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REVIEW

Misconstrued versatility of *Ganoderma lucidum*: a key player in multi-targeted cellular signaling

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Abstract A *Basidiomycetes* fungus belonging to polypore family of mushrooms, *Ganoderma lucidum* (GL), has been known since a long time for their myriad therapeutic indications. Renowned as an invaluable resource of cardinal mycoconstituents they encompass numerous terpenoids polysaccharides and proteins. Possessing the therapeutically potent lanosteroidal skeleton, terpenoids are upheld for their invariable participation in therapeutically diverse bioactivities. Polysaccharides and proteins exhibiting distinguishable bioactivities provide this oriental mushroom with additional edges over immune function and anti-cancer potential. This review is a concerted effort to throw light upon the therapeutic versatility of the fungus, shadowed by various other natural products. An effort has been made towards conglomerating the mycoconstituents decisive for the many activities portrayed by this fungus. More importantly, this review seeks to fathom the inextricable role played by derivatives in modulating signaling cascades such as downregulation of various mitogenic pathways, inhibiting growth factors, or upregulating certain pathways enhancing cellular integrity.

Keywords *Ganoderma lucidum* · Terpenoids · Polysaccharides · Ganoderic acid (GA) · Cancer

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Introduction

Nature has bestowed us incredibly with an armamentarium of lead molecules, many of which—after passing the clinical trials—have become FDA approved drugs whereas others are yet to be explored [1]. Botanically known as *Ganoderma lucidum* (GL), this *Basidiomycetes* fungus has been known since long to be used as herbal medicine [2] especially in Sino-Japanese regions. *Ganoderma lucidum* has derived its name from the Latin word *lucidus* meaning "shiny" or "brilliant" as an acknowledgment for the varnished appearance of the fungus surface. The family *Ganodermataceae* represents polypore *Basidiomycetous* fungi having a double-walled basidiospore with the laccate (shiny) surface, associated with the presence of thick-walled pilocystidia embedded in an extracellular melanin matrix [3]. *Ganoderma* species are found around the globe and characterized by several distinct morphological and anatomical features. This includes the shape and size of the basidiocarp, the color of pileus, and stipe, the pore size, the color of pore the surface and context, the size and shape of the basidiospore, and shape of the apical pilear cells [4]. Morphological features may also vary depending on the host specificity, and geographical origin. *Ganoderma* species are known to have a long history, been used for thousands of years, of maintaining and promoting health and longevity [5]. The extensive use of *Reishi* or *ling Zhi* [6] was attributed to mainly to the immunomodulatory effect and its ability to strengthen the defense mechanisms. The versatility of *Ganoderma* is misconstrued in that where earlier it was acclaimed to have an only immunomodulatory effect, recent research has concluded the participation of various *Ganoderma* constituents (Fig. 2) in a broad spectrum of bioactivities. These mainly include immunity modulator [7], anticancer [8], antioxidant [9–11], antimicrobial [12]. In addition, they have also proven their therapeutic proficiency in

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resolving cardiovascular [13] and neurological [14] complications, wound healing [15] preventing bronchitis, inhibiting platelet aggregations [16]. The pharmaceutical value overrides the nutritional values and being much sought-after this natural product is commercialized in the form of health drinks, soups, tea, tablets, and other products [17]. This clinically beneficial mushroom is known to be a nuisance to plants by acting as parasites on host plants like *Pinus*, *Dalbergia*, *Artocarpus*, *Morus*, *Cedrus*, *Melia*, *Quercus*, and *Populus*, causing butt and root rot diseases [18].

Spores of *G. lucidum* (GLS) also exhibit therapeutic efficiency which can be attributed to various constituents present within methyl ganoderate A acetonide, *n*-butyl ganoderate H, and methyl ganoderic acid B [19]. Spores of *G. lucidum* (GLS) exhibit neuromodulation effect, also confirmed by pharmacological bioassay. The assay showed a reversal of the abnormalities induced by the intracerebroventricular injection of streptozotocin (STZ), thus establishing the applicability of GLS in the remission of Alzheimer's disease [20]. Furthermore, the fungal spore also displays anti-acetyl cholinesterase activity [19] and nerve growth factor-like neuronal survival-promoting effects, highlighting their benefits in neurodegenerative diseases [21].

This multidimensional pharmacological entity portrays its versatility in the signaling pathways involved in the aforementioned anomalies [10]. Despite this, their intrinsic mechanistic binding to the concerned adaptor signaling proteins of respective pathways remains to be explored. Present chemotherapies are facing pitfalls like resistance, selectivity, and toxicity and urgently necessitates new scaffolds and new drug designing approaches. This review is put forward with an aim to put forth worthy insight about the bioactivities portrayed by the various mycoconstituents encompassed within this *Basidiomycetes* fungus. It also discusses the signaling pathways involved directly or indirectly in metabolic and immunological disorders. Major myco-constituents present include terpenoids, polysaccharides, proteins, vitamins, alkaloids, and various minor products. Research and quality assurance depend upon the isolation or purification method used during separation [22].

Ganoderma constituents and their bioactivities

The weight of *G. lucidum* comprises 90 % water, whereas the other constituents such as protein, fat, carbohydrate, fiber, ash, vitamins, and minerals comprise only 10 % [23]. The fungus is composed of numerous mycoconstituents (Fig. 2) but it is dominantly the fruiting body that encompasses significant constituents-terpenoids, polysaccharides, polysaccharide-peptide complex, and proteins along with trace amount of phenols, adenosine, amino acid, vitamin, purine, and pyrimidine derivatives [24, 25]. Among the terpenoids (Fig. 1), ganoderic acid is considered to be a pivotal constituent in modulating the diverse signaling pathways thought plausible for various anomalies. Triterpenoids target the process of proliferation, invasion, metastasis, inflammation, and apoptosis in the cancer cell. They target mainly nuclear factor-kappaB (NF-κB), signal transducer, and activator of transcription 3 (STAT3), tumor necrosis factor (TNF), angiogenesis, PI3K/AKT/mTOR in cancer signaling [26]. In the process, they enhance immunity, arrest cell cycle, and indulge in the process of apoptosis with the help of MMPs, and caspases. In addition to these functions, triterpenes are also reported to participate significantly in the synthesis of cholesterol, neuromodulation, and autophagy (Fig. 2). Immunomodulation role portrayed by polysaccharides enhance immunity by NK, CTL, IL, TNF cells, and acts as an antitumor agent. Polysaccharides potentially act as an antioxidant, scavenging the free radical, also contributing towards autophagy and diabetes. On the other hand, proteins in *Ganoderma* enhances the immunity, with activity in telomerase. Different mycoconstituents perform a different function, but the complexity and multiple roles portrayed by individual protein make it a difficult task to impart single role to an individual component.

