

Chapter 85

Ganoderma lucidum 灵芝 (Lingzhi, Ganoderma)

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85.1 Botanical Identity

Ganoderma, also referred to as Lingzhi in Chinese, is the dried fruiting body of both *Ganoderma lucidum* (Leyss. Ex Fr.) Karst (Chizhi) and *G. sinense* Zhao, Xu et Zhang (Zizhi) belonging to the family of Polyporaceae. Lingzhi has been recorded in the Chinese Pharmacopeia (2010) [1] as one of the most popular Chinese herbal medicines, and is frequently used as an ingredient in dietary supplements. There are more than 200 species of *Ganoderma* in the world, of which 98 species have been found in China. *G. lucidum* and *G. sinense* are two of the most common species to be used for medicinal purposes, and they have been commercially cultivated for the preparation of health products since the 1970s.

Lingzhi is widely distributed in both tropical and temperate geographical regions, growing as a parasite or saprotroph on a wide variety of hardwoods. It grows to the height of 7–15 cm (*G. lucidum*) or 12–22 cm (*G. sinense*), and has a large, perennial, and woody basidiocarps. As shown in Fig. 85.1, the fruit body typically grows in a fan-like (*G. lucidum*) or umbrella-like form (*G. sinense*) on the trunks of living or dead trees. They have double-walled, truncate spores with yellow to brown ornamented inner layers.

Lingzhi are traditionally harvested all year round. After removing the impurities, sediment, and the bottom stalk of in culture, Lingzhi fruiting bodies are dried in shade or at 40–50 °C. The dried fruiting bodies can be stored and marketed as raw material. For further processing, the raw material can be sliced to 5–10 mm thickness or ground to a fine powder in order to form different commercial Lingzhi products.

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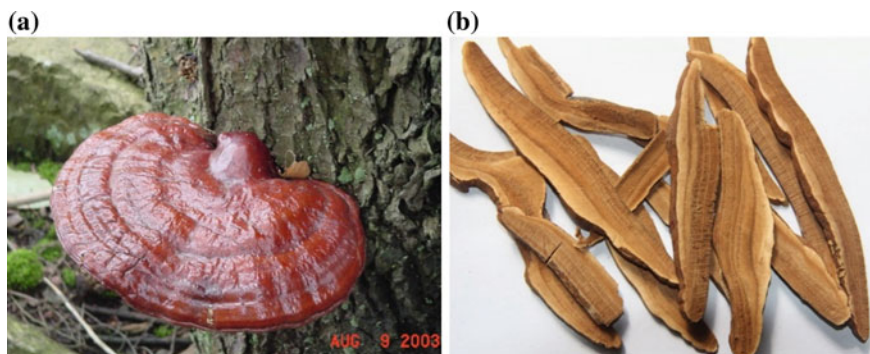


Fig. 85.1 Wild growing state (a) and slices of commercial Lingzhi (b)

85.2 Chemical Constituents

Numerous researches have revealed that Lingzhi contains approximately 400 different bioactive compounds, mainly triterpenoids, polysaccharides, nucleotides, steroids, fatty acids, proteins/peptides, amino acids, and trace elements. These studies have shown that Lingzhi contains properties which can enhance overall health and aid the body in relief of a multitude of diseases, such as hypertension, hepatitis, diabetes, neurasthenia, and cancer. Among the numerous components, triterpenoids and polysaccharides are two major classes of *Ganoderma* fruiting bodies.

85.2.1 Triterpenoids

G. lucidum is the only known source of a particular group of triterpenes, known as ganoderic acids, which have been found to have direct cancer cell cytotoxicity on a wide variety of cancer cell lines, and many of them have been suggested to counter angiogenesis and metastasis [2]. As a major class of bioactive compounds found in Lingzhi, triterpenoids are mainly contained in the spores and are responsible for Lingzhi's bitter taste. Previous studies have shown that triterpenoids exhibit a broad spectrum of anti-cancer effects, including anti-proliferative, anti-metastatic, and anti-angiogenic activities [3]. So far, about 29 triterpenoids [4] have been isolated from the spores and the major bioactive ones were shown in Fig. 85.2. Ganoderic acid T (1) is the most abundant triterpenic acid found in Lingzhi, and Ganoderic acid D (2) has shown significant anti-cancer effects in both in vitro and/or in vivo. Additionally, Ganoderiol F (3), a tetracyclic triterpene found in Lingzhi has also shown cytotoxicity on several kinds of tumor cells, including Lewis lung carcinoma, Meth-A, Sarcoma-180, and T47D cell lines. These triterpenoids are used as

