibiting apoptosis [180,181]. Akt also controls Bcl-2 expression via CREB and directly inhibits caspase-9 activity [182,183]. In addition, Akt suppresses p53 function by activating MDM2, a negative regulator of p53 [184]. I-κB is phosphorylated by Akt, leading to the activation of NF-κB, an antiapoptotic protein [185]. NF-κB activates key antiapoptotic proteins, including Bcl-xL, XIAP, and c-FLIP [186]. It also inhibits cell cycle regulators like p27 and induces the expression of ABCB1 (MDR1) and matrix metalloproteinase-9 (MMP-9), which are involved in cancer cell cycle regulation, drug resistance, and metastasis [187-189]. NF-κB further inhibits TNF-α-induced apoptotic cell death by blocking the JNK signaling cascade, particularly through the action of XIAP, a caspase inhibitor [190]. This antiapoptotic function of NF-κB is linked to its ability to prevent ROS accumulation and modulate the JNK signaling pathway [186].

5.2.4 *Ganoderma Lucidum* Compounds Inducing Apoptosis in GI Cancer

EGLP may induce apoptosis in HCT-116 cells by upregulating the expression of Bcl-2 associated X protein (Bax), phospho-ERK (p-ERK), and cleaved caspase-3, while down regulating Bcl-2, phospho-AKT1, and cyclooxygenase-2 (COX-2) [190-193]. GLP also inhibited the growth and metastasis of HCT-116 cells by increasing the expression of caspase-8, fatty acid synthase (Fas), and caspase-3 through intracellular calcium release and death receptor pathways [192-194]. Jang et al. revealed that EGL promoted apoptosis by activating both the intrinsic caspase pathway and the extrinsic death receptor (DR)-mediated pathway, thereby inhibiting the growth of AGS cells [194].

The abnormal activation of the PI3K/AKT signaling pathway is known to encourage cancer cell proliferation and suppress apoptosis [195]. Shen et al. showed that GLP suppressed the proliferation and migration of SK-HEP-1 and Huh-7 cells by regulating the PI3K/AKT pathway, inducing G1 cell cycle arrest and apoptosis [196]. Similarly, GLSP modulated macrophage polarity and induced apoptosis in hepatocellular carcinoma cells via the PI3K/AKT pathway [2,38,110,149-151,197].

The Ras/Raf/MAPK/MEK/ERK pathway is another crucial regulatory mechanism in tumor cell apoptosis. Zhu et al. confirmed that *G. lucidum* spore powder strongly inhibited cancer cell proliferation in MKN28, NCI, N87, and AGS cells by interfering with autophagic flux [191]. Additionally, *G. lucidum* exerted anti-cancer effects through multi-component, multi-target, and multi-

signaling pathways, with apoptosis being a key mechanism [197-202].

The combination of *G. lucidum* extract and quercetin at low concentrations showed a synergistic reduction in cell viability and induced apoptosis, displaying anti-tumor and anti-viral effects against SNU719 EBV-associated gastric cancer cells. Interestingly, GA-A produced a similar biological effect to *G. lucidum* extract [193]. Furthermore, G85, a triterpenoid-rich extract obtained via high-pressure supercritical CO_2 from *G. lucidum*, significantly inhibited liver cancer cell proliferation and triggered apoptosis by suppressing the Ras/Raf/MEK/ERK signaling pathway [193,194].

Enzymatically hydrolyzed *Ganoderma lucidum* polysaccharide (EGLP) significantly reduced the viability of human colon cancer cells (HCT-116) in a dose- and time-dependent manner with minimal impact on normal colon epithelial cells (CCD18-Co), induced apoptosis with an increasing population to 26.07% [117]. Mechanistic analysis revealed that EGLP downregulated anti-apoptotic proteins like Bcl-2, phospho-Akt1 (p-Akt1), and phospho-ERK (p-ERK), and upregulated pro-apoptotic proteins Bax and cleaved caspase-3 at both protein and mRNA levels suggesting that EGLP induces apoptosis in HCT-116 cells through modulation of the Akt/ERK signaling pathway and regulation of Bcl-2 family proteins, highlighting its potential as a promising therapeutic agent for colorectal cancer treatment [198-204].

Proteoglycan from *Ganoderma lucidum* (FYGL) selectively inhibits the proliferation of PANC-1 and BxPC-3 cells in pancreatic cancer cells in a dose-dependent manner without affecting Mia PaCa-2 pancreatic or HepG2 liver cancer cells. It is absorbed by PANC-1 and Mia PaCa-2 cells, but only inhibits migration and colony formation in PANC-1 cells. FYGL induced apoptosis in PANC-1 cells, increasing apoptotic rates and altering apoptosis-related protein expression, while having no such effects on Mia PaCa-2 cells. Mechanistically, FYGL increased ROS production and reduced mitochondrial membrane potential in PANC-1 cells, activating the caspase-3 cascade and promoting apoptosis. FYGL further modulated autophagy in PANC-1 cells by promoting autophagosome formation but preventing their fusion with lysosomes, leading to dysfunctional mitochondria and increased ROS, suggesting FYGL as a potential therapeutic agent for pancreatic cancer by targeting oxidative stress and autophagy pathways [199-208].

5.3 *Ganoderma Lucidum* in Cell Metastasis

Cell metastasis encompasses a multifaceted process involving several stages, including cytoskeletal restructuring, epithelial-mesenchymal transition, heightened migratory and invasive capabilities, alterations in the microenvironment, and evasion of immune responses (Figure 7). It stands as a primary cause of mortality among cancer patients and significantly influences prognosis. Thus, impeding cancer cell metastasis represents a promising therapeutic approach [198,201].

