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Mycosphere Essays 20: Therapeutic potential of *Ganoderma* species: Insights into its use as traditional medicine

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Abstract

The genus *Ganoderma* (*Ganodermataceae*) has a long history in traditional medicine to improve longevity and health in Asia. *Ganoderma* has been widely used in multiple therapeutic activities as well as dietary supplements to prevent and treat many diseases. Several classes of bioactive substances have been isolated and identified from *Ganoderma*, such as polysaccharides, triterpenoids, nucleosides, sterols, fatty acids, protein and alkaloids. There are numerous research publications, which report the abundance and variety of biological actions initiated by the metabolites of *Ganoderma*. Investigation on different metabolic activities of *Ganoderma* species has been performed both *in vitro* and *in vivo*. In many cases, however, it has been questioned whether *Ganoderma* is solely a nourishment supplement for wellbeing or merely a helpful "medication" for restorative purposes. There has been no any conclusive report of human trials using *Ganoderma* species as a direct control agent for diseases. In addition, there is no evidence supporting the usage of *Ganoderma* species (excluding *G. lucidum*) as potential supplements for cancer or other diseases in humans since no preclinical trials have been performed up to date. In this review, the beneficial medicinal properties of several species of *Ganoderma* (excluding *G. lucidum*) and their secondary metabolites are discussed. *Ganoderma* species can be used as a therapeutic drug, but more direct scientific evidence should be made available in the future. The efficiency of *Ganoderma* in clinical treatments should be substantiated with more biomedical research and their true impact assessed on human health with more standardized clinical evaluations so that the feasibility of biologically active extracts of *Ganoderma* species in alternative treatments can be recommended.

Key words – clinical evidence – medicinal properties – secondary metabolites

Introduction

Ganoderma P. Karst. 1881 is a group of wood degrading mushrooms with hard fruiting bodies, and species are generally not listed among edible mushrooms since their fruiting bodies are thick, corky and tough. They do not have the fleshy texture characteristics (Jong & Birmingham

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1992, Jonathan et al. 2008). The genus *Ganoderma* was established by Karsten (1881) based on *Ganoderma lucidum* (Curtis) P. Karst. Donk (1948) introduced *Ganodermataceae* with the laccate and stipitate white rot fungus *Polyporus lucidus* W. Curtis as its type species (Moncalvo & Ryvarden 1997) and placed the family in Polyporales, Basidiomycetes (Schwarze & Ferner 2003). *Ganoderma* species have a worldwide distribution in green ecosystems both in tropical and temperate geographical regions (Pilotti 2005). These species grow as facultative parasites that can live as saprobes on rotting stumps and roots (Turner 1981). The sexual structure in *Ganoderma* is a basidiocarp and one of the two types of basidiocarps is produced, depending on the species: a laccate fruiting body with a shiny upper surface, or a non-laccate fruiting body with a dull upper surface (Kinge & Mih 2014). Phytochemical and other studies reported varying species numbers in the genus (Li et al. 2013, Yan et al. 2013, Peng et al. 2014). Richter et al. (2015) suggested using a combination of morphological, chemotaxonomic and molecular methods to develop more stable taxonomy for the genus. However, the majority of species in genus *Ganoderma* has not subjected to systematic studies so far (Baby et al. 2015, Hapuarachchi et al. 2015, Zhou et al. 2015a).

Ganoderma is a genus of traditionally used, popular medicinal mushrooms that have been used particularly in China, Japan and Korea for millennia to improve longevity and health (Cheng et al. 2013b). There are a vast number of publications that report the abundance and variety of biological actions triggered by the primary metabolites of *Ganoderma* such as polysaccharides, proteins and triterpenes (Hapuarachchi et al. 2016a). Bioactive compounds from *Ganoderma* hold tremendous structural and chemical diversity (Yang et al. 2013, Hapuarachchi et al. 2016b). These bioactive constituents are reported to be responsible for the anti-cancer, anti-inflammatory, anti-tumor, anti-oxidant, immunomodulatory, immunodeficiency, anti-diabetic, anti-viral, anti-bacterial, anti-fungal, anti-hypertensive, anti-atherosclerotic, anti-aging, anti-androgenic, anti-hepatotoxic, radical scavenging property, neuroprotection, sleep promotion, cholesterol synthesis inhibition, hypoglycemia, inhibition of lipid peroxidation/oxidative DNA damage, hepatoprotective properties, maintenance of gut health, prevention of obesity, and stimulation of probiotics (Paterson 2006, Dai et al. 2009, Cheng et al. 2011, 2012a,b, 2013a, De Silva et al. 2012a,b, 2013, Cao & Yuan 2013, Baby et al. 2015, Bishop et al. 2015, Liu et al. 2015b). *Ganoderma* has been used as functional food to prevent and treat many immunological diseases, such as anorexia, arthritis, asthma, bronchitis, cardiovascular problems, constipation, diabetes, dysmenorrhea, gastritis, hemorrhoids, hepatitis hypercholesterolemia, hypertension, insomnia, lupus erythematosis, migraine, nephritis, neurasthenia, neoplasia and tumorigenesis (Paterson 2006, Cheng et al. 2010, Liu et al. 2012, Wang et al. 2012a, Tan et al. 2015). However, it is not clear if the claimed benefits of taking various forms of *Ganoderma* are substantiated. In this review, we analyse various bioactive compounds produced by the *Ganoderma* species and their metabolic activities. We also present and discuss experimental evidence in connection with those species of *Ganoderma* and its beneficial medicinal properties. Table 1 lists common chemical compounds isolated from *Ganoderma* species.

Beneficial medicinal properties of *Ganoderma* species

Ganoderma applanatum

Some heterogalactans were found in aqueous extracts of *G. applanatum* (Fig. 1) (Usui et al. 1983) and further, exo polysaccharides and glucans were extracted from its fruiting bodies (Nakashima et al. 1979, Usui et al. 1983, Lee et al. 2007). Medicinal properties of *G. applanatum* are anti-tumor (Boh et al. 2000), aldose reductase inhibition (Lee et al. 2006), inhibition of Epstein-Barr virus activation (Chairul & Hayashi 1994) and antibacterial activities (Smania et al. 1999). Anti-tumor activity against transplanted Sarcoma 180 in mice has been exhibited by the β-D-glucan polysaccharides from the basidiocarps of *G. applanatum* (Sasaki et al. 1971). Triterpenoids and malonate half-esters from the basidiocarps of *G. applanatum* inhibit tumor promotion (Tokuyama et al 1991, Lin et al. 1991). However, some esters showed toxicity at high concentrations (Chairul et al. 1990). Steroidal compounds from the basidiocarps were found to have broad-spectrum activities and bactericidal effects (Smania et al. 1999). Huie & Di (2004) reported over 120 volati

Table 1 Chemical compounds isolated from *Ganoderma* species.

Ganoderma species	Chemical compound	References
***G. ambionense* (Lam.) Pat. 1887**	Ganoderic acid AM1, Ergosta-7,22-dien-3β-ol (stellasterol; 5,6-dihydroergosterol), Ergosterol peroxide (5,8-epidioxy-5α-8α-ergosta-6,22E-dien-3-βol), 5α,8α-Epidioxyergosta-6,9(11),22-trien-3β-ol (9,11-Dehydroer-gosterol peroxide), Ergosta-7,22-dien-3β-yl palmitate, 2β-methoxyl-3α,9α-dihydroxyergosta-7,22-diene, Ergos-ta-7,22-dien-3β-yl linoleate, 2β,3α,9α-trihydroxy-5α-ergosta-7,22-diene, Lucidone A	Lin et al. 1993
	Ganoderic acid X and Ganodermacetal	Li et al. 2005
	Ganoderic acid AM, Ganoderic acid DM (Fig.6), Ganoderic acid F, Ganoderic acid H, Ganoderic acid P, Ganodermanontriol, 15-Hydroxy ganoderic acid S, 3β,15α,22β-Trihydroxylanosta-7,9(11), 24-trien-26-oic acid, Methyl ganoderate B, Methyl ganoderate C and Methyl ganoderate E	Yang et al. 2012
***G. annulare* Lloyd) Boedijn 1940**	Applanoxidic acid F, Applanoxidic acid C, Applanoxidic acid G, Applanoxidic acid H, Fungisterol (5α-ergost-7-en-3β-ol), Ergosta-7,22-dien-3β-ol (stellasterol; 5,6-dihydroergosterol) and Ergosterol peroxide (5, 8-epidioxy-5α-8a-ergosta-6, 22E-dien-3-βol	Smania et al. 2003
***G. applanatum* (Pers.) Pat. 1887**	(24S)-24-Methyl-5α-cholest-7-ene-3β-ol and (24S)-24-Methyl-5α-cholest-7, l6-diene-3β-ol	Strigina et al. 1971
	Alnusenone, Furanoganoderic acid, Friedelin, Ganoderenic acid F, Ganoderenic acid G, Ganoderic acid B8, Ergosta-7,22-dien-3β-ol (stellasterol; 5,6-dihydro-ergosterol), Methyl ganoderenate H and Methyl ganoderenate AP	Nishitoba et al. 1989
	Applanoxidic acid A and Applanoxidic acid B	Tokuyama et al. 1991 Yoshikawa et al. 2002
	Applanoxidic acid F, Applanoxidic acid G, Applanoxidic acid H and Applanoxidic acid E	Chairul & Hayashi 1994
	24ξ-Methyl-5α-lanosta-25-one and Ergosta-4, 6, 8(14), 22-tetraen-3-one	Gan et al. 1998a
	Lucidone A, 24ξ-Methyl-5α-lanosta-25-one, Epidioxyergosta-6,9(11), 22-trien-3β-ol (9,11-Dehy-droergosterol peroxide), Ergosta-7, 22-dien-3-one and Ergosta-7, 22-dien-3β-yl palmitate	Gan et al. 1998b
	Ergosterol, Ganoderenic acid A, Ganoderenic acid D, β-Amyrenone, β-Amyrin acetate, *Ganoderma* aldehyde and 2, 5-Dihydroxy benzoic acid	Ming et al. 2002
	Ergosterol; (24S) 24-methyl-5α-cholesta-7, 16-dien-3β-ol; (24S) 24-methylcholesta-7, 22-dien-3-one (Ergosta-7, 22-dien-3-one) as C28 sterols from *G. applanatum*	Cole & Schweikert 2003
	Methyl ganoderenate D, 23-Dihydroganoderenic acid I, 23-Dihydroganoderic acid N, 7β-Hydroxy-3,11,15,23-tetraoxolanosta-8,20E(22)-dien-26-oic acid, methyl ester 3β,7β ,20,23n-Tetrahydroxy-11,15-dioxolanosta-8-en-26-oic acid, 7β,20,23n-Trihydroxy-3,11,15-trioxolanosta-8-en-26-oic acid and 7β,23n-Dihydroxy-3,11,15-trioxolanosta-8,20E (22)-dien-26-oic acid	Shim et al. 2004
	D-mannitol, 2-methoxy fatty acids, cerebrosides, Daucosterol, 2, 5-Dihydroxyacetophenone, 2, 5-dihydro-xyacetophenone, 2,5-dihydroxybenzoic acid and Protocatechualdehyde	Lee et al. 2005
	3α-Carboxyacetoxy-24-methylene-23-oxolanost-8-en-26-oic acid**,** 3α-Carboxyacetoxy-24-methyl-23-oxolanost-8-en-26-oic acid**,** 3α, 16α-Dihydroxylanosta-7,9(11),24-trien-21-oic acid, 16α-Hydroxy-3-oxolanosta-7,9(11), 24-trien-21-oic acid and 3α, 16α, 26-Trihydroxylanosta-7,9(11),24-trien-21-oic acid	De Silva et al. 2006
	Ergosterol peroxide (5,8-epidioxy-5α-8α-ergosta-6,22E-dien-3-βol), 22E,24R-Ergosta-7,22-diene-3β,5α,6β-triol (Cerevisterol)	Lee et al. 2006

Table 1 Continued.

