The American Journal of Chinese Medicine, Vol. 51, No. 3, 1–24

Institute for Advanced Research in Asian Science and Medicine
DOI: 10.1142/S0192415X23500404

The Phytochemistry of *Ganoderma* Species and their Medicinal Potentials

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Published

Abstract: The *Ganoderma* genus is known for its diverse use as a functional food and therapeutic agent. This fungus has over 428 species, with *Ganoderma lucidum* being the most studied. The *Ganoderma* species produce several secondary metabolites and bioactive compounds like polysaccharides, phenols, and triterpenes, which are largely responsible for their therapeutic properties. Throughout this review, several extracts obtained from *Ganoderma* species have been studied to delve into their therapeutic characteristics and mechanisms. Such properties like immunomodulation, antiaging, antimicrobial, and anticancer activities have been demonstrated by several *Ganoderma* species and are supported by a large body of evidence. Although its phytochemicals play a vital role in its therapeutic properties, identifying the therapeutic potentials of fungal-secreted metabolites for human health-promoting benefits is a challenging task. Identification of novel compounds with distinct chemical scaffolds and their mechanism of action could help suppress the spread of rising pathogens. Thus, this review provides an updated and comprehensive overview of the

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March 23, 2023 11:50:08am WSPC/174-AJCM 2350040 ISSN: 0192-415X 1stReading

bioactive components in different *Ganoderma* species and the underlying physiological mechanisms.

Keywords: *Ganoderma*; *G. lucidum*; Therapeutic; Polysaccharides; Triterpenoids.

Introduction

The species complex *Ganoderma* are wood-decaying basidiomycete fungi with hard fruiting bodies called polypores, which bear characteristic double-walled, chambered-looking spores. These species are easily identified in their native habitats due to their unusual fruiting bodies. So far, 428 different species of *Ganoderma* have been identified. Some of the very prominent species of *Ganoderma* are *Ganoderma amboinense*, *G. annulare*, *G. applanatum*, *G. australe*, *G. boninense*, *G. capense*, *G. carnosum*, *G. cochlear*, *G. colossum*, *G. concinna*, *G. fornicatum*, *G. hainanense*, *G. lipsiense* (synonym *G. applanatum*), *G. mastoporum*, *G. neo-japonicum*, *G. orbiforme*, *G. pfeifferi*, *G. resinaceum*, *G. sinense*, *G. theaecolum*, *G. tropicum*, *G. tsugae*, *G. leucocontextum*, and *G. sinense*.

As these *Ganoderma* species are predominantly parasitic and saprophytic on conifers hardwood and are rather selective about their substrates, these species prefer to attack and parasitise specific trees. The fungus' extraordinary ability to produce diverse secondary metabolites (SMs) allows it to thrive in both parasitic and saprophytic modes of the life-cycle. Traditional remedies, as well as functional foods and nutraceuticals, make extensive use of SMs generated from these mushrooms. Meta-information generated via the computational approach of *Ganoderma's* SMs along with its experimental evidence indicates their distinct chemical scaffolds with different biological prowess (Grienke *et al.*, 2015). For its therapeutic capabilities, *Ganoderma* species are also referred to as the 'Mushroom of Immortality (Li *et al.*, 2013).

Furthermore, *Ganoderma lucidum* or lingzhi (Reishi mushrooms), which is one the most studied *Ganoderma* species, is known for its health benefits. Some of these benefits include anti-oxidant, anti-cancer, anti-inflammatory, anti-diabetic, anti-hypertension, and anti-lipidic activities. It has been used in traditional Asian medicine for thousands of years in the form of powder, tea, and dietary supplements to treat different health conditions and diseases and is known in Chinese medicine as the "King of Herbs" or "Miracle Chinese Herb" (Sliva, 2003; Benzie and Wachtel-Galor, 2009; Parepalli *et al.*, 2021b).

Ganoderma extracts contain several bioactive compounds, and the main physiologically active ingredients include polysaccharides, peptidoglycans, proteins, peptides, phenols, and triterpenes (Parepalli *et al.*, 2021a). The *Ganoderma* extracts have been used for decades in traditional Asian medicine, particularly in China and Japan, as the best natural source of anti-oxidants (Koo *et al.*, 2011), an all-cure herb, and an effective medicine in combatting diseases like AIDS and cancer (Cör *et al.*, 2018).

Furthermore, *Ganoderma* is used to strengthen the immune system and to treat viral infections (HIV/AIDS), as well as to treat lung (like asthma and bronchitis), heart, liver, kidney, and cancer diseases (Wachtel-Galor *et al.*, 2011; Kao *et al.*, 2013).

March 23, 2023 11:50:08am WSPC/174-AJCM 2350040 ISSN: 0192-415X 1stReading

Secondary Metabolites of Ganoderma

Ganoderma species possess the capacity to generate more than 450 different SMs with remarkable therapeutic properties. Major secondary compounds isolated are ganoderic acids, C30 lanostanes (aldehydes, alcohols, esters, glycosides, lactones, ketones), C27 lanostanes (lucidenic acids), C27 lanostanes (alcohols, lactones, esters), C24 and C25 lanostanes, C30 pentacyclic triterpenes, meroterpenoids, farnesyl hydroquinones (meroterpenoids), C15 sesquiterpenoids, steroids, alkaloids, prenyl hydroquinone, ganodermanontriol, ganodermaside A, ganodermalactone G, ganoderone A and C, ganoboninone D, benzofurans, benzopyran-4-one derivatives, and benzenoid derivatives (Sharma *et al.*, 2019). In addition, bioactive compounds, such as lectins, beta-glucans, polysaccharide-protein complexes, and lanostanoids, have also been identified in these species (Borchers *et al.*, 2008) (Fig. 1).