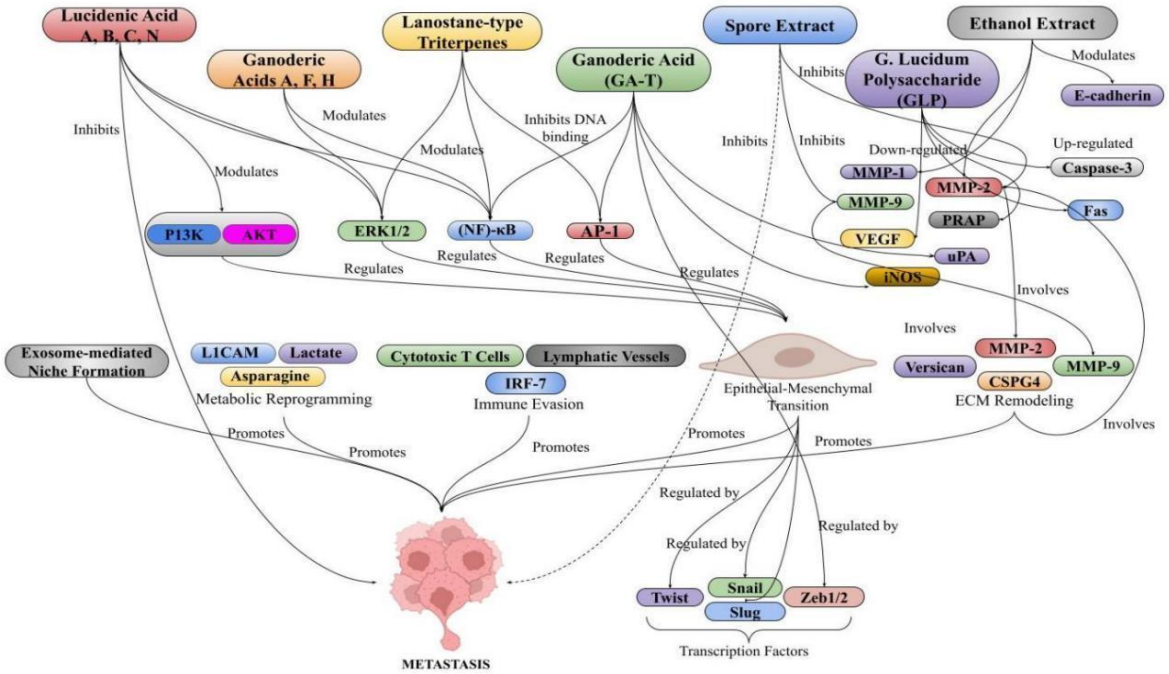


Figure 7. Bioactive compounds derived from *Ganoderma lucidum* and their modulatory effect on signaling pathways, transcription factors, and cellular processes involved in cancer metastasis, immune evasion, metabolic reprogramming, and the formation of a pre-metastatic niche.

Metastasis, which refers to the dissemination of cancer cells from the original tumor site to distant organs, poses a significant challenge in the treatment of gastrointestinal cancers and stands as a key factor contributing to cancer-related deaths. This multifaceted process involves an intricate interplay of cellular events, including

cytoskeletal remodeling, epithelial-mesenchymal transition (EMT), enhanced migratory and invasive capabilities, adaptation to the tumor microenvironment, and evasion of immune surveillance. In gastrointestinal cancers, epithelial-mesenchymal transition (EMT) serves as a critical mechanism, endowing cancer cells with invasive and metastatic characteristics. This phenomenon is managed by a cadre of transcriptional regulators, such as Snail, Slug, Twist, and Zeb1/2, which orchestrate a transcriptional reprogramming event suppressing epithelial gene expression while concomitantly activating mesenchymal gene programs. The ensuing cellular plasticity endows cancer cells with heightened motility, invasiveness, and an ability to resist apoptotic cues [201-208].

Moreover, the extracellular matrix (ECM), which constitutes an intricate framework of proteins with both structural and functional roles, significantly participates in the metastatic process. Proteoglycans such as versican and chondroitin sulfate proteoglycan 4 (CSPG4) facilitate cancer cell invasion by activating signaling pathways like EGFR and PI3K, respectively. Matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9, play a crucial role in degrading the ECM, thereby enabling cancer cell invasion and promoting angiogenesis, a process critical for sustaining tumor growth and dissemination. Primary tumors also secrete exosomes laden with a diverse array of biomolecules, including miRNAs, EMT inducers, and ECM remodeling enzymes having pre-metastatic niche at distant sites, thereby creating a permissive microenvironment for metastatic outgrowth [201]. Notably, metastatic cancer cells undergo metabolic reprogramming to adapt to the unique microenvironmental conditions encountered at distant sites, a process facilitated by factors such as the expression of L1 cell adhesion molecule (L1CAM) in colorectal cancer. This enhances the fatty acid oxidation leading to promote survival and proliferation within the metastatic niche. The availability of specific nutrients, such as asparagine and lactate additionally can influence the metastatic capability of cancer cells. The intratumoral microbiome has also emerged as a crucial factor influencing metastasis in gastrointestinal cancers, with bacterial species like *Fusobacterium nucleatum* and *Gammaproteobacteria* sp. conferring chemoresistance and altering drug metabolism, respectively [202-204]. Metastatic cancer cells also employ sophisticated mechanisms to evade immune surveillance, including reducing the densities of cytotoxic T cells and lymphatic vessels, as well as silencing the interferon regulatory factor (Irf)-7 pathway, thereby facilitating immune evasion and metastatic dissemination [201,204]. *G. lucidum,* in this context, has garnered significant attention for its remarkable anti-metastatic properties in gastrointestinal cancers. The ethanol extract derived from *Ganoderma lucidum* has demonstrated the ability to hinder the migration of colorectal cancer cells. This effect is achieved through the modulation of E-cadherin expression, a critical epithelial marker, along with the downregulation of MMP-1 and MMP-2 expression (E-cadherin plays a major role in cell–cell adhesion and inactivating germline mutations in its encoding gene predispose to hereditary diffuse gastric cancer). Consequently, this extract diminishes the invasive and metastatic capabilities of these cancer cells. The spore extract of *Ganoderma lucidum*, additionally, has shown strong anti-metastatic effects *in vivo*. It reduces the number of mice with metastatic tumors, the number of affected organs, and the number of tumor foci. Simultaneously, it inhibits the activities of MMP-2 and MMP-9 in the serum of these animals [201,205,208].