Bioactive constituents

Terpenes and multifaceted therapeutic role

Terpenes are naturally occurring diverse class of organic compounds with carbon skeletons composed of multiple isoprene units. Terpenoids are categorized into different subclasses depending on the number of isoprene units in the molecule. One of the most important and researched triterpenoids is Ganoderic acid (GA), and its various isoforms represented in Table 1. In the recent times, more than 130 isoforms of ganoderic acid have been isolated from fruiting bodies, spores, and mycelia of *G. lucidum* and characterized [63]. Ganoderic acids, belonging to the triterpenoid class of secondary metabolites, possess six isoprene units constituting mainly of lanostane skeleton with their molecular weight in the range of 400 to 600 kDa [64]. These lanosteroidal skeletons portray significantly diverse therapeutic spectrum (Table 1), inclusive of molecular immunity functionality modifier and anticancer activity [65, 66]. The amalgamation of benefits, devoid of life-threatening detrimental effect, urges the need to discover medicinal properties of this mushroom. These basic steroidal scaffolds with modifications in the chemical functionality groups such as in ganoderic acids make them adept enough to target various subcellular proteins. This confers ganoderic acid with the potential to be used as an invaluable lead molecule in anti-cancer drug discovery. Ganoderic acids (GA) target various adaptor proteins participating in cellular signaling pathways leading to the arrest of cell adhesion, proliferation,

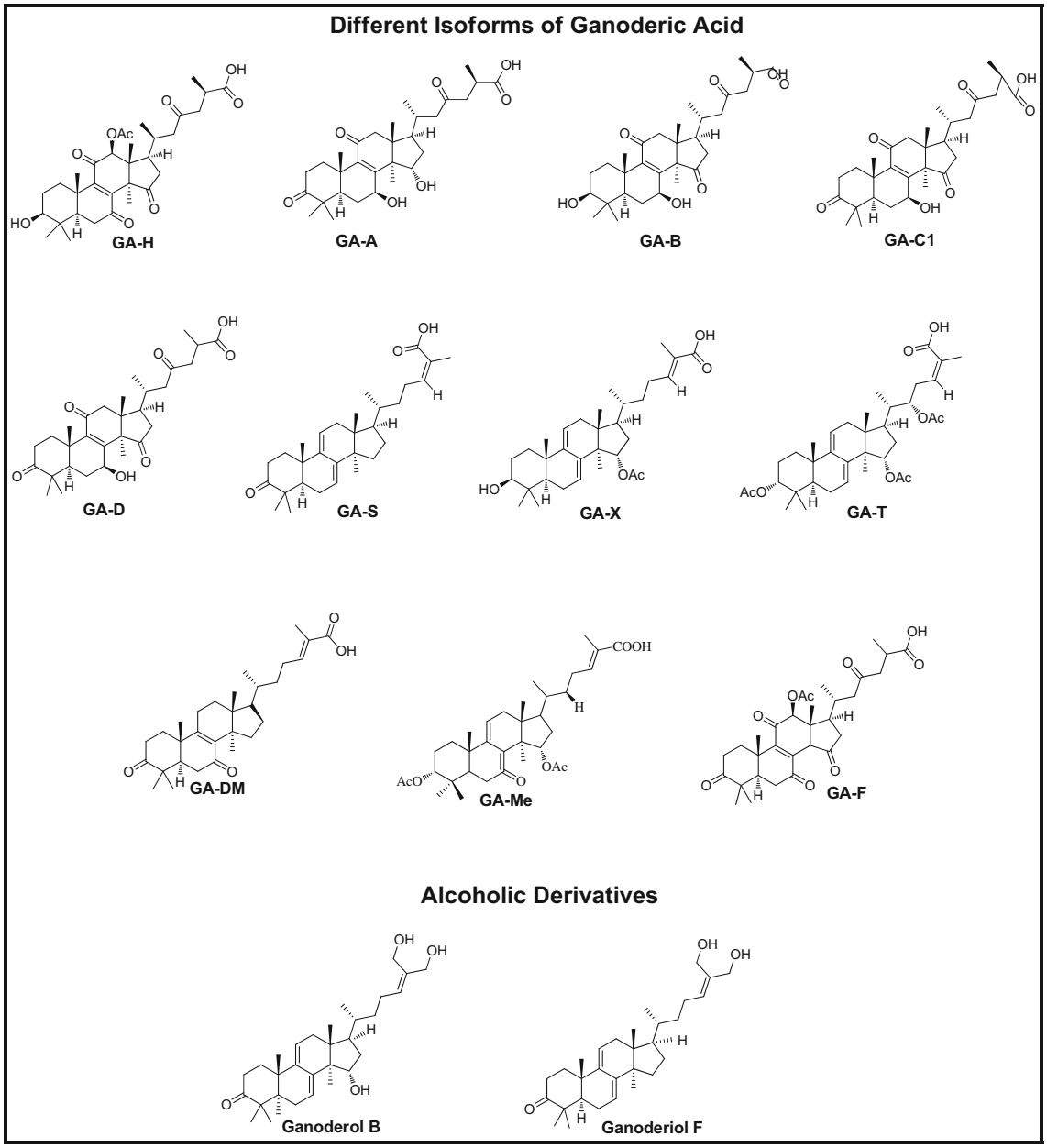

Fig. 1 Chemical structures of various *Ganoderma lucidum* mycoconstituents

survival, invasion, metastasis as well as other mitogenic processes [67–69].

Anti-cancer

Triterpenoid present in *G. lucidum* has been evidenced to play a significant role as an anti-cancer agent. Clinical reports highlight the role of ganoderic acid in cancer, highlighting the potency of GA-A and GA-H (Table 1) in suppressing cell proliferation, metastasis, and adhesion in breast cancer. Through these actions, GA-A and GA-H reverse the aberrant nature of nuclear transcription factors (AP-1 and NF-κB), leading to decreasing the expression of Cdk4 and urokinase-type plasminogen activator (uPA) [70]. In addition, GA-A enhances chemosensitivity and aggravates the cytotoxicity of cisplatin in liver cancer cell lines (HepG2), via suppressing JAK-1 and JAK-2 accessory proteins of JAK-STAT-3 signaling [29]. GA-C was observed to competitively inhibit protein prenyltransferase (PPP), thus, inhibiting the biosynthesis of farnesyl pyrophosphate (FPP), and the subsequent post-translational modification. These modifications become important for cell membrane association and transforming activities. As these processes are involved in the biosynthesis of steroidal hormones and intermediary steps in cholesterol biosynthesis, it is providing an opportunity for rational targeting drug. Owing to this, it can also be employed for steroidal

