Review

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Ganoderma lucidum targeting lung cancer signaling: A review

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Abstract

Lung cancer causes huge mortality to population, and pharmaceutical companies require new drugs as an alternative either synthetic or natural targeting lung cancer. The conventional therapies cause side effects, and therefore, natural products are used as a therapeutic candidate in lung cancer. Chemical diversity among natural products highlights the impact of evolution and survival of fittest. One such neglected natural product is *Ganoderma lucidum* used for promoting health and longevity for a longer time. The major bioconstituents of *G. lucidum* are mainly terpenes, polysaccharides, and proteins, which were explored for various activities ranging from apoptosis to autophagy. The bioconstituents of *G. lucidum* activate plasma membrane receptors and initiate various downstream signaling leading to nuclear factor-κB, phosphoinositide 3-kinase, Akt, and mammalian target of rapamycin in cancer. The bioconstituents regulate the expression of various genes involved in cell cycle, immune response, apoptosis, and autophagy in lung cancer. This review highlights the inextricable role of *G. lucidum* and its bioconstituents in lung cancer signaling for the first time.

Keywords

Ganoderma lucidum, lung cancer, ganoderic acid, signaling, apoptosis

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Introduction

Cancer is a multifactorial disease comprising a complex network of genes causing mortality to large population.[1] Among different kinds of cancer, lung cancer is the second most common disease causing death by various factors ranging from genetic to environmental factors. Non-small-cell lung carcinoma (NSCLC) causes for approximately 75%–85% of lung cancer causing death to a large population.[2] Tobacco is one of the primary sources of smoking causing lung cancer, whereas non-smokers account about 10% of total caused by smoking. Interestingly, women were more prone to lung cancer among never smokers, might be due to more exposure to cooking fumes, heavy metal exposure, human papillomavirus infection, environmental tobacco smoke, and inherited genetic susceptibility. Various commercially available drugs such as gefitinib and erlotinib (epidermal growth factor receptor (EGFR) tyrosine kinase (TK) inhibitors) cause a problem with non-smokers, which was effective among smokers in NSCLC.[3] Ongoing research advancement consequences in the development of plausible candidate for the prevention of lung cancer, but chemoresistance and side effects advocate the development of new preventive and potentially relevant agent. Natural products efficiently fit into the active site of particular site and decrease the time of treatment in low-dose concentration. Natural products were explored for exploiting various adapter molecules in cancer signaling.[4] The cytotoxic nature and side effects of previous therapies enhance the demand for natural products as an alternative to produce or synthesize potential compounds targeting multiple pathways in cancer. Among natural products, terpenes

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emerged as a class of numerous isolated compounds indulged in a network of protein in cancer signaling. *Ganoderma lucidum* is a basidiomycetes fungus renowned for a medicinal value known as the mushroom of immortality. Different species of *Ganoderma* exist in nature, and identification is quite a complicated process, therefore requires proper identification due to high phenotypic plasticity.[5] Species of *G. lucidum* are characterized and identified by their morphological and anatomical features, marked by shape and size of the basidiocarp, pileus color, stipe, and size of the pore.[6] The morphology and chemovariants get influenced by particular geographical location, resulting in prevailing environmental conditions.[7] The commercialization of different *Ganoderma* products enhances its demands of production. Increasing demand of *Ganoderma lucidum* leads the scientist to increases its production artificially by changing various parameters such as temperature, nutrients, and pH. The substrates (paddy straw and tea waste) used were significant, whereas stage control of pH (3–6) improved the mycelial cell growth.[8] Different solvent system (ethanol, methanol, acetone, chloroform, ether, and water) extracts of *G. lucidum* with high-performance liquid chromatography (HPLC) and nuclear magnetic resonance (NMR) were used in metabolomics. *G. lucidum* species is known for maintaining and promoting health and longevity from the longer time.[9] The extract of *G. lucidum* modulates the signaling by targeting NF-κB, RAS-mitogen-activated protein kinase (MAPK), apoptosis, and cell cycle in highly invasive cancer cells.[10] *G. lucidum* extract encompasses myriad constituents with vital activities ranging from anti-cancer and anti-metastatic activities.