Intriguingly, specific bioactive constituents of *Ganoderma lucidum* have also exhibited remarkable anti-metastatic activities. Lanostane-type triterpenes isolated from the fungus have been found to reduce the invasiveness of hepatocellular carcinoma cells by modulating the ERK1/2 signaling pathway. This modulation decreases the DNA-binding activities of the transcription factors AP-1 and NF-κB, resulting in the down regulation of MMP-9 expression. Similarly, *Ganoderma lucidum* polysaccharide (GLP) has shown to inhibit the migration of colorectal cancer cells by upregulating the expression of Fas and caspase-3, while simultaneously downregulating the expression of poly(ADP-ribose) polymerase (PARP) protein. Furthermore, GLP has also been demonstrated to reduce the migration of hepatocellular carcinoma cells by downregulating the expression of vascular endothelial growth factor (VEGF), a crucial mediator of angiogenesis [110,198,201,209].

The triterpenoid fraction of *Ganoderma lucidum* has proven to be a highly effective anti-invasive and anti-metastatic agent against gastrointestinal cancers. Ganoderic acid T (GA-T), a triterpenoid isolated from *Ganoderma lucidum*, has been specifically shown to reduce the metastatic potential of human colon carcinoma cells by promoting homotypic aggregation and inhibiting the adhesion and migration of these cells in a dose-dependent manner. Mechanistically, GA-T downregulates the expression of key metastasis-related genes, including MMP-9, inducible nitric oxide synthase (iNOS), and urokinase plasminogen activator (uPA), in colon carcinoma cells. The anti-metastatic effects of GA-T are attributed to its ability to inhibit the activity of transcription factors AP-1 and NF-κB regulating the expression of various metastasis-associated genes such as MMPs and uPA [198,201,206,207,208]. -

In addition to GA-T, other triterpenoids isolated from *G. lucidum*, such as ganoderic acids A, F, H, and lucidenic acids A, B, C, and N, have also demonstrated potent inhibitory activities against the invasion and migration of different gastrointestinal cancer cell lines, including hepatocellular carcinoma cells. These triterpenoids exert their anti-metastatic effects by modulating key signaling pathways, such as ERK1/2, PI3K/Akt, and NF-κB, which are known to play pivotal roles in regulating the expression of metastasis-associated genes and promoting the metastatic cascade [198,201,208-210] (Table 6).

Table 6. Effect of bioactive compounds of *Ganoderma. lucidum* on the metastatic behavior and underlying mechanisms of various gastrointestinal cancer cell lines and their anti-metastatic activities.

Compound	Signaling Pathway	Transcription Factor	Outcome
Ethanol Extract of *G. lucidum* (EGL)	Upregulated E-cadherin, Downregulated MMP-1, MMP-2	Increased expression and nuclear translocation of E-cadherin transcriptional regulator Snail	Inhibited formation and growth of xenografts in nude mice, Inhibited migration of HCT116 colorectal cancer cells [201,205].
G. lucidum Spore Extract (GLE)	Inhibited MMP-2, MMP-9 activity in mouse serum	Reduced the DNA-binding and transcriptional activity of AP-1 and NF-κB	Reduced number of metastatic tumor-bearing mice Reduced number of affected organs and tumor foci [201].
Lanostane-type Triterpenes from *G. lucidum* (LAB)	Inhibited ERK1/2 phosphorylation	Reduced AP-1 and NF-κB DNA-binding activity	Inhibited PMA-induced invasion of HepG2 hepatocellular carcinoma cells Down Regulated MMP-9 expression [201].
G. lucidum Polysaccharide (GLP)	Upregulated Fas, caspase-3, Downregulated PARP, Down Regulated VEGF	Increased the expression and transcriptional activity of p53 and its target genes Fas and caspase-3, Suppressed the transcriptional activity of HIF-1α, which regulates VEGF expression	Inhibited migration of LoVo colorectal cancer cells Inhibited migration of HepG2 hepatocellular carcinoma cells [110,198].
G. lucidum Polysaccharide Peptide (GL-PP)	Inhibited the phosphorylation of signaling molecules involved in cell migration, such as FAK, Src, and Akt	Reduced the DNA-binding activity of transcription factors like AP-1 and NF-κB	Inhibited migration of Huh7 hepatocellular carcinoma cells [198,201].
Ganoderic Acid A (GA-A)	Downregulated the expression and activity of signaling proteins involved in cell motility, such as Rho GTPases and focal adhesion kinase (FAK)	Suppressed the nuclear translocation and transcriptional activity of NF-κB	Inhibited migration and invasion of HepG2 and SMMC7721 hepatocellular carcinoma cells [198].
Ganoderic Acid T (GA-T)	Downregulated MMP-9, iNOS, uPA	Inhibited AP-1 and NF-κB	Promoted homotypic aggregation, Inhibited adhesion and migration of HCT-116 colon carcinoma cells [198].
Ganoderic Acids F, H Lucidenic Acids A, B, C, N	Modulated ERK1/2, PI3K/Akt, NF-κB signaling	Reduced the DNA-binding and transcriptional activity of AP-1 and NF-κB	Inhibited invasion and migration of HepG2 hepatoma cells [198,201,208].

