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Traditional uses, chemical components and pharmacological activities of the genus *Ganoderma* P. Karst.: a review†

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In recent years, some natural products isolated from the fungi of the genus *Ganoderma* have been found to have anti-tumor, liver protection, anti-inflammatory, immune regulation, anti-oxidation, anti-viral, anti-hyperglycemic and anti-hyperlipidemic effects. This review summarizes the research progress of some promising natural products and their pharmacological activities. The triterpenoids, meroterpenoids, sesquiterpenoids, steroids, alkaloids and polysaccharides isolated from *Ganoderma lucidum* and other species of *Ganoderma* were reviewed, including their corresponding chemical structures and biological activities. In particular, the triterpenes, polysaccharides and meroterpenoids of *Ganoderma* show a wide range of biological activities. Among them, the hydroxyl groups on the C-3, C-24 and C-25 positions of the lanostane triterpenes compound were the necessary active groups for the anti-HIV-1 virus. Previous study showed that lanostane triterpenes can inhibit human immunodeficiency virus-1 protease with an IC₅₀ value of 20–40 μM, which has potential anti-HIV-1 activity. Polysaccharides can promote the production of TNF α and IFN-γ by macrophages and spleen cells in mice, and further inhibit or kill tumor cells. Some meroterpenoids contain oxygen-containing heterocycles, and they have significant antioxidant activity. In addition, *Ganoderma* has been used as a medicine to treat diseases for more than 2000 years, and we also reviewed its traditional uses.

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1. Introduction

With the increasing public awareness of drug safety, people are more inclined to choose medicinal natural products extracted from plants and fungi because of their obvious advantages of being less toxic and having less side effects.¹ Biological natural products are secondary metabolites derived from organisms. These sources can be either complex mixtures extracted from raw materials or single compounds.^{2,3} Among the well-known medicinal fungi, *Ganoderma lucidum* (Curtis) P. Karst. and other species of *Ganoderma* showed greater advantages than other chemical drugs. *Ganoderma* originated from Greek meaning shining skin, *ganos* meaning brightness and *derma* meaning skin. It was named *Ganoderma* by Finnish mycologist Petter Adolf Karsten in 1881.⁴ With the development of molecular biology, the definition of *Ganoderma* species has changed.

For example, *G. lucidum*, which is widely used in commercial cultivation in China, is now considered to be a new species of *G. lingzhi*.⁵ At present, there are 131 species of *Ganoderma* in the world.^{6–8} Among them, 20 kinds of *G. lucidum*, *G. lingzhi* Sheng H. Wu, Y. Cao & Y. C. Dai., *G. sinense* J. D. Zhao, L. W. Hsu & X. Q. Zhang. and others have been proved by modern studies to have medical value.⁹ *Ganoderma* is widely distributed in tropical and subtropical regions in Africa, America, Asia and Oceania, and it is also distributed in Europe (Fig. 1).^{10,11} As shown in Fig. 2, there are many species of *Ganoderma* in southern China, especially in the southern tropical and subtropical regions.^{6,12,13}

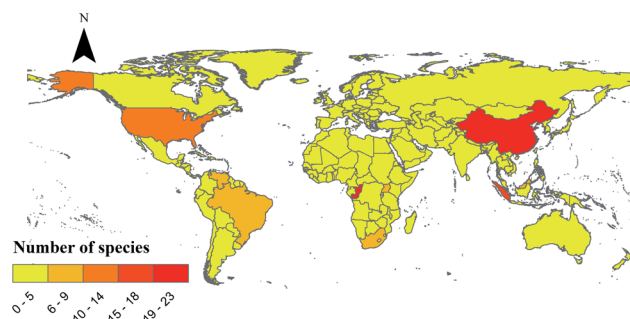


Fig. 1 The distribution information of species of *Ganoderma* in world.

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† Electronic supplementary information (ESI) available: Fig. S1: various mushrooms peddled in the market (*Ganoderma* is marked in red), Table. S1: the main chemical components of *Ganoderma*, Fig. S2: metabolites isolated from various *Ganoderma* species. See DOI: 10.1039/d0ra07219b



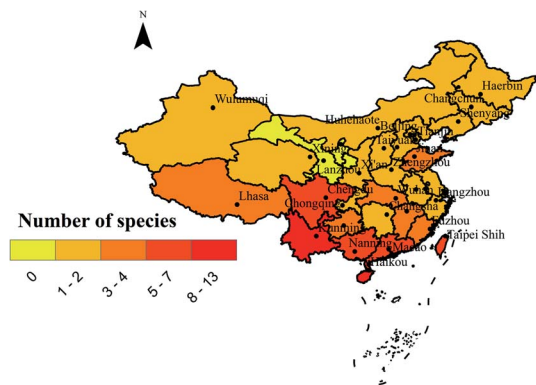


Fig. 2 The distribution information of species of *Ganoderma* in China.

G. lingzhi and other species of *Ganoderma* are medicinal and edible tonic with a history of more than 2000 years in China. There are many traditional appellations of *Ganoderma* such as “Rui-cao”, “Lin-zhi-cao”, “Wan-nian-rong” or “Xian-cao” in China and “Reishi” in Japan due to their efficacy.^{5,14} It mainly regulates human immune function, prolongs longevity and exerts anti-tumor and neuroprotective functions.^{5,14} This is one of the reasons for the increasing demand for *Ganoderma*. The main medicinal part of *Ganoderma* is the fruiting body, however, its spore powder and mycelium can also be used as medicine. Currently, *G. lucidum* and *G. sinense* were considered legal crude drug medicine in the Chinese Pharmacopoeia (2015 edition), and they have the effect of preventing cancer, neurodegeneration and cardiovascular in the clinic.¹⁶ In the United States, *Ganoderma* appears in the US market as a dietary supplement, and it is cataloged in the Dietary Supplements and Herbal Medicines of United States Pharmacopoeia.^{17,18} According to recent studies, the pharmacological activity of this genus is similar to that described in ancient classic monographs.^{19,20} It was recorded as the top grade in the classical Chinese herbal

literature Shennong's herbal classic (Shennong Ben Cao Jing) (Dong Han Dynasty, A.D. 25–220). This literature recorded that *G. lingzhi* has the effect of strengthening and restoring health.²¹ In other medical monographs, *Xin Xiu Ben Cao* records that *G. lingzhi* has the effect of “Buzhong Yiqi, Strengthen muscles and bones, Prolong life”. According to CNKI statistical analysis of patents related to China's “Lingzhi” industry from 1994 to 2019 shows that the number of “Lingzhi” patents had grown rapidly, reaching the highest peak of 1753 in 2016 (Fig. 3). There were 4338 preparation methods, accounting for 40% of the total. The patent focuses on practical applications and provides more valuable information for the development of “Lingzhi” industry. With the development of the industry, the spores and mycelium of *Ganoderma* are also used as new medicinal parts. For example, the spores of *G. lucidum* proved to have satisfactory anti-tumor and antioxidant activities.^{22,23} So far, major compounds have been isolated from the genus *Ganoderma*, including triterpenoids, polysaccharides, meroterpenoids, sesquiterpenoids, steroids and alkaloids.^{24,25} Although the use of *Ganoderma lucidum* in different national medical systems is different, triterpenes and polysaccharides are considered to be the main active ingredients.^{26,27}

