MAJOR BIOACTIVE TRITERPENOIDS FROM GANODERMA SPECIES AND THEIR THERAPEUTIC ACTIVITY: A REVIEW

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ABSTRACT

Ganoderma is a traditional Chinese medicine popularly used for complementary cancer therapy and longevity for centuries. The vast amount of study has been performed on the medicinal properties of Ganoderma lucidum. G. lucidum contains various compounds with a high grade of biological activity, which increase the immunity. Several of these substances belong to the triterpenoids and polysaccharides. Proteins, steroids, phenols, lipids, etc., are also present. Ganoderma triterpenes are important secondary metabolites of G. lucidum. Ganoderma triterpenes are limestone-tetracyclic terpenes which have been reported to possess antioxidant, antitumor, anti-human immunodeficiency virus, anticancer, anti-inflammation, cytotoxic, hepatoprotective, and neuroprotective activities. This review deals with most important triterpenes isolated from Ganoderma and their therapeutic effects.

Key Words: Ganoderma; secondary metabolites; triterpenes; anticancer; antioxidant.

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INTRODUCTION

Ganoderma is a wood-rotting mushroom with hard fruiting body and grows on decaying tree stumps or logs. Ganoderma is known by various popular names as “Reishi” in Japan, “Lingzhi” in China, and “Yeongil” in Korea. The taxonomical studies have reported about 300 species which belong to genus Ganoderma and the majority of which are distributed in tropical regions. Species of Ganoderma are corky, tough, and thick. Ganoderma does not have the fleshy texture and thus do not qualify to be considered as edible mushrooms [1,2]. Some of the important species of Ganoderma on which most of the research work on medical aspects have been carried out are as follows: Ganoderma lucidum, G. sinensis, G. theaeocolum, G. zonatum, G. applanatum, G. pfeifferi, G. tsugae, G. resinaceum, G. factorium, G. colossum, G. formosanum, G. australe, and G. atrium. G. lucidum is the most commonly characterized medicinal mushroom of the genus Ganoderma [3-8]. The more weight of Ganoderma mushroom is due to its high water content up to 90%, which makes extracts of mushroom dehydrated powder and residual 10% of its mass consist of protein (10–40%), carbohydrates (3–28%), fiber (3–32%), fat (28%), and ash (8–10%). Besides, various other compounds such as provitamin D2 [9], C19 fatty acids [10], and essential nutrients such as copper and zinc [11] have also been found to be present. With the minerals potassium, calcium, phosphorous, magnesium, selenium, iron, zinc, and copper represent most of the mineral content [12,13]. Rec, 2014 [14], reported that G. lucidum contains about 72 μg Se/g of dry weight and thus can act as a good source of essential micronutrients such as selenium. G. lucidum is found across the world and is considered as an effective supplement for the prevention and treatment of many diseases since ages. Triterpenes and polysaccharides from G. lucidum have been found to possess anti-inflammatory and antioxidant activity. The polysaccharide and the water extract from G. lucidum have shown to possess immune modulator and antitumor activities. In addition, G. lucidum have a wide variety of bioactive compounds such as terpenoids mostly triterpenoids, carbohydrates including polysaccharides and glycoproteins, steroids, phenolic compounds, nucleotides, and their derivatives. The proteins of Ganoderma mushroom contain different essential amino acids. Lysine and leucine represent the highest percentages. G. lucidum, also contains a large share of polysaturated fatty acids as compared to the total fatty acids, which are the highest contributors for the best human health [6,12].

Ganoderma has been genetically admitted as nutritional supplement across the world due to its long-term safety and tolerance. G. lucidum possess a vast array of medicinal properties. The extremely important G. lucidum in oriental traditional medicine has been used as remedy against various chronic diseases such as antitumor [15,16], antioxidant [17], immunoregulation [18,19], hepatoprotection [20], hypoglycemic effect [21,22], antibacterial activity [23], reduction of blood cholesterol [24,25], inhibition of angiogenesis [26,27], antifibrotic activity [28], anti-human immunodeficiency virus (HIV) activity [29], and reduction of lower urinary tract symptoms [30]. The above bioactivities of Ganoderma have been found due to the important bioactive substances such as polysaccharides and triterpenoids. Despite the vast array of reported medicinal attributes of Ganoderma; however, the pathways and mechanisms of action of these bioactive substances from Ganoderma remain poorly defined. With further advancement in modern research technologies, clear and detailed insights into these pathways and mechanisms of action are becoming increasingly possible in which G. lucidum can influence the observed health benefits. Understanding these mechanisms could lead to more robust use of Ganoderma as an anticarcinogenic agent. With improvement in techniques, better separation and purification methods have proved very beneficial for the isolation and identification of bioactive substances from G. lucidum. However, modern researchers have primarily focused more on two active components, namely triterpenes and polysaccharides. In the foregoing account, emphasis has been given on the research work carried out by different scientists on major bioactive triterpenoids found in G. lucidum and other species of Ganoderma.

TRITERPENES

Triterpenes are biologically active compounds which contribute to the vast array of medicinal and health benefits of G. lucidum [12,31]. Triterpenes are a subtype of terpenes and are composed of six isoprene units. These isoprene units of terpenes usually form linear chains or ring-like structures. Ganoderic acids (GAs) represent a subtype of triterpenes with four cyclic and two linear isoprene units [32]. About 140 subtypes of GAs have been reported and identified from G. lucidum [33]. >130 triterpenoids (Lano-stane type) have been isolated from fruiting bodies, spores, mycelia, and cultures of G. lucidum. They
### Table 1: Triterpenoids from *Ganoderma* and their bioactivity

