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Secondary metabolites from *Ganoderma*

Sabulal Baby *, Anil John Johnson, Balaji Govindan

Phytochemistry and Phytopharmacology Division, Jawaharlal Nehru Tropical Botanic Garden and Research Institute, Pacha-Palode, Thiruvananthapuram 695 562, Kerala, India

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ABSTRACT

Ganoderma is a genus of medicinal mushrooms. This review deals with secondary metabolites isolated from *Ganoderma* and their biological significance. Phytochemical studies over the last 40 years led to the isolation of 431 secondary metabolites from various *Ganoderma* species. The major secondary compounds isolated are (a) C30 lanostanes (ganoderic acids), (b) C30 lanostanes (aldehydes, alcohols, esters, glycosides, lactones, ketones), (c) C27 lanostanes (lucidenic acids), (d) C27 lanostanes (alcohols, lactones, esters), (e) C24, C25 lanostanes (f) C30 pentacyclic triterpenes, (g) meroterpenoids, (h) farnesyl hydroquinones (meroterpenoids), (i) C15 sesquiterpenoids, (j) steroids, (k) alkaloids, (l) prenyl hydroquinone (m) benzofurans, (n) benzopyran-4-one derivatives and (o) benzenoid derivatives. *Ganoderma lucidum* is the species extensively studied for its secondary metabolites and biological activities. *Ganoderma applanatum*, *Ganoderma colossum*, *Ganoderma sinense*, *Ganoderma cochlear*, *Ganoderma tsugae*, *Ganoderma amboinense*, *Ganoderma orbiforme*, *Ganoderma resinaceum*, *Ganoderma hainanense*, *Ganoderma concinna*, *Ganoderma pfeifferi*, *Ganoderma neo-japonicum*, *Ganoderma tropicum*, *Ganoderma australe*, *Ganoderma carnosum*, *Ganoderma fornicatum*, *Ganoderma lipsiense* (synonym *G. applanatum*), *Ganoderma mastoporum*, *Ganoderma theaecolum*, *Ganoderma boninense*, *Ganoderma capense* and *Ganoderma annulare* are the other *Ganoderma* species subjected to phytochemical studies. Further phytochemical studies on *Ganoderma* could lead to the discovery of hitherto unknown biologically active secondary metabolites.

1. Genus *Ganoderma*

Ganoderma is a group of wood degrading mushrooms with hard fruiting bodies. They belong to the kingdom of Fungi, division of Basidiomycota, class of Homobasidiomycetes, order of Aphyllophorales, family of Polyporaceae (Ganodermataceae) and genus of *Ganoderma*. A search for '*Ganoderma*' in the database *Index Fungorum* displayed 428 species records, including synonyms. Taxonomic studies reported more than 300 species in genus *Ganoderma*, and most of them are distributed in the tropical regions (Richter et al., 2015; Seo and Kirk, 2000). Phytochemical and other studies reported varying species numbers in the genus (Li et al., 2013a; Peng et al., 2014b; Yan et al., 2013). *Ganoderma* species are generally not listed among edible mushrooms because their fruiting bodies are thick, corky and tough and do not have the fleshy texture characteristics (Jonathan et al., 2008; Jong and Birmingham, 1992). It is a genus of traditionally used medicinal mushrooms. Crude extracts of *Ganoderma* species are used as remedies for the treatment of a number of ailments including cancer. A recent search for '*Ganoderma*' in SciFinder Scholar gave more than 6500 publications of which nearly half were written in the Chinese language (Adams et al., 2010).

Ganoderma lucidum is the best known medicinal mushroom (Leung et al., 2002; Paterson, 2006; Ríos et al., 2012; Sanodiya et al., 2009; Ziegenbein et al., 2006). It is known as 'Lingzhi' in Chinese, 'Reishi' in Japanese and 'Yeongji' in Korean. It occurs in different colors and shapes. In the Chinese medical texts, six strains of *G. lucidum* are described. Their names are derived from the colors of their fruit bodies: Sekishi (red), Shishi (violet), Kokushi (black), Oushi (yellow), Hakushi (white) and Seishi (blue) (Hirotani et al., 1993; Wang et al., 1993). *G. lucidum*, highly ranked in oriental traditional medicine, has been used as a panacea for chronic diseases such as hepatopathy, nephritis, hypertension, arthritis, insomnia, bronchitis, asthma, diabetes and cancer (Fatmawati et al., 2010; Mizushina et al., 1998a; Nishitoba et al., 1988b; Wasser, 2005; Wasser and Weis, 1999). It is a well known crude drug which has long been used in Traditional Chinese Medicine for the promotion of longevity and maintenance of vitality (Adams et al., 2010; Liew et al., 1992; Wang et al., 2006). Owing to its "magical" medicinal properties, *G. lucidum* was considered as an 'elixir that could revive the dead' (Cheng et al., 2010; Leung et al., 2002).