G. lingzhi and other species of *Ganoderma* has been considered a precious Chinese medicine since ancient times. However, the quality of medicinal materials will be affected by species, cultivation methods and environmental factors, which is one of the important factors for extensive research on medicinal fungi. Summarizing various traditional uses, chemical components and pharmacological activity are important indicators for the quality assessment of medicinal fungi, which can provide better guidance for the rational use of *Ganoderma*. In this review, it mainly introduces the compounds found in the genus of *Ganoderma* fungi in the past 35 years, including the corresponding chemical structure, biological activity and a comprehensive compilation of its traditional uses, cultivation methods and historical culture. Therefore, this study aims to provide a certain

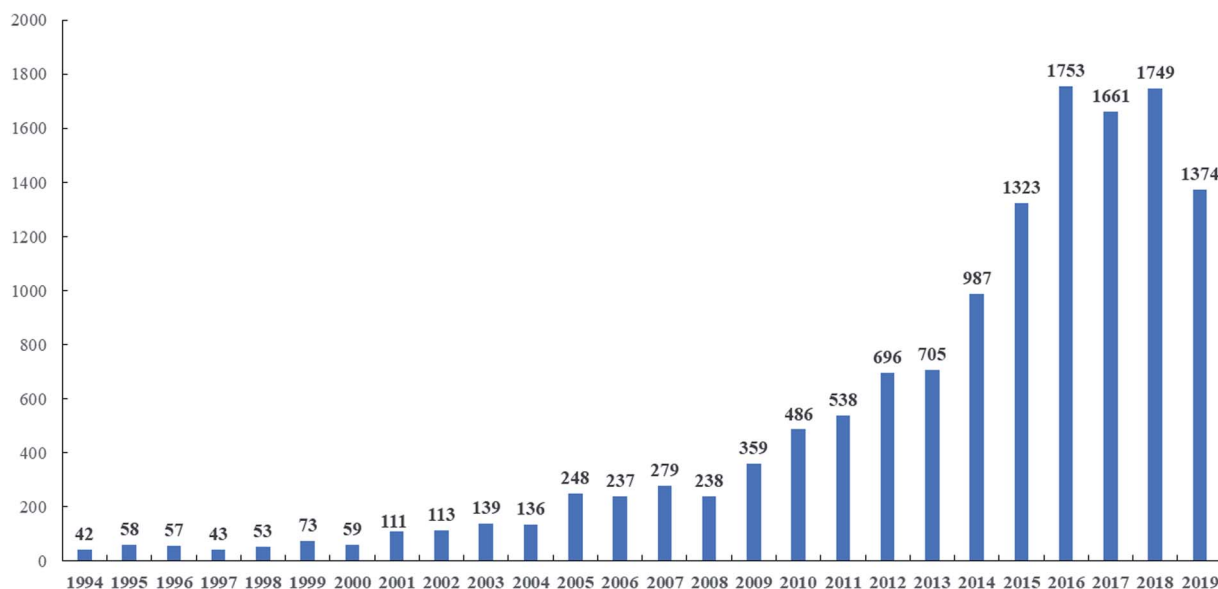


Fig. 3 The number of patents of *Ganoderma* applied in China during 1994–2019.



theoretical basis for the quality control and rational use of *Ganoderma* by searching relevant literature and medicinal historical records, and to tap into potential development value.

2. Medicinal history and experience in ethnic minorities of *Ganoderma*

Ganoderma is a medicinal fungus and has been recorded in Shennong's herbal classic for more than 2000 years. The Shennong's herbal classic recorded "Chizhi", "Qingzhi", "Heizhi", "Baizhi", "Huangzhi" and "Zizhi". These six species of *Ganoderma* have the effects of improving eyesight, strengthen muscles and bones, reinforcing kidney, soothe the nerves.²⁸ Regular consumption of *Ganoderma* has been linked to the relaxed body, alleviate aging and prolong life. However, recent researches have shown that *Ganoderma* can be traced back to more than 6000 years ago. Five prehistoric samples of *G. lucidum* were found from three Neolithic sites in Zhejiang Province, China. The samples in the Tianluoshan site were 6817 ± 44 years old.²⁹ It was speculated that *Ganoderma* was already used by witch doctors at that time. And along with the formation of early agriculture, people have continued exploration and exploitation of *Ganoderma*. During the Dongjin Dynasty, *Ganoderma* was ranked as panacea in an important Taoist work of Ge Hong's Bao Puzi (317 A.D.), and it was believed that the edible *Ganoderma* could extraordinary power and became immortal. Since then, *Ganoderma* has been endowed with a mysterious color, and the praise of *Ganoderma* reached a climax. Due to the limitations of world view and scientific level at that time, people's understanding and research on *Ganoderma* was limited and superstitious. Later, during the Ming Dynasty, some critical views emerged. Li Shizhen's Compendium of Materia Medica (1578 A.D.) believed that *Ganoderma*, which grows on decaying wood, was like a tumour on a human body. But ancients use it as panacea, which is too ridiculous. Li Shizhen denied the rumors that eating *Ganoderma* could live forever, and pointed out the functions of improving eyesight, strengthening muscles and bones, reinforcing kidney and soothing the nerves. *Ganoderma* was even exaggerated to have the function of resurrection and become immortal, in some ancient Chinese legends. However, since the Tang and Song Dynasties, *Ganoderma* is gradually recognized as a medicinal fungus by people's continuous understanding of herbs. Nowadays, *G. lucidum* and *G. lingzhi* are widely cultivated in China and neighboring countries, both of which can be used to soothe the nerves, relieve cough, treat insomnia and anorexia.^{30–32} Since ancient times, people's understanding of *Ganoderma* is a gradual process. From discovery to utilization and then to dialectical understanding, it is a piecemeal process of evolution, which also reflects the process of development and change of Chinese medicine. It shows how the ancients used the surrounding herbs and fungi to prevent and treat various diseases. The medicinal history of *Ganoderma* is summarized in Table 1.

Among the medical local knowledge of ethnic minority communities, *Ganoderma* has a unique value. China is a multi-ethnic country, and all ethnic groups people have accumulated

their own drug experience in long-term life practice. Therefore, they formed rich and colorful national traditional medicine. Due to the influence of the environment, culture and medical theory about the medicinal methods of *Ganoderma* in ethnic minorities, different drug habits and experiences have been formed, such as Shui, Miao, Yi, Jingpo, Achang. In the Jingpo ethnic group, *Ganoderma* is called as Natmauchi, which is used to treat dizziness, insomnia, neurasthenia, hypertension, hypercholesterolemia and hepatitis. The Hani name for *Ganoderma* is Ahonglana, which is used for treating neurasthenia, hypertension, chronic bronchitis, silicosis in Hani medicine. Regarding the Chinese names and usage of *Ganoderma* in different ethnic minorities, Jia and Li summarized the use of this medicinal material by some China ethnic minority groups (Table 2).³³ Some medicinal uses of *Ganoderma* (soothing the nerves, relieving cough and treating insomnia, etc.) were shared by some ethnic minorities and compliance were also record in Chinese Pharmacopoeia. *Ganoderma* has different uses in many ethnic groups. Because different geographical factors and ethnic cultural traditions influence differences in medical knowledge, they have different experiences in using the crude drug.