Ganoderma species	Chemical compound	References
***G. applanatum* (Pers.) Pat. 1887**	Ganoderic acid AP2, Ganoderic acid AP3	Wang & Liu 2008
	Applanatine A, Applanatine B, Applanatine C, Applanatine D and Applanatine E and EchinolactoneD	Fushimi et al. 2010
	Ganodermycin	Jung et al. 2011
	3β,5α-Dihydroxy-(22E,24R)-ergosta-7,22-dien-6-one (6-dehydrocerevisterol), 3β,5α,9α-Trihydroxy-(22E,24R)-ergosta-7,22-dien-6-one and 3β,5α,6β,8β,14α-Pentahydr-oxy-(22E,24R)-ergost-22-en-7-one	Lee et al. 2011
***G. atrum* .D. Zhao, L.W. Hsu & X.Q. Zhang 1979**	Ergosta-4,6,8(14),22-tetraen-3-one	Shen et al. 2008
***G. australe* (Fr.) Pat. 1889**	Ergosta-7,22-dien-3-one, Fungisterol (5α-ergost-7-en-3β-ol), Lanosta-7,9(11), 24-trien-3β, 21-diol	Jain & Gupta 1984
	Applanoxidic acid A, Applanoxidic acid F**,** Applanoxidic acid C**,** Applanoxidic acid G**,** Australic acid and Austrolactone, Ergosterol, Ergosta-7,22-dien-3-ol, stellasterol (5,6-dihydroergosterol)	León et al. 2003
	Methyl australate, 5α-ergost-7-en-3β-ol, 5α-ergost-7, 22-dien-3β-ol, 5, 8-epidioxy-5α, 8α-ergost-6, 22-dien-3β-ol, Methyl australate and Australic acid	Smania et al. 2007
	Two laccase enzymes from *G. australe*	Elissetche et al. 2007
	Fornicatin G (7β-hydroxy-11-oxo-3, 4-seco-25, 26, 27-trinorlanosta-4(28),8-dien-24-oic-3-acetyl ester) Fornicatin H	Peng et al. 2012
	3β, 22S-Dihydroxylanosta-7, 9(11), 24-triene	Peng et al. 2014
***G. boninense* Pat. 1889**	Ergosterol	Choon et al. 2011
	Ganoboninketal A, Ganoboninketal B, Ganoboninketal C	Ma et al. 2014
***G. calidophilum* J.D. Zhao, L.W. Hsu & X.Q. Zhang 1979**	Six new prenylated hydroquinones named Ganocalidin A–F and two new compounds of ganocalicineA and B together with sixteen known compounds Compounds Ganocalidin A and GanocalicineA	Huang et al. 2016b
***G. capense* (Lloyd) Teng 1963**	Ganoderma alkaloid A and Ganoderma alkaloid B	Yang & Yu 1990
	Two novel pyrrole alkaloids, Ganoine and Ganodine and a novel purine alkaloid Ganoderpurine	Yu et al. 1990
***G. carnosum* Pat. 1889**	Carnosodione, 26, 27-Dihydroxylanosta-7, 9(11), 24-trien-3, 16-Dione. Ergosta-7, 22-dien-3β-ol (stellasterol; 5, 6-dihydroergosterol) and Ergosterol peroxide (5, 8-epidioxy-5α-8α-ergosta-6, 22E-dien-3-βol	Keller 1997
***G. cochlear* (Blume & T. Nees) Merr. 1917**	(+)- and (-)-cochlearols A and B, two meroterpenoids with novel polycyclic skeletons	Dou et al. 2014
	Cochlate B, Fornicatin B, Fornicatin D, Fornicatin E**,** Fornicatin F, Friedelin, Ganocin A, Ganocin B, Ganocin C, Ganocin D, Ganodercochlearin A Ganodercochlearin B, Ganodercochlearin C and Inonotsuoxide B	Peng et al. 2014
	Seven new prenylated phenols, five novel phenols with polycyclic skeleton and two new phenols with a carbon chain, along with one known compound were isolated from the fruiting bodies of *Ganoderma cochlear*	Peng et al. 2015b
***G. colossus* (Fr.) C.F. Baker 1920**	Colossolactone A Colossolactone B, Colossolactone C, Colossolactone D, Colossolactone E, Colossolactone F and Colossolactone G	Kleinwächter et al. 2001
	Colossolactone I (22S)-3-β-hydroxylanosta-8,24-dien-26,22-olide), Colossolactone II (22S)-1,3-β-dihydroxylanosta-8,24-dien-26,22-olide, Colossolactone III, Colossolactone IV, Colossolactone V, Colossolactone VI, Colossolactone VIII	El Dine et al. 2008

Table 1 Continued.

Ganoderma species	Chemical compound	References
***G. colossus* (Fr.) C.F. Baker 1920**	Ganomycin B, Ganomycin I, farnesyl hydroquinone, Ganomycin I and another hydroquinone derivative Ganomycin B and schisanlactone A, Colossolactone VII, Ergosterol (El Dine et al. 2008) and Ganorbiformin A	El Dine et al. 2009
	Ganomycin B, Ganomycin I, farnesyl hydroquinone Ganomycin I and another hydroquinone derivative Ganomycin B and schisanlactone A	Isaka et al. 2013
***G. concinnum* Ryvarden 2000**	5α-lanosta-7, 9(11), 24-triene-15α, 26-dihydroxy-3-one, 5α-lanosta-7, 9(11), 24-triene-3β-hydroxy-26-al 8α and 9α-Epoxy-4, 4, 14α-trimethyl-3, 7, 11, 15, 20-pentaoxo-5α-pregnane, Ganodermnonol, Ganodermadiol Ganoderic acid Y, Ganoderiol F, Ganodermatriol, Ganodermanontriol, Ganoderiol A, Ganoderiol B and Fungisterol (5α-ergost-7-en-3β-ol), ergosta-7,22-dien-3-one and ergosterol peroxide	Gonzalez et al. 2002
***G. curtisii* (Berk.) Murrill 1908**	3β, 12β -dihydroxy-7, 11, 15,23-tetraoxo-lanost-8,20-dien-26-oic acid, 15α -hydroxy-3,11,23-trioxo-lanost- 8,20-dien-26-oic acid, 12β -acetoxy- 3,7,11,15,23-pentaoxo-lanost-8,20-dien-26-oic acid, 3β, 7β, 12 β -trihydroxy-11,15,23-trioxo-lanost-8,20-dien-26- oic acid, 3 β,7 β b,15a-trihydroxy-4- (hydroxymethyl)-11,23-dioxo-lanost-8-en-26-oic acid	Jiao et al. 2016
***G. fornicatum* (Fr.) Pat. 1889**	Tsugaric acid	Lin et al. 1997
	Fornicatin A and Fornicatin B	Niu 2004
	Fornicin A, Fornicin B, Fornicin C and Fornicatin C	Niu et al. 2006
	Lucidadiol, Ergosterol, Ergosterol peroxide (5α,8α-epidioxy-ergosta-6, 22E-dien-3β-ol) and Polycarp-ol T	Qiao et al. 2006
***G. hainanense* J.D. Zhao, L.W. Hsu & X.Q. Zhang 1979**	Agnosterol, Ganoderic acid Y, Ganodermic acid T–Q Ganodermanondiol, 16α, 26-Dihydroxy lanosta-8, 24-dien-3-one, Lucidenic acid A (Fig. 4), Lucidenic acid N (Fig. 4), Methyl lucidenate A and Methyl lucidenate N	Ma et al. 2013
	Ganohainanic acid A-E, acetyl ganohainanic acid A and D, Ganohainanic acid B, 3,7, 24-trioxo-5α -lanost-8, 25-dien-26-ol, 24S, 25R-dihydroxy-3,7-dioxo-5α -lanost-8-en-26-ol, 21-hydroxy-3,7-dioxo-5α -lanost-8, 24E-dien-26-ol, 3β,11α -dihydroxy-7-oxo-5α -lanost-8,24E-dien-26-ol, Hainanic acid A and B, hainanaldehyde A	Peng et al. 2015a
G. leucocontextum	Sixteen new lanostane triterpenes, Ganoleucoins A-P with 10 known triterpenes	Wang et al. 2015
	Eighteen new lanostane-type triterpenoids, namely leucocontextins A-R	Zhao et al. 2016a
	Six new lanostane-type triterpenoids, namely leucocontextins S–X	Zhao et al. 2016b
***G. lingzhi* T.H. Li, W.Q. Deng, Dong M. Wang & H.P. Hu 2015**	Spirolingzhines A–D, four meroterpenoids with a spiro[benzofuran-2, 1′-cyclopentane] motif, Lingzhines A–F, six meroterpenoids with diverse ring systems, along with two known compounds; A new oxygenated lanostane-type triterpene, Lucidumol C, together with six known compounds; Lingzhilactones A-C	Yan et al. 2015
***G. lipsiense* sensu auct.**	Ergosterol, Ergosta-7, 22-dien-3-one, Ergosta-7, 22-dien-3β-ol (stellasterol; 5, 6-dihydroergosterol), Ergosta-7-ene-3β-yl linoleate, Ergosta-7, 22-dien-3β-yl linoleate, 3β-Linoleyloxyergosta-7, 24(28)-diene, Ganoderenic acid A, Ganoderenic acid D and their Methyl esters	Rosecke & Konig 2000
***G. mastoporum* (Lév.) Pat. 1889**	Ganomastenol A, Ganomastenol B, Ganomastenol C, Ganomastenol D	Hirotani et al. 1995
	Ganomastenol, Ganomastenol B, Ganomastenol C, and Ganomastenol D	Cole & Schweikert 2003
	Three triterpenoids and five steroids including ergosta-4, 6, 8(14), 22-tetraen-3-one	Thang et al. 2013

Table 1 Continued.

Ganoderma species	Chemical compound	References
***G. neo-japonicum* Imazeki 1939**	Ergosta-7,22-dien-3-one, Ergosta-7,22-dien-3β-ol (stellasterol; 5,6-dihydroergosterol), Ergosta-7,22-diene-2β,3α,9α-triol and Ergosta-7,22-dien-3β-yl palmitate, Furthermore, two lanostanoids Ganoderal A (Fig. 4) and Ganodermadiol, steroid (2*β*, 3α,9α-trihydroxyergosta-7, 22-diene) and four ergosteroids	Gan et al. 1998b
	Two drimane-like sesquiterpenes known as Cryptoporic acids H and I	Paterson 2006
***G. oerstedii* (Fr.) Torrend 1902**	Five sterols (ergosta-7,22-dien-3β-ol, ergosterol peroxide, ergosterol, cerevisterol, and ergosta-7, 22-dien-3-one), three terpene compounds (Ganodermanondiol, Ganoderic acid Sz, and Ganoderitriol M); From the mycelial culture two sterols (ergosterol and cerevisterol), and a new terpene compound (ganoderic acetate from the acid)	Mendoza et al. 2015
***G. orbiforme* (Fr.) Ryvarden 2000**	Ganoderic acid V, Ganorbiformin A, Ganorbiformin B, Ganorbiformin C, Ganorbiformin D, Ganorbiformin E, Ganorbiformin F, Ganorbiformin G. Among the novel lanostane triterpenoids, ganorbiformins A–G, 7-O-Methyl ganoderic acid O, Ganoderic acid R, Ganoderic acid P, Ganoderic acid S, Ganodermic acid T–Q	Isaka et al. 2013
***G. petchii* (Lloyd) Steyaert 1972**	(-)-Petchioics A and B (1 and 2), Petchiates A and B (3 and 4), Petchine and a known compound Petchienes A-E, five new meroterpenoids	Gao et al. 2015
***G. pfeifferi* Bres. 1889**	2,5-dihydroxy benzoic acid and 2,4,5-trihydroxy benzaldehyde, Linolic acid and β-1, 3-glucans	Al-Fatimi 2001
	Applanoxidic acid A (Fig. 4), Applanoxidic acid C, Ergosta-7,22-dien-3-one, Ergosta-7, 22-dien-3β-ol (stellasterol; 5, 6-dihydroergosterol), Ergosterol peroxide (5, 8-epidioxy-5α-8α-ergosta-6, 22E-dien-3-βol, Ergosta-4, 6, 8(14), 22-tetraen-3-one, Lucialdehyde B, Lucialdehyde D, Ganoderol A, Ganoderol B (Fig. 4), Ganoderone A and Ganoderone C.	Niedermeyer et al. 2005
	Ganomycins A and B	Mothana et al. 2000
	Ganodermadiol, Lucidadiol, and Applanoxidic acid G	Mothana et al. 2003
	Lucialdehyde D, Ganoderone A, and Ganoderone C. Ganoderone A and Lucialdehyde B, (and ergosta-7,22-dien-3b-ol)	Niedermeyer et al. 2005
	1-octen-3-ol (amyl vinyl carbinol), 1-octen-3-ol acetate, phenylacetaldehyde and 6-camphenol	Al-Fatimi et al. 2016
***G. philippi* (Bres. & Henn. ex Sacc.) Bres. 1932**	Sixteen compounds were isolated by 2, 5-dihydroxyacetophenone, methyl gentisate, (S)-dimethyl malate, muurola-4, 10 (14)-dien-11β-ol, dihydroepicub-enol, 5-hydroxymethylfuran carboxaldehyde, ergosta-7, 22E-dien-3β-ol, ergosta-7, 22E-dien-3-one, ergosta-7, 22E-diene-2β, 3α, 9α-triol, 6β-methoxyergo-sta-7, 22E-dien-3β, 5α-diol, ergosta-4, 6, 8(14), 22E-tetraen-3-one, ergosta4, 6, 8-(14), 22E-etetraen-3β-ol, 5α, 8α-epidioxy-ergosta-6, 22E-dien-3β-ol, 7α-methoxy-5α, 6α-epoxyergosta-8-(14), 22E-dien-3β-ol (14), ergosta-8, 22E-diene-3β, 5α, 6β, 7α-tetraol, and ergosta-5, 23-dien-3β-ol, acetate.	Yang et al. 2014
***G. resinaceum* Boud. 1889**	3-Epipachymic acid, 3-Oxo-5α-lanosta-8, 24-dien-21-oic acid and 3α-(3-Hydroxy-5-methoxy-3-methyl-1, 5-dioxo-pentyloxy)-24-methylene-5α-lanost-8-en-21-oic acid	Niu et al. 2007
	7-Oxo-ganoderic acid Z, 7-Oxo-ganoderic acid Z2, 7-Oxo-ganoderic acid Z3, Ganoderic acid Y, Ganoderesin B, Ganoderesin A, Lucidone D, Lucidone E, Lucidone F, Lucidone G and Lucidone H	Peng et al. 2013

Table 1 Continued.

