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REVIEW ARTICLE

Ganoderma Lucidum (Reishi Mushroom) and cancer

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Summary

Having a long historical past in traditional Chinese medicine, Ganoderma Lucidum (G. Lucidum) is a type of mushroom believed to extend life and promote health. Due to the increasing consumption pattern, it has been cultivated and marketed intensively since the 1970s. It is claimed to be effective in the prevention and treatment of many diseases, and in addition, it exerts anticancer properties. Almost all the data on the benefits of G. Lucidum are based on laboratory and preclinical studies. The few clinical studies conducted are questionable. Nevertheless, when the findings obtained from laboratory studies are considered, it turns that G. Lucidum is likely to have some benefits for cancer patients. What is important at this point is to determine the components that will provide these benefits, and use them in drug development, after testing their reliability. In conclusion, it would be the right approach to abstain from using and incentivizing this product, until its benefits and harms are set out clearly, by considering its potential side effects.

Key words: *ganoderma lucidum, Reishi, mushroom of immortality, cancer, alternative medicine, complementary medicine*

Introduction

Ganoderma Lucidum (G. Ludicum), also known as Reishi, Ling-zhi, mannentake or mushroom of immortality, is a type of mushroom that has been used in Chinese medicine for approximately 2000 years. It has a bright surface, a woody texture and a deep red color. Its name has been derived from the word 'lucidus' that means bright [1]. Lucidum began to find a wide place in art and religion since the 1400s. It has been associated with Taoism, and has been involved in certain art elements such as painting, carving, and accessory items. G. Lucidum, described as holy mushroom, has been believed to be a mushroom growing in the "houses of immortals" [2,3].

Since G. Lucidum growing in natural environments is very rare, it has initially been a product available to only noble people. But afterwards, it has begun to be cultivated as a result of the difficulty in its accession due to its irregular distribution in nature as well as the increasing demand, and since the 1970, the cultivation of G. Lucidum has been the main source of this mushroom [2,4]. G. Lucidum products of more than 90 brands have been registered and entered the international market in the last 15 years. Every year thousands of tons of G. Lucidum are consumed across the world, as the product that has gained a rapidly increasing consumption pattern [5]. In a statistical study conducted in 2002, it has been stated that the worldwide annual production of G. Lucidum has been 4700 tons, 3800 of which have been produced in China [6]. G. Lucidum products are sold in a variety of forms such as powder, nutritional supplements, tea, syrup, cream, hair tonic, and particularly capsule or tablet after being turned into powder [1,6]. These

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products can be produced from different parts of the mushroom, such as micella, spore, and stem [1].

G. Lucidum, considered to be the plant of spiritual power and also shown as a the symbol of health, longevity, success and divine power in China, comes into prominence with its pharmaceutical properties rather than its nutritional value, differing from other cultivated mushrooms [1]. These mushrooms, generally cultivated on oak trees and plum trees, are commonly used in Chinese medicine, with the thought that they are effective in energy enhancement, stimulation of the immune system, and prolongation of life [7]. The effect of G. Lucidum on cancer is based on glucan and triterpenes that it contains. Beta glucans are thought to activate the immune system, and triterpenes are thought to have a cytotoxic effect against various cancer cells [8-10]. Triterpenes are also alleged to inhibit tumor invasion by reducing the expression of matrix metalloproteinases and inhibit tumor metastasis by limiting the binding to endothelium [11,12].

Laboratory studies on the effects of ganoderma lucidum on cancer

For years, G. Lucidum has been alleged to be effective in the treatment and prevention of many, cancer in particular. These claims are basically based on laboratory and animal studies. In the literature, there are laboratory and animal studies that show the immunomodulatory, anti-inflammatory and hepatoprotective effects of G. Lucidum extract [13-18]. In laboratory and animal experiments investigating the anti-cancer properties, it was reported that G. Lucidum has an anti-proliferative effect [19], shows a cytotoxic effect by stopping the cycle of tumor cells, inducing apoptosis [20-23], and also inducing NK (natural killer) cell cytotoxicity against various cancer cell lines [24]. Besides, in two studies carried out on mice, G. Lucidum was also alleged to have also an anti-angiogenic activity [25,26]. In another study carried out on prostate cancer cell lines, G. Lucidum was stated to inhibit VEGF and TGF-β1, which are among the angiogenic factors [27]. Similar results were found in a study carried out on lung cancer cell lines [28]. In a study that involved the testing of the mixture of G. Lucidum and Agaricus Blazei Murill on endometrial cancer cell lines, the viability of cells, probably through autophagy induction as well as the inhibition of their proliferation, were reported [29]. In another study carried out on mice, it has been stated that a G. Lucidum's component called polysaccharide facilitates cancer immunotherapy by antagonizing the suppression of melanoma cells on macrophages [30]. Besides, there are some other studies indicating that G. Lucidum enhanced the effectiveness of radiotherapy, reduced chemotherapy-induced nausea, and increased the sensitivity of ovarian cancer cells to cisplatin [31-33].