Therapeutic Capabilities of Ganoderma Species

An extensive variety of medicinal and pharmacokinetic properties have been observed from metabolites extracted from *Ganoderma* species, and these metabolites are being used as anti-cancer agents and anti-oxidants, and possess anti-ageing, anti-inflammatory, and anti-immunomodulatory activities, amongst others (Fig. 2). In addition, their use in regulating blood cholesterol, treating respiratory diseases, and lowering anxiety levels has also been observed (Nishitoba *et al.*, 1998; Ikekawa *et al.*, 1992; Liu *et al.*, 1998). Due to their versatility, *Ganoderma* extracts are frequently used for treating hepatitis, hypercholesterolemia, diabetes, neoplasms, immunodeficiency, leukopenia, atherosclerosis, haemorrhoids, chronic fatigue, cancer, bronchitis, hypertension, insomnia, and

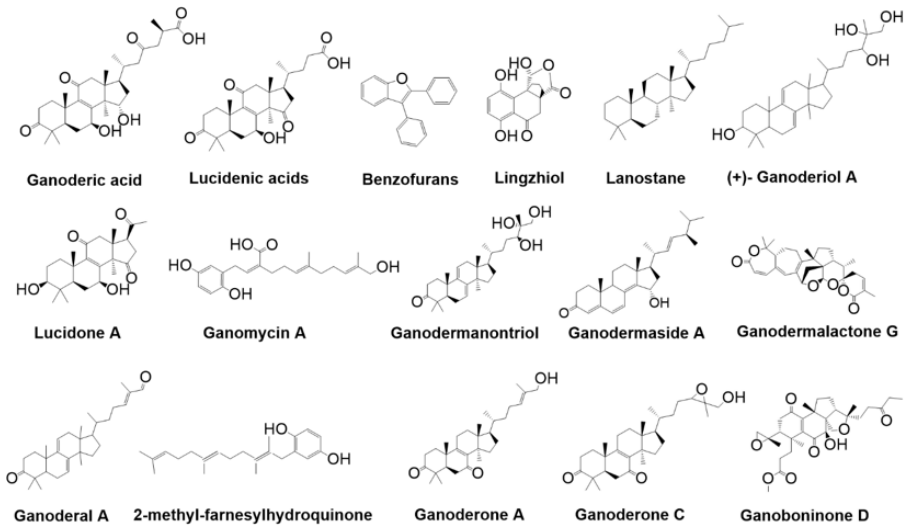

Figure 1. Selected secondary metabolites biosynthesized by Ganoderma species.

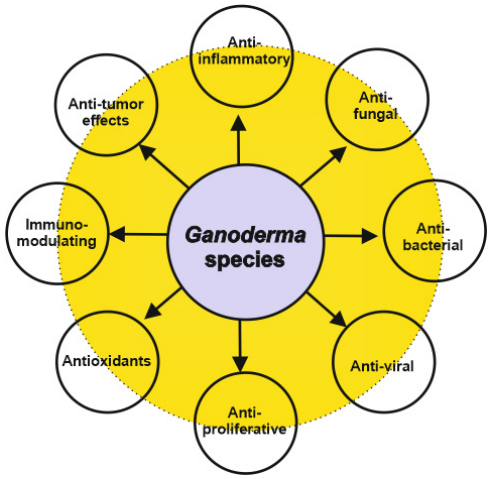

Figure 2. Therapeutic applications of *Ganoderma* metabolites.

dizziness (Gao *et al.*, 2002; Fujita *et al.*, 2005; Hajjaj *et al.*, 2005; Wang and Ng, 2006). Furthermore, the chemicals found in these species are efficient anti-oxidizing agents as well as inhibitors of sarcoma development (Jones and Janardhanan, 2000).

Anti-Tumor Properties

Different extracts of *Ganoderma* species were found to have an inhibitory effect on different types of cancers, such as prostate, lung, glioma, breast cancers, and malignant melanoma, as seen in Table 1 (Chen *et al.*, 2016; Kao *et al.*, 2016; Smina *et al.*, 2017; Zheng *et al.*, 2018), by inhibiting the cell cycle, inducing apoptosis, reducing tumor progression, and decreasing the expression and activity- of cell cycle regulators (Yang *et al.*, 2019). Furthermore, the bioactive compounds of *Ganoderma* also exhibit anti-angiogenic, multidrug resistance reversal, and anti-proliferative and apoptosis inductive activities by involving the intrinsic and extrinsic initiated apoptotic pathway in association with cell cycle arrest, telomerase inhibition, autophagy, and oxidative stress, in addition to the inhibition of tumor cell adhesion, invasion, and migration. The antitumor activities may be due to the inhibition of ATP-dependent transmembrane drug transporters such as P-glycoprotein on the surface of resistance tumor cells to prevent reduction of the intracellular accumulation of anticancer drugs (Sun and Sun, 2019).

Triterpenes in mushrooms possess chemo-preventive and tumoricidal activities (Leskosek-Cukalovic *et al.*, 2010). Triterpenes activate the capase cascade, which helps to prevent cancer metastasis by directing matrix metalloproteinase and interleukin (IL)-8 and reduces pro-inflammatory cytokine production in macrophage cells. Polysaccharides, on the other hand, can boost the immunological response of the host by promoting the growth of macrophages, natural killer cells, and T-lymphocytes. This may stop tumor-derived

Table 1. A Summary of the Components and/or Extracts Obtained from *Ganoderma* Species that Can be Used to Combat Melanoma