3. Cultivation methods and cultural connotations of *Ganoderma*

As a widely distributed fungus, *Ganoderma* has attracted extensive attention for its economic value. *Ganoderma* was developed into a variety of products such as powders, teas and dietary supplements, with global sales of these products estimated to exceed \$2.5 billion,³⁴ with sales growing at an annual rate of 18%.^{35,36} The wild fungus resources are abundant in Yunnan, China. Local residents often collect various wild fungus in the mountains and sell them in the mushroom market as part of their economic income. *Ganoderma* is also an important part of wild fungus resources, and it often appears in these markets (Fig S1†). *Ganoderma* appears in the modern market in the form of health care products or ornamentals. Due to the high medicinal and ornamental value of *Ganoderma*, people try to grow it. Before the 1990s, there were not any reports on artificial cultivation of *Ganoderma* in the world. Although some people tried to cultivate it, they failed because it could not form pileus. As shown in Fig. 4a and b, wild *Ganoderma* usually grows on the trunks, stumps, fallen and rotten wood of broad-leaved trees in diffused sunlight woodland with high humidity requirements. In the natural environment, they can easily form a complete fruit body, but cannot form a cap in the laboratory. The Fungal Research Laboratory of the Institute of Microbiology, Chinese Academy of Sciences firstly discovered in 1991 that high air relative humidity (85–95%) was the key factor for the formation of basidiocarps and the release of the spores of *Ganoderma*.³⁷ The method and technology of large-scale artificial cultivation of *Ganoderma* were realized in 1992, and it was also the first example of the successful use of modern scientific methods to cultivate *Ganoderma*. The research institute popularized this method free of charge, which has made an important contribution to the rapid development of *Ganoderma*



Table 1 Medicinal history of *Ganoderma*

Date of origin	Chinese ancient literatures	Medicinal part	Application
About 206 B.C. to 220 A.D.	Shennong's herbal classic	Fruiting body	Adjusting the function of spleen and stomach, amnesia, prolong life
About 317 A.D.	Bao puzi	Fruiting body	Live forever and become an immortal
About 492 A.D. to 536 A.D.	Shennong's herbal classic ji zhu	Fruiting body	Adjusting the function of spleen and stomach, amnesia, prolong life, improving eyesight, soothe the nerves
659 A.D.	Xin xiu ben cao	Fruiting body	Cure deafness, lubricate joints, tonifying middle-jiao and qi, strengthen muscles and bones, prolong life
682 A.D.	Qian jin yi fang	Fruiting body	Improving eyesight, nourishing the liver, soothe the nerves
992 A.D.	Tai ping sheng hui fang	Fruiting body	Relax physically and psychologically
1098 A.D.	Zheng lei ben cao	Fruiting body	Cure deafness, lubricate joints, tonifying middle-jiao and qi, strengthen muscles and bones, prolong life
1406 A.D.	Pu ji fang	Fruiting body	Treatment of gingival bleeding
1436 A.D.	Dian nan ben cao	Fruiting body	Tonifying middle-jiao and qi, relieve cough, oppression in chest
1505 A.D.	Ben cao ping hui jing yao	Fruiting body	Strengthen muscles and bones, improving eyesight, soothe the nerves, nourishing the liver.
1565 A.D.	Materia medica companion	Fruiting body	Relax physically and psychologically, oppression in chest
1578 A.D.	Compendium of materia medica	Fruiting body	Tonifying middle-jiao and qi, strengthen muscles and bones, lubricate joints, protecting the kidney,
1604 A.D.	Wai ke qi xuan	Fruiting body	Carbuncle-abscess
1647 A.D.	Ben cao cheng ya ji	Fruiting body	Cure deafness, lubricate joints, strengthen muscles and bones, protecting the kidney, prolong life
1765 A.D.	Compendium of materia medica shi yi	Fruiting body	Relax physically and psychologically, rectal prolapse
1769 A.D.	Ben cao qiu zhen	Fruiting body	Purging heat

industry in China. Rani *et al.* found that the sawdust supplemented with dextrose medium improved the quality and biological efficiency of *G. lucidum* because dextrose provided a good carbon source for the Mycelial growth.³⁸ Using wheat straw as substrate to form *G. lucidum* fruiting bodies shorter time, higher yield, higher biological efficiency and lower cost.³⁹ *Ganoderma* is not only used as traditional Chinese medicine but also has a high ornamental value. Contemporarily, shapely *Ganoderma* is made into the potted landscape in the home for viewing. In traditional Chinese culture, *Ganoderma* symbolizes auspiciousness and fortune, and "ruyi" (a kind of ornament that represents auspicious) is made according to the shape of *G. lucidum*. The image of *Ganoderma* also appears in paintings, railings, furniture, wood carvings, carpets and handicrafts.⁴⁰ It is precise because of the medicinal value and cultural symbols of *Ganoderma* that it is deeply loved by people, which makes the *Ganoderma* industry flourish.⁴¹

The successful tamed of *Ganoderma* had laid the foundation for the rapid development of the *Ganoderma* industry. In

addition, it is beneficial to the human body and has ornamental value, making it a popular medicinal fungus. *Ganoderma* culture has a major and far-reaching impact on the cultural fields of philosophy, medicine, literature, and art in China. However, modern pharmacological research is mainly focused on the chemical constituent activity of *Ganoderma*. Many studies proved that *Ganoderma* has a variety of pharmacological activities, and chemical components are the premise for studying these pharmacological activities and their mechanisms.^{24,42,43} Therefore, it is necessary to review the chemical components and pharmacological activities of *Ganoderma*.

4. Chemical components of *Ganoderma*

In the past 35 years, chemical components have been separated from the fruiting bodies, sporophytes and mycelia of

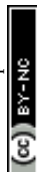


Table 2 Medicinal record of *Ganoderma* in ethnic minority

Ethnic minorities	Name	Chinese name	Medicinal part	Indications	Record
<i>G. sinense</i>					
Yi (彝)	Zilingzhi	紫灵芝	Fruiting body	Testicular swelling, prostatitis	<i>Ai Lao Ben Cao</i>
Miao (苗)	Zilingzhi	紫灵芝	Fruiting body	Cough, asthma, insomnia, dyspepsia	<i>Hunansheng Lanshanxian Zhong Cao Yao Zi Yuan Kao Cha Yu Yan Jiu</i>
Tibetan (藏)	Guoxia mobu	过夏莫布	Fruiting body	Neurasthenia, chronic bronchitis, insomnia, hypertension, dizziness, hepatitis, trachitis, arthralgia	<i>Zhong Hua Zang Ben Cao</i>
<i>G. lucidum</i>					
Aching (阿昌)	Maone	毛呢	Fruiting body	Dizziness, insomnia, neurasthenia, hypertension, hypercholesterolemia, hepatitis	<i>De Hong Ming Zu Yao Lu</i>
Lisu (傈僳)	Miqiguo	米其果	Fruiting body	Stomachache, neurasthenia, chronic bronchitis, detoxification of mycotoxins	<i>Nu Jiang Zhong Cao Yao</i>
Hani (哈尼)	Ahong lana	阿烘喇拿	Fruiting body	Dizziness, insomnia, neurasthenia, hypertension, chronic bronchitis, silicosis	<i>Yuan Jiang Ha Ni Zu Yao</i>
Tibetan (藏)	Guoxia saibu	过夏塞布	Fruiting body	Neurasthenia, stomachache, chronic bronchitis, insomnia, hypertension, dizziness, hepatitis, trachitis, arthralgia	<i>Zhong Hua Zang Ben Cao</i>
Chaoxian (朝鲜)	Lingzhi/bulaocao	灵芝/不老草	Fruiting body	Asthenia, neuropathy, arteriosclerosis/dizziness, insomnia, neurasthenia, hypertension, hepatitis, chronic bronchitis, asthma, silicosis, rheumatic arthritis, rhinitis, asthenia, neuralgia, arteriosclerosis	<i>Chao yao zhi/Chao Xian Zu Ming Zu Yao Cai Lu</i>
Man (满)	Shabingacan	沙炳阿参	Fruiting body	Coronary heart disease, trachitis, bronchial asthma	<i>Man Zu Chang Yong Yao Jian Jie</i>
Bai (白)	Lingzhi/lingzhi cao	灵芝/灵芝草	Fruiting body	Dizziness, insomnia, cough, neurasthenia, bronchitis, dyspepsia	<i>Da Li Zhong Yao Zi Yuan Zhi</i>
De' ang (德昂)	Diguozhong	地果众	Fruiting body	Dizziness, insomnia, neurasthenia, hypertension, hypercholesterolemia, hepatitis	<i>De Hong Ming Zu Yao Lu</i>
Jingpo (景颇)	Natmauchi	Natmauchi	Fruiting body	Dizziness, insomnia, neurasthenia, hypertension, hypercholesterolemia, hepatitis	<i>De Hong Ming Zu Yao Lu</i>
Jinuo (基诺)	Mulumuka	母鲁母卡	Fruiting body	Hypertension, hepatitis, rheumatic arthritis, body aches	<i>Ji Nuo Zu Yi Yao</i>