| Mushroom         | Bioactive compound | Bioactivity                                                                 | References |
|------------------|--------------------|------------------------------------------------------------------------------|------------|
| *G. lucidum*     | GA T               | Shows anticancer activity against lung: 95D, liver: KB-A:1- KB-3-1, cervix: SMMC7721, epidermis: HCT-116 melanoma, HeLa colon: Lo174, lung: A375, colon: LLC cell lines. It inhibited the growth and proliferation of these cancer cells. | [41,42,120,121] |
| *G. lucidum*     | GA D               | Shows apoptotic activity against cervical: HeLa cell line and inhibited cell proliferation | [33,34,100] |
| *G. lucidum*     | GA F               | Shows cytotoxic activity.                                                   | [36,44-46,122,123] |
| *G. lucidum*     | GA Me              | It shows cytotoxic activity against breast: MDA-MB-231, lung: 95-D, colon: HCT-116, HCT-8 cell lines. It arrests cell cycle, targets p53, and inhibited cell proliferation, migration, invasion, and induced apoptosis | [91,124-128] |
| *G. lucidum*     | GA Me              | Shows apoptotic activity against cervical: Hela cell line.                  | [132] |
| *G. lucidum*     | Lucialdehydes A C  | Shows cytotoxic activity.                                                   | [45] |
| *G. lucidum*     | 3β, 22β-diacetoxy-7α-hydroxyl-5α-lanost-8, 24E-dien-26-oic acid | It shows cytotoxic activity against lung: 95D, cervical: HeLa cell lines. | [130] |
| *G. lucidum*     | GA MK              | Shows cytotoxic activity.                                                   | [130,131] |
| *G. lucidum*     | GA MF/S            | It shows cytotoxic activity against lung: 95D, cervical: HeLa cell lines.  | [124,129] |
| *G. lucidum*     | GA R               | Shows cytotoxic activity against lung: 95D, cervical: HeLa cell lines.      | [130] |
| *G. lucidum*     | Colossolactone H   | Shows apoptotic activity.                                                   | [132] |
| *G. lucidum*     | Ganodermanontetrol| Shows cytotoxic activity.                                                   | [133] |
| *G. lucidum*     | Ganodermanontriol | It inhibited cell proliferation in the breast: MDA-MB-231, colon: HCT-116, HT-29 cell lines. | [134] |
| *G. lucidum*     | 3β, 24S, 25R, 26-tetradroxy-7α-methoxy-8-ene-lanost-ol | Shows cytotoxic activity.                                                   | [133] |
| *G. lucidum*     | 12β-methoxy-ganodermanontriol | Shows cytotoxic activity.                                                   | [133] |
| *G. lucidum*     | 15β-hydroxy-lucidumol A | Shows cytotoxic activity.                                                   | [133] |
| *G. lucidum*     | 15α-hydroxy-ganodermanontriol | Shows cytotoxic activity.                                                   | [133] |
| *G. lucidum*     | Lucidinic acid, O and lucidinic lactones | Inhibited HIV Type 1 reverse transcriptase. | [87] |
| *G. lucidum*     | Ganodermic acid S  | Induction of platelet aggregation.                                          | [135] |
| *G. lucidum*     | 26-oxygenosterols, ganoderol A, ganoderol B, ganoderol A, and GA Y | Lowering of blood cholesterol. | [136] |
| *G. pfeifferi*   | Ganoderone A       | Inhibitory activity against herpes simplex virus.                           | [137] |
| *G. lucidum*     | Lucialdehyde B     | Shows cytotoxic activity.                                                   | [45] |
| *G. lucidum*     | 15α, 26 dihydroxy-5α-lanostane-7, 9, 24(E)-triene-3-one | It shows cytotoxic activity against human HeLa cervical cancer cell line. | [95] |
| *G. lucidum*     | 23β-hydroxy-3, 7, 11, 15- tetraoxolanost-8, 24E-dien-26-oic acid | It shows cytotoxic activity against HeLa, p388, SGC-7901, BEL-7402 human cancer cell lines | [48] |
| *G. lucidum*     | 12β-Acetoxy-3β-hydroxy-7β,11,15,23-tetraoxolanost-8, 20 E-diene-26-oic acid | It shows cytotoxic activity against HeLa, p388, SGC-7901, BEL-7402 human cancer cell lines | [48] |
| *G. lucidum*     | GA y, γ, ε, ζ, η | Studied against Meth-A and LLC tumor cell lines.                            | [36] |
| *G. sinensis*    | GA Je              | Showed selective inhibition against HL-60 cells.                            | [9] |
| *G. lucidum*     | Ganoderol E        | Shows cytotoxic activity against MCF-7 cells.                               | [138] |
| *G. lucidum*     | GA A               | Strong cytotoxic activity against breast: MDA-MB-231. Inhibited growth and invasive behavior of breast cancer cells | [100,110,123] |
| *G. lucidum*     | GA, H              | Strong cytotoxic activity against breast: MDA-MB-231. Inhibited growth and invasive behavior of breast cancer cells | [123] |
| *G. lucidum*     | GA C1              | Strong cytotoxic activity.                                                   | [45] |
| *G. pfeifferi*   | Lucialdehyde D     | Strong cytotoxic activity.                                                   | [137] |
| *G. lucidum*     | Lucialdehyde E     | Strong cytotoxic activity.                                                   | [139] |
| *G. tsugae*      | Tsugaric acid A    | Significant activity against T-24 and HT-3 cells.                           | [140] |
| *G. tsugae*      | Tsugariside A      | Activity against T-24 cells.                                                | [51] |
| *G. tsugae*      | 3β-Hydroxy-5α-lanosta-8,24-diene - 21-oic acid | Activity against CaKi cells. | [51] |
| *G. amboinense*  | GA X               | Activity against liver: HuH-7, colon: HCT-116 cell lines and inhibits topoisomerase and induces apoptosis of cancer cells | [68] |
| *G. resinaceum*  | 3α-(3-Hydroxy-5- methoxy-3-methyl-1,5-dioxygenomethylene)-24 methylene-5α-lanost-8-en-21-oic acid | Significant cytotoxic activity. | [47] |

(Contd..)
Table 1: (Continued)

