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Ganoderma lucidum: A Review with Special Emphasis on the Treatment of Various Cancer

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Abstract

Ganoderma lucidum, commonly referred to as Lingzhi or Reishi, is a basidiomycete rot fungus which has been used for centuries in East Asia for promotion of good health and longevity. The main bioactive components of *G. lucidum* can be broadly grouped into polysaccharides and triterpenes. The anticancer properties of *G. lucidum* have been proved in both *in vitro* and *in vivo* studies using human and murine cell lines. Various pharmacological activities have been reported such as, hepatoprotective, anti-diabetic, anti-hypertensive, cardioprotective, immune modulatory, antioxidant, anticancer, etc. Regardless of polysaccharides and triterpenes have been used for treatment of different types of cancers the mechanism by which they exert their anticancer effect remains undefined.

The aim of this paper is to summarise the treatment of various cancer with respect to various mechanisms that have been suggested for the anticancer properties of polysaccharides and triterpenes extracted from *G. lucidum*.

Keywords: *Ganoderma lucidum*; Basidiomycete; Polysaccharides; Triterpenes; Anticancer properties; Murine

Introduction

Ganoderma lucidum is a basidiomycete white rot fungus [1] that belongs to the family Polyporaceae (or Ganodermataceae) of Aphyllophorales [2]. It is commonly known as "Lingzhi" in Chinese, "Reishi" in Japanese and "Youngzhi" in Korean [3]. Its medicinal values has been documented in the Chinese literature which can be dated back nearly two thousand years to the Shen Nong Materia Medica (102–200AD). It is regarded as a symbol of happiness, good fortune, good health and even immortality in Chinese traditional culture [4].

More than 120 species of *Ganoderma* have been reported in the world out of which 98 species were found in China. However, only two species of *Ganoderma* (Figure 1) i.e., *G. lucidum* (Leyss.ex Fr.) Karst. and *Ganoderma* sinense Zhao, Xu et Zhang, are documented in Chinese Pharmacopoeia (2010) as Lingzhi [5]. The fungus is commonly used in East Asian countries for the promotion of health and longevity and as a remedy for illness. *Ganoderma* is consumed for its medicinal value rather than nutritional value. Lingzhi has been reckoned to extend the life span and to increase youthful vigour and vitality [6].

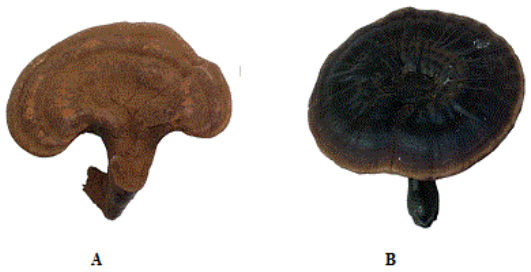

Figure 1: Raw materials of (A) *Ganoderma lucidum* and (B) *Ganoderma sinense* [5].

Chemistry

Ganoderma contains various bioactive components which are mainly located in the shiny fruiting body, mycelium and spores [7]. It has been indicated that *G. lucidum* might produce as many as ~400 different bioactive compounds [8]. The primary active ingredient of *G. lucidum* is polysaccharides [9]. It also contains secondary metabolites such as triterpenoids [10,11], alkaloids [12], proteins [12], coumarin [13], flavonoid [7], phenols [7], lignocellulose degrading enzymes [1] and nucleosides [14].

Pharmacological Activities

The polysaccharides fraction of *G. lucidum* has been manifested to activate immune effector cells and supress the growth of several cancer

cells *in vivo* [15]. According to recent studies β-(1→3) D-glucan of polysaccharide fraction was found to be carcinistatic substance present in *G. lucidum* [16]. The mushroom contains glycans as a large group of polysaccharide. Glycans consists of arabinose, mannose, fucose, galactose, xylose, glucuronic acid and also glucose [17]. The other pharmacological properties of polysaccharides were reported such as, hepatoprotective [18], neuroprotective effect [19], anti-amnesic effect [20], anti-epileptic effect [21], anti-obesity effect [22], anti-depressant [23], anti-microbial [24-26], anticancer effect [27,28] and ant diabetic [29].

