Therapeutic applications of *Ganoderma lucidum*: Progress and Limitations
Ganoderma lucidum presents different nomenclatures that change according to the countries where it is used. This mushroom has been used for more than 4 thousand years to treat different pathologies. It is used in different presentations and the dosage varies according to the pathology treated. There are many compounds that form its chemical constitution. *In vitro* assays emphasize its antitumor, immunomodulatory and antioxidant properties. *In vivo* studies highlight its properties of hepatoprotection and antiglycemic are also described. Although its therapeutic use is variable, its toxicity and safety in pregnancy, childhood and in the elderly is still unknown. Thus, many studies are necessary to determine their safe and rational use in therapeutic.

**Keywords:** *Ganoderma Lucidum*, Mushrooms, Pathologies, Therapeutic Effect.
INTRODUCTION


It is geographically distributed on the Pacific, USA and Canada, Finland, Europe, India, China, Japan, Korea and the Central African Mountains. The basidiocarp may be supported by a stipe, or sessile, umbilicated or non-umbilicated [4,5,6]. It has a cuticle, which can be lacquered and bright with a reddish-brown color or opaque with dark-brown coloration. The surface of the pores shows cream coloration, where the spores are produced. These pores have regular sizes of 4-7 mm, stratified tubes, and may be variable staining, duplex or having several bands or zones. The normal basidiocarp is attached laterally to the stipe, but central and sessile connections can also be developed. The color of the internal structure (context) varies from white to dark brown [7,8].

Traditional medicinal uses around the world

The mushroom *Ganoderma lucidum* has historical medicinal use dating back at least four thousand years. In these millennia, it has been used in Chinese and Japanese medicine especially for the treatment of diabetes, chronic hepatitis, nephritis, liver disease, neurasthenia, arthritis, bronchitis, asthma, gastric ulcer [9,10]. In addition to this, *G. lucidum* is widely used in food products to increase human vitality and longevity. *G. lucidum* is classified according to Chinese medicinal encyclopedias as “Shen Nong’s Ben Cao Jing” and “Ben Cao Gang Mu” described by Li Shingzhen, as precious and rare; However, it is nowadays an important mushroom on several continents [6]. In Korea, China and Japan it is used as food, but also
present miraculous longevity properties in asiatic countries [11]. The use of *G. lucidum* has also been described in documents on the treatment of cancer in ancient Egypt [12].

According to Liu [13] in traditional chinese medicine, *G. lucidum* was considered for thousands of years, a nostrum. This author claims that *Ganoderma* aqueous extract has a sedative effect on the central nervous system, improves cardiocerebral circulation, lowers hyperlipidemia, modulates immune system functions, combats weakness, antiaging and antitumor properties. Clinically, according to these authors, *G. lucidum* can be used as food or medicine, in the form of granules, capsules and tablets. For several decades in Chinese medicine, the blend of natural products “Fuzheng Guben”, with *Ganoderma lucidum* as one of the main components, has been used as preventive therapy or adjuvant for cancer [14]. Traditionally in India, *G. lucidum* has also been widely used for the treatment of hepatopathy, chronic hepatitis, nephritis, hypertension, arthritis, insomnia, bronchitis, asthma and gastric ulcer. Scientific studies have confirmed that the substances extracted from this mushroom can reduce blood pressure, cholesterol, plasma sugar levels and inhibit platelet aggregation [15,16,17]

Oyetayo [18] reported that in the last four decades, researchers in Nigeria are collecting information on the medicinal uses of mushrooms in that country where the use of mushrooms varies from one ethnic group to another. Ethnomicological uses of edible and medicinal species for the treatment of arthritis and neoplasms by the Yoruba peoples of South-West Nigeria, Ibos in the Southeast and by Igalas in central-northern Nigeria are well evidenced [19] also found that this mushroom can be used in treatment prostate hyperplasia.

Among the products commercially available are: (1) Hydro-alcohol extract (hot aqueous extraction and subsequent alcoholic extraction) [20,21,22]; 2 (Dry extract capsules: 360 mg (equals 13.2 g of fresh mushrooms and 1.44 g of dried mushroom) [23,24], 250 mg (70% dry extract and 20% spores, with 10% polysaccharides) [25] ou 500 mg (1.89% terpenoids and 15.8% polysaccharides) [26,27]; (3) Dried extract tablet (0.075 mg, 0.75 mg, 3 mg e 7.5 mg of extract) [28,29]; (4) spore powder ( capsules of 100 0 mg) [30].