| Mushroom          | Bioactive compound | Bioactivity                                                                 | References |
|-------------------|--------------------|------------------------------------------------------------------------------|------------|
| *G. lucidum*      | GA E               | Cytotoxic activity against HepG2 HepG2, 2, 15 and P-338 cell lines          | [74,122]   |
| *G. lucidum*      | Lucindinic acid N  | Cytotoxic activity against HepG2 HepG2, 2, 15, P-338, and leukemia: HL 60 cell lines | [74,141,142] |
| *G. lucidum*      | Lucindinic acid A  | Cytotoxic activity against HepG2 HepG2, 2, 15, P-338, leukemia: HL 60 cell lines and decreases cell population growth, cell cycle arrest of these cell lines | [142,143] |
| *G. lucidum*      | Lucindinic acid B  | Induces apoptosis in leukemia: HL 60, liver: HepG2, lymphoma: CA46 cell lines | [142,144] |
| *G. lucidum*      | Lucindinic acid C  | Decreases cell population growth, cell cycle arrest of leukemia: HL 60 cell lines | [142]       |
| *G. lucidum*      | Ethyl lucidenates A| Cytotoxic activity against HL-60 and CA 46 cancer cell lines                  | [129]       |
| *G. applanatum*   | Applanoxic acid A, applanoxic acid B, applanoxic acid C, applanoxic acid D| Antitumor promoters                                                   | [50]       |
| *G. zonatum*      | GA γ               | Cytotoxic activity against liver and lung cancers                           | [145]       |
| *G. applanatum*   | Applanoxic acid G, applanoxic acid F, applanoxic acid C | Inhibition of viability and growth of the HL-60 cell lines                  | [50,146]   |
| *G. australis*    | Austroactone, austroacic acid | Inhibition of viability and growth of the HL-60 cell lines                  | [147]       |
| *G. colussum*     | Collosolactone E collosolactone G, collosolactone VIII, collosolactone V, collosolactone VI | Inhibitory activity against HIV-1 protease                                 | [88,148]   |
| *G. lucidum*      | Ganolucidic acid A | Inhibitory activity against HIV-1 protease                                  | [149]       |
| *G. lucidum*      | GA B               | Inhibitory activity against HIV-1 protease                                  | [86]       |
| *G. lucidum*      | Lucidumol B        | Inhibitory activity against HIV-1 protease                                  | [86]       |
| *G. lucidum*      | GA B               | Hepatoprotective activity                                                  | [100]       |
| *G. lucidum*      | Granosporic acid A | Hepatoprotective activity                                                  | [102]       |
| *G. lucidum*      | α-Butyl lucidenate B| Antioesity activity                                                          | [150]       |
| *G. lucidum*      | Lucidadiol         | Cytotoxic activity against human HeLa cervical cancer                       | [113]       |
| *G. lucidum*      | Ganoderiol F       | Cytotoxic activity against human HeLa cervical cancer, lung: LLC Meth A, sarcoma: Sarcoma-180, carcinoma: T-47D, lung: LLC cell lines. Active anti-HIV-1 agent | [36,46,138] |
| *G. theaeolum*    | GA XL, GA XL₂, 20-hydroxy-GA AM₁ | Hepatoprotective activity                                                     | [103]       |
| *G. pfeifferi*    | Ganoderone C       | Antiviral activity against influenza virus A                                 | [137]       |
| *G. pfeifferi*    | Lucaldehyde C      | Antiviral activity against herpes simplex virus, antiviral activity against influenza virus A | [137] |
| *G. pfeifferi*    | Applanoxic acid G  | Antiviral activity against influenza virus A                                 | [151]       |
| *G. pfeifferi*    | Lucidadiol         | Antiviral activity against influenza virus A                                 | [151]       |
| *G. lucidum*      | Lucaldehyde C      | Shows cytotoxic activity                                                     | [45]       |
| *G. lucidum*      | Ganodermenonol     | Shows cytotoxic activity                                                     | [152]       |
| *G. lucidum*      | Ganodermonandiol   | Shows cytotoxic activity and inhibitory activity against HIV-1 protease       | [107]       |
| *G. lucidum*      | GA DM1 and DM2     | Inhibition of the proliferation and metastasis of the aggressive human prostate cancer cell line PC3 | [70,153] |
| *G. lucidum*      | Methyl ganoderate B| Neurotrophic activity                                                       | [100,110] |
| *G. lucidum*      | Methyl ganoderate A| Neurotrophic activity                                                       | [100]       |
| *G. lucidum*      | GA A               | Neurotrophic activity                                                       | [112]       |
| *G. lucidum*      | GA T-Q             | Neurotrophic activity                                                       | [111]       |
| *G. lucidum*      | α-Butyl ganoderate H| Neurotrophic activity                                                       | [114]       |
| *G. lucidum*      | Methyl ganoderate acetoxide | Neurotrophic activity                                                       | [114]       |
| *G. lucidum*      | Lucadadiol         | Neurotrophic activity                                                       | [113]       |
| *G. lucidum*      | Ganodermonandiol   | Neurotrophic activity                                                       | [107]       |
| *G. lucidum*      | 4, 4, 14α-trimethyl-5α-chol-7,9 (11)-diene-3-oxo-2,4-oxo-acid | Neurotrophic activity                                                       | [112]       |

HeLa: Human epithelial cell line, HepG2: Hydroperoxide in human hepatic, HIV: Human immunodeficiency virus, *G. lucidum*: Ganoderma lucidum, GA: Ganoderic acids

have molecular weights ranging from 400 to 600 KDa. Triterpenes isolated from *Ganoderma* species show remarkable therapeutic and pharmacological properties on a number of human diseases including cancer pharmacological properties [1,16,18,20,31,33]. The triterpene extracts of *G. lucidum* are known to induce apoptosis of multiple human cancer cell lines [16]. However, the cytotoxic activity of triterpenes varied significantly across different subtypes of triterpenes [16]. Most triterpenoids extracted and identified from *Ganoderma* have shown robust biological activities (Table 1). The GAs isolated from *Ganoderma* have shown antiviral, anticancer, antioxidant, hepatoprotective, cytotoxic, antiplatelet aggregation, and inhibition of histamine release and hypcholesterolemic activities [7,34-40]. The most abundant triterpenic acid from *G. lucidum* is GA T which shows significant anticancer activity both in vivo and in vitro experiments [41,42]. GA has been found to inhibit tumor invasion by inhibiting matrix metalloproteinase (MMP)-9 expressions [42]. Another triterpenic acid GA D has been shown to directly bind to 14-3-3¢ protein [43] and this binding may contribute to the facilitation of apoptosis observed in human epithelial cell line (HeLa) cell [43]. Ganoderiol F (GA-F) a tetracyclic triterpene found in *Ganoderma lucidum* [36,44] has shown...
significant cytotoxic activity against Sarcoma-180, Lewis lung carcinoma (LLC), Meth-A and T-47D cancer cell lines [36,45]. GA-F has also been demonstrated in vivo in rats with LLC tumor cells [46]. The other forms of the isolated triterpenes from *Ganoderma lucidum* have been reported to show cytotoxic activity in the p388, HeLa, human hepatoma cell line (BEL-7402), and human gastric cancer cell line (SGC-7901) [47,48]. Recently, Hsu et al., 2018 [49], tested a novel empyreumatic effect of *G. lucidum*, an arterial condition which is associated with chronic oxidative stress and inflammation, using a carotid artery ligation mouse model. In this study, the ligation of the artery generated disturbed blood flow, a critical atherogenic factor with no cure currently. These authors studied that *G. lucidum* protected arteries from disturbed flow-induced atherogenesis and the triterpenoid fraction is the critical constituents for these effects. *Ganoderma* triterpenoids alleviated oxidative stress and inflammation, thereby preventing neointimal hyperplasia in the ligated arteries through daily oral dosage after 2 weeks. Specific triterpenes or a mixture of triterpenes have been isolated and identified from *G. lucidum* and other species of *Ganoderma* with various health benefits, the results of which have been published. The various health benefits of *Ganoderma* triterpenes are as follows.