G. lucidum and its constituents

Chemically *G. lucidum* comprises of terpenes, proteins, polysaccharides, amino acids, flavonoids, alkaloids, steroids, mannitol, and others minor compounds (Figure 1). The extract of *G. lucidum* contains numerous bioactive compounds engaged in various proteins in cancer signaling. The methanolic extract of fruiting bodies results in a two-fold increase in cytotoxic activity in J558 (BALB/C mouse myeloma) cells as compared to hot water extract.[11] The anticancer property of *G. lucidum* in environmental stress condition was evaluated resulting in enhancing the amount of chemovariants to cope with prevailing stress conditions. The study conducted concludes the interdependence of *G. lucidum* on the host plant such as *Acacia, Azadirachta, Bauhinia, Dalbergia*, and *Melia*. The enhanced amount comprises sugars, reducing sugars, starch, protein antioxidant, phenolics, and flavonoid contents with high efficiency of inhibiting cancer signaling.[7] Immunomodulatory effects of alkali-extracted *G. lucidum* polysacchrides (GLPS) are pronounced, which stimulate the mouse macrophages and increase macrophage volume and its capability to phagocytize latex beads.[12] Furthermore, enhancement of the NO production; cellular respiratory burst activity, and interleukin (IL)-1β, IL-12p35, and IL-12p40 gene expressions were reported.[13] Among different triterpenes present in *G. lucidum*, ganoderic acid occupies a significant position with substantial biological activity. Triterpenes arrest the process of the cell cycle at G1 phase by modulating cyclin D1 which induced the mitochondrial-dependent process of apoptosis. Triterpene enhanced the potential of the immune system by activating the expression of macrophages, NK cells, and T-lymphocytes.[14] Increasing evidence suggests the anti-cancer or anti-metastatic effect of the polysaccharides and polysaccharopeptides in these mushrooms associated with immunostimulant activities. More than 100 isoforms of ganoderic acids were reported and checked for their biological activity. Terpenes, proteins, and polysaccharides are the major classes present in *G. lucidum*.[10] Ganoderic acid (GA) is one of the most explored terpenes of the *G. lucidum* in cancer, in which GA-A and GA-H effectively suppress the process of cell proliferation, metastasis, and adhesion in breast cancer by modulating the expression of nuclear transcription factors (AP-1 and NF-κB) which results in decrease in Cdk4 and urokinase-type plasminogen activator (uPA) expression.[15] GA-X controls the process of apoptosis by modulating the expression of topoisomerases, ERK, JNK, Bcl-xL, and MAPKs, changing the mitochondrial membrane potential ($\Delta\psi_m$), and releasing the cytochrome-c.[16] Similarly, in melanoma cells, GA-DM increases the expression of bax proteins, Apaf-1, cytochrome-c, Beclin-1, and cleaved caspases 9 and 3, ultimately resulting in orchestrating autophagic and apoptotic cell death.[17] Some of the isoforms which have structural differences show cytotoxic activity against lung cancer cells particularly ganoderic acid 3a, 22β-diacetoxy7a-hydroxyl-5a-lanost-8, 24E-dien-26-oic acid, GA-Mc, GA-Mk, GA-Mf, and GA-S (Table 1).

Role of *G. lucidum* in lung cancer

Anticancer

Different receptors present in the membrane are divided on the basis of specificity of recognition by ligand, their structure, and response upon stimulation. Receptor tyrosine kinases (RTKs) are transmembrane glycoprotein's which are activated by external stimulus and stabilize the receptor dimerization producing downstream signals.[24] RTKs are indulged in various cellular processes, advancing in cell proliferation, differentiation, and migration. RTK family comprises of receptor for insulin growth factor, vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and nerve growth factor (NGF).[25] Structurally, RTKs exist as both monomeric and multimeric subunits, which are activated by the process of phosphorylation of phosphotyrosine-binding (PTB) and Src homology 2 (SH2) domains.[4] Importantly, non-RTKs also become an integral part of signaling cascade controlled by RTKs.[26] RTK subfamily comprises Src family involved in activation of B and T cells and cytoskeleton modeling. Jak family indulged