***Ganoderma* Spp.**	***Ganoderma* Components**	**Effects**	**References**
Ganoderma lucidum	*Ganoderma lucidum* extracts	The possible use of *Ganodermalucidum* extract for the therapeutic management of melanoma	(Barbieri *et al.*, 2017)
Ganoderma Lucidum	9,11-Dehydroergosterol peroxide [9(11)-DHEP] from *Ganoderma Lucidum* mycelium	Myeloid cell leukemia-1 (MCL-1) in regulating apoptosis of melanoma cells induced by the steroid.	(Zheng *et al.*, 2018)
Ganoderma lucidum	*Ganoderma lucidum* polysaccharide peptide (GL-pp)	GL-pp significantly reduced B16-F10-luc-G5 melanoma tumor metastasis	(Xian *et al.*, 2021)
Ganoderma microsporum	Immunomodulatory proteins of *Ganoderma microsporum (GMI)*	GMI-induced decrease in proliferation and migration of A375.S2 melanoma cells in a concentration-dependent manner.	(Lu *et al.*, 2019)
Ganoderma lucidum polysaccharides	*Ganoderma lucidum* polysaccharides	Polysaccharides extracted from G. lucidum inhibit the adhesion of fibrinogen to melanoma cells, and reverse the blocking effect of the fibrin coat on NK cytotoxicity against melanoma cells.	(Zheng *et al.*, 2011)
Ganoderma lucidum	*Ganoderma lucidum* spore and fruiting body GLSF	GLSF reduced skin tumor incidence and multiplicity. GLSF attenuated UV-induced epidermal thickening, expression of Ki-67, COX-2 and NF-κB, while in tumor tissues, GLSF increased expression of CD8 and Granzyme B. GLSF prevents skin cancer probably via attenuating UV-induced immunosuppression	(Shahid *et al.*, 2022)

March 23, 2023 11:50:15am WSPC/174-AJCM 2350040 ISSN: 0192-415X 1stReading

angiogenesis by lowering human umbilical vein endothelial cell proliferation and angiogenic factors, including Vascular Endothelial Growth Factor and transforming growth factor beta 1 (TGF-β1) production. The triterpenes act as anti-oxidants by scavenging free radicals and activating anti-oxidant enzymes, whereas polysaccharides reduce oxidative damage caused by reactive oxygen species and prevent the breaks of DNA strands (Kao *et al.*, 2013).

G. lucidum extracts are carcinostatic in a variety of cancer cell lines, including pancreatic, lung, colon, skin, breast, prostate, and liver cancer cell lines (Suprasert, 2015; Yu *et al.*, 2017; Zhang, 2017). Furthermore, the compounds from *G. lucidium* (Xu *et al.*, 2011) and *G. applanatum* have been shown to exhibit immunomodulatory, anti-angiogenic, and cytotoxic properties (Elkhateeb *et al.*, 2018). Triterpenes such as ganoderic acids U-Y and F are cytotoxic to hepatoma cells (O. Toth *et al.*, 1983) and inhibit the angiotensin-converting enzyme (Morigiwa *et al.*, 1986; Zhang *et al.*, 2009), respectively.

Furthermore, the ganoderic acid DM possesses anti-proliferative properties against human malignant growth cells by altering androgen or oestrogen receptors (Liu *et al.*, 2006; Wu *et al.*, 2012) and has apoptotic effects in Michigan Cancer Foundation (MCF)-7 breast cancer cells; additionally, it hinders testosterone change to dihydrotestosterone through 5 α-reductase inhibitory activity (Liu *et al.*, 2006; Suárez-Arroyo *et al.*, 2017). Anti-proliferative effects of ganoderiol A, ganoderiol F, ganoderol B, lucidumol B, ganodermatriol, and ganodermanontriol against prostrate cells have also been discovered (Jiang *et al.*, 2011).

Immunomodulation

Ganoderma exerts immunomodulation effects by enhancing humoral and cellular immunity (Wang and Lin, 2019). These effects may be due to its bioactive molecules, particularly polysaccharides. It was found that the polysaccharide contents of *G. lucidum* play a role in promoting the function of antigen-presenting cells, humoral immunity, mononuclear phagocyte system, and cellular immunity (Lin, 2005). Many studies reported that *Ganoderma* exhibits significant antitumor and anti-inflammatory activity and promotes the activity of most immune effector cells, including lymphocytes and myeloid cells (Ren *et al.*, 2021). Numerous studies linked the antitumor effects and enhanced immune system by *Ganoderma* supplements or extracts. In addition, the aqueous extracts of *Ganoderma* stimulate the production of cytokines, such as interleukins IL-2, IL-10, IL-1β- IL-6 and tumor necrosis factor alpha (TNF-α) and interferon – Y (INF-Y) (Sanodiya *et al.*, 2009; Wang *et al.*, 2018).

Smina *et al.* (2017) reported that total triterpenes induced apoptosis in human breast adenocarcinoma cells by regulating the levels of cyclin D1 and B cell lymphomas, and by upregulating the levels of Bax and caspase-9. Furthermore, Zheng *et al.* (2018) reported that the antitumor effects may be due to the effect of Ganoderma as a dehydroergosterol peroxide enzyme by its role in the process of decreasing the expression of the myeloid leukemia cell differentiation protein, releasing cytochrome-c and damaging the mitochondrial membrane. In addition, *Ganoderma* promotes the function of phagocytes, natural killer cells, antigen-presenting cells, lymphocytes, and cytotoxic T- lymphocytes, and promotes the production of cytokines (Zhibin Lin and Sun, 2019).

March 23, 2023 11:50:15am WSPC/174-AJCM 2350040 ISSN: 0192-415X 1stReading

Moreover, β-D-glucans, the Zhi-8 proteins, and triterpenoids are the known immunomodulating agents identified from *Ganoderma*. These compounds stimulate immune effectors and cause cytokine production (Wang *et al.*, 1997). They additionally prevent systemic anaphylaxis in mice (Kino *et al.*, 1989), stimulate immune regulation (Tanaka *et al.*, 1989), are an adjuvant for the DNA vaccine via dendritic cells activation (Lin *et al.*, 2011), and stimulate cancer cell death (Li *et al.*, 2014; Hsin *et al.*, 2015).

