

# Reishi or Ling Zhi (*Ganoderma lucidum*)

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## INTRODUCTION

*Ganoderma lucidum* (reishi mushroom, Ling Zhi) has been an economically important species, particularly in the Far East countries (China, Japan, Korea, etc.), for over 4000 years. It is widely grown on a commercial scale and is commonly purchased for its medicinal and spiritual properties.

## NAME AND GENERAL DESCRIPTION

In Latin, *lucidum* means shiny or brilliant and aptly describes this mushroom's fruiting body, which has a modeled, sculptured, varnished appearance. The Chinese and Koreans know it as Ling Zhi (mushroom of herb and immortality), whereas the Japanese call this mushroom reishi or manntake (10,000 year mushroom). The virtues of *G. lucidum* extracts, handed down from generation to generation, include it as a "cancer cure" and a symbol of happy augury, good fortune, good health, longevity, and even immortality. Beginning with the Yuan Dynasty (1280–1368 A.D.), *G. lucidum* has been endlessly represented in art—in paintings, carvings of jade and deer's antlers, furniture and carpet designs, balustrades, jewelry, women's hair combs, perfume bottles—in short, wherever an artistic urge found an outlet. The earliest mention of Ling Zhi was in the era of the first emperor of China, Shing-huang of the Ch'in Dynasty (221–207 B.C.). Subsequently, depictions of this fungus proliferated through Chinese literature and art. The mushroom is known by many in North America and Europe as one of the "artist's conk" fungi (the true artist conk is *Ganoderma applanatum*).

A detailed description of the reishi mushroom and its taxonomy can be found in Refs.<sup>[3,10]</sup> (Fig. 1).

## Habitat

This annual mushroom grows on a wide variety of dead or dying trees, e.g., deciduous trees especially oak, maple, elm, willow, sweet gum, magnolia,

and locust (*Quercus*, *Acer*, *Alnus*, *Betula*, *Castanea*, *Corylus*, *Fagus*, *Fraxinus*, *Populus*, *Pyrus*, *Magnolia*, *Tilia*). *G. lucidum* is less frequently found on coniferous trees (e.g., *Larix*, *Picea*, *Pinus*) in Europe, Asia, and North and South America (in temperate rather than subtropical regions). In the Orient, it grows primarily on plum trees. It is also found on stumps, generally near the soil surface, and occasionally on soils arising from buried roots.

## Edibility

The mushroom is too tough to be edible.

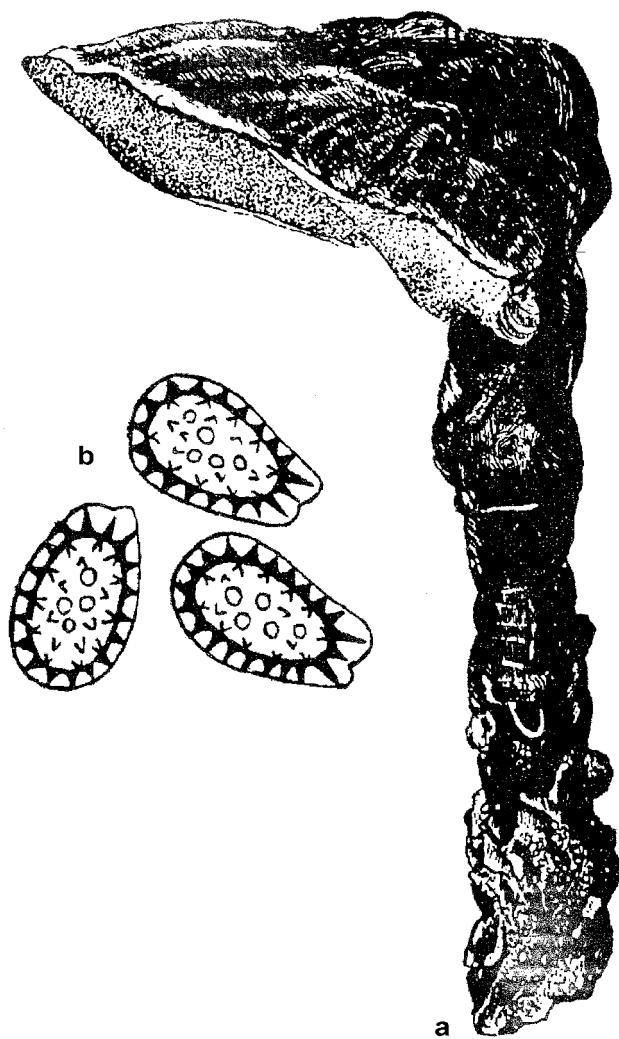
## RELATED SPECIES AND ARTIFICIAL CULTIVATION

Ling Zhi encompasses several *Ganoderma* species, which are widely used for medicinal purposes, e.g., *G. lucidum*, *G. luteum* Steyaert, *G. atrum* Zhao, Xu and Zhang, *G. tsugae* Murrill, *G. applanatum* (Pers.: Wallr.) Pat., *G. australe* (Fr.) Pat., *G. capense* (Lloyd) Teng, *G. tropicum* (Jungh.) Bres., *G. tenue* Zhao, Xu and Zhang, and *G. sinense* Zhao, Xu and Zhang. According to two famous Chinese plant medical books, *Shen Nong Ben Cao Jing* (25–220 A.D., Eastern Han Dynasty) and *Ben Cao Gang Mil* by Li Shi-Zhen (1590 A.D., Ming Dynasty), six Ling Zhi species/varieties were known in China at that time. Worldwide, more than 250 *Ganoderma* species have been described.<sup>[2,3]</sup> However, in therapeutic practices and literature citations, *Ganoderma* usually refers to the species of *G. lucidum*.

Besides being treasured for its medicinal value in China for more than 1000 yr, the lack of availability of *G. lucidum* was also largely responsible for it being so highly cherished and expensive. During ancient times in China, any person who picked the mushroom from the natural environment and presented it to a high-ranking official was usually well rewarded. Even in the early 1950s, it was presented to Chinese leaders in Mainland China and Taiwan, following the occasional discovery in the wild. In the past, *G. lucidum* grew in small quantities only in the wild; therefore, it was very expensive.

Artificial cultivation of this valuable mushroom was successfully achieved in the early 1970s, and since

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**Fig. 1** *Ganoderma lucidum*: (a) fruit body, (b) spores.

1980, production of *G. lucidum* has developed rapidly, particularly in China. The process of producing *G. lucidum* fruiting bodies is the same as for other cultivated edible mushrooms and can be divided into two major stages. The first involves the preparation of the fruiting culture, stock culture, mother spawn, and planting spawn, while the second entails the preparation of growth substrates for mushroom cultivation. Currently, the methods most widely adopted for commercial production are the wood log, short wood segment, tree stump, sawdust bag, and bottle procedures (for cultivation details, see Refs.<sup>[4,5]</sup>).

## HISTORY AND TRADITIONAL USES

*G. lucidum* has been used in folk medicine of China and Japan, especially in the treatment of hepatopathy,

chronic hepatitis, nephritis, hypertension, arthritis, neurasthenia, insomnia, bronchitis, asthma, and gastric ulcers.<sup>[6,8–11]</sup> In China, *G. lucidum* has been cherished for over 4000 yr as a longevity-promoting tonic.<sup>[6]</sup> According to Hikino,<sup>[12]</sup> “the most important elixirs in the Orient” are ginseng (*Panax ginseng* C.A. Meyer) and the fruit bodies of *G. lucidum*.

Fascination with *Ganoderma* began under the name of *ling chih*, later transliterated to *reishi* in Japanese. The fungus first appeared in Chinese literature during the Han Dynasty (206 B.C.–220 A.D.). Emperor Wu associated growth of the fungus in an inner chamber of the Imperial Palace with a plant of immortality—known simply as the *chih* plant or *chih* fungus.<sup>[1]</sup> The Han Dynasty chronicler, Pan Ku, wrote a poem using the term *ling chih*.<sup>[1]</sup> However, the association between the original *chih* fungus and *G. lucidum* had clearly derived from legends of an earlier mysterious *chih* fungus or *chih* plant of immortality recorded in India. Indeed, versions of Indian legends concerning this mushroom are found later, in almost identical form in the Chinese literature, in reference to what would be *ling chih* (*reishi*), while the identity of the true *chih* plant or fungus of immortality remains in dispute.<sup>[1]</sup> In addition to its medicinal properties, *reishi* has been used in the Orient as a talisman to protect a person or home against evil.<sup>[6]</sup>

Medicinal uses of *G. lucidum* in ancient Far East countries included the treatment of neurasthenia, debility from prolonged illness, insomnia, anorexia, dizziness, chronic hepatitis, hypercholesterolemia, mushroom poisoning (antidote), coronary heart disease, hypertension, prevention of altitude sickness, treatment of “deficiency fatigue,” carcinoma, and bronchial cough in the elderly.<sup>[3,6,7,9–11]</sup> Chinese research during the past decade has focused on much the same uses, whether in the fields of antiaging/life prolongation, brain ischemia/reperfusion injury, chronic viral hepatitis, male sexual dysfunction, hypercholesterolemia, immunological function in the elderly, chemotherapy-induced toxicity, narcotic-induced immunosuppression, anticarcinogenic and antitumor activity, and immunostimulation.<sup>[6,8,13–18,55]</sup> Different types of *G. lucidum*, according to Traditional Chinese Medicine (TCM), have different tastes and thus affect different organs. Based on their color, six different types of *G. lucidum* have been classified,<sup>[19]</sup> each with different uses (Table 1).