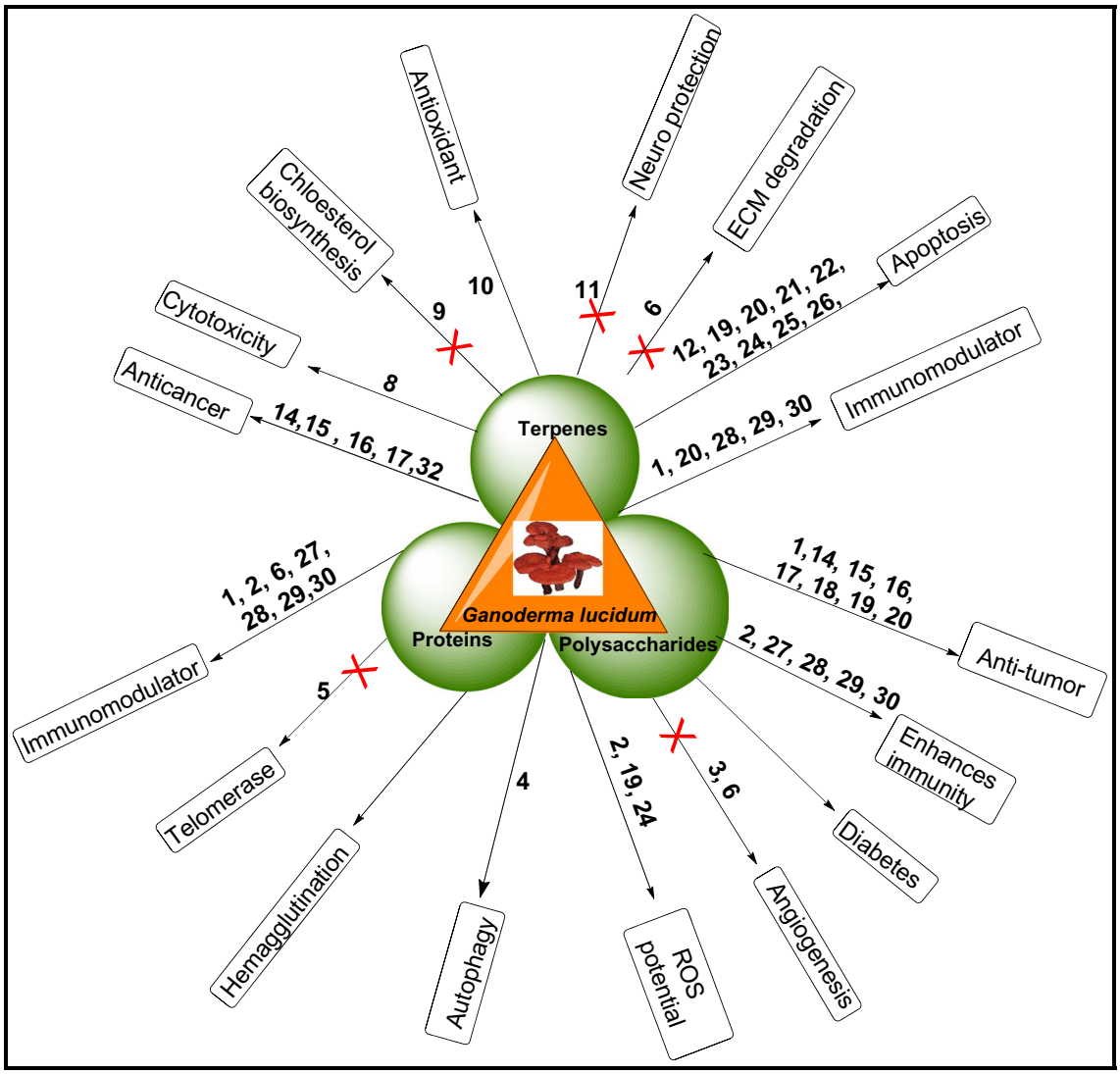

Fig. 2 Mechanism of action for bioactivities exhibited by major mycoconstituents of *G. lucidum*. **1** = enhance natural killer (NK), cytotoxic T-lymphocyte (CTL) **2** = enhance tumor necrosis factor (TNF), interleukin (IL), NK **3** = inhibit capillary morphogenesis **4** - = activation of endoplasmic reticulum-associated degradation (ERAD) **5** = inhibit c-myc **6** = modulate matrix metalloproteinase (MMP) **7** - = inhibit protein kinase C (PKC), β catenin **8** = mitochondrial dependent **9** = inhibit farnesyl pyrophosphate (FPP) **10** = caspases **11** = inhibit microglial cell activation **12** = inhibit topoisomerase **13** - = immunomodulator **14** = nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) **15** = activator protein 1 (AP-1) **16** - = downregulates urokinase-type plasminogen activator (μPA) **17** = JAK-STAT **18** = inhibit protein prenyltransferase (PPP) **19** = modulate cell cycle **20** = T, B lymphocytes **21** = histamine release **22** = topoisomerase **23** - = extracellular-signal-regulated kinases (ERK) **24** = c-Jun N-terminal kinases (JNK) **25** = Bcl2 **26** = mitochondrial potential **27** = antigen promoting cells (APC) **28** = cellular immunity **29** = interleukin (IL) **30** = natural killer (NK) cells **31** = apoptotic protease activating factor-1 (apaf-1) **32** = p53 **33** = c-myc

hormone-dependent cancer patient suffering from hypercholesterolemia as a secondary complication [71, 72]. Similar cytotoxicity was also reported with methyl lucidenic acid; lucidenic acid A, C, and N; and GA-E against hepatic carcinoma (HepG2, HepG2. 2.15) and leukemia (P-388) [73]. Furthermore, *G. lucidum* in combination with conventional therapies acts as an important supplement to enhance the immunity in cancer patients. The anti-proliferative effect of *Ganoderma* in human (HepG2) cell lines was also demonstrated as was arresting cell cycle at the G1 phase [74]. Several in vitro and in vivo molecular studies have shown the antiproliferative potency of GA-T in colon (HCT-116 ($p53^{+/+}$ and $p53^{-/-}$)) and lung (95-D, Lewis Lung Carcinoma, (LLC)) cancer cell lines. GA-T modulates variety of functions involving uPA, matrix metalloproteinase-2/9 (MMP-2/9), inducing nitric oxide synthase (iNOS/NOS2) and their corresponding proteins levels [38, 40, 49, 51, 75] and arrest G_1 cell cycle in 95-D cell lines. Moreover, ganoderic acids like GA-F, K, B, AM1 have been characterized by their potential anti-cancer activity against HeLa human cervical carcinoma [27]. GA-F,

Table 1 List of different ganoderic acid along with their biological activity

Ganoderic acid (GA)	Biological effect	References
Ganoderic acid, GA-F, K, B, D, GAAM1, DM, and A	Anti-tumor activity	[27–30]
Ganoderic acid, GA α, β, C1, H, GS-2, and B	Anti-HIV 1, 2 activity	[31–33]
GA-R, S	Antihepatotoxic activity	[34]
B, C2, and G	Anti-ageing activity	[35, 36]
Ganoderic acid, GA- A, B, C, and D	Antioxidative activity	[37]
GA-A, B, G, and H	Antinociceptive activity	[38]
GA-Me	Arrest cell cycle, apoptosis	[39, 40]
Ganoderic acid, GA-C, and D	Histamine inhibition	[38, 41, 42]
Ganoderic acid, GA-A, F, and DM	Anti-inflammatory activity	[43–45]
GA-Y, F, H, B, D, K, and S	Antihypertensive activity	[46]
GA-Me, Mf, and Y	Hypercholesterolemic activity	[38, 47]
GA-Sz	Anticomplement activity	[48]
GA-T	Anti-metastatic, anti-invasion	[38, 40, 49]
GA-Mf, S, A, DM, and Me	Apoptosis	[43, 50, 51]
GA-Df, GA-C2, and ganoderenic acid A	Inhibits aldose reductase	[52]
GA-R, T	Cytotoxicity	[53, 54]
Ganoderic acid	Anti-hepatitis B	[55]
7-*O*-Ethyl ganoderic acid O (7-*O*-ethyl GA-O), Ganodermanontriol (GDNT)	Anti-cancer	[56, 57]
GA-DM	Tubulin-inhibition	[58]
GA-E	Neuroprotective effect	[59]
Ganoderol B	Inhibits α- Glucosidase	[60]
Ganoderic acid	Antiviral activity	[61, 62]

ganoderic acid γ, ganoderic acid ε and ganoderic acid ϕ were also found to have inhibitory effect on primary solid tumor growth in the spleen and liver metastasis and secondary metastatic tumor growth in the liver in intrasplenic LLC-implanted mice [38] and even their synthetic analogues showed cytotoxicity in LLC, Meth-A, Sarcoma-180, and T-47D cell lines [70, 76, 77].

Anti-oxidant

Reactive oxygen species are generated in the body in response to normal cell metabolism, but an imbalance resulting from high concentration leads to oxidative stress. Ganoderic acids have demonstrated commendable anti-oxidant activity as scavengers of free radical that occur as a consequence of altered gene expression in stress conditions. GA-A, B, C, D (Fig. 1) displayed potent antioxidant activity against the pyrogallol-induced erythrocyte membrane oxidation and Fe^{2+}-ascorbic acid-induced lipid peroxidation [78]. Fatmawati et al. has reported ganoderic acid-Df inhibitory activity (IC_{50} = 22.8 μM) against NADPH-dependent human aldose reductase known to play a significant role in catalyzing the reduction of glucose to sorbitol [52], a fundamental step in polyol biosynthetic pathway. These reports demonstrate the mechanism of antioxidant activity to be via the inhibition of NADPH-dependent enzymes, proving to be critical in the regulation of polyol biosynthesis.