**Anticancer activities**

The triterpene extracts identified from *G. lucidum* and other *Ganoderma* species have shown anticancer property under in vivo conditions [12,23,50-52]. The carcinogenic effects shown by various types of extracts from *G. lucidum* include various cancer cell lines (breast, colon, lung, pancreas, prostate, and skin) [12,52]. The known mechanisms through which the extracts of *G. lucidum* exhibit anticancer activities include direct inhibition of cell proliferation through cancer-specific cell cycle arrest and apoptosis [41,53-55]. *G. lucidum* extracts, in addition, can lead to downregulation of cell cycle-associated proteins, resulting in cell cycle arrest [54,56,57]. Studies of the triterpene extracts from *G. lucidum* have shown that these extracts can arrest the cell cycle at the G1 phase [54,55]. The mechanism for this inhibition of cell cycle at G1 phase is by the downregulation of cyclin D1 through the modulation of the β-catenin pathways [58]. Cyclin D1 is the key regulator of cyclin-dependent kinase which is very important for the transition of G1/S phase of the cell cycle [59]. About 30% of colon cancer has overexpression of cyclin D1, due to the abnormal β-catenin signaling pathway [60]. The triterpene from *G. lucidum*, ganodermanortriol has been found to inhibit the proliferation of human colorectal carcinoma cell lines (HCT116 and HT-29) by inhibiting the expression of cyclin D1, thus controlled levels of cyclin D1 is expressed [54]. The triterpene extracts from *Ganoderma* can also cause inhibition of G2/M transition, apart from inhibiting G1 phase of cell cycle [38]. It has been studied that the triterpene extract of *Ganoderma* can suppress the activity of protein kinase C (PKC), leading to a prolonged G2 phase, by treatment with the triterpene-enriched ethanol soluble fractions (WEES-G6). PKC is selectively activated during G2 phase of the cell cycle and belongs to the class of serine-threonine protein kinases [61]. During the G2 phase of the cell cycle, PKC has been found to be involved in the regulation of nuclear disassembly [62]. Various studies have reported that the use of PKC inhibitors can arrest the G2 phase of the cell cycle [63,64]. In addition, the level of cyclin B, a kinase, which is responsible for the transition from G2 to M phase, is reduced by WEES-G6 [38]. Due to the activity of WEES-G6, the c-Jun N-terminal kinase (JNK) and p38 kinase, both of which are mitogen-activated protein kinase which responded to cellular stress are activated [38]. JNK is considered very critical regulator of transcription which can activate stress-related genes as p53 [65-67]. Johnson and Lapadat [67] observed cell cycle arrest in triterpene-treated human hepatoma (HuH-7) carcinoma, but no effect has been seen in a normal human liver cell line, which further supports the use of triterpenes as therapeutic anticancer agent. Jiang et al., 2004 [52], reported that *G. lucidum* suppress the growth of breast cancer cells through the inhibition of Akt/NF-Kappa B signaling. How the triterpene-induced G2 phase cell cycle arrest occurs. Li et al., 2005 [68], identified the inhibition of DNA synthesis through the inhibition of topoisomerase as the possible mechanism of GA X-induced cell cycle arrest. Tang et al., 2006 [41], observed that GA from *G. lucidum* mycelia induces mitochondria-mediated apoptosis in lung cancer cells. Similarly, Chen et al., 2010 [42], revealed that GA T from *G. lucidum* inhibits the tumor growth through inhibition of MMP expression.

A recent study by researchers reported that gold nanoparticles (Au-NPs) synthesized from *G. lucidum* and then conjugated with drug doxorubicin show robust and significant anticancer drug accumulation and cytotoxic activity against MCF-7-doxbreast cancer cell line. Au-NPs efficiently inhibited the growth of MCF-7-doxbreast cancer cell line at higher concentration (400 µM/ml) by 97%. mRNA expression of ABCB1 gene and CDNA synthesized from human breast cancer cell line (MCF-7) showed reduced expression. It is important to conclude that the pharmacological activity of *G. lucidum* exhibits the anticancer activity of newly synthesized Au-NPs conjugated with drug doxorubicin. However, further research is required under in vivo conditions to report toxicity if any, due to newly synthesized Au-NPs. Au-NPs synthesized from *G. lucidum* conjugated with drug doxorubicin could prove as possible and strong source of drug delivery for anticancer inducing drug preparation which can benefit treatment of breast cancers [69].

**Cytotoxic activities**

The triterpene extracts identified from *G. lucidum* have been shown to exhibit cytotoxic effects under *in vitro* conditions on cancer cell lines [12]. Various cytotoxic compounds from *Ganoderma* species have been found to trigger apoptosis, leading to programmed cell death [52,53]. The triterpenes from *G. lucidum* also observed to cause apoptosis of various cancer cell lines, and this has been found to be due to the increase of proapoptotic proteins and decrease of antiapoptotic proteins [41,53]. The structure–activity relationship of GA-DM was investigated and it was shown to inhibit the proliferation of the aggressive human prostate cancer cell line PC3 [70].

The mechanisms by which triterpenes from *G. lucidum* induce apoptosis in human cancer cell lines include mitochondria-dependent pathway followed by activation of caspase cascade [70,71]. The mitochondrial-dependent apoptotic pathway also known as intrinsic apoptotic pathway involves the decrease in mitochondrial potential followed by the release of cytochrome c from the mitochondria [72,73]. The cytochrome c which is released from the mitochondria into the cytosol is known to trigger the caspase cascade which leads to apoptosis. This caspase cascade involves caspase 9 and caspase 3 which have been studied to have higher expressions in different human cancer cell lines when treated with the triterpenes extract from *G. lucidum* [41,71,74]. The release of cytochrome c depends on the ratio of Bax/Bcl-2 balance [75]. It has also been observed that when the ratio of Bax/Bcl-2 is increased, apoptosis is triggered. The Bcl-2 family proteins can be either proapoptotic or antiapoptotic. Bcl-2 associated X protein (Bax) and Bcl-2 associated death promoter (Bad) are proapoptotic while as Bcl-2 is antiapoptotic. Various studies have revealed that during the treatment of different human cancer cell lines with the triterpenes of *G. lucidum*, the ratio of Bax/Bcl-2 is increased which, therefore, increases Bax expression while downregulating Bcl-2 expression [71]. Liu et al., 2012 [70], observed cytotoxic and proapoptotic effect of GA derivatives on human cervical cancer cells under *in vitro* conditions.

**Antioxidant activity**

The major contributor to increased cancer risk is known to be the oxidative stress. Reactive oxygen species (ROS) and free radicals are produced as by-products of normal metabolism which can result in oxidative damage to proteins and DNA. However, this has been observed that excessive oxidative stress can override the innate protective system, leading to a variety of physiological disorders including cancer [78]. These cancer
cells further contribute to cancer progression by generating increased levels of free radicals relative to normal cells [78]. Various studies have suggested that this cancer-causing damage might be reduced or prevented with the help of antioxidants from the extracts of Ganoderma species [78,79].

