Biologically active metabolites of the genus *Ganoderma*: Three decades of myco-chemistry research

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REVISIÓN

Metabolitos biológicamente activos del género *Ganoderma*: tres décadas de investigación mico-química

Resumen. Desde la antigüedad en la medicina tradicional de oriente, hasta los tiempos modernos, los hongos pertenecientes al género *Ganoderma* se han utilizado para el tratamiento y la prevención de diversas enfermedades como cáncer, hipertensión y diabetes, entre muchas otras afecciones. Así, a partir de los cuerpos fructíferos, micelio y esporas de diferentes especies de *Ganoderma* se han aislado más de 140 triterpenoides biológicamente activos y 200 polisacáridos, al igual que proteínas y otros metabolitos diversos. Por lo que el objetivo de este trabajo, es mostrar un panorama general de los principales metabolitos biológicamente activos aislados de los miembros de este género hasta la fecha, aunque sin pretender constituir una revisión exhaustiva, ya que tal cosa sería imposible dado el impresionante dinamismo del tema de investigación.
Palabras clave: compuestos bioactivos, hongos medicinales, metabolitos terapeúticos, polisacáridos, triterpenoides.

Abstract. The fungi belonging to the genus *Ganoderma* have been used since ancient times in Eastern traditional medicine in the treatment and prevention of several diseases such as cancer, hypertension and diabetes, among many other conditions. More than 140 biologically active triterpenoids and 200 polysaccharides, as well as proteins and miscellaneous metabolites have been isolated from the fruiting bodies, mycelium and spores of different species of *Ganoderma*. The aim of this study is to summarize the main biologically active metabolites isolated from members of this genus to date, yet without pretending to be an exhaustive review, since that would be impossible due the dynamism of the field.
Key words: bioactive compounds, medicinal mushrooms, polysaccharides, therapeutic metabolites, triterpenoids.

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Introduction

The fungi belonging to the genus *Ganoderma* (especially *G. lucidum*), have been used since ancient times in Eastern traditional medicine, until modern days in the treatment and prevention of several diseases such as cancer, hypertension, chronic bronchitis and asthma, among many other conditions, as well as being a key ingredient in the formulation of tonics and sedatives (Lee *et al*., 2005). More recently, different preparations made from mycelium, fruiting bodies and spores of *G. lucidum* have been marketed as nutriceuticals or dietary supplements due their antitumor, immunomodulatory and free radical scavenging abilities (Mau *et al*., 2002; Wachtel-Galor *et al*., 2004; Wasser *et al*., 2000). The market for dietary supplements made from *G. lucidum* has been estimated at about 5 to 6 billion dollars per year, of which 1.6 billion

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correspond only to its consumption within the United States (Zjawiony, 2004). In addition to *G. lucidum*, some other species belonging to this genus have be seen to exert diverse salutary effects on human health, including G. *tsugae, G. applanatum, G. colossum, G. concinna, G. pfeifferi* and *G. neo-japonicum* (Gan *et al*., 1998; González *et al*., 2002; Kleinwächter *et al*., 2001; Lee *et al*., 2005; Mau *et al*., 2002; Mothana *et al*., 2000; Zjawiony, 2004).

The genus *Ganoderma* has been studied from many different points of view, depending on the interests of each research group:

a) As a source of drugs and nutraceuticals (Boh, *et al.*, 2007; Fujita *et al.*, 2005; Han and Yuan, 2005; Joseph *et al*., 2009; Lindequist *et al*., 2005; Mau *et al*., 2002; Mizuno *et al*., 1995; Suárez-Medellín *et al*., 2007; Sliva *et al.*, 2003; Tang *et al*., 2005; Tasaka *et al.*, 1988; Trigos and Suárez-Medellín, 2010; Wachtel-Galor *et al*., 2004; Wang *et al*., 2005; Wasser *et al*., 2000; Yang, 2005).

b) As plant pathogens on crops like oil palm, coconut, rubber, tea, coffee, cocoa and forest trees (Karthikeyan *et al*., 2009; Paterson, 2007; Zakaria *et al*., 2005).

c) As a cause of asthma due to the airborne dispersal of spores (Craig and Levetin, 2000).

d) As a source of ligninolytic enzymes with potential applications in pulping, textile dyes, detoxification of polluted water and other biotechnological procedures (Hong and Jung, 2004; Songulashvili *et al*., 2006; Teerapatsakul *et al*., 2007; Wang and Ng, 2006).

e) And even as a dietary supplement for farm chickens (Ogbe *et al*., 2008).

The aim of this study, is to summarize the main biologically active metabolites isolated from members of *Ganoderma* genus to date, in order to show an overview of the state of art about the mycochemical research of this genus and its potential use as a natural resource.

The text is divided into two main sections. First are presented the biologically active metabolites isolated from *Ganoderma lucidum* complex, including non-polar metabolites (mostly lanosterol derivatives and related compounds) and polar metabolites (polysaccharides, peptides and proteins). Then are listed the metabolites isolated from other members of this genus, yet without pretending to be an exhaustive review, since that would be impossible due the dynamism of the field.

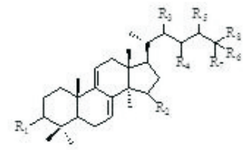
Biologically active compounds isolated from *Ganoderma lucidum* complex

The most studied members of Ganodermataceae family are without any doubt, the laccate species belonging to *Ganoderma lucidum* (Curtis) complex. These fungi, named Reishi in Japan and Ling-zhi in China, have been known since ancient times, and were even mentioned in the famous medical books *Shen Nong Ben Cao Jing*, (written during the Eastern Han Dynasty) and *Ben Cao Gang Mu* (written around 1590 A.C.). Among the wide range of diseases claimed to be successfully treated by *G. lucidum* are found be: hepatitis, hypercholesterolemia, diabetes, neoplasm, immunodeficiency, leukopenia, atherosclerosis, hemorrhoids, chronic fatigue, insomnia and dizziness caused by neurasthenia, in addition to the previously mentioned cancer, bronchitis and hypertension (Bao *et al*., 2001; Fujita *et al.*, 2005; Gao *et al*., 2002; Hajjaj *et al*., 2005; Lu *et al*., 2003; Sliva *et al.*, 2003; You and Lin, 2002).

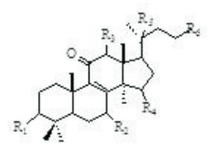
This surprising versatility is due to the large number of bioactive compounds isolated from this fungus. Overall, most of the biologically active metabolites reported for *G. lcidum* fall into two main groups: those derived from lanosterol (mostly ganoderic acids and related compounds) and polysaccharides (Cole and Schweikert, 2003; Paterson, 2006). However, there are also reports of low molecular weight peptides and proteins (Sripuan *et al*., 2003; Sun *et al*., 2004; Wang and Ng, 2006). It has been shown that aqueous extracts of *G. lucidum* are particularly effective in inhibiting the growth of sarcoma, while non-polar extracts are not, although the latter show strong activity against lipid peroxidation as well as scavenging hydroxyl and superoxide free radicals, among other properties (Jones and Janardhanan, 2000; Lu *et al*., 2003).

Triterpenoids derived from lanosterol (ganoderic acids and related compounds)

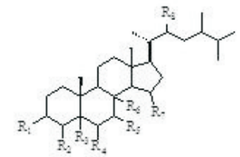
From the non-polar fractions of *G. lucidum* extracts, more than 130 different triterpenoids have been isolated. All of them are highly oxygenated lanosterol derivatives with



	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8
1	α-OAc	α-OAc	-H	-H	Δ^{24-25}		-Me	-COOH
2	β-OAc	α-OAc	-H	-H	Δ^{24-25}		-Me	-COOH
8	α-OH	α-OAc	-H	-H	Δ^{24-25}		-Me	-COOH
9	β-OH	-H	-H	-H	Δ^{24-25}		-Me	-COOH
11	β-OAc	α-OAc	β-OAc	-H	Δ^{24-25}		-Me	-COOH
12	α-OH	α-OAc	-H	=O	Δ^{24-25}		-Me	-COOH
13	α-OAc	α-OAc	-H	=O	Δ^{24-25}		-Me	-COOH
14	α-OAc	α-OH	-H	=O	Δ^{24-25}		-Me	-COOH
15	α-OAc	α-OH	β-OAc	-H	Δ^{24-25}		-Me	-COOH
19	β-OH	-H	-H	-H	α-OH	-OH	$-CH_2OH$	-Me
20	=O	α-OH	-H	-H	Δ^{24-25}		$-CH_2OH$	$-CH_2OH$
21	=O	-H	-H	-H	Δ^{24-25}		$-CH_2OH$	$-CH_2OH$
22	=O	-H	-H	-H	α-OH	-OH	$-CH_2OH$	-Me
31	β-OH	-H	-H	-H	Δ^{24-25}		-Me	$-CH_2OH$
32	=O	-H	-H	-H	Δ^{24-25}		-Me	$-CH_2OH$
47	β-OH	-H	-H	-H	Δ^{24-25}		-Me	-CHO
51	β-OH	-H	-H	-H	α-OH	-OH	-Me	-Me
52	β-OH	-H	-H	-H	Δ^{24-25}		$-CH_2OH$	$-CH_2OH$
60	=O	-H	-H	-H	Δ^{24-25}		-Me	-CHO
61	=O	α-OH	-H	-H	Δ^{24-25}		-Me	-COOH
67	=O	-H	-H	-H	Δ^{24-25}		-COOH	-Me
70	=O	β-OH	-H	-H	Δ^{24-25}		-Me	-COOH
71	=O	α-OH	-H	-H	Δ^{24-25}		-CHO	-Me
72	-OH	-H	-H	-OH	Δ^{24-25}		-COOH	-Me