## General Nutritional Components of *Ganoderma lucidum*

*G. lucidum* contains mainly protein, fat, carbohydrate, and fiber. Artificially cultivated variety has similar contents of nutritional components compared with



**Table 1** The six types of reishi

| Color            | Taste            | Japanese name | Use  |
|------------------|------------------|---------------|--|
| Blue             | Sour             | Aoshiba       | Improves eyesight and liver function; calms nerves           |
| Red <sup>a</sup> | Bitter           | Akashiba      | Aids internal organs; improves memory; enhances vitality     |
| Yellow           | Sweet            | Kishiba       | Strengthens spleen function; calms the "spirit" (shen)       |
| White            | Hot (or pungent) | Shiroshiba    | Improves lung function; gives courage and strong will        |
| Black            | Salty            | Kuroshiba     | Protects kidneys   |
| Purple           | Sweet            | Murasakishiba | Enhances function of ears, joints, muscles; helps complexion |

<sup>a</sup>The red-colored variety of *G. lucidum* is generally regarded as the most potent and medicinal.<sup>[19]</sup>

wild types, and the extraction significantly increases the amounts of crude protein and carbohydrates and deleted crude fiber. Mizuno<sup>[20]</sup> reported the composition of *G. lucidum* extract (% of dry weight), which consisted of folin-positive material (68.9%), glucose (11.1%), protein (7.3%), and metals (10.2%) (K, Mg, and Ca are the major components with Ge having the 5th highest metal concentration at 489 µg/g). These results generally agree with those reported by other authors.<sup>[4,5,10]</sup> However, there are qualitative and quantitative differences in the chemical composition of *G. lucidum* products depending on the strain, origin, extracting process, and cultivation conditions.<sup>[3,5,10,11,20]</sup>

### Major Bioactive Constituents

Over 300 reports have been published concerning the chemical constituents of *G. lucidum* and related species. The fruiting body, mycelia, and spores of *G. lucidum* contain approximately 400 different bioactive compounds, which mainly include triterpenoids, polysaccharides, nucleotides, sterols, steroids, fatty acids, proteins/peptides, and trace elements.<sup>[11,16,20,21,55]</sup>

### TERPENOID COMPOUNDS

#### Triterpenes

At least 140 different triterpenes have been identified in *G. lucidum*.<sup>[3,6,10,11,20,21]</sup> The majority are bitter tasting and largely occur as ganoderic acid.<sup>[21]</sup> A new triterpenoid, named ganosporeric acid A, was recently isolated from the ether-soluble fraction of the spores.<sup>[22]</sup> Min et al.<sup>[23]</sup> reported the isolation of six new lanostane-type triterpenes, and also from the spores (ganoderic acids γ, δ, ε, ζ, η, and θ). Preliminary studies indicate that the spores contain considerably higher contents of ganoderic acids than other parts of the fungus and that triterpene composition of the fruit body varies according to the area in which it is grown.<sup>[22]</sup> The

spores also contain triterpene lactones,<sup>[21]</sup> and documented triterpenoids have been divided into 10 groups based on the structural similarities and known biological and medicinal properties (Fig. 2).

### CARBOHYDRATES

#### Polysaccharides

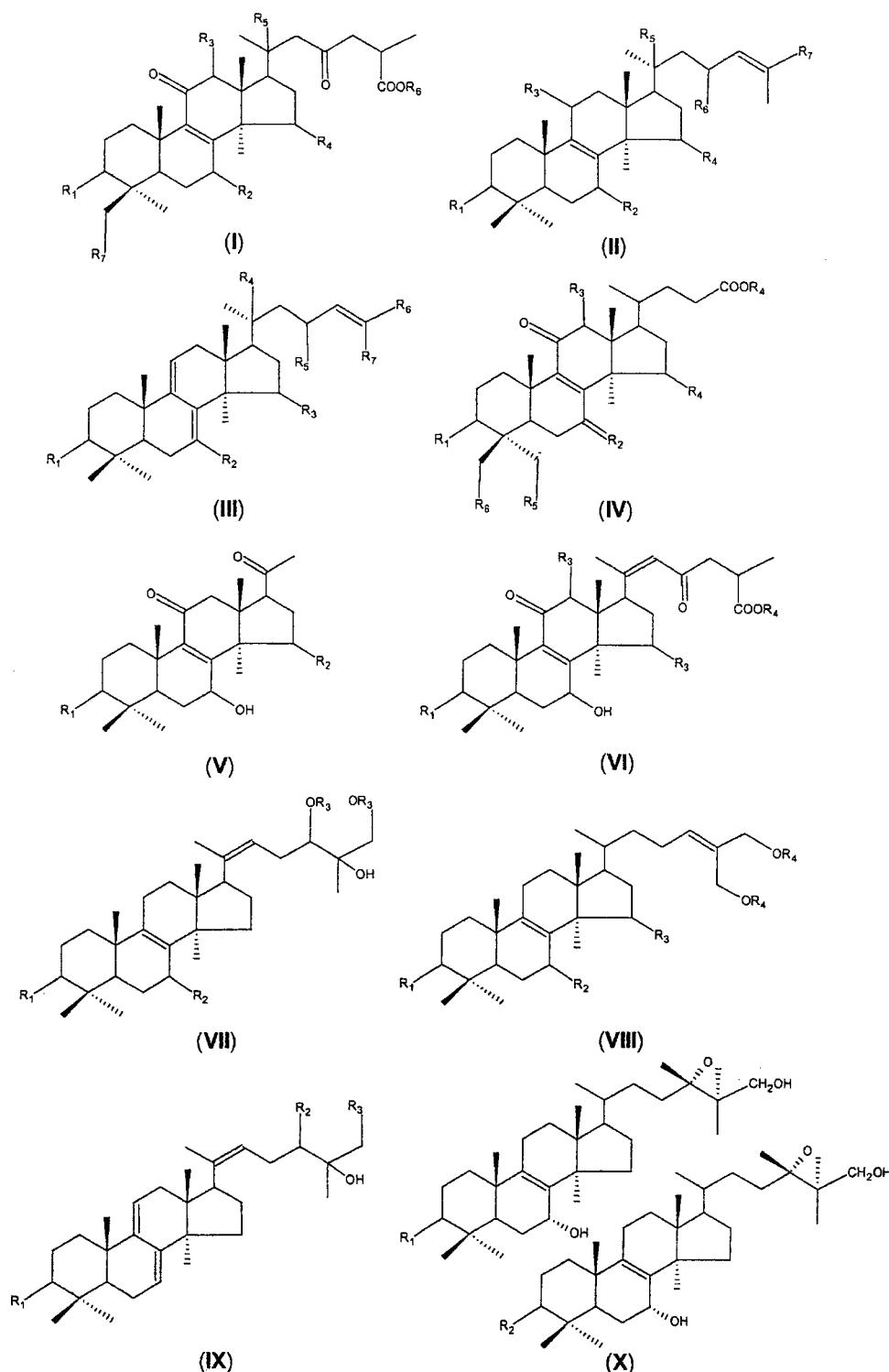
More than 100 types of polysaccharides have been isolated from the fruiting body, spores, and mycelia, or separated from the broth of a submerged liquid culture of *G. lucidum*. Most have a molecular weight ranging from  $4 \times 10^5$  to  $1 \times 10^6$  in the primary structure. They comprise one of the major sources of *G. lucidum*'s pharmacologically active compounds.

*G. lucidum* polysaccharides such as β-D-glucans, heteropolysaccharides, and glycoprotein have been isolated and characterized and are considered the major contributors of bioactivity of the mushroom. β-D-glucans consist of a linear backbone of β-(1 → 3)-linked D-glucopyranosyl groups with varying degrees of branching from the C6 position. In addition to water-soluble β-D-glucans, β-D-glucans also exist with heteropolysaccharide chains of xylose, mannose, galactose, uronic acid, and β-D-glucans–protein complexes that are present at 10–50% in dry *G. lucidum*.<sup>[16,24–26]</sup> Some protein-bound polysaccharides and fucose-containing glycoprotein with bioactivity have been isolated.<sup>[18,27,28]</sup>

### PROTEINS

Some proteins with bioactivity have also been isolated from *G. lucidum*. The LZ-8 is one such protein isolated from *G. lucidum*, which was shown, by sequencing studies, to be similar to the variable region of the immunoglobulin heavy chain in its sequence and in its predicted secondary structure. Major biological activities of LZ-8 resemble those of lectins, with mitogenic capacity toward mouse spleen cells and human peripheral lymphocytes





**Fig. 2** The lanostane-type triterpenoids of *Ganoderma lucidum*. These triterpenoids are divided into ten groups based on structural similarity.

and agglutination of sheep red blood cells in vitro. Neither was inhibited by the mono- or dimeric sugars examined, indicating that LZ-8 is not a lectin per se. It did not agglutinate human red blood cells but could

function as a potent suppressor of bovine serum albumin-induced anaphylaxis in CFW mice in vitro. It appears to be related to an ancestral protein of the immunoglobulin superfamily.<sup>[29]</sup>



## NITROGENOUS COMPOUNDS

### Nucleotides and Nucleosides

Nucleosides include adenosine and 5-deoxy-5' methylsulfinyladnosine.<sup>[20]</sup>

## OTHER CONSTITUENTS

Reishi also contains sterols, amino acids, soluble proteins, oleic acid, cyclo-octasulfur, an ergosterol peroxide (5,8-epidioxy-ergosta-6,22E-dien-3-ol), and the cerebrosides (4E',8E)-N-D-2'-hydroxystearoyl-1-O- $\beta$ -D-glucopyranosyl-9-methyl-4-8-sphingadienine, and (4E,8E)-N-D-2'-hydroxypamitoyl-1-O- $\beta$ -D-glucopyranosyl-9-methyl-4-8-sphingadienine.<sup>[3,11,17,18,20]</sup>

Regarding the inorganic ions, the mushroom contains Mg, Ca, Zn, Mn, Fe, Cu, and Ge. The spores themselves contain choline, betaine, tetracosanoic acid, stearic acid, palmitic acid, ergosta-7, 22-dien-3-ol, nonadecanoic acid, behenic acid, tetracosane, hentriacontane, ergosterol, and  $\beta$ -sitosterol. One of the lipids isolated from *G. lucidum* is pyrophosphatidic acid.<sup>[13,17,20]</sup>

## THERAPEUTIC APPLICATIONS

### Preclinical and Clinical Studies

*G. lucidum* has been reported to have a number of pharmacological effects including immunomodulating, antiatherosclerotic, anti-inflammatory, analgesic, chemopreventive, antitumor, radioprotective, sleep-promoting, antibacterial, antiviral (including anti-HIV), hypolipidemic, antifibrotic, hepatoprotective, diabetic, antioxidative and radical-scavenging, anti-aging, hypoglycemic, and anti-ulcer properties.<sup>[3,6,9–11,16,25,30,55]</sup>

Reishi has now become recognized as an alternative adjuvant in the treatment of leukemia, carcinoma, hepatitis, and diabetes.<sup>[9–11,14–18,25,30,55]</sup> Clinical studies, to date, lack the controls needed to make a scientific assessment of its efficacy in a given application, a situation expected to change with increasing interest from Western scientific communities. It was only since the last decade that clinical trials on the use of *G. lucidum* preparation used to treat cancer and other diseases have been reported in international peer-reviewed journals.