Various other studies have also shown that the triterpene extracts of *G. lucidum* have antioxidant activity and have the potential to reduce oxidative damage by directly scavenging free radicals generated in the cell due to the increase in the activity of superoxide dismutase and catalase which are enzymes involved in removing harmful free radicals and ROS [80,81]. Smina et al., 2011 [82,83], revealed in mice that triterpenes from *G. lucidum* showed antioxidant activity which may be due to increased activity of antioxidant enzymes and they further observed that total terpenes from *G. lucidum* prevent radiation-induced DNA damage and apoptosis in splenocytes of mice under *in vitro* conditions. In a recent study by Smina et al., 2016 [84], total triterpenes from *G. lucidum* were highly effective in reducing the levels of lipid peroxidation and protein oxidation to near normal values in both liver and brain tissues in Swiss albino mice under *in vivo* conditions. Total triterpenes, when administered under *in vivo* conditions, were also found to be successful in restoring the antioxidant enzyme activities and glutathione level in liver and brain of irradiated mice. Administration of total triterpenes, before radiation exposure, significantly decreased the DNA strand breaks.

**Anti-HIV activity**

HIV, which induces a lethal and incurable condition known as acquired immunodeficiency syndrome (AIDS), is a highly infectious virus affecting an estimated 35 million people all over the world [85]. The treatment strategies for HIV, which are currently in use, involve delaying the progression of disease into AIDS [85]. Various compounds that exhibit inhibitory effects against AIDS have been identified from *G. lucidum*, and related species of *Ganoderma* such as triterpenes have shown anti-HIV-1 protease activity [22,86]. Mizushima et al., 1999 [87], observed the inhibition of HIV Type 1 transcriptase due to lucidic acid and lucidicin lactones isolated from *G. lucidum*. El-Mekkawy et al., 1998 [29], have assayed 13 compounds for anti-HIV activity isolated from *G. lucidum*. El Dine et al., 2008 [88], observed anti-HIV-1 protease activity of triterpenoids from *G. colosseum*. The inhibitory activity of triterpenoids isolated from *Ganoderma* species against HIV has also been reported by Casset and Asencio, 2011 [89]. Various compounds out of these have shown anti-HIV-1 activity, which includes GA A which showed robust activity against HIV proteases. However, much-extended research is to be carried out to ascertain a mechanistic basis for *G. lucidum* extracts and other species of *Ganoderma* as anti-HIV agents. In addition, determination of the structure–activity relationship between triterpenes from *G. lucidum* and HIV proteases must be performed as well.

**Antimetastatic potential**

Cancer metastasis is a very complex phenomenon in which cancer cells split from the primary tumor cells and invade other tissues, thereby leading to the formation of secondary tumors. Cancer metastasis dramatically reduces the rate of survival and cure, when left untreated [90]. Several key proteins which are involved in metastasis of cancer may be regulated by triterpenes of *G. lucidum* and other species of *Ganoderma* [64,91]. MMP is a family of proteins which cause degradation of extracellular matrix and thereby promote cancer metastasis [32,92,93]. The triterpenoid GA-Me extracted from *G. lucidum* suppressed the invasion of 95-D, LLC, and HCT-116 metastatic cancer cell lines through inhibition of MMP-9 expression [75,94]. Chen et al., 1995 [95] revealed that GA-T extracted from *G. lucidum* inhibits the tumor invasion through inhibition of MMP expression. Interleukin (IL-8) and various angiogenic factors such as vascular endothelial growth factor (VEGF) caused induction of angiogenesis and resulted in the promotion of metastasis [96]. It is further suggested that the expression of IL-8 is upregulated during oxidative stress, and therefore, overexpression of IL-8 is involved in the metastasis of breast cancer cells lines [97,98]. Studies have reported that oxidative-induced IL-8 expression was reduced in breast cancer cells lines after treatment with triterpenoid extracts of *G. lucidum* [99].

**Hepatoprotective activity**

It has been studied that GA B isolated from *Ganoderma* species showed significant hepatoprotective property [100]. However, it was observed that when the doses of GA B were increased 10 times than the normal, it did not further reduce glutamic oxaloacetic transaminase and glutamic pyruvic transaminase levels in the serum of the mice [101]. Chen and Yu, 1993 [102], have reported that ganosomic acid A has shown significant activity of lowering the levels of GPT in mice with liver injury by carbon tetrachloride (CCL₄) and exhibits hepatoprotective effect. Lin et al., 2003 [88], and Liu et al., 2014 [103], observed that triterpenoids such as GA XL, XI2, and ganoderic in from the extracts of *G. lucidum* and *G. roseum* have good hepatoprotective properties suppress the growth of hepatoma cells. Wu et al., 2016 [104], observed the hepatoprotective effects and mechanism of the action of triterpenoids from *G. lucidum* on α-amanitin-induced liver injury in mice. Wu et al., 2016 [105], studied the hepatoprotective effect of *Ganoderma* triterpenoids against oxidative damage induced by tert-butyl hydroperoxide in human hepatic cells. GAs, namely, GAs R and S, from the cultured mycelium of *G. lucidum* have shown strong hepatoprotective activity in galactosamine-induced cytotoxicity in cultured rat hepatocytes. The triterpenoid extracts from *Ganoderma* can prevent liver damage induced by CCL₄ and galactosamine in rats [106]. The triterpenoids from *G. lucidum* have shown significant protection against immunological liver damage in mice *in vitro* and *in vivo*.

**Neurotrophic activity**

Several studies have confirmed the neuroprotective activity of triterpenoids from *Ganoderma* species [107-109], Zhou et al., 2012 [109], reported neuroprotective effect of pre-administration of *G. lucidum* spores on rat hippocampus. Various studies have reported that the compounds, 4,4,14α-Trimethyl-5α-chol-7,9-(11)-diene-3-oxo-24-oic-acid and methyl ganodenate B, have showed nerve growth factor-like neuronal survival-promoting effects [100,110], whereas the compounds 4,4,14α-Trimethyl-5α-chol-7,9-(11)-diene-3-oxo-24-oic-acid, methyl ganodenate B, methyl ganodenate A, GA S1, and GA T-Q showed brain-derived neurotrophic factor-like neuronal survival-promoting activities [100,110-112]. Compounds such as n-butyl ganodenate H and methyl ganodenate A acetone have shown specific anticytoxine terase activity and have been examined as possible drug candidates for the treatment of Alzheimer’s and other related neurodegenerative diseases. The compounds lucidadiol, ganoderamondiol, and other *Ganoderma* triterpenes have shown moderate acetylcholinesterase inhibitory activity [113]. These observations indicate that these lanostane triterpenes are potential inhibitors of acetylcholine esterase and may be considered as preferential drug candidates [114].

**Anti-inflammatory potential**

About 20% of the cancers are considered to be the result of inflammation [115,116]. The carcinogenesis is promoted due to the chronic overexpression of inflammatory cytokines such as IL-6, VEGF, and tumor necrosis factor-α [117,118]. The administration of a triterpene extract of *G. lucidum* is known to suppress the inflammatory cytokine secretion in macrophage cells, therefore, reducing the level of inflammation [119].