Furthermore, polysaccharides promote cancer and viral immunity by increasing the expression of the major histocompatibility complex in a melanoma cell line, which improves antigen presentation (Sun *et al.*, 2010). *G. microsporum* extracts also cause apoptosis in urothelial cancer cells (Huang *et al.*, 2018). As a result, the proteins implicated in Ganoderma immunomodulation might be used to develop immunotherapy.

Anti-Oxidative and Radical Scavenging Activity

Ganoderma anti-oxidants protect cellular components from oxidative damage, lowering the likelihood of mutations and carcinogenesis, as well as immune cells, allowing them to maintain immune surveillance and responsiveness as shown in Table 2. Furthermore, *G. lucidum* polysaccharides safeguard immune cells from oxidative stress, while the ethanolic extract breaks cellular DNA by boosting the generation of hydrogen peroxide (H_2O_2), causing considerable cell death. Additionally, *G. lucidum* methanolic extracts protect kidneys from cisplatin-induced kidney injury by restoring the renal anti-oxidant defence system (Sheena *et al.*, 2003).

Table 2. A Summary of the Main Components in *Ganoderma* Species that Exhibit Anti-Oxidant Activity

***Ganoderma* Spp.**	***Ganoderma* Component**	***Ganoderma* Activity**	**References**
Ganoderma lucidum	*Ganoderma lucidum* polysaccharides (GLP)	Anti-oxidant	(Xu *et al.*, 2019)
Ganoderma lucidum	*Ganoderma lucidum* triterpenes and aromatic meroterpenoids	Anti-oxidant	(Wang *et al.*, 2019)
Ganoderma lucidum	*Ganoderma lucidum* chitosan extracts	Anti-oxidant, cytotoxic, antimicrobial activity.	(Savin *et al.*, 2020)
Ganoderma lucidum	*Ganoderma lucidum* extract	Anti-oxidant	(Kebaili *et al.*, 2021)
Ganoderma spp.	*Ganoderma* spp. extracts	Anti-oxidant	(Obodai *et al.*, 2017)
Ganoderma lucidum	*Ganoderma* extracts	Anti-oxidant activity and protective effects in oxidatively injured DNA in cell-free analyses	(Saltarelli *et al.*, 2019)
Ganoderma lucidum	*Ganoderma lucidum* spores	Antitumor, anti-oxidation, and cell protecting	(Xu *et al.*, 2019)
Ganoderma lucidum	GLP	Anti-oxidant activity	(Zheng *et al.*, 2018)
Ganoderma lingzhi	Exopolysaccharides	Anti-oxidant activity	(Si *et al.*, 2019)

March 23, 2023 11:50:15am WSPC/174-AJCM 2350040 ISSN: 0192-415X 1stReading

Antibacterial Activity

Ganomycin and triterpenoids have a broad-spectrum of antibacterial activity against Gram-positive and Gram-negative bacteria (Suay, 2000; Gao *et al.*, 2003). Organic extracts of *G. lucidum* have antibacterial activities against *Bacillus subtilis*, *Corynebacterium diphtheria*, *Enterobacter aerogenes*, *Escherichia coli*, *Pseudomonas aeruginosa, Salmonella* sp., *Staphylococcus aureus* (Sheena *et al.*, 2003; Keypour *et al.*, 2008), *S. aureus*, and *B. cereus* (Heleno *et al.*, 2013). Moreover, *G. pfeifferi* extracts also inhibited the growth of pathogenic bacteria such as *Aeromonas hydrophila*, *Aeromonas salmonicida*, *Vibrio anguillarum,* and *Yersinia ruckeri* (Monthana, 1999).

Based on our previous studies, it can be concluded that the antimicrobial activity of pure compounds should be below 1000 μg/ml. We have shown that the strong activity is for MICs below 300 μg/ml, medium activity for MICs 300–500 μg/ml, and poor activity for MICs $>$ 500 to 1000 μg/ml (Adamczak *et al.*, 2020; Karpiński *et al.*, 2021). The values of MIC above 1000 μg/ml should be considered as very poor activity or lack of activity ($>$ 5000 μg/ml). Extracts and fractions of *Ganoderma* have mainly poor or lack of activity. Regardless of the *Ganoderma* species, the MIC values for extracts most often range from 500 μg/ml to even 512 mg/ml (Sa-Ard *et al.*, 2015; El Zawawy and Ali, 2016; Ergun, 2017; Costa *et al.*, 2020; Savin *et al.*, 2020; Serrano-Márquez *et al.*, 2021). For single strains, incl. *Enterococcus faecalis*, extract of *G. lucidum* has a strong activity with an MIC of 200 μg/ml (Ergun, 2017). Some isolated compounds exhibit poor or no significant antimicrobial activity, e.g. chitosan from *G. lucidum* (MICs 625–2500 μg/ml) (Savin *et al.*, 2020) and sulfated (1,3)-β-d-glucan from *G. lucidum*, for which the MIC values are 1000–5000 μg/ml (Wan-Mohtar *et al.*, 2016). Similarly, exopolysaccharide from *G. applanatum* shows poor activity with an MIC of 1000 μg/ml (Osińska-Jaroszuk *et al.*, 2014). Lanostane triterpenoids and farnesyl hydroquinones are the most active. The MIC values for the former start from 0.391 μg/ml (Isaka *et al.*, 2016; Chinthanom *et al.*, 2021), and for the latter from 2.5 μg/ml (Mothana *et al.*, 2000).

Some antibacterial studies presented the disk diffusion method (ZOI) instead of MIC. The authors present the activity, unfortunately, without specifying the MIC value or the active concentration. The disc diffusion test provides qualitative results showing if bacteria are susceptible or resistant (Benkova *et al.*, 2020). Consider that this research extracted freeze-dried culture fluids of *G. lucidum* extracts that have activity against *Acidovorax avenae*, *Agrobacterium tumefaciens*, *Brenneria quercina*, *Erwinia carotovora*, *Pantoea herbicola*, *Pseudomonas syringae*, and *Xanthomonas campestris* (Robles-Hernández *et al.*, 2021). Extracts of *G. boninense* in ZOI method are active against coagulase-negative Staphylococci (CoNS), methicillin-resistant *Staphylococcus aureus*, and *Streptococcus pyogenes* (Chan and Chong, 2022).