## ANTITUMOR EFFECT

Polysaccharides ( $\beta$ -D-glucans, heteropolysaccharides, and glycoproteins) isolated from *G. lucidum* demonstrated antitumor activity against Sarcoma 180 in

mice.<sup>[3,10,11,13,14,16,20,25,27,28,30]</sup> Triterpenoids, such as ganoderic acids T-Z isolated from *G. lucidum*, showed cytotoxic activity in vitro on hepatoma cells.<sup>[31]</sup> A lanostanoid, 3 $\beta$ -hydroxyl-26-oxo-5 $\alpha$ -lanosta-8,24-dien-11-one, and a steroid, ergosta-7,22-diene-3 $\beta$ ,3 $\alpha$ ,9 $\alpha$ -triol, isolated from fruiting bodies of *G. lucidum*, demonstrated potent inhibitory effects on KB cells and human PLC/PRF/5 cells in vitro.<sup>[32]</sup>

The polysaccharide-mediated potentiation of immune function is thought to be the major mechanism of antitumor action by *G. lucidum*. Among the multiple polysaccharides, active  $\beta$ -D-glucans are responsible for the antitumor effect.<sup>[3,10,11,13,20,28,30]</sup> This polysaccharide appears to act by binding to leukocyte surfaces or serum-specific proteins leading to activation of macrophages, T-helper, natural killer (NK) and other effector cells.<sup>[33–35]</sup> All of these increase the production of cytokines such as tumor necrosis factor (TNF- $\alpha$ ) interleukins (IL) and interferon (IFN), nitric oxide (NO), and antibodies by the activated effector cells. Tumor regression in various animal models can be ascribed to vascular damage to tumor blood flow and necrosis caused by T cells and local TNF- $\alpha$  production.

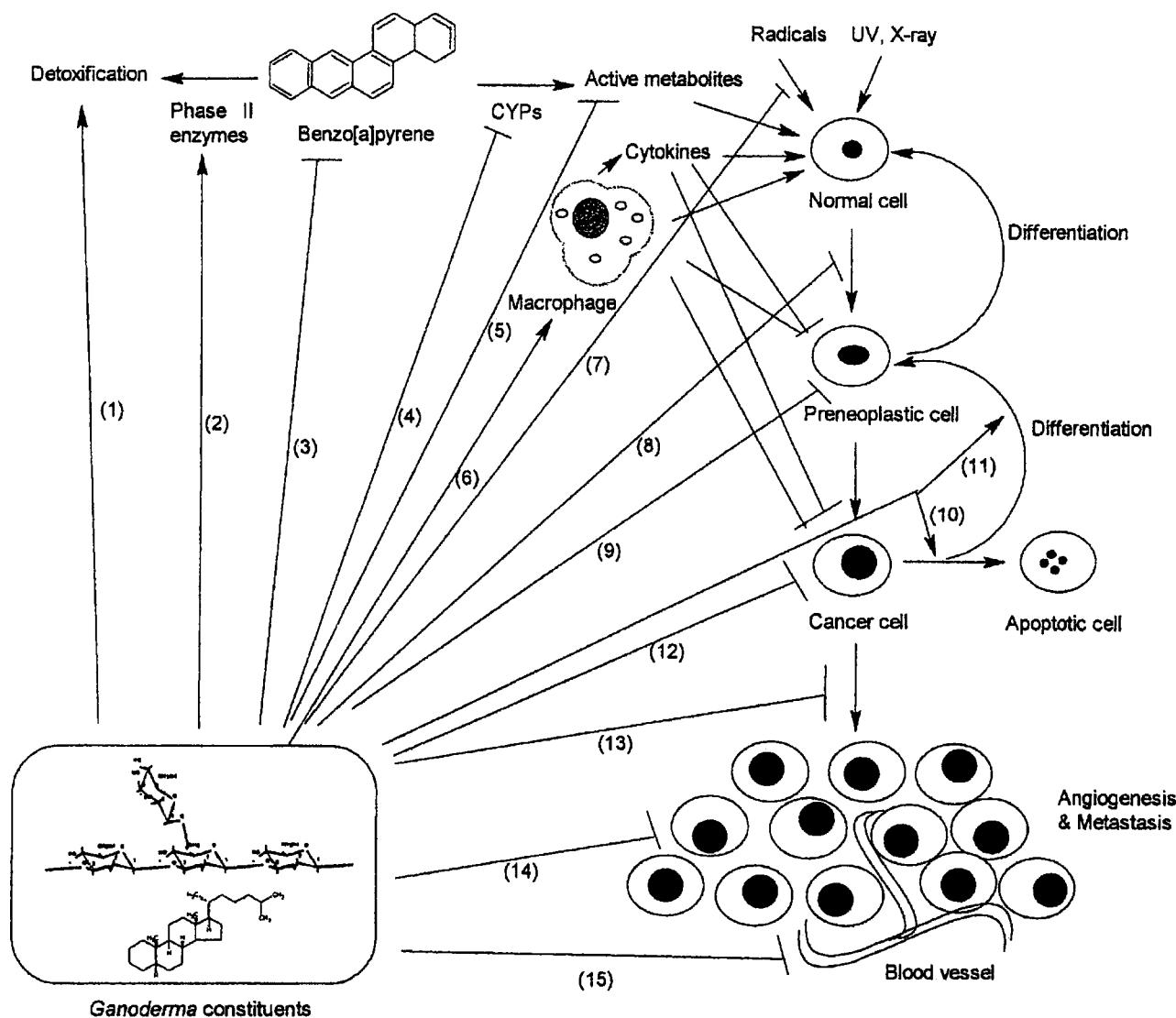
In addition to host defense potentiation, other mechanisms are also involved in the antitumor effect. A compound from *G. lucidum* suppressed the growth of K562 leukemic cells in a dose- and time-dependent manner and induced their differentiation into more mature erythrocytic cells.<sup>[36]</sup> The conditioned medium from PS-stimulated human blood mononuclear cells (PSG-MNC-CM) significantly inhibited the growth of U937 cells and induced their differentiation into mature monocytes/macrophages, which had functions of phagocytosis and producing cytoplasmic superoxide.<sup>[37]</sup> Inhibition of DNA polymerase and posttranslational modification of oncoproteins may contribute to the antitumor activity of reishi.<sup>[38]</sup> The organic germanium may also contribute to its antitumor activity.<sup>[39]</sup> The mechanisms for tumor prevention and antitumor effect of *G. lucidum* are shown in Fig. 3.

In clinical studies, *G. lucidum* products have been widely used as a single agent or in combination with other herbal medicines or chemotherapeutic drugs for many years, mainly in Asian countries. However, randomized, placebo-controlled and multicancer clinical studies using reishi alone have rarely been reported.

### *Ganoderma lucidum* as a Single Agent

In a randomized, placebo-controlled clinical study, 143 patients with advanced previously treated cancer were given an oral *G. lucidum* polysaccharide extract (Ganopoly) of 1800 mg three times daily for 12 weeks.<sup>[16]</sup> Twenty-seven patients were not assessable





**Fig. 3** The mechanisms for the tumor preventive and antitumor effect of *G. lucidum*. Active constituents from *G. lucidum* may operate through several mechanisms including enhancement of detoxification of carcinogens (line 1), increased expression and activity of Phase II enzymes (line 2), inhibition of organ exposure of carcinogens due to reduced absorption or increased excretion (line 3), decreased expression and activity of Phase I (e.g., CYPs) enzymes (line 4), decreased formation of toxic metabolites and adduct formation with macromolecules (line 5), enhanced host immune responses (e.g., activation of macrophages, T lymphocytes, and natural killers producing various cytokines such as TNF- $\alpha$ , IFNs, and ILs, which improve immunosurveillance and kill preneoplastic and cancer cells) (line 6), antioxidative and radical-scavenging effects (line 7), antipromotion effect (line 8), antiproliferation (line 9), apoptosis induction of tumor cells (line 10), induction of differentiation (line 11), direct cytotoxicity, induction of cell-cycle arrest, antiproliferation and modulation of signaling transduction molecules (line 12), antiprogression and tumor growth inhibition (line 13), antimetastasis (line 14), and anti-angiogenesis (line 15).<sup>[16]</sup>

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for response and toxicity, because they were lost in the follow-up or refused further therapy before the 12 weeks of treatment. Of the 100 fully assessable patients, 46 (32.2%) had progressive disease before or at the 6-week evaluation point (range: 5 days–6 weeks).

Sixteen subjects (11.2%) developed progressive disease between 6 and 12 weeks of therapy. No objective (partial or complete) responses were observed, but 38

of 143 cases (26.6%) had stable disease for 12 weeks or more (range: 12–50 weeks). There was no significant change in the Functional Assessment of Cancer Therapy-General (FACT-G) scores in 85 assessable patients. However, palliative effects on cancer-related symptoms, such as sweating and insomnia, have been observed in many subjects. In the group with stable disease, FACT-G scores improved in 23 patients, were



unchanged in five, and declined in one. Within this group, the median change from the baseline score to the 6- and 12-week score was +7.6 and +10.3, both statistically significant ( $P < 0.05$ ). For the 38 patients with SD, the median change from the baseline score was  $28.1 \pm 10.2$  weeks. The prostate-specific antigen (PSA) levels in the five prostate cancer patients were reduced significantly ( $P < 0.05$ ) during SD. Ganopoly was well tolerated with five moderate adverse events recorded. The results indicate that Ganopoly may have an adjunct role in the treatment of patients with advanced cancer although objective responses were not observed in this study.

### ***Ganoderma lucidum*-Containing Herbal Mixture: PC-SPES**

PC-SPES has been used as an alternative in the treatment of prostate cancer.<sup>[47]</sup> Several clinical trials have been completed with patients having advanced prostate cancer.<sup>[48,49]</sup> Small et al.<sup>[49]</sup> included 70 subjects with androgen-dependent ( $n = 33$ ) and androgen-independent ( $n = 37$ ) disease, which was refractory to surgery, radiotherapy, and hormone therapy. Treatment of PC-SPES at a dose of 3 capsules (320 mg/capsule) orally resulted in  $\geq 80\%$  decrease in PSA levels in all 32 patients with androgen-dependent cancer, while it was undetectable in 26 patients (81%). The median duration of PSA response was 57 weeks. In the 35 patients with androgen-independent cancer, 19 (54%) had a PSA decrease of  $\geq 50\%$  with median duration of PSA response of 18 weeks. The study by Pfeifer et al.,<sup>[48]</sup> which included only 16 patients with androgen-independent disease for just a 20-week follow-up, showed an improvement in quality of life for the patients. PC-SPES was generally well tolerated by prostate cancer patients, but they exhibited a dose-dependent toxicity similar to that of diethylstilbestrol.<sup>[49]</sup> Side effects include reduced libido, hot flashes, diarrhea, dyspepsia, leg cramps, nipple tenderness, and gynecomastia.<sup>[48,49]</sup> More life-threatening adverse events are pulmonary emboli in 4–5% of patients and deep vein thrombosis in 2% of patients. Overall, the clinical responses to PC-SPES compare favorably with second-line hormonal therapy with agents, such as estrogens and ketoconazole.<sup>[50]</sup> However, it must be noted that the adulteration of PC-SPES products has become a serious problem. Further details may be obtained at the website of the NIH National Center for Complementary and Alternative Medicine at <http://nccam.nih.gov/health/alerts/spes/>.