Ganoderma species	Chemical compound	References
***G. sinense* J.D. Zhao, L.W. Hsu & X.Q. Zhang 1979**	Ergosta-7,22-dien-3β-ol, ergosterol, 6, 9-epidi-oxyergosta-7, 22-dien-3beta-ol, 5, 8-epidioxiergosta-6, 22-dien-3beta-ol, ergosta-7, 22-dien-3-one, β-sitosterol (6), α-Hydroxytetracosanoic acid, cyclo (D-Pro-D-Val)	Liu et al. 2007
	Ganoderiol A triacetate, Ganolactone B, Lucidenolactone, Ganolactone B	Qiao et al. 2007
	Ergosta-7, 22-dien-3β-ol (stellasterol; 5,6-dihydroergos-terol), Ergosterol peroxide (5,8-epidioxy-5α-8α-ergosta-6,22E-dien-3-βol, 22E,24R-Ergosta-7,22-diene-3β,5α,6β-triol (Cerevisterol), Lucidenic acid D2, Ganoderic acid GS-1, GS-2, GS-3, Ganoderic acid β, Ganoderiol A, Ganodermanontriol, Ganosinensin A, Ganosinensin B, Ganosinensin C, 20-Hydroxy lucidenic acid A, 20-Hydroxy lucidenic acid N, 20(21)-Dehydrolucidenic acid A, 20(21)-Dehydrolucidenic acid N	Sato et al. 2009b
	Methyl ganosinensate A, Ganosinensic acid A, Ganosinensic acid B	Wang et al. 2010
	Sinensine, Sinensoic acid	Liu et al. 2010
	Ganoderiol J, Ganoderiol E, Ganolucidic acid B, Ganolucidic acid γa, Ganolucidate F, Ganoderic acid Jc, Ganoderic acid Jd, Ganosinoside A, Sinensine B, Sinensine C, Sinensine D and Sinensine E	Liu et al. 2011
	Ganosinensine, Ganosineniol A, Ganodermatetraol, Lucidadiol, Lucidumol B, Methyl lucidenate Ha, Tsugarioside A (3α-acetoxy-5α-lanosta-8, 24-dien-21-oic acid ester β-D-glucoside), 20(21)-Dehydrolucidenic acid N and 20-Hydroxylucidenic acid A	Liu et al. 2012
***G. theaecola* J.D. Zhao 1984**	Five new lanostane triterpenoids, Ganoderic acid XL1, Ganoderic acid XL2, 20-hydroxy-ganoderic acid AM1, Ganoderenic acid AM1 and Ganoderesin C, and five other known triterpenoids	Liu et al. 2014
***G. tropicum* (Jungh.) Bres. 1910**	3β,7β,15β-trihydroxy-11,23-dioxo-lanost-8,16-dien-26-oic acid, 3β,7β,15β-trihydroxy-11,23-dioxo-lanost-8,16-dien-26-oic acid methyl ester, and 3β,15β-dihydroxy-7,11,23-trioxo-lanost-8,16-dien-26-oic acid methyl ester	Hu et al. 2013
	26-Nor-11, 23-dioxo-5α-lanost-8-en-3β, 7β 15α, 25-tetrol, 3β, 7β, 15β -Trihydroxy-11, 23-dioxo-lanost-8, 16-dien-26-oic acid methyl ester, 3β, 15β-Dihydroxy-7, 11, 23-trioxo-lanost-8, 16-dien-26-oic acid methyl ester and Lucidone D	Hu et al. 2014
	Ganotropic acid, 3β, 7β, 15α, 24-tetra- hydroxy-11, 23-dioxo-lanost-8-en-26-oic acid and 3β, 7β, 15α, 28-tetrahydroxy-11, 23-dioxo-lanost-8, 16-dien-26-oic acid	Zhang et al. 2015
***G. tsugae* Murrill 1902**	Lucidone A, Lucidenol	Su et al. 1993
	Three antitumor-active polysaccharides	Mizuno 1995
	Tsugaric acid A, Tsugaric acid B, Ergosta-7, 22-dien-3β-ol (stellasterol); 5,6-dihydroergosterol;	
	Two novel lanostanoids, 3α-acetoxy-5α-lanosta-8, 24-diene-21-oic acid (tsugaric acid A) and 3α-acetoxy-16α-hydroxy-24-methyl-5α-lanosta-8, 25-diene-21-oic acid (tsugaric acid B)	Lin et al 1997
	Ergosta-7,22-diene-2β,3α,9α-triol	Gan et al. 1998a
	New lanostanoid ester glucoside, 3R-acetoxy-5R-lanosta-8, 24-dien-21-oic acid ester β-D glucoside and a known steroid, 2β, 3R, 9R-trihydroxy-5R-ergosta-7, 22-diene	Gan et al. 1998a

Table 1 Continued.

Ganoderma species	Chemical compound	References
***G. tsugae* Murrill 1902**	Tsugarioside B, Tsugarioside A and 3β-Hydroxy-5α-lanosta-8,24-dien-21-oic acid; 3-oxo-5α-lanosta-8,24-dien-21-oic acid, Oxo-5α-lanosta-8,24-dien-21-oic acid and 2β, 3α, 9α-trihydroxy-5α-ergosta-7,22-diene, Tsugaric acid C, Tsugarioside C; (24*R*,*S*)-3R-acetoxy-24-hydroxy-5R-lanosta-8,25-dien-21-oic acid, named tsugaric acid C, 3R-acetoxy-5R-lanosta-8,24-diene-21-*O*-β-D-xyloside, named tsugariosi-de B, and 3R-acetoxy- (*Z*)-24-methyl-5R-lanosta-8,23,25-trien-21-oic acid ester β-D-xyloside, named tsugarioside C, and a mixture of two known steroids	Su et al. 2000
	Lucidenic acids and Colossolactones A	Kleinwächter et al. 2001
	Ganoderic acids A, B, C1, C5, C6, D, E, G and Ganoderenic acid D	Chen & Chen 2003
	Two novel heteropolysaccharides (EPF1 & EPF2) from the crude extracellular polysaccharide	Peng et al. 2003
	Extracted a novel water soluble polysaccharide–protein complex	Peng & Zhang 2003
	Six water-soluble polysaccharides	Peng et al. 2005
	Ganodone	La Clair et al. 2011
	Ergosterol peroxide (5, 8-epidioxy-5α-8α-ergosta-6, 22E-dien-3-βol), Epidioxyergosta-6, 9(11), 22-trien-3β-ol (9, 11-Dehydroergosterol peroxide) Tsugaric acid D and Tsugaric acid E	Lin et al. 2013
	3β-acetoxy-16α-hydroxy-24ξ-methyl-5α-lanosta-8,25-dien-21-oic acid, named tsugaric acid F and a novel palmitamide, N-(3'α,4'β-dihydroxy-2'β-(hydroxymethyl)-1'β-(cyclobutyl) palmitamide	Lin et al. 2016

flavor compounds, mostly alcohols, aldehydes, ketones, esters, phenols, and very-long-chain fatty acids with more than 23 carbon atoms from *G. applanatum* at trace levels (1–2%). Water-soluble preparations from carpophores of *G. applanatum* exhibited potent antiviral activity against vesicular stomatitis virus Indiana serotype VSV (IND) (Zjawiony 2004).

In vitro evaluation of antioxidant activities of *G. applanatum* showed significant inhibition of lipid peroxidation, and potent hydroxyl radical scavenging activity when compared with the standard drug Catechin. Furthermore, crude, boiled and ethanolic extracts also significantly increased nitric oxide production over the control (Acharya et al. 2005). Studies of Jung et al. (2005) suggested that *G. applanatum* might possess constituents with antidiabetic and inhibitory effects on diabetic complications. Polysaccharides of *G. applanatum* (PGA) could strengthen gastric mucosa barrier by improving the level of PGE2, GMBF and the secretion of gastric mucus, which may be one of the mechanisms underlying the protective effect of PGA on the gastric mucosa during the gastric ulcer (Yang 2005). Bhattacharyya et al. (2006) demonstrated *in vitro* antimicrobial activity against *Acitenobacter aerogenes, Acrobacter aerogenes, Arthrobacter citreus, Bacillus brevis, B. subtilis, Corynebacterium insidiosum, Escherichia coli, Proteus vulgaris, Clostridium pasteurianum, Micrococcus roseus, Mycobacterium phlei, Sarcina lutea* and *Staphylococcus aureus.* Moradali et al. (2007) reported antibacterial activity only against gram-negative bacteria. The antitumor effect of exo-biopolymer (EXP) produced was investigated

using sarcoma-180 bearing mice. EXP, when administered (10–80 mg/kg body weight: BW) intraperitoneally, significantly inhibited the growth of solid tumor and increased the natural killer (NK) cell activity (Jeong et al. 2008).

CXCL10 (inducible protein-10) contributes for the actions of macrophages and T-lymphocytes, and helps in chronic inflammatory conditions. Ganodermycin, isolated from fermentations of *G. applanatum* inhibited lipopolysaccharide (LPS)/interferon (IFN)-γ-induced CXCL10 promoter activity in transiently transfected MonoMac6 cells. Ganodermycin reduced LPS/IFN-γ-induced CXCL10 protein synthesis and excretion (Junget al. 2011).

Ganoderma applanatum extract could enhance the sensitivity of SGC-7901 cells to the c-jun, p53, Bax and Bcl-2 induced apoptosis and provided a promising approach to anti-human gastric cancer therapy (Ma et al. 2011). Trigos & Medelline (2011) mentioned that Applanoxidic acids A, B C, D, E, F, G and H, isolated from a non-polar fraction of this fungus, proved to be effective against skin tumors in mice. Furthermore, it has been reported that extracts have an inhibitory effect on metaloendopeptidase encefalinase EC 3.4.24.11, a potential application for pain treatment. Vazirian et al. (2014) showed considerable anti-inflammatory effects due to polysaccharide components (β-glucan) of the extracts. *Ganoderma applanatum* mycelium extracts and its active component, Protocatechualdehyde (PCA) may suppress adipogenesis by inhibiting differentiation of 3T3-L1 preadipocytes, and in part through altered regulation of PPARγ, C/EBPα, and SREBP1 in order to confirm anti-obesity property (Kim et al. 2014).

Reports from Osińska-Jaroszuket al. (2014) revealed that, exopolysaccharide preparation of *G. applanatum* (GpEPS) may exhibit selective activity against tumor cells (cell lines SiHa) and stimulate production of TNF-α THP-1-derived macrophages. Moreover, the GpEPS showed antibacterial properties against *S. aureus* and a toxic effect against *Vibrio fischeri* cells. Further, GpEPS showed high cholesterol-binding capacity and triglycerides-binding capacity. FGAP and SGAP were typical polysaccharides with different molecular weights, monosaccharide components, and functional groups isolated from *G. applanatum* and FGAP exhibited a better antitumor activity than SGAP. Inhibition of CSGAP against Sarcoma 180 *in vivo* was significantly enhanced by comparison to the native SGAP and even higher than that of FGAP, suggesting that the carboxylate groups played a major role in antitumor activity of *G. applanatum* polysaccharide (Sun et al. 2014). A β-carotene-degrading enzyme activity was observed in liquid cultures and the new enzymes may replace common bleaching agents to produce environmentally more compatible detergent formulations (Lanfermann et al. 2015).

Exopolysaccharides could scavenge hydroxyl radicals (HR) and superoxide anion radicals (SAR), and the concentration of exopolysaccharides was positively related to the antioxidant activity (Liu et al. 2015c). Applanatumin A, a novel meroterpenoid dimer, exhibited potent antifibrotic activity in TGF-β1-induced human renal proximal tubular cells (Luo et al. 2015). Aqueous extracts from fruiting bodies are also active against influenza viruses (Teplyakova & Kosogova 2015). The ethanol and methanol extract of *G. lipsiense* (synonymized as *G. applanatum*) showed antibacterial activity against *Vibrio cholera* (Singdevsachan et al. 2015).
Zengin et al. (2015) revealed methanol and water extracts of *G. applanatum* possess weak antibacterial and antifungal activities. Spiroapplanatumines A-Q, along with three known compounds, spirolingzhines A, B, and D, were isolated from the fruiting bodies of the fungus. Moreover, Spiroapplanatumines G and H compounds inhibited JAK3 respectively (Luo et al. 2017). (±)-Ganoapplanin a pair of novel meroterpenoid enantiomers was isolated from *G. applanatum*. Biological studies showed that (±)-1 and its enantiomers exhibited different inhibitory activities on T-type voltage-gated calcium channels (Li et al. 2016a). Manayi et al. (2016) suggested the potential ability of *G. applanatum* aqueous extract to activate immunologic parameters in rainbow trout fish. Crude exopolysaccharides from *G. applanatum* (GpEPS) can be safely used in anticancer therapy without side effects or damage to healthy cells (Prendecka et al. 2016). *Ganoderma lipsiense* extract could inhibit malignant proliferation of tumor cells by suppressing angiogenesis of blood vessels in tumor tissues and regulating cell cycles, thereby

inhibiting triple-negative breast cancer (TNBC) cell line MDA-MB-231-HM in a mouse model (Qi et al. 2016).