Immunomodulator

Literature evidences ganoderic acid to be an efficient immunomodulator. In vitro and animal studies further confirmed these evidence that mycoconstituent stimulate proliferation of B and T lymphocytes, splenic mononuclear cells, NK cells, and dendritic cells [79]. In 1985, Kohda and his research group demonstrated GA-C and GA-D (Fig. 1) to inhibit histamine release from the rat peritoneal mast cells [80]. Literature also reveals the central role played by ganoderic acids in controlling asthma and other hypersensitivity-related diseases. In asthma, GA-β displayed promising results in the cultures of peripheral blood mononuclear cells (PBMCs) isolated from the asthma patient. This was attributed to the ability of the isoform to suppress Th2 responses and induce Th1/Tregs [81]. Th2 plays a pivotal role in the pathogenesis of the allergic disease [82], whereas Th1 and T inhibit the Th2 responses, thus, inducing immune tolerance. Also, GA-β has been seen to exhibit immune-modulator action decreasing the burden of the active immune system by reducing IL-5, but increasing $CD8^+$, IFN-γ, IL-10, and IL-12 production of specific allergen-stimulated PBMCs. These effects have been observed to be significant for attaining immune competence in

asthmatic patients [81]. In addition, GA-S is known to suppress the thromboxanes and prostaglandins exhibiting the amphipathic effect on the platelets aggregation [77, 83, 84].

Topoisomerases and apoptosis activity

Isoforms of ganoderic acid exhibit potent inhibitory activity against topoisomerases. Topoisomerases are the enzymes which cleave the phosphate backbone of the DNA, regulating the overwinding or underwinding of DNA ultimately leading to programmed cell death (apoptosis). Various drugs operate through interference with the mechanism of topoisomerases. GA-X (Fig. 1) impedes the function of topoisomerases, ERK, JNK, mitogen-activated protein kinases, and Bcl-xL which result in the disruption of mitochondrial membrane potential ($\Delta\psi_m$). This, in turn, initiates the release cytochrome-c, ultimately culminating in activation of apoptosis in the cancer cells [85]. GA-D and GA-T bind to14-3-3ζ protein, annexin A5, and aminopeptidase B [86]. As seen in HeLa human cervical carcinoma cells, this causes cell cycle arrest at G2/M phase, precipitation of pro-apoptotic proteins p53, IL-2, IFN-γ, NF-κB, Bax, and alleviation of Bcl-2 expression leading to caspase-dependent apoptotic cell death [86, 87]. GA-T (Fig. 1) specifically inhibits the activity of topoisomerase-I by interfering with the interaction of telomerase 1 with DNA preventing the complex formation [88]. GA-B, C2, and G exhibit anti-aging effect [36] indicating that ganoderic acid are possibly responsible for telomerase-mediated the anti-ageing activity of GL.

Apoptotic agent

Ganoderic acid-DM (Fig. 1), in melanoma cells, has been seen to increase Bax proteins expression, elevating the level of Apaf-1, cytochrome-c, Beclin-1, and LC3 proteins. These events facilitate the cleavage of caspases 9 and 3, thereby, orchestrating autophagic and apoptotic cell death. GA-DM enhances the expression of high-level HLA class II proteins with antigen presenting cell and T cell recognition, which increases the cancer cell immune-susceptibility. This further confirmed the role of GA-DM in stimulating autophagy and apoptosis and generating an immune response in melanoma [89]. Other isoforms like GA-Mf and S also bring about mitochondrial-mediated apoptosis by enhancing the caspase-3 and caspase-9 activity resulting in increased ratio of Bax/Bcl-2 and cell cycle arrest at S and G1 phase, as seen in HeLa cells [50]. Despite the role of ganoderic acid in DNA damage and cleavage of poly (ADP-ribose) polymerase (PARP), it also modulates immune functionality, activity of CDK2, CDK6, cycle D1, and nuclear transcription factor (p-Rb and c-Myc) in MCF-7 breast cancer cell lines [43].

Multi-drug resistance (MDR) inhibitory activity

Recent findings highlight the efficacy of lanosteroids in overcoming multiple drug resistance (MDR), where reports disclose their mechanism to be the induction of cytotoxicity and apoptosis in tumor and sensitive cell lines as in GA-R. Likewise, GA-Me (Fig. 1) also directs the apoptosis in MDR colon cancer cells (LLC) by (a) improvising the chemotactic movement of IL-2, IFN-γ, NK cells [79], (b) exacerbating apoptotic proteins (p-p53, p53, Bax, caspase-3, caspase-9), (c) suppressing the expression of anti-apoptotic protein, Bcl-2 [50], (d) downregulating MMP-2/9 gene expression [75], (e) reducing $\Delta\psi_m$ and variations in apoptosis proteins expression stimulating the release of cytochrome into cytosol [40, 50]. These factors, taken together, causes mitochondrial dysfunction and p53-mediated sub-G_1 arrest in human colon carcinoma cells. Furthermore, it diminishes hMDR1 promoter activity and prevents other protein expression (MDR1) which ultimately recedes the colonization, migration, adhesion, and induces apoptosis [75]. However, Chen et al. reported the role of GA-Me in G_1 arrest in wild-type p53 human tumor cells, and G_1/S transition arrest in the p53-null cell [39]. This result surmises p53 to be a promising target of GA-Me and exploring further might divulge their role as a potent clinical agent against the multi-drug-resistant colon cancer cells.

Miscellaneous roles

The objective of the research is to combat microorganism particularly viral and bacterial infection. Modulating multiple signaling pathways without side effect makes progress of new antibiotics and provides the researchers to work in this direction. Polysaccharides or triterpenoids from *Ganoderma* showed antimicrobial activity against Herpes simplex virus, Hepatitis B virus, HIV, and Epstein-Barr virus in vitro or animal models [90]. Keypour et al. investigated the antibacterial effect of chloroform extract of *Ganoderma* on *Bacillus subtilis*, *Staphylococcus aureus*, *Enterococcus faecalis*, *Escherichia coli,* and *Pseudomonas aeruginosa* [91]. Interestingly, ganoderic acid has been proven to be cytotoxic against both androgen-independent or dependent prostate cancer cells with decreased incidences of osteoclastogenesis in late metastatic stage [92]. This is directed at suppressing c-Fos and nuclear factor of activated T cells c1 (NFATc1). This brings about a decrease in activity of the dendritic cell-specific transmembrane protein (DC-STAMP) expression, reducing the osteoclast fusion [93]. This is quite convenient to target simultaneously with steroidal hormone-dependent tumors associated with osteoclast atrophy by the ganoderic acid [93].

Signaling network influenced by *Ganoderma* Cell signaling is rightly defined in terms of receptor activation causing phosphorylation of transducer proteins or involving closing and

opening channels for cations or anions to move inside or outside the cell. In normal physiology of the cell receptors embedded in the plasma membrane are in an inactive form which on receiving signal, get phosphorylated and activated. In complex diseases such as in cancer, gene networks and receptor get interlinked playing a significant role in such diseases. Cross talk among different proteins and their adapter molecules makes it challenging to hold responsible any single pathway, as aberration in more than one pathway may be causing the debilitating condition. This is more so in the case of cancer where at times multiple signaling cascades need to be targeted to effect recuperation. Herein, the signaling pathways occurring in normal cell physiology have been discussed viz (a) apoptosis, (b) NF-κB pathway, (c) RAS-MAPK, (d) PI3K-AKT, (e) mTOR, and (f) cell cycle (Fig. 3). The figure also points out various fungal constituents that interact with the proteins of these pathways, thus, modulating the pathway.