	R_1	R_2	R_3	R_4	R_5	R_6
44	β-OH	β-OH	-H	=O	-H	-COOH
45	=O	=O	-H	=O	-H	-COOMe
53	=O	β-OH	-H	=O	Δ^{20-21}	-COOH
54	=O	β-OH	-H	=O	Δ^{20-21}	-COOMe
55	=O	=O	β-OAc	=O	-OH	-COOH
56	=O	=O	-H	=O	-OH	-COOH
57	β-OH	=O	β-OAc	=O	-OH	-COOH
58	β-OH	β-OH	-H	=O	-OH	-COOH
59	β-OH	β-OH	β-OAc	=O	-OH	-COOH
69	=O	β-OH	-H	α-OH	-H	-COOH
78	β-OH	β-OH	-H	=O	-H	-COOBu
79	=O	β-OH	-H	=O	-H	-COOBu



	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8
23	β-OH	-H	Δ^{5-6}	-H	Δ^{7-8}	-H	-H	Δ^{22-23}
25	β-OH	-H	α-OH	β-OH	Δ^{7-8}	-H	-H	Δ^{22-23}
26	β-OH	-H	α-OH	β-OMe	Δ^{7-8}	-H	-H	Δ^{22-23}
27	=O	-H	-H	-H	Δ^{7-8}	-H	-H	Δ^{22-23}
28	β-OH	-H	Δ^{5-6}	-H	Δ^{7-8}	-H	-H	-H
29	β-OH	-H	-H	-H	Δ^{7-8}	-H	-H	-H
30	=O	Δ^{4-5}			Δ^{6-7}	Δ^{8-14}	-H	Δ^{22-23}
74	=O	Δ^{4-5}			Δ^{6-7}	Δ^{8-14}	α-OH	Δ^{22-23}
75	=O	Δ^{4-5}			Δ^{6-7}	Δ^{8-14}	β-OH	Δ^{22-23}

Figure 1. Some metabolites isolated from *Ganoderma lucidum.*

Table1. Biological activity of some non-polar metabolites isolated from *Ganoderma lucidum*

Metabolite	Bioactivity	Reference
Ergosterol	Inhibition of angiogenesis induced by solid tumors; growth-inhibition of bladder cancer in rats; inhibition of iron-dependent lipidic peroxidation of membranes; reduction of pain associated to inflammation; reduction in the incidence of cardiovascular diseases and antimicrobial activity; Anti-complement activity against the classical pathway of the complement system	Wiseman, 1993; Yazawa *et al.,* 2000 Takaku *et al.*, 2001; Yuan *et al*., 2006; Kobori *et al*., 2007; Seo *et al*., 2009
Ergosterol peroxide	Cytostatic effect on HT29 cells; suppression of inflammatory response; suppression of LPS-induced TNF- secretion and IL-1 expression in RAW264.7 cells; suppression of LPS-induced DNA binding activity of NF- B and C/EBP inhibition of the phosphorylation of MAPKs; down-regulation of the expression of LDL receptor in RAW264.7 cells; induction of the expression of oxidative stress-inducible genes; suppression of STAT1 and interferon inducible genes; Anti-complement activity against the classical pathway of the complement system; Inhibition of cancer cell prolifieration	Yuen and Gohel, 2005; Kobori *et al*., 2007; Seo *et al*., 2009
Cerevisterol	*In vitro* inhibition against mammal -DNA polymerase	Mizushina *et al*., 1999
Ergosta-7,22-diene-2 ,3 ,9 -triol;	Inhibition of cancer cell prolifieration	Yuen and Gohel, 2005
Ganoderic acid A	Modulation of AP-1 and NF- B signaling, leading to suppression of growth and invasive behavior in cancer; suppression of the growth and invasive behavior of breast cancer cells through the inhibition of transcription factors AP-1 and NF- B; antiinflammatory activity in mice; inhibition of farnesyl protein transferase	Sliva, 2003; Jiang *et al*., 2008; Weng *et al.* 2008; Shiao, 2003
Ganoderic acid F	Suppression of angiogenesis *in vitro* and inhibition of growth and liver metastasis of lung carcinoma cells in mice; suppression of the growth and invasive behavior of breast cancer cells through the inhibition of transcription factors AP-1 and NF- B; antiinflammatory activity in mice	Morigiwa *et al*., 1986; Sliva, 2003; Jiang *et al*., 2008; Weng *et al.* 2008
Ganoderic acid DM	*In vitro* inhibiting effect against 5 -reductase; prevention of androgen related diseases; antiinflammatory activity; inhibition of osteoclastogenesis in RAW 264 cells; Antiplasmoidal activity	Liu *et al*, 2006 a and b;Liu *et al*., 2009; Xu *et al*., 2010; Adams *et al*., 2010
Lucidimol A	*In vitro* cytotoxic effect on Meth-A and LLC tumor cell lines; activity against HIV-1 protease	Min *et al*., 2000; Sato *et al*., 2009

Continue Table1

Metabolite	Bioactivity	Reference
Ganoderic acids R, T, U, V, W, X, Y and Z, lucidimol A and B, and ganodermanondiol	Cytotoxic-based carcinostatic effects on cancer cells	Toth *et al*., 1983; Sliva, 2003; Yuen and Gohel, 2005
Ganoderic acids C1, G, , and , ganolucidic acid A, lucidenic acid , lucidimol B; ganodermanondiol, ganodermenonol, ganodermadiol, lucialdehydes A, B and C	Direct cytotoxicity on Meth-A and LLC tumor cell lines	Min *et al.*, 2000; Yuen and Gohel, 2005
Ganoderic acid Me	Enhancement of IL-2 and IFN- expression and NK cells activity; Enhancement of IL-2, IFN- and NK cells and inhibition of lung metastasis in C57BL/6 mice implanted with LLC tumors; inhibition of adhesion, migration and MMP2/9 genes expressions on 95-D lung tumor cells	Wang *et al.*, 2007; Weng and Yen, 2010
Ganoderic acids TR, and S, ganoderic aldehyde TR and ganodermanondiol	Antiplasmoidal activity	Adams *et al*., 2010
Ganoderic acid X	Topoisomerases inhibition and apoptosis of cancer cells induction; Cytotoxic-based carcinostatic effects on cancer cells; Activation of ERK and JNK kinases and induction of apoptosis of human hepatoma cells	Toth *et al*., 1983; Sliva, 2003; Yuen and Gohel, 2005; Li *et al.*, 2005
Ganoderiol F	Induction of premature senescence on hepatoma cells, cytotoxicity against Meth A; Direct cytotoxicity on Meth-A and LLC tumor cell lines, LLC, Sarcoma 180 and T-47D cancer cell lines; 5 -reductase inhibitory activity; Anti HIV-1 activity; Inhibition against HIV-1 PR	El-Mekkawy *et al*., 1998; Min *et al.*, 2000; Sliva, 2003 Yuen and Gohel, 2005; Chang *et al*., 2006; Gao *et al.*, 2006; Liu *et al*., 2006; Zhang *et al*., 2009; Sato *et al*., 2009
Ganodermasides A and B	Anti-aging effect	Weng *et al.*, 2010
Ganoderic acid H, lucidenic acid B	Modulation of AP-1 and NF- B signaling, leading to suppression of growth and invasive behavior in cancer	Jiang *et al*., 2008; Weng *et al.* 2008
Ganoderic acids D, ganoderiol A, lucidumol B, ganodermadiol, and 5 -lanosta-7,9(11),24-triene-15 ,26-dihydroxy-3 -one	5 -reductase inhibitory activity	Liu *et al.*, 2006;Liu *et al*., 2009
Lucialdehydes A, B and C; lucidimols A and B; ganodermadiol; ganodermanondiol; ganodermenonol	Cytotoxicity against Meth A, LLC, Sarcoma 180 and T-47D tumor cells	Gao *et al.*, 2002
Protocatechualdehyde	Rat lens aldose reductase inhibitor	Lee *et al.*, 2005
Ganoderol B	Suppression of androgen-induced growth of prostate cancer cells	Sliva, 2003