**CONCLUSION**

The beneficial health attributes of *Ganoderma* species are due to the presence of various bioactive compounds. *Ganoderma* genus, in general, and *G. lucidum*, in particular, can be considered as a natural pharmacy store besides being natural therapeutic machinery. There are two main groups of bioactive substances triterpenes and polysaccharides that can be extracted from the mycelium of *G. lucidum* and can be considered as a natural pharmacy store besides being natural therapeutic machinery. There are two main groups of bioactive substances triterpenes and polysaccharides that can be extracted from the mycelium of *G. lucidum* and can be considered as a natural pharmacy store besides being natural therapeutic machinery.
did not show any toxic side effects, the demand for this mushroom as health fortifying food, a natural remedy, and dietary food is increasing day by day and attracting the interests of the scientific community and industrial community as well. However, due to the lack of results, intense investigation needs to be performed in the field (e.g., human clinical trials). Till now, the available data support that G. lucidum has a high potential to be accepted as a good health food supplement for patients experiencing cancer therapy. This available knowledge and further investigation would facilitate the development of new nutraceuticals and pharmacological formulations.

CONFLICTS OF INTEREST

It is hereby stated that the above article is consented for publication by all authors in this journal and, therefore, declares no conflicts of interest.

REFERENCES

1. Jong SC, Birmingham JM. Medicinal benefits of the mushroom *Ganoderma*. Adv Appl Microbiol 1992;37:101-34.
2. Jonathan SG, Kidigira LT, Ohimain E. Evaluation of the inhibitory potentials of eight higher Nigerian fungi against pathogenic microorganisms. Afr J Biomed Res 2008;11:197-202.
3. Leung SW, Yeung KY, Ricky YL, Man YK. Lingzhi (Ganoderma) Research the Past, Present and Future Perspectives in *Ganoderma*: Genetics, Chemistry, Pharmacology and Therapeutics Proceedings of International Symposium on Ganoderma Research. Beijing: Beijing Medical University Press; 2002. p. 1-9.
4. Paterson RR. *Ganoderma* a therapeutic fungal biofactory. Phytochemistry 2006;67:1985-2001.
5. Ziegenbein FC, Hanssen HP, König WA. Secondary metabolites from *Ganoderma lucidum* and *Spongiporus leucomallellus*. Phytochemistry 2006;67:207-12.
6. Sanodiyia BS, Thakur GS, Baghel RK, Prasad GB, Bisen PS. *Ganoderma lucidum*: A potent pharmacological macrofungus. Curr Pharm Biotechnol 2009;10:717-42.
7. Rios JL, Andujar I. Lanostanoids from fungi as potential medicinal agents. Fungal Metab 2009;73:59-69.
8. Rios JL, Andujar I. Lanostanoids from fungi as potential medicinal agents. Fungal Metab 2009;73:59-69.
9. Liu JQ, Wang CF, Li Y, Luo HR, Qiu MH. Isolation and bioactivity evaluation of terpenoids from the medicinal fungus *Ganoderma sinense*. Planta Med 2012;78:368-76.
10. Gao P, Hirano T, Chen Z, Yasuhara T, Nakata Y, Sugimoto A, et al. Identification and isolation of C-19 fatty acids with anti-tumor activity from the spores of *Ganoderma lucidum* (reishi mushroom). Fitoterapia 2012;83:490-9.
11. Matute RG, Serra A, Figals D, Curvetto N. Copper and zinc bioaccumulation and bioavailability of *Ganoderma lucidum*. J Med Food 2011;14:1273-9.
12. Wachtel-Galor S, Benzie IFF. Triterpene-enriched extracts from *Ganoderma lucidum* with different growth stages using high-performance liquid chromatography for evaluation of their 5α-reductase inhibitory properties. Food Chem 2012;134:303-8.
13. Sonoda Y, Sekigawa Y, Sato Y. In vitro effects of oxygenated lanosterol derivatives on cholesterol biosynthesis from 24,25-dihydromelatonin. Chem Pharm Bull (Tokyo) 1986;34:646-33.
14. Komoda Y, Shimizu M, Sonoda Y, Sato Y. Ganoderic acid and its derivatives as cholesterol synthesis inhibitors. Chem Pharm Bull (Tokyo) 1989;37:531-3.
15. Min BS, Gao JJ, Nakamura N, Hattori M. Triterpenes from the spores of *Ganoderma lucidum* and their cytotoxicity against meth-A and LLC tumor cells. Chem Pharm Bull (Tokyo) 2000;48:1026-33.
16. González AG, León F, Rivera A, Padrón JI, González-Plata J, Anda A, et al. In vitro evaluation of terpenoids from *Ganoderma lucidum* against human cancer cell lines (Curt: Fr.) P. Karst. (Tokyo) 1989;37:531-3.
17. Yuen JY, Wu JY, Leung VW, Chan CH, Lee KH, Lo SC, et al. Characterization of the cytotoxicity mechanism of ganoderic acid...
D and computer-automated estimation of the possible drug target network. Mol Cell Proteomics 2008;7:949-61.
4. Chang UM, Li CH, Lin LI, Huang CP, Kan LS, Lin SB, et al. Gaesinol F, a Ganoderma triterpene, induces senescence in hepatoma hepG2 cells. Life Sci 2006;79:1120-9.
5. Gao JJ, Min BS, Ahn EM, Nakamura N, Lee HK, Hattori M, et al. New triterpene aldehydes, laucildehydes A-C, from Ganoderma lucidum and their cytotoxicity against murine and human tumor cells. Chem Pharm Bull (Tokyo) 2002;50:837-40.
6. Gao JJ, Hirakawa A, Min BS, Nakamura N, Hattori M. In vivo antitumor effects of bitter principles from the antlered form of fruiting bodies of Ganoderma lucidum. J Nat Med 2006;60:42-8.
7. Niu XM, Li SH, Xiao WL, Sun HD, Che CT. Two new lanostanoids from Ganoderma lucidum. J Asian Nat Prod Res 2007;9:659-64.
8. Gau SH, Xiao YM, Yang WX, Wang XM, Liu X, Guo DA, et al. Cytotoxic lanostanoid triterpenes from Ganoderma lucidum. J Asian Nat Prod Res 2008;10:705-10.
9. Hsu PL, Lin YC, Ni H, Mo FE. Ganoderma triterpenoids exert antiangiogenic properties in mice by alleviating disturbed flow-induced oxidative stress and inflammation. Oxid Med Cell Longev 2018;2018:3491703.
10. Tokuyama T, Hayashi Y, Nishizawa M, Tokuda H, Chairul SM, et al. New lanostanoid triterpenoids of Ganoderma tsugae. J Nat Prod 2008;71:847-53.
11. Tokuyama T, Hayashi Y, Nishizawa M, Tokuda H, Chairul SM, et al. New lanostanoid triterpenoids of Ganoderma tsugae. J Nat Prod 2008;71:847-53.
12. Wu G, Qian Z, Guo J, Hu D, Nakamura N, Hattori M. Triterpenes from Ganoderma lucidum suppresses growth of breast cancer cells through the inhibition of Akt/NF-kB signaling. Nutr Cancer 2004;49:209-16.
13. Fukuzawa M, Yamaguchi R, Hara Y, Hayashi S, Ikezoe Y, et al. Antiproliferative activity of the triterpenoids from Ganoderma tsugae. J Ethnopharmacol 2003;88:299-304.
14. Wug Q, Gao Z, Guo J, Hu D, Bao J, Xie J, et al. Ganoderma lucidum extract induces G1 cell cycle arrest, and apoptosis in human breast cancer cells. Am J Chin Med 2012;40:631-42.
15. Wu GS, Guo JJ, Bao JL, Li XW, Chen XP, Lu JJ, et al. Anti-cancer properties of triterpenoids isolated from Ganoderma lucidum a review. Expert Opin Investig Drugs 2013;22:981-92.
16. Sliva D, Loganathan J, Jiang J, Jedinaik A, Lamb JG, Terry C, et al. New lanostanoids from Ganoderma resinaceum. Phytochemistry 2001;58:761-7.
17. Jiang J, Silverman D, Bovey K, Valachovcova T, Sliva D. Ganoderma lucidum suppresses growth of breast cancer cells through the inhibition of Akt/NF-kB signaling. Nutr Cancer 2004;49:209-16.
18. Gao JJ, Min BS, Ahn EM, Nakamura N, Hattori M, et al. New lanostanoid triterpenoids from Ganoderma tsugae. J Nat Prod Res 2008;10:705-10.
19. Bartkova J, Lukas J, Strauss M, Bartek J. The PRAD-1/cyclin D1 pathway. Science 2007;316:1346-50.