Ganoderma lucidum and its bioactive constituents, particularly triterpenoids and polysaccharides, have exhibited remarkable anti-metastatic properties in gastrointestinal cancers by targeting various steps in the metastatic cascade, including EMT, ECM remodeling, MMP activation, exosome-mediated niche formation, and the expression of metastasis-associated genes. These effects are facilitated by modulating crucial signaling pathways and transcription factors, including ERK, PI3K/Akt, AP-1, and NF-κB, which are pivotal in controlling the metastatic process. The ability of *Ganoderma lucidum* and its bioactive components to inhibit metastasis underscores their therapeutic promise in preventing and treating gastrointestinal cancers with metastatic potential, a disease setting that continues to pose significant clinical challenges [198,201,208].

Ganoderma lucidum triterpenoids significantly inhibited cancer metastasis in human hepatocellular carcinoma (HCC) SMMC-7721 cells lines in a dose dependent manner with suppressed cell proliferation and induced cell cycle arrest (G1/G2 phase). Evidently, apoptosis is promoted with increased Annexin V/PI-positive and TUNEL-positive cells. *G. lucidum* triterpenoids also significantly reduced the migratory and invasive abilities of SMMC-7721 cells with wound healing. Mechanistically, these effects were linked to the downregulation of the metastasis-associated protein E-cadherin and suppression of the MAPK, FAK, and PI3K/Akt signaling pathways highlighting the potent anti-metastatic properties of *G. lucidum* triterpenoids and their therapeutic potential for targeting metastatic progression in gastrointestinal and hepatocellular carcinoma [209,210].

The anticancer and anti-metastatic properties of a *Ganoderma lucidum* triterpene extract (GLT) was investigated in a mouse model of colitis-associated colorectal cancer using a combination of the carcinogen PhIP and the inflammatory agent DSS [205]. GLT treatment significantly reduced aberrant crypt foci, focal hyperplasia, and colonic tumors in a dose-dependent

manner. Mechanistic investigations revealed that GLT slowed the growth of colonic epithelial cells by reducing Ki-67 expression and downregulating pro-carcinogenic and pro-inflammatory proteins *viz.* cyclin D1 and COX-2. GLT also exhibited anti-inflammatory effects by reducing colon inflammation and macrophage infiltration induced by DSS. These anti-inflammatory effects were linked to the regulation of transcription factors like AhR and PXR modulating xenobiotic-metabolizing enzymes CYP1A2 and CYP3A4. This regulation mitigates the production of carcinogenic compounds, effectively suppressing colon cancer development and metastasis [81,211].

5.4 The Effects of *Ganoderma Lucidum* in Cell Autophagy

The involvement of *Ganoderma lucidum* in cellular autophagy is pivotal for maintaining intracellular equilibrium. Autophagy, governed by specific genes, orchestrates the removal of defective organelles and large molecules via lysosomes (Figure 8**)**. Its impact on cancer is complex, as it can either bolster or hinder tumor survival, contingent upon tumor stage and tissue type emphasizing the viability of autophagy regulation as a promising strategy for cancer therapy [198,209,211-215].

