VOLUME 9 ISSUE 2 2023

ISSN 2454 – 3055

INTERNATIONAL JOURNAL OF ZOOLOGICAL INVESTIGATIONS

Forum for Biological and Environmental Sciences

Published by Saran Publications, India

International Journal of Zoological Investigations Vol. 9, No. 2, 524-533 (2023)

International Journal of Zoological Investigations

Contents available at Journals Home Page: www.ijzi.net

Editor-in-Chief: Prof. Ajai Kumar Srivastav

Published by: Saran Publications, Gorakhpur, India

ISSN: 2454-3055

Anti-Cancer Properties of *Ganoderma lucidum*'s Active Constituents and Pathways

Sharma Kaushal, Srivastav Alok Kumar* and Das Priyanka

Department of Health Science, University of the People, Pasadena, CA 91101, United States

**Corresponding Author*

Received: 18th June, 2023; **Accepted:** 25th July, 2023; **Published online:** 7th September, 2023

https://doi.org/10.33745/ijzi.2023.v09i02.060

Abstract: *Ganoderma lucidum*, also known as Lingzhi, has been utilized in Asia to promote health for centuries. In both *in vitro* and *in vivo* investigations, *G. lucidum's* anticancer properties have been demonstrated. In addition, the anti-cancer effects of *Ganoderma* have led to its use alongside chemotherapy by cancer patients. Triterpenes and polysaccharides constitute the two most important bioactive components of *G. lucidum.* Although triterpenes and polysaccharides are well-known as the primary active constituents, the biological pathways through which they exert their anti-cancer effect remain inadequately defined. Therefore, comprehending the mechanisms of action may contribute to a more widespread use of *Ganoderma* as an anticancer agent.

This study aims to summarize the numerous bioactive mechanisms that have been postulated for the anti-cancer properties of triterpenes and polysaccharides extracted from *G. lucidum.* The terms "Ganoderma" and "cancer" were used to perform a literature search of published papers on NCBI. Studies examining the anticancer effects of *Ganoderma* triterpenes and polysaccharides were chosen for inclusion in this review article.

Ganoderma triterpenes are associated with five potential anti-cancer mechanisms, while Ganoderma polysaccharides are associated with three potential anti-cancer mechanisms. In addition, *G. lucidum* has been combined with established anti-cancer agents to enhance their anti-cancer efficacy. This indicates that Ganoderma bioactive pathways may complement anti-cancer agents. In this study, we describe several potential anti-cancer mechanisms of Ganoderma triterpenes and polysaccharides that can be used to develop *Ganoderma* as an anti-cancer agent.

Keywords: *Ganoderma lucidum*, Cancer, Bioactive pathways, Triterpene, Polysaccharide

Citation: Sharma Kaushal, Srivastav Alok Kumar and Das Priyanka: Anti-cancer properties of *Ganoderma lucidum*'s active constituents and pathways. Intern. J. Zool. Invest. 9(2): 524-533, 2023.

https://doi.org/10.33745/ijzi.2023.v09i02.060

Introduction

Ganoderma lucidum (*G. lucidum*), also known as Lingzhi, is a fungus that has been extensively used for centuries in Asian countries to promote overall health and longevity. Numerous pharmacological

effects, such as immunemodulating, anti-inflammatory, anti-cancer, anti-diabetic, anti-oxidative and radical-scavenging, and anti-aging, have been attributed to it (Srivastav *et al.,* 2014). .

The majority of mushrooms are composed of 90 per cent water by weight. The remaining 10% of *G. lucidum* is made up of 26–28% carbohydrates, 3–5% crude fat, 59% crude fibre, and 7–8% crude protein. In addition, *G. lucidum* contains numerous bioactive compounds, including terpenoids, steroids, phenols, glycol-proteins, and polysaccharides. Triterpenes and polysaccharides are the main physiologically active components of *G. lucidum*.

In this review, we focused on the numerous bioactive pathways believed to be associated with the anti-cancer properties of *G. lucidum*, specifically the two major active ingredients: triterpenes and polysaccharides.