Ganoderma (Table S1†) including triterpenoids (1–561), meroterpenoids (562–792), sesquiterpenoids (793–815), steroids (816–875), alkaloids (876–906), polysaccharide, volatile oils and

other types. These chemical structural formulas are listed (Fig. S2†). Clinical studies have been confirmed that triterpenoids and polysaccharides have a good effect. According to the



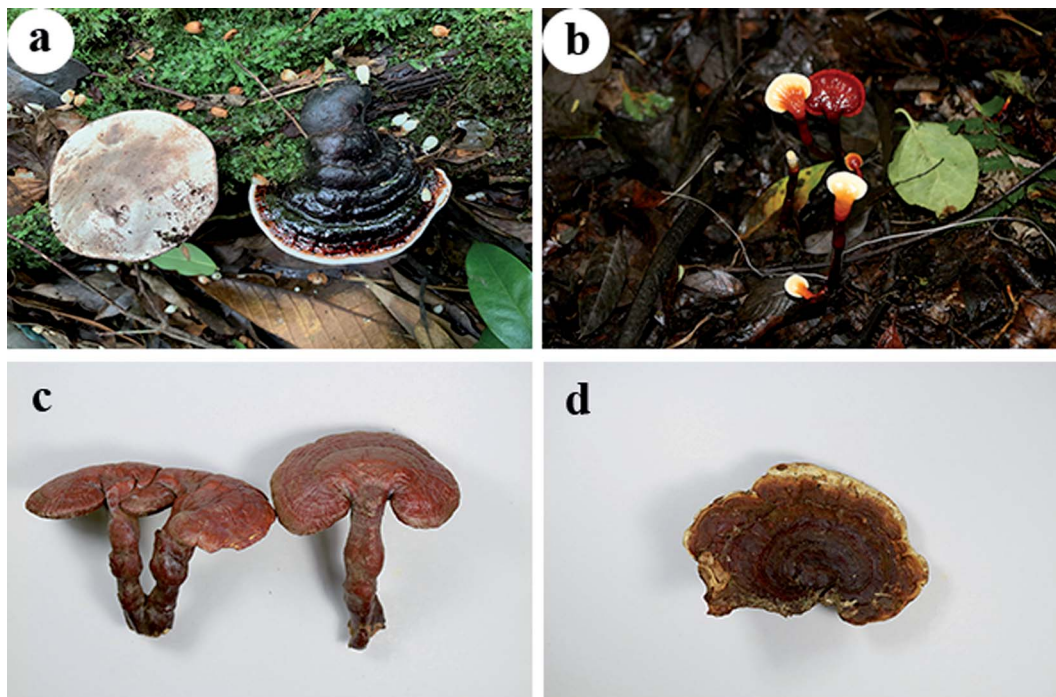


Fig. 4 Fruiting body of *Ganoderma*. (a) *G. cochlear*; (b) *G. kunmingense* J.D. Zhao.; (c) *G. lingzhi*; (d) *G. tropicum* (Jungh.) Bres.

Chinese Pharmacopoeia (2015 edition), the dry fruiting body of *Ganoderma*, polysaccharides shall not be less than 0.90%, and the triterpenoids not be less than 0.50%.³⁰

4.1 Triterpenoids

Most triterpenoids are a class of terpenoids with a basic mother nucleus of 30 carbon atoms, which can be considered to polymerize from six isoprene units. Most of the triterpenoids that have been discovered so far are tetracyclic triterpenoids and pentacyclic triterpenoids, and a few are chain, monocyclic, bicyclic and tricyclic triterpenoids.^{44,45} The tetracyclic triterpenes of *Ganoderma* are highly oxidized lanosteran-type triterpenoids derivatives. Depending on the structure and functional groups, it is further divided into ganoderic acid, methyl ganoderate, ganodermic acid, ganosporeri acid, ganodsporelactone, ganolucidic acid, ganoderal, lucidenic acid, methyl lucidenate, lucidone, ganolactone, lucialdehyde. The double bonds on the ring are mostly located at C8-9, C9-11, C22-23, and C24-25. There is often a methyl group on C25, and the carbonyl group is mostly located at C11 and C23, C3, C7 and C15 are also often replaced by carbonyl or hydroxyl.⁴⁶

Ganoderma contains a large number of triterpenoids, most of which have a bitter taste. More than half of triterpenoids are isolated from *G. lucidum*. Among the common species *G. lucidum*, *G. Lingzhi*, *G. sinense* and *G. leucocontextum*, 61 percent of 561 triterpenoids were isolated (as shown in Fig. 5). It is found in *Ganoderma* fruit bodies and spores, such as ganoderic acid A (10), ganoderic acid B (11), ganoderic acid G (17), ganoderic acid H (18).⁴⁷ Pharmacological studies have confirmed that *Ganoderma* triterpenes (GTs) can inhibit tumor cells, lower blood pressure, protect the liver, lower cholesterol, and resist

biological activities such as human immunodeficiency virus.^{42,48} The structural changes of the side chains of lanostane-type triterpenoids have significant effects on their hypoglycemic activity, especially the OH substituents at C-3 and the double bond parts at C-24 and C-25.⁴⁹ In addition, ganoderic acid MK (92) and T (111) have the same parent ring structure, but their structures have different degrees of acetylation. 92 has 2 acetyl groups and 111 has 3 acetyl groups. These structural changes have varying degrees of influence on the pharmacological activities of triterpenes.⁵⁰

4.2 Meroterpenoids

Meroterpenoid is a natural product widely distributed in plants, fungi and marine invertebrates. The biosynthesis of meroterpenoids originates from a mixed pathway of the shikimate pathway and the polyisoprene pathway.⁵¹ Meroterpenoids are often introduced into many heteroatoms in the process of biosynthesis, which makes the molecular structure form different polar centers, the molecular properties are more active and have strong reactivity. *Ganoderma* meroterpenoids are a class of meroterpenoids containing 1,2,4-trisubstituted phenyl and polyunsaturated terpenoid part.⁵² Some meroterpenoids contain oxygen-containing heterocycles, and these compounds were mainly concentrated in oxygen-containing five-membered heterocycles and oxygen-containing six-membered heterocycles. They generally have good biological activity, for example, the oxygen-containing five-membered heterocyclic compound fornicin E (590) had a stronger antioxidant effect than the positive control vitamin E.⁵³