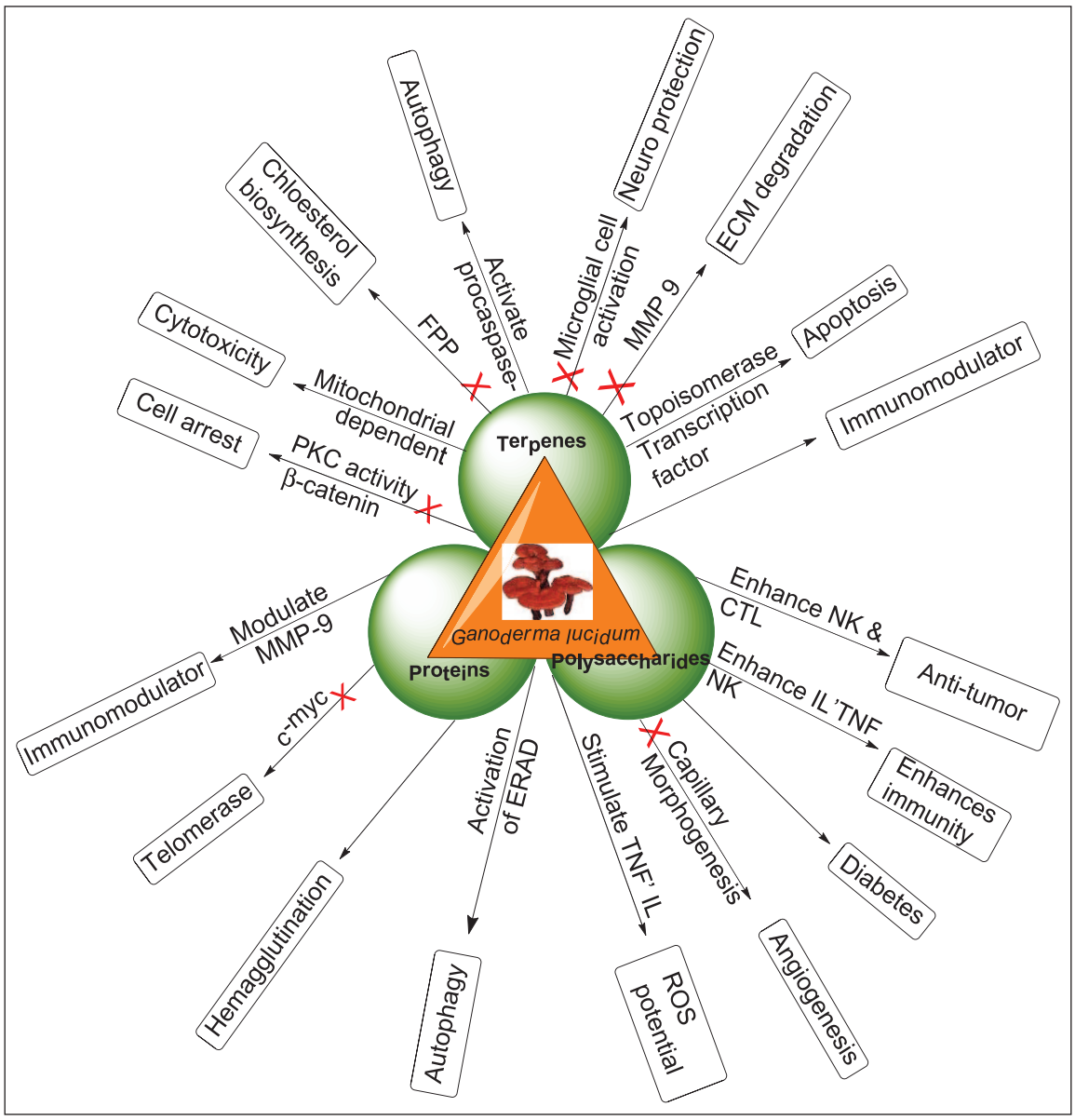

Figure 1. Action of mechanism of myco-constituents of *Ganoderma lucidum* in signaling in cancer. Major constituents of *G. lucidum* are terpenes, polysaccharides, and proteins involved in cancer signaling. Terpenes arrest cell cycle and apoptosis and enhance the immune system and exhibit anti-cancerous property with involving different adapter molecules. Multifunctional nature of various terpenes stimulates the immune system and target apoptosis through activating caspases (mitochondrial-dependent). Protein and polysaccharides stimulate the expression of various factor in immune system and scavenging free radicals vital in cancer signaling and diabetes.

FPP: farnesyl pyrophosphate; IL: interleukin; NK: natural killer; ECM: extracellular matrix; MMP: matrix metalloproteinase; ERAD: endoplasmic reticulum–associated degradation; TNF: tumor necrosis Factor; PKC: protein kinase C; CTL: cytotoxic T-lymphocyte.[10]

in the phosphorylation of cytokine receptors involving interferon-γ receptors. Methanolic extract of *Ganoderma tsugae* causes inhibition in the activation of epidermal EGFR and VEGF in human epidermoid carcinoma A-431 cells.[27] Ju research group explained the mechanism of resistance acquired by EGFR tyrosine kinase inhibitors (EGFR TKIs) in NSCLC. New human NSCLC cell line PC9/AB2 was established with a 576-fold decrease in gefitinib sensitivity.[28] *G. lucidum* modulates the functioning of RTKs, such as extracellular heteropolysaccharide fraction PS-F2 stimulates TNF-α and immunomodulatory activities. PS-F2 modulates the different adapter molecules such as MAPKs JNK, p38, ERK, and NF-κB, critical for activation of TNF-α in cancer signaling.[29] Immunomodulatory protein from *Ganoderma microsporum* (GMI) evinces role in RTK as it inhibits epidermal growth factor–mediated migration and invasion in A549 lung cancer cells. GMI inhibits the process in a dose-dependent manner by

Table 1. *Ganoderma lucidum* terpenoids and their activities in lung cancer.