The posology and frequency vary according to the type of pathology: (1) Adjuvant in the treatment of cancer: capsules containing 600 mg (9 g of dried mushroom), dose: 1 capsule 3 times daily for 12 weeks [20,21]; (2) Treatment of diabetes: capsule containing 360 mg (13.2 g of dried mushroom), dose: 1 capsule twice daily for 12 weeks[23]; (3) Treatment of symptoms of the lower urinary tract: tablets containing 0.75 to 3 mg extract, dose: 1-2 tablets once daily for 4-12 weeks [31,29]. For all treatments, the period of use is from 04 to 06 months [20,21,23,28,31].

No studies on contraindications, particularly with children, pregnant and breastfeeding women and elderly people were found in the literature. On the other hand, two case reports
about exposure to *G. lucidum* related to some and/or toxic effects were found. One of the studies described the hepatotoxicity of *G. lucidum*; however, the authors attribute this toxicity to the preparation of medicinal products based on the mixing of several Chinese plants [32]. In the other study, bullous vesicle was reported in the hands of the patient exposed to *G. lucidum*. However, the patient was also exposed to other agents concomitantly [33].

Concerning the mushroom-drug interaction, Poppenga [34] reported drug interactions of *G. lucidum* with acyclovir, anticoagulants, antihypertensives, antibiotics, cefazolin, immunosuppressants, insulin, oral hypoglycemic agents and interferon. Overdosage information was not found in the literature.

Considering package and store, the mushroom extract should be preserved in tightly closed containers, protected from light, and store at room temperature. The label should also indicate the part of the mushroom that was used to prepare the extract.

**Chemical constituents**

There are numerous bioactive molecules in *G. lucidum*, such as glycoproteins, sterols, steroids, proteins, peptides, C2 ganodermic acid, ganodermic acid B, ganodermic acid AM1, ganodermic acid K, ganodermal acid H [35,36,37], triterpenoids and Polysaccharides [9]. The mushroom must contain, at room temperature, 0.3% terpenoid acids calculated on the dry basis. Lanthans are the main group of tetracyclic triterpenoid derivatives of lanosterol present in *G. lucidum* [35,38]. Rios et al. [39] compiled the organometallic complexes of lanthanides. Lanthanides are elements of the most relevant periodic table isolated from *G. lucidum* and studied between 2000 and 2011, indicating 81 isolated compounds. This mushroom also has essential elements such as copper, zinc, manganese, magnesium, phosphorus, sulfur, potassium, and selenium [40,41].

**Quality control of main derivatives**

The analysis of fruiting bodies of *G. lucidum* cultures, from various sources for medicinal use, by the identification and quantification of ganodermic, nucleoside and nucleobase acids can be used to differentiate the various species of this mushroom [42,43,44,45,46]. The *G. lucidum* derivatives are described in the “Herbal Medicines Compendium” that are 50 monographic records about fruiting body of *G. lucidum* powder and dry extract, broken spores and mycelium [47]. The dry alcholic extract can be observed for the presence of ganoderenic acid C, ganodermic acid C2, ganoderenic acid B, ganodermic acid B, ganodermic acid A, ganodermic acid H, ganoderenic acid D, ganodermic acid D, ganodermic acid F, ganodermic acid G (Rejection: less than 0.3% of each acid in calculation of dry basis) and polysaccharides (Acceptance criterion: above 0.7% of each monosaccharide on a dry basis). In broken
spores is possible observe the presence of polysaccharides, polysaccharide-peptide complex, β-glucans, lectins, organic germanium, adenosine, triterpenoids and combined nucleotides.

**Pharmacological reports**

The popular indication of *G. lucidum* for the treatment of cancer reflects in the high number of studies found in the literature about antitumor and immunomodulatory activities. For the pharmacological studies, the fruiting body, spores or mycelium were used in distinct extraction preparations such as water, ethanol, methanol and petroleum ether. In some studies, commercial products (Pharmanex, Reishimax) have been used. Pharmacological reports were divided into two sections: *in vitro* and *in vivo* assays.

