Evidence-Based Herbal Medicine: 
My Experience with the Lingzhi
(Ganoderma lucidum)

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1. **Our Clinical Trials for *G. lucidum***

*Ganoderma lucidum* (Ling-Zhi) is a very important traditional medicinal mushroom which has been used extensively by Asians in the treatment of a variety of chronic diseases like hepatic cirrhosis, hypertension, diabetes and cancer. A number of preclinical studies done by our group have revealed that polysaccharides are the major active component in *Ganoderma lucidum*. These components had antiulcer, antitumor, hypoglycemic, and hypolipidemic effects in rodent models. However, the scientific rationale of optimal dose and therapeutic regimen, and safety profiles for the use of *G. lucidum* have not been identified in humans. To provide an insight into the pharmacological basis and to identify a strategy for the research of *G. lucidum*, we have extensively investigated its clinical activities in several diseases and its potential side effects.

We have completed nine clinical trials of *G. lucidum* in several diseases like cancer, Type II diabetes, coronary heart disease, chronic hepatitis B, and neurasthenia. Most of these studies were randomized, double-blind, multi-centered and placebo-controlled. Some of them were before-and-after comparison studies to investigate the effect of *G. lucidum* on the immune system in patients with solid tumor and lung cancer, respectively. The diagnosis of the diseases was confirmed using World Health Organization ICD-10 criteria. Different end points were adopted to evaluate the clinical results for different diseases. The tested *G. lucidum* product contains 25% water-soluble polysaccharides extracted from the fruiting bodies of *G lucidum* grown in the south China. The common dose used for all trials was three capsules, three times per day (each capsule has 600 mg extract, i.e. 5400 mg/day).

The clinical outcomes arising from these studies have been reported in peer-reviewed international journals. The treatment of *G. lucidum* for 12 weeks showed hypoglycemic activity in Type II diabetes. It improved the symptoms/signs of patients with coronary heart disease or neurasthenia, and produced some antiviral and liver protective effects in patients with chronic hepatitis B infection. However, the same treatment regimen did not result in any objective response in late-stage cancer patients. Although some stable disease status was observed. *G. lucidum* appeared to enhance the immune functions in some cancer patients, the results have yet to be confirmed. The treatment of advanced lung cancer patients with *G. lucidum* at 5.4 g/day for 12 weeks did not significantly alter the immune functions. *G. lucidum* was generally well tolerated. In all completed studies, Ganopoly was generally well tolerated and was not associated with hematologic, vital organ, or biochemical toxicity. No patients developed hepatitis or abnormal liver function tests. Toxicity of *G. lucidum* was generally mild.
2. Challenges and Approaches for Clinical Trials of Medicinal Herbs

2.1 Regulation Issue

Many Western and Asian countries have adopted different regulation systems for herbal medicines. Most Western countries follow the rules of the Dietary Supplement Health and Education Act (DSHEA) in which plant extracts are defined as dietary supplements and rigorous clinical studies (Phase I-IV) are not required before their introduction to the market, while China defines many herbs as drugs and Phase I-IV studies are needed (Fig. 1). *G. lucidum* has been treated as a therapeutic agent for cancer in China. As required by the State Food and Drug Administration of China, Phase I-IV studies have to be conducted for herbal medicines before being claimed to be therapeutic and safe. Such studies aim to obtain sufficient data on herbal efficacy and safety. Phase I study explores the general acceptance of the human being after consumption of the herbal preparation; Phase II study focuses on the safety and efficacy while working out the effective dosage; and Phase III and IV studies expands on Phase II study to collect more reliable data of efficacy and safety.

2.2 Endpoint and Biomarker Identification

Suitable end points are needed for clinical studies of medicinal mushrooms. For the clinical studies of the synthetic drugs, well-accepted end points are usually measured. However, these end points may render great difficulties in herbal clinical studies, this is because most herbal medicines are used as biological response modifiers or adaptogens. Therefore, some complementary end points may be included in the evaluation of medicinal mushrooms. For example, *G. lucidum* has exhibited beneficial effects on the symptoms such as pain, fever, and anorexia in many cancer patients in this study, subsequently this results in an improvement of quality of life. Although the effect of *G. lucidum* on patient’s survival time has not been investigated, end point parameters such as quality of life have been accepted in a novel paradigm to evaluate the salutary effects of investigational anticancer agents, particularly those from natural sources, in patients with advanced-stage cancer. As many natural biological response modifiers have shown beneficial effects when they are used as adjuvant therapy to standard modules, an adjuvant role should be expected for *G. lucidum* in the treatment of cancer.