S. no	Target	Mechanism	Reference
1	Ganoderic acid Me	Target MMP-2/9, p53, arrest cell cycle, inhibits cell migration	Chen et al.[18] Chen and Zhong[19]
2	Ganoderic acid Mc	Cytotoxic	Li et al.[20]
3	Lucialdehydes A C,	Cytotoxic	Gao et al.[21]
4	3a, 22β-diacetoxy-7ahydroxyl-5a-lanost-8, 24E-dien-26-oic acid	Cytotoxic	Li et al.[20]
5	Ganoderic acid MK	Cytotoxic	Li et al.[20]
6	Ganoderic acid Mf/S	Cytotoxic	Li et al.[20]
7	Ganoderic acid T	Apoptosis	Tang et al.[22]
8	Colossolactone H	Apoptosis	Chen et al.[23]

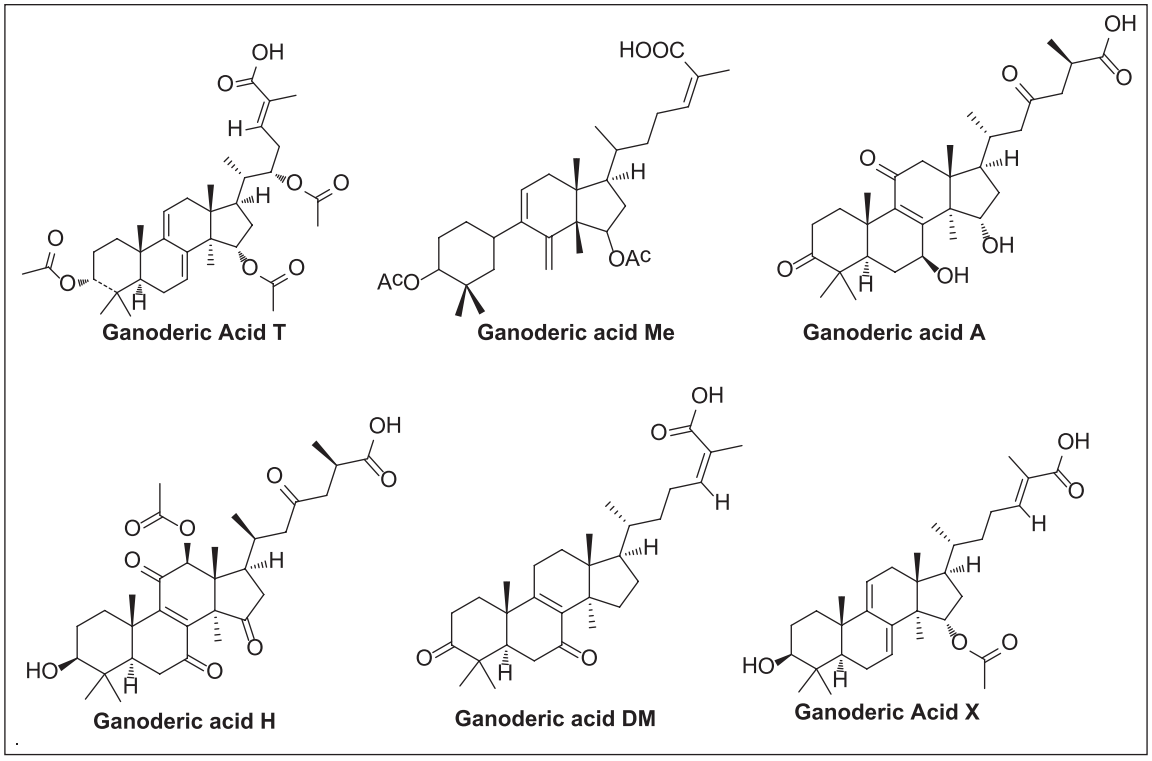

Figure 2. Chemical structure of different isoforms of ganoderic acid.

phosphorylation induced by EGF and activation of EGFR and Akt pathway kinases. Additionally, GMI also inhibited the EGF-induced microfilament depolymerization.[30]

Apoptosis

The process of apoptosis is marked as morphological and biochemical changes in the cell gradually culminate in apoptosis and dysregulation in the process results in cancers. The different adapter molecules and pathway decide the type of apoptosis caused which is either intrinsic or extrinsic. Intrinsic pathways mainly target anti-apoptotic and pro-apoptotic factor of the bcl-2 family.[1] GA-T suppresses the tumor formation by inhibiting apoptosis and cell cycle at G1 phases and thus inhibits proliferation in lung cancer cells. The induction during apoptosis is caused by the reduction of mitochondrial membrane potential ($\Delta\psi m$) and the release of cytochrome c with an increase in p53 and Bax expression in 95-D cells (Figure 2).[22] Pentacyclic triterpene dilactones and colossolactone H (colo H) isolated from the fruiting bodies of *Ganoderma colossum* enriched with anticancer potential in lung cancer. Gene expression profiling indicates the upregulation of 252 genes and downregulation of 398 genes in lung cancer. Colo H elevates the cellular reactive oxygen species with decreases in cell growth, inducing cell apoptosis, and increases the ability of tumor suppressor p53 protein in lung cancer.[23] GA-Me promoted cell homotypic aggregation and inhibits cell adherence matrix metalloproteinases