In laboratory studies intended to identifying G. Lucidum's effects on cancer, the strongest results were obtained in breast cancer cell lines. In a study conducted on mice, published in 2014, highly invasive human breast cancer cells were implanted into the breast tissues of mice, and G. Lucidum was administered to mice every other day. In conclusion, G. Lucidum was observed to suppress breast-to-lung metastasis through the inhibition of pro-invasive genes [34]. According to a study published in the Journal of Cancer Research in April 2015, G. Lucidum, when used in conjunction with Lapatinib in HER2 + inflammatory breast cancer cells, was effective on SUM190 and KPL-4 cell lines, and reduced the viability of the cells [35]. In another study, G. Lucidum extract reduced the tumor growth by reducing the E-cadherin and eIF4GI expression in inflammatory breast cancers [36] (Table 1).

Clinical studies on the effects of G. Lucidum on cancer

There are few clinical studies that involve testing G. Lucidum on cancer patients, and their results have been reported incompletely in certain aspects. In some clinical studied conducted in China, certain positive results were obtained. However, these studies were unreliable because they were not standardized enough, in terms of patient selection and the extract methods used [37[. In one of these, polysaccharide extract of G. Lucidum was observed to provide an increase in the plasma levels of interleukin (IL)-2, IL-6, interferon γ (IFN-γ), which are immunological markers, and in NK cell activities [38,39]. In another study, more positive responses were attained in those using G. Lucidum in combination with chemotherapy/radiotherapy, compared to those using only chemotherapy/radiotherapy. An increase, to a certain extent, was also observed in the immunological markers CD3, CD4, CD8 [37]. In another study, G. Lucidum was reported to suppress the growth of colorectal adenomas [40].

In a study published in 2012 in PLoS One, the effect of using Ginseng and/or G. Lucidum after the diagnosis of breast cancer on the quality of

life was investigated. In that study conducted on 4,149 breast cancer patients, 14.2 and 58.8% of whom used Ginseng and G. Lucidum respectively after diagnosis, the use of Ginseng showed a significant effect on the quality of life. G. Lucidum has created a socially positive effect but in the physical sense, it has negatively affected the quality of life [41].

In a compilation made by Cochrane Collaboration in 2012, only 5 studies could meet the criteria for inclusion. The polysaccharide contents have not been defined adequately in these studies as well. In addition, all of the participants were selected from Asian countries. In conclusion, the researchers have concluded that there were not adequate data supporting the usability of G. Lucidum in cancer patients [37]. In another compilation intended for the evaluation of the anti-cancer effects of G. Lucidum, it has been concluded that some clinical studies support the use of G. Lucidum in conjunction with chemotherapy and/or radiotherapy, but that the methodologies of these studies were questionable as well [42]. In another compilation intended for investigating the anti-cancer properties of triterpenes, which are among the active components of G. Lucidum, it has been stated that there are some findings indicating that triterpenes have certain anti-cancer properties, such as stopping the cell cycle in cancer cells, apoptosis and autophagy induction, metastasis and angiogenesis suppression etc., but that these findings needed to be supported by clinical studies and the molecular mechanisms needed to be clarified [43]. In a compilation published by Cheng and Sliva in 2015, it was concluded that "although positive results were obtained in laboratory studies and preclinical studies, clinical studies are still inadequate, and further clinical studies should be conducted on active components such as D-Glucan, triterpene"; and it was emphasized that "this information should be used in drug development after its benefits are clearly shown" [44] (Table 1).

Potential side effects on G. Lucidum

Although G. Lucidum is alleged to be free from toxicity, there are many cases of adverse effects and drug interactions reported in the literature. In one of such cases, G. Lucidum extract was even held responsible for a fulminant hepatitis that resulted in death. A 47-year-old woman with schizophrenia developed fatal fulminant hepatitis two months after starting to take G. Lucidum, in the form of 400 mg capsules. Investigations that followed showed that the responsible factor was G. Lucidum [45]. In another case presentation, G. Lucidum tablets were held responsible for causing the development of lethargy and anorexia, leading to hepatotoxicity [46]. G. Lucidum also caused vesiculobullous lesions covering the entire palms and soles as well as an anagen effluvium and aplastic crisis in a 66-year-old male patient [47]. G. Lucidum was held responsible for aplastic anemia in two other cases [48]. In another case report, the authors stated that G. Lucidum led to chronic diarrhea [49] and in a laboratory study, it was stated that G. Lucidum could be toxic to immune cells, contrary to the assertions [50].

There are also studies on drug interactions with G. Lucidum. G. Lucidum extract may affect the concentrations of drugs metabolized by cytochrome P450 enzymes by inhibiting these enzymes [51] and reducing the efficiency of chemotherapeutic drugs [52], leading to increased risk of bleeding by interacting with anticoagulant/antiplatelet drugs [53], and reducing the efficiency of immunosuppressive drugs [39]. It can also lead to misleading results by affecting the levels of certain cancer markers such as CA72-4 [54]. In a study involving the presentation of 5 cases, G. Lucidum spores caused an increase in the level of serum CA72-4, one of the most valuable markers for the assessment of responses to treatments administered to patients for gastrointestinal cancer [55].