Recently, great attention has been drawn to the clinicians to choose proper biomarkers for the assessment of both Western drugs and herbal medicines. Biomarkers enable the characterization of patient populations and quantitation of the extent to which new drugs reach intended targets, alter proposed pathophysiological mechanisms and achieve clinical outcomes. However, the challenge is to identify unique biomarkers in complex biological mixtures that can be unambiguously correlated to biological events in order to validate novel drug targets and predict drug or herbal response. Biomarkers are particularly useful in disease-modification studies in poorly served areas such as cancer and neurodegenerative diseases. There is no doubt that clinically useful biomarkers are required to inform regulatory and therapeutic decision making bodies regarding candidate drugs or herbs and their indications in order to help bring new medicines to the right patients faster than they are today.
2.3 How Much to Use? How are the Herbs Disposed by the body?

The dosage for humans is a complicated issue for all herbal medicines as the dose-response relationships for all herbal medicines are not established. Generally, the dosage used in folk medicine is empirical, depending on the patients (e.g. age, gender, and body weight), diseases treated (e.g. type, period and previous treatment history), and combined herbal medicines.

Pharmacokinetics is about with the absorption, distribution, metabolism and excretion of drugs and herbs. Thus, it can answer the question of how the herbs are disposed in our body. For all synthetic drugs, detailed preclinical and clinical pharmacokinetic studies are needed by regulatory authority to assess the toxicity of the drug candidate. However, the pharmacokinetic data for almost all herbal medicines are scanty or lacking, probably due to the fact that herbal medicine has relied on tradition, the existence of multiple components, trace or low level of the active components \textit{in vivo}, and regulation reason. For \textit{G. lucidum}, as its major active constituent is polysaccharides, of particular interest is the question of bioavailability to assess to what degree and how fast the polysaccharides are absorbed after oral administration. It is also important to elucidate the metabolic pathways, the elimination routes (biliary and/or urinary) and their kinetics \textit{in vivo}. These data become an important issue to link data from pharmacological assays and clinical effects.

2.4 Preclinical-clinical scaling

Detailed preclinical studies including those in at least two species of animals are required for all synthetic drugs. Proper pharmacokinetic and pharmacodynamic principles are then applied to extrapolate the efficacy and the safety resultant data to humans before entering Phase I study. Such scaling process is generally reasonable and accepted, despite the presence of inter-species discrepancy. However, for herbal medicines, particular caution should be taken when extrapolating data from preclinical studies to humans. For example, most preclinical studies using and animal models indicate that \textit{G. lucidum} polysaccharides are able to activate macrophages, T lymphocytes, and natural killer cells, and to induce the production of cytokines such as tumor necrosis factor in human immune cells and \textit{in vivo} in mice. However, significant effects as such are not observed in cancer patients. This inconsistency in efficacy observed may be due to the differences in dose levels, immune status, and species difference in response to \textit{G. lucidum} polysaccharides. Minimal beneficial effects of herbal medicine are tested, in advanced stage of lung cancer patients with low immune functions, limited sample size and marked inter-individual variability in the measured variables might contribute to the lack of drug response in lung cancer patients.

2.5 Toxicity issue

Toxicity of herbal medicines is becoming an important concern. Some herbal medicines have been found to cause substantial injuries to human organs. Herbal toxicity may arise from its toxic constituents and/or metabolites, unfavorable cellular responses induced by herbal constituents/metabolites, or interactions with co-administered drugs. For example, methyl eugenol and estragole from some herbal medicines caused renal and liver carcinogenesis, through toxic 1’-hydroxy metabolite in laboratory animals. A number of herbal constituents have been reported to alter the clearance and response of co-administered drugs. All our clinical studies indicate that \textit{G. lucidum} was safe in patients involved, without significant toxicity. However, it is important to monitor any possible toxicity of \textit{G. lucidum} products when it is chronically used or in combination with synthetic drugs including warfarin, anti-HIV agents, digoxin and other drugs.
3. Conclusions

Although the activities are minor, moderate, or lacking due to many factors such as inappropriate dosage regimen; difficulties in finding suitable biomarkers and endpoints; large inter-patient variability in responses to the treatment and the unknown mode of action, the findings from all these clinical studies suggest that *G. lucidum* may have multiple pharmacological activities. The clinical studies of medicinal mushrooms may encounter great difficulties as such medicinal mushrooms always contain dozens of active components; there are problems in the standardization and the quality control of their preparations; pharmacokinetic studies are difficult and dose-response relationship is hard to establish; and medicinal mushrooms themselves are always used as adaptogens and thus acceptable clinical biomarkers are often lacking. Further well-designed clinical studies are needed to identify the efficacy and safety of *G. lucidum* in patients.

Fig. 1. Objectives of clinical trials for herbal medicines.

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