2/9 (MMP2/9) gene expressions in 95-D cells (Figure 2).[18] GA-Me arrested cell cycle at G1 phase in 95-D and HCT-116 $p53^{+/+}$ cells, whereas H1299 cells and HCT-116 $p53^{-/-}$ cells were arrested in S phase or G1/S transition, respectively.[19] Mao research group explained the role of active fraction of donkey milk in A549 human lung cancer cells. Donkey milk active fractions in a dose-dependent manner reduce the viability, in which fraction-IV with >10 kDa accumulates cell cycle at G0/G1 and G2/M phases, leading to cell death by process of apoptosis. It stimulates the secretion of IL-2, IL-1b, IL-6, interferon-g (IFN-g), and tumor necrosis factor a (TNF-a).[31]

Recombinant fungal immunomodulatory protein (reFIP-gts), isolated from *G. tsugae*, exhibits anti-telomerase activity (A549 cell) in human lung adenocarcinoma. Flow cytometry revealed cell-cycle arrest at G1 phase leading to premature senescence of A549 cells.[32] reFIP-gt localization in endoplasmic reticulum and cell results in stress, leading to enhanced endoplasmic reticulum stress markers (CHOP/GADD153) and release of intracellular calcium in A549 cells. This study demonstrates the use of calcium chelator in restoring reFIP-gts-mediated reduction in telomerase activity.[33] Recombinant fungal immunomodulatory protein (GMI) isolated from *G. microsporum* illustrates the inhibitory effect on epidermal growth factor activation. GMI inhibits phosphorylation, activation of EGFR, and Akt pathway kinases in cancer signaling.[30]

Immunomodulation

Functioning of the immune system is critically engaged in the progression of the tumor, and immunotherapy is the foremost strategy for oncotherapy. Cancer therapy highlighted the role of B, T (lymphocytes), dendritic, natural killer (NK), and mononuclear phagocyte cells. Polysaccharides isolated from *G. lucidum* strengthen the building of immune system, such as two heteroglycans (PL-1 and PL-4) and one glucan (PL-3) enhance the proliferation of T and B lymphocytes. The structural difference makes PL-1 more effective than PL-3 and PL-4 and therefore stimulates the proliferation of T- and B-lymphocytes and the production of antibodies.[34] GLPS activate cell membrane Ig (mIg) and toll-like receptor 4 (TLR4) which send signals to activate B cells and initiate the process of macrophage activation with ribosomal protein S7 and transcriptional co-activator (intracellular proteins).[35] GLPS inhibits the proliferation of human umbilical vein endothelial cell (HUVECs) but not in PG cell (a human lung carcinoma cell line). Tumor-bearing mice were treated with GLPS peptide for 33 days, which showed inhibition of PG cell proliferation. Along with this, GLPS peptide also shows its behavior as anti-angiogenic by reducing xenograft (human lung carcinoma cell PG) in BALB/c nude mice.[36] Effect of ganopoly at 0.05–1.0 mg/mL for 48 h exhibits slight cytotoxic effects in CaSki, SiHa, Hep3B, HepG2, HCT116, HT29, and MCF7 cancer cells.[37]

Cancer cells resist and adapt to inhibit immune system by releasing immunosuppressive mediators (prostaglandin E2 (PGE2), transforming growth factor beta (TGF-β), IL-10, and VEGF) against immune surveillance. *G. lucidum* polysaccharides counteract this immune inhibition and control the tumor formation by suppressing cell proliferation and activation of CD69 expression, perforin, and granzyme B production.[38] Lingzhi-8 (LZ-8) is the first protein isolated from *G. lucidum*, which functions as immunomodulatory protein in lung cancer cells.[39] Immunomodulatory protein of *Ganoderma* (GMI) induces cell death by activating autophagy (self-digestive process), but no effect on apoptotic cell death in lung cancer.[40] In lung cancer cell, *G. lucidum* polysaccharides-peptide (Gl-PP) inhibits the growth of vascular endothelial cell and induction of VEGF expression. Gl-PP treatment of HUVECs reduces bcl-2 and increases Bax and thus induces apoptosis in HUVECs.[41] Polysaccharides exhibit the ability to protect lung cancer patient against plasma-induced suppression of lymphocytes. The plasma of lung cancer patients shows repression in the process of proliferation, CD69 expression, and perforin and granzyme B production in lymphocytes.[38] Ganopoly, polysaccharides fractions extracted from *G. lucidum*, plays a role in the immune function of advanced-stage cancer patients. Clinical studies performed in 34 advanced-stage cancer patients with 1800 mg ganopoly for 12 weeks exhibit enhanced immune parameters such as cytokines, T cells, and NK activity. Along with this, ganopoly increases the concentrations of interleukin (IL-2), IL-6, and interferon (IFN)-γ and decreases the level of IL-1 and tumor necrosis factor (TNF-α). GLIS (a proteoglycan) activates IL-1β, TNF-α, and reactive nitrogen intermediates like NO and stimulates the immune system in tumor-bearing mice. GLIS marked the increase in both humoral and cellular immune activities and inhibits tumor growth.[42] Thus, it indicates the immune strengthening capacity of polysaccharides present in *G. lucidum*.[43] Amino-polysaccharide fraction (designated as "G009") isolated from *G. lucidum* protects against oxidative damage by free radicals. G009 inhibits the iron-induced lipid peroxidation and inactivation of free radicals in a dose-dependent manner in rat brain homogenates. Fraction reduced single strand breakage of φX174 caused by free radicals in human promyelocytic leukaemia (HL-60) cells.[44]