Ganoderma amboinense

Lanostanoid triterpenesisolated from *G. amboinense* (Fig. 3) inhibited the growth of numerous cancer cell lines, and the activities of topoisomerases I and IIa (Li et al. 2005). Furthermore, Ganoderic acid X inhibits topoisomerases and sensitizethe cancer cells toward apoptosis and acts as a potential anti-cancer drug. *Ganoderma amboinense* has been shown to exert a preventive effect on acetaminophen-induced acute liver injury (Hsu et al. 2008).

Ganoderma atrum

Chen et al. (2007) found that *G. atrum* (Fig. 3) polysaccharide (PSG-1) had strong antioxidant potential based on *in vitro* evaluation of the free radical-scavenging and self-oxidation of 1, 2, 3-phentriol inhibitory activities, which may be comparable to vitamin C. PSG-1 protects cardiomyocytes against oxidative stress induced by anoxia/reoxygenation by attenuating ROS production, apoptosis and increasing activities and protein expressions of endogenous antioxidant enzymes (Li et al. 2009). PSG-1 significantly attenuates anoxia/reoxygenation-induced oxidative stress and improves cell survival in cardiomyocytes through mitochondrial pathway, furthermore it inhibited tumor growth in S180-bearing mice via the induction of apoptosis and immunoenhancement effects through the same pathway (Li et al. 2010a) and also enhanced the cyclophosphamide-induced anti-tumor effect (Li et al. 2011a). Administration of PSG-1 significantly reduced apoptosis in the mouse brain in a dose-dependent manner. PSG-1-evoked reduction of apoptosis was associated with the decrease of MDA and GSSG contents, and the increase of SOD, CAT, GPx and GSH-Rd activities, and GSH contents. PSG-1 treatment was also found to attenuate ROS production and calcium accumulation (Li et al. 2011b). PSG-1 significantly decreased lipid peroxidation in liver, brain, and spleen, but concomitantly increased the activities of superoxide dismutase, catalase, and glutathione peroxidase compared with the d-gal group. Elevation of glutathione contents and attenuation of glutathione disulfide contents were also found in PSG-1-treated animals. Furthermore, the results showed that PSG-1 treatment increased basal lymphocyte proliferation as well as T cell and B cell proliferation and enhanced interleukin-2 production (Li et al. 2012a).

Ethanol-soluble acidic components (ESAC) exhibited antimicrobial activity against bacteria (*S. aureus, E. coli, B. subtilis* and *P. vulgaris*), and exerted antioxidant activities by 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging, total reducing power and β-carotene bleaching assays. ESAC (at concentrations of 0–100 μg/mL) did not show any cytotoxic effects in RAW264.7 murine macrophage cells (Li et al. 2012b). Mitogen-activated protein kinase (MAPK) pathways were simultaneously activated and involved in PSG-1-induced TNF-α secretion in RAW264.7 cells and phosphoinositide 3-kinase (PI3K)/Akt pathway was stimulated and played an important role in the PSG-1 induced TNF-α secretion. Nuclear factor (NF)-κB activation by PSG-1 was triggered by PI3K/Akt/MAPK pathway and NF-κB participated in PSG-1 stimulated TNF-α production. This showed the potential of PSG-1 as a novel immunomodulating agent (Yu et al. 2012a). *Ganoderma atrum* polysaccharide increased the production of NO, and the level of mRNA expression of inducible nitric oxide synthase in a dose-response manner and polysaccharide dose-dependently induced the release of TNF-α and interleukin-1β. Generation of reactive oxygen species was promoted by PSG-1. Furthermore, PSG-1 induced nuclear factor-κB activation by elevation of p65 nuclear translocation, suggesting that PSG-1 probably stimulated macrophage activities by activating the nuclear factor-κB pathway (Yu et al. 2012a).

Zhang et al. (2013a) found PSG-1 increased macrophage phagocytosis and the levels of cytokines and nitride oxide through TLR4-mediated NF-*κ*B and MAPK signaling pathways in S180 tumor bearing mice model. Furthermore, a similar mode of action was demonstrated, as polysaccharides did not kill CT26 colorectal carcinoma cells directly but exerted inhibitory effects on proliferation of CT26 cells by activating peritoneal macrophages and tumor growth was also

inhibited in mice with CT26 xenografts (Lin et al. 2015). Zhu et al. (2013) revealed oral administration of PSG-1 at 200 or 400 mg/kg body weight significantly reduced fasting blood glucose and serum insulin levels. Moreover, PSG-1 significantly decreased the levels of serum total cholesterol, triglyceride, low-density lipoprotein cholesterol, free fatty acid and insulin resistance, and increased high-density lipoprotein cholesterol level and insulin sensitivity. PSG-1 inhibited the expression of pro-apoptotic protein, Bax and increased the expression of anti-apoptotic protein, Bcl-2 in pancreatic cells, suggesting that PSG-1 exerted a protective role in the pancreas of diabetic rats. Chen et al. (2014) was able to modify a water-soluble polysaccharide (PSG) extracted from *G. atrum* to obtain its acetylated and carboxymethylated derivatives and then evaluated their antioxidant and immunomodulatory activities *in vitro* and characterized the relationship between bioactivity and chemical characteristics.

PSG-1 induced apoptosis in CT26 cells and enhances the antitumor immune response, induces apoptosis in CT26-bearing mice, and could be a safe and effective adjuvant for tumor therapy or functional food. Furthermore, PSG-1 could inhibit the tumor growth, possibly in part by enhancing the induction of apoptosis through cAMP-PKA signaling pathway and down-regulation of Ca (2+)/PKC signal pathway, activating host immune function in S180-bearing mice (Zhang et al. 2014). PSG-1 induces TNF-α secretion through TLR4/ROS/PI3K/Akt/MAPKs/NF-κB pathways during macrophage activation and thus provides a molecular basis for the potential of PSG-1 as a novel immunomodulatory agent (Yu et al. 2014a). Yu et al. (2014b) revealed PSG-1 treatment accelerated recovery dose-dependently of peripheral red blood cells, white blood cells and platelets, enhanced splenic natural killer cell activity and cytotoxic T lymphocyte activity in Cy-treated mice. PSG-1 elevated CD4 (+) T lymphocyte counts and CD4 (+)/CD8 (+) ratio dose-dependently. Furthermore, PSG-1 restored the levels of IL-2, INF-γ, IL-10, IgA, IgM and IgG and hemolysin in the sera. PSG-1 can also significantly increase the total antioxidant capacity, activities of superoxidase dismutase, catalase and glutathione peroxidase, and decrease the malondialdehyde level *in vivo*. Zhu et al. (2014) revealed that the protective effects of PSG-1 against endothelial dysfunction may be related to activation of the PI3K/Akt/eNOS pathway. *Ganoderma atrum* sulfated polysaccharides with C-2 position (S-PSG-2) derived could be served as immunomodulator and free-radical inhibitors (Chen et al. 2015). Huang et al. (2016a) revealed that PSG-1stimulated macrophages resulted in an increase in phosphorylation of NF-κB, Akt and MAPK family proteins, which are indicative of activations of NF-κB pathway activation. Furthermore, the levels of TNF-α protein and TNF-α mRNA expression were significantly suppressed when macrophages were pretreated with various inhibitors, including NF-kB inhibitors, IkB inhibitors, MAPK inhibitors and PI3K/Akt inhibitors.

Li et al. (2015) revealed PSG-1 in reactive oxygen species (ROS) generation and mitochondrial function in hyperglycemia-induced angiopathy. PSG-1, mPTP blocker, or caspase inhibition can reduce apoptosis and ROS generation. Experimental results show that exposure of survival of human umbilical vein cells (HUVECs) to 35.5 mmol/L glucose increases the proportion of cells undergoing apoptosis. PSG-1 also increases mitochondrial Bcl-2 protein formation and mitochondrial membrane potential (ΔΨm) but inhibits Bax translocation, cytochrome c release, and caspase activation. Lin et al. (2015) revealed that polysaccharides isolated from *G. atrum* considerably enhanced cell surface expression of Toll-like receptor-4 in macrophages and induced intracellular signaling. *In vitro* tests showed that sulfated modification of water-insoluble polysaccharide from *G. atrum* improved its antioxidant activities and anti-proliferative ability against S-180 tumor cells (Zhang et al. 2015).

PSG-1 may induce activation of spleen lymphocytes at least in part via the Ca2+/CaN/NFAT/IL-2 signaling pathway and the PKC/NFAT/IL-2 signaling pathway cooperatively regulated PSG-1-induced activation of spleen lymphocytes. Furthermore, the antitumor activity of PSG-1 is mediated by Toll-like receptor 4 (TLR4) (Yu et al. 2015). There was evident nuclear accumulation of the p65 subunit of NF-κB and degradation of IκBα. FIP-gat, an immunomodulatory protein isolated from *G. atrum*, is a new member of the FIP family. This protein could reduce MDA-MB-231 cells cell viability dose-dependently with a median inhibitory

Figure 1 – Medicinally important *Ganoderma* species. a *Ganoderma australe* (GACP 14081321). b *G. annulare* (GACP HNU5456). c *G. applanatum* (GACP 14081511). d *G. calidophilum* (GACP HNU86). e *G. sinense* (GACP 14081236). f *G. tropicum* (GACP 14081328).

Figure 2 – Medicinally important *Ganoderma* species. a *G. lingzhi* (GACP HNU10). b *G. fornicatum* (GACP 14081329). c *G. orbiforme* (GACP14081310). d *G. mastoporum* (GACP 14081136). e *G. fornicatum* (GACP 14081136). f *G. leucocontextum* (www.cembn.com) [accessed 22 February 2017].

Figure 3 – Medicinally important *Ganoderma* species. a *Ganoderma atrum* (GACP 16072832). b *G. amboinense* (GACP 16082544). c *G. neo-japonicum* (GACP 17072725). d *G. tropicum* (GACP HNU21). *GACP – The Herbarium of Guizhou University

concentration (IC_{50}) of 9.96 μg/mL and agglutinate the MDA-MB-231 cells at a concentration as low as 5 μg/mL. Furthermore, FIP-gat at a concentration of 10 μg/mL can induce significant growth inhibition and cell death in MDA-MB-231 cells. FIP-gat treatment triggers significant cell cycle arrest at the G1/S transition and pronounced increase in apoptotic cell population (Xu et al. 2016).

Zhu et al. (2016) revealed PSG-1 decreased the activities of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT), while increasing hepatic glycogen levels. PSG-1 also exerted strong antioxidant activities, together with unregulated mRNA expression of peroxisome proliferator-activated receptor-γ (PPAR-γ), glucose transporter-4 (GLUT4), phosphoinositide 3-kinase (PI3K), and phosphorylated-Akt (p-Akt) in the liver of diabetic rats. The improvement of PSG-1 on liver function in type 2 diabetic rats may be due to its antioxidant effects, SCFA

excretion in the colon from PSG-1, and regulation of hepatic glucose uptake by inducing GLUT4 translocation through PI3K/Akt signaling pathways. Five new lanostanoid triterpenes were isolated from the ethanol extract of the fruiting bodies of *G. atrum*. Two of the isolated compounds exhibited potent neuroprotective activity against 6-OHDA-induced cell death in SH-SY5Y cells while other compounds possessed significant neuroprotective activity. All tested compounds showed the comparable free radical scavenging activities with the standard drug trolox in both ABTS (+) and DPPH experiment (Qiu et al. 2016). PSG-1 protected mice against CTX-mediated immunosuppression, as evidenced by enhancing the ratios of thymus and spleen weights to body weight, promoting T cell and B cell survival, and increasing levels of TNF-α and IL-2. Apoptosis, ROS generation and lipid peroxidation in the immune organs of the immunosuppressed animals were ameliorated by PSG-1 and further, it may play an important role in PSG-1-evoked immune protection. Hence, these findings have demonstrated that PSG-1 may ameliorate CTX-induced immunosuppression through reducing apoptosis and oxidative damage in immunological system (Li et al. 2017a).

Mannose receptor (MR) was crucial for the immune response to a *Ganoderma atrum* polysaccharide (PSG-1), as evidenced by elevation of MR in association with increase of phagocytosis and concentrations of interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) in normal macrophages. Elevation of MR triggered by PSG-1 also led to control lipopolysaccharide (LPS)-triggered inflammatory response via the increase of interleukin-10 (IL-10) and inhibition of phagocytosis and IL-1β (Li et al. 2017b).

