MEDICINAL MUSHROOM REISHI (*GANODERMA LUCIDUM*). MAIN TOXICITY AND ALLERGENICITY STUDIES. DOSAGE, POSOLOGY AND SIDE EFFECTS.

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Medicinal mushroom *Ganoderma lucidum* has been subjected to intensive scientific research since the 80s, showing the multiplicity of its possible medicinal uses. Nowadays, *Ganoderma* is artificially cultivated in more than 10 countries, being China the first one in relation to its major production, followed by Korea, Taiwan, Japan, USA, Malasya, Vietnam, Indonesia and Sri Lanka. Also, its cultivation has recently begun in some Latin American countries like Colombia and Brazil.

INTRODUCTION

From a medicinal point of view, the important compounds found in *Ganoderma lucidum* are mainly polysaccharides (β-D-glucans), sterols (particularly ergosterol), triterpenes (ganoderic acids), glycosides, riboflavin, ascorbic acid and aminoacids[14].

Furthermore, it possesses dietary fiber (quitin, polysaccharides), i.e. high molecular weight compounds which are not absorbed or transformed into the digestive tract, and hence directly excreted. These compounds exhibit carcinostatic activity, due to their capacity to absorb and excrete carcinogenic substances.

More than 2000 years ago that *Ganoderma* has been used in China, Japan, Korea and Taiwan as a popular medicine for treating various illnesses such as hepatitis, hypertension, hypercholesterolemia and gastric cancer[55] and it is widely consumed in the

belief that it promotes health and longevity, lowers the risk of cancer and heart disease and boosts the immune system [2,48].

Studies on medicinal higher mushrooms in west science began around thirty years ago. From that time until nowadays, it could be demonstrated a series of interesting biological activities for *Ganoderma lucidum*, including antitumor and anti-inflammatory effects and cito-toxicity to hepatoma cells[32,37].

Antitumor effects of *G. lucidum* were associated with triterpenes[6,30], polysaccharides[7,19,26,31,35,37] or immuno-modulatory proteins[25].

The specialist Alice W. Chen in Mushroom Growers´Handbook 1. Oyster Mushroom Cultivation (Publ. MushWorld –Heinart Inc. ISSN 1739-1377, Seoul. Korea), refers to Reishi mushroom health benefits as follows:

"*Ganoderma lucidum*, the most famous species in this group is a legendary mushroom in China, with a long fascinating history dating back over two thousand years. Not only is a sparkling beautiful woody mushroom, but more importantly, *G. lucidum* is known as the mushroom of immortality and is the number one medicinal mushroom in China. Dr. Andrew Weil, a most popular authority in the West on Eastern medicine, recently advised readers of his daily health tip to consume Reishi to prevent cancer. Reishi is the Japanese name for *G. lucidum*, while Ling Zhi is the Chinese name. Dr. B. K. Kim, a world leader in research on *Ganoderma* in Korea, showed that *G. lucidum* has an anti-AIDS property. AIDS is a worldwide problem, particularly in Africa and Asia.

Best known as an immune system enhancer and modulator with health benefits, *Ganoderma lucidum* is generally safe for long-term use. The LD 50 (letal dose to kill 50% of the studied subjects) for a single intraperitoneal injection dose of *Ganoderma* extract in rodents was as high as 38g/kg . The LD 50 of a water-soluble polysaccharide fraction of *G. lucidum* in rodent was higher than 5g/kg. Since the toxic/lethal doses in rodent are quite high relative to conventional human dosages, they do not indicate significant limitations for clinical dosages of *Ganoderma*[1]".

TOXICITY

Ganoderma lucidum mushroom does not present cito-toxicity and has demonstrated to be safe due to its long history of oral administration not associated with toxicity[17,43].

In animal experiments, *Ganoderma lucidum* extracts showed a very low toxicity[42,50]. There are few reported data about the possibility of adverse effects on long-term consumption of *G. lucidum* and/or its commercial varieties. In a clinical trial, 88 men

over the age of 49 years, who had slight-to-moderate lower urinary tract symptoms, were randomly assigned to 12 weeks of treatment with *G. lucidum* extract (6 mg once a day) or placebo. Evaluation of the changes in the International Prostate Symptom Score (IPSS) and variables of uroflowmetry was done. *G. lucidum* was effective and significantly superior to placebo for improving total IPSS. Overall treatment was well tolerated with no severe adverse effects. There were not observed hematological, hepatic or renal toxicity[33].

The aqueous extract of Reishi administered to mice (5 g/kg during 30 days) produced no changes in body weight, organ weight or hematological parameters[50].

The mushroom produced no changes in the estrus cycles of ovariectomized mice from a dosage of 10 g/kg and no increase in the weight of levator cavernosa and testicles in male mice from the same dosage[50].