In a normal cell, mitochondria display the protein Bcl-2 on their surface which inhibits apoptosis (Fig. 3a). When the normal mechanisms are disrupted, Bax migrates to the mitochondria inhibiting Bcl-2 leading to of cytochrome c release. The cytochrome c forms apoptosomes by binding to protein Apaf-1 (apoptotic protease activating factor-1) which, in turn, bind to and activate caspase-9, which initiates a cascade of cleaving and activating other caspases with proteolytic activity. The nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) described in (Fig. 3b) produces a free form of its subunits in response to any signaling directed towards phosphorylation of NF- κB complex and translocates it to the nucleus for expression and activation of other genes. NF-kB activates the urokinase-type plasminogen activator receptor (uPAR) enabling it to interact better with its endogenous ligand, uPA. Thus, enhancing adhesion and migration of cancer cells and improving their survival chances. Third signaling pathway is RAS-MAPK, mitogen-activated protein kinases (Fig. 3c), which, on receiving any external stimulus. converts GDP to GTP, activates Ras. This leads to phosphorylation and activation of MAP3K which activates MAP2K, and this subsequently activates MAPK. These Ras-regulated signal pathways control various cellular processes such as proliferation, differentiation, cell adhesion,

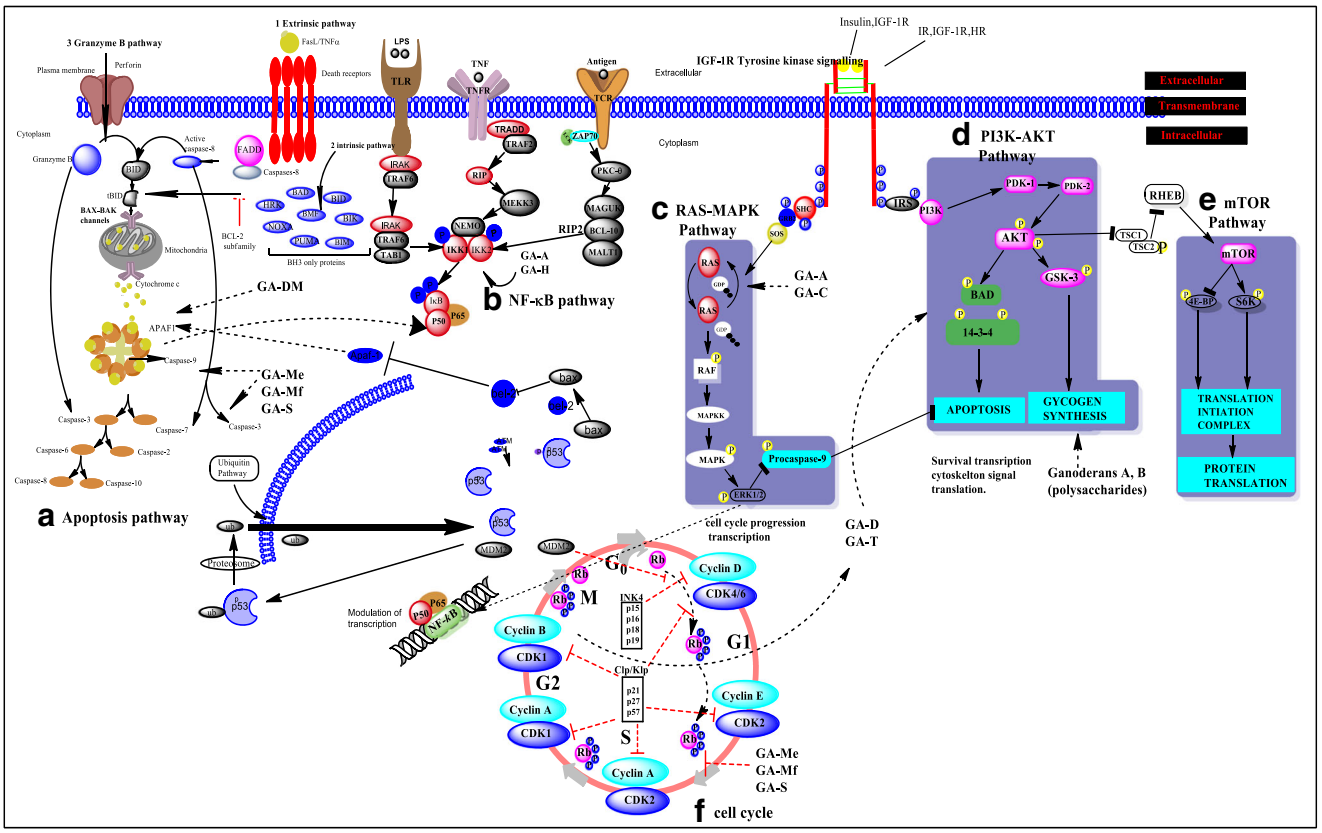

Fig. 3 Signaling network influenced by *G. lucidum* and its constituents. Six major cellular pathways prominent in cancer signaling have been discussed. They are **a** apoptosis pathway [50], **b** NF-κB pathway [70], **c** RAS-MAPK pathway, **d** PI3K-AKT pathway, **e** mTOR pathway, and **f** cell cycle and its regulation [74]. *G. lucidum's* constituent ganoderic acid when administered appropriately modulates the signaling pathway in cancer. Ganoderic acid targets the cancer signaling pathway which is initiated by getting external stimulus on receptors and its downstream signaling

apoptosis, and cell migration. Minute aberration in this pathway may culminate in increased metastasis ultimately leads to cancer [94].

Fourth and fifth signaling pathway together forms the PI3K/AKT/mTOR pathway (Fig. 3d, e). RTKs activate phosphatidylinositol 3-kinase (PI3K) through direct binding of scaffolding adaptors such as insulin receptor substrate 1 (IRS1), which binds to and activates PI3K. PI3K phosphorylates, phosphatidylinositol biphosphate (PIP2) resulting in the formation of phosphatidylinositol (3, 4, 5)-trisphosphate (PIP3). PDK1 (3-phosphoinositide-dependent protein kinase 1) aides the activation of AKT (Protein kinase B) by PIP3 and subsequent phosphorylation of the activation loop of AKT at T308. Furthermore, RTK signaling also activates mammalian target of rapamycin complex 1 (mTORC1), phosphorylates S6K1, and inhibits eIF4E-binding protein (4EBP). mTOR Complex 2 (mTORC2) phosphorylates hypoxia-inducible factor 1-alpha (HIF-1α) and regulates the growth translation. On the other hand, RTK gets stimulated by glucose, amino acids, ATP, and AMP, which phosphorylates PKA and further AMPK, which act on mTOR. Literature survey significantly highlights the contribution of mTOR in both cancer and diabetes Type 2 [95–97].

Cell cycle (Fig. 3f) is mediated by a complex series of molecular and biochemical signaling pathways controlling division and growth. Sequential process in the cell cycle leads to the normal functioning, whereas, even a minute error incorporation results in apoptosis. The cell cycle is regulated by the help of cyclin-dependent kinases or CDKs which uses signals to activate the cell cycle progression. CDKs themselves are activated by regulatory protein (cyclins), present only for a short period in the cell cycle [98].