Ganoderma australe

Ganoderma australe (Fr.) Pat. (Fig. 1) has triterpenoids with cytostatic activity against tumor cells (León et al. 2003). Both australic acid and methyl australate have antibacterial and antifungal activities against bacteria and fungi. Elissetche et al. (2007) isolated two laccase enzymes from *G. australe* and the former has been reported to have potential antibacterial activities (Luna-Acosta et al. 2011). De Melo et al. (2016) revealed the biological effect of the β-glucan from *G. australe* via *in vitro* cell cultures of peritoneal macrophages isolated from Swiss mice. Biological assays confirmed that there was an increase in interleukin-6 by approximately 111% with 1.0 μg/mL of polysaccharide, and phagocyte activity was increased in all concentrations examined, obtaining 52.3% with 0.25 μg/mL polysaccharide. The results indicate that a β-(1→3)-glucan isolated from *G. australe* can be classified as a biological response modifier. Applanoxidic acid A isolated from *G. annulare* (synonymized as *G. australe*) showed weak antifungal activity against *Trichophyton mentagrophytes* which are well known to occur as dermatophytes (Smania et al. 2003).

Ganoderma capense

Isolation of nucleotides and nucleosides from the mycelia of *G. capense* was first reported in 1979 by Yu & Zhai (Huie & Di 2004). Uridine and uracil were found to be capable of lowering the serum aldolase level of mice, suffering from experimental Myotonia. Adenosine has also been shown to inhibit platelet aggregation (Shimizu et al. 1985). Lanosta-7, 9(11), 24-trien-3β, 15α, 22-triacetoxy-26-oic acid showed mitogenic activities toward mouse splenocytes and anti-proliferative activity toward leukemia cells and hepatoma cells *in vitro*. The lectin exhibited more potent mitogenic activity than that of concanavalin A (Ngai & Ng 2004). A novel water-soluble polysaccharide (GCP50-1) was obtained from the dried powder of submerged fermentation mycelia of *G. capense* by extraction with hot water (Li et al. 2013). Preliminary anti-radical *in vitro* studies of Yan et al. (2013) indicated that the four crude polysaccharides showed concentration-dependent scavenging abilities on DPPH and hydroxyl radicals. GCGP (*G. capense* Glycopeptide) had inflammatory modulation effects on macrophage cells to maintain NO production and iNOS expression at the normal level and the underlying mechanism of immunomodulatory effect of GCGP involved NF-κB p65 translation, I κB phosphorylation, and degradation. Furthermore, GCGP could inhibit LPS from binding to macrophage cells (Zhou et al. 2014).

Jiang et al. (2016) revealed a novel polysaccharide, designated as GCPB-1b, from the alkaline extract of the submerged fermentation culturing mycelium powder of *G. capense*. Furthermore, GCPB-1b had 1-diphenyl-2-picryl-hydrazyl (DPPH) radical-scavenging ability according to antioxidant activity tests which was greater than other antioxidants. These data suggest that GCPB-1b holds promise as an anti-aging functional food. Eight aromatic meroterpenoids including Ganocapensins A and B were isolated from *G. capense*. All isolated compounds showed significant antioxidant effects with IC_{50} values ranging from 6.00±0.11 to 8.20±0.30μg/ml in the DPPH radical scavenging assay (Peng et al. 2016). Huang et al. (2015) revealed a novel heteropolysaccharide (GCPB-2), isolated from the submerged fermentation culturing mycelia powder *G. capense*. In the *in vitro* antioxidant assay, GCPB-2 was found to possess 1-diphenyl-2-picryl-hydrazyl (DPPH) radical-scavenging activity, which provided an experimental evidence to support *G. capense* as a functional food in some Asian countries.

Ganoderma colossus

Kleinwächter et al. (2001) extracted triterpenoids from a Vietnam specimen named *G. colossum* and they mentioned this species was synonymised as *Polyporus colossus* and *Dendrophagus colossus*. This was subsequently followed by few researchers (El Dine et al. 2008, 2009, Weng et al. 2010, Ofodile et al. 2012). However, according to Index Fungorum (accessed 22 February 2017) the latter species were synonymized as *G. colossus* not as *G. colossum*. Therefore, we used the accepted scientific species name to avoid confusion. Colosolactones from *G. colossus* showed moderate cytotoxicity against L-929, K-562 and HeLa cells. As well, 3α-hydroxysteroid dehydrogenase (3α-HSD) showed anti-inflammatory properties. Furthermore, the farnesyl hydroquinone Ganomycin I and another hydroquinone derivative Ganomycin B and schisanlactone A isolated from *G. colossus* showed significant anti-HIV activity (Kleinwächter et al. 2001). Colossolactone E, Colossolactone V, and colossolactone VII inhibit HIV-1 protease with IC50 values of 8.0, 9.0, and 13.8 lg/mL, respectively (El Dine et al. 2008). When HepG2 cells were treated with the ethanol extract of *G. colossus* (EEGC), the PMA-induced invasion was reduced in a dose-dependent manner and the PMA-induced matrix metalloproteinase (MMP)-9 was also suppressed at the transcriptional level. The EEGC also showed an inhibitory effect on the PMA-induced phosphorylation of extracellular signal-regulated kinase (ERK1/2) and protein kinase B (Akt) in cytosol, as well as the activator protein-1 (AP-1) and nuclear factor-kappa B (NF-kappa B) levels in the nucleus of HepG2 cells. This study provides the first evidence demonstrating that the EEGC is an effective inhibitor on the PMA-induced invasion of hepatoma cell. The EEGC could be further tested by an *in vivo* model to verify whether it is effective for the prevention of hepatoma invasion or metastasis (Weng et al. 2010). Ofodile et al. (2012) isolated and tested antimicrobial activity of three Colossolactones, colossolactone E, colossolactone B and 23-hydroxycolossolactone E. The results showed that colossolactone E and 23-hydroxycolossolactone E were active against *B. subtilis* and *Pseudomonas syringae*, however, colossolactone B was not active against the bacteria.

Ganoderma cochlear

(+)- and (-)-cochlearols A and B, two meroterpenoids with novel polycyclic skeletons, were isolated from the fruiting bodies of the fungus *G. cochlear*. Biological studies showed that (-) -cochlearols are strong inhibitors of p-Smads, exhibiting renoprotective activities (Dou et al. 2014). All compounds found by Peng et al. (2015b) showed antioxidant effects in radical scavenging assays via a plausible biosynthetic pathway. Wang et al. (2016b) reported six novel meroterpenoids cochlearoids F-K using isolated by utilizing phytochemical approaches. Biological evaluation shows that compounds exhibit potent inhibitory activity on fibronectin overproduction in TGF-β1-induced HKC-8 cells. Seven pairs of new alkaloid enantiomers, Ganocochlearines C-Iand three pairs of known alkaloids were isolated from the fruiting bodies of *G. cochlear* (Wang et al. 2016c).

Ganoderma calidophilum, G. carnosum, G. chalceum* and *G. concinnum

Ganoderma calidophilum (Fig. 1) is a rare wild fungus in the *Ganodermataceae* family, distributed in tropical areas of China, and its fruiting body is traditionally used to treat allergic asthma, eczema, and allergic rhinitis. Compounds Ganocalidin A and GanocalicineA showed inhibitory activityeffects on β-hexosaminidase activity and significantly reduced the production of IL-4 and LTB4 by RBL-2H3 cells in response to antigen stimulation and therefore demonstrated anti-allergic activity (Huang et al. 2016b). Akar et al. (2006) reported utilization of a macro-fungus *G. carnosum* as a biosorbent material for the removal of lead (II) ions from aqueous solutions. Water, Methanol and Ethanol extracts of *G. chalceum* showed selective antibacterial activity against *P. aeruginosa* and *E. coli*. The spent mushroom substrate of *G. balabacense* (synonymized as *G. chalceum*) cultivation (SMSGB) contains a large amount of bioactive substances. Hot water extract with SMSGB treatment is effective in improving milk yield and hematology parameters of dairy cows, and may be useful as a functional feed additive (Liu et al. 2015a).

Gonzalez et al. (2002) isolated lanosta triterpenoids from a species named *Ganoderma concinna*. These isolated triterpenoids exhibit apoptosis-inducing activity against myeloid leukemia HL-60 cells. In contrast, three triterpenoids from *G. concinnum* inhibited calf and rat DNA polymerases implicated in DNA repair, recombination and DNA replication (Mizushina et al. 1999).

Ganoderma formosanum*, *G. fornicatum* and *G. hainanense

Wang et al. (2011) revealed that D-mannose and D-galactose are the major constituents of *G. formosanum* polysaccharides. Furthermore, they demonstrated extracellular polysaccharides of this mushroom have the potential to be used as immuno-stimulatory and antibacterial agents against *Listeria monocytogenes* injected in mice. Extracellular polysaccharides produced by *G. formosanum* stimulate macrophages via the engagement of multiple pattern-recognition receptors including Dectin-1, CR3 and TLR4, resulting in the activation of Syk, JNK, p38, ERK, and NK-κB and the production of TNF-α (Wang et al. 2012b). PS-F2, a polysaccharide fraction purified from the submerged culture broth of *G. formosanum*, stimulates the activation of dendritic cells and primes a T helper 1 (Th1)-polarized adaptive immune response. BALB/c mice were sensitized by repeated immunization with chicken ovalbumin (OVA) and alum, followed by intranasal challenge of OVA to induce acute asthma. PS-F2 administration during the course of chicken ovalbumin (OVA) sensitization and challenge effectively prevented AHR development, OVA-specific IgE and IgG1 production, bronchial inflammation, and Th2 cytokine production. Hence, PS-F2 has a potential to be used for the prevention of allergic asthma (Pi et al. 2014a).

PS-F2 functions as an adjuvant capable of inducing a Th1-polarized adaptive immune response, which would be useful in vaccines against viruses and tumors (Pi et al. 2014b). The polysaccharide fraction purified from a culture broth of *G. formosanum* has been shown to have notable anticancer activity. When administered intraperitoneally or orally, the polysaccharide fraction efficiently inhibited tumor growth in xenografted mice (Wang et al. 2014). The three prenylated phenolic compounds extracted from *G. fornicatum* (Fig. 2) Fornicin A Fornicin B and Fornicin C showed moderate cytotoxic activity in Hep-2 cells (Qiao et al. 2006). Li et al. (2016b) showed five new lanostane-type triterpenoids, ganoderenses A-E (two new lanostane nor-triterpenoids, ganoderenses F and G) along with 13 known analogues were isolated from the fruiting body of *G. hainanense*. All compounds were evaluated for inhibitory activity against thioredoxin reductase (TrxR), a potential target for cancer chemotherapy with redox balance and antioxidant functions.

Ganoderma leucocontextum

Some Ganoleucoins and triterpenes extracted from *G. leucocontextum* (Fig. 2) showed much stronger inhibitory activity against HMG-CoA reductase and few presented potent inhibitory activity against α-glucosidase. Furthermore, the cytotoxicity was exhibited against the K562 and PC-3 cell lines by the MTT assay with IC_{50} values in the range 10-20 μM (Wang et al. 2015). Leucocontextins R exhibited weak cytotoxicity against K562 and MCF-7 cell lines with IC_{50} of 20–

30 μM. Wang et al. (2016d) found three new meroterpenoids, Ganoleucin A-C, together with five known meroterpenoids from the fruiting bodies of *Ganoderma leucocontextum*. Ganomycin I showed stronger inhibitory activity against HMG-CoA reductase than the positive control atorvastatin. Other compounds presented potent noncompetitive inhibitory activity against α-glucosidase from both yeast and rat small intestinal mucosa. Ganomycin was synthesized and evaluated for its *in vivo* bioactivity. Pharmacological results showed that Ganomycin I exerted potent and efficacious hypoglycemic, hypolipidemic, and insulin-sensitizing effects in KK-Aymice.

Ganoderma lingzhi

Tran et al. (2014) used *G. lingzhi's* own proteases to hydrolyze its protein and obtained auto-digested Reishi (ADR) extract to determine its potential for use as a hypotensive medication. The results showed that ADR could be a good source of hypotensive peptides that could be used for antihypertensive medication or incorporation into functional foods. Yan et al. (2015) revealed Lingzhilactone B could inhibit ROS generation in a dose-dependent manner, inhibit mRNA expression of collagen IV, fibronectin, IL-6 and increase expression of Nrf 2 in rat tubular epithelial cells. The *in vitro* and *in vivo* results suggested that Lingzhilactone B could protect against renal injuries by increasing the activities of antioxidants and inhibiting inflammation. The inhibition of Smad3 phosphorylation suggested that this substance displays *in vivo* anti fibrotic activity by a mechanism that is dependent on disruption of Smad3. Studies of Fatmawati et al. (2013) revealed a series of lanostane-type triterpenoids, identified as *Ganoderma* alcohols and *Ganoderma* acids from the fruiting body of *G. lingzhi*. Some of these compounds were confirmed as active inhibitors of the *in vitro* human recombinant aldose reductase. Structure-activity studies of *Ganoderma* alcohols showed that the OH substituent at C-3 and the double-bond moiety at C-24 and C-25 are necessary to increase α-glucosidase inhibitory activity. The structure-activity relationships of *Ganoderma* acids revealed that the OH substituent at C-11 is an important feature and that the carboxylic group in the side chain is essential for the recognition of α-glucosidase inhibitory activity. Moreover, the double-bond moiety at C-20 and C-22 in the side chain and the OH substituent at C-3 of *Ganoderma* acids improve α-glucosidase inhibitory activity.