Anti-Fungal Activity

Extracts of *G. lucidum* are active against *Botrytis cinerea*, *Physalospora piricola*, and *Fusarium oxysporum* (Wang and Ng, 2006), and against *Trichoderma viridae* that exceed

March 23, 2023 11:50:16am WSPC/174-AJCM 2350040 ISSN: 0192-415X 1stReading

more than the standards, i.e., bifonazole and ketoconazole (Heleno *et al.*, 2013). Antifungal characteristics are found in sterols derived from *G. annulare*, such as 5α-ergost-7-en-3β-ol, 5α-ergosta-7,22-dien-3β-ol, and 5,8-epidioxy-5α,8α-ergosta-6,22-dien-3β-ol and five triterpenes, applanoxidic acids A, C, F, G and H (Smania *et al.*, 2003). The terpenoids were found to be active against *Microsporum cannis* and *Trichophyton mentagrophytes* (Smania *et al.*, 2003).

Furthermore, in terms of antifungal activity, the best activity is shown by triterpenoids obtained from *G. gibbosum*. The MIC_{50} of these triterpenoids against *Candida albicans* is 3.8–129.1 μg/ml (Pu *et al.*, 2019). Benzolactones isolated from *G. lucidum* also have a strong activity. Their MIC_{90} against *Microsporum gypseum* ranges from 18.5 up to > 128 μg/ml (Lu *et al.*, 2020). Unfortunately, there is little research into the antifungal activity of *Ganoderma* species. In addition, one of the studies on farnesyl hydroquinones from *G. pfeifferi* showed no activity. However, MIC values were only determined up to 100 μg/ml (Mothana *et al.*, 2000). This means that hydroquinones should also be tested at higher concentrations, which would clearly show activity or lack thereof.

Antiviral Activity

Compounds of gray level histogram width (GLhw) and GLMe-1, 2, 4, and 7 from *G. lucidum* significantly inhibited cytopathic effects of the vesicular stomatitis virus and herpes simplex virus (HSV) (Sharma *et al.*, 2019). GLhw inhibited plaque formation of HSV-2 and HEp-2 cells, while GLMe-4 showed cytotoxicity (Liu *et al.*, 2004; Sharma *et al.*, 2019). Furthermore, terpenoids derived from *G. pfeifferi* have antiviral properties against influenza and *Herpes simplex virus* (Lindequist *et al.*, 2015). Moreover, applanoxidic acid G, lucialdehyde, lucidadiol, and ergosta-7,22-diene-3β-ol compounds from *Ganoderma* possess antiviral properties against influenza virus A (Mothana *et al.*, 2003; Niedermeyer *et al.*, 2005). The combination of ganomycin B and ganomycin I from *G. colossum* inhibits HIV-1 protease (El Dine *et al.*, 2009).

Most studies of the antiviral activity of *Ganoderma* species indicate good activity. Lanostane triterpenoids have been shown to inhibit HIV-1 protease at IC_{50} concentrations from 5 μg/ml or from 20 μM (El Dine *et al.*, 2008; Sato *et al.*, 2009). Triterpenoids also show strong inhibitory activity against H1N1 influenza virus neuraminidase (IC_{50} from 4.6 μM), H5N1 influenza virus neuraminidase (IC_{50} from 1.2 μM), HSV-1 (ED_{50} 0.068 mM/l), and influenza virus type A (ED_{50} 0.19–0.22 mM/l) (Mothana *et al.*, 2003; Zhu *et al.*, 2015). However, the activity of triterpenoids against Dengue virus NS2B-NS3 protease was confirmed in silico analysis (Bharadwaj *et al.*, 2019). Extracts from *Ganoderma* against Dengue virus serine protease and enterovirus A71 show a lower antiviral activity (over 25 μg/ml) (Lim *et al.*, 2020; Ang *et al.*, 2021). Thus, as seen, *Ganoderma* has extensive antimicrobial properties.

In Tables 3 and 4, the antimicrobial activities of extracts or compounds from some *Ganoderma* species are presented.

Table 3. A Summary of the Main Components in *Ganoderma* Species that Demonstrate Antimicrobial Activity

Ganoderma Spp.	Compound/s	Target Microorganisms	Active Concentration	Reference
G. applanatum	Exopolysaccharide	*Staphylococcus aureus*	MIC 1000 μg/ml	(Osińska-Jaroszuk *et al.*, 2014)
G. australe	Natural lanostane triterpenoid: ganodermic acid	*Mycobacterium tuberculosis*	MIC 0.391 μg/ml	(Chinthanom *et al.*, 2021)
	Semisynthetic lanostane triterpenoids		MIC from 0.0977 to > 50 μg/ml	
G. colossum	Lanostane triterpenes	HIV-1 protease	IC_{50} from 5 up to > 100 μg/ml	(El Dine *et al.*, 2008)
G. curtisii	Extract	*Staphylococcus aureus*	MIC from 500 up to > 1000 μg/ml	(Serrano-Márquez *et al.*, 2021)
		Enterococcus faecalis	MIC > 1000 μg/ml	
		Escherichia coli	MIC > 1000 μg/ml	
		Pseudomonas aeruginosa	MIC > 1000 μg/ml	
G. gibbosum	Triterpenoids: gibbosicolids	*Candida albicans*	MIC_{50} 4.7–129.1 μg/ml	(Pu *et al.*, 2019)
	Triterpenoids: gibbosic acids		MIC_{50} 3.8–70 μg/ml	
G. lingzhi	Triterpenoids: ganoderic acids, ganoderenic acids, ganolucidic acid, ganoderiols, ganodermanondiol, lucialdehydes	H1N1 influenza virus neuraminidase	IC_{50} 4.6 up to > 200 μM	(Zhu *et al.*, 2015)
		H5N1 influenza virus neuraminidase	IC_{50} 1.2 up to > 200 μM	
G. lipsiense	Crude extract	*Escherichia coli*	MIC > 1000 μg/ml	(Costa *et al.*, 2020)
		Pseudomonas aeruginosa	MIC 500 μg/ml	
		Staphylococcus aureus	MIC > 1000 μg/ml	
	Fractions	*Escherichia coli*	MIC 1000 μg/ml	
		Pseudomonas aeruginosa	MIC 500 up to > 1000 μg/ml	
		Staphylococcus aureus	MIC 500 up to > 1000 μg/ml	