TRITERPENES:

Triterpenes are among the putative pharmaceutically active compounds that contribute to *G. lucidum's* medicinal properties. Triterpenes are a subtype of Terpenes, a class of organic compounds composed of one or more isoprene units. Terpenes are prevalent throughout the plant kingdom. Numerous subtypes of Terpenes have anti-inflammatory, anti-tumorigenic, and hypolipidemic properties. Triterpenes comprise six isoprene units. The isoprenes may form either linear chains or ring-like structures (Srivastav *et al.*, 2015). Ganoderic acid is a subclass of triterpenes that contains four cyclic and two linear isoprenes. More than 140 species of triterpenes and triterpenoids have been identified in *G. lucidum.*

Triterpenes are predominantly isolated from the spores of *G. lucidum* and have demonstrated extraordinary pharmacological and therapeutic activities against a variety of human maladies, including cancer. Triterpenes are typically extracted using methanol, ethanol, acetone, chloroform, ether, or a combination of these solvents.

Numerous subtypes of *G. lucidum* triterpene extracts have been shown to directly induce apoptosis in multiple human cancer cell lines. The cytotoxic effect of various subtypes of triterpenes varied considerably. Several subspecies of triterpenes have demonstrated potent cytotoxic effects at modest concentrations in diverse human cancer cell lines

Ganoderic acid T is the most abundant triterpenic acid found in *G. lucidum*, and it demonstrates significant anti-cancer effects in both *in vitro* and *in vivo* investigations. Ganoderic acid T inhibits tumour invasion by inhibiting Matrix Metalloproteinase (MMP)-9 expressions (Chen *et al.*, 2010). Yue *et al.* (2018) demonstrated that ganoderic acid D binds directly to 14-3-3 protein and this binding may contribute to the apoptosis observed in HeLa cells. Ganoderiol F (GA-F) is a tetracyclic triterpene that is discovered in Ganoderma species. GA-F has demonstrated cytotoxicity *in vitro* against cell lines derived from Lewis lung carcinoma (LLC), Meth-A, Sarcoma-180, and T-47D. In rodents implanted with LLC tumour cells, GA-F's antitumor activity has also been demonstrated *in vivo*. Additional triterpenes isolated from *G. lucidum* have demonstrated cytotoxicity in p388, HeLa, BEL-7402, and SGC-7902 human cancer cell lines.

Cell Cycle Arrest:

A deregulated cell cycle leads to uncontrolled cell proliferation in cancer cells. Anti-cancer compounds can halt the cell cycle in the G0/G1, S, or G2/M phases, thereby reducing the rate of proliferation (Das *et al.*, 2021). Triterpene extracts from *G. lucidum* have been shown to arrest the cell cycle at the G1 phase. ß-catenin pathway modulation is the probable mechanism of action for cell cycle inhibition at the G1 phase. Cyclin D1 is a regulator of Cyclin Dependent Kinase (CDK), which is essential for cell cycle G1/S transition. The promoter of Cyclin D1 contains transcription factor (TCF)/Lef-binding sites that can be activated by ß-catenin/Lef-1/TCF. As a consequence of abnormal ß-catenin signalling, approximately 30% of colon carcinoma cells

exhibit an over expression of Cyclin D1. Ganodermanontriol, a triterpene extract of *G. lucidum*, inhibits the proliferation of HCT116 and HT-29 colon cancer cells by inhibiting the expression of ß-catenin.

In addition to arresting the cell cycle in the G1 phase, triterpene extracts can also inhibit the G2/M transition. Triterpene-enriched ethanol soluble fractions (WEES-G6) can inhibit protein kinase C (PKC) activity, resulting in a protracted G2 phase. PKC is a class of serine-threonine protein kinases that are activated selectively during the G2 phase of the cell cycle. PKC is involved in regulating the degradation of nuclear lamina during the G2 phase. According to studies, the use of PKC inhibitors can also result in cell cycle arrest at the G2 phase. WEES-G6 can also decrease the level of Cyclin B, a kinase that is essential for the transition from G2 to M phase. WEES-G6 also activates c-Jun N-terminal kinase (JNK) and p38 kinase, which are both stress-responsive mitogen-activated protein kinases (MAPK). JNK is an essential transcription regulator that can activate tumour suppressors such as p53. To further support the use of triterpenes as a therapeutic anti-cancer agent, Johnson and Lapadat (2012) observed cell cycle arrest in triterpene-treated HuH-7 human hepatocellular carcinoma cells, but no effect in normal human liver cell lines. Li *et al.* (2015) identified inhibition of DNA synthesis via inhibition of topoisomerase as the probable cause of Ganoderic acid X- induced cell cycle arrest in an attempt to determine the cause of the triterpene-induced G2 phase cell cycle arrest.