Continue Table1

Metabolite	Bioactivity	Reference
Ganoderic acids T-Q and lucideinic acids A, D2, E2, and P	Antiinflammatory activity in mice	Sliva, 2003
Ganodermanontriol	Anti HIV-1 activity; Cytotoxicity against Meth A, LLC, Sarcoma 180 and T-4 D tumor cells; 5 -reductase inhibitory activity	El-Mekkawy *et al*., 1998; Min *et al.*, 2000; Gao *et al*., 2002; Sliva, 2003; Yuen and Gohel, 2005; Liu *et al*., 2006; Liu *et al*., 2009;
Ganoderic acids B, C1, GS-2 and H; ganoderiols A and B; 20-hydroxylucidenic acid N, 20(21)-dehydrolucidenic acid N and 3 -5 -dihydroxy-6 -methoxy-ergosta-7,22-diene	Inhibition against HIV-1 PR;	El-Mekkawy *et al*., 1998; Sato *et al.*, 2009
Ganoderone A, lucialdehyde B, and ergosta-7,22-dien-3 -ol	Potent inhibitory activity against herpes simplex virus	Niedermeyer *et al*., 2005
Australic acid and methyl australate	Antimicrobial activity against fungi and Gram-positive bacteria	Albino-Smania *et al*., 2007
Lucidenic acids N and A, and ganoderic acid E	Cytotoxic activity against Hep G2, Hep G2,2,15, and P-388 tumor cells	Wu *et al.*, 2001
Ganoderols A and B, ganoderal A and ganoderic acid Y	Inhibition of cholesterol synthesis pathway	Hajjaj *et al.*, 2005
Ganoderic acid T	Induction of apoptosis in metastatic lung tumor cells through intrinsic pathway related to mitochondrial dysfunction and p53 expression	Tang *et al.*, 2006; Weng and Yen, 2010
Ganomycines A and B	Antimicrobial activity against Gram-positive and Gram-negative bacteria	Mothana *et al.*, 2000
Ganoderic aldehyde A.	Cytotoxic against hepatoma PLC/PRF/5 and KB	Lin *et al.*, 1991
Ganoderic acids C and D	Antihistamine releasing activity in rat mast cells	Kohda *et al.*, 1985
Ganoderic acids S1 and C1	Glucosyltransferase inhibitory activity	Hada *et al*., 1989
Ganoderic acid A	Hepatoprotective activity	Kin *et al*., 1998
Ganoderic acid D	Inhibition of the proliferation of HeLa human carcinoma cells and induction of the G2/M cell cycle arrest and apoptosis	Yue *et al*., 2008
Ganoderic acid Sz	Anti-complement activity against the classical pathway of the complement system	Seo *et al*., 2009
5 -lanosta-7,9(11),24-triene-3 -hydroxy-26-al; 5 -lanosta-7,9(11),24-triene-15 -26-dihydroxy-3-one; and 8 ,9 -epoxy-4,4,14 -trimethyl-3,7,11,15,20-pentaoxo-5 -pregnane	Induction of apoptosis in human promyelocytic leukemia HL-60 cells	González *et al.*, 2002
Ganodermic acid S	Induction of platelet aggregation at high dosages, and inhibition of agonist-induced platelet aggregation at low dosages	Su *et al.*, 1999 Shiao, 2003
Ganoderic acid C	Inhibition of farnesyl protein transferase	Shiao, 2003
2 ,3 ,9 -trihydroxy-5 -ergosta-7,22-diene	Induction of apoptosis in HL-60 human premyelocytic leukemia cells and inhibition of LLC tumor growth	Lee *et al* 2011
Butyl ganoderate A, butyl ganoderate B, butyl lucidenate N and butyl lucidenate A	Down-regulation of SREBP-1c gen, leading to inhibitory effects on adipogenesis in 3T3-L1 cells	Lee *et al*., 2010a and 2010b
Methyl 7β,15α-isopropylidenedioxy-3,11,23-trioxo-5α-lanost-8-en-26-oate and n-butyl 12β-acetoxy-3β-hydroxy-7,11,15,23-tetraoxo-5α-lanost-8-en-26-oate	Specific anti-acetylcholinesterase activity	Lee et al., 2011

pharmacological activity, known as ganoderic acids, ganoderiols, ganolucidic acids, lucidones and lucidenic acids (Cole and Schweikert, 2003).

According to Shiao (2003), among the triterpenoids isolated from this fungus, are predominate pairs of C-3 stereoisomers and C-3/C-15 positional isomers. Ganodermic acids S (**1**) and R (**2**) (Figure 1) are a good example of this. The biological activity of the main compounds of this group is summarized in Table 1.

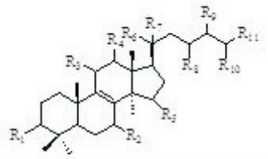
The Isolation of ganoderic acids A (**3**) and B (**4**) (Figure 2), was first reported by Kubota *et al*. (1982) from the chloroform extract of dried fruit bodies of *G. lucidum*. Since then, the discovery of new lanosterol derivatives in this group of fungi, has carried on with almost no interruption until today.

Toth *et al*. (1983) showed the occurrence of six poly-oxygenated lanostanoids in fruit bodies of *G. lucidum*, which were named ganoderic acids T (**5**), V (**6**), W (**7**), X (**8**), Y (**9**) and Z (**10**), respectively and Shiao *et al.* (1988) identified the five compounds from basidiocarps of *G. lucidum:* Lanosta-7,9(11),24-trien-3 ,15 ,22 –triacetoxy-26-oic acid (**11**), lanosta-7,9(11),24-trien-15 -acetoxy-3 -hydroxy-23-oxo–26-oic acid (**12**), lanosta-7,9(11), 24-trien-3 ,15 -diacetoxy-23-oxo-26-oi cacid (**13**), lanosta-7,9 (11), 24-trien-3 acetoxy-15 -hydroxi-23-oxo-26-oic acid (**14**), and lanosta-7,9(11),24-trien-3 acetoxy-15 22 -dihydroxy-26-oic acid (**15**) (Figures 1 and 2).

El-Mekkawy *et al.* (1998) later reported the isolation of 13 metabolites from *G. lucidum*, which were identified as ganoderic acids (**16**), A (**3**), B (**4**), C1 (**17**) and H (**18**); ganoderiols A (**19**), B (**20**) and F (**21**); ganodermanontriol (**22**), ergosterol (**23**), ergosterol peroxide (**24**), cerevisterol (**25**) and 3 -5 -dihydroxy-6 -methoxyergosta-7,22-diene (**26**). This research group found also that ganoderiol F, ganodermanontriol and to a lesser extent ganoderic acids B, C, and H, ganoderiols A and B, as well as 3 -5 -dihydroxy-6 -methoxyergosta-7,22-diene, showed antiviral activity against HIV-1.

One year later González *et al.* (1999), reported the isolation of ergosta-7,22-dien-3-one (**27**); ergosta-5,7-dien-3 -ol,(**28**) fungisterol (**29**); ergosterol (**23**), ergosterol peroxide (**24**), ergosta-4,6,8(14),22-tetraen-3-one (**30**), ganodermadiol (**31**), ganodermenonol (**32**); ganoderic acid DM (**33**), lucidadiol (**34**) and lucidal (**35**) from *G. lucidum*.

Another report was made by Min *et al.* (2000), on the isolation of ganoderic acids (**36**) (**37**) (**38**) (**39**) (**40**) and (**41**), in addition to ganolucidic acids D (**42**) and C2 (**43**) from spores of *G. lucidum*, as well as their citotoxic