* Corresponding author. Tel.: +91 472 2869226x214; fax: +91 472 2869646.
E-mail address: sabulal@gmail.com (S. Baby).

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The use of *G. lucidum* even to cure major disease conditions prompted extensive phytochemical and biological studies (Ríos et al., 2012). So far, over 240 secondary compounds have been isolated from *G. lucidum* (Chen et al., 2012; Paterson, 2006; Qiao et al., 2007; Shiao, 2003) (Table 1, Fig. 1). Triterpenoids are the major constituents in *G. lucidum* and they play a critical role in its biological effects. *G. lucidum* has a strong bitterness which originates from its triterpenes and it depends on the strain, cultivation conditions and manufacturing processes (Seo et al., 2009). Several recent systematic studies have established the therapeutic potential of this mushroom as an anticancer agent (Gao et al., 2002; Joseph et al., 2011b; Kimura et al., 2002; Liu et al., 2009a; Muller et al., 2006; Ríos et al., 2012; Yuen and Gohel, 2005). *G. lucidum* was also found to possess antiviral especially anti-HIV (El-Mekkawy et al., 1998; Eo et al., 1999a,b; Min et al., 1998), immunomodulating (Chen et al., 2006), antiinflammatory (Joseph et al., 2009, 2011b; Ko et al., 2008), antiandrogenic (Fujita et al., 2005; Liu et al., 2007), cholesterol synthesis inhibitory (Hajjaj et al., 2005; Komoda et al., 1985), hypoglycemic (Hikino et al., 1989), hepatoprotective (Kim et al., 1999), inhibition of lipid peroxidation/oxidative DNA damage (Joseph et al., 2009; Lee et al., 2001), antimicrobial (Yoon et al., 1994) and anti-aging (Shie et al., 2001) activities. *G. lucidum* is also safe because oral administration of its extracts did not show any toxicity (Kim et al., 1986). Dried powder of *G. lucidum* is currently used worldwide as a dietary supplement. The annual sale of products derived from *G. lucidum* was estimated to be more than 2.5 billion U.S. dollars (Cao et al., 2012; Li et al., 2013a).

The genome sequence of *G. lucidum* has been recently elucidated by next generation sequencing and optical mapping approaches (Chen et al., 2012). The 43.3 Mb *G. lucidum* genome sequence revealed an array of genes encoding cytochrome P450s (CYPs), transporters and regulatory proteins that cooperate in secondary metabolism. The genome encoded one of the richest sets of wood degradation enzymes among the sequenced basidiomycetes. *G. lucidum* genome analysis led to the identification of 24 CYP gene clusters. Totally 78 CYP genes were found to be co-expressed with lanosterol synthase and 16 of them showed high similarity with fungal CYPs that specifically catalyze the hydroxylation of testosterone, suggesting their possible roles in triterpenoid biosynthesis (Chen et al., 2012). Recent molecular studies found the commercially cultivated '*G. lucidum*' ('Lingzhi') in East Asia as a different species from the *G. lucidum* originally described from Europe. Cao et al. proposed a new species *Ganoderma lingzhi* Sheng H. Wu, Y. Cao & Y. C. Dai for 'Lingzhi' which has an East Asia distribution (Cao et al., 2012; Liu et al., 2012a).

Medicinal properties of *Ganoderma applanatum* are antitumor (Boh et al., 2000), aldose reductase inhibition (Lee et al., 2006), inhibition of Epstein–Barr virus activation (Chairul et al., 1994) and antibacterial activities (Smania et al., 1999). *Ganoderma australe* and *Ganoderma capense* showed antimicrobial (Smania et al., 2007) and mitogenic (Ngai and Ng, 2004) activities, respectively. *Ganoderma colossum* was reported to possess anti-HIV-1 protease activity (El Dine et al., 2008a). *Ganoderma neo-japonicum* showed radical scavenging and antihepatotoxic activities (Lin et al., 1995). *Ganoderma pfeifferi* possessed antimicrobial (Mothana et al., 2000) and antiviral (Mothana et al., 2003) activities. An Indonesian unidentified *Ganoderma* species was reported to have antitumor promoting activity (Chairul et al., 1990). *Ganoderma tsugae* showed cytotoxicity (Gan et al., 1998a; Su et al., 2000), anti-inflammatory (Ko et al., 2008), antitumor (Wang et al., 1993) and antioxidant activities (Mau et al., 2005). Recent reviews on the chemical constituents and biological activities of *Ganoderma* described the genus as a therapeutic biofactory (Paterson, 2006). This review is a compilation of secondary metabolites isolated from various *Ganoderma* species. Biological activities of secondary compounds, chemotaxonomical and biosynthetic aspects are also described briefly.