Lucidumol C showed potent selective cytotoxicity against HCT-116 cells and high cytotoxic activities against Caco-2, HepG2 and HeLa cell lines (Amen et al. 2016). Twenty nine lanostane triterpenoids were obtained from the EtOH extract of fruiting bodies of *G. curtisii* including a new lanostane triterpenoid and four known other compounds were isolated from the genus *Ganoderma* for the first time (Jiao et al. 2016). Wang et al. (2016c) revealed the triterpene acid extract (TAE) from *G. lingzhi* mycelia was found to be cytotoxic to the SMMC-7721 and SW620 cell lines *in vitro*, and the TAE exhibited dose-dependent antitumor activity against the solid tumor sarcoma 180 *in vivo*. Chemical analysis revealed that the key active triterpene compounds, Ganoderic acid T (Fig. 4) and ganoderic acid Me, predominated in the extract. Amen et al. (2017) suggest that the traditional uses of *G. lingzhi* might be in part due to the ROCK-I and ROCK-II inhibitory potential of this mushroom. Structure-activity relationship studies revealed lanostane triterpenes potentiate their Rho-kinase inhibition.

Zhang et al. (2017) revealed Ganoderic acids (GAs) in *G. lingzhi* exhibit anticancer and antimetastatic activities. GA yields can be potentially improved by manipulating *G. lingzhi* through genetic engineering. In this study, a putative lanosterol synthase (LS) gene was cloned and overexpressed in *G. lingzhi*.Results showed that its overexpression (OE) increased the ganoderic acid (GA) content and the accumulation of lanosterol and ergosterol in a submerged *G. lingzhi* culture. This study demonstrated that OE of the homologous LS gene could enhance lanosterol accumulation. A large precursor supply promotes GA biosynthesis.

Ganoderma microsporum

A new recombinant immunomodulatory protein (GMI) was purified from *G. microsporum* (Fig. 4), with anti-metastatic effect and it can inhibit epidermal growth factor mediated migration and invasion in A549 lung cancer cells (Lin et al. 2010). GMI induces lung cancer cell death by

activating autophagy, but does not induce apoptotic cell death. Using VZV-G pseudotyped lentivirus-shRNA system for autophagy-related genes silencing, the capabilities of GMI to reduce cell viability and colony formation were abolished in autophagy-defective cells. Furthermore, GMI did not stimulate apoptosis after blocking of autophagy by 3-MA or shRNA knockdown system. Oral administration of GMI inhibited the tumor growth and induced autophagy significantly in nude mice that had received a subcutaneous injection of A549 cells (Hsin et al. 2011).

Autophagosome accumulation induces autophagic cell death in a GMI, and ATP6V0A1 plays an important role in mediating autophagosome-lysosome fusion (Hsin et al. 2012). GMI, elevates the intracellular calcium level and reduces the growth of MDR subline via autophagy and apoptosis, regardless of p-glycoprotein (P-gp) overexpression, in mice xenograft tumors. Furthermore, autophagy plays a pro-death role in acquired MDR and upregulation of autophagy by GMI via Akt/mTOR inhibition provides a potential strategy for overcoming MDR in the treatment of lung cancers (Chiu et al. 2015). GMI and cisplatin induce apoptosis via autophagy/caspase-7-dependent and survivin- and ERCC1-independent pathway. GMI may be a potential cisplatin adjuvant against lung cancer (Hsin et al. 2015).

Ganoderma orbiforme and *G. mastoporum*

The C-3 epimer of ganoderic acid T isolated from *G. orbiforme* (Fig. 2) exhibited significant antimycobacterial activity with *Mycobacterium tuberculosis* H37Ra (Isaka et al. 2013). Ergosta-4, 6, 8(14), 22-tetraen-3-one (3) by *G. mastoporum* (Fig. 2) exhibited the most significant inhibition towards superoxide anion generation and elastase release (Thang et al. 2013).

Ganoderma neo-japonicum

The Malaysian indigenous tribes use *G. neo-japonicum* (Fig. 3) to treat various diseases such as asthma, cancer, diabetes, epilepsy and fever. Lin et al. (1995) demonstrated that the scientific validation of the medicinal value of this mushroom has not been extensively investigated and has been reported as a potent radical scavenger and showed hepatoprotective activity *in vivo*. The therapeutic effect of *G. japonicum* mixture on thrombosis and its mechanism were studied. The results showed that *G. japonicum* mixture inhibited thrombus formation *in vitro* and *in vivo* (Wen et al. 1997). Methionine enhanced the Ergothioneine by using the mycelia culture of *G. neo-japonicum* (Lee et al. 2009). Production Tryptophan was the best amino acid in accumulation of total phenolic compound in the mycelial culture of *G. neo-japonicum* (Park & Lee 2010).

This mushroom has strong β-glucosidase and avicelase activities (Jo et al. 2011a). Jo et al. (2011b) performed an experiment to determine the laccase activity for *G. neo-japonicum* and results revealed that optimum detection of cellulase activity was reported at 25 °C for Congo red dye at pH 7.0. Wheat grains fermented by mycelia of *G. neo-japonicum* enhanced antioxidant activities and adipogenesis (Tan et al. 2015) and that PPARγ expression in 3T3-L1 cells was modulated (Subramaniam et al. 2014, 2015). The aqueous extracts of *G. neo-japonicum* had a significant effect on neurite outgrowth stimulatory activities when compared to nerve growth factor (Seow et al. 2013). The aqueous extracts of basidiocarps of *G. neo-japonicum* showed the involvement of MEK/ERK1/2 and P13K/Akt signaling pathways for neuritogenesis in PC-12 cells *in-vitro* (Seow et al. 2013).

Ganoderma pfeifferi

Sterols from *G. pfeifferi* (Komoda et al. 1989) and oxygenated triterpenes (Shiao 2003) have been shown to inhibit cholesterol synthesis *in vitro*. Mothana (1999) first reported the anti-bacterial activity of *G. pfeifferi*. His studies demonstrated CH_2Cl_2, EtOH and hot aqueous extracts of the fruiting bodies of the mushroom exhibited antibacterial activity against Gram-positive (*B. subtilis*, *S. aureus*, *S. epidermides* and *Micrococcus flavus*) and Gram-negative (*E. coli*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *P. maltophilia* and *Serratia marcescens*) bacteria. Furthermore, these extracts from *G. pfeifferi* also inhibited the growth of the fish pathogenic bacteria *Aeromonas hydrophila* and *A. salmonicida*, while the hot aqueous extract was also active against fish

pathogenic species *Vibrio anguillarum* and *Yersinia ruckeri* (Mothana 1999, Mothana et al. 2000). Ganomycins A and B, from *G. pfeifferi* exhibited antibacterial activity against Gram-negative and Gram-positive bacteria (Mothana et al. 2000). Al-Fatimi (2001) revealed 2, 4, 5-trihydroxy Benzaldehyde isolated from *G. pfeifferi* inhibited the growth of Gram-positive and Gram-negative bacteria, fish pathogenic bacteria and yeasts and the compound was active against multi-resistant strains of *S. aureus* and enterococci. 2, 5-Dihydroxy benzoic acid exhibited no antibacterial activity, but showed antifungal activity against *Candida maltosa*. Lanostane type triterpenes named Ganodermadiol, Lucidadiol, and Applanoxidic acid G from *G. pfeifferi* have also been shown to exhibit activity against HSV-1 and influenza A virus (Mothana et al. 2003).

Four sterols and 10 triterpenes from the fruiting bodies of *G. pfeifferi* were isolated, including three new triterpenes: Lucialdehyde D, Ganoderone A, and Ganoderone C. Ganoderone A and Lucialdehyde B, (and ergosta-7, 22-dien-3β-ol) were found to exhibit potent inhibitory activity against herpes simplex virus (Niedermeyeret al. 2005). The analysis of antiviral activity of the extract of *G. pfeifferi* against influenza virus type A, HSV-1, HIV-1, revealed that the major antiviral component of the extract were triterpenoids: Ganodermadiol, Lucidadiol and Aplanoxin acid G (Teplyakova & Kosogova 2015). Farnesyl hydroquinone and Ganomycin K were also reported from this mushroom and the former have not been shown any antibacterial activity while the latter showed antibacterial activity with its free carboxylic acid group (Niedermeyer et al. 2013). Al-Fatimi et al. (2016) obtained four volatile oil, 1-octen-3-ol (amyl vinyl carbinol), 1-octen-3-ol acetate, phenylacetaldehyde and 6-camphenol from *G. pfeifferi*. They demonstrated the strong antimicrobial activity of the oil against *S. aureus* and *Candida albicans*. It was found that the Gram-positive bacteria species are more sensitive to the essential oil than Gram-negative bacteria. Furthermore, the oil exhibited strong radical scavenging activity in the DPPH assay.

Ganoderma petchii* and *G. resinaceum

Ganoderma petchii provided five new compounds, (−)-petchioics A and B, petchiates A and B and Petchine (5), and a known compound. The structures of the new compounds were elucidated on the basis of spectroscopic data. The absolute configurations of 1 and 2 were assigned by computational methods. Biological activities of these isolates towards human cancer cells, COX-1/2, and influenza virus were evaluated. Five new compounds, Petchienes A-E, were isolated from the fruiting bodies of *G. petchii*. Biological evaluation showed that compounds Petchiene B and racemic Petchiene D could increase intracellular free calcium concentration at 10 μM in HEK-293 cells (Gao et al. 2015). *Ganoderma resinaceum* tolerated sodium chloride (NaCl) salt stress within a range of 0 mM till 300 mM. It responded to salt stress with fluctuation in Proline formation at different NaCl concentrations (Mahmoud et al. 2007). Ganoderol exhibited a vital activation for PXR-induced CYP3A4 expression. Thus it suggested *Ganoderma* triterpenoids exhibited hepatoprotective activities by lowering ALT and AST levels (Peng et al. 2013). *Ganoderma praelongum* was synonymized as *G. resinaceum* according to Index Fungorum.This species was evaluated against 30 strains of clinical isolatesof methicillin-resistant and -sensitive *S. aureus*. The ethyl acetate extract of this speciescontainingsesquiterpenoids exhibited the maximum activity (35.67±0.62 μm) and minimum inhibitory concentration (MIC) of 0.390–6.25 mg/mL (Ameri et al. 2011). Coletto & Mondino (1991) demonstrated methanolic extracts of the mycelia and culture extracts of *G. resinaceum* inhibited *B. subtilis* and *Staphylococcus aureus*. But Zengin et al. (2015) showed methanol and water extracts of *G. resinaceum* possess weak antibacterial and antifungal activities.

Ganoderma sinense

Both AFGS (artificial and fermentative *G. sinense*) and natural *G. sinense* (Fig. 1) (NGS) have obvious anti-inflammatory and analgesic effects for arthritis in rats induced by carrageenan and the pain reaction in mice induced by hot scalding as well as HAC-induced writhing. AFGS also can reduce the edematous swelling of mice's ears, reduce the capillary permeability of mice skin and obviously inhibit cotton pellets granuloma implanted in rats. It can promote cytophagy capacity

of the reticular endothelial cells in mice (Wan & Huang 1992). Triterpenoid-enriched lipids have emerged due to their immunomodulatory and cytotoxic effects. Dose-dependent suppression of proliferation of leukemia and hepatoblastoma cells has been described for a lipid extract of this *G. sinense* mushroom, known as GL6. Furthermore, the same GL6 was shown to induce human monocytes and immunosuppressive M2 macrophages to release pro-inflammatory cytokines (Yue et al. 2008).

Studies of Liu et al. (2009) concluded ethanol extracts of *G. sinense* responsible for activities on human breast cancer, hepatoma and myeloid leukemia, anti-proliferation effect through apoptosis pathway and cell cycle arrest effect. *Ganoderma sinense* have anti-tumoral proliferation effect through both apoptosis pathway and cell cycle arrest effect, and some other compounds such as sterols and/or nucleosides may contribute to their activity besides triterpenoids. Ganoderic acids GS-2 and 20(21)-dehydrolucidenic acid N, inhibited the human immunodeficiency virus-1 protease with IC values of 20 to 40 mM (Sato et al. 2009a). The recombinant FIP-gsi protein could be expressed in *E. coli* and got the yield of about 25% of the soluble form in the total soluble protein. The FIP-gsi protein was composed of 111 amino acids, and the sequence of homologous rate was 88.6% with FIP-glu (LZ-8). Furthermore, it could enhance the levels of interleukin (IL)-2, IL-3, IL-4, interferon gamma, tumor necrosis factor alpha, and IL-2 receptor (IL-2R) in mouse spleen cells (Li et al. 2010b).