A large number of meroterpenoids are currently found in the fruiting bodies of *Ganoderma*. The meroterpenoids isolated from *G. cochlear*, *G. applanatum*, *G. lucidum* and *G. theaeacolum*

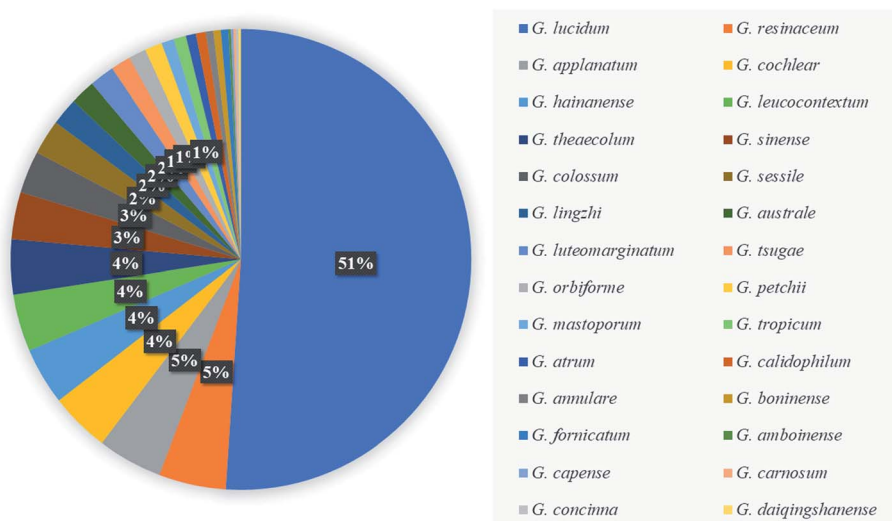


Fig. 5 The percentage of triterpenes isolated from 28 species of *Ganoderma*.

accounted for 74% of the 231 meroterpenoids (as shown in Fig. 6). The meroterpenoids isolated from *G. cochlear* have received widespread attention and proved to have a wide range of biological activities. The fungal-derived meroterpenoids have various biological activities such as antibacterial,⁵⁴ antifibrotic, cytotoxic and NO production inhibitory.^{55,56} Wang *et al.* found that cochlearoid F-I, K (669–672, 674) have significant renoprotective activity to reduce oxidative stress through Nrf2 activation.⁵⁷ At present, there are few studies on meroterpenoids, but they have great potential to be developed into a new framework for epigenetic agents.⁵⁸ It can be used as one of the important research objects to evaluate the efficacy of *Ganoderma* in the future.

4.3 Sesquiterpenoids

The basic carbon frame of sesquiterpenoids is composed of 15 carbon atoms, that is, 3 isoprene units. It is a volatile oil component, and the sesquiterpene oxygenated derivatives have strong aroma and biological activity. Farnesyl pyrophosphate (FPP) is a precursor of sesquiterpene biosynthesis. Pyrophosphate group is removed from *cis*, *trans*-FPP and *trans* and *trans*-FPP, and cyclize with their corresponding double bonds to form appropriate cyclic positive carbon ions. Finally, the Wagner–Meerwein rearrangement or the 1, 2-displacement (or elimination) of the methyl group results in the formation of sesquiterpenoids of various carbon framework types. The sesquiterpenoids can be classified into acyclic sesquiterpenoids, monocyclic sesquiterpenoids, bicyclic sesquiterpenoids and tricyclic sesquiterpenoids. Most of *Ganoderma* is a double-

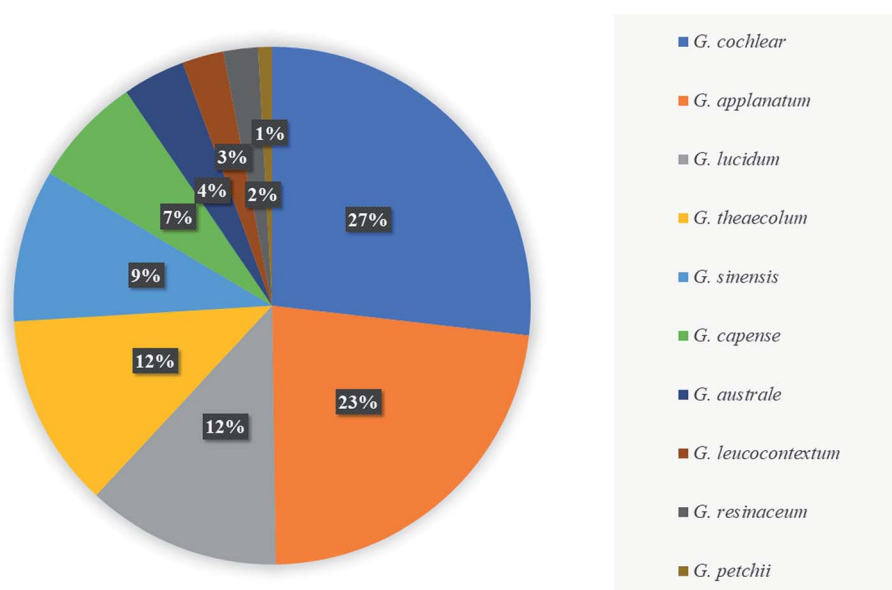


Fig. 6 The percentage of triterpenes isolated from 10 meroterpenoids of *Ganoderma*.



ringed sesquiterpenoid, and Zhen *et al.* isolated 11 sesquiterpenoids from the mycelium of *G. lucidum*, ganodermanol A–K (796–806).⁵⁹ Among them, 796–803 are cadinane-type sesquiterpenoids, and 804–806 are eudesmane-type sesquiterpenoids. The sesquiterpene in *Polyporus brumalis* has antifungal activity,⁶⁰ but there are few studies on the sesquiterpene of *Ganoderma* and it is worthy of further study.

4.4 Steroids and alkaloids

Steroids are found in *Ganoderma* fruit bodies and spores. The B/C rings of natural steroid compounds are trans, C/D rings are mostly trans, and A/B rings are *cis* and reverse. Therefore, the steroids can be divided into two types, the A/B ring *cis*-fused mode. That is the hydrogen atom on C5 and the horn methyl group on C10 extend to the front of the ring plane, on the same side, which is a β configuration. The A/B ring *trans*-fused mode (allo), that is, the hydrogen atom on C5 extends to the rear of the plane of the ring, and is not on the same side as the horn methyl group on C10, which is an α configuration. The C10, C13 and C17 side chains of steroids are mostly β configurations, C3 has hydroxyl group, and most of them are β configuration.⁶¹

Alkaloids are a class of nitrogen-containing organic compounds, most of which have complex cyclic structures. The nitrogen atoms are bound in the ring and are mostly alkaline, which can react with acids to form salts. Two novel pyrrole alkaloids ganoine and ganodine have been isolated from the mycelium of *G. capense* obtained by submerged fermentation.⁶² In the biosynthetic pathway of alkaloids, amino acids are generally considered to be their starting substances. Most of the skeleton of these amino acids remains in the alkaloids synthesized. At present, there are few alkaloids isolated from *G. lucidum*. The 32 alkaloids collected in this paper are listed in Table S1,[†] including pyrrolidine alkaloids, indoles alkaloids, quinolones alkaloids.