2. Secondary metabolites of *Ganoderma*

G. lucidum, *G. applanatum*, *G. colossum*, *Ganoderma sinense*, *Ganoderma cochlear*, *G. tsugae*, *Ganoderma amboinense*, *Ganoderma orbiforme*, *Ganoderma resinaceum*, *Ganoderma hainanense*, *Ganoderma concinna*, *G. pfeifferi*, *G. neo-japonicum*, *Ganoderma tropicum*, *G. australe*, *Ganoderma carnosum*, *Ganoderma fornicatum*, *Ganoderma lipsiense* (synonym *G. applanatum*), *Ganoderma mastoporum*, *Ganoderma theaecolum*, *Ganoderma boninense*, *G. capense* and *Ganoderma annulare* are the *Ganoderma* species subjected to phytochemical studies so far (Table 1, Fig. 1). Most studies for biologically active molecules in *Ganoderma* species were carried out on the extracts of their fruiting bodies, spores and cultured mycelia. Triterpenes, steroids and polysaccharides are the major constituents in *Ganoderma* species (Boh et al., 2007). Proteins, peptides, amino acids, nucleosides, fatty acids, alkaloids and inorganic elements are also biologically significant constituents in *Ganoderma* (Li et al., 2013b). Secondary metabolites are a diverse group of organic molecules biosynthesized by plants, fungi, bacteria and algae. They are not involved in the normal growth, development and reproduction of an organism, but they contribute to its survival through signaling and defense. Triterpenoids are a major group of secondary metabolites found in terrestrial and marine flora and fauna (Hill and Connolly, 2012, 2013). They are composed of six isoprene units (C30) and they exist as acyclic, mono-, di-, tri-, tetra- or pentacyclic carbon skeletons. Among these pentacyclic triterpenoids are the widely distributed and most studied group (Mahato and Kundu, 1994). Triterpenoids occur in free form or as either their ether, ester, or glycoside derivatives. Many studies established the potential pharmacological effects of triterpenoids (Hill and Connolly, 2012, 2013). Triterpene structures in *Ganoderma* evolved from the intermediate lanosterol skeleton. Cyclization of squalene-2,3-epoxide leads to a protosterol, which on subsequent backbone rearrangement gives rise to lanosterol. Lanostane skeleton ($C_{30}H_{54}$) is tetracyclic (Hill and Connolly, 2013). It acts as the intermediate molecule in the biosynthesis of various lanostane type triterpenoids (Ríos et al., 2012). Squalene and lanosterol synthases are the two major enzymes controlling the formation of squalene and lanosterol, respectively (Shi et al., 2010; You et al., 2013). Lanostane type triterpenoids are characteristic of the trans junction of rings A/B, B/C and C/D, β-oriented methyls at C10, C13, α-oriented methyl at C14, β-oriented side-chain at C17 and R configuration for C20. Most lanostanes isolated from *Ganoderma* species show a high degree of oxidation (Fig. 1).

Secondary metabolites isolated from various *Ganoderma* species belong to the following groups, (a) C30 lanostanes (ganoderic acids) (**1**–**171**), (b) C30 lanostanes (aldehydes, alcohols, esters, glycosides, lactones, ketones) (**172**–**284**), (c) C27 lanostanes (lucidenic acids) (**285**–**319**), (d) C27 lanostanes (alcohols, lactones, esters) (**320**–**343**), (e) C24, C25 lanostanes (**344**–**353**), (f) C30 pentacyclic triterpenes (**354**–**357**), (g) meroterpenoids (**358**–**365**), (h) farnesyl hydroquinones (meroterpenoids) (**366**–**370**), (i) C15 sesquiterpenoids (**371**–**379**), (j) steroids (**380**–**413**), (k) alkaloids (**414**–**420**), (l) prenyl hydroquinone (**421**), (m) benzofurans (**422**–**423**), (n) benzopyran-4-one derivatives (**424**–**428**) and (o) benzenoid derivatives (**429**–**431**). Several compounds were reported from more than one *Ganoderma* species (Table 1, Fig. 1). Previous studies reported inconsistent numbers of secondary metabolites isolated from *Ganoderma* (Boh et al., 2007; Kim and Kim, 1999; Paterson, 2006; Ríos et al., 2012; Shiao, 2003).

Of the 431 secondary compounds reported from various *Ganoderma* species (Table 1, Fig. 1), 240 were isolated from

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