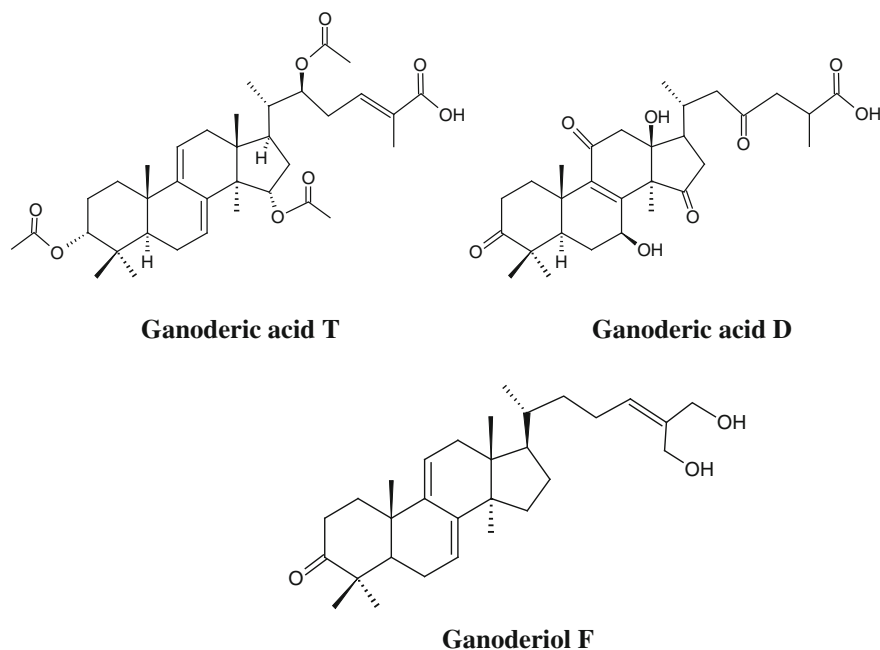


Fig. 85.2 Chemical structures of ganoderic acid T, D, and ganoderiol F from Lingzhi

chemical markers for quality evaluation of crude drug Lingzhi and related pharmaceuticals, as well as some natural health products containing Lingzhi.

85.2.2 Polysaccharides

Polysaccharides, a class of structurally-diverse biological macromolecules with wide-range physiochemical properties, were extracted from Lingzhi with water, based on the traditional use of Lingzhi (decoction), and followed by alcohol precipitation. Because of their various bioactivities, and very low to even no cytotoxicity, polysaccharides have attracted much attention of researchers. Up to now, many polysaccharides have been isolated from fruiting bodies, mycelium, spores, and culture medium of *G. lucidum*, including homo- or hetero-glucans, and heterosaccharides with different combinations of glucose, galactose, mannose, xylose, arabinose, as well as fructose. Among them, (1 → 3)- β -D-glucans branched at O-6 position as shown in Fig. 85.3, mainly existing in spores, and are considered to be the major active polysaccharides. Additionally, β -D-glucans consisting of (1 → 3)-, (1 → 4)-, and (1 → 6)- β -D linkages are reported to have a stronger anti-tumor potency and better absorption than other polysaccharides in *G. lucidum* [5].