	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	R_{10}	R_{11}
3	=O	β-OH	=O	-H	α-OH	α-Me	-H	=O	-H	-COOH	-Me
4	β-OH	β-OH	=O	-H	=O	α-Me	-H	=O	-H	-COOH	-Me
5	α-OH	α-OH	-H	-H	-H	α-Me	-H	-H	Δ^{24-25}	-Me	-COOH
6	=O	α-OH	-H	-H	α-OAc	α-Me	-H	-H	Δ^{24-25}	-Me	-COOH
7	α-OAc	α-OH	-H	-H	α-OAc	α-Me	-H	-H	Δ^{24-25}	-Me	-COOH
10	β-OH	-H	-H	-H	-H	α-Me	-H	-H	Δ^{24-25}	-Me	-COOH
16	β-OH	=O	=O	β-OAc	β-OH	α-Me	-H	=O	-H	-COOH	-Me
17	=O	β-OH	=O	-H	=O	α-Me	-H	=O	-H	-COOH	-Me
18	β-OH	=O	=O	β-OAc	=O	α-Me	-H	=O	-H	-COOH	-Me
33	=O	=O	-H	-H	-H	α-Me	-H	-H	Δ^{24-25}	-Me	-COOH
34	β-OH	=O	-H	-H	-H	α-Me	-H	-H	Δ^{24-25}	-Me	$-CH_2OH$
35	β-OH	=O	-H	-H	-H	α-Me	-H	-H	Δ^{24-25}	-Me	-CHO
36	=O	β-OH	=O	-H	α-OH	α-Me	-H	β-OH	Δ^{24-25}	-Me	-COOH
37	=O	α-OH	=O	-H	α-OH	α-Me	-H	β-OH	Δ^{24-25}	-Me	-COOH
38	β-OH	β-OH	=O	-H	=O	α-Me	-H	β-OH	Δ^{24-25}	-Me	-COOH
39	β-OH	=O	=O	-H	=O	α-Me	-H	β-OH	Δ^{24-25}	-Me	-COOH
40	β-OH	β-OH	=O	β-OH	=O	α-Me	-H	β-OH	Δ^{24-25}	-Me	-COOH
41	β-OH	=O	=O	β-OH	=O	α-Me	-H	β-OH	Δ^{24-25}	-Me	-COOH
42	=O	-H	=O	-H	α-OH	α-Me	-H	β-OH	Δ^{24-25}	-Me	-COOH
43	β-OH	β-OH	=O	-H	α-OH	α-Me	-H	=O	-H	-Me	-COOH
46	=O	=O	=O	-H	=O	α-Me	-H	=O	-H	-COOH	-Me
48	=O	=O	-H	-H	-H	α-Me	-H	-H	Δ^{24-25}	-H	-CHO
49	=O	α-OH	=O	-H	α-OH	α-Me	-H	=O	-H	Me	-COOH
50	=O	α-OH	=O	-H	α-OH	α-Me	-H	=O	-H	-H	-COOH
62	β-OH	α-OH	=O	-H	α-OH	α-H	-H	=O	-H	-Me	-COOH
63	=O	β-OH	=O	-H	=O	α-H	-H	=O	-H	-Me	-COOH
64	β-OH	β-OH	=O	-H	=O	α-OH	-H	=O	-H	-Me	-COOH
65	=O	=O	=O	-H	=O	α-Me	-H	β-OH	Δ^{24-25}	-Me	-COOH
66	β-OH	=O	=O	β-OAc	=O	-Me	Δ^{20-22}	=O	-H	-Me	-COOH
68	=O	β-OH	=O	-H	α-OH	α-Me	-H	=O	-H	-Me	-COOH
76	=O	β-OH	=O	-H	α-OH	α-Me	-H	=O	-H	-Me	-COOBu
77	β-OH	β-OH	=O	-H	=O	α-Me	-H	=O	-H	-Me	-COOBu
81	β-OH	=O	=O	β-OAc	=O	α-Me	-H	=O	-H	-Me	-COOBu
82	=O	=O	=O	β-OAc	=O	α-Me	-H	=O	-H	-COOH	-Me
83	-OH	β-OH	=O	-OH	=O	α-Me	-H	=O	-H	-COOH	-Me
84	=O	=O	=O	-H	α-OH	α-Me	-H	=O	-H	-COOH	-Me
85	β-OH	=O	=O	-H	α-OH	α-Me	-H	=O	-H	-COOH	-Me
86	β-OH	β-OH	=O	-H	α-OH	α-Me	-OH	=O	-H	-COOH	-Me
87	α-OAc	α-OAc	-H	-H	α-OH	α-Me	-H	-H	Δ^{24-25}	-Me	-COOH
88	-OH	α-OH	-H	-H	-H	α-Me	-H	-H	Δ^{24-25}	-Me	-COOH

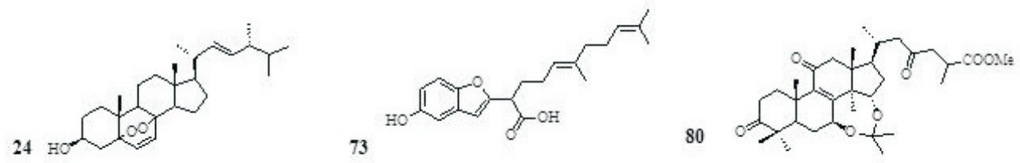


Figure 2. More metabolites isolated from *Ganoderma lucidum*.

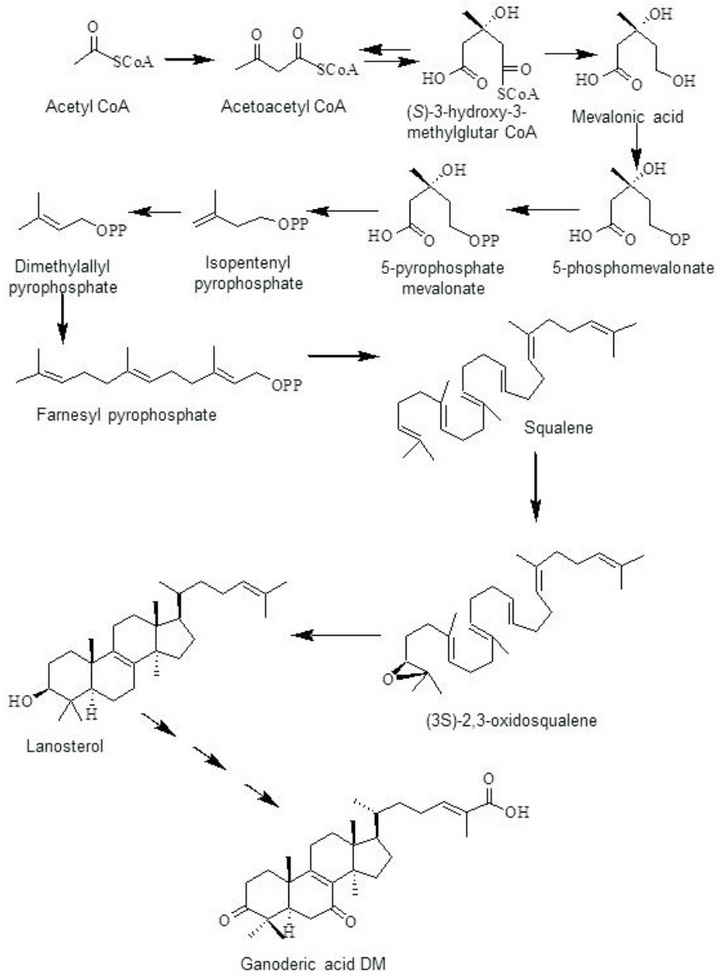


Figure 3. General scheme of ganoderic acids biosynthesis from acetyl CoA by the mevalonate/isoprene pathway (Brown, 1998; Shiao, 2003; Xu *et al*., 2009, 2010).

activity against tumor cell lines Meth-A and LLC.

Wu *et al*. (2001) then isolated lucidenic acids A, C, N (**44**), lucidolactone, methyl lucidenate F (**45**) and ganoderic acid E (**46**) from dried basidiocarps of *G. lucidum*. Lucidenic acids A and N, and ganoderic acid E showed citotoxic activity against tumor cell lines Hep G2, Hep G2.2.15 and P-388 and Gao *et al.* (2002) isolated three lanosterol derivatives from fruit bodies of *G. lucidum*, known as lucialdehydes A (**47**), B (**48**) and C, which was previously named lucidal (**35**) by González *et al*., (1999), respectively. This research group also reported the finding of ganodermanonol (**32**), ganodermadiol (**31**), ganodermanondiol (**49**), ganodermanontriol (**22**), ganoderic acid A (**3**), ganoderic acid B8 (**50**) and ganoderic acid C1 (**17**). Lucialdehydes B and C (or lucidal), as well as

ganodermanonol and ganodermanondiol showed citotoxic effects *in vitro* against Lewis lung carcinoma cells, sarcoma 180, tumor cell lines T-47D and Meth-A (Gao *et al*., 2002). In a subsequent study performed on antler shaped basidiocarps, these researchers also found lucidimol B (**51**) and ganodermatriol (**52**), which showed citotoxicity against Lewis lung carcinoma cells (Gao *et al*., 2006).

Akisha *et al.* (2005) reported the occurrence of seven triterpenoids in basidiocarps of *G. lucidum*, which were identified as: 20(21)-dehydrolucidenic acid A (**53**), methyl-20(21)-dehydrolucidenate A (**54**), 20-hydroxilucidenic acid D2 (**55**), 20-hydroxilucidenic acid F (**56**), 20-hydroxilucidenic acid E2 (**57**), 20-hydroxilucidenic acid N (**58**), and 20-hydroxilucidenic acid P (**59**).

During that same year Hajjaj *et al*. (2005) isolated ganoderol A (**32**) and ganoderol B (**31**), also known as ganodermanonol and ganodermadiol respectively (González *et al*., 1999), ganoderal A (**60**) and ganoderic acid Y (**9**), from the methanol extract of *G. lucidum*. These metabolites showed an inhibitory effect on in vitro cholesterol synthesis, by inhibiting the enzyme lanosterol-14 -desmetilase, which transforms 24,25-dihydrolanosterol into cholesterol.

Liu and co-workers (2006a, 2006b), described the inhibitory effect on the enzyme 5 -reductase, induced by lanosterol derivatives such as ganoderic acids TR (**61**), DM (**33**), A (**3**), B (**4**), C2 (**62**), D (**63**), I (**64**) and 5 -lanosta-7,9 (11),24-trien-15 ,26-dihydroxi-3-one (**120**). These researchers found that compounds with a carbonyl group at C-3 and a carbonyl group unsaturated at C-26, exhibited greater inhibitory effect against that enzyme, which might give them therapeutic and preventive qualities against androgen related diseases such as prostate cancer, male baldness and acne.