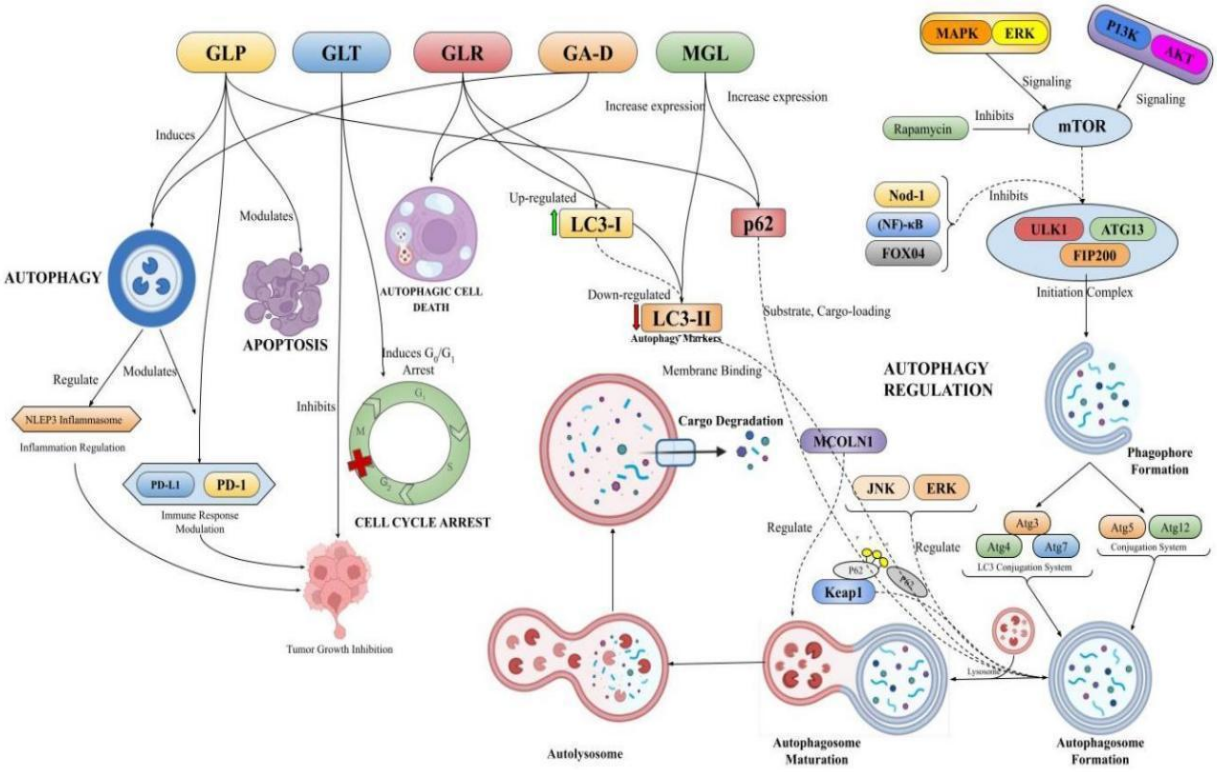


Figure 8. Potential impact of *Ganoderma lucidum* biomolecules viz. GLP, GLT, GLR, GA-D, and MG on cellular process in modulating autophagy through various signaling pathways; the intricate network of molecules explain their involvement in regulating autophagy initiation, cargo degradation, and autophagosome formation.

Proteins derived from *Ganoderma lucidum*, such as GLR, exhibit inhibitory effects on colorectal cancer (CRC) [198,211]. Studies indicated that GLR suppresses autophagy activation in HT29 and HCT116 cells, leading to the accumulation of P62, upregulation of LC3-I, and downregulation of LC3-II. Conversely, GA-D demonstrates autophagy activation in esophageal squamous cell carcinoma (ESCC) cells, promoting autophagosome formation while impeding autophagy-lysosome fusion, thereby inducing autophagic cell death. Moreover, MGL induces autophagosome formation in gastric cancer (GC) cells, with increased expression of p62 and LC3-II when combined with lysosomal protease inhibitors, confirming its role as an autophagy inducer. GLP has additionally been observed to trigger both autophagy and apoptosis in colorectal cancer (CRC) cells by activating the MAPK/ERK pathway. *In vivo* studies support its capacity to hinder tumor growth and autophagic flux. Similarly, GLT suppresses the growth of CRC cells by arresting the cell cycle at the G0/G1 phase and inducing programmed cell death Type II, i.e., autophagy. Notably, GLT also exhibits tumor growth inhibition in a colon cancer xenograft model [212,213,215].

The autophagy pathway can be broadly divided into several stages, each involving a unique set of regulatory proteins and signaling cascades. The onset of the initiation stage is prompted by diverse cellular stresses, including nutrient scarcity, depletion of growth factors, or the accumulation of damaged organelles or misfolded proteins. This stage involves the formation of the phagophore, a cup-shaped double-membrane structure that serves as the precursor to the autophagosome [212,213]. The nucleation of the phagophore is mediated by a multi-protein complex known as the initiation complex, which includes various autophagy-related proteins [215]. This complex is regulated by upstream signaling pathways, such as the mTOR (mechanistic target of rapamycin) pathway, which acts as a major negative regulator of autophagy

[216]. Under nutrient-rich conditions, active mTOR inhibits the initiation complex, thereby suppressing autophagy. However, upon nutrient deprivation or other stress signals, mTOR is inactivated, allowing the initiation complex to promote phagophore formation [211,212,214-216].

Following the initiation stage, the phagophore undergoes elongation and expansion, facilitated by two ubiquitin-like conjugation systems involving several autophagy-related proteins. These conjugation systems mediate the recruitment and incorporation of lipids and proteins into the growing phagophore membrane [213,217].

The initial conjugation system entails the covalent bonding of a ubiquitin-like protein to a lipid molecule, which is subsequently integrated into the phagophore membrane. This sequence is facilitated by a cascade of enzymes, including an E1-like activating enzyme, an E2-like conjugating enzyme, and an E3-like ligase. The resultant lipid-protein conjugate plays a pivotal role in shaping the curvature and enlargement of the phagophore membrane [213,218]. The subsequent conjugation system comprises the covalent binding of another ubiquitin-like protein to a soluble protein, resulting in the formation of a complex that binds to the phagophore membrane. This complex serves as a scaffold for recruiting additional proteins engaged in elongating and sealing the phagophore, ultimately culminating in the creation of the double-membraned autophagosome [218]. Once the autophagosome is formed, it undergoes maturation and fusion with lysosomes, a process mediated by various trafficking proteins and membrane fusion machinery. The fusion of the autophagosome with the lysosome results in the formation of an autolysosome, where the sequestered cargo is degraded by lysosomal hydrolytic enzymes [213].

The degradation products, including amino acids, lipids, and nucleotides, are then released back into the cytoplasm through membrane permeases, allowing for their recycling and utilization across a range of cellular processes, including protein synthesis, energy generation, and biosynthetic pathways [213]. Autophagy plays a complex and multifaceted role in gastrointestinal cancers (Figure 8**)**, with both tumor-promoting and tumor-suppressing effects reported in different contexts [219]. In esophageal cancer, autophagy has been associated with chemoresistance and the promotion of cancer cell survival and growth. Nevertheless, it has also been associated with inducing cell cycle arrest and autophagy-linked cell death, hinting at a possible tumor-suppressive function [213,220]. In gastric cancer, autophagy has been associated with modulating immune responses, including the regulation of programmed cell death-1 (PD-1) and its ligand (PD-L1), which play pivotal roles in immune checkpoint inhibitor therapy [221]. Additionally, autophagy has been demonstrated to contribute to gastric cancer metastasis and cell survival through diverse signaling pathways. Conversely, autophagy has also been implicated in safeguarding against *Helicobacter pylori* infection, a significant risk factor for gastric cancer onset [222,223].