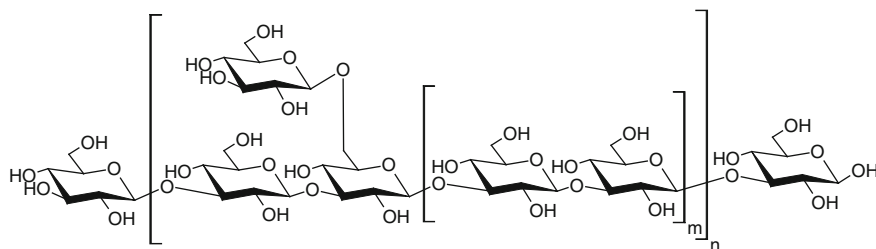


Fig. 85.3 structure of (1 → 3)- β -D-glucans branched at O-6 position

85.3 Pharmacological Studies

In Asian countries, Lingzhi has been widely used for centuries to promote general health and longevity. Modern pharmacological studies have reported that Lingzhi has a number of pharmacological effects including immune-modulating, anti-cancer, anti-oxidant, anti-hypertensive, anti-atherosclerotic, anti-inflammatory, anti-diabetic, anti-aging, radical-scavenging, neuroprotective, hepatoprotective, and sleep promoting effects [6, 7]. Among them, Lingzhi's anti-cancer effect is the most extensively studied. Numerous researchers have demonstrated that triterpenes and polysaccharides are responsible for the major physiologically activity of Lingzhi. Further studies have revealed that ganoderic acids, which are composed of highly oxygenated triterpenes, exert antitumor activity by directly acting on a wide variety of neoplastic cells, such as murine Lewis lung carcinoma (LLC) and Meth-A, and many of them have been suggested to counter angiogenesis and metastasis [3]. In contrast to the actions of triterpenes, polysaccharides are reported to trigger an indirect antitumor mechanism, in which the host immune system is altered to target the tumor cells. It has been demonstrated that β -glucans have the ability to induce both innate and adaptive immune responses by targeting immune cells including macrophages, neutrophils, monocytes, natural killer cells, and dendritic cells [3].

85.4 TCM Applications and Dietary Usage

85.4.1 TCM Applications

In traditional Chinese medicine, as well as Chinese legend and history, Lingzhi is described as a miraculous drug. Lingzhi is mainly used to treat tightness of the chest, boost the heart's *Qi*, and improve memory. Long-term administration may tonify *Qi* to tranquilize the mind, suppress cough and relieve panting [1]. Modern pharmacological research has mainly focused on Lingzhi's immunomodulating and anti-tumor effects. It exerts therapeutical actions in the following aspects: enhancing anti-tumor immunity, direct cytotoxicity against tumor cells, anti-angiogenesis,

anti-inflammation, and anti-oxidant actions. Clinically, Lingzhi is most often used as an alternative adjunct to conventional therapy in cancer treatment; especially to decrease the side effects resulting from chemical drugs, radiotherapy, and surgery.

Common Lingzhi preparations clinically used include the following forms: (1) Decoction: Thinly sliced or pulverized Lingzhi is added to boiling water and simmered for 2 h. The resulting liquid is fairly bitter in taste and dark, in which the red Lingzhi (*G. lucidum*) is more active and bitter than black Lingzhi (*G. sinense*). (2). Powder and capsule forms: There are many manufactures making this product. Some of them consist of the raw powder of Lingzhi or spores, such as Lingzhi broken spores powder. Dongfang Lingzhi Bao developed by Beijing Hengji Tang has been approved by State Food and Drug Administration for the treatment of cancer patients, which is a water extract preparation of fruiting bodies and broken spores. Additionally, other products such as Yunfeng, Tian'an, and Handu Lingzhi capsules, are used to enhance immunity, promote sleep, and improve memory. (3) Zhengqin Lingzhi Pills: This is the only one Lingzhi product available in market as OTC medicine for the treatment of insomnia, neurasthenia, and asthenic, which is manufactured by Hunan Zhengqin Pharmaceutical Group Co. LTD. (4) Lingzhi syrup: It is also sold as OTC medicine for the treatment of insomnia, neurasthenia, and asthenic. Finally, Lingzhi is also used as an ingredient in clinical decoctions or used to make an extract in liquid or powder form.

85.4.2 Dietary Usages

Due to its reputation of safety and efficacy, many dietary products containing Lingzhi are widely available, such as Lingzhi wine, Lingzhi tea, Lingzhi yoghurt, and Lingzhi soup. With a thorough investigation of Lingzhi, as well as development of new technology, highly processed Lingzhi products, such as Lingzhi extract, spore powder, and β -gluans are now commercially available. The following dietary forms can be easily made at home.

85.4.2.1 Lingzhi Tea

Lingzhi tea consumed as a functional product, made of Lingzhi alone or mixed with other herbs is the most common way to use Lingzhi. It has the function of modulating immunity to keep the body in balance. As the raw material of Lingzhi tea, Zizhi is thought to be better than Chizhi as it is less bitter. There is a recommended formula to make Lingzhi tea, i.e. Lingzhi, Dangui (*Orange osmanthus*), Jinyinhua (*Lonicera japonica* Thunb.), Shanzha (*Crataegus pinnatifida*) and Gouqi (*Lycium barbarum* L.). There are also many kinds of products of Lingzhi tea available in the market, such as Bairentang Lingzhi Tea composed of Lingzhi spore powder alone; Jingchuntang Lingzhi Tea composed of Lingzhi and honey; Zhirentang Lingzhi Tea composed of Chizhi, Huangqi (*Astragalus mongolicus*), Taizishen (*Pseudostellaria*

heterophylla), and Yunling (*Pachyma cocos*); Enhuatang Lingzhi Tea composed of Lingzhi spore powder, Lingzhi polysaccharides, and Lu'an Melon Seed Tea, etc. To make the herbal tea, it is recommended to use soft water, as it has a lower mineral content and is therefore less alkaline, which is important to reduce the decomposition of phenolic acids.