Guan and co-workers found two novel triterpenoids in *G. lucidum* fruiting bodies, identified as 23*S*-hydroxy-3,7,11,15-tetraoxo-lanost-8,24*E*-diene-26-oic acid (**65**) and 12 -acetoxy-3 -hydroxy-7,11,15,23-tetraoxo-lanost-8,20*E*-diene-26-oic acid (**66**) (Guan *et al.*, 2008).

Seo and co-workers isolated three steroids and five triterpenoids from the fruiting bodies of *G. lucidum*, which were identified as ergosterol (**23**), ergosterol peroxide (**24**), stella sterol, also known as ergosta-7,22-dien-3 -ol (**96**), ganoderic acids A (**3**), C1 (**17**) and Sz (**67**), methyl ganoderate A (**68**) and lucidenic acid A (**69**). (Seo *et al.*, 2009).

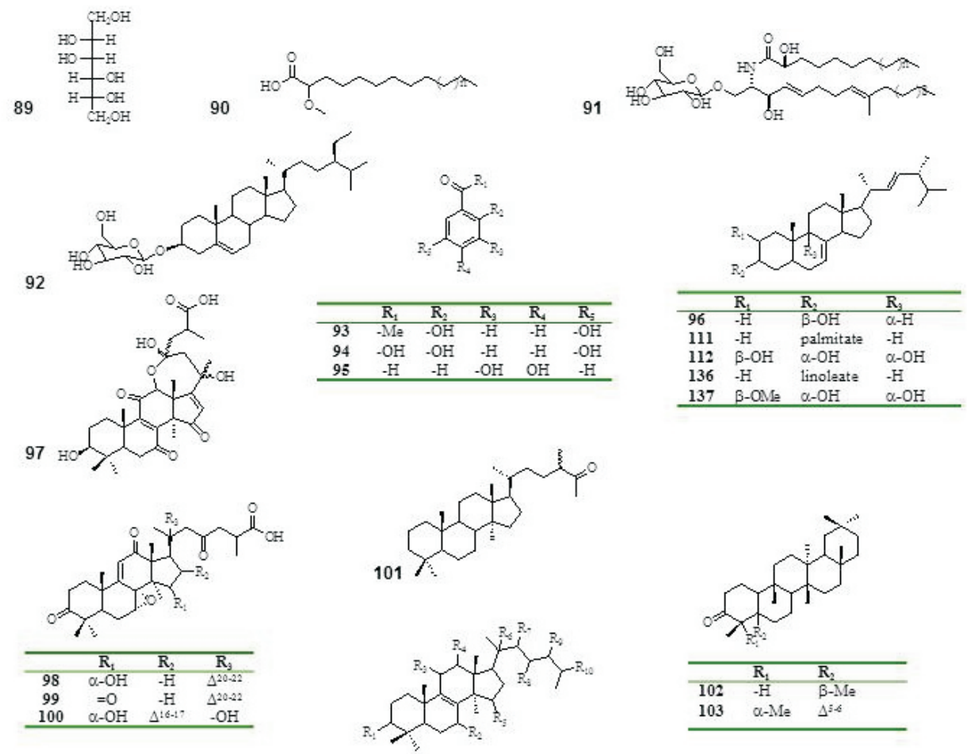
Adams *et al.* (2010) isolated three new lanostanoids and a benzofuran derivative from the fruiting bodies of *G. lucidum*, which were named ganoderic acid TR1 (**70**), ganoderic aldehyde TR (**71**), 23-hydroxyganoderic acid S (**72**) and ganofuran B (**73**).

Weng and co-workers (2010) found two novel sterols with anti-aging effect on yeast, which were identified as ganodermasides A (**74**) and B (**75**).

Lee an co-workers (2010a), reported the isolation of four new lanostane triterpenes, known as butyl ganoderate A (**76**), butyl ganoderate B (**77**), butyl lucidenate N (**78**), and butyl lucidenate A (**79**), from the fruiting bodies of *Ganoderma lucidum*, which exhibited considerable inhibitory effects on adipogenesis in 3T3-L1 cells. This effect was achieved through down-regulation of SREBP-1c (Lee *et al*., 2010a and 2010b). The same research team, isolated methyl 7β, 15α-isopropylidenedioxy-3,11,23-trioxo-5α-lanost-8-en-26-oate (**80**) and *n*-butyl 12β-acetoxy-3β-hydroxy-7,11,15,23-tetraoxo-5α-lanost-8-en-26-oate (**81**). Both compounds exhibiting specific anti-acetylcholinesterase activity (Lee *et al*., 2011).

In addition, Cole and Schweikert (2003), reported several other metabolites isolated from basidiocarps, spores and mycelium of *G. lucidum*, (like) such as ganoderic acids E (**46**), F (**82**), G (**83**), J (**84**), K (**85**), L (**86**), Ma (**87**) and U (**88**), among many others (Figures 1 and 2).

Moreover, all ganoderic acids (G.A) and related compounds are bio-synthesized by the mevalonate/isoprene pathway, which involves the conversion of farnesyl di-phosphate to squalene and then to 2,3 epoxysqualene. The



	R_1	R_2	R_3	R_4	R_5
93	-Me	-OH	-H	-H	-OH
94	-OH	-OH	-H	-H	-OH
95	-H	-H	-OH	OH	-H

	R_1	R_2	R_3
96	-H	β-OH	α-H
111	-H	palmitate	-H
112	β-OH	α-OH	α-OH
136	-H	linoleate	-H
137	β-OMe	α-OH	α-OH

	R_1	R_2	R_3
98	α-OH	-H	Δ^{20-22}
99	=O	-H	Δ^{20-22}
100	α-OH	Δ^{16-17}	-OH

	R_1	R_2
102	-H	β-Me
103	α-Me	Δ^{5-6}

	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	R_{10}
104	=O	β-OH	=O	-H	α-OH	Δ^{20-22}	-H	=O	-H	-COOH
106	β-OH	-H	=O	β-OAc	α-OAc	-H	-H	-H	Δ^{24-25}	-COOH
107	=O	=O	=O	-H	α-OH	-OH	-H	=O	-H	-COOH
108	β-OH	β-OH	=O	-H	=O	Δ^{20-22}	-H	=O	-H	-COOH
109	=O	β-OH	=O	-H	=O	Δ^{20-22}	-H	=O	-H	-COOH
110	=O	=O	=O	-H	α-OH	Δ^{20-22}	-H	=O	-H	-COOH
124	=O	=O	=O	-H	-H	-H	-H	-H	Δ^{24-25}	-COOH
125	=O	=O	-H	-H	-H	-H	-H	-H	Δ^{24-25}	-CH_2OH
138	β-OH	=O	=O	-H	=O	-H	-H	=O	-H	-COOH
147	=O	-H	=O	α-OH	=O	-H	-H	=O	-H	-COOH
148	β-OH	β-OH	=O	=O	=O	-H	-H	=O	-H	-COOH
151	=O	β-OH	=O	-H	=O	-H	-H	-H	Δ^{24-25}	-COOH
152	=O	β-OH	=O	-H	α-OH	-H	-H	-H	Δ^{24-25}	-COOH
153	β-OH	β-OH	=O	β-OAc	=O	-H	-H	-H	Δ^{24-25}	-COOH
162	β-OH	β-OH	=O	-H	=O	-H	-OH	=O	-H	-COOH

Figure 4. Metabolites isolated from other species of *Ganoderma* genus.

enzyme (*S*) 3-hydroxy-3-methylglutaryl-CoA reductase (HMGR) catalyzes the first specific step of the isoprenoid biosynthesis, the squalene synthase (SQS) catalyzes the first enzymatic step from the central isoprenoid pathway to the sterol and triterpenoid bio-synthesis and the lanosterol synthase (LS) catalyzes the cyclization of 2,3 epoxysqualene to yield lanosterol, which is the basic skeleton of ganoderic acids and related compounds (Figure 3). Even when it is known that ganoderic acids are synthesized from lanosterol, the final steps of their bio-synthetic pathway include several acylation, oxidation and reduction reactions, which are not yet fully understood. However, it is known that stereoisomers belonging to 3 series are obtained from 3 (Brown, 1998, Shiao, 2003; Xu *et al*., 2009, 2010).

According to Shiao (2003), the action of ganoderic acids against tumor cell growth might be related to their inhibitory effect on cholesterol synthesis. It is known that several triterpenoids found in *G. lucidum* inhibit cholesterol bio-synthesis at a postmevalonate step. Mevalonate is an obligatory intermediate step required by normal and cancer cells for cholesterol synthesis, protein prenylation (Ras and G proteins), and DNA synthesis. Deprivation of mevalonate causes cell growth arrest and apoptosis. Since the demands of mevalonate may not be equal between normal and cancer cells, the sensitivity to mevalonate deprivation is greater among the latter, thus causing the observed reduction in tumor cell growth. In addition, *G. lucidum* triterpenoids inhibit farnesyl protein transferase (FPT) the catalyzed post translational farnesylation of Ras protein. FPT inhibitors have been demonstrated to block Ras dependent cell transformation and therefore represent a potential therapeutic strategy for the treatment of human cancer.