A polysaccharide (GSP-6B) was isolated from the fruiting bodies of *G. sinense*. An *in vitro* immunomodulating activity assay revealed that GSP-6B could significantly induce the release of IL-1β and TNF-α in human peripheral blood mononuclear cell (PBMC) and showed no toxicity to either PBMC or a human macrophage cell line THP-1. GSP-6B could also activate dendritic cells (DC) by stimulating the secretion of IL-12 and IL-10 from DC (Han et al. 2012a). A protein-bound polysaccharide (GSP-4) was isolated from the water extract of the fruiting bodies of *G. sinense*. GSP-4 could significantly stimulate the production of the immunomodulatory markers tumor necrosis factor α (TNF-α), interleukin (IL)-1β, IL-12, and granulocyte-macrophage colony-stimulating factor (GM-CSF) in PBMCs. This observation was further substantiated in RAW 264.7 cells, as indicated by the increase of nitric oxide (NO), TNF-α and IL-6 production. GSP-4 also enhanced the expression of inducible NO synthase mRNA in dose-dependent manner (Han et al. 2012b).

Ganoderic acid Jc displayed selective inhibitory activity against HL-60 and Ganoderiol E exhibited selective cytotoxic activity against MCF-7 cells. Meanwhile, Ganodermatetraol, Ganolucidate, and Ganolucidic acids B and C showed induction ability of hPXR-mediated CYP3A4 expression (Liu et al. 2012). Polysaccharide-enriched fraction of *G. sinense* hot water extract (400 μg/ml) exhibited significant stimulatory effects on PBMC proliferation. When the fruiting bodies of *G. sinense* were divided into pileus and stipe parts and were separately extracted, the *G. sinense* stipe polysaccharide-enriched fraction (50–400 μg/ml) showed concentration-dependent immunostimulating effects in human peripheral blood mononuclear cells (PBMC). The productions of tumor necrosis factor-α, interleukin (IL)-10, and transforming growth factor -β were significantly enhanced by this fraction. The proportion of CD14 (+) monocyte subpopulation within the PBMC was specifically increased. The IL-10 and IL-12 productions in monocyte-derived dendritic cells were significantly enhanced by *G. sinense* stipe fraction (Yue et al. 2013). The recombinant proteins FIP-SN15 and FIP-glu (reFIPs) on U-251 MG cell cycle indicated that reFIPs could inhibit cell cycle progression by retardation of G1/S transition. The efforts in this assay would lay the foundation for further development of reFIPs products and research on the anti-tumor mechanisms of FIP-SN15 (Cong et al. 2014).

A polysaccharide GSP-2 was isolated from the fruiting bodies of *G. sinense*. Immunological assay exhibited that GSP-2 significantly induced the proliferation of BALB/c mice splenocytes with target on only B cells, and enhanced the production of several cytokines in human peripheral blood mononuclear cells and derived dendritic cells (Han et al. 2014). Furthermore, they revealed FIP-gsi could enhance the production levels of cytokinine, including interleukin-2, 3 and 4 interferon gamma, TNF-α, and interleukin receptor-2 in mouse spleen cells. Four new farnesyl

phenolic compounds, Ganosinensols A–D and two pairs of enantiomers were isolated from the 95% EtOH extract of the fruiting bodies of *G. sinense*. All of these isolated compounds showed potent inhibitory activity against LPS-induced nitric oxide production in RAW 264.7 macrophages (Wang et al. 2016a). Zizhines A-F, six pairs of new meroterpenoid enantiomers and a known meroterpenoid were isolated from the fruiting bodies of *G. sinensis* (Cao et al. 2016). (+)- and (-)-Sinensilactam, novel hybrid metabolites were isolated from the fruit bodies of *G. sinensis*. (-)-1 Sinensilactam was found to be a Smad3 phosphorylation inhibitor in TGF-β1 induced human renal proximal tubular cells (Luo et al. 2015). Chan et al. (2016) first reported the presence of 9- and 13-oxo-octadecadienoic acids in the stipe of *G. sinense* and they might be responsible for the anti-tumor activities. Further studies will be needed to confirm their activities.

Ganoderma tsugae

Ganoderma tsugae is one of the popular traditional medicines used in China due to its various beneficial medicinal properties (Wasser & Weis 1999). The fruiting bodies and cultured mycelia of *G. tsugae* have been reported to be effective in the treatment of many diseases, such as chronic hepatopathy, hypertension, and neoplasia (Kimura & Tamura 1988, Lin et al. 1993). Splenic NK activity and serum IFN (IFN-(alpha+beta) and IFN-gamma) titers are elevated by *G. tsugae* mycelium extracts in mice (Won et al. 1992). Moreover, it has been reported many pharmacological properties, such as anti-autoantibody formation (Lai et al. 2001), anti-fibrosis (Wu et al. 2004), anti-inflammation (Ko et al. 2008), anti-oxidation characteristics (Mau et al. 2002) and anti-mutagenic activities (Zheng et al. 2005). Among the biologically active components, the polysaccharides, protein-bound polysaccharides and their derivatives have been demonstrated to be responsible for its antitumor activities, which are based on enhancing the host-mediated mechanism (Mizuno et al. 1985, Wang et al. 1993, Zhang et al. 1994, Gao et al. 2000, Seong 2000). This mushroom has growth-inhibitory effects in a variety of human cancer cells such as A431 epidermoid carcinoma cells (Hsu et al. 2009), COLO 205 colorectal cancer cells (Hsu et al. 2008), H23 and H23/0.3 lung adenocarcinoma cells (Yu et al. 2012b), Hep3B hepatoma cells (Gan et al. 1998a), MDA-MB-231 and MCF-7 breast cancercells (Yue et al. 2006). Crude extracts *G. tsugae* can be used as a treatment for the enhancement of splenic natural killer cell activity and serum interferon production in mice (Won et al. 1992). Mizuno (1995) extracted three antitumor-active polysaccharides from *G. tsugae*. They showed substantial survival ratio on Sarcoma 180/mice.

Gan et al. (1998a) found new lanostanoid ester glucoside, 3R-acetoxy-5R-lanosta-8, 24-dien-21-oic acid ester β-D glucoside and a known steroid, 2β, 3R, 9R-trihydroxy-5R-ergosta-7, 22-diene were isolated from the fruit bodies of *G. tsugae*. These two compounds are responsible for cell death by apoptosis and the activity of cell cycle inhibition respectively. Su et al. (1999) showed Sacchachitin membrane, prepared from the residue of the fruiting body of *G. tsugae*, was effective on wound healing and the proliferation and migration of fibroblast cells in female guinea pigs. The methanolic extract from *G. tsugae*, was found to be high in antioxidant abilities (Yen & Wu 1999). The water-soluble polysaccharides of *G. tsugae* mycelium have bidirectional immunomodulatory effects on cytokine production in different stimulatory conditions in a dose-dependent manner. Compared with FI0-b, FI0-b-H has more marked effects on human proinflammatory cytokine production (Gao et al. 2000).

Su et al. (2000) examined the cytotoxic activity of lanostanoids from *G. tsugae* and found activity against three cancer cell lines. Kleinwächter et al. (2001) found Lucidenic acids and Colossolactones A inhibit HepG2 cancer cell invasion by acting as inhibitor on the phorbol-12-myristate-13-acetate (PMA)-induced matrix metalloproteinase (MMP-9) expression. *Ganoderma tsugae* extracts improved the survival rate of lupus mice, decreased the amount of proteinuria, decreased serum levels of anti-dsDNA autoantibody, and showed evidence of decreased perivascular and parenchyma mononuclear cell infiltration in vital organs (Lai et al. 2001). Lin et al. (2003) demonstrated triterpenoids extracted from mycelia of *G. tsugae* caused a rapid decrease in the activity of cell growth regulative protein, PKC, and the activation of JNK and p38 MAP kinases, which resulted in a prolonged G2 cell cycle phase and strong growth inhibition of the

hepatoma cells. Peng et al. (2003) obtained two novel heteropolysaccharides (EPF1 & EPF2) from the crude extracellular polysaccharide of *G. tsugae* mycelium and the samples were exhibited high inhibition ratio against Sarcoma 180 in mice, and the crude extracellular polysaccharide has higher inhibition effect both *in vivo* and *in vitro* than heteropolysaccharides.

Peng & Zhang (2003) extracted a novel water soluble polysaccharide-protein complex from the mycelium of *G. tsugae*. Methanolic, hot water and cold water extracts from *G. tsugae* possessed good antioxidant properties (Mau et al. 2005a, b, Tseng & Mau 2007). Crude extracts of *G. tsugae* (GTE) has hepatoprotective and anti-fibrotic activities (Wu et al. 2004). Jinn et al. (2006) revealed, compared with the rFIP-gts produced in *Escherichia coli* cells, the rFIP-gts produced in Sf21 cells possessed evidently higher specific immunomodulatory activity. Lin et al. (2006) reported a therapeutic application for *G. tsugae* in allergic asthma. *Ganoderma tsugae* supplementation *in vivo* modulated the Th1/Th2 balance and enhanced macrophage immune responses. However, the supplementation diet could not fully reverse the Th2-skewed responses to level of Th1-skewed responses. ReFIP-gts suppresses telomerase activity and inhibits transcriptional regulation of hTERT via a c-myc-responsive element-dependent mechanism (Liao et al. 2006). The nm23-H1gene suppresses cervical cancer cell migration, activities of MMP-2 and MMP-9 and enhances the inhibition of FIP-gts upon migration (Wang et al. 2007). ReFIP-gts inhibits telomerase activity in lung cancer cells through nuclear export mechanisms, which might be mediated by Endoplasmic Reticulum stress-induced intracellular calcium level (Liao et al. 2007). Hsiao et al. (2008) introduces a FIP-gts immunomodulatory which having anti-cancer activities.

Hsu et al. (2008) studied the anti-tumour effects of *G. tsugae* extracts on colorectal adenocarcinoma cell proliferation. Tumorigenesis study in mice revealed the extracts caused tumor shrinkage. *In vitro and in vivo* experiments showed that colorectal adenocarcinoma cells are inhibited by induction of G2/M cell cycle arrest. Possibly through downregulation of cyclin A and B1 and up-regulation of p21 and p27. Also, no significant physiological changes as a result of treatment with *G. tsugae* extracts were observed in the animal model. Furthermore, Tseng et al. (2008) revealed hot water and hot alkali extracted polysaccharides from *G. tsugae* possessed good antioxidant properties except for scavenging ability on hydroxyl radicals. In addition to their therapeutic effects, *G. tsugae* could be used in human diets to suppress oxidative damage and hot water and hot alkaline extracted polysaccharides preparations could be developed as a new dietary supplementand functional food. Moreover, both extracted polysaccharidescould be added in emulsion to prevent anti-oxidation (Kishk & Al-Sayed 2007) or formulated into bread as a health-promoting functional food (Fan et al. 2007).

Ko et al. (2008) revealed tsugaric acid A isolated from *G. tsugae* exhibited significant inhibitory effects on fMLP/CB-induced superoxide anion generation and 3-oxo-5α-lanosta-8, 24-dien-21-oic acid showed inhibitory effects on release of β-glucuronidase stimulated with fMLP/CB from rat neutrophils and accumulation of NO in the culture media of N9 cells in response to LPS/IFNc. The tsugaric acid A has a protective effect on keratinocytes against photodamage induced by ultraviolet B light and could be used as an agent for skin care. Liao et al. (2008) found that purified recombinant fungal immunomodulatory protein from *Ganoderma tsugae* (reFIP-gts) has anti-telomerase effects in human lung adenocarcinoma A549 cells. The reFIP-gts-treated lung cancer cells are arrested at G1 phase by flow cytometry and possess morphological phenotype consistent with cellular senescence. The A549 cells treated with reFIP-gts grew significantly slower than cells treated with PBS alone in an *in vivo* mouse model revealing that lung tumor can be inhibited by reFIP-gts. La Clair et al. (2011) reported the isolation and characterization of an unprecedented benzofuran, Ganodone from the fruiting bodies of mature *G. tsugae*. *Ganoderma tsugae* inhibits the viability of H23/0.3 cells *in vitro* and *in vivo* and sensitizes the growth suppression effect of doxorubicin on H23/0.3 cells and induces S phase arrest by interfering with the protein expression of cyclin A, cyclin E, CDK2, and CDC25A. Furthermore, GT induces cellular apoptosis via induction of a mitochondria/caspase pathway and suppression of cell proliferation by through down-regulation of the PI3K/Akt signaling pathway (Yu et al. 2012a).

Kuo et al. (2013) revealed *G. tsugae* extract inhibits cancer cell growth and induces cell cycle arrest via modulation of the HER2/PI3K/Akt signaling pathway. Furthermore, combining *G. tsugae* extract with taxol or cisplatin significantly slows the growth of HER2-overexpressing cancer cells. Two new lanostanoids, Tsugaric acid D and Tsugaric acid E were isolated from the fruit bodies of *G. tsugae* and former compound with other two known compounds exhibited significant inhibitory effects on xanthine oxidase (XO) activity. Moreover, one known compound was able to protect human keratinocytes from photo damage and the other compound combined with cisplatin enhanced the cytotoxicity induced by cisplatin (Lin et al. 2013). *Ganoderma tsugae* possesses anti-apoptotic and hepatoprotective potential after exhaustive exercise (Huang et al. 2013). Kuok et al. (2013) revealed that oral administration of *G. tsugae* can protect the mice from ISO-induced myocardial injury and the triterpenoid fraction of *G. tsugae* containing Ganoderic acids, provided cardio protection by inhibiting the ISO-induced expression of Fas/Fas ligand, oxidative stress, and apoptosis. Ganoderic acids dissipated the cellular reactive oxygen species imposed by H_2O_2 and prevented cell death. Lin et al. (2006) performed an experiment to show supplementation of *G. tsugae* significantly decreased total infiltrating leukocytes and lymphocyte percentage in BALF in the experimental groups. Supplementation of *G. tsugae* also significantly reduced inflammatory mediators in BALF including histamine, prostaglandin E2, and eotaxin. *Ganoderma tsugae* phosphorylates the human epidermal growth factor receptor 2 (HER2) which activates the variety of proteins such as PI3K/Akt and Ras/mitogenactivated protein kinase (MAPK) proteins in downstream signaling in cancer (Baselga & Swain 2009). *In vitro* studies of *G. tsugae* indicated that administration of *G. tsugae* extract (GTE) induced G1 phase arrest via modulating cyclins D1, E, p21, and p27 in the cell cycle in ovarian cancer and breast cancer cells. Furthermore, *G. tsugae* arrests cyclin and cdks in HER2/ PI3K/Akt signaling which inhibit the growth of HER2 overexpressing cancer cells (Kuo et al. 2013).