Cancer is a multifactorial disease involving uncontrolled cell growth and proliferation. Dynamic nature and gene network in cancer renders the researchers with the challenging task of designing therapy. Natural products are endowed by multifaceted therapeutics values, in which triterpenes are momentously involved in combating cancer and other anomalies. Ganoderic acid and its isoforms, when administered, appropriately modulates the above signaling pathway in cancer. GA-DM has been observed to inhibit apaf-1, whereas, GA-Me, GA-Mf, GA-S target different caspases in the apoptosis process in cancer (Fig. 3a). In addition, GA-Me, GA-Mf, GA-S also interfere with the G1 phase of the cell cycle (Fig. 3f). In the NF-κB pathway (Fig. 1b), GA-A and GA-H target the NF-κB subunits involved in the activation of the pathway [30]. In RAS-MAPK pathway (Fig. 3c), GA-A and GA-C were reported to affect the first steps in the signaling cascade that leads to cell cycle progression and translation. Isoforms of ganoderic acid, GA-T, and GA-D interfere in signaling of the PI3K/AKT/mTOR pathway (Fig. 3d, e). Furthermore, ganoderic acid play a significant role in the signaling cascade related to BCL-family, BAX, *BH3 interacting-domain* (BID), Fas-associated protein with death domain (FADD), and TNF-α. They also alter the growth factor assisted cellular proliferation via exploiting various subcellular kinases of signaling pathway. Ganoderic acid acts by impeding the nuclear transcription factor associated signaling dominantly involved in various cellular mitogenic effects. Polysaccharides, ganoderans A and B, interfere with glycogen synthesis resulting from the AKT pathway.

In vivo and in vitro studies, highlighted the ganoderic acid potential in the dissemination of signaling related to kinases (ERK 1/2), PI3K or AKT but involving various subcellular proteins. These include growth factor receptor, matrix metalloproteases (MMP), nuclear transcription factors i.e. urokinase-type plasminogen activator (uPA and uPA receptors), and activator protein-1 (AP-1) and (NF-κB). It also contributes towards the cytotoxicity of the natural killer cells (NKC) which together with immune functions act against the secondary complications resulting from the hijack of the immune system in cancer [99]. Clinical reports state the utilization of *Ganoderma* in inflammatory breast cancer (IBC) reduces the expression of mTOR and eIF4G levels, decreases aberrant protein translation [100], controls chemotherapy-induced emesis [101]. This strongly highlights its prowess in improving the anticancer chemotherapy status and, in turn, the quality of life of cancer patients [102].

Ganoderic acid-infused nanoparticles (GAIN) formulation

Ganoderic acid-infused nanoparticles (GAIN) formulation is the nanoparticle-based drug delivery approach found to be more advantageous due to enhanced efficacy and lesser incidence of toxicity [103]. Nanoparticle drug delivery of ganoderic acid can be seen as a comprehensible technique as hydrophobic residues associating in appropriate length facilitate their release in tumor cells [92]. Specifically, GA-A showed excellent results, devoid of any adverse effects, when incorporated with nanoparticle against cancer. Receptor-mediated cellular uptake of nanoparticles targets cancer treatment without harming the healthy cells such as folic acid. This becomes important because cancer cells consume large amounts of folic acids and therefore, nanoparticles accumulate near tumor site before releasing their drugs [104]. The nanoparticle prepared from polysaccharides of *Ganoderma* exhibit cytotoxicity in tumor cells of HepG2, HeLa, and A549 cancer cell lines and mouse spleen cells [105].

Alcoholic derivatives

Ganodermanontriol (GDNT) is an alcoholic isoform which has been observed to inhibit the proliferation of invasive breast cancer cells [106] via downregulating cell division cycle 20 (CDC20) and uPA [57]. GDNT escalates the expression of E-cadherin and ß-catenin in human colon adenocarcinoma

cells (HT-29). This increased expression becomes useful as a research tool in animal modeling of colorectal cancer wherein in xenograft implantation of HT-29 cells can be carried out in nude mice without any adverse effects [107]. Alcoholic derivatives including ganoderiols, ganodermatriol, ganoderol B, ganoderiol F, and lucidumol inhibit androgen-independent human prostate cancer cell proliferation [108]. Lucidumol A along with ganoderic acid-β exhibited potent anti-HIV activity [31]. Ganoderiol F was seen to potentially inhibit topoisomerases I, II, and DNA synthesis, causing cell cycle arrest at G2 phase in hepatic (HepG2, Huh7) and leukemic cancer cell lines (K562) [109]. Ganoderol B has been implicated in prostate cancer by downregulating the antigen-specific activity important in controlling morbidity due to prostate cancer [110]. This constituent also acts as a glycosidase inhibitor which is a core target for diabetes mellitus type 2 [60]. Similarly *Ganoderma FYGL* (Fudan–Yueyang *G. lucidum*) has been accredited as an efficacious protein tyrosine phosphatase 1B (PTP1B) inhibitor ($IC_{50} = 5.12 \pm 0.05$ μg/mL) as compared to metformin, a common anti-diabetic in mice model [111]. As a protein tyrosine kinase phosphate inhibitor it has also been indicated in cancer [112]. Additionally, it also reduces the glycated hemoglobin (Hb1ac) level, phosphoenolpyruvate carboxykinase and improves the catalytic activity of glucokinase with the reduction in hepatic glucose transporter protein expression level [112]. These studies suggest the use of *Ganoderma FYGL* rational targeting of both cancer and diabetes robustly. Others bioactive compounds such as butyl lucidenate P, butyl lucidenate D_2, butyl lucidenate E_2, and butyl lucidenate have been observed to suppress Nitric Oxide (NO) production [113], implicated in different disorders including arthritis, asthma, and neurodegeneration.

Ganoderma lucidum polysaccharides (GLP)

Polysaccharides constitute the cellular structural components encompassed within all domains of life. Fungi enclose high-molecular-weight polysaccharide structures with wide-ranging physiochemical properties. In the process of isolating various constituents from *Ganoderma*, researchers came across the skeleton of molecules bearing similar pharmacological profile but which were also specific in its bioactivity. Later on, these moieties were characterized as polysaccharides which are currently more than 200 in number [22]. These chemical entities require a temperature of 25–30 °C, pH 4.0–6.0, and a biochemical C: N ratio of ~ 18:1 and 25:1 for optimum growth [114]. Structurally, these polysaccharides (GLP) are heteropolymers ranging from 4×10^5 to 1×10^6 Da in molecular weight [115] with specific physiochemical properties [64]. To a large extent, their therapeutic efficacy depends mainly on their structure and distinct molecular weight [116]. Their pharmacognostic values contain ample derived products of xylose, fructose, glucose, sucrose, mannose at varied concentration of approximately 0.4, 14.4, 12.8, 0.7, 50.9 %, respectively [117].

Numerous studies have concluded their contribution either as an efficient anti-oxidative agent or an apoptosis inducer. Yang et al. highlighted the anti-oxidant enzyme activity of polysaccharides to be mainly governed by the expression of Bax/bcl-2 ratio [117]. In vitro and in vivo studies of enriched polysaccharide GL extract substantiated the immune function of antigen promoting cells (APC), humoral immunity, cellular immunity, and mononuclear phagocyte system [69]. Further reports clarified the participation of individual polysaccharide in immune responses. Among these, three polysaccharides viz two heteroglycans (PL-1 and PL-4) and one glucan (PL-3) are known to show in vitro proliferation of T and B lymphocytes. These studies lucidly indicate their involvement in humoral and cellular-mediated immunity as PL-1, which has been found to be an immune stimulator in mice, though not yet confirmed in humans [118]. Polysaccharides also induce macrophage-like differentiation in human leukemia THP-1 cells via caspases and p53 activation [119]. GLP also increases in vitro dose, and time-dependent TNF-α and IFN-γ release [120] providing effective results in free radical scavenging and Fe^{+2} chelation pertaining activities [121]. Studies involving the administration of *Ganoderma* polysaccharides for 12 weeks concluded that *Ganoderma* polysaccharides enhanced the plasma concentration of IL-2, IL-6, IFN-γ, $CD56^+$, cell number, natural killer cell activity and low-level IL-1, and TNF-α level when compared to the baseline value and after treatment value. This process cumulatively escalated the immune response in cancer patients [122]. However, branching pattern of monomers and solubility of these polysaccharides was found to be the limiting factor for anticancer activity [123].