**In vitro assay**

*In vitro* assays *Ganoderma lucidum* extracts were used for evaluation of antitumor, immunomodulatory, antioxidant, and other activities.

**Studies on Anti-tumoral cells**

Non-Hodgkin lymphoma cells (NK92) [48,49] human colon cells (Colon-205), prostate cancer cell (LNCaP) [50], prostate (DU-145 and PC-3), lung cells (A-549), ovary cells (IGROV-1), neuroblastoma cells (IMR-32), breast cells (MCF-7) and promyelocytic leukemia cells (HL-60) [51,52], human breast cancer cells (MCF-7: estrogen dependent breast cancer cell and MDA-MB-231: estrogen independent breast cancer cell) [53,54,55,56,57], gastric carcinoma cells (AGS) [58,59,60], human colon adenocarcinoma cells (SW620), leukaemic cells (K562), leukaemic murine cells line (L12110) [51], premalignant urothelial cells (HUCPC) [61,62], epithelial ovarian cells (IOSE-398, EOC, OV2008, C13*, A2780s e 2780-cp, NIH:OVCAR-3) [63,64], human cervical cancer cells (HeLa) [65], cells DA-1 [66], promyelocytic leukemia cells (NB4) [67] e (HL-60) [68,49,69], neuroblastoma cells (SH-SY5Y) [70] multi-drug-resistant leukemic cells line (K562 e K562/ADM) [71] human hepatoma cells (Hep3B) [58] murine skin carcinoma cells (CH72) [72], tumor cells (HT-29) [73]. These studies refer to cytotoxicity, growth inhibition, cell migration, apoptosis, evaluation of macrophages and lymphocytes, dosage, receptors on target cells. Some studies propose IC$_{50}$ values for the different tumor cells lines. In all articles the authors report in vitro antitumor activity [74]. In a review article, the effects of *G. lucidum* on tumor cell invasion and metastasis, conclude that these effects occur through the modulation of extracellular signal-regulated phosphorylation of kinase (ERK1/2), phosphatidylinositol 3-kinase (PI 3 Kinase) or Akt kinase (protein kinase
B). These authors claim, in these models with multiple cell lines, that *G. lucidum* may be an effective nutraceutical for prevention of metastases.

**Immunomodulatory activity.**

Immunological activity assays were used: tumor cells[75,76], cells of primary cultures of mice [77,78,79,80,81,82] human macrophages and neutrophils [80,83,84]. The biological markers evaluated were cytokines, mRNA, interleukins, evaluation of cell proliferation. All studies indicated the positive effects of *G. lucidum* extracts on immunomodulation.

**Antioxidant activity.**

Human plasma, enzymes, epitelial, tumor cells and lymphocytes were used as models of antioxidant activity [85,86,87,88,89,90,91,92]. All studies indicated the antioxidant activity of *G. lucidum*.

**Other Activities.**

Neuronal cell protection was observed, indicating possible use of the extract in the treatment of neurodegenerative diseases [93,94,95]; antimicrobial and antifungal activity [96,97]; indication of MIC (minimal inhibitory concentration) for fungal and bactérias [97]. Control over adipocyte differentiation [98,99] and anti-androgenic activity [99]. *In vitro* assays have also indicated that the extracts of the body and the mycelia of *G. lucidum* showed an antimutagenic activity [58,100].

**In vivo assay**

The most commonly used route for administration was the oral route, however the doses used were quite varied. Only two articles of preclinical pharmacokinetics with extracts were found in the researched literature; one identified the presence of terpenoids in the bile [101] and the other defined the curve “dose x plasma concentration” for these compounds evaluation of a [102]. Although most of the studies show models for antitumoral and immunomodulatory activities, other pharmacological actions are also described in the literature, as follows:

**Antitumoral activity and protective effects on the idiosyncrasies of antitumor treatments.**

The models used: breast tumors (tumor induction by IB cell inoculation, SUM-19 cells, or DMBA-7,12-dimethyl benzanthracene) [103,104]. Lung tumors (tumor induction by the inoculation of LLC-1 cells, S180 sarcoma cells, or BHP-N-nitrosobis (2-hydroxypropyl) amine agent
[105,106,107,108]; Leukemia (induction by WEHI-3 cell inoculation) [109]. In all these articles, the antitumor activity was evidenced. Grant e Ramasamy [110] described that *G. lucidum* has testosterone inhibition activity, reducing the malignancy of prostate cancer. On the other hand, studies showed protection effects of *G. lucidum* extracts in idiosyncrasies induced by antitumor agents such as azoxymethane, methotrexate, 5-FU (5-fluroacyl), UFT (Tegafur-uracil), CDDP (cisplatin), CPA ) and IRESSA [111,112,113] and the effect of radioprotection [114]. Haniadka et al. [115] in their review article on natural products with anti-emetic properties as adjuvants in the treatment of cancer, considered *G. lucidum* a promising agent for this purpose.

**Immunoregulator activity**

Immunomodulatory activity was assessed by quantification of cytokines, NK cells and autoimmune pathologies, such as salivary gland activity [116,117,118,119]. In all the studies, authors reported that extracts of *G. lucidum* have immunoregulatory activity.

**Hepatoprotective effect**

In the various models found, induction of hepatotoxicity was performed by CCl4, benzoyprene or CdCl2; And the biological markers evaluated were ALT, AST, ALP, albumin and albumin globuline, evaluation of malondialdehyde (MDA) and hydroxyproline enzymes. Reduced glutathione - GSH, glutathione peroxidase - GPX, glutathione s-transferase - GST, superoxide desmutase - SOD, and catalase - CAT, in addition to spleen and liver weight [120,121,100,122,123]. In all studies hepatoprotective effect was reported.

**Hypoglycemic activity**

The models used were streptozotocin-induced diabetes mellitus (STZ) *Ganoderma lucidum* promoted the synthesis of glycogen and inhibited gluconeogenesis [124]. Repairing the induced lesions in β-pancreatic cells, promoting an increase in insulin synthesis and a decrease in plasma glucose levels [125,126,127,128]. Comparative studies of the efficacy of metformin, rosiglitazone and glibenclamide in rats and mice with DM-STZ show that *Ganoderma lucidum* was more effective than the drugs, promoting the increase of insulin receptor levels in the beta subunit in Skeletal muscles, reduction of glycated hemoglobin, reduction of triglyceride levels, total cholesterol and low-density proteins, and promoted the increase of high density lipoprotein levels [129,130,131,132,133]. *Ganoderma lucidum* also promoted reduction of oxidative injury and inhibition of apoptosis [130].
Antioxidant activity

The assays with the extract indicated that it has antioxidant activity when compared to the protective effect with DL-\(\alpha\)-lipoic acid and also show a protective effect when exposed to alcohol [134,135,136,137].

Other activities.

Activities on degenerative neuropathies were observed, indicating neuronal protection effect [138,62,139]; protection in allergic processes [140,141] effectiveness in treating malaria when compared to chloroquine [142]; anti-inflammatory activity in the induction of colitis by the sulfonic acid trinitrobenzene [143] superior cardioprotection compared to \(\alpha\)-tocopherol [144]; anti-influenza activity [145]; protection against retinopathy induced by n-methyl n-nitrosourea [146] hypnotic effect [147] reduction of LDL [148].

**CONCLUSION**

*Ganoderma lucidium* is known by variable names in different countries. Its use in several diseases emphasize its therapeutic properties, which are associated with different molecules and constituents acting concomitantly and synergistically. Commercially diverse pharmaceutical presentations are employed, with varying dosages. However, the safety of their use in pregnancy, lactation and children are still poorly reported. Its pharmacological properties are attributed to different parts of its structure including fruiting body, spores or mycelia, used in different extraction preparations. Much is already known about its pharmacological properties and action in different organs and systems; however, there is pressing need to study its a safe and rational use in therapeutics.

**ACKNOWLEDGMENT**

The authors are grateful for financial support from Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP- 2015/24566-9) and the Programa de Suporte à Pós-Graduação de Instituições de Ensino Particulares (PROSUP/CAPES) and the Post Graduate Program in Pharmaceuticals Sciences from University of Sorocaba, Sorocaba, SP, Brazil.

**COMPLIANCE WITH ETHICAL STANDARDS**

Conflicts of interest Authors indicate that there is no conflict of interest.
REFERENCES