Li *et al.*[22] in a study of acute and genetic toxicity of *Ganoderma lucidum* Spore Powder Capsule, found that LD50 was higher than 10 g/kg; Ames test, Micronucleus test of bone marrow cell in mice and sperm shape abnormality test in mice had negative reaction and a lack of toxicity, hence indicating that *Ganoderma lucidum* Spore Powder Capsule has non-toxicity.

No toxicity was observed in the organs of rabbits who took a syrup preparation of Reishi in progressive doses of 4-140 mL/kg daily during 10 days or in dogs (2 mL/kg and 4 mL/kg during 10 days). When an alcoholic extract was administered to young rats (1.2 and 12 g/kg daily during 30 days), no signs of toxicity were produced in major organs, hepatic function, growth or development. In the case of dogs administered with an alcoholic extract (12 g/kg daily during 15 days and 24 g/kg daily during 13 days), there were no toxic reactions but they displayed lethargy[12,29].

In a rural area of Hong Kong, the toxicity of wild Reishi was evaluated by preparing harvested fruit bodies as a freeze-dried powder extract (1 g/20 g of freeze-dried fruit bodies and 50 mL of extract solution/100 g of freeze-dried fruit bodies). Acute toxicity was tested administering the extract solution to male mice at a dosage equivalent to that one commonly recommended by manufacturers of commercial concentrated extracts. Neither evidence of acute toxicity was found, nor was abnormal serum contents of urea, GOT or GPT compared to controls. No abnormalities were found in histological examinations of livers and kidneys, organ weights (liver, kidney, heart, lung and spleen) or organ/body weight ratios compared to controls[3,50].

In other work, *G. lucidum* toxicity was evaluated by feeding 70 rats with *G. lucidum.* No significant toxicity was detected in the rats[24].

In a double-blinded, placebo-controlled, cross-over intervention study, the effects of 4 weeks Reishi supplementation on a range of biomarkers for antioxidant status,

coronary human disease risk, DNA damage, immune status, and inflammation, as well as markers for liver and renal toxicity were investigated. In this study, blood and urine from healthy, consenting adults (n 18; aged 22–52 years) were collected before and after 4 weeks supplementation with a commercially available encapsulated Reishi preparation (1·44 g Reishi/day; equivalent to 13·2 g fresh mushroom/day) or placebo. No significant change in any of the studied variables was found, although a slight trend toward lower lipids was observed, while antioxidant capacity in urine increased. The results showed no evidence of liver, renal or DNA toxicity with Reishi intake[49]. The previous study was performed as a follow-up to a study which showed that antioxidant power in plasma increased after Reishi ingestion, and that 10 days supplementation was associated with a trend towards an improved CHD biomarker profile.

As regards long term toxicity, rats of three experimental groups were given *Ganoderma lucidum* capsule at doses of 0.47, 0.94 and 1.87, g/kg·day-1 during twenty-six weeks. There was not found abnormality induced by *Ganoderma lucidum* capsule in all results, and the pathological figures of major organs were normal. There is no toxicity of *Ganoderma lucidum* capsule given to rats for long term, indicating that it is safe to administrate *Ganoderma lucidum* capsule continuously[8].

To observe the long term toxic reactions of *Ganoderma* spores on rats, 80 rats were randomly divided into 4 groups of 20 each, i.e. blank group and 3 treating groups. The low, middle and high dosages of *Ganoderma* spores were perfused respectively to the three treating groups for 30 days, continuously, and the body weight of rats were weekly measured. The hematological and biochemical indexes, organ coefficient and patho-histology changes were tested after stopping administration. No evident abnormal change of every index was observed in every group, indicating that the administration of the dosage of 4.50g/kg of *Ganoderma* spores to rats during 30 days is safe[53].

ALLERGENICITY

Although mushrooms are commonly consumed worldwide, the overall extent of mushroom allergy is not known. It may be very slight (1%) from eating, but could, alternatively, be as prevalent as pollen and mould allergy (10-30% of an allergic population)[18]. The importance of fungal spores as the causing agent of airborne respiratory allergies has been established[13]; thus it should be considered in the protection of workers in mushroom industrial production. Although Basidiomycetes edible mushrooms are extensively consumed worldwide, food allergies caused by

these mushrooms have generally not been reported, excepted those ones referred to the mushroom *Boletus edulis*[34,45].

In 2002, the first case of food allergy caused by the cultivated edible mushroom *Agaricus bisporus* (white champignon) was reported, and mannitol was described as the low molecular weight allergen[10].

In 2005, two cases of hyper-sensibility to champignon basidiocarps and spores experienced by workers related with the cultivation of champignons, who previously suffered asthma, were informed[46].

