Published in final edited form as:

Anticancer Agents Med Chem. 2018 ; 18(5): 667–674. doi:10.2174/1871520617666171113121246.

Ganoderma lucidum Polysaccharides as an anti-cancer agent

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Abstract

The mushroom *Ganoderma lucidum* (*G. lucidum*) has been used for centuries in Asian countries to treat various diseases and to promote health and longevity. Clinical studies have shown beneficial effects of *G. lucidum* as an alternative adjuvant therapy in cancer patients without obvious toxicity. *G. lucidum* polysaccharides (GLP) is the main bioactive component in the water soluble extracts of this mushroom. Evidence from *in vitro* and *in vivo* studies has demonstrated that GLP possesses potential anticancer activity through immunomodulatory, anti-proliferative, pro-apoptotic, anti-metastatic and anti-angiogenic effects. Here, we briefly summarize these anticancer effects of GLP and the underlying mechanisms.

Keywords

Ganoderma lucidum polysaccharides; Reishi; anti-cancer; immunomodulatory; anti-proliferative; pro-apoptotic; anti-metastatic; anti-angiogenic

1. INTRODUCTION

Ganoderma lucidum (*G. lucidum*) is a kind of mushroom, which belongs to *Ganodermataceae* family and is known as *Lingzhi* in China and *Reishi* in Japan. It has been commonly referred as the “mushroom of immortality”, “mushroom of spiritual potency”, and “spirit plant” [1–2]. Due to its magical medicinal properties such as tonifying effects, enhancing vital energy, and strengthening cardiac function, *G. lucidum* has been used as a traditional Chinese medicine for promoting good health, perpetual youth, vitality, and longevity for thousands of years [3–6].

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CONFLICT OF INTEREST

No potential conflicts of interest were disclosed.

G. lucidum is listed in American Herbal Pharmacopoeia and Chinese Pharmacopoeia. According to Chinese Pharmacopoeia, *G. lucidum* acts to restore *Qi* ("life energy" or "life force" in traditional Chinese medicine) ease the mind, and relieve cough and asthma, so it is recommended for the treatment of dizziness, insomnia, palpitation, and shortness of breath [7]. Modern medicinal studies have demonstrated that this mushroom possesses a broad range of bioactivities, including anti-inflammatory, anti-oxidant, anti-glycemic, anti-ulcer, anti-cancer, and immunostimulating effects [8–13]. Hence, *G. lucidum* has been used to treat a variety of chronic diseases such as hepatopathy, nephritis, hypertension, arthritis, migraine, insomnia, bronchitis, asthma, diabetes and cancer [6, 14]. Especially, it has also been recognized as an alternative adjuvant therapy for cancer and diabetes [11, 15].

G. lucidum contains a wide variety of constituents such as glycoproteins, polysaccharides, triterpenoids, meroterpenoids, sesquiterpenoids, steroids, alkaloids, benzopyran derivatives, and benzoic acid derivatives [16, 17]. It also contains some minerals, e.g. potassium, calcium, phosphorus, magnesium, selenium, iron and zinc [6]. The composition of *G. lucidum* extracts depends on whether polar or apolar solvents are used for extraction. Polysaccharides and triterpenes are the main constituents of polar and apolar extracts, respectively. It has been found that the anticancer properties of *G. lucidum* are primarily attributed to its polysaccharides and triterpenes [6, 18, 19]. *G. lucidum* polysaccharides (GLP) is composed of (1→3), (1→6)-α/β-glucans, glycoproteins and water soluble heteropolysaccharides [17]. GLP executes the anti-cancer actions through inhibiting tumor growth and metastasis, as well as boosting immune function of patients, by various mechanisms, such as anti-proliferative, pro-apoptotic, anti-metastatic, anti-angiogenic, anti-inflammatory, anti-oxidant, and immunomodulatory effects (Fig 1) [20–22]. This review will focus on discussing the anticancer effects of GLP and the underlying mechanisms.

2. ANTICANCER EFFECTS OF GLP

2.1. Immunomodulatory effect

Host immune surveillance plays a crucial role in recognizing and destroying not only invading pathogens but also host cells that become cancerous, so immunotherapy has become one of the major strategies for cancer prevention and treatment [23, 24]. Accumulating evidence implicates that GLP exerts the anticancer action in part by stimulating the immune function [20, 21, 25]. This is primarily attributed to the fact that GLP can activate T and B lymphocytes, macrophages, dendritic cells (DCs) and natural killer (NK) cells, which promotes proliferation of lymphocytes, enhances phagocytosis, increases production of cytokines, and augments NK cell-mediated cytotoxicity (Fig 2) [8, 14, 18, 25, 26].

2.1.1. Effect of GLP on T lymphocytes—T lymphocytes (also known as T cells) are essential for cellular immunity. There are several subtypes of T cells with distinct functions, such as T helper cells, cytotoxic T cells, memory T cells, suppressor T cells, natural killer T cells, and mucosal associated invariant T cells [27]. Numerous studies have suggested that GLP is an activator of T lymphocytes. It has been described that treatment with GLP significantly promotes concanavalin A (ConA)-induced mouse lymphocyte proliferation and

IL-2 production [28]. GLP can also enhance the DNA synthesis in mouse spleen cells in a mixed lymphocyte culture by inducing the expression of DNA polymerase α [29]. GLP increases the expression of IFN-γ in the T-lymphocytes [30] and IL-1, IL-2, and IFN-γ in mouse spleen cells [31]. GLP increases the production of inositol triphosphate (IP_3) and diacylglycerol (DAG) in resting T cells, although it does not influence the production of IP_3 and DAG in ConA-activated T cells [32], suggesting that both IP_3/Ca^{2+} and DAG/ protein kinase C (PKC) pathways may be involved in the immunomodulatory effect of GLP on T cells. Further studies have shown that GLP can activate both PKC and protein kinase A (PKA) in murine T cells [33].