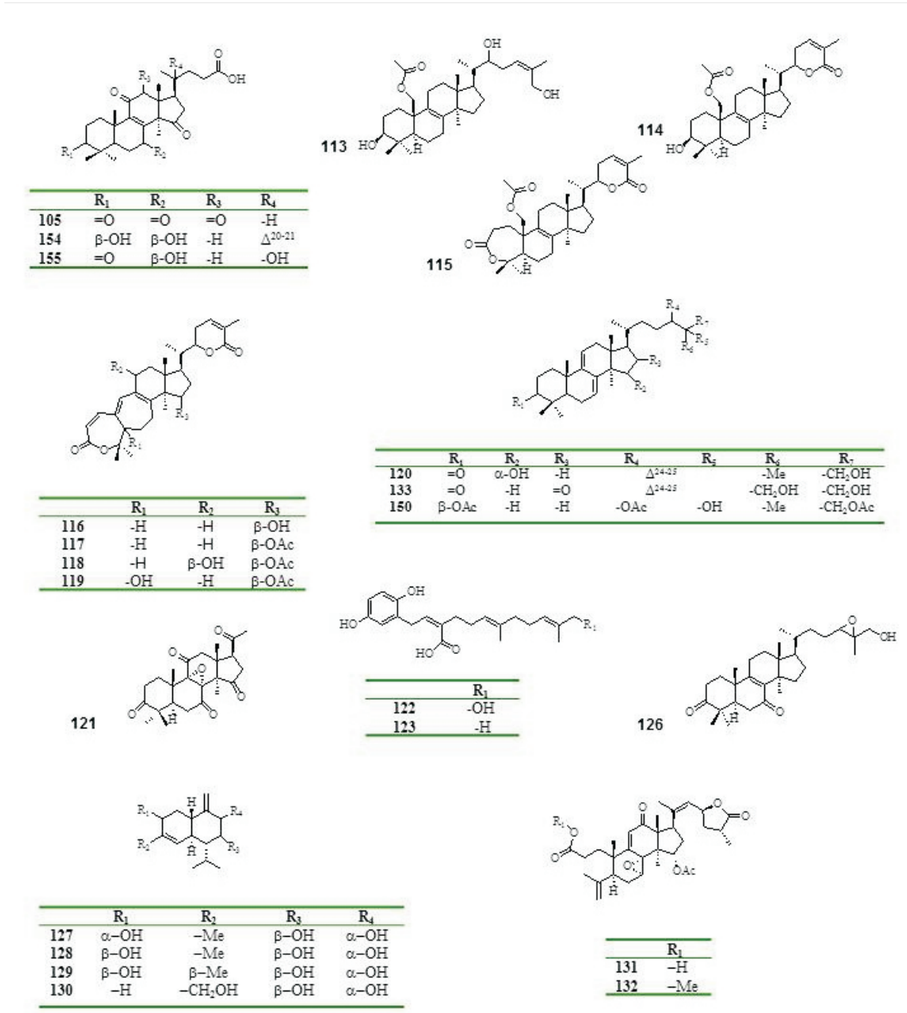
Ganoderma lucidum polysaccharides

Besides the previously discussed triterpenoids, the occurrence of more than 200 polysaccharides has been reported with antitumor and immunomodulatory activity, in the polar extracts of *G. lucidum*. The main bioactive polysaccharides isolated from this fungus are D-glucanes with -1-3 and -1-6 glycosidic bonds. The basic structure of these carbohydrates is conformed by 1-3-D-glucopyrane and side chains with 1 to 15 units of 1-6 monoglucosyls with an average molecular weight of 1,050,000 Da (Sone *et al*., 1985; Yuen and Gohel, 2005).

It is generally accepted that the antitumor activity of Ganoderma polysaccharides is due to their positive effect on the consumer's immune system, rather than direct citotoxicity against cancer cells (Lin and Zhang, 2004).

Among the biological activities reported for the polysaccharides fraction obtained from this fungus the following are to be found: immunomodulation, antihepatotoxicity, free radical scavenging, influence on cell cycle and transduction of cell signals, inhibition of leukemic cell growth, induction of leukemic cells differentiation into monocyte/macrophages, inhibition of blood platelets aggregation, inhibition of the interaction between virus and cell membranes with an increase in the production of IL-2. It was also found that the water-soluble extract of *G. lucidum* mycelium, and in a dose dependent manner, significantly reduces the incidence and size of tumors induced by azoxymethane and N,N'- dimethylhydrazine in male F344 rat colon cells (Lu *et al*., 2003; Paterson, 2006; Shiao *et al*., 2003; Sripuan *et al*., 2003).

Bao *et al.,* (2001, 2002), reported the occurrence of a D-glucose polysaccharide known as PSGL-I-1A, isolated from water-soluble extract of *G. lucidum* spores, which exerts a stimulating effect on T-lymphocytes. Previously, the same research group found another polysaccharide named PGL, which had a distinct structure with -D (1-6) bonds, branched with glucosyl side chains linked by (1-3) and (1-4) bonds. According to these authors, PGL supresses the proliferation of T-lymphocytes. Hung and co-workers (2008) analyzed the polysaccharide fraction of *G. lucidum*, and confirmed the presence of 1-3 and 1-6 linkages.



	R_1	R_2	R_3	R_4
105	=O	=O	=O	-H
154	β-OH	β-OH	-H	Δ^{20-21}
155	=O	β-OH	-H	-OH

	R_1	R_2	R_3	R_4	R_5	R_6	R_7
120	=O	α-OH	-H	Δ^{24-25}		-Me	$-CH_2OH$
133	=O	-H	=O	Δ^{24-25}		$-CH_2OH$	$-CH_2OH$
150	β-OAc	-H	-H	-OAc	-OH	-Me	$-CH_2OAc$

	R_1	R_2	R_3
116	-H	-H	β-OH
117	-H	-H	β-OAc
118	-H	β-OH	β-OAc
119	-OH	-H	β-OAc

	R_1
122	-OH
123	-H

	R_1	R_2	R_3	R_4
127	α–OH	–Me	β–OH	α–OH
128	β–OH	–Me	β–OH	α–OH
129	β–OH	β–Me	β–OH	α–OH
130	–H	$-CH_2OH$	β–OH	α–OH

	R_3
131	–H
132	–Me

Figure 5. More metabolites isolated from other members of *Ganoderma* genus.

Some other effects attributed to *G. lucidum* polysaccharides are: antiviral, anti-inflammatory, antioxidant, hypoglycemic, and protection against radiation and DNA damage (Paterson, 2006).

Peptides and proteins

A protein with mitogenic activity named LZ-8 was isolated from *G. lucidum* mycelium. This polypeptide consists of 110 amino-acid residues with an acetylated amine ending, and has a molecular weight of 12 kDa (Paterson, 2006).

You and Lin (2002) reported the occurrence of a polysaccharide-protein complex known as GLPP that has the ability of neutralizing the damage caused by Reactive Oxygen Species (ROS) in rat macrophages. GLPP has an average molecular weight of 5.13×105 Da and includes the following amino-acids: Asp 8.49, Thr 3.58, Ser 3.93, Glu 5.81, Gly 3.50,

Ala 3.84, Cys 1.06, Val 2.68, Met 5.33, Iso-Leu 0.25, Leu 1.5, Phe 1.99, Lys 3.30, His 1.21, Arg 3.94, Pro1.22 (mg/g). The polysaccharide in the complex is made of ramnose, xylose, fructose, galactose and glucose with a molarity of 0.549:3.614:3.167:0.556:6.89, linked by -glycosidic bonds.

Sripuan *et al.* (2003) isolated from wild *G. lucidum* basidiocarps, a galactosidase enzyme, able to hydrolyze *p*-nitrophenyl D-galactopyranoside, as well as melibiose, raffinose and stachyose. In addition to this, a peptideglycan with a hypoglycemic activity known as ganoderan C has been isolated from this fungus. The glycan of this molecule is composed of D-glucose (69.6% of peptideglycan) and D-galactose (2.9 %). Both the backbone and side chains of ganoderan C contained D-glucopyranosyl 1-3 and 1-6, linkages as well as a D-galactopyranosil 1-6 linkage.

Additionally, the occurrence of a low-weight peptide has been proven known as GLP, in the water-soluble extract of this fungus, which is believed to be the main element responsible for *G. lucidum* antioxidant activity. GLP has shown to play an important role in the inhibition of lipid peroxydation *in vivo*, due their antioxidant, metal-chelating and free radical scavenging activities (Sun *et al*., 2004).