4.5 Polysaccharides

Polysaccharide is a polymer compound composed of ten or more monosaccharides which are polymerized by glycosidic bond, and is usually composed of several hundred to several thousands of monosaccharides and has a large molecular weight. GPs can be isolated from fruiting bodies, mycelia and spore powders, such as heteropolysaccharides ($1\beta \rightarrow 6, 1\beta \rightarrow 3$ bindings of arabinogalactan), dextran ($1\beta \rightarrow 6, 1\beta \rightarrow 3$ binding), peptide polysaccharides, mannose and galactose. Bao *et al.* found that the degree of substitution in the main chain and the length of the side chain may be important factors affecting the conformation and biological activity of *G. lucidum* polysaccharides (GLPs).⁶³ In general, the molecular weight of GPs is generally greater than 1×10^4 to be biologically active. There is no significant difference in the activity between these GPs, but the disruption of the three-dimensional helical structure affects its activity.

GPs are divided into two types, α -type and β -type. The former has no biological activity, and the β -type structure of GPs has biological activity. The glycosidic bond is linked by $\beta(1 \rightarrow 3)$, $(1 \rightarrow 6)$, or $\beta(1 \rightarrow 4)$, $(1 \rightarrow 6)$. Biological activity is not only related to the primary structure but also largely affected by secondary

and tertiary structures, in which intra- or extra-chain hydrogen bonding is an important factor in determining the level of biological activity.⁶⁴

4.6 Others

There are also a large number of volatile oils such as alcohols, aldehydes and ketones, hydrocarbons and their derivatives, acids, esters, *etc.*, which are found in *Ganoderma* fruit bodies and spore powders. Among them, the spore powder has many volatile components and little amount, most of them are aliphatic compounds.^{65–67} Al-Fatimi *et al.* reported for the first time the composition and biological activity of volatile oils from *G. pfeifferi*, indicating that volatile oils have strong free radical scavenging activity.⁴³ *Ganoderma* contains various trace elements such as Al, B, Ca, Cu, Fe, K, Na, Mg, Mn, Pb, Zn, P, Ni, Co, Mo, Li, V, Sn, Ge, Ti, Se, Cr, containing a variety of human essential elements. This *Ganoderma* organic selenium is deserved a further study of pharmacological effect.^{68,69} *Ganoderma* also contains nucleosides, vitamins C and E, carotene, *etc.*⁷⁰

5. Pharmacological activities

Ganoderma is a popular traditional Chinese medicine, and people pay attention to its true pharmacological effects. Several recent systematic studies have established the therapeutic potential of *Ganoderma* as antitumour, hepatoprotective, anti-inflammatory, immunomodulatory, antioxidant and antiviral.^{15,24,71}

5.1 Antitumour activity

The anti-tumor activity of *Ganoderma* have gradually attracted the attention of researchers. The anti-tumor effect is related to promoting tumor cell apoptosis and enhancing the immune regulatory function of host cell.

Ganoderma extract (GES) and *Ganoderma* spore oil (GSO) proved definite anti-tumor effects in the *in vitro* and *in vivo* studies. GES and GSO inhibited the growth of human leukemia cells (K562 and HL60) and human gastric cancer cells (SGC-7901). Topoisomerases I and II may be the target of GES and GSO actions.⁷² Triterpenoids plays an important role in the anti-tumor activity of *Ganoderma*. Wu *et al.* isolated two new triterpenoids from *G. lucidum*, lucidenic acid N (162) and methyl lucidenate F (173). It was confirmed that 162, lucidenic A (154) and ganoderic acid E (15) had obvious cytotoxicity to Hep G2, Hep G2, 2, 15 and P-388 tumor cells.⁷³ The lanosteranes triterpenes isolated from *G. lucidum* showed good cytotoxic activity to gastric cancer cells HGC-27, cervical cancer cells HeLa, lung cancer cells A449, liver cancer cells SMMC-7721 by MTT method.⁷⁴ The results showed that most of the triterpenoids inhibited the proliferation of four kinds of cancer cells. Among them, (5 α ,24E)-3 β -acetoxyl-26-hydroxy lanosta-8,24-dien-7-one (241) showed good cytotoxic activity against four kinds of cancer cells, and the IC₅₀ value of inhibiting cervical cancer HeLa proliferation could reach 1.29 μ M. At the same time, the study also showed that the C-26 and C-3 substituents of



triterpenes in *G. lucidum* affected cytotoxic activity.⁷⁵ For example, when the hydroxyl group or acetoxy group of C-3 was oxidized to ketone, the cytotoxicity was weakened. Nguyen *et al.* found that lucidadiol (265) and ganodermanondiol (318) have significant cytotoxic activity in anti-tumor *in vitro* tests, and ganoderic acid F (16) can control cancer by inhibiting angiogenesis.⁷⁶ In addition, the alkaloid compound lucidimine B (904) with nitrogen-containing heterocycles and oxygen-containing heterocycles induces DNA fragmentation to arrest the cell cycle of human breast cancer MCF-7 in S phase, thereby reducing the mitochondrial membrane potential. It has the effect of inhibiting the proliferation of MCF-7 cells, with an EC50 value of $0.27 \pm 0.02 \mu\text{mol mL}^{-1}$.⁷⁷

GPs also plays an important role in anti-tumor activity. Huang *et al.* found that *G. lucidum* polysaccharide has no direct inhibitory effect on tumor cells cultured *in vitro*, but has an obvious inhibitory effect on tumor cells *in vivo*.⁷⁸ It indicates inhibitory activity may be achieved by enhancing immune function to achieve antitumour activity. GLPs can promote the production of TNF α and IFN- γ by macrophages and spleen cells in mice, and further inhibit or kill tumor cells.⁷⁹ Cao and Lin proved that GLPs have the effect of inhibited growth of Sarcoma 180 in tumor-bearing mice *in vivo*.⁸⁰ GLPs still have high antitumor activity in immune-deficient mice. It is suggested that the anti-tumor activity of GPs involves other pathways, and anti-angiogenesis may be one of the mechanisms of antitumour effect of GPs. Triterpenoids and polysaccharides play an important role in antitumor activity, and the specific antitumour mechanism is still unclear, which needs further study.

5.2 Hepatoprotective activity

The liver of the human body has the function of degrading alcohol, but frequent and excessive drinking will cause alcoholic liver damage. Triterpenoids are the main components of the ethanol extract of *G. lucidum*, which can regulate the conversion of CYP2E1 to regulate the conversion of ethanol into acetaldehyde/acetate and up-regulation alcohol dehydrogenase 1 of tautomerism between aldehydes and alcohols or ketone in humans.⁸¹ Peng *et al.* found that fornicatin A, D, and F (392, 394, 398) can effectively lower the alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels in H₂O₂-treated HepG2 cells.⁸² The detection indexes of liver injury include ALT, AST and lactate dehydrogenase,⁸³ which suggests that *Ganoderma* has liver protective activity *in vivo*. GPs have hepatoprotective activity against carbon tetrachloride-induced liver cell damage in carp by inhibiting lipid peroxidation, increasing antioxidant enzyme activity and inhibiting apoptosis.⁸⁴

5.3 Anti-inflammatory activity and anti-microbial activity

GTs have anti-inflammatory activity against mouse macrophage line (RAW264.7) inflammation caused by lipopolysaccharide. Wu *et al.* isolated six triterpenoids from *G. lucidum*.⁸⁵ Among them, the compound methyl lucidenate L (198) has a strong inhibitory effect on the NO-induced by LPS and

attenuates the production of pro-inflammatory cytokines including IL-6 and IL-1 β in RAW264.7 cells. At the same time, 198 effectively reduced the expression levels of iNOS, COX-2 and NF- κ B, and inhibited the phosphorylation of I κ B α and IKK β in LPS-induced macrophages. Li *et al.* showed that triterpenoids isolated from *G. lucidum* have anti-inflammatory activity, which could significantly reduce the accumulation of cadmium in chicken liver, thereby reducing oxidative stress and inflammatory response.⁸⁶ In the future, the total triterpenoids of *G. lucidum* are expected to become a functional food for preventing inflammation.