B16F10 melanoma cells can secrete a large amount of interleukin 10 (IL-10), transforming growth factor β1 (TGF-β1) and vascular endothelial growth factor (VEGF) in the cell culture medium. It has been shown that treatment with the B16F10 cell culture supernatant prevents phytohemagglutinin (PHA) from stimulating the production of perforin and granzyme B, as well as the proliferation in lymphocytes. Interestingly, addition of GLP can fully or partially antagonize the inhibitory effects of the B16F10 cell culture supernatant on lymphocytes [34]. GLP also prevents B16F10 cells from reducing the expression of CD71 and Fas ligand (FasL) in lymphocytes [35]. Furthermore, the plasma of lung cancer patients inhibits proliferation, CD69 expression, and perforin and granzyme B production in lymphocytes activated by PHA, which can also fully or partially reversed by GLP treatment [36]. GLP treatment of the co-culture of B16F10 melanoma cells and lymphocytes increases the production of CD69 (a co-stimulatory molecule for T cell activation and proliferation), FasL and interferon (IFN)-γ in the medium [26].

2.1.2. Effect of GLP on B lymphocytes—B lymphocytes (also known as B cells) play an important role in the humoral immunity. Different from T or NK cells, B cells express B cell receptors on their cell membrane, which allow the B cell to bind a specific antigen and produce an antibody against the antigen. Besides, B cells also present antigen and secrete cytokines [37]. GLP can activate B cells by increasing their proliferation and differentiation [4]. It has been reported that GLP not only increases the percentage of B cells by 2.5–4 fold, but also increases the size of B cells [38]. Similarly, *in vivo* treatment with GLP also activates spleen and bone marrow-derived B lymphocytes from sarcoma S180 bearing mice, and induces proliferation of the B cells and production of large amounts of immunoglobulins in mice [39]. Mechanistically, GLP can induce the expression CD71 and CD25 on B cell surface, and increase the secretion of immunoglobulins by B cells, through directly stimulating the expression of PKCα and PKCγ in B cells [38].

2.1.3. Effect of GLP on DCs—DCs are important professional antigen-presenting cells, which are necessary for the initiation of primary immune response of both helper and cytotoxic T lymphocytes [40]. GLP has the ability to stimulate the maturation of normal human monocyte-derived DCs and leukemic monocyte-derived DCs [5, 8, 41]. GLP increases cell-surface expression of CD80, CD86, CD83, CD40, CD54, and human leukocyte antigen-DR (HLA-DR) [42]. It also enhances the production of IL-12 p70, IL-12 p40, and IL-10 [43]. The GLP-induced activation and maturation of human monocyte-derived DCs are mediated by the nuclear factor kappa-light-chain-enhancer of activated B

cells (NF-κB) and p38 mitogen-activated protein kinase (MAPK) pathways [44]. GLP (0.8, 3.2, or 12.8 mg/ml) increases the co-expression of CD11c and I-A/I-E molecules on the surface of cultured bone morrow derived DCs [45]. It elevates mRNA expression of cytokine IL-12 p40 in DCs and increases protein production of IL-12 p40 in culture supernatants. GLP also enhances the lymphocyte proliferation of mixed lymphocyte culture induced by mature DCs [41]. Treatment of leukemic monocytic cell-lines THP-1 and U937 with GLP (100 μg/mL) significantly increases the expression of HLA-DR, CD40, CD80 and CD86 [8]. GLP induces the differentiation of THP-1 leukemia cells to macrophage-like cells by enhancing cell adherence, superoxide production, cell cycle arrest and expression of differentiation markers such as CD11b, CD14, CD68, matrix metalloproteinase-9 (MMP-9) and myeloperoxidase. Also, GLP-induced activation of caspases and p53 contributes to this differentiation [46].

2.1.4. Effect of GLP on macrophages—Macrophages are the “big eaters” of the immune system, which engulf and digest apoptotic cells and pathogens (called phagocytosis), and produce immune effector molecules [47]. *In vivo* treatment with GLP activates bone marrow-derived macrophages from sarcoma S180-bearing mice, resulting in production of immunomodulatory substances, such as IL-1β, TNF-α and nitric oxide (NO) [39]. GLP increases phagocytosis of macrophages significantly, and enhances the macrophage-mediated tumor cytotoxicity. Also, GLP activates macrophages *in vitro*, and increases the levels of various cytokines including IL-1β, tumor necrosis factor (TNF)-α, IFN-γ and IL-6 in the culture medium [48]. GLP has been shown as an inducer of MAPKs- and Syk-dependent TNF-α and IL-6 secretion in murine resident peritoneal macrophages. Dectin-1 is stimulated by GLP, but toll like receptor (TLR)-4 signaling is not involved in biological activities of GLP [49]. However, this is controversial, since GLP has been found to directly bind to TLR-4, mIg of B cells, 7S ribosomal protein, and bZIP enhancer [50], and to transduce certain signalings via the TLR-4 [3]. Apart from the effects of GLP on the expression of the cytokines and chemokines mentioned above, GLP also induces the expression of inflammatory cytokine IL-1, which, in part, links to its anticancer activity. It has been described that GLP up-regulates the secretion of IL-1, and the expression of pro-IL-1 (precursor of IL-1) and IL-1-converting enzyme in human macrophages and murine macrophages (J774A.1). This is attributed to the activation of protein tyrosine kinase/protein kinase C/MEK1/extracellular signal-regulated kinase (ERK) and protein tyrosine kinase/Rac1/p21-activated kinase/p38 pathways [3].