Liu and co-workers (2004) reported the isolation of a proteoglycan with a carbohydrate ratio of 10.4:1 from the cultivated mycelia of *G. lucidum*. This proteoglycan showed antiviral activities against herpes simplex virus types 1 and 2. According to this research group, the proteoglycan inhibits viral replication by interfering with the early events of viral adsorption and entry into target cells (Liu *et al*., 2004).

Wang and Ng (2006) described the isolation of a ligninolytic enzyme from *G. lucidum* fresh fruiting bodies, which also exerted a potent inhibitory effect against HIV-1 reverse transcriptase. In addition, there are previous reports of the isolation and characterization of some other laccase isozymes (Ko *et al*., 2001).

Du *et al*. (2006) showed that *G. lucidum* is able to bio-transform inorganic selenium into organic selenium, which is stored in a water-soluble protein. These researchers isolated a selenium-containing protein, belonging to the family of D I N G proteins.

This protein in its native state was identified as a monomer of 36,600 Da and has a remarkable quality in scavenging superoxide and hydroxyl radicals.

Biologically active compounds isolated from other members of *Ganoderma* genus

G. lucidum is not the only member of the *Ganoderma* genus able to produce bioactive metabolites. There are several other species of *Ganoderma* that have proven to be a valuable source of substances with pharmacological potential.

For instance, Lee *et al*. (2005) reported the occurrence of several substances that are shown to exert potent rat lens aldose reductase inhibition *in vitro,* in the ethyl acetate extract of *G. applanatum* (Pers.) basidiocarps. Among those compounds can be found: D-mannitol (**89**), 2-methoxy fatty acids (**90**), cerebrosides (**91**), daucosterol (**92**), 2,5-dihydroxyacetophenone (**93**), 2,5 dihydroxybenzoic acid (**94**) and protocatechualdehyde (**95**) (Figure 4).

The same fungus, commonly known as "artist's conk", has the sterols 5 -ergost-7-en-3 -ol (**29**), 5 -ergost-7,22-dien-3 -ol (**96**), 5,8-epidioxy-5 ,8 -ergost-6,22-dien-3 -ol (**24**) and a lanostanoid (**97**) that showed remarkable antibiotic activity against gram positive bacteria. Although some polysaccharide have been isolated from the water-soluble extract of *G. applanatum*, none of them has shown antitumor activity, unlike those isolated from *G. lucidum.* However, applanoxidic acids A (**98**), B (**99**), C, D, E, F, G (**100**) and H, isolated from a non-polar fraction of this fungus, proved to be effective against skin tumors in mice. On the other hand, it has been reported that *G. applanatum* extracts have an inhibitory effect on metaloendopeptidase encefalinase EC 3.4.24.11, which might suggest a potential application for this fungus in pain treatment. Furthermore, the occurrence of ergosterol (**23**), 24 -methyl-5 -lanosta-25-one (**101**), ergosta-7,22-dien-3-one (**27**), friedelin (**102**), alnusenone (friedoolean-5-en-3-one) (**103**), ganoderic acid F (**82**), ganoderenic acid A (**104**) and lucidenic acid D1 (**105**) has been reported *for G.applanatum* (Boh *et al*., 2000; Chairul and Hayashi, 1994; Cole and Schweikert, 2003; Gan *et al*., 1998; Melzig *et al*., 1996; Zjawiony, 2004).

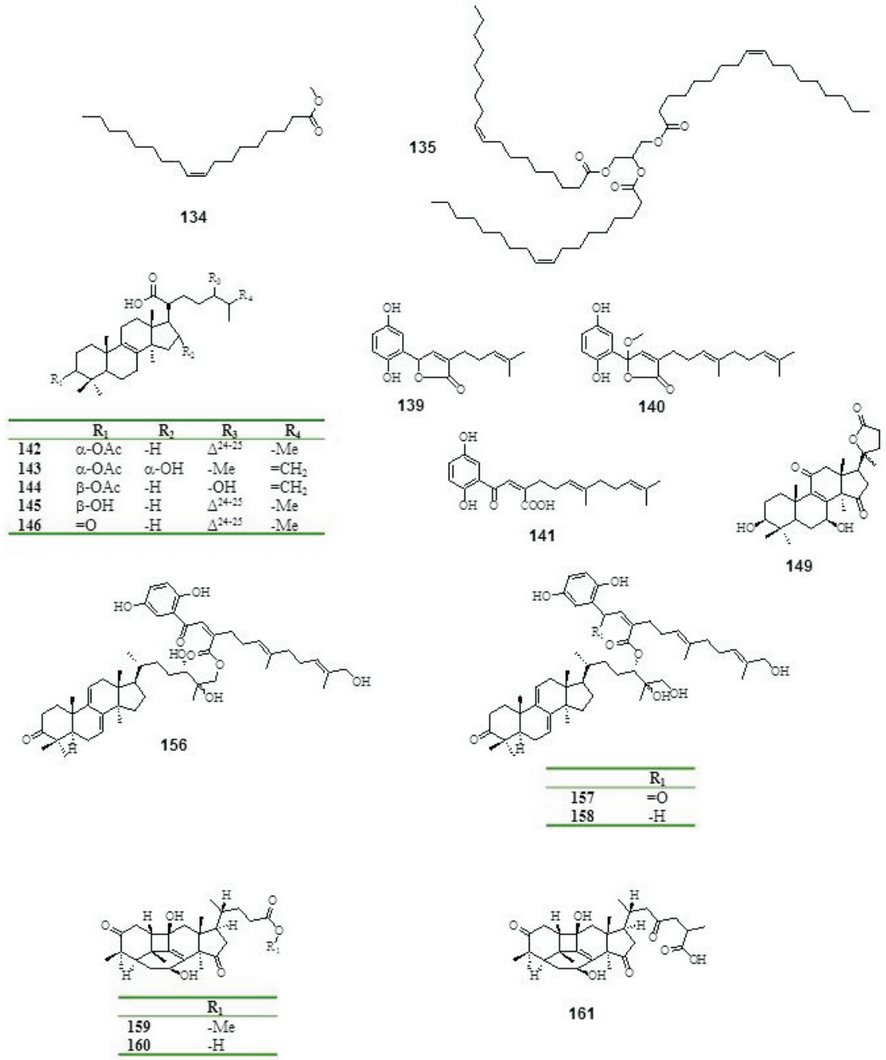


Figure 6. More metabolites isolated from other members of *Ganoderma genus*.

Wang and Liu (2008), found two new highly oxygenated lanostane type triterpenoids named ganoderic acid AP2 (**106**) and AP3 (**107**) from the fruiting bodies of the fungus *G. applanatum*. In addition, these researchers reported the isolation of ganoderenic acids A (**104**), B (**108**), D (**109**) and G (**110**) (Figure 17) and Gan *et al*., (1998) isolated from

Ganoderma neojaponicum (Imazeki) the following metabolites: ganoderal A (**60**), ganodermadiol (**31**), ergosta-7,22-dien-3 -yl palmitate (**111**), ergosta-7,22-dien-3-one (**27**), ergosta-7,22-dien-3 -ol (**96**), ergosta-4,6,8(14),22-tetraen-3-one (**30**), and a steroid identified as 2 ,3 ,9 trihydroxyergosta-7,22-diene (**112**). Besides, Paterson (2006) reports that two drimane-like sesquiterpenes known as cryptoporic acids H and I, have been isolated from this fungus.

Kleinwächter *et al*. (2001) reported the occurrence of seven triterpenoids in *G. colossus* (Fr.), which were named colosolactones A (**113**), B (**114**), C (**115**), D (**116**), E (**117**), F (**118**) and G (**119**) (Figure 5). These colosolactones did not show antibiotic activity, but showed moderate citotoxicity against L-929, K-562 and HeLa cells, with IC_{50} values from 15 to 35 g/mL. Beside, these substances the 3 -hydroxysteroid dehydrogenase (3 -HSD) inhibited in concentrations comparable to indomethacin as a standard drug, suggesting anti-inflammatory properties.

According to González *et al.* (2002), 15 compounds have been isolated from *G. concinnum* (Ryvarden), 12 of them have been previously reported: ganodermanonol (**32**), ganodermadiol (**31**), ganoderic acid Y (**9**), ganoderiol F (**21**), ganodermatriol (**52**), ganodermanontriol (**22**), ganoderiol A (**19**), ganoderiol B (**20**), ergosta-7,22-dien-3-one (**27**), fungisterol (**29**) and ergosterol peroxide (**24**). Several of these compounds have proven to exert biological activity in *G. lucidum* based studies. The other three metabolites were identified as 5 -lanosta-7,9(11),24-trien–3 -hydroxy-26-al (**47**), 5 -lanosta-7,9(11), 24-trien-15 -26-dihydroxy-3-one (**120**), and 8 9 -epoxy-4,4,14 trimethyl-3,7,11,15,20-pentaoxo-5 -pregnane (**121**), and exhibit apoptosis-inducing activity against myeloid leukemia HL-60 cells.