Cell-cycle arrest

The cell cycle is a regulated series of events leading to differentiation, crucial for the survival of cell. Anti-cancer drugs target cell cycle at G0/G1, S, or G2/M phase and control division process. The ethanolic extract of sporoderm-broken spores of *G. lucidum* (SBGS) exhibits

antitumor activities against human lung cancer. It arrests cell cycle at G2/M phase with decreases in the activity of cyclin B1 and cdc2 and anti-apoptotic proteins Bcl-2 and Bcl-xl. Oral administration suppresses the tumor in mice and suppressed the activation of Akt, mechanistic target of rapamycin (mTOR), S6 kinase, and 4E-BP1 (downstream molecules) in tumor cells.[45] Triterpenes of *G. lucidum* inhibit tumor growth in mice by enhancing the expression of various components of immune system. Triterpenes stimulate the expressions of IL-6 and TNF-α, and arrest cell cycle at G2/M phase in A549 cells. Also, triterpenes induce apoptosis by decreasing the expression of Bcl-2 and pro-caspase 9 with increases in caspase 9 level.[46]

Autophagy

Autophagy is a regulated, orderly self-digestion process of cellular components *via* lysosomal degradation pathway and regarded as an adaptive response to stress in cell survivability. *In vivo* studies of recombinant Ling Zhi-8 (rLZ-8) from *G. lucidum* effectively check the lung cancer cell proliferation. rLZ-8 modulates the functioning of epithelial–mesenchymal transition (EMT) by regulating the expression of cell adhesion and focal adhesion kinase (FAK) in lung cancer cells. rLZ-8 downregulates the expression of Slug (transcription factor), represses E-cadherin transcription, and induced FAK inactivation, resulting in repression of tumor mobility.[47] Intracellular calcium level in multidrug resistance (MDR) causes sensitization, which may cause cell death and creates chemoresistance in cancer therapy. GMI elevates the intracellular calcium level and inhibits cell growth through autophagy and apoptosis in mice xenograft tumors in A549 cells. GMI causes inhibition in the process of phosphorylation of Akt/S473 and p70S6K/T389 and plays a role in autophagy in lung cancers.[48]

Anti-inflammation

Inflammation is self-protection from irrelevant material through the activation of immune system. GMI reduced the expression of TNF-α-induced MMP-9 activities by inhibiting MMP-9 transcriptional activity and induced antitumor and anti-inflammatory effects. GMI modulates the NF-κB/MMP-9 pathways through blocking the process of phosphorylation and degradation of IκBα, resulting in suppression of the nuclear translocation of p65.[49]

Anti-proliferation

Oral administration of *G. lucidum* extract inhibits breast-to-lung cancer metastases through downregulating the genes regulating invasive behavior (HRAS, VIL2, S100A4, MCAM, I2PP2A, and FN1).[50] Ganoderiol F (GA-F) is a tetracyclic triterpene, exhibiting cytotoxicity in vitro against Lewis lung carcinoma (LLC) cell lines.[51] Khz is a compound derived by fusing mycelia of *G. lucidum* and *Polyporus umbellatus* which inhibits the cancer cells. Khz arrested cell cycle at G1 and reduced MMP and Bcl-2 protein levels but increased reactive oxygen species (ROS) generation, apoptosis, and p53 and pro-apoptotic proteins. This study indicates antiproliferative and proapoptotic effects of Khz and can be used as chemotherapeutic agent.[52]

Signaling in lung cancer

The process of cell signaling involves the activation of receptors by phosphorylation in the plasma membrane and subsequent activation of the downstream protein acting as a gateway for signaling. Multifactorial disease cancer involves complex networking of gene interlinking various pathways in cancer signaling, and the crosstalk among different adapter molecules makes cancer mechanism unrevealed. Majorly, cancer comprises different pathways targeting apoptosis, NF-κB pathway, RAS-MAPK, PI3K-AKT, mTOR, and cell cycle (Figure 3).