G. pfeifferi and other species of *Ganoderma* have been confirmed to have broad spectrum activity and bactericidal effects.⁸⁷ The meroterpenoids compound ganomycins A and B (720 and 721) isolated from *G. pfeifferi* showed antibacterial activity against Gram-negative and Gram-positive bacteria. Especially for Gram-positive bacteria, such as *Bacillus subtilis*, *Staphylococcus aureus* and *Micrococcus flavus*, the inhibition zone is 15–25 mm.⁸⁸ D-glucose is the main component of GLPs and plays an important role in inhibiting the growth of pathogenic bacteria.²⁴ GLPs also show broad-spectrum activity and bactericidal effects, among which *Micrococcus luteus* was the most sensitive, with a minimal inhibitory concentration (MIC) value of 0.63–1.25 mg mL⁻¹.⁸⁹ The volatile oil of mushroom seldom had antibacterial activity, but the volatile oil extracted from *G. Pfeifferi* showed strong antibacterial activity against *S. aureus* (30 mm, MIC 0.3 mg mL⁻¹) and *B. subtilis* (20 mm, MIC 0.6 mg mL⁻¹). In addition, it had a significant inhibitory effect on *Candida albicans* (MIC 0.6 mg mL⁻¹). The natural products of *G. pfeifferi* and other species of *Ganoderma* may have a synergistic effect, which means that the clinical effect usually depends on the combination of several ingredients.

5.4 Immunomodulatory activity

There have been many studies on the characteristics that *Ganoderma* can improve the immune ability, among which GPs have an important effect on immune regulation. The immune system is an important system to perform immune response and immune function, which is composed of immune organs, immune cells and immune molecules. GLPs can achieve immunomodulatory activity by activating a variety of immune-related cells, such as B lymphocytes, T lymphocytes, dendritic cells (DCs), macrophages and natural killer cells (NKs).⁹⁰ The immune regulation mechanism of *Ganoderma lucidum* mainly depends on the following aspects.

5.4.1 Effect on macrophages. The macrophage is an important kind of immune cell in the body. The phagocytic ability of macrophages reflects the immune level of the body. Macrophages can directly destroy bacteria or cancer cells, or presenting them to T cells. The levels of interleukin-1 β , tumor necrosis factor (TNF)- α and IL-6 in cultured macrophages treated with GLPs (100 mg mL⁻¹) were significantly higher than those in the control group.⁹¹ These cytokines enhance the immune ability of the body and play the role of anti-inflammation and antitumour. Yu *et al.* studied the



immunomodulatory effects of polysaccharides isolated from *G. atrum* on mouse macrophage cell line RAW264.7, and found that *G. atrum* polysaccharides can promote macrophage phagocytosis and increase NO production.⁹² In addition, GLPs have a protective effect on macrophage injury induced by reactive oxygen species.⁹³

5.4.2 Effects on natural killer cells and dendritic cells. NKs are immune cells that can directly kill pathogens. It can be used as one of the indicators for judging the body's anti-tumor and anti-viral infections. The amount of it and the strength of its activity have a very close relationship with the body's ability to resist disease. Zhu *et al.* showed that the cytotoxic activities of NKs and lymphokine-activated killer (LAK) were enhanced after the intragastric administration of GLPs for 7–9 days.⁹⁴ NKs can enhance the expression of the domain (CD86) on DCs, which plays an important role in tumor response.^{95,96}

DCs are a kind of leukocyte derived from bone marrow pluripotent hematopoietic stem cells. Wang *et al.* found that polysaccharide (PSG-1) isolated from *G. atrum* could stimulate the maturation of DCs in mice.⁹⁷ DCs were induced to produce cytokines (IL-12p70, IL-10 and IL-6) to enhance immune regulation. Besides, GLPs combined with gold to form nanocomposites can efficiently induce (DC) activation in dendritic cells.⁹⁸

5.4.3 Effects on T lymphocytes and B lymphocytes. Both T cells and B cells are derived from pluripotent stem cells of bone marrow. T cells play various roles in immunity, such as directly killing target cells, assisting or inhibiting B cells from producing antibodies and producing cytokines. In the presence of PSG-1, the release of IFN- γ in T cells is greatly promoted.⁹¹ PSG-1 has an immunomodulatory effect on splenic lymphocytes. Xiang *et al.* (Xiang *et al.*, 2017). found that the polysaccharide PSG-1 extracted from *G. atrum* has the function of promoting the proliferation of T lymphocytes, and the content of IL-12, IL-2 and IFN- γ is increased. In addition, PSG-1 increased intracellular Ca²⁺ concentration, calcineurin activity and increased expression levels of p-ERK, p-JNK and p-p38 in the cell.⁹⁹ Zhang *et al.* used successful chromatographic steps to extract a biologically active component from *G. lucidum*.¹⁰⁰ The biologically active component-treated mouse spleen lymphocytes showed a significant increase, increasing the percentage of B cells by 3–4 times and activation.

5.5 Antioxidant activity

Free radicals can cause lipid peroxidation, which can damage cell membranes, damaged tissue cells and cell death lead to great harm to the human body. Studies have confirmed that *Ganoderma* is a very promising fungus with antioxidant activity. Seven new compounds isolated from *G. cochlear*.¹⁰¹ Among them, ganocochlearin A (627), ganocochlearin B (628), ganocochlearin C (629), and ganocochlearin D (630) have strong scavenging effects on DPPH radical, ABTS⁺ radical and hydroxyl radical. The volatile oil component isolated from *G. pfeifferi* and the alkaloid component isolated from *G. lucidum* also have a strong scavenging effect on DPPH radical, such as nitrogen-

containing heterocyclic compounds lucidimines B and C (904 and 905).^{43,77}

These nitrogen-containing heterocycles may play a crucial role. In chicken liver, GTs had resistance to cadmium-induced peroxidation damage. The contents of superoxide dismutase and glutathione peroxidase in chicken liver treated with GTs were significantly higher than those in the control group, and had better antioxidant activity.⁸⁶ The meroterpenoids compounds fornicin E (590), ganocapensin A (711), B (712) and ganomycin F (723) isolated from *G. capense* can effectively scavenge DPPH free radicals with IC₅₀ values of 6.00 ± 0.09 , 7.79 ± 0.15 , 8.20 ± 0.13 , 7.44 ± 0.13 $\mu\text{g mL}^{-1}$, respectively.⁵³ In addition, *Ganoderma* polysaccharides reduce the oxidation of low-density lipoproteins and exhibited antioxidant properties by scavenging reactive oxygen species in mice.¹⁸