The isolation of ganomycin A (**122**) and B (**123**) (Figure 5) has been reported from the European fungus *Ganoderma pfeifferi* (Bres.). These metabolites showed antibiotic activity against *B. subtilis*, *S. aureus*, and *Micrococcus flavus*, among other bacteria. There were also reports on the isolation of ganodermadiol**,** and lucidadiol, both showing antiviral activity against influenza virus type A and HSV-1 (Mothana *et al*., 2000; Zjawiony, 2004).

In addition, Niedermeyer *et al*. (2005), isolated from *G. pfeifferi* basidiocarps, the previously known metabolites: ergosta-7,22-dien-3-one (**27**); ergosta-4,6,8(14),22-tetraen-3-one (**30**), 5 ,8 -epidioxy-ergosta-6,22-dien-3 -ol (**24**), lucialdehyde B (**48**), ganoderol A (**32**), ganoderol B (**31**), ganoderal A (**60**), ergosta-7,22-dien-3 -ol (**96**) and applanoxidic acids A (**98**), C and G (**100**), as well as the new triterpenoids lucialdehyde D (3,7,11-trioxo-5 -lanosta-8,24-dien-26-al) (**124**), ganoderone A (5 -lanosta-8,24-dien-26-hydroxy-3,7-dione) (**125**) and ganoderone C (5 -lanosta-8-en-24,25-epoxi-26-hydroxy-3,7,-dione) (**126**).

As regards to *Ganoderma mastoporum* (Lév.), Cole *et al.* (2003), reported the occurrence of ganomastenol A (*rel*-3 ,8 ,9 -trihydroxycadin-4,10(15)-diene) (**127**), ganomastenol B (*rel*-3 ,8 ,9 -trihydroxicadin-4,10(15)-diene) (**128**), ganomastenol C (*rel*-3 ,8 ,9 -trihydroxicadin-10(15)-ene) (**129**) and ganomastenol D (*rel*-8 ,9 -dihydroxycadin-4-hydroxymethylcadin-4,10(15)-diene) (**130**).

Meanwhile, *Ganoderma australe* (Fr.) has triterpenoids with citostatic activity against tumor cells, as ganoderic acids Z (**10**), Y (**9**), X (**8**), W (**7**), V (**6**) and T (**5**), as well as lucialdehydes A (**47**), B (**48**) and C (**35**) (León *et al*., 2003). From the same fungus Albino-Smania *et al*. (2007) isolated 5 -ergost-7-en-3 -ol (**29**), 5 -ergost-7,22-dien-3 -ol (**96**), 5,8-epidioxy-5 8 -ergost-6,22-dien-3 -ol (**24**), applanoxidic acids A (**98**), C, F, G (**100**) and H; as well as australic acid (**131**) and methyl australate (**132**) (Figure 5). Both australic acid and methyl australate have activity against bacteria and fungi. In addition to that, Elissetche *et al.* (2007) isolated two laccase enzymes from *G. australe*.

During an exhaustive bibliographic review of that genus, Paterson (2006) mentions that from *G. lipsiense* (Batsch) the following compounds: ergosterol (**23**); 5 -ergosta-7,22-dien-3 -ol (**96**), ergosta-7,22-dien-3-one (**27**), as well as ganoderic acids A (**3**) and D (**63**) and their methyl esters have been isolated. The same author, reported on the occurrence of ergosta-7,22-dien-3 -ol (**96**), ergosta-7,22-dien-3 -yl palmitate (**111**), 26,27-dihydroxy-lanosta-7,9(11),24-trien-3,16-dione (**133**), methyl oleate (**134**) and glyceryl trioleate (**135**) in *G. carnosum* (Pat.) (Figure 25). Beside, in *G. amboinense* (Lam.) has been described the occurence of: ergosta-7,22-dien-3 -ol (**96**), ergosta-7,22-dien-3 -yl palmitate (**111**), ergosta-7,22-dien-3 -yl linoleate (**136**), 2 ,3 ,9 -trihydroxy-5 -ergosta-7,22-diene (**112**), 5 ,8 -epidioxy-ergosta-6,9(11),22-trien-3 -ol (**24**), 2 -methoxyl-3 ,9 -dihydroxy-ergosta-7,22-diene (**137**) and ganoderic acid AM, also known as 3 -hydroxy-7,11,15,23-tetraoxo-lanosta-8-en-26-oic acid (**138**) (Figures 5 and 6) (Paterson, 2006). The powder made by grounding the basidiocarps of *Ganoderma amboinenese*, has shown to excert a preventive effect on acetaminophen-induced acute liver injury (Hsu *et al.*, 2008).

Meanwhile, Shen *et al*. (2008) reported the isolation and identification of the sterol ergosta-4,6,8(14),22-tetraen-3-one (**30**), from *G. atrum* (Zhao).

Niu and co-workers (2006), found three new prenylated phenolic compounds named fornicins A (**139**), B (**140**) and C (**141**) with moderate cytotoxic activity in Hep-2 cells, in the mushroom *Ganoderma fornicatum* (Fr.).

The fungus *Ganoderma tsugae* (Murr.), which was also used in Eastern traditional medicine just like *G. lucidum*, has a high antioxidant activity, reducing power, scavenging and chelating abilities and total phenol content. There were reports about the isolation of several lanostanoids with citotoxic activity *in vitro* from *G. tsugae* basidiocarps (Figure 6), including tsugaric acids A (**142**), B (**143**) and C (**144**), and tsugarosids A, B and C, in addition to four previously known metabolites: 3 -hydroxy-5 -lanosta-8,24-dien-21-oic acid (**145**), 3-oxo-5 -lanosta-8,24-dien-21-oic acid (**146**), ergosta-7,22-dien-3 -ol (**96**), and 2 ,3 ,9 -trihydroxy-5 -ergosta-7,22-diene (**112**). On the other hand, Chen and Chen (2003) reported the isolation of ganoderic acids A (**3**), B (**4**), C1 (**17**), C5 (**147**), C6 (**148**), D (**63**), E (**46**) and G (**83**), as well as ganoderenic acid D (**109**), from *G. tsugae* fruiting bodies (Chen and Chen, 2003; Mau *et al*., 2002; Su *et al*., 2000).

Qiao *et al*. (2007) isolated two triterpenoids from *Ganoderma sinense* (Zhao), which were identified as ganolactone B (**149**) and ganoderiol A triacetate (**150**). Sato *et al.* (2009b) reported that five new highly oxygenated lanostane-type triterpenoids known as ganoderic acid GS-1 (**151**), ganoderic acid GS-2 (**152**), ganoderic acid GS-3 (**153**), 20(21)-dehydrolucidenic acid N (**154**) and 20-hydroxylucidenic acid A (**155**) were isolated from the fruiting body of *G. sinense*, together with known compounds including six triterpenoids and three sterols. Among these, ganoderic acids GS-2 and 20(21)-dehydrolucidenic acid N, inhibited the human immunodeficiency virus-1 protease with IC_{50} values of 20 to 40 M.

The same research group, also isolated three new lanostane-type triterpenoids having farnesyl hydroquinone moieties, named ganosinensins A (**156**), B (**157**) and C (**158**), from the same fungus (Sato *et al*., 2009a). Subsequently, Wang *et al.* (2010) reported on the isolation of three new triterpenoids containing a four-membered ring from the same fungus named methyl ganosinesate A (**159**), ganosinesic acid A (**160**) and ganosinesic acid B (**161**) (Figure 6).

Finally, Welti *et al*. (2010), reported the isolation of ganoderic acid FWI (**162**) (Figure 4) from *Ganoderma tuberculosum* (Murr.). According to these researchers *G. tuberculosum* extracts might inhibit the growth of cancer cells as well as or even better than those from *G. lucidum*. Since it has been isolated only from *G. tuberculosum*, ganoderic acid FWI might be used also as a chemotaxonomic marker.

Conclusions

As we can see, during the last thirty years or so, the genus *Ganoderma* has been extensively researched in order to find new therapeutic metabolites. This research has lead to the isolation of hundreds of new compounds with medicinal value, most of them being either lanosterol derivatives (ganoderic acids and related molecules) or polysaccharides. Among the main biological activities exerted by the lanosterol derivatives are cytotoxicity against several lines of cancer cells, anti-inflammatory, antiviral and hepatoprotective activity, as well as inhibition of 5 -reductase and cholesterol biosynthesis. The polysaccharides on the other hand, are known to enhance the immune system and exert free radical scavenging activity. However, since this genus is one of the largest belonging to the ganodermataceae family, there is still plenty of room for further research.

Even though there is a strong body of evidence suggesting the curative potential of some substances occurring in most members of this genus, it does not necessarily mean that every *Ganoderma* fungus is always a panacea. First, because those compounds that would exert a positive effect on human health, might actually not be there at all in certain preparations, since the conditions needed for their production are not yet clear (which is by the way, what happens with many secondary metabolites). Second, as Paterson (2006) pointed out, because the toxicology of each particular fungal species has received little attention or none at all. Nevertheless, it is evident that further myco-chemical and pharmacological research will lead to a better understanding (and hence safer use) of these and other related issues.

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