March 23, 2023 11:50:17am WSPC/174-AJCM 2350040 ISSN: 0192-415X 1stReading

Table 3. (*Continued*)

***Ganoderma* Spp.**	**Compound/s**	**Target Microorganisms**	**Active Concentration**	**Reference**
Ganoderma neo-japonicum	Crude extracts	enterovirus A71	25–1250 μg/ml	(Ang *et al.*, 2021)
G. orbiforme	Lanostane triterpenoids	*Mycobacterium tuberculosis*	MIC 0.781 up to > 50 μg/ml	(Isaka *et al.*, 2016, 2017)
Ganoderma pfeifferi	Ganomycins a and b, new antimicrobial farnesyl hydroquinones	*Micrococcus flavus*	MIC 2.5 μg/ml	(Mothana *et al.*, 2000)
		Staphylococcus aureus	MIC 25 μg/ml	
		Candida albicans	MIC > 100 μg/ml	
		Candida maltosa	MIC > 100 μg/ml	
	Lanostanoid triterpenes ganodermadiol	HSV type 1	ED_{50} 0.068 mM/l	(Mothana *et al.*, 2003)
		Influenza virus type A	ED_{50} 0.22 mM/l	
	Lucidadiol	Influenza virus type A	ED_{50} 0.22 mM/l	
	Applanoxidic acid g	Influenza virus type A	ED_{50} 0.19 mM/l	
Ganoderma sinense	Lanostane-type triterpenoids	Inhibited human immunodeficiency virus-1 protease	IC_{50} 20-40 μM	(Sato *et al.*, 2009)

March 23, 2023 11:50:19am WSPC/174-AJCM 2350040 ISSN: 0192-415X 1stReading

Table 4. A Summary of the Main Components in *Ganoderma Lucidum* that Demonstrate Antimicrobial Activity

Compound/s	Target Microorganisms	Active Concentration	Reference
Extracts	*Staphylococcus aureus*	MIC 625–2500 µg/ml	(Savin *et al.*, 2020)
Extracts	*Pseudomonas aeruginosa*	MIC 400–2500 µg/ml	(Savin *et al.*, 2020) (Ergun, 2017) (El Zawawy and Ali, 2016)
Extract	*Enterococcus faecalis*	MIC 200 µg/ml	(Ergun, 2017)
Mycelia protein extract	*Staphylococcus epidermidis*	MIC 20000–512500 µg/ml	(Sa-Ard *et al.*, 2015)
	Bacillus cereus	MIC 20000–81500 µg/ml	
	Escherichia coli	MIC 81500 µg/ml	
Extract	Dengue virus serine protease	25 to 400 µg/ml	(Lim *et al.*, 2020)
Mycelium	*Salmonella Typhi*	25–60 µg	(Mishra *et al.*, 2018)
	Escherichia coli	30–55 µg	
Fruiting body	*Salmonella Typhi*	30–65 µg	
	Escherichia coli	40–55 µg	
Sulfated (1,3)-β-d-glucan	*Escherichia coli*	MIC 1000–3000 µg/ml	(Wan-Mohtar *et al.*, 2016)
	Shigella sonnei	MIC 3000 µg/ml	
	Pseudomonas aeruginosa	MIC 3000 µg/ml	
	Salmonella enteritidis	MIC 3000 µg/ml	
	Salmonella enterica Typhimurium	MIC 3000 µg/ml	
	Listeria monocytogenes	MIC 3000 µg/ml	
	Staphylococcus aureus	MIC 2000–3000 µg/ml	
	Staphylococcus epidermis	MIC 5000 µg/ml	
Triterpenoid	*Staphylococcus aureus*	MIC 68.5 µM	(Li *et al.*, 2014)
	Bacillus subtilis	MIC 123.8 µM	
Benzolactones, ganodumones c and e	*Microsporum gypseum*	MIC_{90} 18.5 up to > 128 µg/ml	(Lu *et al.*, 2020)
Triterpenoids: ganodermanontriol, lucidumol a, ganoderic acid c2, ganosporeric acid a	Dengue virus NS2B-NS3 protease	in silico analysis, −6.291 to −5.983 kcal/mol	(Bharadwaj *et al.*, 2019)
Chitosan	*Staphylococcus aureus*	MIC 625–2500 µg/ml	(Savin *et al.*, 2020)
	Pseudomonas aeruginosa	MIC 1250–2500 µg/ml	