2.1.5. Effect of GLP on NK cells—NK cells, unlike cytotoxic T-cells, can recognize stressed cells in the absence of antibodies and major histocompatibility complex (MHC), allowing for a much faster immune reaction, so NK cells are critical to the innate immunity [51]. It has been shown that treatment with GLP increases the population of $CD14^+CD26^+$ monocyte/macrophage, $CD83^+CD1a^+$ DCs, and $CD16^+CD56^+$ NK cells by 2.9, 2.3, and 1.5 fold, respectively, in human umbilical cord blood mononuclear cells. Also, GLP enhances NK cell-mediated cytotoxicity by 31.7% [52]. Oral administration of *G. lucidum* extract increases the levels of T-helper type 1 and macrophage cytokines (IL-6 and IFN-γ), and enhances the NK cell activities and phagocytosis in BALB/c mice [25, 53]. A GLP fraction binds to TLR-4 receptor and activates ERK, c-Jun N-terminal kinase (JNK) and p38 MAPK.

GLP can stimulate the expression of IL-1, IL-6, IL-12, IFN-γ, TNF-α, granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte-colony stimulating factor (G-CSF) and macrophage colony-stimulating factor (M-CSF) in mouse splenocytes [18]. In addition, a GLP fraction increases in the number of DCs as well as CD4, CD8, regulatory T, B, plasma, NK and natural killer T (NKT) cells in the spleen of mice. *In vivo* treatment of mice with this fraction elevates the levels of 12 cytokines and chemokines including KC (CXCL1), MCP-1 (CCL2), IL-6, MIP-1β (CCL3), IL-1 β, IL-12p40, IL-12p70, RANTES (CCL5), IL-1α, TNF-α, IL-10, and IL-13 in the serum of mice [42, 53].

G. lucidum mitigates cyclophosphamide-induced decrease in body weight, NK activity, IFN-γ production, and cytotoxic T lymphocyte activity, and inhibits the abnormal increase or decrease in IL-4 level due to cyclophosphamide administration [54]. Chronic administration of 2.5 mg/kg GLP accelerates recovery of bone marrow cells, red blood cells and white blood cells, as well as splenic NK cells and NKT cells, and enhances T and B cell proliferation responses compared to the treatment with vehicle. It also augments the phagocytosis and cytotoxicity of macrophages without any obvious side effect. Thus, the low-dose GLP treatment accelerates the recovery of immunosuppressed mice from leukopenia, myelosuppression and immunosuppression, which should be beneficial to cancer chemotherapy [55].

2.2. Anti-proliferative and pro-apoptotic effects on tumor cells

Increasing evidence has suggested that GLP functions as an anticancer agent not only by stimulating the immune response, but also by displaying direct cytostatic and cytotoxic effects on tumor cells (Fig 3) [14]. It has been described that GLP inhibits proliferation of mouse melanoma cells (B16F10), rat adrenal medulla pheochromocytoma cells (PC12) [56, 57] and human bladder cancer cells (HUC-PC and MTC-11) [58]. GLP down-regulation of cyclin D1 is associated with the growth inhibition and cell cycle arrest in human ovarian OVCAR-3 cells [59]. Studies have also revealed that both phosphoinositide 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) and MAPK signaling pathways are involved in the anticancer effect of GLP. For instance, GLP reduces the expression of some signaling molecules in the PI3K/AKT/mTOR and MAPK pathways at both gene and protein levels. Treatment of inflammatory breast cancer cells (SUM-149) with the commercial GLP (Pharmanex ReishiMax GLp™) down-regulates the expression of mTOR downstream effectors at early time points of treatment *in vitro*. Particularly, GLP reduces the level of eukaryotic initiation factor (eIF) 4G (eIF4G), increases the binding of eIF4E to eIF4E-binding protein 1 (4E-BP1), and decreases the formation of eIF4F complex, thereby inhibiting protein synthesis [60].

Also, GLP has been found to reduce cell viability in human colon cancer cells (HCT-116 and SW 480) in a concentration-dependent manner [61, 62]. GLP can induce apoptosis by enhancing the release of lactate dehydrogenase (LDH) and increasing the level of intracellular Ca^{2+}, leading to activation of Fas-mediated caspase, mitochondrial and JNK pathways in HCT-116 cells [61, 63]. A GLP fraction triggers apoptosis in THP-1 leukemia cells by up-regulating expression of death receptor (DR3 and DR4/5) ligands (TNF-α and

TRAIL), resulting in death receptor oligomerization, recruitment of specialized adaptor proteins, and the activation of caspase pathway [64].

A commercial *G. lucidum* extract, Ganopoly®, at 10 mg/ml, shows a remarkable cytotoxic effect on CaSki, SiHa, Hep3B, HepG2, HCT116, and HT29 cells [20]. Treatment with another commercial *G. lucidum* extract, ReishiMax GLp®, at 0.5 or 1.0 mg/ml, dramatically reduces the cell number of inflammatory breast cancer cells (SUM-149) by 67% and 98%, respectively, whereas treatment with ReishiMax GLp® does not alter the cell number of noncancerous mammary epithelial cells (MCF10A) at 0.5 mg/ml, and only slightly (by 11%) decreases the number of MCF10A at 1.0 mg/ml [65] suggesting the tumor selective effect of GLP. GLP induces apoptosis of SUM-149 and suppresses tumor spheroid formation, which is correlated with the reduced expression of some key proteins responsible for tumor survival and invasion such as BCL-2, BCL-xL, eIF4G, E-cadherin, MMP-9, p120-catenin and c-Myc in the cells [65].