In summary, animal studies have demonstrated the antitumor activity of *G. lucidum* administered by different routes at different stages of tumor growth.<sup>[3,10,16,20]</sup> Polysaccharides and triterpenoids

are the major contributors to the anticancer effect of *G. lucidum*, but other constituents, such as proteins, also play a role (Fig. 4).<sup>[20]</sup> Several recently published reports have found that *G. lucidum* or *G. lucidum*-containing herbal mixtures (PC-SPES) had biological activities (e.g., cancer biomarker alteration) and beneficial effects (e.g., palliative effects in cancer patients) although striking objective responses were not observed.<sup>[16,47]</sup>

### **CHEMO- AND RADIOPREVENTIVE EFFECTS**

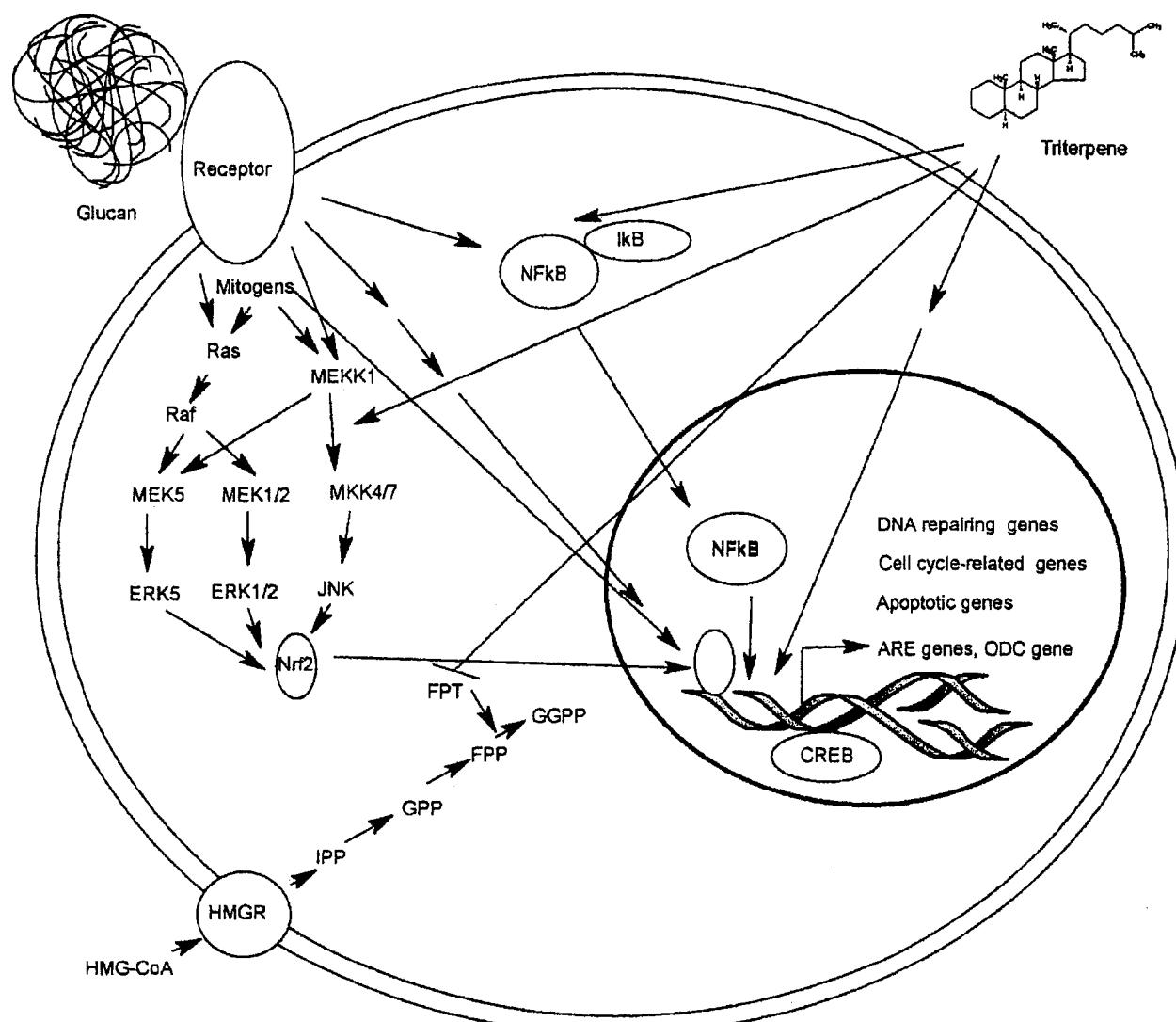
The chemo- and radiopreventive effect of *G. lucidum* may result from its effects on the immune system. *Ganoderma* polysaccharides restored the TNF- $\alpha$  production inhibited by cyclophosphamide to normal levels in mice. Both the *G. lucidum* extract and krestin (protein-bound  $\beta$ -glucan isolated from *Trametes versicolor*) were beneficially effective in the recovery of cellular immunocompetence, measured by [<sup>3</sup>H] thymidine incorporation with splenic cells stimulated through mitogens, such as phytohemagglutinin (PHA) and concanavalin A. The extract (400 mg/day/kg body weight) appears more effective than krestin (500 mg/day/kg body weight) in repairing the damage of subset T cells in the spleens of  $\gamma$ -irradiated mice, as the relative thymus weight and CD4 and CD8 splenocytes were higher in *G. lucidum* extract-treated mice compared with krestin-treated mice.<sup>[16]</sup>

In morphine-dependent mice, a polysaccharide peptide from *G. lucidum* could restore several immunologic parameters depressed by morphine treatment to normal levels or even beyond.<sup>[40]</sup> Both c-myb and c-myc mRNA expression in splenocytes of repetitive morphine-treated mice was significantly decreased, and the polysaccharide peptide could induce the expression of these genes indicating that the one from *G. lucidum* could be of a potential application in controlling abuse of opiate-induced immunodeficiency.

### **ENZYME-INHIBITING ACTIVITY**

Triterpenoids of *G. lucidum* have been reported to exert various enzyme inhibitory activities. Inhibitors of farnesyl protein transferase (FTP) have been demonstrated to inhibit Ras-dependent cell transformation and thus represent a potential therapeutic strategy for the treatment of human cancers. Ganoeric acids A and C were identified to be inhibitors of FTP.<sup>[41]</sup> Ergosterol peroxide, 5,8-epidioxy-5 $\alpha$ , 8 $\beta$ -ergosta-6,22E-dien-3 $\beta$ -ol, from *G. lucidum*, was reported to selectively enhance the inhibitory effect of linoleic acid on DNA polymerase- $\beta$ , but not on the type  $\alpha$  enzyme. Ergosterol peroxide itself was





**Fig. 4** Possible molecular targets of *G. lucidum*. *G. lucidum* constituents (e.g.,  $\beta$ -D-glucan and triterpenoid) modulated Ras/Erk, c-myc, CREB protein and mitogen-activated protein kinases, which may provide an explanation for the cancer preventive and anticancer effect of *G. lucidum*.<sup>[16]</sup>

ineffective but completely blocked rat DNA polymerase- $\beta$  in the presence of linoleic acid.<sup>[38]</sup> Inhibitors of phospholipase A<sub>2</sub>(PLA<sub>2</sub>) can be developed as potential anti-inflammatory agents for the treatment of rheumatic arthritis, asthma, and psoriasis. Ganoderic acid T was found to inhibit secreted PLA<sub>2</sub> from pig pancreas, human synovial fluid, and bee venom, but no such effect was observed with ganoderic acids AA, O, R, S, T-OH, and T-OH-H<sub>2</sub>.<sup>[16]</sup>

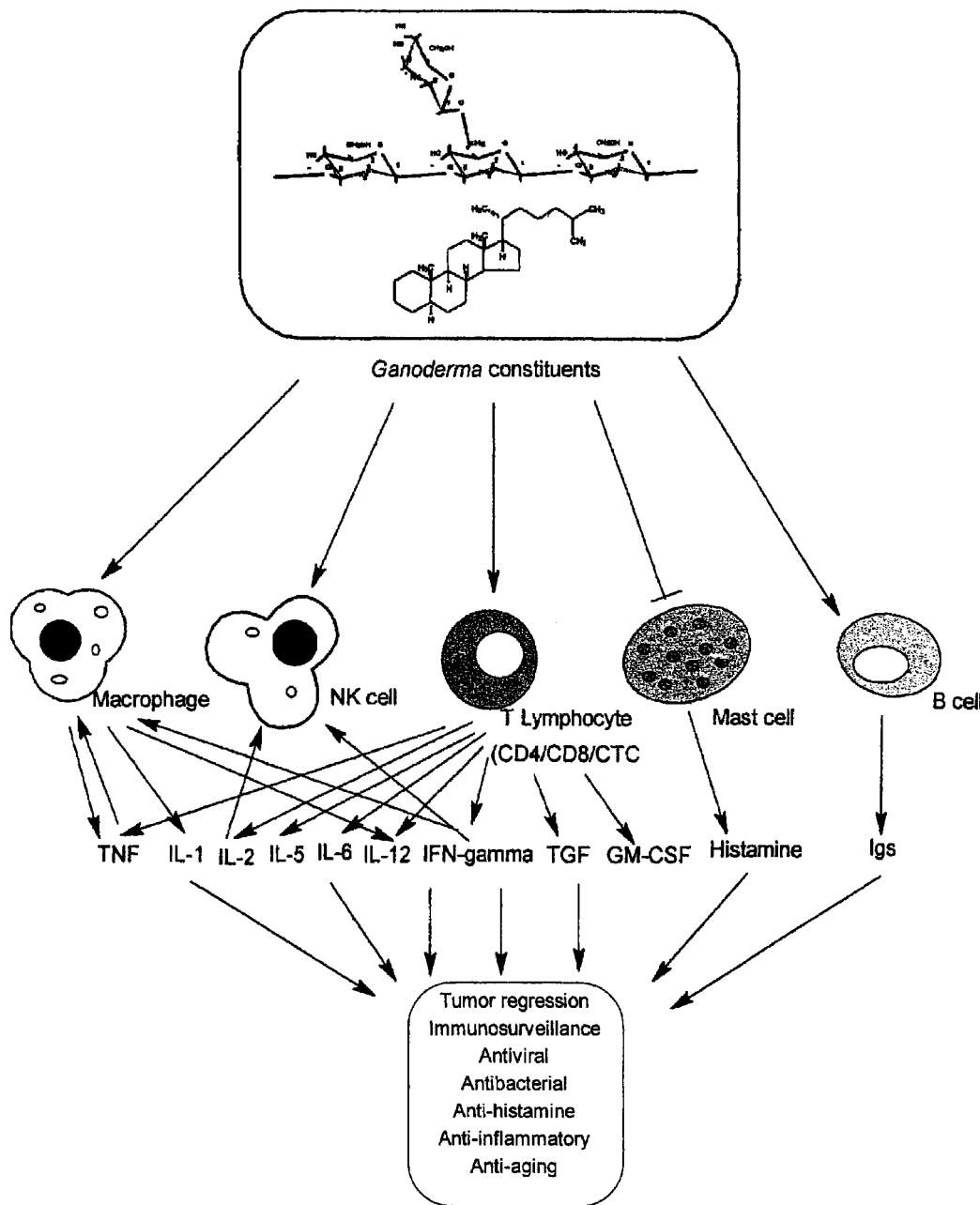
### IMMUNOMODULATING EFFECTS

The immunomodulating effects of *G. lucidum* are shown in Fig. 5.