Cytotoxicity:

Cytotoxic substances can directly induce apoptosis, resulting in programmed cell death. Triterpenes induce apoptosis in human cancer cell lines through a mitochondria-dependent pathway, followed by caspase cascade activation.

The intrinsic apoptotic pathway, also known as the mitochondria-dependent apoptotic pathway, entails the decrease of mitochondrial potential, followed by the release of cytochrome c from mitochondria. The release of cytochrome c into the cytosol initiates the caspase cascade, which ultimately leads to apoptosis. Human cancer cells treated with *G. lucidum* triterpenes exhibit increased expression of caspase 9 and caspase 3.

The release of cytochrome c from mitochondria is dependent on the permeability of the mitochondrial outer membrane, which is tightly regulated by proteins from the B-cell lymphoma 2 (Bcl-2) family. Pro-apoptotic or anti-apoptotic proteins can be found in the Bcl-2 family. Bcl-2 is anti-apoptotic, whereas Bax and Bad are pro-apoptotic. The ratio of Bax/Bcl-2 equilibrium determines the release of cytochrome c in response to an apoptotic stimulus. Increasing the ratio of Bax to Bcl-2 facilitates apoptosis. Studies have demonstrated that *G. lucidum* triterpenes increase the ratio of Bax/Bcl-2 in human cancer cells by increasing Bax expression and decreasing Bcl-2 expression. However, various triterpene subtypes have distinct impacts on Bax and Bcl-2. According to a study by Tang *et al.* (2006), Ganoderic acid T treatment up-regulates Bax expression while Bcl-2 expression remains unchanged.

The 14-3-3 proteins are a family of conserved regulatory proteins that regulate protein kinase signalling cascades. They are involved in a variety of cellular processes, including cell cycle progression and apoptosis. Protein Bad is a target of 14-3-3 protein. Bad-induced cell death is prevented by the binding of 14-3-3 to Bad. Ganoderic acids have been shown to bind directly to 14-3-3 protein, thereby inhibiting its activity.

Reduced Metastatic Potential:

Cancer metastasis is a complex process in which cancer cells divide from the primary tumour, invade surrounding tissues, and create secondary tumors. When left untreated, cancer metastasis drastically reduces the likelihood of survival and cure. *G. lucidum* triterpenes may modulate a

number of crucial proteins implicated in cancer metastasis.

Matrix Metalloproteinase is a protein family that degrades the extracellular matrix and promotes cancer metastasis. Ganoderic acid extracted from *G. lucidum* was found to inhibit the expression of MMP-9, thereby inhibiting the invasion of 95-D, LLC, and HCT-116 metastatic cancer cells.

Interleukin (IL)-8 and other angiogenic factors, including vascular endothelial growth factor (VEGF), can induce angiogenesis and promote metastasis. Oxidative stress can increase IL-8 expression, and IL-8 over expression is linked to the metastatic phenotype of breast cancer cells. After treatment with *G. lucidum*, oxidative stress-induced IL-8 expression in a breast cancer cell line was reduced.

Anti-Inflammation:

Approximately 20% of malignancies have been attributed to inflammation as a causal factor. Chronic over expression of pro-inflammatory cytokines, including VEGF, IL-6, and tumour necrosis factor (TNF)-α, can promote carcinogenesis. According to Dudhgaonkar *et al.* (2019), administration of *G. lucidum* triterpene extract inhibited inflammatory cytokine secretion in macrophage cells, thereby reducing the level of inflammation.