In colorectal cancer, autophagy plays a significant role in regulating inflammatory and immune responses, which are closely linked to tumor development and progression. Autophagy has been demonstrated to protect regulatory T cells (Treg cells) and induce anti-tumor adaptive immunity, suggesting a potential tumor-suppressive role [224]. Nevertheless, specific genetic variations in autophagy-related genes have been linked to enhanced overall survival in colorectal cancer patients, suggesting a potential tumor-promoting effect in certain circumstances [225,226].

Autophagy plays a role in driving gastric cancer progression by influencing the regulation of immune responses. It has been demonstrated to regulate the expression of programmed cell death-1 (PD-1) and its ligand (PD-L1), which are key components in immune checkpoint inhibitor therapy. Specifically, inhibition of autophagy has been demonstrated to enhance the expression of PD-L1, thereby promoting the sensitivity of gastric cancer cells to PD-L1-targeted immunotherapy. Autophagy has been implicated in gastric cancer metastasis through the unfolded protein response (UPR) pathway. The UPR-induced activation of autophagy, mediated by Sec62, a membrane protein of the endoplasmic reticulum involved in protein transport, has been shown to significantly contribute to the metastatic potential of gastric cancer cells [199-202]. The lysosomal cation channel mucolipin TRP cation channel 1 (MCOLN1) has been identified as a regulator of oncogenic autophagy in gastric cancer cells. MCOLN1 has been demonstrated to control the influx of zinc into the cytosol, thereby modulating autophagy and contributing to the survival and proliferation of gastric cancer cells [227-229].

Indeed, the impact of autophagy on gastric cancer appears to be influenced by the presence of *Helicobacter pylori* infection, a widely recognized risk factor for gastric cancer development [230]. Autophagy has been revealed to have a protective role against *H. pylori* infection. Evidence suggests that *H. pylori* toxin vacuolating cytotoxin (VacA) and genetic deficiencies in autophagy promoted *H. pylori* infection and contributed to gastric cancer pathogenesis [213,231]. Prolonged exposure to *H. pylori* has, additionally, been documented to impede the autophagy process in gastric epithelial cells, partly through the Nod1-nuclear factor (NF)-κB/mitogen-activated protein kinase (MAPK)-ERK/forkhead box O 4 (FOXO4) signaling pathway. Conversely, the activation of autophagy degradation functions by vitamin D3 has been demonstrated to safeguard gastric epithelial cells against *H. pylori* infection [231-233].

Extract from Ganoderma lucidum (GL) can potently induce autophagy leading to the breakdown and recycling of damaged organelles and macromolecules [231]. GL reduced fibrillarin levels with an increase in autophagosomal marker LGG-1, in the nematode Caenorhabditis elegans, extending the nematodes' lifespan. This effect was dependent on the autophagy

and stress resistance genes atg-18, daf-16, and sir-2.1. GL induced autophagy in human cell lines viz. Huh7 hepatoma cells and IMR-90 lung fibroblasts by decreasing mTOR phosphorylation and increasing LC3B-I to LC3B-II conversion. Microscopic analysis confirmed the formation of autophagosomes and autolysosomes. The ability of GL to induce autophagy is relevant to gastrointestinal cancers, where autophagy plays a complex role in tumor suppression and therapy resistance. Therefore, Ganoderma lucidum and its autophagy-inducing compounds hold potential as adjunct therapies for treating these malignancies, warranting further investigation [211,233].

Autophagy exerts its tumor-suppressive effects by regulating regulatory T cells (Treg cells) in colorectal cancer which has been documented to integrate environmental cues and metabolic balance, thereby preserving the lineage and survival integrity of Treg cells. Consequently, this prevents tumor resistance and the onset of inflammatory disorders associated with colorectal cancer. Autophagy has also been implicated in promoting anti-tumor adaptive immunity through a process known as mitophagy, a form of selective autophagy targeting damaged or dysfunctional mitochondria. Mitophagy induction is known to elicit an anti-tumor immune response during tumorigenesis, thereby further enhancing the tumor-suppressive effects of autophagy in colorectal cancer [199]. Autophagy serves a critical function in intestinal epithelial cells in averting tumorigenesis by repairing DNA damage, curbing cell proliferation, and dampening inflammation whereas its deficiency has been linked to heightened tumor advancement in colorectal cancer, underscoring the significance of preserving appropriate autophagic activity in these cells [199]. Additionally, the activation of autophagy through specific small molecule agents provide protection against colorectal cancer linked to colitis by inhibiting the activation of the NLR family pyrin domain containing 3 (NLRP3) inflammasome. The NLRP3 inflammasome plays a pivotal role in regulating inflammatory reactions, and its dysfunction is associated with a range of inflammatory conditions and autoimmune disorders, including colorectal cancer [213].

Autophagy plays a crucial role in curbing the proliferation and spread of colorectal cancer by regulating neutrophil extracellular traps (NETs) and inflammasomes [231-233]. NETs, which are released by activated neutrophils, have been implicated in driving tumor growth and metastasis. Autophagy potentially counters the inflammatory environment that fuels colorectal cancer progression through elimination of NETs and inflammasomes. Furthermore, certain variations in genes associated with autophagy have also been linked to enhance overall survival rates among colorectal cancer patients as therapeutic benefits in selected cases [213].

i. Esophageal Cancer

GA-D, a compound derived from *Ganoderma lucidum*, facilitates the formation of autophagosomes while impeding their fusion with lysosomes and ultimately inducing autophagic cell death in esophageal squamous cell carcinoma (ESCC) cancer. The ability of GA-D to induce autophagy suggests a potential therapeutic approach for addressing esophageal cancer by manipulating autophagy pathways [230].