### MITOGENIC ACTIVITY

Extracts from *G. lucidum* (e.g., polysaccharide fractions, methanolic extracts, and LZ-8) have mitogenic effects on mouse splenocytes and human peripheral blood mononuclear cells (PBMCs) in the presence of various immunostimulating or immunosuppressive agents (e.g., PHA and 12-O-tetradecanoylphorbol 13-acetate).<sup>[42,43]</sup> Treatment of the PBMCs with cyclosporin A (CsA) led to blockage of the cell proliferation. The methanolic fraction from *G. lucidum* recovered the CsA-induced inhibition of the cell proliferation, which might be due to the inhibition of the protein kinase C signal pathway and acceleration of the CsA signal pathway.





**Fig. 5** The immune-modulating effects of *G. lucidum*. The major immunomodulating effects of active substances derived from *G. lucidum* include mitogenicity and activation of immune effector cells such as T lymphocytes, macrophages, and NK cells leading to the production of cytokines including ILs, TNF- $\alpha$ , and IFNs. Other effects, such as inhibition of mast cells, activation of B lymphocytes, and the complement system have also been reported.<sup>[15]</sup>

## EFFECTS ON IMMUNE EFFECTOR CELLS

### Splenocytes

In vitro and in vivo studies in mice indicated that *G. lucidum* water extract stimulates the production of IL-2 by splenocytes in the presence of hydrocortisone.<sup>[3,7,10,11]</sup>

### T Cells

Extracts from *G. lucidum* are potent activators of T cells, inducing the production of a number of cytokines, in particular IL-2. In human PBMC (primarily T cells) in vitro, the crude *G. lucidum* water extract induced the expression of cytokines including IL-10 and TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and IL-2.<sup>[43]</sup> Crude



polysaccharide fractions isolated from fresh fruiting bodies potentiated the release of IFN- $\gamma$  from human T cells.<sup>[37]</sup> A polysaccharide fraction (GL-B) promoted the production of IL-2 in a dose-dependent manner and markedly enhanced the cytotoxicity of cytotoxic T lymphocytes, which was increased by 100% at a concentration of 200  $\mu$ g/ml. GL-B also restored the mixed lymphocyte response to alloantigen, automatic proliferation, and IL-2 production of splenocytes in aged mice declined as compared with that in young adult mice *in vitro*.

LZ-8 is also a potent T-cell activator mediating its effects via cytokine regulation of integrin expression. Stimulation of human peripheral blood lymphocytes with LZ-8 resulted in the production of IL-2 and a corresponding upregulation of IL-2 receptor expression.<sup>[44]</sup> In addition to T-cell proliferation, microscopic examination of LZ-8-stimulated peripheral blood lymphocytes revealed that LZ-8 induced cellular aggregate formation. This formation correlated with a dramatic rise in ICAM-1 expression and an increased production of IFN- $\gamma$ , TNF- $\alpha$ , and IL-1 $\beta$ , molecules associated with regulation of ICAM-1 expression. Both the aggregate formation and the proliferative effects of LZ-8 were blocked by the addition of a monoclonal antibody to either CD18 or CD11a, the counter-receptor complex components for ICAM-1. Furthermore, addition of neutralizing antibodies to both IL-2 receptor and TNF- $\alpha$  blocked aggregate formation, cellular proliferation, and ICAM-1 expression.

### Natural Killer (NK) Cells

A water-extracted polysaccharide fraction from *G. lucidum* enhanced the cytotoxicity of splenic NK cells in tumor-bearing mice.<sup>[3,16,37]</sup>

### Macrophages

Macrophages are responsible for killing pathogens in the body. Activation of macrophages by substances from *G. lucidum* results in the release of cytokines, NO, and other mediators.<sup>[37,45]</sup> All of these responses are associated with the antitumor, antimicrobial, and anti-inflammatory effects of *G. lucidum*.

Polysaccharides from *G. lucidum*, in particular  $\beta$ -D-glucans, are potent stimulators of murine and human macrophages *in vitro* and *in vivo*.<sup>[37,45]</sup> CR3 receptors on macrophages are bound by  $\beta$ -D-glucans and internalized, priming a series of molecular events. Crude water-extracted polysaccharides isolated from fresh fruiting bodies of *G. lucidum* potentiated the production of cytokines including IL-1 $\beta$ , IL-6, IFN- $\gamma$ , and TNF- $\alpha$  by human macrophages, which

were antiproliferative, differentiated and apoptosis inductive to the HL-60 and the U937 leukemic cells.<sup>[37]</sup> IFN- $\gamma$  and TNF- $\alpha$  released from macrophages act synergistically to inhibit the growth of leukemic cells as shown by the antibody-neutralization studies. GLB7, a *G. lucidum* polysaccharide, decreased the production of oxygen-free radicals and antagonized the respiratory burst induced by PMA in murine peritoneal macrophages. These observations suggest that GLB7-decreased production of oxygen-free radicals in murine peritoneal macrophages plays an important role in the anti-aging effect of *G. lucidum* polysaccharides.<sup>[45]</sup>

Ganoderan (GAN), a  $\beta$ -D-glucan isolated from *G. lucidum*, enhanced the production of NO in the RAW 264.7 macrophages.<sup>[45]</sup> The ability of GANs to produce NO was based on differences in the chemical composition of GANs obtained from the mycelium on various carbon sources and mycelial fractionation. The highest NO production was observed in the polysaccharide, which was extracted from the mycelial wall. Partial removal of the protein in the extracellular GAN by TCA treatment did appreciably reduce its capacity to secrete NO. The cell proliferation of GAN-treated RAW 264.7 cell lines was inhibited compared to its control. Of the culture supernatant of macrophage activated by this glycan, the percentage of cytotoxicity against mouse leukemia L1210 cells was slightly dependent on the amount of NO in the culture supernatants of the activated macrophages. These results indicate that the  $\beta$ -glucan-related polysaccharides of the higher fungus activate macrophages and release NO, which is an important chemical messenger for the induction of many biological responses.

A protein-polysaccharide fraction (GLB) from the growing tips of *G. lucidum* is a strong stimulator to the macrophages.<sup>[46]</sup> When analyzed using a flow cytometer, GLB (100  $\mu$ g/ml) increased the phagocytic activity of the BALB/c mouse peritoneal macrophages as well as chicken macrophage BM2CL cells against FITC-labeled *Candida albicans* by 55.2% and 21.2%, respectively. It also enhanced the spreading and expression of MHC class II molecules of BM2CL cells as well as the mouse peritoneal macrophages.

### Mast Cells

Some substances from *G. lucidum* can act on mast cells. A water extract of the fruit body had inhibitory activity on histamine release from rat peritoneal mast cells, induced by compound 48/80 or antigen (egg white albumin)-antibody reaction and on passive cutaneous anaphylaxis reaction in guinea pigs and rats. Two ganoderic acids (C and D) isolated from the fruit body by methanol inhibited the histamine release from



rat mast cells, induced by compound 48/80 and concanavalin A. A chloroform extract from *G. lucidum* broth also significantly inhibited histamine release from rat peritoneal mast cells induced by A-23187 and compound 48/80. The mechanism for the inhibitory activity on histamine release from mast cells was further studied. Palmitic acid, stearic acid, oleic acid, and linoleic acid were isolated from the active fractions. Of these, oleic acids induced membrane stabilization in model membrane systems. Cyclo-octasulfur extracted from the culture medium of *G. lucidum* may decrease calcium uptake from the extracellular medium by a disulfide exchange reaction in the cell membrane leading to inhibition of histamine release from mast cells.<sup>[3,10,11,14,16]</sup>

## COMPLEMENT SYSTEM

An alkali extract isolated from cultured mycelium of *G. lucidum* activated classical and alternative pathways of a complement system. Activated complement C3 was observed by crossed immunoelectrophoresis in mice. This fraction also activated the reticuloendothelial system of mice in the carbon clearance test and increased hemolytic plaque forming cells of the spleen. The alkali extract consisted of 10% carbohydrate and 49% proteins. A clinical study in elderly patients with insomnia and palpitations recently showed that taking *G. lucidum* essence for 4–6 weeks increased their serum C3 levels.<sup>[3,10,20]</sup>

## HISTAMINE RELEASE INHIBITION

The fruiting bodies have been traditionally used as anti-inflammatory agents for the treatment of asthma or allergy. In the course of a screening test for the inhibition of histamine release from rat mast cells, it was found for the first time that ganoderic acids C and D inhibited histamine release from rat mast cells (that were induced by compound 48/80 and concanavalin A). Other than the triterpenoid compounds, cyclo-octasulfur from this fungus also effectively inhibited histamine release from rat peritoneal mast cells and interacted with membrane proteins to inhibit Ca uptake causing a blockade of histamine release.<sup>[7,13,55]</sup>