Ganoderma yields oxygenated triterpenoids (especially ganoderic acids) which has wide range of biological activities. These include differential effects on the inhibition of eukaryotic DNA polymerases, thromboxane A2-signaling pathways in human platelets, inhibition of tumor invasion *in vitro* and *in vivo*, cytotoxicity to several cancer cells *in vitro*, anti-human immunodeficiency virus-1 protease activity and regulation of osteoclastogenesis [14]. The other pharmacological properties of triterpenoids were reported such as, antihypertensive [30], antianemia [31], cardioprotective [32,33], antifibrotic effect [34,35], anti-oxidant [36], anti-HIV-1 activity [37] and anticancer [38,39].

In this article, we laid emphasis on the treatment of various cancers with *G. lucidum* as well the bioactive pathways which might be associated with the anticancer activity.

Anticancer Activity and Mechanisms of *G. lucidum*

Effect of *G. lucidum* on human colorectal cancer cells

Zengenni et al. reported that cell viability on HCT-116 cells was reduced by GLP in a time- and dose-dependent manner which in turn induced cell apoptosis. Apoptosis was characterized by morphological changes, DNA fragmentation, mitochondrial membrane potential decrease, S phase population increase, and caspase-3 and -9 activation. GLP-induced apoptosis was further decreased by inhibition of c-Jun N-terminal kinase (JNK) by SP600125. Western blot analysis revealed that GLP influenced the expression of Bax/Bcl-2, caspase-3 and poly (ADP-ribose) polymerase (PARP). It has been reported that activation of mitochondrial and mitogen-activated protein kinase (MAK) pathways proved the apoptosis stimulated by GLP in human colorectal cancer cells [40].

Effect of *G. lucidum* on mouse hepatoma, sarcoma S-180 and reticulocyte sarcoma L-II cells

Xin Liu et al. showed the inhibitory effects of dormant spores, the germinating spores, the sporoderm-broken germinating spores (SBGS) and the lipids extracted from the germinating spores of *G. lucidum* on the growth of mouse hepatoma, sarcoma S-180 and reticulocyte sarcoma L-II cells. The sporoderm-broken spores indicated much higher bioactivities than the whole spores. The bioactivities of the spores were enhanced by germinating the dormant spores. The lipids extracted from germinating spores and the sporoderm-broken germinating spores of *G. lucidum* inhibited three tumors in dose-dependent manner with an inhibition of 80-90% [28].

Effect of *G. lucidum* on Lewis lung carcinoma bearing mice

Shiu-Nan et al. showed the effect of mushroom β-glucans (MBGS) by analyzing size of primary tumor and rate of metastasis in Lewis lung carcinoma (LLC) bearing mice (C57BL/6). MBGS was derived from solid culture of Ganodermalucidum and was administered orally along with radiation therapy. MBGS enhances NK cell-mediated cytotoxicity in mice without LLC bearing mice. When MBGS is administered in conjugation with radiation therapy it serves as a protective factor for the hair loss and wounds due to the overgrowth of primary tumor in LLC bearing mice. It is also effective in controlling tumor growth and rate of metastasis [41].

Effect of *G. lucidum* on colitis associated carcinogenesis in mice

Daniel et al. demonstrated anticancer and anti-inflammatory activity of triterpene extract isolated from G. lucidum. It was reported that mice exposed to PhIP/DSS was treated with *G. lucidum* triterpene (GLT) which suppressed focal hyperplasia, aberrant crypt foci (ACF) formation and tumor formation in mice. Further decreased staining with Ki-67 in colon tissues confirmed the anti-proliferative effect of GLT. PhIP/DSS-induced colon inflammation in mice was proved by shortening of the large intestine and macrophage infiltrations. GLT treatment forbade the shortening of colon length and reduced macrophage infiltration. It also decreased PhIP/DSS-dependent expression of cyclin D1, COX-2, CYP1A2 and CYP3A4 in colon tissues [38].