Oral administration of *G. lucidum* extract (at a dose of 28 mg/kg/day) for 13 weeks does not obviously affect the body weight of mice, but inhibits breast SUM-149 xenograft volume and tumor weight by 58% and 45%, respectively [60]. This is related to reduced expression of E-cadherin, mTOR, eIF4G, and p70 S6 kinase (S6K), and activity of ERK1/2. Administration of GLP (100 mg/kg) 24 h after tumor implantation with Ehrlich's ascites carcinoma cells shows 80.8 and 77.6% reduction in tumor volume and tumor mass, respectively; while administration of GLP at the same dose before tumor inoculation exhibits 79.5 and 81.2% inhibition of tumor volume and tumor mass, respectively [66]. Different administration protocols of GLP can lead to up to 60 % inhibition of S180 xenografts in mice without obvious adverse effect on body weight [39, 53]. In Yoshida AH-130 ascites hepatoma cells implemented mice, administration of an aqueous extract of *G. lucidum* reduces the tumor weight in a dose dependent manner compared to the control group, with inhibition rates of 25% and 47% at 200 and 400 mg/kg, respectively [67]. GLP significantly suppresses tumor growth in hepatoma-bearing mice associated with an increase of the ratio of regulatory T cell (Treg) and effector T cell (Teff). Moreover, GLP induces miR-125b expression and attenuates the inhibitory effect of Treg on Teff proliferation by increasing IL-2 secretion [68].

Of interest, it has been noticed that mice immunized with an L-fucose enriched GLP fraction is able to produce IgM antibodies specific to tumor-associated glycans, which have cytotoxicity and reduce the production of tumor-associated inflammatory mediators in murine Lewis lung carcinoma cells [69]. In addition, *in vivo* administration of GLP increases the Con A-induced proliferative response of splenocytes and induces anti-tumor activity against Lewis lung cancer in mice [49].

In addition, GLP can enhance the anti-cancer effects of chemotherapeutic agents. For instance, combination of GLP and chemotherapeutic agents (cisplatin and arsenic trioxide) displays synergistic cytotoxicity in human urothelial carcinoma cells including parental NTUB1; cisplatin-resistant, N/P(14); and arsenic-resistant, N/As (0.5). It has been proposed that GLP enhances the cytotoxicity of these compounds by activation of p38 MAPK, down-regulation of AKT and XPA, induction of Fas, activation of caspases 3/8, up-regulation of

BAX and BAD, down-regulation of Bcl-2 and Bcl-xL, and increase of cytochrome c release [70]. Besides, combination of cyclophosphamide and *G. lucidum* has been found to inhibit tumor growth more potently than cyclophosphamide alone in MM 46-bearing mice [54]. This is attributed to GLP's alleviation of cyclophosphamide-induced decrease in body weight, NK activity, IFN-γ production, and cytotoxic T lymphocyte activity, and inhibition of cyclophosphamide-induced abnormal expression of IL-4.

2.3. Anti-metastatic effect on tumor cells

Cancer metastasis, one of the characteristics of malignant tumors, is the primary cause of death in most cancer patients. Tumor cell migration is a prerequisite for metastasis [71]. Thus, targeting tumor cell motility has received great attention for cancer therapy. Studies have shown that GLP can inhibit tumor cell motility and invasion *in vitro* and tumor metastasis *in vivo* (Fig 4). For example, GLP inhibits cell adhesion and/or motility in HCT-116 [63], human lung carcinoma PG cells [22], and MT-1 human breast carcinoma cells [72]. GLP inhibits cell adhesion in MT-1 breast cancer cells by reducing β1-integrin expression [72]. The water extract of *G. lucidum* inhibits cell motility in breast MDA-MB-231 and prostate PC-3 cancer cells in a concentration-dependent manner [73]. This is associated with inhibition of constitutive activation of NF-κB and AP-1, reducing the expression of the urokinase-type plasminogen activator uPA and the uPA receptor (uPAR) in the cells. Besides, GLP inhibits oxidative stress-induced migration of MCF-7 cells by suppressing ERK1/2 signaling, resulting in down-regulation of c-fos expression and inhibition of NF-κB and AP-1 [74]. GLP also inhibits 4-aminobiphenyl-induced migration, by inducing actin polymerization and focal adhesion complex formation in human bladder cancer cells (HUC-PC and MTC-11) [58]. Reishi extract, ReishiMax GLp®, inhibits cell invasion by downregulation of MMP-9 [65]. In a Lewis lung carcinoma cell mouse xenograft model, administration of cyclophosphamide increases metastasis of the tumor cells to the lung in C57BL/6 mice, which can be effectively suppressed by pre-feeding with the *G. lucidum*-containing diet [54].

2.4. Anti-angiogenic effect

Angiogenesis refers to the formation of new blood vessels from pre-existing vessels, which plays a key role in promoting tumor growth and metastasis [75]. Thus, targeting angiogenesis has become an attractive intervention for cancer therapy. Many studies have demonstrated that GLP has the ability to inhibit angiogenesis. It has been shown that GLP suppresses VEGF overexpression and tumor angiogenesis in metastatic mouse melanoma B16F10 cells *in vitro* and Yoshida AH-130 ascites hepatoma xenografts *in vivo* [34, 67]. GLP peptide markedly reduces the microvessel formation as detected by chorioallantoic membrane assay [76]. A *G. lucidum* extract (standardized to 13.5% polysaccharides and 6% triterpenes) suppresses prostate-cancer dependent angiogenesis by inhibiting the secretion of VEGF and TGF-β1. This is through by inhibiting AKT/ERK-mediated AP-1 activity [77].