Cancer, aging, and atherosclerosis have been known since long to be associated with oxidative stress thus making the role of anti-oxidants imperative. Polysaccharides and their derivatives have been reported to possess antioxidant effect with the ability to reduce oxidative stress and providing beneficial results in various disorders [124]. Moreover, polysaccharides enriched extract have been observed to reduce lipid peroxidation and blood glucose level in diabetic rats [125, 126] and the exposed polysaccharide1 (PSG-1) appreciable antioxidative activity through biochemical assays further supports their potential to overcome the oxidant stress [127]. Amino-polysaccharides (G009) fraction has shown significant free radical scavenging activity against iron-induced lipid peroxidation in rat brain as well as against hydroxyl radicals and superoxide anions. It decreases the breakage of ϕX174 supercoiled DNA and attenuates differentiated human promyelocytic leukemia (HL-60) cells by UV-induced photolysis of hydrogen peroxide [128]. Recent clinical studies have found that polysaccharide fractions induce the insulinotropic

and anti-hyperglycemic effect in type-II diabetic patients [129, 130]. Ganoderans A, B, and other polysaccharides have been observed to show potent hypoglycemic results in normal and alloxan-induced hyperglycemic mice. Ganoderans B amplified hyperinsulinemia conditions irrespective of the normal and glucose loaded physiology of mice but interestingly reduced the glycogen content without altering the hepatic/plasma cholesterol profile or the insulin binding to the adipocyte cell [131]. Delving deeper into its mechanism has revealed its ability to increase hepatic glucokinase, phosphofructokinase, and glucose-6-phosphate dehydrogenase and simultaneously, decreases the catalytic activity of hepatic glucose-6 phosphatase, glycogen synthetase and phosphoenolpyruvate carboxykinase (PEPCK) gene expression signifying the behavior of ganoderans B in the glycolytic pathway. It is now well-stated fact that diabetic complications induce cardiopathy and nephropathy that is mainly manifested by the aberrant glycosylation in cardiac, smooth muscle cells and nephron [132]. Ganoderic polysaccharides attenuate the myocardial collagen cross-linking, advanced glycation end product (AGE), augmenting the antioxidant enzyme activities in diabetic rats [133, 134]. On the other hand, decreasing triglyceride and glucose levels in diabetic nephropathy in mice, thus highlighting their invaluable role as hypoglycemic in diabetes associated complication [135]. Furthermore, Fenglin Li and his group evaluated the hypoglycemic effect of *Ganoderma* polysaccharides exhibiting dominant anti-diabetic role. The study performed by the research group revealed that polysaccharides increased the serum insulin level, at the same time, decreasing total cholesterol, triglyceride, and low-density lipoprotein. These events taken together significantly increased the level of high-density lipoprotein cholesterol which is beneficial in humans [136]. Polysaccharides extract also reduce LPS-induced adhesion molecule expression and monocytes adherence [137]. Besides, its immunomodulating actions, they exhibit moderate anti-viral activity, especially in herpes simplex virus such as proteoglycan of *Ganoderma* encumber the viral replication, viral adsorption and its entry into the target cells [138]. GLPs like GLhw, GLhw-01, GLhw-02, and GLhw-03 have been validated for their antiviral activities against herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2). These polysaccharides are also capable of being administered as potential therapeutics against aging and age-related neurodegeneration [139].

Ganoderma lucidum proteins

Amino acid content in the *Ganoderma* spores has been found to be higher than the fruiting bodies. In a study carried out by Wang and research group, it was estimated that crude extract of GL contains 15.6 % proteins [140]. In this study, the crude extract of Reishi, prepared by alkaline precipitation, was dissolved in hydrochloric acid and trifluoroacetic acid which on heating to 140 °C affected the dry residue used for the analysis. The amino acid composition was, thus, analyzed by the method given by Spackman and his team [140, 141].

Proteins are the chief actors within the cell, carrying out the information encoded by the genes. The diversity of the proteins in terms of functioning is based on the ability to bind other molecules specifically and tightly. Proteins isolated from *Ganoderma* display plethora of biological activities by utilizing different adapter proteins at different stages of immune modulation, inflammation, and cancer signaling. These immune-modulatory proteins or GMI decreases the TNF-α induced matrix metalloproteinase-9 phosphorylation and the degradation of IκBα resulting in suppression of phosphorylation along with nuclear translocation of p65 in the NF-κB signaling in non- small cell lung cancer cell line (NSCLC; A549) [142].

Ganoderma protein LZ-8 is the first immunomodulatory protein which was isolated from the mycelial extract by employing chromatographic and electrophoretic techniques [143]. Although, LZ-8 is physicochemically stable enough to withstand the harsh pH, it is highly susceptible to a temperature above 55 °C. Different techniques such as gel filtration, ion-exchange, affinity chromatography, SDS-PAGE have been employed for the isolation of LZ-8, lectin (low sugar content), LZP-1, LZP-2, and LZP-3 protein for different properties. Denaturation or native state does not affect the anti-inflammatory activity of LZ-8 [144]. In addition to its role as an immunomodulator, it exhibits anti-inflammatory activity supported by enhanced expression of CDllb brought about by exerting its effect on modulating adhesion molecules on immune-competent cells [145]. It also affects another functionality of inflammatory immune sub-cellular protein i.e., FOXP3+ (indispensable for the control of pathogenic autoreactivity and maintenance of immune homeostasis) via CD45-dependent pathway and elevates acute intestinal inflammation [146]. Furthermore, the application of ribosomal DNA (rDNA) technology also assisted in the retrieval of recombinants LZ-8 (rLz-8) obtained through rDNA technology. It activate p53, p21 induced ribosomal protein S7-MDM2-p53 and also induce cell cycle arrest at G1 phase in p53 dependent cells in lung cancer cell proliferation [147]. It also induces autophagy, enhances ER stress and the ATF4-CHOP (activating transcription factor 4-C/EBP homology protein pathway). Among the synthetic or naturally derived drug known till now, *Ganoderma* is the first natural product to exhibit selectivity towards this target ER. rLz-8 also leads to the activation of the ubiquitin/proteasome ER-associated degradation (ERAD) system switch to over-autophagic response in the human gastric cancer cell line SGC-7901 that cause cell death [148]. These proteins also have been reported for their cardiotonic effects attributed to the various anti hypertensive-related proteins produced by the

mycelial part of *G. lucidum*. These proteins are known to possess diuretic as well as anti-angiotensin converting enzyme functionality include cystathionine beta synthase-like protein, paxillin like protein, and alpha/beta hydrolase-like protein DEAD/DEAH box helicase-like protein [149].