Basidiospores are prevalent in the air worldwide[9,20]**.** Thus, basidiospores are potentially the major source of aeroallergens[11]. López *et al.*[28] and Sprenger *et al*.[39] demonstrated that extracts from selected *Basidiomycetes* mycelia or liquid fluid which were grown *in vitro* resulted allergenic for humans and antigenic in rabbits. Human sensitization for *Ganoderma* antigen was first reported in the *Journal of Allergy and Clinical Immunology,* in 1979, in a work performed in Ontario[44]. The researchers found that 8.2% of allergic patients positively reacted to *Ganoderma lucidum* antigen. In a similar work in Auckland, this allergic reaction occurred in the 16% of the patients studied[4]. In India, sensitization was also reported in 1995[36]. It was found that 28 % and 17% of atopic patients showed marked skin reactivity to spores extract and whole fruit bodies, respectively.

On the other hand, from the point of view of food immuno-modulation, it was seen that diet and nutrition can affect the functioning of various immune parameters. This concept can be utilized in attempts to prevent or mitigate allergic reactions via the development of targeted food products or ingredients. In this sense, there are food products and ingredients that show potential, with special emphasis on pro- and prebiotics, i.e. β-glucans and fungal immunomodulatory proteins[52]. Beta-glucans bind to immunological system cells such as macrophages and NK cells. β-Glucans appear to exert their immunomodulatory effects via the activation of innate pathways, e.g. in macrophages[16,47] and were found to stimulate the production of TNF-α, IFN-γ and IL-12.

Mitigant effects to peanut allergy were observed in a rat model after application of a preparation containing β-glucans from *Ganoderma lucidum*[21,40], even providing long term protection from anaphylaxis by inducing a beneficial shift in allergen-specific immune responses mediated largely by elevated CD81, T-cell, IFN- γ production[41].

The biological relevance of fungal immunomodulatory proteins (FIPs), for allergy mitigation lies in the observation that they were able to inhibit food allergic and respiratory-allergic reactions in mouse models when applied orally or nasally[52].

When *G. lucidum* LZ-8 FIP preparations were orally applied to 50 male rats, it could be observed that they were effective in immunotherapy in cases of inflammation caused by respiratory allergy to *Dermatophagoides pteronyssinus*[27].

In a double-blind trial, 91 subjects with moderate-severe, persistent asthma with prednisone therapy were studied to compare the efficacy, safety, and immunomodulatory effects of ASHMI treatment (formula which contains *Ganoderma lucidum*) in comparison with prednisone therapy, during 4 weeks[51]. In this study, the authors concluded that the antiasthma herbal medicine intervention appeared to be a safe and effective alternative medicine for treating asthma. In contrast with prednisone, ASHMI had no adverse effect on adrenal function and had a beneficial effect on Th1 and Th2 lymphocyte balance.

It was recently completed a study to examining the safety, tolerability and immunological effects of complementary ASHMI administration (which includes *Ganoderma lucidum*) to standard therapy of corticosteroid (Budesonide -Pulmicort Turbohaler) in 5-14 years old children with persistent asthma with or without allergic rhinitis in China[23]. The results showed that ASHMI was safe and well tolerated in children. As expected, both standard and ASHMI plus standard groups significantly improved clinical symptoms. However, symptom scores improvement was greater in the ASHMI plus group than in standard therapy alone group, particularly in the nasal symptoms. Furthermore, ASHMI plus standard group showed significantly greater reductions in serum total IgE ($p<0.05$) and serum eosinophil cationic protein ($p<0.05$) but higher serum IFN-γ levels ($p<0.001$) after 3 months of treatment as compared to the standard therapy.

A great quantity of treatments commonly used in Western medicine are linked with allergies, penicillin is one such example. It does not seem surprising therefore that *G. lucidum* have been also related to some cases of allergies, too. However, it is important to bear this downside in mind when considering the various healing claims made of *Ganoderma,* as it occurs with the case of penicillin[5].

DOSAGE FORMS

Ganoderma lucidum is usually prescribed in various forms. It may be injected as a solution of powered spore. Mushroom mycelia can be ingested in diverse forms as soup, syrup, tea, tablets, capsules, tincture or bolus[50]. The dose in tincture form (20%) is 10 mL three times daily; that of tablet is 1 g tablets three times daily and syrup is 4-6 mL/day[12,29,42].

SIDE EFFECTS

In oral dosages of 1.5-9 g/day, some patients when initially took a powder extract of Reishi have experienced temporary symptoms of sleepiness, thirst, rashes, bloating, frequent urination, abnormal sweating and loose stools, reactions which were considered to be a response to the detoxyfying effect of Reishi[38,50]. Large oral doses of vitamin C (6-12 g/day) taken at the same time as Reishi powder extract (2-10g/day) counteracted loose stools[12,15,29,38,50].

Because Reishi potentiates the immune system, it may be advised precaution in people who receive immunosuppressive therapies.

The platelet aggregation inhibition activity demonstrated in Reishi[12,29] may present an additive effect in those taking blood thinning medications such as daily aspirin or warfarin[50,51].

Synergistic antimicrobial activity was shown with an aqueous extract of Reishi in combination with cefazolin against *Klebsiella oxytoca* ATCC 8724 and *Bacillus subtilis* ATCC 6603, *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25933 and *Salmonella Typhi* ATCC 6509[50,54].

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