Effect of *G. lucidum* on human ovarian cancer cells

Shuyan et al. reported that treatment with G. lucidum reduced proliferation of human ovarian cancer cells (HOCC). It was accounted that decrease in VEGF expression and increase in Cx43 expression in the cancer cells was followed by inhibition of proliferation. The concentration of *G.* lucidum used was correlated for the extent of immune-reactivity of Cx43 or VEGF in cancer cells. The decreased expression of Cx43 in HOCC abolished the effect of *G.* lucidum on cell proliferation without the change of *G.* lucidum-induced attenuation of VEGF expression. The inhibition of HOCC was brought about by decreasing the expression of VEGF and increasing the expression of Cx43 [39].

Effect of *G. lucidum* on inflammatory breast cancer

Ivette et al. showed the mechanism of *G. lucidum* concentrating on the phosphoinositide-3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway. Early treatment of Inflammatory breast cancer (IBC SUM-149) with Reishi reduces expression of mTOR, reduced eIF4G level coupled with increased levels of eIF4E bound to 4E-BP as well as consequential protein synthesis reduction. Reishi treated severe combined immunodeficient mice injected with IBC cells for 13 weeks showed reduction in tumor growth and weight by 50%. It also showed reduction in the expression of E-cadherin, mTOR, eIF4G and p70S6K and activity of extracellular regulated kinase (ERK1/2). Thus it is evidenced that Reishi suppresses protein synthesis and tumor growth by affecting survival and proliferative signalling pathways [42].

Effect of *G. lucidum* on LNCaP prostate cancer cells

Ben et al. reported that ethanol and ethyl acetate extracts from *Coprinus comatus* and *G. lucidum* inhibit dihydrotestosterone-induced LNCaP cell viability, supress levels of secreted prostate-specific antigen in a dose-dependent manner. It also causes a G1 phase arrest in LNCaP. When used in combination *C. comatus* and *G. lucidum* decreased androgen and glucocorticoid receptors

transcriptional activity in breast cancer MDA-kb2 cells. It also suppressed androgen receptor (AR) protein level in LNCaP and MDA-kb2 cells in a dose-dependent manner [43].

Effect of *G. lucidum* on human osteosarcoma MG63 cell line

Sun et al. reported the effect SCGLP1 on human osteosarcoma MG63 cell line. The treatment with SCGLP1 showed inhibitory effect on cell proliferation and cell viability of MG63 cells in a dose-dependent manner. It also caused apoptotic death in MG63 cells through an increase in G0/G1 phase arrest. SCGLP1 induced apoptosis was related with protein expression of pro-apoptotic Bax and Bad, decreased expression of anti-apoptotic Bcl-2 and Bcl-XL, loss of mitochondrial membrane potential, the release of mitochondrial cytochrome C to cytosol, and cleavage of caspase-9, caspase-3, and poly (ADP ribose) polymerase (PARP). Pre-treatment with pan-caspase inhibitor had blocked SCGLP1 induced apoptosis in MG63 cells. Hence it was suggested that SCGLP1 induced apoptosis was related to caspase-3 and caspase-9-dependent apoptotic pathway [44].

Effect of *G. lucidum* on mouse myeloma cancer cell line

Tong et al. reported that morphological changes and apoptosis were observed in J558 cells when treated with *G. lucidum* extract at a dose of 150 μg/mL. But when the dose was increased to 200 and 400 μg/mL there was no significant reduction in cell viability. Necrosis occurred which was characterized by small fragments with uniformly stained red nuclei when the dose was increased to 400 μg/mL. After treatment the viable cells decreased by 45.6% whereas the apoptotic and necrotic cells increased by 16.5 and 29.1% respectively. But there was no changes observed in 3T3 cells. Thus it was confirmed various necrotic and apoptotic changes of cells by scanning electron microscopy and transmission electron microscopy [45].

Effect of *G. lucidum* on microRNA miR-378-mediated tumor cells

Wu et al. reported that miR-378 cells were transfected into tumor cells which acquired aggressive properties of cancer cells. Enhanced cell survival and colony formation was observed due to over expression of miR-378 cells which led to multiple drug resistance. To accelerate the death of miR-378-transfected cells higher concentration of chemotherapeutic agents were required rather than control cells. The active ingredient from *G. lucidum* was purified and isolated as ergosterol peroxide which increased the death of miR-378 cells than GFP cells. Thus from here it was shown that lower concentration of ergosterol peroxide was required to enhance death of miR-378-transfected cells compared to chemotherapeutic agents. Thus it serves as a promising new agent which can overcome the resistance of chemotherapeutic agents in cancer cells [46].