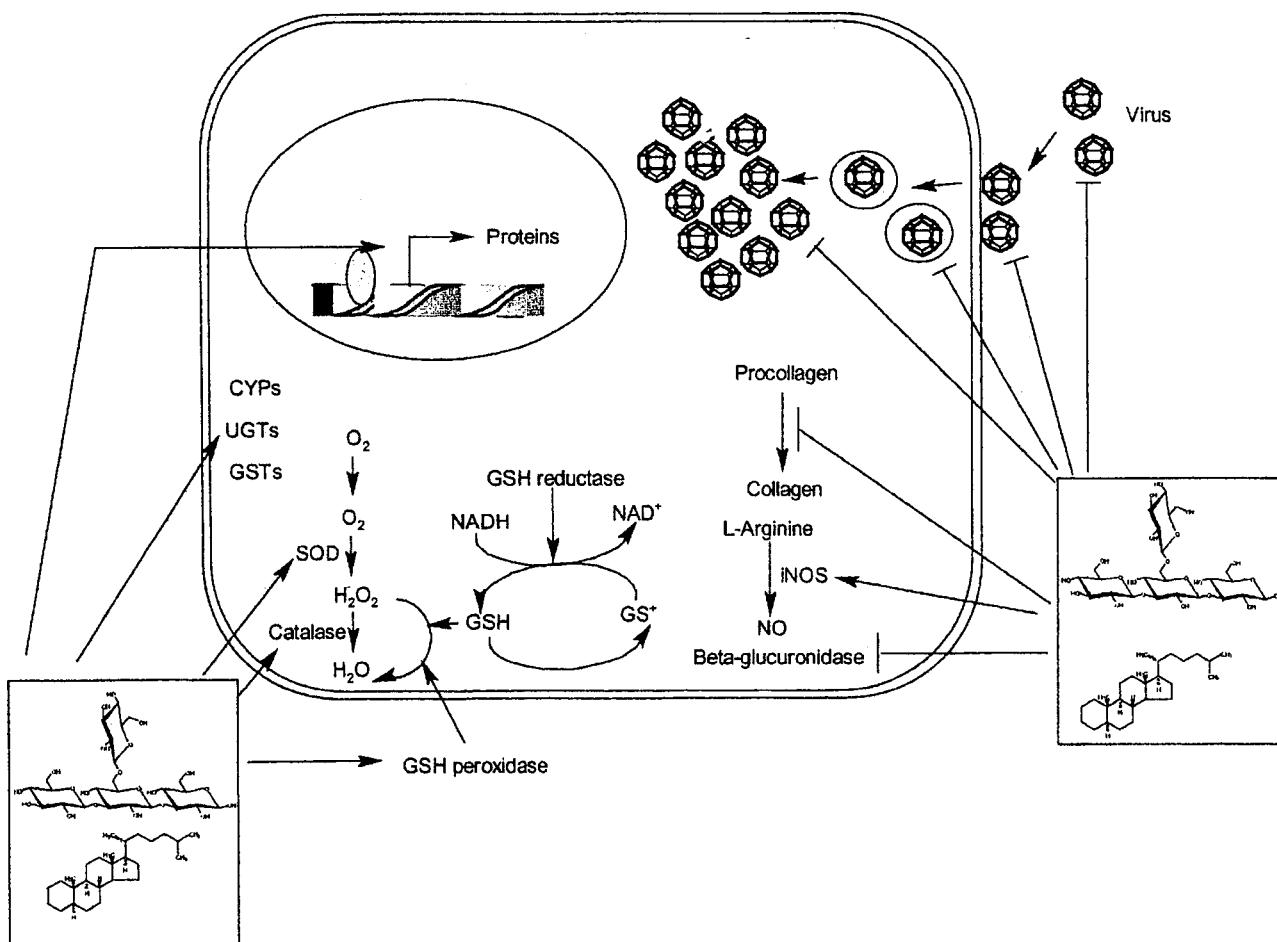
## HEPATOPROTECTIVE ACTIVITY

*G. lucidum* has been widely used for the treatment of chronic hepatopathy of various etiologies. Data from

in vitro and animal studies indicate that *G. lucidum* extracts (mainly polysaccharides or triterpenoids) exhibit protective activities against liver injury induced by toxic chemicals (e.g., CCl<sub>4</sub>) and *Bacillus Calmette-Guerin* (BCG) plus lipopolysaccharide (LPS). Reishi also showed antihepatitis B-virus (HBV) activity in a duckling study. Recently, a randomized placebo-controlled clinical study<sup>[15,17]</sup> showed that treatment with *G. lucidum* polysaccharides for 12 weeks reduced hepatitis B e antigen (HBeAg) and HBV DNA in 25% (13/52) patients with HBV infection. The mechanisms of the hepatoprotective effects of *G. lucidum* have been largely undefined. However, accumulating evidence suggests several possible mechanisms. These include antioxidant and radical-scavenging activity, modulation of hepatic Phase I and II enzymes, inhibition of β-glucuronidase, antifibrotic and antiviral activity, modulation of NO production, maintenance of hepatocellular calcium homeostasis, and immunomodulating effects (Fig. 6). The mushroom could represent a promising approach for the management of various chronic hepatopathies. Further studies are needed to explore the kinetics and mechanisms of action of its constituents with hepatoprotective activities.

The polysaccharide fractions and triterpenes isolated from *G. lucidum* have shown protective effects on the liver in animal and human studies. Ninety patients with chronic hepatitis B, hepatitis B viral (HBV) DNA positivity, and aminotransferase elevation were included in this multicenter prospective randomized Phase I/II study. Subjects were randomized to be given Ganopoly ( $n = 60$ ) or a placebo ( $n = 30$ ) for 12 weeks, then followed up for 13 weeks. Effect of therapy on levels of HBV DNA and aminotransferase activities in serum and HBeAg status were investigated. There were 78 assessable patients who entered the trial for efficacy and safety; 13 of 52 (25%) receiving Ganopoly responded by reducing HBeAg and HBV DNA compared to 10 of 26 (4%) patients in the control group ( $P < 0.05$ ). Among those with serum aspartate aminotransferase (AST) values  $<100$  U/L ( $n = 29$ ), 41% (12/29) responded, and among those with AST values  $>100$  U/L ( $n = 23$ ), 65% (15/23) responded. Within the 6-mo study period, 33% (17/52) of treated patients had normal aminotransferase (ALT) values, and 13% (7/52) had cleared hepatitis B surface antigen (HBsAg) from serum, whereas none of the controls had normal ALT values or had lost HBsAg. Eight of the 60 patients in the Ganopoly group and 4 of the 30 in the controls were unable to be followed up due to loss or withdrawal. Our study indicates that Ganopoly is well tolerated and appears to be active against HBV patients with chronic hepatitis B.<sup>[3,10,15,17]</sup>





**Fig. 6** Possible mechanisms for the hepatoprotective effects of *G. lucidum*. These include antioxidative and radical-scavenging effects, downregulation of activating enzymes, and upregulation of detoxifying enzymes, antiviral activities, inhibition of  $\beta$ -glucuronidase, enhanced hepatic nucleic acid and protein synthesis, inhibition of hepatic collagen synthesis, immunomodulating effects, and modulation of nitric oxide (NO) production. GSH = glutathione; GSSG = oxidized glutathione; INOS = inducible NO synthase; SOD = superoxide dismutase; CYP = cytochrome P450; UGT = uridine diphosphate glucuronosyltransferases. (From Ref.<sup>[17]</sup>.)

## ANTIDIABETIC EFFECT

Animal studies have demonstrated that the polysaccharide fractions of *G. lucidum* have potential hypoglycemic and hypolipidemic activities.

A water extract of reishi reduced the increase in blood glucose and blood insulin levels in rats (50 mg p.o.) following oral glucose test. Following adrenaline (i.v.) or oral glucose in rats, the mushroom inhibited increases in blood glucose without raising blood insulin levels. Glycans (ganoderans B and D) have shown significant hypoglycemic activity in mice.

A clinical study aimed at evaluating the efficacy and safety of polysaccharide fractions extracted from *G. lucidum* (Ganopoly) by a patented technique<sup>[18]</sup> in 71 patients with confirmed type II diabetes mellitus (DM) was carried out. Eligibility criteria included

type II DM of  $>3$  mo duration during which patients did not receive insulin; age  $>18$  yr; normal vital signs for age and disease state; normal electrocardiogram (ECG); and fasting plasma glucose (FPG) level of 8.9–16.7 mmol/L in sulfonylurea-naïve patients or an FPG  $< 10$  mmol/L before washout in sulfonylurea-treated patients. They were randomly grouped and given either Ganopoly or an oral placebo of 1800 mg three times daily for 12 weeks. The subjects underwent 4 weeks of dose adjustment, followed by 8 weeks of dose maintenance. Fasting and stimulated glycosylated hemoglobin (HbA<sub>1c</sub>), plasma glucose, insulin, and C-peptide were monitored at predetermined intervals. Adverse events and hypoglycemic episodes were recorded. Treatment with Ganopoly significantly decreased the mean HbA<sub>1c</sub> from 8.4% at baseline to 7.6% at 12 weeks. Significant changes in mean FPG



and PPG levels at the last visit paralleled the changes in mean HbA<sub>1c</sub> levels. At baseline, the mean FPG and PPG values for patients treated with Ganopoly were 12.0 and 13.6 mmol/L, respectively. At week 12, mean PPG values had decreased to 11.8 mmol/L. However, these parameters did not change or slightly increased for patients receiving placebos. The between-group difference in PPG levels at week 12 was significant ( $P < 0.05$ ). Changes in fasting insulin, 2-hr postprandial insulin, fasting C-peptide, and 2-hr postprandial C-peptide were consistent with the between-group differences in these end points being significant at the last visit. Overall, Ganopoly was well tolerated. This study demonstrated that Ganopoly is efficacious and safe in lowering blood glucose concentrations.<sup>[18]</sup>

A 2-mo open label comparative clinical study of a reishi powder extract (1 g t.i.d.) for eight diabetic patients (four with NIDD and four with IDDM) found hypoglycemic effects comparable to those found in controls who were administered insulin (100 IU/ml for 60 days) or oral hypoglycemic agents (250 mg/day for 60 days).<sup>[3,10,11,18]</sup>

## CARDIOVASCULAR AND CIRCULATORY FUNCTIONS

### Cholesterol and Lipid Metabolism

The powdered mycelium of reishi, at 5% of the diet of spontaneously hypertensive rats for 4 weeks, caused plasma total cholesterol to decrease significantly (by 18.6%) compared to controls. Total liver triglyceride and total liver cholesterol levels were also significantly lower in the reishi-fed group (by approximately 46% and 56%, respectively).<sup>[51,52]</sup>

### Hypertension

A water extract of the mycelium administered to rats and rabbits (3–30 mg/kg i.v.) produced significant hypotensive effects; an activity the researchers suggested is secondary to the primary effect that suppresses sympathetic outflow of the central nervous system.<sup>[53]</sup> The powdered mycelium of reishi, at 5% of the diet of spontaneously hypertensive rats for 4 weeks, caused systolic blood pressure to be significantly lower (approximately 10 mmHg) without causing a significant difference in the heart rate<sup>[51]</sup> Jin et al.<sup>[54]</sup> conducted a double-blind, placebo-controlled clinical study of *G. lucidum* in 54 patients with primary stage-II hypertension who had not responded to previous drug treatment (captopril 25 mg t.i.d. or nomodipine 20 mg t.i.d.). In the group which was

administered administrated *G. lucidum* extract tablets (2 tablets b.i.d. or 220 mg/day), systemic blood pressure significantly improved in 82.5%, with capillary and arterial blood pressure showing significant improvements in as little as 14 days. No changes of any significance were found in the placebo group. According to Soo<sup>[52]</sup> in treating hypertension, *G. lucidum* was shown to be highly effective in a very large number of treated cases. In the more successful cases, blood pressure was back to normal within 2 mo, and in some cases, within 2 weeks.