Microspherule protein (MSP58) present in *Ganoderma* represses human telomerase reverse transcriptase (hTERT) gene expression and cell proliferation by interacting with telomerase transcriptional element-interacting factor (TEIF) [150]. In addition to LZ-8 from *G. lucidum*, another fungal immunomodulatory protein FIP-gts has been isolated from allied genus, *Ganoderma tsugae*. This protein transcriptionally inhibits telomerase in the A549 non-small lung cancer cells by suppressing telomerase activity and inhibiting the catalytic activity of telomerase (hTERT), thereby further preventing the binding of c-*myc* nuclear transcriptional factor to E-box sequence on the hTERT promoter, proving to be a promising chemopreventive agent [151]. Another novel protein, lectins (glycoproteins that bind carbohydrates) which are hexameric with a molecular weight of 114 kDa were isolated from the fruiting body. Lectins have been found to exhibit the mitogenic potential of the mouse splenocytes and antiproliferative activity towards leukemia cells and hepatoma cells [152].

Clinical trials

Despite extensive research on medicinal mushrooms, these are still lacking in strong clinical data. Clinical trials of GL have been performed on cancer, Type II diabetes, coronary heart disease, chronic hepatitis B, and neurasthenia [153]. In a study carried out over a period of 12 weeks in humans with Type II diabetes, hypoglycemic activity was observed, along with improved immunity against chronic hepatitis B infection. It was noted that dose–response in case of cancer patients depended on the stage of cancer and was devoid of any objective response during the late stage [153]. The meta-analysis results demonstrated a more positive outcome with combinatorial effect of GL with chemo/radiotherapy as compared to chemo/radiotherapy or GL administered individually (RR 1.50; 95 % CI 0.90 to 2.51, $P = 0.02$). Combination therapy increased CD3, CD4 and CD8 by 3.91, 3.05, and 2.02 %, respectively, with little increase in leukocyte, NK-cell activity and CD4/CD8 ratio [154]. Furthermore, phase I/II clinical trials were performed for Ganopoly to assess its safety profile in the treatment of chronic hepatitis B in ninety patients. Among 90 human patients, 78 who fulfilled the criteria were selected for further tests. These patients were administered Ganopoly for 12 weeks, at the end of which, Ganopoly was observed to be well tolerated and active against hepatitis B virus (HBV) in patients with chronic hepatitis B [155]. Another controlled study was carried out in 16 humans to evaluate the safety and tolerance of oral administration of *G. lucidum*. After administration, no change in levels of CD4, CD8, and CD19 cells were observed [156]. In a study with *G. lucidum* extract, different extracts were administered for 12 weeks to 88 men (over 49 years) suffering from low to moderate lower urinary tract symptoms (LUTS). Subsequent evaluation of International Prostate Symptom Score (IPSS) revealed a well-tolerated and effective treatment without any side effect [157]. Thus, it was concluded that GL and its bio-constituents exhibit commendable therapeutic potency but require a more detailed study to outline a mechanistic approach for combating different anomalies.

Side effects

Ganoderma potently exhibits wide ranges of bioactivities, but akin to other natural products are not completely devoid of side effects. *Ganoderma* derived natural products have been observed to exhibit mild side-effects ranging from short to long term [42]. Literature survey reveals numerous in vivo and in vitro tests conducted to ascertain the toxicity of the various dosage forms of *Ganoderma* derivatives. Most of the available dosage forms such as spore powder capsule, freeze dried powder, soup, syrup, and tablets or in solution form display dose-dependent activities with their toxicities varying with the dosage of ingestion. The oral dosages (1.5 g/day) have been seen to cause mild side-effects, such as sleepiness, thirst, rashes, bloating, frequent urination, that occur as a consequence of its detoxifying effect [158]. *G. lucidum* extract was administered to 88 men (over 49 years) suffering from low to moderate lower urinary tract symptoms (LUTS) for 12 weeks. Subsequent evaluation of International Prostate Symptom Score (IPSS) revealed a well-tolerated and effective treatment devoid of side effect [157]. Among the extracts, alcoholic extract (1.2 and 12 g/kg daily during 30 days) of *Ganoderma* showed no effect on major organs growth and development. Co-treatment of lithium, perphenazine, and trihexyphenidyl with *Ganoderma* boiled slices was used in treating schizophrenia in 47-year old women without any side effects. Changing of boiled *Ganoderma* to capsule form (400 mg/day) resulted in jaundice and coma due to fulminant hepatitis [159]. This medicinal mushroom is renowned for its stimulatory immune response and inhibiting platelets aggregation which may also hamper the signaling cascade of immunosuppressive therapies such as aspirin or warfarin drugs useful in controlling different anomalies [160]. *Ganoderma* shows allergenicity to pollen and basidiocarp, the major contributor of aeroallergens.

Conclusion

Ganoderma lucidum, a basidiomycete's fungus, owing to its indisputable multi-facetedness and versatility has of late successfully reversed its "neglected" status. This natural product accredited with a broad spectrum of activity, is well-defined as a large reservoir of indispensable mycoconstituents, mainly encompassing ganoderic acid along with its alcoholic derivatives, polysaccharides, and proteins. This review has been put forward with a motivation to congregate the information obtained about the fungus over the last few years. This endeavor highlighted the determining properties it possesses and the significant bioactivities it exhibited. Portraying myriad activities, attributed to the lanosteroidal skeleton, ganoderic acid has proven to be a momentous constituent. *Ganoderma* formulation, GAIN, possessing superior efficacy and toxicity lowering property has irrefutably become a panacea for life-threatening diseases. In addition, *G. lucidum* is known to be a fundamental participant in various signaling cascades proving to be an efficacious and consequential entity to target various signaling mechanisms going awry in cancer. In future, in silico and structure-associated relationship (SAR) studies, if and when, carried out may prove to be an important platform to reveal new mycoconstituents which could be classified as FDA approved drugs. Moreover, there is an urgent need to delve deeper to explore more regarding proteins and their structure, interaction, folding, known to play a tantamount role in a various drug interactions.

GA ganoderic acid, GL *Ganoderma lucidum*, GAIN ganoderic acid-infused nanoparticles, MDR multi-drug resistance, GLP *Ganoderma lucidum* polysaccharides, RTKs receptor tyrosine kinases, NF-κB nuclear factor kappa-light-chain-enhancer of activated B cells, uPAR urokinase-type plasminogen activator receptor, TNF tumor necrosis factor, PI3K phosphatidylinositol 3-kinase, PIP2 phosphatidylinositol biphosphate, PIP3 phosphatidylinositol (3,4,5)-triphosphate, PTEN phosphatase and tensin homolog, PDK1 3-phosphoinositide-dependent protein kinase 1, PKC protein kinase C, S6K ribosomal protein S6K, SGK serine/threonine-protein kinases, ASK1 apoptosis signal-regulating kinase 1, FKHR forkhead protein, MDM2 mouse double minute 2 homolog, GSK3β glycogen synthase kinase 3 beta, mTORC1 mammalian target of rapamycin complex 1, 4EBP eIF4E-binding protein, mTORC2 mTOR Complex 2, HIF-1α hypoxia-inducible factor 1-alpha, NKC natural killer cells, NTF nuclear transcription factor, STAT3 signal transducer and activator of transcription 3, FPP farnesyl pyrophosphate, IL interleukin, ECM extracellular matrix, MMP matrix metalloproteinase, ERAD endoplasmic reticulum-associated degradation, PKC protein kinase, CTL cytotoxic T-lymphocyte, PPP protein prenyltransferase, PARP poly (ADP-ribose) polymerase, GDNT ganodermanontriol, APC antigen promoting cells, PEPCK phosphoenolpyruvate carboxykinase, AGE advanced glycation end product, NO nitric oxide, hTERT human telomerase reverse transcriptase

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Compliance with ethical standards

Conflicts of interests None

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