GLP peptide inhibits angiogenesis by directly inhibiting cell proliferation of human umbilical cord vascular endothelial cells (HUVEC) [76]. GLP peptide can also directly induce cell death of HUVEC by reducing Bcl-2 anti-apoptotic protein expression and increase Bax pro-apoptotic protein expression. Furthermore, GLP peptide treatment

decreases the secretion of VEGF in human lung carcinoma cells under hypoxia condition [78]. The above results suggest that GLP peptide inhibits angiogenesis through directly inhibiting cell proliferation and inducing cell death in vascular endothelial cells, as well as by indirectly suppressing VEGF production in tumor cells.

2.5. Anti-inflammatory effect

Chronic inflammation triggers cellular events that can promote malignant transformation of cells and carcinogenesis [79]. Several inflammatory mediators, such as TNF-α, IL-6, TGF-β, and IL-10, have been shown to participate in both the initiation and progression of cancer [80]. GLP possesses anti-inflammatory effect in a dose-dependent manner. Administration of GLP (100 mg/kg) results in 58% inhibition of inflammation, as evaluated by carrageenean-induced (acute) and formalin-induced (chronic) inflammation assays [66].

2.6. Anti-oxidant effect

GLP possesses potent scavenging activities against O_2^-, SO, $HO^{\cdot}$, H_2O_2, and 2,2-diphenyl-1-picrylhydrazyl (DPPH) *in vitro* and *in vivo* [56, 81]. It has been shown that 5 mg/ml of GLP extract can reduce DPPH radical strikingly within 2 minutes and completely scavenge the radical in 15 minutes [62]. GLP extract induces the superoxide dismutase (SOD), catalase, phase II detoxification enzyme NAD(P)H:quinone oxidoreductase 1 (NQO1) and glutathione S-transferase P1 (GSTP1) via the Nrf2-mediated signaling pathway in colorectal cancers *in vitro* [59]. GLP also enhances the activities of SOD, and glutathione peroxidase, and reduces the malonaldehyde level *in vivo* in a dose-dependent manner either in mice exposed to γ-irradiation or rats with cervical carcinoma [81, 82].

2.7. Other activities related to cancer

GLP protects mouse bone marrow from ^{60}Co γ-irradiation, and diminishes the occurrence of micronuclei as a sign of γ-irradiation induced DNA damage in the bone marrow [82]. It has been observed that a GLP fraction possesses radio-protective activity and facilitates DNA repair, which may be attributed to its antioxidant effect [83]. Furthermore, a *G. lucidum* extract (SunRecome®) decreases cisplatin-induced kaolin intake dose-dependently as a reflection of cisplatin's nausea and vomiting action. It also alleviates cisplatin-induced food intake reduction in rats in a dose dependent manner [84].

3. CLINICAL STUDIES RELATED TO ANTICANCER EFFECTS OF GLP

GLP administration increases immune responses in patients with advanced-stage cancer. In a non-randomized open clinical trial, 74 advanced colorectal cancer patients were administered GLP at a dose of 5.4 g/day for 12 weeks. It was found that treatment with GLP increased the mitogenic reactivity to PHA, counts of CD3, CD4, CD8 and CD56 lymphocytes, plasma concentrations of IL-2, IL-6 and IFN-γ, and activity of NK, but decreased plasma concentrations of IL-1 and TNF-α [15]. In another clinical trial, 34 advanced-stage cancer patients were given 1,800 mg Ganopoly® (GLP extract) three times daily for 12 weeks. This resulted in an increase in the mean plasma concentrations of IL-2, IL-6, and IFN-γ, and a decrease in the plasma levels of IL-1 and TNF-α. The mean absolute number of CD56+ cells also increased and the number of CD3+, CD4+, or CD8+ only

marginally increased compared to the base levels, with the CD4:CD8 T cell ratios unchanged. Furthermore, the treatment led to a significant increase in the mean NK activity compared to baselines [85]. A randomized, placebo-controlled, multi-centered study was conducted on advanced lung cancer patients with the same treatment protocol by Ganopoly®. The GLP treatment enhanced the immune parameters including total T cells, NK cells, and CD4/CD8 ratio. Moreover, the quality of life in terms of Karnofsky score was improved in approximately 65% of those patients [86].

A meta-analysis of the randomized-controlled trials evaluated the effect of *G. lucidum* on the long-term survival of cancer patients, tumor response, immunological system, improvement in quality of life, and adverse effects. The results showed that chemotherapy/radiotherapy combined with *G. lucidum* enhanced tumor response by 1.27 fold. *G. lucidum* increased host immune functions, especially the percentage of CD3, CD4, and CD8 lymphocytes. It was concluded that *G. lucidum* improves long-term survival in patients with advanced cancer. It should not be used as first-line therapy, but because of the general stimulatory effect on the host immune system and enhancement in tumor response, it can be used as an adjuvant therapy [87]. Although the number of clinical trials conducted is limited so far, it can be concluded that GLP has the advantage in enhancing the effects of conventional cancer therapy and improving immune functions of cancer patients. Undoubtedly, more evidence from properly designed randomized clinical trials on the treatment of specific types of cancer is needed.