## ANTIBACTERIAL AND ANTIVIRAL VALUE

### Antibacterial Effect of *Ganoderma lucidum* on Gram-Positive and Gram-Negative Bacteria

Recently, more studies demonstrated that *G. lucidum* contained antibacterial constituents that are able to inhibit gram-positive and/or gram-negative bacteria.<sup>[3,5,10,11,17,55,56]</sup> The aqueous extract from the carpophores of *G. lucidum* inhibited 15 types of gram-positive and gram-negative bacteria. Further studies indicate that the antimicrobial combinations of *G. lucidum* extract with four antibiotics (ampicillin, cefazolin, oxytetracycline, and chloramphenicol) resulted in additive effects in most instances: synergism in two instances when combined with cefazolin against *Bacillus subtilis* and *Klebsiella oxytoca*,<sup>[57]</sup> and antagonism in two instances.

### *Helicobacter pylori*

*Helicobacter pylori* is associated with human gastroduodenal diseases such as gastritis, peptic ulcer, and gastric carcinoma. The extracts of many mushrooms inhibited the growth of this bacterium.<sup>[17,58]</sup> The extract of *G. lucidum* and some other species of higher Basidiomycetes arrested the growth of this pathogen. When their extracts were fractionated, the ether fractions of *G. lucidum* and *Agaricus bisporus* (J. Lge) Imbach were the most effective. Among seven components separated from the ether fraction of *G. lucidum* extract by silica gel column chromatography, P3 was the most potent with a minimum inhibitory concentration of 200 µg/ml.

It appears that some constituents such as ganomycin, triterpenoids, and aqueous extracts from *Ganoderma* species have a broad spectrum of in vitro antibacterial activity against gram-positive and gram-negative bacteria and *H. pylori*. Thus, it is possible that the antibacterial activity of *Ganoderma* species may be beneficial for those patients with chronic infection (e.g., chronic bronchitis) and those with *H. pylori*-positive



peptic ulcer diseases, though clinical studies are required to confirm this.

### **Antihuman Immunodeficiency Virus (HIV) Activity**

HIV was isolated as an etiological agent of acquired immunodeficiency disease syndrome in 1983.<sup>[59]</sup> Acquired immunodeficiency syndrome caused by HIV infection has recently become an important social and medical problem. Anti-HIV therapy by nucleoside analogues, such as 3'-azido-thymidine, is the major effective approach for the treatment of acquired immunodeficiency syndrome.<sup>[60]</sup> These agents are potent inhibitors of HIV reverse transcriptase (RT) and protease.<sup>[61]</sup> However, the emergence of drug-resistant variants of HIV and toxicities severely limits the long-term effectiveness of these drugs. Recent studies have indicated that many natural products are active as anti-HIV agents. These compounds belong to a wide range of different structural classes, e.g., coumarins, flavonoids, tannins, alkaloids, lignans, terpenes, naphtho- and anthraquinones, and polysaccharides.<sup>[62]</sup>

In vitro studies indicate that various triterpenoids from *G. lucidum* had potent inhibitory activity against HIV. Lucidenic acid O and lucidenic lactone, isolated from the fruiting body of *G. lucidum*, not only inhibited the activities of calf DNA polymerase- $\alpha$  and rat DNA polymerase- $\beta$ , but also those of HIV-1 RT.<sup>[17]</sup> Ganoderiol F and ganodermanontriol isolated from the fruiting bodies of *G. lucidum* are active against HIV-1 growth with an IC<sub>100</sub> of 7.8  $\mu\text{g}/\text{ml}$ .<sup>[10,11,17]</sup> Ganoderic acid B and ganoderol B showed potent inhibitory effect on HIV protease with an IC<sub>50</sub> value of 0.17 mM. Other triterpenoids including ganoderic acid C1, 3 $\beta$ -5 $\alpha$ -dihydroxy-6 $\beta$ -methoxyergosta-7,22-diene, ganoderic acid- $\alpha$ , ganoderic acid H, and ganoderol A had moderate activity against HIV-1 protease with IC<sub>50</sub> values of 0.17–0.23 mM.<sup>[10,11,17,50]</sup> In addition, ganoderic acid- $\beta$ , lucidumol B, ganodermanon-diol, ganodermanontriol, and ganolucidic acid A showed significant anti-HIV-1 protease activity with IC<sub>50</sub> values of 20, 59, 90, 70, and 70  $\mu\text{M}$ , respectively.<sup>[22]</sup> Ganoderic acid A, B, and C1 had minor inhibitory activity against HIV protease with IC<sub>50</sub> values of 140–430  $\mu\text{M}$ . It appears that there is a structure-activity relationship for triterpenoid showing anti-HIV protease activity. The C3, C24, or C25 atoms are vital for the anti-HIV activity.<sup>[22]</sup>

The aqueous low-molecular-weight fraction extracted from *G. lucidum* also exhibited anti-HIV activity using the XTT [2,3-bis (2-methoxy-4-nitro-5-sulfo-phenyl)-5-[(phenylamino) carbonyl]-2H-tetrazolium hydroxide] antiviral assay, which can quantitatively measure cytopathic effects of HIV-1 on CEM cells,

a human T lymphoblastoid cell line.<sup>[63]</sup> The IC<sub>50</sub> and EC<sub>50</sub> values were 125 and 11  $\mu\text{g}/\text{ml}$ , respectively, resulting in a therapeutic index of 11.4. This aqueous low-molecular-weight extract was further fractionated to eight subfractions by methanol: GLA (methanolic extract), GLB (hexane soluble), GLC (acetic ether soluble), GLD (water soluble), GLE (neutral), GLF (acidic), GLG (alkaline), and GLH (amphoteric). All subfractions except GLD, GLF, and GLH exhibited anti-HIV activity with IC<sub>50</sub> and EC<sub>50</sub> values of 22–44  $\mu\text{g}/\text{ml}$  and 14–44  $\mu\text{g}/\text{ml}$ , respectively. GLC and GLG inhibited HIV RT. Showing consistency, incubation of GLC at 50  $\mu\text{g}/\text{ml}$  or GLG (100  $\mu\text{g}/\text{ml}$ ) with Jurkat T cells gave a 75% and 66% inhibition of HIV growth, respectively. However, the high-molecular-weight fraction did not inhibit any HIV-induced cytopathic effect. Both low-molecular-weight and high-molecular-weight fractions from *G. lucidum* had negligible toxicities to CEM cells. The results indicate that the aqueous low-molecular-weight fraction from the fruiting bodies of *G. lucidum*, and the neutral and alkaline subfractions from the methanolic extract might contain small molecular weight polysaccharides.

### **Epstein-Barr Virus**

Virus-induced carcinogenesis is considered a complicated process with multiple steps involving a number of cellular signaling pathways. A few polyoxygenated lanostanoid triterpenes isolated from *G. applanatus* inhibited the 12-O-tetradecanoylphorbol-13-acetate induced Epstein-Barr virus early antigen in Raji cells. Similar effects have been observed with *Zingiberaceae rhizomes*, a commonly used traditional medicine in Malaysia. These results indicate that herbal medicines, such as *Ganoderma* species, may behave as antitumor promoters.<sup>[17]</sup>

### **Other Viruses**

The antiviral effects of two water-soluble substances (GLhw and GLlw) and eight methanol-soluble substances (GLMe-1-8) isolated from the carpophores of *G. lucidum*, were investigated on influenza A virus strains and vesicular stomatitis virus Indiana and New Jersey in vitro. These activities were evaluated by the cytopathic effect inhibition assay and plaque reduction assay using Vero and HEp-2 cells. Five substances, GLhw, GLMe-1, -2, -4, and -7 significantly inhibited the cytopathic effects of vesicular stomatitis virus. GLMe-4 did not exhibit cytotoxicity up to 1000  $\mu\text{g}/\text{ml}$ , while it displayed potent antiviral activity on the vesicular stomatitis virus New Jersey strain with a therapeutic index of more than 5.43.<sup>[64,65]</sup>



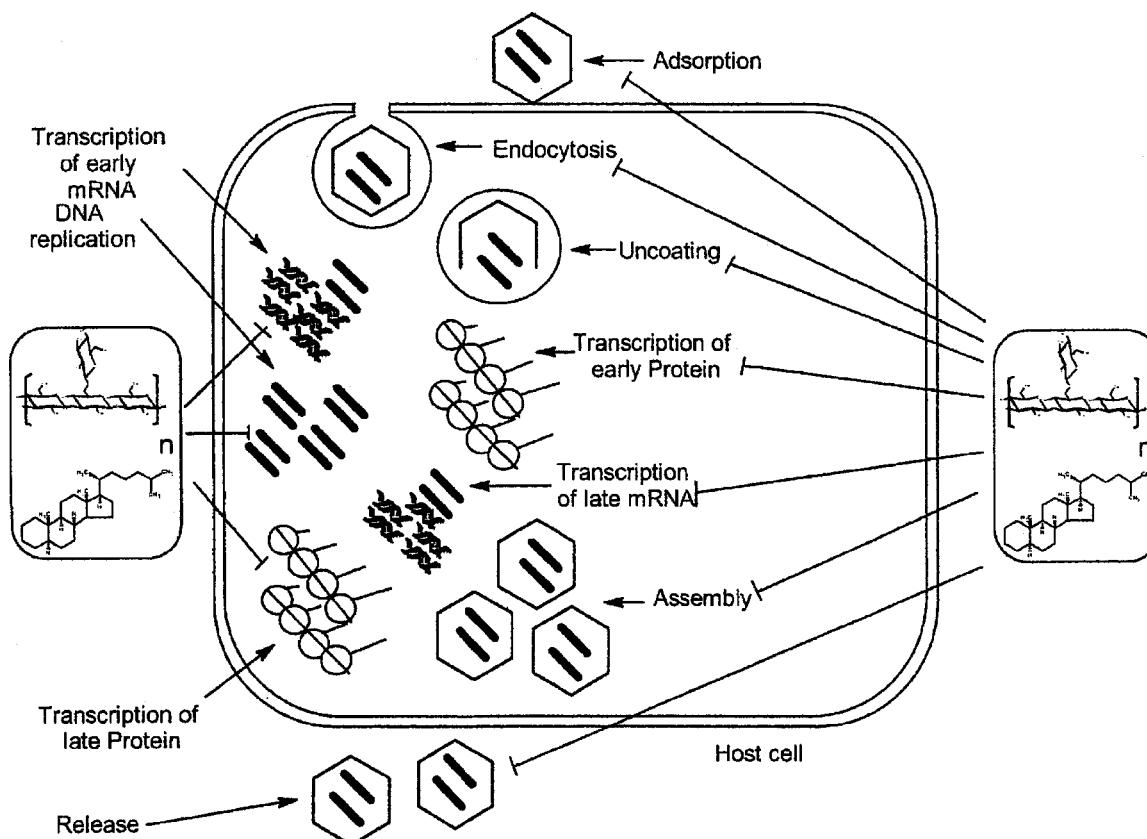
## Mechanism Consideration

The mechanisms for the antibacterial and antiviral activity of *Ganoderma* species are largely undefined. Gao et al.<sup>[17]</sup> suggest that multiple mechanisms may be involved. For example, the *Ganoderma* species constituents (e.g., polysaccharides and triterpenoids) may inhibit viral replication of HSV, HBV, HIV, and other types of viruses by interfering with their adsorption, virus–hepatocyte fusion and endocytosis, viral integration, assembly, and release (Fig. 7).