Chiang et al. (2014) prepared nano/submicrometer particles from *G. tsugae* and both nano/submicrometer and hot-water extract *G. tsugae* exhibited no mutagenic potential to *Salmonella typhimurium* tester strains. Cell toxicity test also confirmed the safety of both nano/submicrometer and hot water extract *G. tsugae*. Li et al. (2014) reportedFIP-gts may have the potential to be utilized as a therapeutic adjuvant for the treatment of resistant urothelial cancer down-regulating Beclin-1 to activate autophagic cell death. *Ganoderma tsugae* exhibited antibacterial activity against *S. aureus*, *B. subtilis* and *E. coli* (Singdevsachan et al. 2015). DMSO extractof *G. tsugae* (GTDE) prevents particulate matter (PM) transmigration into the bloodstream, and the resultant dysfunction, by inhibiting oxidative stress production and endothelial permeability and thus decrease myocardial infarctions (Tseng et al. 2016). Lin et al. (2016) isolated anew lanostanoid, a novel palmitamide and three novel seco-lanostanoids and results indicated that some of the compounds may be used as cancer chemo preventive agents. *Ganoderma tsugae* ethyl acetate extract (GTEAE) showed high potential by inhibiting reporter activity. Results demonstrated that GTEAE had a strong effect on inhibitory protein κBα level in the higher concentration used (200 gg/mL), which could be compared with the effect of parthenolide. Furthermore, GTEAE demonstrated strong inhibition of IκBα phosphorylation (Chan et al. 2015). Hot water extracts, from immature *G. tsugae*, could be of used as an alternative cancer therapy since it has anti-proliferation effects on HL-60, Hep 3B, and C6 cells (Chien et al. 2015). Triterpenoids (Gt-TRE) and polysaccharide (Gt-PS) extracts from *G. tsugae* shows anti-allergic effects. Gt-TRE significantly suppressed histamine secreted from activated RBL-2H3 mast cells and interleukin- (IL-) 4 secreted from activated EL4 cells but not Gt-PS (Chen et al. 2015). Moreover, triterpenoids fraction of *G. tsugae* might be the main constituents to alleviate allergic asthma.

Ganoderma tuberculosum, G. theaecola* and *G. tropicum

Welti et al. (2010) reported the isolation of Ganoderic acid FWI from *G. tuberculosum* and its extracts might inhibit the growth of cancer cells however, it has been isolated only from *G. tuberculosum*, Ganoderic acid FWI might be used also as a chemotaxonomic marker. Ganoderic acid XL1, Ganoderenic acid AM1, Ganoderesin C and three other known triterpenoids isolated by

G. theaecola exhibited hepatoprotective activities against DL-galactosamine-induced cell damage in HL-7702 cells (Liu et al. 2014).

The 3β, 7β, 15β-trihydroxy-11, 23-dioxo-lanost-8, 16-dien-26-oic acid methyl ester extracted from *G. tropicum* (Fig. 3) exhibited definite inhibitory activity against AChE (Hu et al. 2013).

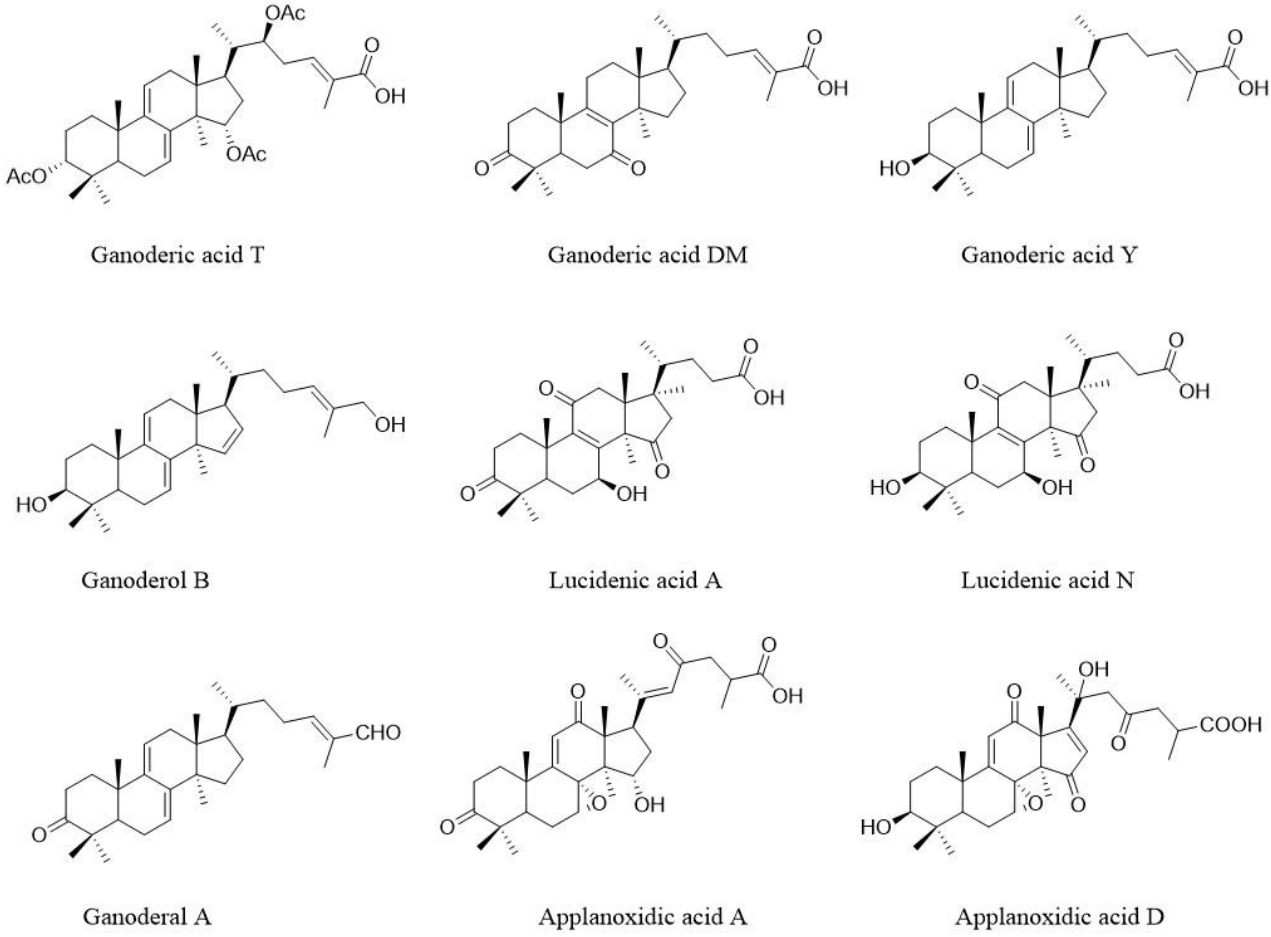

Figure 4 – Typical Chemical structures of common compounds found within *Ganoderma* spp. (Hapuarachchi et al. 2016a).

Ganoderma weberianum* and *G. zonatum

Ganoderma weberianum, a tropical white-rot fungus with great economic and environmental importance, has been used as a traditional Chinese medicine with anticancer and antivirus properties (Gao & Zhou 2003). *Ganoderma weberianum* TZC-1 was able to produce a high yield of laccase, which exhibited the strong ability to decolorize different dyes (Chen et al. 2010a,b). Mycelia pellets could also decolorize indigo carmine, indigo dye, and its effluents efficiently (Zhou et al. 2011b, Tian et al. 2013). Zhou et al. (2015b) established a simple and efficient genetic transformation method of *G. weberianum* via ATMT. This method included the growing mycelia of the fungus, *Agrobactrium tumefaciens*strain GV3101, vector pBIH1 harboring the cauliflower mosaic virus (CaMV) 35S promoter and the selective hpt marker. The hygromycin phosphotransferase (hpt), β-glucuronidase (uidA), and enhanced green fluorescent protein (egfp) genes have been efficiently expressed in transgenic mycelia and spores of *G. weberianum* through co-cultivation of *Agrobacterium* lawn and fungal mycelia at 28 °C on yeast extract agar medium. Kinge & Mih (2011) demonstrated the cytotoxicity of three lanostane-type triterpenoids, Lanosta-7, 9(11), 24-trien-3-one15, 26-dihydroxy, Lanosta-7, 9(11), 24-trien-26-oic, 3-hydroxy and Ganoderic acid Y (Fig. 4), isolated from fruiting bodies of *G. zonatum*, against five human tumor cell lines.

Discussion

Are the beneficial medicinal properties of *Ganoderma* truly substantiated?

Ganoderma is now becoming accepted as a natural supplement to enhance the healing effects by supporting the immune system in combination with other therapies. Large number of scientific articles and patents from *Ganoderma* originate from research laboratories of Asian countries, such as Japan, China, and Korea. Recent *in vitro* and *in vivo* studies demonstrate the beneficial effects of species on various diseases. But, very few studies have been conducted with *Ganoderma* in human patients owing to poor methodological quality of these trials. In more recent studies, purified substances isolated from *Ganoderma* have been investigated to reveal the molecular mechanisms responsible for the antitumor and immunosupportive activities. One of the primary reactions of radiation and chemotherapy in the treatment of disease patients is the advancement of leukopenia, which fundamentally expands the danger of contaminations. Consequently, a few late reviews have looked into whether *Ganoderma* mushroom concentrates or constituents can upgrade hematopoiesis by investigating ideal dosing, viability and security, alone or in blend with chemotherapy or radiotherapy (Ulbricht et al. 2010).

In spite of the fact that recent studies focusing on molecular targets of chemical compunds yielded promising results, details of the disease mechanisms involved and the active components of *Ganoderma* extracts need to be further characterised. Besides, preclinical or clinical invistigations must be carried out to determine the potential of these compounds in disease prevention or therapy. Systematic, standardized research and the utilization of FDA administrative conventions and defined clinical trials are are still very constrained and should be effectively sought after. In the mean time, it is vital to researchers to effectively consider how to make novel, enhanced, or modified clinical surveys, studies, and trial mechanisms. More consideration needs to be paid to proper explanation of clinical results, which are of significance to patient care and clinical basic leadership including survival times, extent of relapse and quality of life. Utilizing dietary supplements from *Ganoderma* for specific diseases should be done with caution.

It has been reported that the concentration and composition of active ingredients of *Ganoderma* depends on upon a number of factors, e.g. the harvesting techniques, strains, cultivating areas, age, manipulation, and storage of the mushrooms and spores which in turn largely influence biological activities (Hattori 2001). Hence, it is largely recommended to take these into account whenever any of these chemical compounds are being extracted for medicinal purposes. Submerged liquid or solid state biotechnological processes in bioreactors under controlled conditions offer a quicker alternative for the production and isolation of *Ganoderma* pharmaceutically active substances (Zhou et al. 2011a). Many authors have postulated that *Ganoderma* preparations induce many biological activities *in vitro* and *in vivo* on animal models. However, potential promising findings, their efficacy and safety have not yet been supported by any single human clinical evidence up to now. Further research, scientific support and a deeper scientific understanding of the mechanisms are needed to confirm these effects. Hence well designed *in vivo* tests and randomized controlled clinical studies with *Ganoderma* can provide statistically significant results to confirm the efficacy and safety of *Ganoderma* applications. Further, standardization and quality control of *Ganoderma* species, cultivation processes, extracts and commercial formulations, are needed to accept these speciesas natural product for potential use in the prevention and treatment of various diseases.

Conclusion

Ganoderma has been used as a food supplement to prevent and treat many immunological diseases over the last 30 years. Some *in vitro* and *in vivo* studies of medicinal properties of *Ganoderma* appear to be promising, but careful investigation and accurate scientific evidences needed for establishing the safe and efficient use of *Ganoderma.* Experimental, epidemiological, and clinical studies should be carried out on identification of the molecular targets and investigate the association between *Ganoderma* intake and disease risk. Moreover, the efficacy dosage,

efficacy of the drug, and safety, alone or in combination with chemotherapy or radiotherapy should also be researched in the future.

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