Effect of *G. lucidum* on bladder cancer cells

Lu et al. reported chemotherapeutic activity of *G. lucidum* with the help of *in vitro* human urothelial cell (HUC) model which consisted of HUC-PC cells and MTC-11 cells. *G. lucidum* was used to analyse growth inhibition, actin polymerization status, and impact of actin remodelling on cell migration and adhesion. The growth inhibition was associated with G2/M arrest as shown by cell cycle analysis. In less concentration the extract of *G. lucidum* showed actin polymerization. It leads to inhibition of carcinogen 4-aminobiphenyl induced migration in HUC-PC and MTC-11 cells. The expression of matrix metalloproteinase-2 and focal adhesion kinase were unchanged which suggests that other mechanism may be involved [47].

Effect of *G. lucidum* on lung cancer patient

Sun et al. reported that plasma-induced suppression of lymphocytes in lung cancer patients can be treated with *G. lucidum* polysaccharides (Gl-PS). Various immunosuppressive mediators such as, PGE2, TGF-β, IL-10 and VEGF are released by cancer cells to inhibit the immune response. Gl-PS antagonises the immune inhibition to facilitate tumor control in animal model. Hence, with the treatment of Gl-PS it was possible to supress proliferation, CD69 expression, and perforin and granzyme B production in lymphocytes which was activated by Phytohemagglutinin (PHA) in the plasma of lung cancer patients. An observation was made that Gl-PS can fully or partially reverse those effects [48].

Effect of *G. lucidum* on gastric cancer cell line

Oliveira et al. reported the inhibition of the growth of a gastric cancer cell line (AGS) by interfering with cellular autophagy and cell cycle. *G. lucidum* extract was found to possess antitumor activity. The phytochemical constituent of the various extract of *G. lucidum* from fruiting body and spores were investigated [49].

Current Scenario and Future perspectives

G. lucidum has been used all over the world for centuries as a source of health food supplements and nutraceuticals. It has various pharmacological benefits, such as, hepatoprotective, ant diabetic, antimicrobial, neuroprotective, antihypertensive, cardioprotective, anti-oxidant, anti-HIV-1 activity, immune-modulating, anticancer, etc. The effectiveness of *G. lucidum* reckons mainly on its chemical constituents, namely, polysaccharides and triterpenes that make up the fruiting body, mycelium or spores.

Polysaccharides have been shown to activate immune effector cells and supress the growth of several cancer cells *in vivo*, enhance the host's immune response by stimulating the production of macrophages, NK cells and T-lymphocytes, etc. It precludes tumor metastasis by various mechanisms such as inhibition of c-Jun N-terminal kinase (JNK) by SP600125, inhibition of VEGF expression, reduced expression of mTOR, reduced eIF4G level, suppressed androgen receptor (AR) protein level; inhibit immunosuppressive mediators such as, PGE2, TGF-β, IL-10, etc.

Triterpenes have shown to inhibit eukaryotic DNA polymerases, thromboxane A2-signaling pathways in human platelets, inhibition of tumor invasion *in vitro* and *in vivo*, cytotoxicity to several cancer cells *in vitro*, anti-human immunodeficiency virus-1 protease activity and regulation of osteoclastogenesis. It also prevented tumor metastasis by inhibiting the expression of cyclin D1, COX-2, CYP1A2 and CYP3A4, regulating MMp and IL-8, suppressed inflammatory cytokine secretion in macrophage cells, down regulation of cyclin D1, etc.

Recently, anticancer activities of polysaccharides and triterpenoids have received much attention in cancer treatment. Various *in vitro* and *in vivo* studies in human and murine cell lines have been demonstrated for its anticancer activity. However, the mechanism responsible for the anticancer activity of *G. lucidum* on cancer treatment lies inconclusive. The current studies provide new insights for cancer prevention and treatment based on various *in vitro* and *in*

vivo studies. *Ganoderma lucidum* represent a promising approach for the development of novel class of anticancer drugs.

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