Data from in vitro studies indicate that *Ganoderma* polysaccharides have direct anti-HBV activity through inhibition of HBV DNA polymerase. The extract from *G. lucidum* inhibited the HBV DNA polymerase activity in PLC/PRF/5 cells by 80%, 70%, and 60%, respectively, with a 28–41% decrease in HBV DNA contents. Some constituents isolated from *G. lucidum* showed inhibitory effect on eukaryotic DNA polymerase. For example, two cerebrosides from the fruiting bodies selectively inhibited the activities of replicative DNA polymerases (especially the  $\alpha$  and  $\delta$  type) with a  $IC_{50}$  of 12–57  $\mu$ M. However, these

cerebrosides hardly influenced the activities of DNA polymerase- $\beta$ , prokaryotic DNA polymerases, terminal deoxynucleotidyl transferase, HIV RT, RNA polymerase, deoxyribonuclease I, and ATPase. Linoleic acid from *G. lucidum* inhibited the activities of mammalian DNA polymerases.<sup>[38,66]</sup>

Immunomodulating effects of *G. lucidum* are considered to play a role in antimicrobial activity.<sup>[15,17]</sup> Activation of immune effector cells (e.g., T cells, macrophages, and natural killer cells) by both pathogen infection and *G. lucidum* administration caused an enhanced production of cytokines, radicals, and NO facilitating the killing of viruses and bacteria. For example, activation of Kupffer cells by *G. lucidum* polysaccharides and triterpenoids within the liver facilitate the killing of HBV. In addition, a study of the mouse indicates that a proteoglycan with a carbohydrate protein ratio of 11.5 : 1 isolated from *G. lucidum* stimulated the proliferation of mouse spleen lymphocytes, resulting in a three-to-four fold increase in the percentage of B cells. These B cells were enlarged, expressed CD71 and CD25 on the cell surface, and showed an increase in the production of



**Fig. 7** Possible mechanisms for the antiviral effects of *G. lucidum*. Polysaccharides and triterpenoids may inhibit viral replication of HSV, HBV, HIV, and other types of viruses by interfering with their adsorption, and virus–hepatocyte fusion and endocytosis, viral integration, assembly, and release. (From Ref.<sup>[17]</sup>.)



immunoglobulins. Therefore, *Ganoderma* species may stimulate B cells in vivo, producing immunoglobulins, which can neutralize HBV.<sup>[15,17]</sup>

Furthermore, the immunosuppressive activity of *G. lucidum* constituents may decrease tissue and cellular damage following infection. Ling-Zhi-8 at 8 and 12 mg/kg by intraperitoneal injection significantly blocked the production of antibody to HBsAg (83.3–96.8% inhibition) in mice treated with twice the sensitization of the antigen. As Ling-Zhi-8 did not alter the mitogen responsibility of spleen cells and the T-cell subset population in mice, and prevented systemic anaphylaxis and Arthus reactions, these immunosuppressive activities may be ascribed to the blocking of antigen-specific antibody production. The immunosuppressive effect might ameliorate the immune response to HBV infection.<sup>[15,17]</sup>

#### Potential role in the treatment of HBV infection in combination with antiviral nucleoside analogues

Further studies are required to identify the molecular targets of *G. lucidum* constituents for viruses and bacteria. Herbal medicines often contain multiple active substances with individual constituents possibly contributing to the bioactivity observed in vitro and in vivo. Therefore, multiple important molecules might be the targets of a herbal medicine. The identification of these targets may provide molecular evidence of the pharmacological activity and toxicity of herbs.<sup>[67]</sup> *G. lucidum* may play an adjunct role in the management of infectious diseases. However, further experimental clinical studies are needed to identify mechanisms of action, optimal dosing, efficacy, and safety, alone or in combination with chemotherapeutic agents.

#### DOSAGE FORMS

*G. lucidum* is usually prescribed in various forms. It may be injected as a solution of powdered spore. It may be ingested as a soup, syrup, tea, tablets, capsules, tincture, or bolus (powdered medicine in honey). 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. As an antidote for ingestion of poisonous mushrooms, dried *G. lucidum* (120–200 g) is decocted in water and given as a drink 3–5 times daily.<sup>[3,5,10,11]</sup>

#### SAFETY PROFILE

Contraindications. None known.

#### Drug Interactions

Because reishi potentiates the immune system, caution is advised for those receiving immunosuppressive therapies.

#### SIDE EFFECTS

In oral dosages of 1.5–9 g/day, some patients, when initially taking a powder extract of reishi, have experienced temporary symptoms of sleepiness, thirst, rashes, bloating, frequent urination, abnormal sweating, and loose stools.<sup>[52]</sup> Large oral doses of vitamin C (6–12 g/day) taken at the same time as reishi powder extract (2–10 g/day) reportedly counteracted loose stools.<sup>[9,10,11,52]</sup>

The inhibition of platelet aggregation by *G. lucidum*<sup>[3,10,11]</sup> may present an additive effect in those taking blood thinning medications such as daily aspirin or warfarin.

Synergistic antimicrobial activity was shown with an aqueous extract of *G. lucidum* 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.<sup>[57]</sup>

#### TOXICITY

In animal experiments, *G. lucidum* extracts showed a very low toxicity.<sup>[3,5,10,11]</sup> There are few reported data on the long-term adverse effects on *G. lucidum* and its derivatives.

The aqueous extract of reishi administered to mice (5 g/kg p.o. for 30 days) produced no changes in body weight, organ weight, or hematological parameters. The polysaccharide fraction at the same dosage produced no lethal or serious effects.<sup>[21]</sup> The mushroom produced no changes in the estrus cycles of ovariectomized mice from a dosage of 10 g/kg p.o. and no increase in the weight of levator cavernosa and testicles in male mice from the same dosage. The LD<sub>50</sub> in mice of the reflux percolate was 38.3 ± 1.048 g/kg i.g. No organ toxicity was found in rabbits taking a syrup preparation of reishi (progressively dosed with 4–140 ml/kg p.o. daily for 10 days), or in dogs (2 ml/kg and 4 ml/kg p.o. daily for 10 days). An alcoholic extract (1.2 and 12 g/kg i.g. daily for 30 days) produced no signs of toxicity in young rats in DCG, major organs, hepatic function, growth, or development. Toxic reactions were absent in dogs administered an alcoholic extract (12 g/kg i.g. daily for 15 days and at 24 g/kg i.g. daily for 13 days); however, they did display lethargy.<sup>[10,11]</sup>



**Table 2** Current biomedical applications of *G. lucidum*

| <b>Applications</b>   | <b>Observed effects</b>   |
|---|---|
| A. Cosmonaut training in Russia                               | 1. Improves work capacity<br>2. Rapid recovery of normal physiology   |
| B. Usage with conventional treatment in cancer therapy        | 1. Maintains leukocyte counts<br>2. Enhances the immune system<br>3. Reduces chemotherapy toxicity and elimination of induced leucopenia (low blood leukocytes) by chemotherapy and radiation<br>4. Accelerates postsurgical recovery<br>5. Sedation, pain relief and reduction of morphine dependence in terminal cancer patients<br>6. Usage during remission to prevent relapses |
| C. Cardiovascular disorders including                         | 1. Coronary dilation and increasing coronary circulation<br>2. Increases frequency and amplitude of heart contraction<br>3. Blood pressure regulation together with other medication<br>4. Antihyperlipidemic, antihypoglycemic and antiplatelet aggregation (blood clots)<br>5. Relief from oxygen deprivation   |
| D. Immunomodulation effects                                   | 1. Anticancer<br>2. Antiviral (e.g., anti-HIV)<br>3. Antibacterial<br>4. Anti-inflammatory<br>5. Therapy of autoimmune disorders<br>6. Inhibition of histamine release in allergy and prevention of anaphylactic shock  |
| E. Usage during remission of cancer and hepatitis B treatment |   |
| F. Enhancing oxygen utilization                               | 1. Relief from discomfort of high-altitude stress, headaches, dizziness, nausea, and insomnia<br>2. Relief of oxygen deprivation caused by coronary arteries blocked by atheromas, spasms, or clots<br>3. Tolerance to hypobaric (low pressure) conditions  |
| G. Other examples   | 1. Usage in combination with other medication<br>2. Anti-aging, antioxidant free radical scavenger<br>3. Antidiabetic   |

(From Refs.<sup>[3,5,10,11,15–18,68]</sup>.)

To test the toxicity of wild reishi, fruit bodies harvested in a rural area of Hong Kong were prepared as a freeze-dried powder extract (yield: 1 g/20 g of freeze-dried fruit bodies and 50 ml of extract solution/100 g of freeze-dried fruit bodies). Examining acute toxicity, the extract solution (0.9259/kg) was administered to male mice at a dosage equivalent to the one commonly recommended by manufacturers of commercial concentrated extracts. Neither evidence of acute toxicity was found, nor was serum contents of

urea, GOT, or GPT significantly different 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 the control.<sup>[39]</sup>

Summarized data about *G. lucidum* biomedical applications are shown in Table 2. The observed effects include both clinical and preclinical observations, and the reader should refer to the preceding discussion of the various applications for more details.



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