Anti-Oxidant:

It is well known that oxidative stress is a significant contributor to an increased risk of cancer. Free radicals and reactive oxygen species (ROS) are byproducts of metabolic processes involving redox enzymes and bioenergetics electron transfer, as well as exposure to certain exogenous compounds (Srivastav *et al.*, 2023). Antioxidant enzymes and repair mechanisms can mitigate oxidative stress caused by free radicals and reactive oxygen species. Nonetheless, excessive oxidative stress can overwhelm the body's natural defence mechanisms, resulting in a variety of physiological disorders, including cancer. Compared to normal cells, cancer cells produce a greater number of free radicals, which contributes to the progression of the disease. Anti-oxidants may be able to prevent or reduce cancer-causing oxidative damage (Srivastav *et al*., 2019). Antioxidants may mediate their effect by directly reacting with reactive oxygen species, scavenging them, or chelating the catalytic metal ions.

Smina *et al.* (2011) demonstrated that triterpenes extracted from *G. lucidum* have anti-oxidative properties *in vitro* and can reduce oxidative damage by directly scavenging cell-derived free radicals. Moreover, administration of triterpenes to mice increased the activity of anti-oxidant enzymes and decreased radiation-induced oxidative DNA damage in mice splenocytes. Triterpenes are a highly effective anti-oxidant due to their ability to scavenge free radicals and enhance inherent anti-oxidant enzymes (Srivastav *et al*., 2021).

POLYSACCHARIDES:

Polysaccharides consist of extended chains of sugar molecules held together by glycosidic bonds. Various kinds of polysaccharides with molecular weights spanning from 4×10^5 to 1×10^6 Da have been identified in *G. lucidum*; the majority have been identified in the fruiting body and mycelia, while a few have been identified in the spores.

All *G. lucidum* polysaccharides are heteropolymers, according to structural analysis. Glucose constitutes the majority of sugar molecules, with xylose, mannose, galactose, and fucose exhibiting different conformations. It is hypothesized that polysaccharides extracted from various portions of *G. lucidum* induce distinct immune responses with diverse immune potency. The anti-tumorigenic properties of these polysaccharides are influenced by the branching conformation and solubility characteristics. *G. lucidum* -D-glucans containing (1-3)-, (1-4)-, and (1-6)-β-D linkages are known to have a higher antitumor activity and greater assimilation compared to other polysaccharides.

In addition to a high concentration of polysaccharides with a high molecular weight,

mushrooms contain a matrix of the polysaccharide chitin, which is largely indigestible and partially responsible for the mushroom's physical rigidity.

Improve Immune Response:

In contrast to triterpenes, numerous studies have demonstrated that polysaccharides exert their anti-cancer effect by enhancing the host's immune system, as opposed to through a direct cytotoxic impact. This entails the activation of macrophages, natural killer (NK) cells, and cytotoxic T-lymphocytes (CTL) along with their secretory products, such as TNF, reactive nitrogen and oxygen intermediates, and interleukins. Wang *et al.* (2002) demonstrated that polysaccharides extracted from the fresh fruiting bodies of *G. lucidum* stimulate the production of IL-1β, IL-6, TNF-α, and interferon-γ (IFN-γ) in human monocyte-macrophages and T-lymphocytes.

It is well known that macrophages play a significant role in numerous primary defence mechanisms via phagocytosis and the secretion of immune cytokines in response to microenvironmental signals. The immune-modulating substance of *G. lucidum* (a proteoglycan isolated from the fruiting body of *G. lucidum*) activates macrophages derived from bone marrow in a dose-dependent manner. The phagocytosis activity and production of IL-1β and nitric oxide of these activated macrophages increased significantly.

All cell surfaces express the Major Histocompatibility Complex (MHC) protein. Antigen presentation is the process by which MHC displays a molecular fraction of proteins that are synthesised within the cell. Antigen presentation by immune cells leads to CTL-mediated apoptosis when cancer cells with anomalous proteins or altered protein expression levels are detected. To avoid CTL-mediated apoptosis, cancer cells may down regulate MHC expression. NK cells can detect and elicit apoptosis in cancer cells expressing minimal levels of MHC.