Table 5. How *Ganoderma* Species Exert their Anti-ageing Properties

***Ganoderma* Spp.**	**Effects**	**References**
Ganoderma lucidum	The results indicate that *Ganoderma lucidum* polysaccharide can increase wound healing, the epidermal and dermal thickness, improve the skin tissue structure, and enhance the superoxide dismutase levels and the expression of CuZn-superoxide dismutase mRNA.	(Xiang *et al.*, 2013)
Ganoderma lucidum	Inhibition of tyrosinase activity (IC_{50} value 0.32 mg/ml)	(Chien *et al.*, 2008)
Ganoderma applanatum	Fruiting bodies of *G. applanatum* had good anti-tyrosinase, good anti-collagenase, and moderate anti-elastase activities, which might be useful for developing novel skin-whitening and anti-wrinkle agents.	
Ganoderma lucidum	Antiperoxidative, anti-inflammatory, and antimutagenic activities of the ethanol extract of the mycelium of a medicinal mushroom, *Ganoderma lucidum*.	
Ganoderma weberianum	Ethyl acetate fraction of *G. formosanum* mycelium ethanol extract (GFE-EA) demonstrated tyrosinase inhibitory activity in both *in vitro* cell-free and cellular tyrosinase system, and *in vivo* zebrafish model. These studies showed the anti-melanogenic activity of *Ganoderma* and more tyrosinase inhibitors might be found from *Ganoderma*.	(Lai *et al.*, 2019)
Ganoderma leucocontextum	No data available	(Yu *et al.*, 2019)
Ganoderma lucidum spore oil	GLS have potential anti-inflammatory and wrinkle improves, skin moisture effect.	
Ganoderma lucidum polysaccharide (GLP)	It has been found in the experiments of UVB-induced skin pigmentation in zebrafish that GLP is capable of inhibiting UVB-induced skin pigmentation. Meanwhile, it can greatly relieve erythema reaction in guinea pig skin caused by high-dosage UVB irradiation. In conclusion, this study shows that GLP can inhibit UVB-induced melanogenesis by antagonizing cAMP/PKA and ROS/MAPK signaling pathways and is a potential natural safe whitening sunscreen additive.	(Hu *et al.*, 2019b)
Ganoderma lucidum	Results demonstrate that GL-PS protects fibroblasts against photoaging by eliminating UVB-induced ROS. This finding indicates GL-PS treatment may serve as a novel strategy for antiphotoaging.	(Zeng *et al.*, 2017)
Ganoderma lucidum polysaccharides	*Ganoderma lucidum* polysaccharides may play an important role in boosting cell growth and against skin aging.	(Shaoqiong *et al.*, 2008)
Ganoderma formosanum mycelium	No data available	(Hsu *et al.*, 2016)
Ganoderma lucidum	*Anti-aging*	(Li *et al.*, 2015)
Ganoderma lucidum	As the most potent adaptogen present in nature, and its anti-inflammatory, anti-oxidant, immunomodulatory and anticancer activities are well known of its capability to accelerate the healing processes enhancing re-epithelialization and to protect cells from free-radical action.	
Ganoderma pfeifferi	*Ganoderma pfeifferi* extract is active at both sites it might be the ideal supplement and demonstrate that natural products are a potential source for skin-protecting or antiaging formulations.	(Harms *et al.*, 2008)
	Ganoderma Tsugae, Tsugaric Acid, Prevents the UV-induced Damage on HaCaT Keratinocytes.	(Li *et al.*, 2018)

Table 6. A Summary of *Ganoderma* Species' Phytochemistry and their Health Benefits

***Ganoderma* Spp.**	**Effects and Compounds**	**References**
Ganoderma pfeifferi	Antimicrobial activities *in vitro* and *in vivo* against multi-resistant bacteria, such as MRSA. Antiviral properties, UV-protection abilities and other activities are also known. Extracts of *Ganoderma pfeifferi* have positive effects on human keratinocytes. Farnesylhydroquinones named ganomycins and triterpenoids. sesquiterpenoids	(Lindequist *et al.*, 2015)
Ganoderma concinna	5α-lanosta-7,9 (11),24-triene-3β-hydroxy-26-al (**1**), 5α-lanosta-7,9(11),24-triene-15α-26-dihydroxy-3-one (**2**), and 8α,9α-epoxy-4,4,14α-trimethyl-3,7,11,15,20-pentaoxo-5α-pregnane (**3**),	(González *et al.*, 2002)
Ganoderma weberianum	Anti-melanogenic agent. *Ganoderma* extracts	(Lai *et al.*, 2019)
Ganoderma formasanum	• Tyrosinase inhibitor and antitumoral activity. *Ganoderma formasanum.* • Suppression of tyrosinase activity. *Ganoderma formosanum* mycelium extracts	(Hsu *et al.*, 2016; Kuo *et al.*, 2021)
Ganoderma applanatum	• Cytostatic and Antibacterial Properties (against Staphyloccoccus aureus). *Ganoderma applanatum* exopolysaccharide (GpEPS). • Tyrosinase inhibitor and exhibited an SPF value of ∼ 9. *G. applanatum* extract. • Good anti-tyrosinase, good anti-collagenase, and moderate anti-elastase activities, which might be useful for developing novel skin-whitening and anti-wrinkle agents. Flavonoids.	(Osińska-Jaroszuk *et al.*, 2014; Sułkowska-Ziaja *et al.*, 2021; Yoo *et al.*, 2021)
Ganoderma leucocontextum	GLP-1 could be explored as a potential anti-oxidant agent. *Ganoderma leucocontextum* fruiting bodies low-molecular-weight polysaccharides (GLP-1 and GLP-2)	(Gao *et al.*, 2021)

Table 6. (*Continued*)