Therefore, *G. lucidum* and its bioconstituents may target these pathway, but these are still unexplored. Very few studies were conducted targeting lung cancer with *G. lucidum* and its bioconstituents. Till now, researchers were focused only on apoptosis and cell cycle, without exploring much on other pathways in cancer signaling. Previously, our research group determines the anticancer property of *G. lucidum* growing under abiotic stress conditions. The potent anticancer activity was reported owing to the higher content of phytochemical release to combat stress conditions.[7] Different isoforms of ganoderic acid (more than 50) were studied on membrane receptor RTKs (insulin receptor (IR), insulin-like growth factor (IGFR), VEGR1, VEGFR2, and estrogen receptor (ER)) and disclose the mechanistic binding with ganoderic acid in liver cancer. The mechanistic binding depends on the overall effect of binding interactions which comprises lipophilic hydrogen bonding, pi-pi stacking interactions, and non-covalent bonding. Ganoderic acid has lanosterol scaffold, and functionality varies in their isoforms with a change in the functional side chain.[53] Furthermore, ganoderic acid A inhibits the expression of STAT3 by inhibiting proliferation, viability, and ROS. The activity of antioxidant was enhanced with ganoderic acid A with the role of SOD1, SOD2, and SOD3 in a PC-3 cell in a dose-dependent manner.[54] The ganoderic acid modulates the A Wnt signaling and controls the development, proliferation, migration, cell fate specification, and pattern of the body axis. Ganoderic acid A inhibits the cell proliferation, viability, and ROS of pancreatic cancer in a dose-dependent manner in pancreatic cancer cells.[55] Previously, isoforms GA-A and H were critically involved in NF-κB, a transcription factor which has pivotal role in cell proliferation and apoptosis.[56]