20. Liu YX, Nakagawa H, Lee MH, Rustgi AK. Transforming growth factor alpha activates the cyclin D1 protein in human gastric cancer cells. J Natl Cancer Inst 1999;91:1066-74.
21. Bartkova J, Lukas J, Strauss M, Bartek J. The PRAD-1/cyclin D1 pathway. Science 2007;316:1346-50.
22. Paydary K, Khaghani P, Emamzadeh-Fard S, Alinaghi SA, Baesi K, et al. Intracellular reactive oxygen species determine the induction of apoptosis by reishi mushroom extracts in the myeloid leukemia cells. Bioorg Med Chem 2014;22:5857-64.
23. Shtutman M, Zhurinsky J, Simcha I, Albanese C, D’Amico M, et al. Differential activation of ERK, JNK/SAPK and P3/CSBP/RK maps to distinct regions of the cell cycle. J Cell Biochem 1998;70:381-90.
24. Hofmann J, O’Connor PM, Jackman J, Schubert C, Ueberall F, et al. Hematopoietic cell cycle failure is observed in mice with a targeted disruption of c-myc. Cell 1997;88:471-82.
25. Liu RM, Yu YB, Jiang ZJ. Cytotoxic and pro-apoptotic effects of novel ganoderic acid derivatives on human cervical cancer cells in vitro. Eur J Pharmacol 2012;673:23-33.
26. Liu RM, Zhong JJ. Ganoderic acid mf and S induce mitochondria mediated apoptosis in human cervical carcinoma HeLa cells. Phytotherapy 2011;18:349-55.
27. Green D, Kroemer G. The central executioners of apoptosis. Caspases or mitochondrial pathways? Trends Cell Biol 1998;9:267-71.
28. Green DR, Reed JC. Mitochondria and apoptosis. Science 1998;281:1309-12.
29. Wang SM, Shih LS, Kao SC. Cytotoxicity of Ganoderma lucidum extracts. J Nat Prod 2001;64:1200-2.
30. Kumar DS, Senthilkumar P, Surendran L, Sudhagar B, et al. Protective effect of fenugreek (Trigonella foenum-graecum L.) on ethanol induced liver damage and apoptosis in splenic lymphocytes in vivo. Toxicol Lett 2011;212:188-94.
31. Ajith TA, Sudheesh NP, Roshathy D, Abishek G, Janardhanan KK, et al. Effect of Ganoderma lucidum on the activities of mitochondrial superoxide dismutase and catalase, and mitochondrial membrane potential. Phytomedicine 2011;18:349-55.
32. Lobo V, Patil A, Phatak A, Chandra N. Free radicals, antioxidants and functional foods: Impact on human health. Pharmacogn Rev 2010;4:118-26.
33. Dreher D, Junod AF. Role of oxygen free radicals in cancer development. Eur J Cancer 1996;32A:30-8.
34. Peng XR, Liu QJ, Han ZH, Yuan XX, Luo HR, Qiu MH, et al. Protective effects of triterpenoids from Ganoderma resinsaeum on the O2 - induced toxicity in human cervical cancer HeLa cells. Food Chem 2013;141:920-6.
35. Cheiran E, Sudheesh NP, Janardhanan KK, Patani G. Free-radical scavenging and mitochondrial antioxidant activities of reishi (Ganoderma lucidum) extract. J Agric Food Chem 2005;53:6731-7.
36. Cherian E, Sudheesh NP, Janardhanan KK, Patani G. Free-radical scavenging and mitochondrial antioxidant activities of reishi (Ganoderma lucidum) extract. J Agric Food Chem 2005;53:6731-7.
37. Cherian E, Sudheesh NP, Janardhanan KK, Patani G. Free-radical scavenging and mitochondrial antioxidant activities of reishi (Ganoderma lucidum) extract. J Agric Food Chem 2005;53:6731-7.
38. Stojanovic B, Tebyes MS, Pascual-Mendez M, et al. Ganoderma lucidum mediates anti-inflammatory and anti-fibrotic effects in a murine lung fibrosis model. Eur Respir J 2016;48:1245-57.
39. Stojanovic B, Tebyes MS, Pascual-Mendez M, et al. Ganoderma lucidum mediates anti-inflammatory and anti-fibrotic effects in a murine lung fibrosis model. Eur Respir J 2016;48:1245-57.
40. Stojanovic B, Tebyes MS, Pascual-Mendez M, et al. Ganoderma lucidum mediates anti-inflammatory and anti-fibrotic effects in a murine lung fibrosis model. Eur Respir J 2016;48:1245-57.
41. Stojanovic B, Tebyes MS, Pascual-Mendez M, et al. Ganoderma lucidum mediates anti-inflammatory and anti-fibrotic effects in a murine lung fibrosis model. Eur Respir J 2016;48:1245-57.
42. Stojanovic B, Tebyes MS, Pascual-Mendez M, et al. Ganoderma lucidum mediates anti-inflammatory and anti-fibrotic effects in a murine lung fibrosis model. Eur Respir J 2016;48:1245-57.
43. Stojanovic B, Tebyes MS, Pascual-Mendez M, et al. Ganoderma lucidum mediates anti-inflammatory and anti-fibrotic effects in a murine lung fibrosis model. Eur Respir J 2016;48:1245-57.
44. Stojanovic B, Tebyes MS, Pascual-Mendez M, et al. Ganoderma lucidum mediates anti-inflammatory and anti-fibrotic effects in a murine lung fibrosis model. Eur Respir J 2016;48:1245-57.
expression. J Pharmacol Sci 2008;108:212-6.
92. Bielawski K, Bielawskia B, Sadowski T, Bolkun-Skornicka U, Muszyńska A. Proline-linked nitrosoureas as proline-converting antitumor agents. Human Cancer Cell 2008;20:171-82.
93. Moss LA, Jensen-Taubman S, Stetler-Stevenson WG. Matrix metalloproteinases: Changing roles in tumor progression and metastasis. Ann J Pathol 2012;181:1895-9.
94. Chen NH, Zhong JJ. P53 is important for the anti-invasion of ganoderic acid T in human carcinoma cells. Phytochemistry 2011;81:719-25.
95. Cheng CR, Yue QX, Wu QY, Song XY, Tao SJ, Wu XH, et al. Cytotoxic triterpenoids from Ganoderma lucidum. Phytochemistry 2010;71:1759-85.
96. Brown NS, Jones A, Fujiyama C, Harris AL, Bicknell R. Thymidine phosphorylase induces carcinoma cell oxidative stress and promotes secretion of angiogenic factors. Cancer Res 2000;60:6298-302.
97. Bendres M, Gaddy-Kurten D, Mon-Foote T, Akel NS, Skinner RA, Nicholas RW, et al. Expression of interleukin-8 and not parathyroid hormone-related protein by human breast cancer cells correlates with mammosphere formation in vitro. Cancer Res 2002;62:256-65.
98. Freude A, Chauveau C, Brouillet JP, Lucas A, Lairoux M, Lieznar A, et al. IL-8 expression and its possible relationship with estrogen-receptor-negative status of breast cancer cells. Oncogene 2003;22:256-65.
99. Thyagarajan A, Jiang J, Hopf A, Adamec J, Sliva D. Inhibition of oxidative stress and invasiveness of cancer cells by Ganoderum lucidum is mediated through the suppression of interleukin-8 secretion. Int J Mol Med 2006;18:657-64.
100. Kohda H, Tokumoto W, Sakamoto K, Fujii M, Hirai Y, Yamasaki K, et al. Antiproliferative and antipromigratory activities of two new lanostanoids from Ganoderma lucidum (Fr.) Karst. Histamine release-inhibitory triterpenes. Chem Pharm Bull (Tokyo) 1985;33:1367-74.
101. Su CH, Lai MN, Chan MH. Hepato-protective triterpenoids from Ganoderma tsugae Merrill. In: Mushroom Biology and Mushroom Products. Hong Kong, China: The Chinese University Press; 1993. p. 275-83.
102. Chen RY, Yu DQ. Studies on the triterpenoid constituents of the spores of Ganoderma lucidum Karst. J Chin Pharm Sci 1993;2:91-6.
103. Liu LY, Chen H, Liu C, Wang HQ, Kang J, Li Y, et al. Triterpenoids of Ganoderma lucidum and their hepatoprotective activities. Fitoferapia 2014;98:254-9.
104. Wu H, Tang S, Huang Z, Zhou Q, Zhang P, Chen Z, et al. Hepatoprotective effects and mechanisms of action of triterpenoids from lingzhi or reishi medicinal mushroom Ganoderma lucidum (Agaricomycetes) on α-amanitin-induced liver injury in mice. Int J Med Mushrooms 2016;18:841-50.
105. Wu JG, Kan YJ, Wu YB, Yi J, Chen TQ, Wu JZ, et al. Triterpenoids with neurotrophic activity from Ganoderma tsugae (Agaricomycetes) on α-amanitin-induced liver injury in mice. J Antibiot 2016;71:256-9.
106. Birbach A, Eisenbarth D, Kozakowski N, Ladenhauf E, Schmidt-
MAPK/ERK signal transduction pathway and reducing binding activities of NF-kappaB and AP-1. Carcinogenesis 2008;29:147-56.