Conclusion

Certain benefits of G. Lucidum were observed in some laboratory and animal experiments. However, such results were not confirmed in clinical studies conducted on humans. Moreover, literature contains some cases in which this product led to certain harms. In conclusion, the available evidence indicates that G. Lucidum cannot be used as a primary treatment for cancer. However, it is likely to have some effects such as enhancing the response of tumors to standard treatment, regulating the immunity, or relieving certain side effects induced by cancer or cancer treatment. What is important at this point is to determine the components that will provide these benefits, and use them in drug development, after testing their reliability. For now, the right approach would be to stay away from this product, until its efficiency, side effect profile, and impact area are set out clearly.

Conflict of interests

The authors declare no confict of interests.

Table 1. Selected laboratory and clinical studies

Reference	*Type of study*	*Type of cancer*	*Results*	*Potential mchanism of action*
Liao SF et al. (2013) [9]	laboratory	lung carcinoma	Increased antibody-mediated cytotoxicity and reduced production of tumor-associated inflammatory mediators	Inducing antibodies against murine Lewis lung carcinoma cells
Lin SB et al. (2003) [10]	laboratory	hepatoma	Inhibited growth of hepatoma cells	Suppressing protein kinase C, activating mitogen-activated protein kinases and G2-phase cell cycle arrest
Chen NH et al. (2008) [11]	laboratory	lung carcinoma	Inhibited tumor invasion	Down-regulating matrix metalloproteinases 2/9 gene expression
Li YB et al. (2008) [12]	laboratory	prostate carcinoma	Inhibited the adhesion ability of human prostate carcinoma cells to human umbilical cord vascular endothelial cells.	Up-regulating SAA protein expression
Müller CI et al. (2006) [21]	laboratory	a panel of 26 human cancer cell lines.	Caused apoptosis in leukemia, lymphoma and multiple myeloma cells	Unclear
Hong KJ et al. (2004) [23]	laboratory	Colonic carcinoma	Had pro-apoptotic and anti-inflammatory functions, as well as inhibitory effects on cytokine expression during early inflammation in colonic carcinoma cells	Unclear
Chang CJ et al. (2014) [24]	laboratory	leukemia	Stimulated naturel killer cell cytotoxicity	Inducing NKG2D/NCR activation, phosphorylation of intracellular MAPKs and secretion of perforin and granulysin
Stanley G et al. (2005) [27[	laboratory	prostate cancer	Suppressed angiogenesis	Inhibiting of secretion of VEGF and TGF-beta1
Hahne JC et al. (2014) [29]	laboratory	endometrial cancer	Inhibitory effect on cell viability and proliferation	Induction of autophagy
Lu J et al. (2014) [30]	laboratory	melanoma	Facilitated cancer immunotherapy	Antagonising suppression of melanoma cells in macrophages
Wang CZ et al. (2005) [31]	laboratory	none	Attenuated cisplatin-induced nausea and vomiting	Unclear
Zhao S et al. (2011) [32]	laboratory	ovarian cancer	Enhanced the effect of cisplatin on epithelial ovarian cancer cells	Unclear
Kim KC et al. (2008) [33]	laboratory	leukemia	Enhanced radiation-induced apoptosis and overall cell death	Inhibition of cyclin-dependent kinase 1 (CDK1) phosphorylation and the dephosphorylation of retinoblastoma protein (pRB)
Loganathan J et al (2008) [34]	laboratory	breast cancer	Suppressed breast-to-lung cancer metastasis	Inhibition of pro-invasive genes
Yismeilin FM et al. (2015) [35]	laboratory	breast cancer	Inhibited KPL-4 and SUM190 cell viability and sensitized inflammatory breast cancer cells to lapatinib therapy	Unclear

Continued on next page

Reference	*Type of study*	*Type of Cancer*	*Results*	*Potential mchanism of action*
Suarez-Arroyo IJ et al. (2013) [36]	laboratory	breast cancer	Suppressed protein synthesis and tumor growth	Reducing E-cadherin and eIF4GI expression
Gao YH et al (2003) [38]	clinical	lung cancer	Increased CD3 percentage, and natural killer cell activity; a marginal increase in the CD_4 percentage and CD_4/CD8ratio; but a marginal reduction of CD_8	Unclear
Gao YH et al (2003) [39]	clinical	various advanced-stage cancers	Increased the mean plasma concentrations of interleukin (IL-2), IL-6, and interferon (IFN)-gamma	Unclear
Oka S et al (2010) [40]	clinical	none	Suppressed the development of colorectal adenomas	Unclear
Ping-Ping B et al (2012) [41]	clinical	breast cancer	Post-diagnosis G. lucidum use was associated with better social well-being scores, but poorer physical well-being scores.	Unclear

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