5.6 Antiviral activity

AIDS is a highly harmful infectious disease caused by HIV infection. There is currently no way around the world to cure it completely, and it can only be controlled to become AIDS by limiting and reducing the concentration of HIV. GTs are potent anti-HIV drugs that can effectively inhibit HIV-1 protease activity. Ganoderiol F (142), ganodermanontriol (322), ganolucidic acid A (38), ganolucidic acid B (39), ganoderic acid GS-2 (84), 15 α -acetoxy-3 α -hydroxylanosta-8,24-dien-26-oic acid (445), colossolactone V (297) and ganoderiol F (142) have anti-HIV-1 activity.^{102–105} The hydroxyl groups at positions C-3, C-24 and C-25 in lanostane triterpenoids are the necessary active groups for anti-HIV-1 virus.¹⁰⁶ Among them, compounds 84 and 142 inhibit human immunodeficiency virus-1 protease with IC₅₀ values of 20–40 μM .¹⁰⁷ Ganoderic acid Y (113) isolated from *G. lucidum* inhibits virus replication by preventing virus from uncoating, with a maximum inhibition rate of 83.9% at 20 $\mu\text{g mL}^{-1}$, thereby preventing enterovirus 71 infection.¹⁰⁸ Besides, *Ganoderma* has certain inhibitory effects on the dengue virus¹⁰⁹ and influenza virus,¹¹⁰ but the antiviral mechanism needs further study.

5.7 Anti-hyperglycemic and anti-hyperlipidemic

Ganoderma has the effect of improving pancreatic blood circulation, reducing blood glucose and improving the symptoms of diabetic patients, as well as reducing blood lipids and improving various symptoms of hyperlipidemia. Sarker *et al.* showed that *G. lucidum* had good anti-hyperglycemic and anti-hyperlipidemic activity on alloxan and glucocorticoid-induced diabetic rats.¹¹¹ Petroleum ether extract and methanol extract of *G. lucidum* can significantly increase plasma insulin levels in rats and reduce fasting plasma glucose. It is speculated that *G. lucidum* extract enabled cells to continuously produce insulin, restores normal cholesterol and triglyceride levels in rats, and has the function of significantly lowering blood lipids. *G. atrum* polysaccharide PSG-1 has the effect of lowering blood sugar and blood lipids. In high-fat diet and streptozotocin-induced type 2 diabetic rats, PSG-1 can significantly reduce fasting blood glucose and total cholesterol.⁷¹ The structural changes of the side chain of lanostane triterpenoids have a more significant effect on the activity than



the structural changes of the four-ring skeleton. The carboxyl group on the side chain is the key to identifying the inhibitory activity of α -glucosidase, and it has the effect of reducing blood sugar.¹¹² Seven compounds 40, 41, 136, 138, 139, 142 and 265 showed stronger activity than the positive control acarbose, with IC_{50} values of 15.75, 29.30, 33.52, 19.51, 24.98, 28.04 and 10.99 μ M, respectively.⁴⁹ The OH substituent at C-3 and the double bond at C-24 and C-25 are necessary conditions to increase the inhibitory activity of α -glucosidase. In addition, the double bond portion of C-20 and C-22 on the side chain of ganoderic acid and the hydroxyl substituent on C-3 increase the inhibitory activity of α -glucosidase.¹¹³ Diabetes leads to a chronic complication – diabetes foot ulcer, which leads to difficulty in healing wounds.¹¹⁴ The water extract of *G. lucidum* was abundant in polysaccharides, which can increase the antioxidant capacity *in vivo* and promote wound healing in diabetic rats.¹¹⁵ Meroterpenes also showed strong inhibitory activity on α -glucosidase, but the mechanism of action needs further study.^{116,117} Hu *et al.* found that *G. lucidum* triterpenes might improve hyperlipidemia by regulating intestinal flora and promoting the growth of beneficial bacteria.¹¹⁸ Xu *et al.* compared the natural polysaccharides and degraded polysaccharides of *G. lucidum* found that the structure of ultrasonic degradation polysaccharides did not change, and the hypolipidemic activity of degrading polysaccharides was higher than that of natural polysaccharides.¹¹⁹ GLPs significantly decreased fasting plasma glucose and fasting serum insulin in diabetic mice. The mechanism of action of GLPs may be related to the reduction of hepatic glucose regulator enzyme mRNA levels through activation of AMPK, which improves insulin resistance.¹²⁰

6. Summary and future perspectives

Ganoderma widely distributed in Africa, North America, Asia, and has a long history of medicinal use in Asia. Although there are many reports on the chemical composition and pharmacological activity of *Ganoderma*, according to the latest edition of the Chinese Pharmacopoeia (2015 Edition), the content of triterpenoids and polysaccharides is the main evaluation index. This has led to the current research on *Ganoderma* mainly focusing on the pharmacological effects of triterpenoids and polysaccharides, which is similar to the method of chemical drug research. This method ignores the integrity of Chinese medicine, which means a clinical efficacy usually depends on the combination of multiple components. However, the quality of *Ganoderma* is affected by a variety of factors, such as cultivated varieties, cultivation substrate, processing methods, storage time. Only through the two types of components can not accurately reflect the quality of *Ganoderma*. Therefore, it is imperative to establish a more scientific and systematic evaluation system for quality evaluation of *Ganoderma* drugs and health products. Nowadays, the *Ganoderma* industry has great potential because of its medicinal and cultural values. In the future, *Ganoderma* is expected to become natural medicine source for treating various diseases. In this paper, 906 chemical components of *Ganoderma* medicinal fungi were reviewed, which were divided into triterpenoids, polysaccharides, meroterpenoids, sesquiterpenoids, steroids, alkaloids and their

biological activities and pharmacological effects were reviewed. Among them, the meroterpenoids compound has a variety of biological activities and is worthy of further study. This provides a basis for further research into its quality control, chemical components and pharmacological mechanisms.

Abbreviations

AMPK	Adenosine 5'-monophosphate (AMP)-activated protein kinase
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
COX-2	Cyclooxygenase-2
CYP2E1	Cytochrome P450 2E1
DCs	Dendritic cells
ERK	Extracellular regulated protein kinases
FPP	Farnesyl pyrophosphate
GEs	Ganoderma extracts
GLPs	<i>Ganoderma lucidum</i> polysaccharides
GP _s	Ganoderma polysaccharides
GSO	Ganoderma spores oil
GT _s	Ganoderma triterpenes
HIV	Human immunodeficiency virus
IC_{50}	Half inhibitory concentration
IFN- γ	Interferon γ
IKK β	Inhibitor kappa B kinase β
IL	Interleukin
iNOS	Nitric oxide synthase
I- κ B	Nuclear factor kappa B inhibitor
JNK	C-Jun amino terminal kinase
LAK	Lymphokine-activated killer
LPS	Lipopolysaccharide
MTT	3-(4,5)-Dimethylthiazoliazolo (-z-y1)-2,5-diphenyltetrazolium bromide
MIC	Minimal inhibitory concentration
NF- κ B	Nuclear factor kappa B
NK _s	Natural killer cells
NO	Nitric oxide
TNF	Tumor necrosis factor

Author contributions

Li Wang, Jie-qing Li, Ji Zhang, Zhi-min Li, Hong-gao Liu and Yuan-zhong Wang conceived the review. Li Wang, Jie-qing Li and Zhi-min Li collected literature and drafted manuscript. Ji Zhang, Hong-gao Liu and Yuan-zhong Wang helped in manuscript revision. All authors read and approved the final manuscript for publication.

Conflicts of interest

The authors declare that there is no conflict of interest regarding publication of this paper.

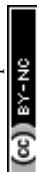
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