***Ganoderma* Spp.**	**Effects and Compounds**	**References**
Ganoderma weberianum	Anti-melanogenic activity. mycelial culture of Ganoderma weberianum	(Lai *et al.*, 2019)
Ganoderma lucidum	• Inhibition of cAMP/PKA and ROS/MAPK signaling pathways. *Ganoderma lucidum* polysaccharide. • Inhibition of the MAPK cascade and cAMP-dependent signal pathway. Ganodermanondiol • Antibacterial activity towards pathogenic strains Staphylococcus epidermidis and Pseudomonas aeruginosa and also had an interesting α-amylase inhibitory activity. Culture broth of Ganoderma lucidum • Anti-oxidative. Chemical isolation of the terpene fraction resulted in the detection of ganoderic acids A, B, C and D, lucidenic acid B and ganodermanontriol as major ingredients and *Ganoderma* polysaccharides (GL-PS) and *Ganoderma lucidum* water-soluble glycopeptide (PGY). • Melanogenesis Inhibitor. Ganodermanondiol • Cytotoxic activity against Hep G2, Hep G2,2,15, and P-388 tumor cells. Lucidenic acid N (**1**) and methyl lucidenate F (**2**), together with four known compounds, lucidenic acid A, lucidenolactone, lucidenic acid C, and ganoderic acid E. • Anti-androgenic and Tyrosinase-inhibiting activity. Ganoderol B. • Inhibited UVB-induced MMP-1 expression and increased procollagen expression in HDF cells. We also determined for the first time that the activated MAPK signaling, especially p38, was inhibited by treatment with GLE in UVB-irradiated HDF cells. *G. lucidum* extract (GLE). • Anti-aging effects mainly through anti-oxidation, immunomodulation and anti-neurodegeneration. • Protect human skin fibroblasts from oxidative damage caused by H_2O_2 peroxide by enhancing enzyme activity and activating Keap1-Nrf2/ARE signaling pathway. GLP will act as a natural anti-oxidant to protect the skin from oxidative stress damage. *Ganoderma lucidum* polysaccharides (GL-PS). • Accelerate skin wound healing. *Ganoderma lucidum* spore oil (GLSO) • Anti-oxidant effect, protecting from H_2O_2-induced cytotoxicity; preventing activation of AKT (protein kinase B), ERK (extracellular signal-regulated kinase), p53 and p21; and reducing the number of apoptotic cells. Ethanol extracts • GL-PS protects fibroblasts against photoaging by eliminating UVB-induced ROS. *Ganoderma* polysaccharides (GL-PS)	(Zhu *et al.*, 1999; Wu *et al.*, 2001; Liu *et al.*, 2007; Lee *et al.*, 2015; Kim *et al.*, 2016; Sarnthima *et al.*, 2017; Wang *et al.*, 2017; Zeng *et al.*, 2017; Cör *et al.*, 2018; Hu *et al.*, 2019a, b; Abate *et al.*, 2020; Jiao *et al.*, 2020; Lee *et al.*, 2020; Seweryn *et al.*, 2021; Shi *et al.*, 2021)

March 23, 2023 11:50:21am WSPC/174-AJCM 2350040 ISSN: 0192-415X 1stReading

Neuroprotective Effects

Ganoleucoin Q and R from *G. leucocontextum* display neuroprotective and neurotrophic activities (Chen *et al.*, 2018). Neuroprotective effects of *G. lucidum* on Spinal Cord Injury (SCI) of a model organism rat have also been observed (Ekinci *et al.*, 2018). *G. lucidum* reduces SCI-induced oxidative stress and promotes neuroprotection by lowering lipid peroxidation and glutathione depletion (Ekinci *et al.*, 2018).

The bioactive molecules in *Ganoderma* play a crucial role in neuroprotective effects or diseases by sedative, hypnotic, anti-nociceptive, analgesic, neuroprotective, anti-epileptic, and anti-depressant effects (Cui and Zhang, 2019). Some studies demonstrated that *Ganoderma* extracts, especially its content of polysaccharides, have increased neuron viability, reduced malondialdehyde content and reactive oxygen species levels, increased the manganese dismutase activity, and blocked the translocation of nuclear factor-kappa B (Zhao *et al.*, 2004).

Other Medicinal Attributes of Ganoderma

Triterpenoids and steroids from *G. lucidum* and *G. tsugae* inhibit the effect of the chemical mediators liberated from neutrophils, mast cells, and macrophages (Ko *et al.*, 2008). The release of β-glucuronidase from rat neutrophils induced with formyl-Met-Leu-Phe (fMLP)/ cytochalasin B was significantly inhibited by 3-oxo-5-lanosta-8, 24-dien-21-oic acid (Ko *et al.*, 2008). This confirmed *Ganoderma*'s anti-inflammatory properties.

Furthermore, according to previous studies, many digestive system diseases can be ameliorated by natural products such as *Ganoderma* supplements. In these studies, the *Ganoderma* extracts play a role in improving the symptoms of gastric mucosal congestion and bleeding, decreasing inflammatory factors, serum histamine, and myeloperoxidase whilst increasing the anti-oxidant activity and defence factors such as nitric oxide (NO) and endothelial growth factor (EGF) (Tian *et al.*, 2022).

Additionally, different *Ganoderma* extracts were used for decades as an elixir for lifespan elongation since they exert many functions in improving health and longevity (Wang *et al.*, 2017). These extracts enhance the anti-ageing properties such as helping to fight off skin-damaging free radicals, repair collagen in the body. and reduce inflammation as demonstrated in Table 5.

Unsurprisingly, the highly biologically active constituents of *Ganoderma* extracts have been shown to have hypoglycemic effects. The extracts have been reported to exhibit anti-diabetic activity by increasing plasma insulin levels, decreasing plasma glucose levels, decreasing lymphocyte infiltration and inhibiting aldolase reductase, a-glucosidase, and protein tyrosine phosphatase 1B (Ma *et al.*, 2015). Thus, as summarized in Table 6, *Ganoderma* species have a wide spectrum of medicinal attributes.

Concluding Remarks and Future Perspectives

As demonstrated throughout this review, the phytoconstituents of *Ganoderma* species contribute to their therapeutic properties. Whilst each bioactive compound within the

fungus has its own properties and benefits, the cumulative effect of several bioactive compounds contributes to many of the medicinal benefits discussed throughout such as being chemo-preventive, tumoricidal, antimicrobial, and anti-inflammatory. This work substantially contributes to the understanding of *Ganoderma's* core pharmacologically active compounds and illustrates the immense therapeutic potential of SMs generated from this fungus. The opine is that the understanding of the SMs of *Ganoderma* might help to further establish it as a pharmacologically applicable medication.

Acknowledgments

This research did not receive any specific grant from funding agencies on the public, commercial, or not-for-profit sectors.

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