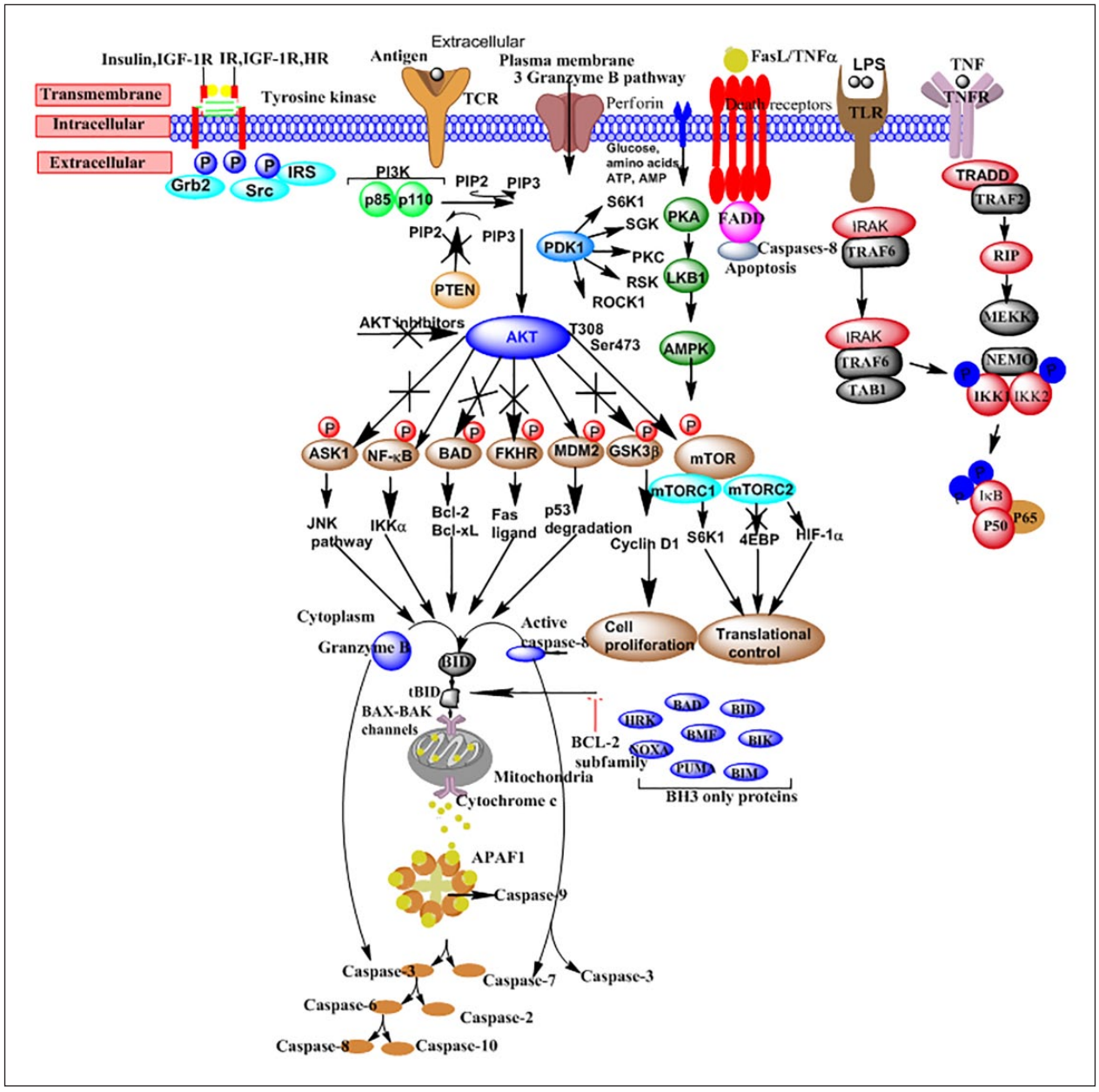

Figure 3. Signaling cascade initiated by *Ganoderma lucidum* and its bioconstituents in cancer. Upon receiving stimulus such as growth factor initiates the activation of different receptors in the plasma membrane particularly RTKs. RTK phosphorylation leads to dimerization and activation of adapter molecules, initiating the process of apoptosis in cancer. Upon stimulus, RTKs activates PI3K/Akt/mTOR pathway with other proteins modulating the behaviour of action in cancer signaling. *G. lucidum* modulates and control the expression of various signaling factors in both intrinsic and extrinsic apoptosis, depending upon a signal received.

Side effects

G. lucidum has high medicinal values and this causes increased demand for commercial use. The increase in demand and use of the artificial method for cultivation enhance its productivity, modulating the parameters responsible for cultivation. Multifarious uses of *G. lucidum* also bring its function to decrease or inhibit the toxicity caused by other products. Previous chemotherapeutic agent, cisplatin (platinum-containing anticancer drugs) which is effective in treating the tumor, causes the side effect of renal impairment with a decrease in glomerular filtration.[57] *G. lucidum* administration induces the antioxidant capacity (superoxide dismutase, catalase, and glutathione peroxidase activities), reduces glutathione, and prevents nephrotoxicity induced by cisplatin.[58] Recent radiation-damage cryoprotectant causes an undesirable side effect; however, use of *G. lucidum* overcomes this effect with the recovery of cellular immune competence

Table 2. Clinical trial of different compounds from natural products in cancer.

S. no	Compound	Cancer used	Status
1	Vincristine	Leukemia, breast, lung, and pediatric solid cancer	Phase III/IV
2	Irinotecan	Colorectal and lung cancer	Phase II/III
3	Paclitaxel	Ovary, lung, neck, and breast cancer	Phase II/III
4	Bruceantin	Experimental	Preclinical/phase I
5	Docetaxel	Breast and lung cancer	Phase III
6	Topotecan	Ovarian, lung, and pediatric cancer	Phase II/III

from gamma-irradiation.[59] Use of dosage in the form of spore capsule, freeze dried powder, tablets, soup, and syrup display dose-dependent toxicities varying with the dosage of ingestion. The oral dosages (1.5 g/day) cause mild side effects of sleepiness, thirst, rashes, bloating, and frequent urination.[60] *G. lucidum* hampers the efficacy of aspirin or warfarin drugs (immunosuppressive therapies) in various anomalies.[61] The use of alcoholic extract (1.2 and 12 g/kg daily during 30 days) of fungus do not exhibit any effect on organs responsible for the growth and development. Combined therapy of lithium, perphenazine, and trihexyphenidyl with *Ganoderma* slices was used to treat schizophrenia, which do not have any side effects.[62]

Clinical trials

Plants are enriched with numerous phytochemicals, and their level changes with the prevailing environmental condition to make their survival easier. These phytochemicals defend the plants from predators initiating the activation of the signal for releases of harmful chemicals for predators. Plant-derived drugs are effective in combating cancer; some are in different phases of clinical trials (Table 2). Vincristine, also known as leurocristine, is an alkaloid available commercially under brand name Oncovin and is used in chemotherapy for curing leukemia by inhibiting microtubule assembly.[63] Antitumor activity of taxanes (paclitaxel and docetaxel) exhibits impressive effects in the breast, ovarian, and other tumor types.[64] Also, camptothecin derivatives irinotecan and topotecan have an inhibitory role in colorectal and ovarian cancer.[65]

Conclusion

Lung cancer is the leading cause of death and needs some alternative drugs to the commercially available drugs. *G. lucidum* and its active compounds explicit their role in cancer signaling, targeting different adapter molecules crucial in maintaining physiology of the cell. *G. lucidum* is well known for promoting health and referred as "herb of spiritual potency," but only few studies were conducted in the field of lung cancer. The isolated bioactive constituents present in *G. lucidum* exhibit potential in cancer therapy and its expression in lung cancer needs to be studied. Till now, ganoderic acid and some other compounds isolated were targeted for the process of apoptosis, cell cycle, and autophagy. This review indicates prospects regarding the expression of different isoforms of ganoderic acid and lanosterol compounds in lung cancer. This might produce some effective compounds or can synthesize new compounds in lung cancer targeting multiple genes in lung cancer. The present research group is engaged in determining the anticancerous property of *G. lucidum* and active compounds in cancer.

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Declaration of conflicting interests

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