142. Hsu CL, Yu YS, Yen GC. Lucidenic acid B induces apoptosis in human leukemia cells via a mitochondria-mediated pathway. J Agric Food Chem 2008;56:3973-80.

143. Nishitoba T, Sato H, Kasai T, Kawagishi H, Sakamura S. New bitter C27 and C30 terpenoids from the fungus *Ganoderma lucidum* (Reishi). Agric Biol Chem 1985;49:1793-8.

144. Weng CJ, Chau CF, Chen KD, Chen DH, Yen GC. The anti-invasive effect of lucidenic acids isolated from a new *Ganoderma lucidum* strain. Mol Nutr Food Res 2007;51:1472-7.

145. Kinge TR, Mih AM. Secondary metabolites of oil palm isolate of *Ganoderma zonatum* Murrill from Cameroon and their cytotoxicity against five human tumor cell lines. Afr J Biotechnol 2011;10:8440-7.

146. Chairul SM, Hayashi Y. Lanostanoid triterpenes from *Ganoderma applanatum*. Phytochemistry 1994;35:1305-8.

147. Leon F, Valencia M, Rivera A, Nieto I, Quintana J, Estevez F et al. Novel cytostatic lanostanoid triterpenes from *Ganoderma australis*. Helv Chim Acta 2003;86:3088-95.

148. Kleinwächter P, Anh N, Kiet TT, Schlegel B, Dahse HM, Härtl A, et al. Collossolaetone, new triterpenoid metabolites from a Vietnamese mushroom *Ganoderma colossum*. J Nat Prod 2001;64:236-9.

149. Kikuchi T, Kanomi S, Murai Y, Kudota S, Tsuneyoshi K, Ogita ZI. Constituents of the fungus *Ganoderma lucidum* (FR.) KARST. III. Structures of ganolucidic acids A and B, new lanostane-type triterpenoids. Chem Pharm Bull 1986;34:4030-6.

150. Lee J, Kim H, Youn U, Kim J, Min B, Jung H, et al. Effect of lanostane triterpenes from the fruiting bodies of *Ganoderma lucidum* on adipocyte differentiation in 3T3-L1 cells. Planta Med 2010;76:1558-63.

151. Mothana RA, Ali NA, Jansen R, Wegner U, Mentel R, Lindequist U, et al. Antiviral lanostanoid triterpenes from the fungus *Ganoderma pfeifferi*. Fitoterapia 2003;74:177-80.

152. Arisawa M, Fujita A, Saga M, Fukumura H, Hayashi T, Shimizu M, et al. Three new lanostanoids from *Ganoderma lucidum*. J Nat Prod 1986;49:621-5.

153. Johnson BM, Doonan BP, Radwan FF, Haque A. Ganoderic acid DM: An alternative agent for the treatment of advanced prostate cancer. Open Prost Cancer J 2010;3:78-85.