4. SAFETY, TOXICITY AND INTERACTIONS

Hot water extract of *G. lucidum* administered orally 5,000 mg/kg to mice for 30 days does not affect body weight, organ weight, and hematological parameters [7]. A *G. lucidum* extract (equivalent to 220 g/kg *G. lucidum*) does not produce any genotoxicty as chromosomal breakages or cytotoxic effects in mouse lymphocytes [88]. These data suggest that the water extract of *G. lucidum* or GLP is considerably safe in mice.

However, *G. lucidum* or its extract should be taken carefully, when patients receive treatment with anti-diabetics or anti-coagulants, as *G. lucidum* may augment the effects of these drugs, because of its blood glucose lowering and anti-coagulant effects. Similarly, patients who have gastric ulcers or active gastrointestinal bleeding, or will have operation soon should consult with their health providers before taking *G. lucidum* [89]. Furthermore, as *G. lucidum* possesses anti-hypertensive effect, it may also potentiate the effects of anti-hypertension drugs [90, 91]. GLP has anti-bacterial effect as well and it can increase the activity of some antibiotics (e.g. tetracycline and cefazolin) [92, 93].

5. CONCLUSIONS

Preclinical and clinical studies have demonstrated that GLP not only has anti-proliferative, pro-apoptotic and anti-migratory effects on cancer cells, but also possesses anti-angiogenic and immunomodulatory effects. Hence, combined use of GLP could be beneficial to cancer patients receiving conventional chemotherapy and/or radiotherapy, and help improve patient's immune function and alleviate the toxicity of conventional therapy. Moreover,

according to literatures, it appears to be safe. However, more studies are still required to further elucidate the mechanisms of the immunomodulatory effect as well as the direct anti-cancer effects of GLP. Especially, more properly designed clinical trials for different patient groups are also warranted.

ACKNOWLEDGEMENTS

This work was supported by TUBITAK 2219 grant (D. Sohretoglu), National Institutes of Health (CA115414; S. Huang), and the Eastern Star Award of Louisiana State University Health Sciences Center-Shreveport (S. Huang).

Abbreviations

DCs	dendritic cells
DPPH	2,2-diphenyl-1-picrylhydrazyl
GLP	*Ganoderma lucidum* polysaccharides
HUVEC	human umbilical cord vascular endothelial cells
IFN	interferon
MAPK	mitogen-activated protein kinase
mTOR	mammalian target of rapamycin
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
SOD	superoxide dismutase
TNF	tumor necrosis factor
VEGF	vascular endothelial growth factor

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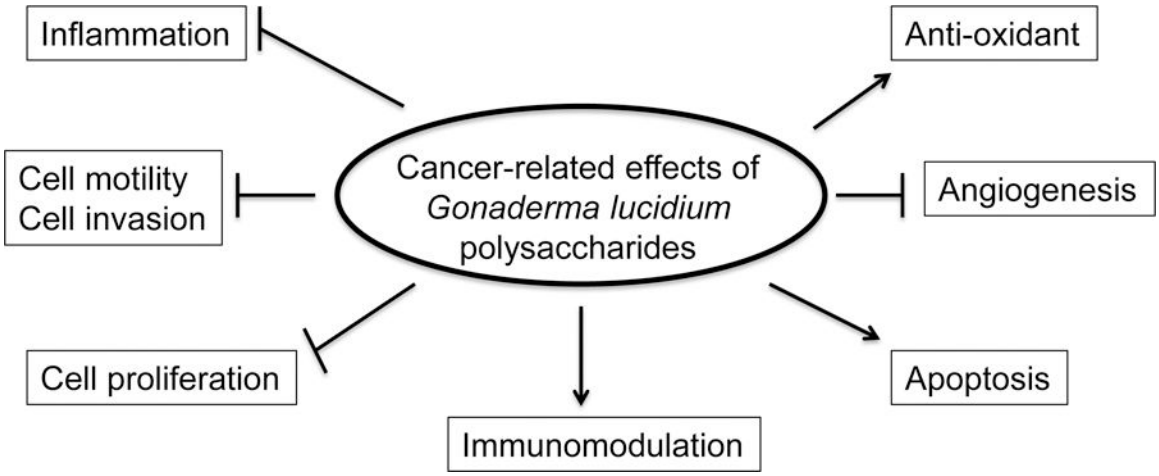

Fig 1.

Cancer-related effects of *Gonaderma lucidium* polysaccharides. Arrows represent activation, whereas bars represent inhibition.