ii. Gastric Cancer

Autophagy's role in gastric cancer is complex, with evidence suggesting both tumor-promoting and tumor-suppressing functions, influenced by factors such as *Helicobacter pylori* infection. A compound from *Ganoderma lucidum*, MGL, has been demonstrated to prompt autophagosome formation in gastric cancer (GC) cells, leading to heightened expression of autophagy markers like p62 and LC3-II. This induction of autophagy by MGL could contribute to its anti-cancer effects in gastric cancer, potentially by triggering autophagic cell death or modulating the inflammatory and immune responses linked to *H. pylori* infection [230-233].

iii. Colorectal Cancer

Autophagy plays a pivotal role in regulating inflammatory and immune responses in colorectal cancer (CRC), with evidence pointing to both tumor-promoting and tumor-suppressing effects. Compounds derived from *Ganoderma lucidum*, such as GLR and GLP, have been shown to modulate autophagy in CRC cells. GLR inhibits autophagy activation in HT29 and HCT116 cells, resulting in the accumulation of p62 and altered LC3 expression patterns. Conversely, GLP induces both autophagy and apoptosis in CRC cells through the MAPK/ERK pathway, demonstrating an inhibitory effect on tumor growth and autophagic flux *in vivo* [232].

GLT has been identified as a suppressor of colorectal cancer (CRC) cell growth by inducing autophagic cell death, also known as programmed cell death Type II, and halting the cell cycle at the G0/G1 phase. Moreover, GLT demonstrates inhibition of tumor growth in a colon cancer xenograft model, potentially mediated through autophagy modulation. Various bioactive components within *Ganoderma lucidum* may exert their anti-cancer effects in gastrointestinal cancers through diverse mechanisms involving autophagy regulation. While compounds like GA-D and MGL induce autophagy to promote autophagic cell death, others such as GLR inhibit autophagy activation, potentially disrupting cancer cell survival mechanisms. Furthermore, the autophagy-modulating properties of *Ganoderma lucidum* compounds may contribute to the regulation of inflammatory and immune responses, crucial factors in gastrointestinal cancer progression [213,230].

5.5 The Effects of *Ganoderma Lucidum* in Immunotherapy

Tumor immunotherapy, recognized as the fourth approach in cancer treatment after surgery, chemotherapy, and radiotherapy, functions by activating the patient's immune system to enhance anti-

tumor responses, thereby targeting and eliminating cancer cells. It is regarded as a highly promising method, with the potential to fully eradicate tumors, offering a significant advantage in comprehensive cancer treatment [234]. Research has demonstrated that an increase in regulatory T cells (Treg cells) in both peripheral blood and tumor environments is linked to poorer outcomes in hepatocellular carcinoma (HCC) patients, making Treg cells a key therapeutic target in HCC [235].

Ganoderma lucidum polysaccharides (GLP) have shown notable tumor-suppressing effects in hepatoma-bearing mice by decreasing the percentage of Treg cells in tumors in a dose-dependent manner. Additionally, when tumor-infiltrating Treg cells were inactivated, the anti-tumor effects of GLP were diminished, underscoring its direct role in inhibiting liver tumor growth by reducing Treg cell accumulation and activation [236].

Key pro-inflammatory markers such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), secreted by M1 macrophages, are essential in promoting cellular immunity [237,238]. According to Xia et al., GLP stimulates the release of TNF-α, IL-6, and IL-1β through the induction of CD68 macrophages, while also reducing the immunosuppressive effects of interleukin-13 (IL-13), secreted by natural killer T cells. This process enhances immune function, thereby inhibiting the growth of distant tumors in HCC models [239].

Moreover, Song et al. demonstrated that *Ganoderma lucidum* spore polysaccharides (GLSP) could reconfigure the tumor microenvironment by promoting the polarization of primary macrophages towards the M1 type, boosting the secretion of inflammatory factors like TNF-α, IL-1β, IL-6, and TGF-β1 [240]. Additionally, GLP mitigated the development of colitis and tumors in AOM/DSS-induced mice. In these models, macrophage surface markers (CD68 and F4/80) were significantly increased compared to controls. In vitro studies further indicated that GLP inhibited the activation and inflammation of RAW264.7 macrophages induced by lipopolysaccharides (LPS), likely through the regulation of the TLR4/MyD88/NF-κB and MAPK pathways [241].

The polysaccharide extracted from sporoderm-removed spores of *Ganoderma lucidum* (GLP) exhibits notable effects against AOM/DSS-induced colitis and tumorigenesis. GLP significantly mitigated colitis and tumor formation in AOM/DSS-induced mice models. The polysaccharide decreased the disease activity index (DAI) scores and reduced the total number and size of tumors in a dose-dependent manner. Importantly, GLP reversed gut microbiota dysbiosis and increased the production of short-chain fatty acids (SCFAs), specifically butyrate and propionate, both of which play a protective role in gut health [241]. The anti-inflammatory properties of GLP were further demonstrated through its ability to inhibit macrophage infiltration and downregulate key inflammatory markers such as IL-1β, iNOS, and COX-2 in colon tissues. GLP also suppressed lipopolysaccharide (LPS)-induced activation and inflammation in RAW264.7 macrophages by modulating the TLR4/MyD88/NF-κB and MAPK pathways. This effect was associated with a decrease in CD68 and F4/80 macrophage surface markers, suggesting a significant reduction in macrophage-mediated inflammation [241].

Additionally, GLP treatment improved gut barrier function, as evidenced by increased tight junction protein expression (ZO-1 and occludin) and goblet cell number, which are critical for maintaining intestinal integrity. The study also highlighted GLP's impact on gut microbiota composition, particularly the increase in beneficial bacteria such as *Bifidobacterium* and *Lactobacillus*, while reducing harmful bacteria like *Oscillibacter* and *Desulfovibrio*, both associated with CRC progression [241]. These findings suggest that GLP could serve as a promising therapeutic agent for modulating inflammation and preventing colorectal cancer through gut microbiota regulation. Furthermore, *Ganoderma lucidum* triterpenes (GLT) inhibited colon tumor development in a mouse model induced by foodborne carcinogens, reducing focal hyperplasia and aberrant crypt foci. GLT also demonstrated anti-inflammatory effects by reducing macrophage infiltration in the colon [242].