85.4.2.2 Lingzhi Wine [8]

Lingzhi alone or combined with other herbs can be used to prepare herbal wine for balancing the body and slowing down the aging process. To produce this wine, Lingzhi (5 g) is combined with Chinese spirit (500 g) and left sealed for 7 days. Drinking 20–40 ml twice daily in early morning and evening could enhance memory and strengthen the body. For the treatment of phthisis chronic cough through nourishing lung *Qi*, a Lingzhi wine [9, 10] composed of Lingzhi (75 g), ginseng (25 g), crystal sugar (250 g), and Chinese spirit (1500 ml) can be consumed. Lingzhi can also be used to make herbal wines in combination with many other herbs such as Huangqi, Shanyao (*Dioscorea opposita*), Wuweizi (*Schisandra chinensis*), and Roucongrong (*Cistanche deserticola* or *C. tubulosa*), Dazao (*Ziziphus jujuba* Mill.), depending on the specific functions needed. The daily intake amount is based on the content of Lingzhi, other herbs, and alcohol.

85.4.2.3 Lingzhi Used in Medicated Foods

In terms of the miraculous and versatile functions without toxicity, Lingzhi is also commonly used as the material of functional food in daily life. It can be used to make soups with meat, corn powder, rice, and/or with other herbs depending on different body status. The taste of Lingzhi-contained foods can be adjusted based on personal preferences.

One example of such soups is as follows: a medicated Lingzhi soup is cooked by boiling slices of Lingzhi (6 g), Heimuer (black fungus, 6 g), Baimuer (Tremella, 6 g), Mizao (6 honey dates) and lean pork (200 g) for 30 min. Consumption of this soup is said to nourish the lung and stomach, promote blood circulation, strengthen heart *Qi*, prevent and treat cancer, lower blood pressure, and prevent coronary heart disease.

85.5 Clinical Evidences

As a therapeutic medicine, Lingzhi is usually recommended as an alternative adjunct to conventional therapy in cancer treatment in terms of its potential to enhance anti-tumor response and stimulate host immunity, to improve the quality of life and prolong the survival time. There are thousands of clinical related reports or

observational studies published on the effects of Lingzhi and combinations. Ganopoly [11] is an aqueous polysaccharide fraction extracted from *G. lucidum* by patented biochemical technique and has been marketed as an OTC product for chronic diseases including cancer and hepatopathy in many Asian countries. A clinical research on immune functional evaluation of ganopoly on 34 advanced-stage cancer patients revealed that the treatment with 1800 mg ganopoly three times daily orally before meals for 12 weeks resulted in a significant ($P < 0.05$) increase in the mean plasma concentrations of IL-2, IL-6, IFN- γ , phytochemagglutinin response, and NK activity compared to baselines. The product ganopoly was also evaluated in patients with advanced lung cancer in a randomized double-blind, placebo-controlled, multicenter clinical trial. The results indicated that ganopoly may have an adjunct role in the treatment of patients with advanced lung cancer [12]. Lingzhi was generally well tolerated by most participants with only a scattered number of minor adverse events. No severe toxicity was observed across these studies.

85.6 Safety Evaluation and Toxicity Data

Lingzhi, a famous herbal medicine that has been used in TCM for thousands of years, is being used as an adjunctive to chemotherapy to help boost the immune system. Few clinical reports on the toxicity or side effects of the use of Lingzhi are available. Although laboratory research is being carried out to determine its immunostimulatory properties, no essential data on toxicity were observed in animal models in addition to few reports on cells [13].

In conclusion, Lingzhi is definitely a relative safe herbal medicine. It is often taken alone or together with other herbs in many forms for the treatment of asthenic, neurasthenia, insomnia, and prevention of cancers and coronary heart diseases.

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