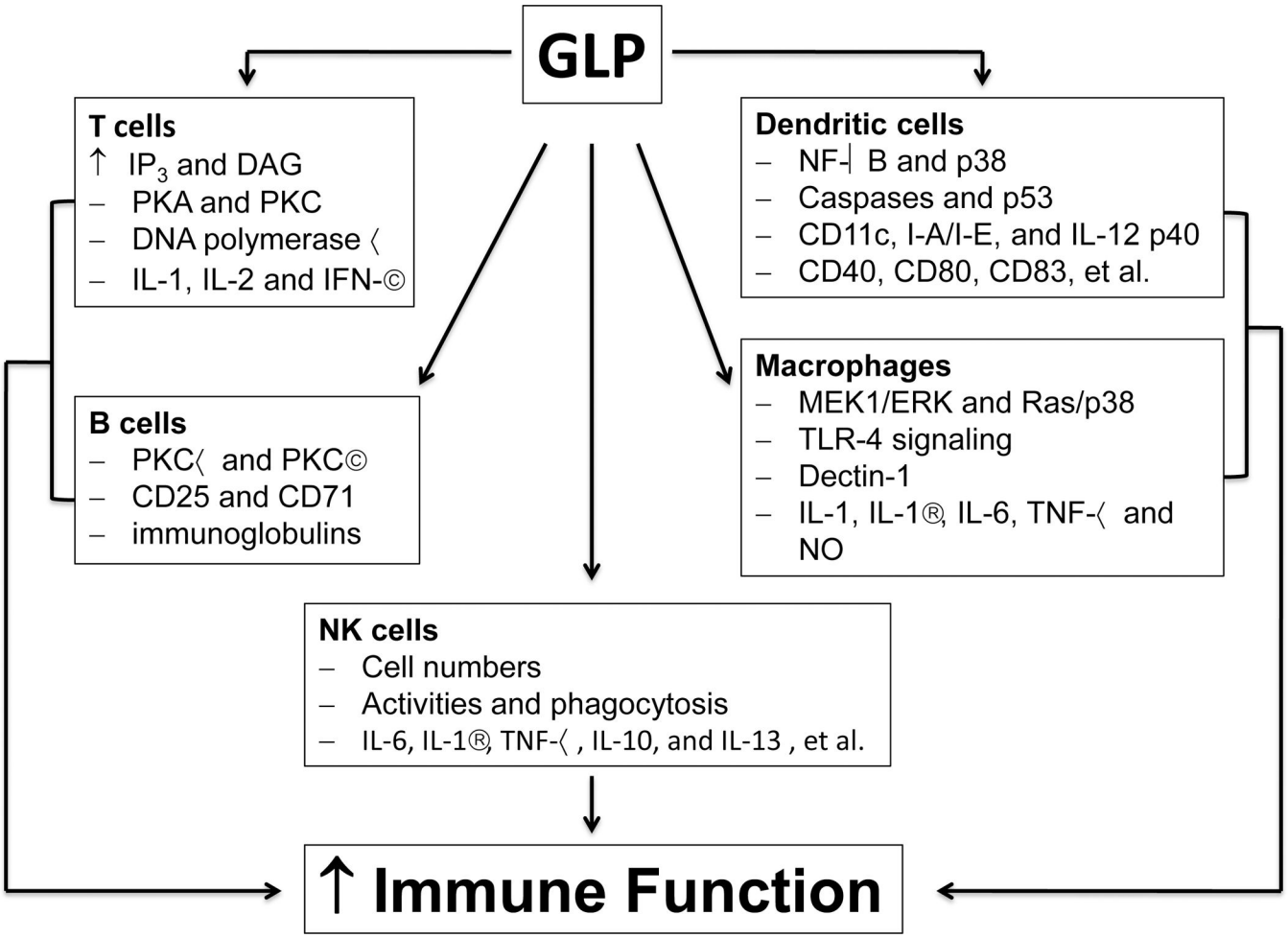

Fig 2.

Mechanisms of immunomodulatory action of *Gonaderma lucidium* polysaccharides. ↑: increasing or activating.