Polysaccharides from *Ganoderma lucidum* (GLPS) are key players in its immunomodulatory effects. GLPS can enhance the function of immune cells, particularly dendritic cells (DCs), T cells, macrophages, and natural killer (NK) cells. In liver cancer models, GLPS promotes the differentiation of dendritic cells, leading to increased antigen presentation and activation of cytotoxic T cells, thereby enhancing the body's antitumor response [243]. Moreover, GLPS has been found to reduce the population of regulatory T cells (Tregs), known to suppress immune responses in the tumor microenvironment, thereby allowing a more robust attack on tumor cells [244].

Triterpenoids, another active component of *Ganoderma lucidum* GL, target specific pathways involved in immune cell regulation. In colon cancer models, triterpenoids have been shown to inhibit the expression of immune-suppressive molecules such as indoleamine 2,3-dioxygenase (IDO), which suppresses T cell activity [245]. This inhibition enhances the cytotoxic function of CD8+ T cells, leading to improved tumor clearance. Triterpenoids also reduce tumor-associated inflammation, thus inhibiting the growth and spread of cancer cells [246]. The NF-κB and MAPK pathways are critical to the immunomodulatory effects of GL. Activation of these pathways by GLPS leads to increased production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IFN-γ, which enhance the immune response against cancer cells [247]. Additionally, GL downregulates the expression of key tumor-promoting cytokines, reducing the inflammatory milieu that supports tumor growth in the gastrointestinal tract [248-249].

In liver cancer models, *Ganoderma lucidum* GLPS enhances immune surveillance by upregulating the expression of major histocompatibility complex (MHC) class I molecules, essential for recognizing tumor antigens by cytotoxic T cells [248-251]. This leads to more effective immune-mediated destruction of hepatocellular carcinoma cells. Moreover, GLPS modulates gut microbiota, playing a crucial role in liver cancer progression by reducing systemic inflammation that contributes to liver cancer development [249-253].

6. Future Directions

Exploring bioactive molecules from natural sources like *Ganoderma lucidum* (*G. lucidum*) holds promise for gastrointestinal (GI) cancer treatments. Future research should focus on understanding the molecular mechanisms of *G. lucidum*'s anti-cancer effects, including apoptotic pathways, autophagy, and signaling pathways like PI3K/Akt and MAPK/ERK. Examining synergistic effects with traditional chemotherapeutics could enhance efficacy and reduce side effects. Transitioning to clinical applications requires well-designed trials to assess the safety, efficacy, and optimal dosing of *G. lucidum* extracts alongside standard cancer therapies. Validating biomarkers such as circulating tumor DNA (ctDNA) for treatment monitoring and early detection of recurrence is crucial. Prioritizing targeted and personalized therapies based on individual tumor profiles, and identifying specific molecular targets affected by *G. lucidum* compounds, can improve treatment outcomes. Additionally, exploring novel bioactive compounds from various natural sources for their anti-cancer properties and conducting comparative studies in different GI cancer models can identify promising candidates. Integrating multi-omics technologies like genomics, proteomics, and metabolomics will provide insights into how these compounds affect cancer cells, helping to identify new biomarkers and resistance mechanisms.

Using network pharmacology and molecular docking techniques can reveal the complex interactions between bioactive compounds and cellular targets, aiding in the design of effective therapeutic regimens. In conclusion, advancing GI cancer therapeutics requires a multidisciplinary approach combining natural bioactive molecules with advanced technologies for more effective, safe, and personalised treatments.

7. Conclusion

The review highlights the promising role of *Ganoderma lucidum* as a supportive treatment for gastrointestinal (GI) tract cancers. The bioactive compounds in *G. lucidum*, particularly polysaccharides and triterpenes, exhibit significant anti-tumor effects by influencing crucial cellular processes *viz.* proliferation, apoptosis, metastasis, and autophagy. The literature reviewed underscores *G. lucidum's* capacity to induce oxidative DNA damage and halt the cell cycle selectively in cancer cells, while preserving healthy cells. This highlights its potential as a safe and efficient complement to conventional chemotherapy. The review additionally clarifies the various mechanisms by which *G. lucidum* exerts its anti-cancer effects, including inducing apoptosis through both intrinsic and extrinsic pathways, inhibiting metastasis by modulating epithelial-mesenchymal transition, and regulating autophagy to maintain cellular balance. These insights lay a strong groundwork for future research into the clinical applications of *G. lucidum* in GI cancer treatment.

Incorporating *G. lucidum* into existing treatment protocols could improve therapeutic outcome and mitigate the adverse effects of standard treatments. However, further clinical studies are necessary to validate these preclinical findings and comprehensively understand the therapeutic effectiveness and safety of *G. lucidum* in humans. As our knowledge of *G. lucidum's* role in cancer therapy grows, it holds the promise of becoming a vital part of the comprehensive management of GI cancers, bridging traditional Chinese medicine with modern Western oncology.

Credit Authorship Contribution Statement

Kaushal K. Sharma: Conceptualization, supervision, computational analysis, formal analysis, visualization, writing - review and editing.

Saksham Gupta: Investigation, data analysis, software development, visualization, literature collection and extending help in writing the original draft.

Prakash S. Bisen: Conceptualization, methodology, developing illustrations, supervision, writing review and editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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