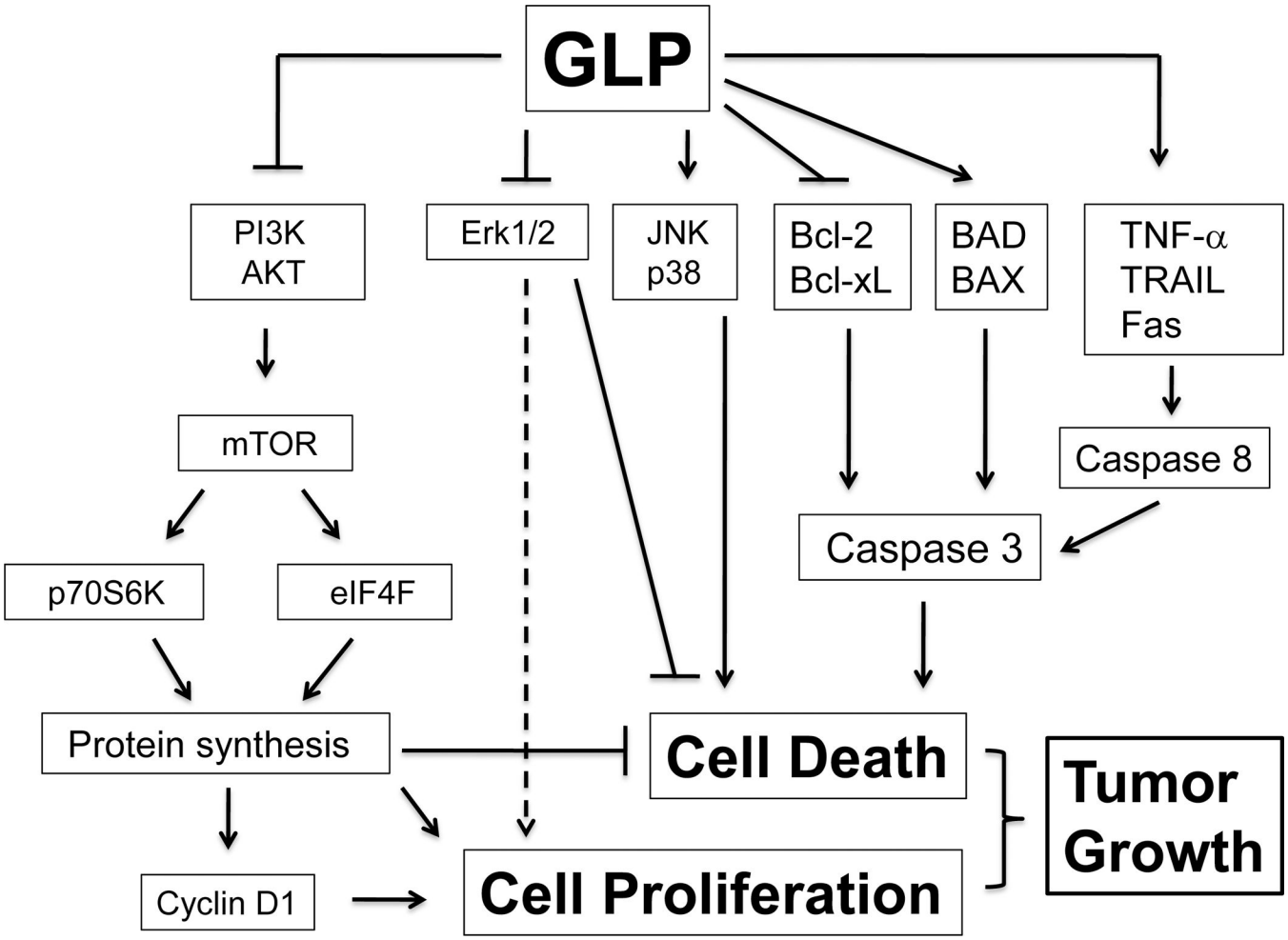

Fig 3.

Signaling pathways involved in anti-proliferative and pro-apoptotic effects of *Gonaderma lucidium* polysaccharides on tumor cells. Arrows represent activation, whereas bars represent inhibition.

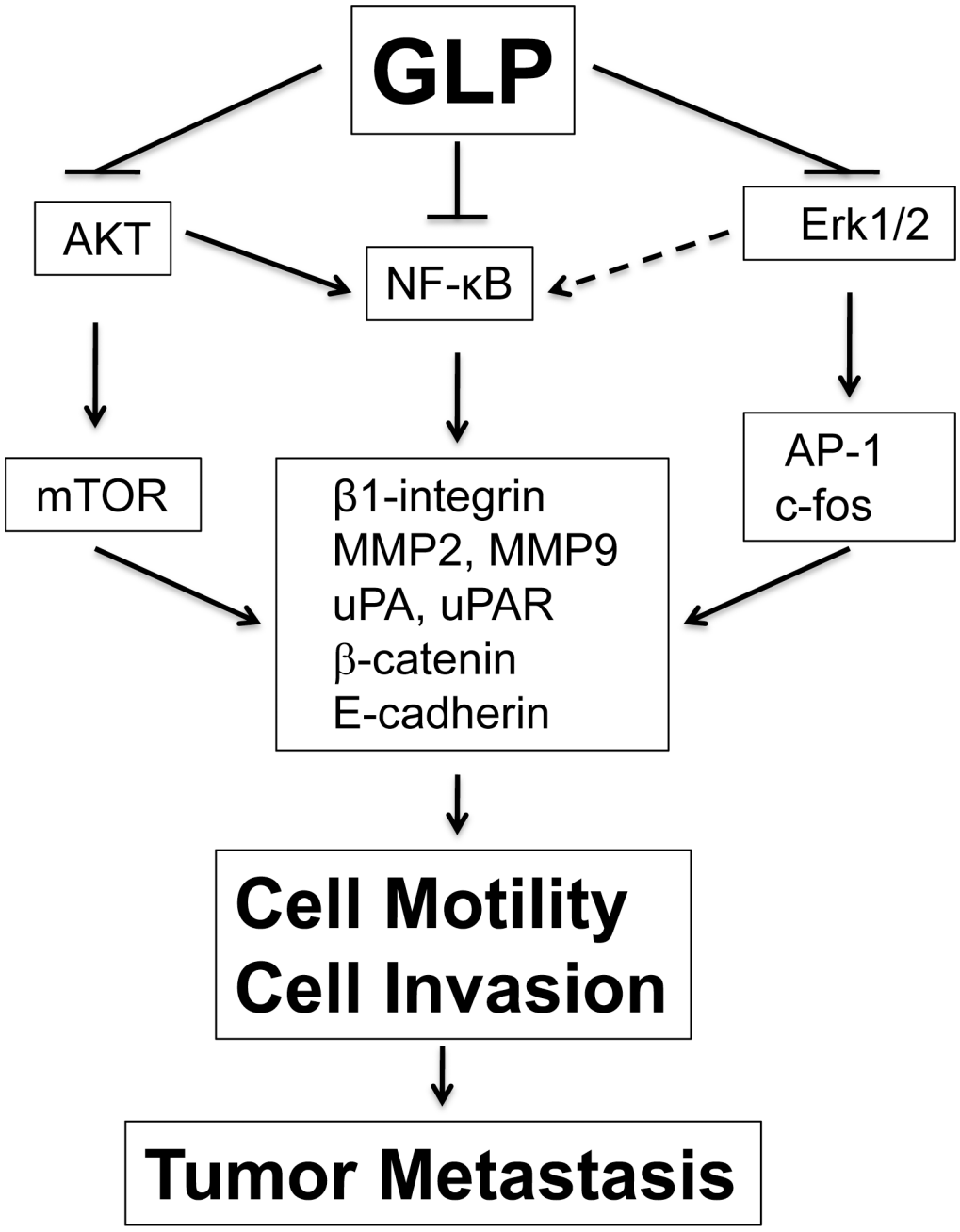

Fig 4.

Signaling pathways involved in anti-metastatic effect of *Gonaderma lucidium* polysaccharides. Arrows represent activation, whereas bars represent inhibition.