Fraction-3 (F3), a fucose-containing glycoprotein extracted from *G. lucidum*, stimulated the proliferation of murine spleen cells and the expression of numerous cytokines, such as IL-1, IL-2, and IFN-γ. Chien *et al.* (2004) found that F3 treatment of human umbilical cord blood-derived mononuclear cells stimulated their differentiation into macrophages and NK cells by 2.9 and 1.5 times, respectively. Another study revealed that F3 treatment of THP-1 human acute monocytic leukaemia cells enhanced macrophage differentiation by activating caspases and p53. Changes in cell adherence, cell cycle arrest, an increase in the expression of differentiation markers, and a downregulation of myeloperoxidase (MPO) were indicators of this differentiation. Only myeloid and monocytic cells produce the enzyme MPO, and macrophage differentiation is characterized by the downregulation of MPO activity.

By modulating cytokine production, these results demonstrated that polysaccharides derived from *G. lucidum* can efficiently enhance cellular immune activity *in vitro* and *in vivo*.

Anti-Oxidative Activity:

Lu *et al.* (2001) demonstrated that dietary treatment with a Ganoderma mycelium-derived polysaccharide extract inhibits the formation of colonic aberrant crypt foci in rats, presumably by reducing the oxidative damage induced by ROS. In addition, the 'G009' amino-polysaccharide fraction of *G. lucidum* inactivates hydroxyl radicals and superoxide anions and dose-dependently reduces DNA strand breaks. This study demonstrated that G009 inhibited iron-induced lipid peroxidation in rat brain homogenates and inactivated hydroxyl radicals and superoxide anions in a dose-dependent manner. In differentiated HL-60 (human promyelocytic leukaemia) cells, it also decreased DNA strand disruption caused by UV-induced photolysis.

Suppression of Angiogenesis:

Angiogenesis is a physiological process that involves the formation of new blood vessels from existing blood vessels. The normal regulation of angiogenesis is governed by a delicate equilibrium

between factors that stimulate the formation of blood vessels and those that inhibit this process. An imbalance in this equilibrium results in pathological angiogenesis. Tumour cells are known to induce angiogenesis by secreting various growth factors, such as VEGF, which induce capillary growth into the tumour, supplying it with necessary nutrients and allowing for tumour growth and metastasis.

Studies have demonstrated that *G. lucidum* has anti-angiogenic properties and can also inhibit the production of nitric oxide, an angiogenesis-inducing agent that is overexpressed in tumors. Cao *et al.* (2006) demonstrated that a polysaccharide peptide (G*l*-PP) isolated from *G. lucidum* inhibits the proliferation of human umbilical cord vascular endothelial cells (HUVEC) dose-dependently. A high dose of G*l*-PP administered to human lung carcinoma cells for 18 h under hypoxic conditions decreased the amount of secreted VEGF. G*l*-PP decreased Bcl-2 expression and increased Bax expression in HUVECs, which induces apoptosis in vascular endothelial cells. G*l*-PP may therefore inhibit angiogenesis by inhibiting the secretion of pro-angiogenic factors and the proliferation of vascular endothelial cells. It is plausible that the bioactive pathways underlying the cytotoxic effect and the inhibition of proliferation observed in polysaccharide and triterpene extracts are identical.

According to a study by Stanley *et al.* (2015), *G. lucidum* inhibits capillary morphogenesis, a crucial phase in angiogenesis linked to the development and progression of cancer. By inhibiting the secretion of the angiogenic factors VEGF and Transforming Growth Factor (TGF)-β1, *G. lucidum* significantly suppressed capillary morphogenesis. It has been demonstrated that *G. lucidum* inhibits prostate cancer angiogenesis by modulating MAPK and Protein Kinase B signalling and modifying the phosphorylation of extracellular signal-regulated kinases 1/2 and Akt kinases.

Extraction Methods:

G. lucidum's entire spores, fruiting bodies, and cultured mycelia, as well as its triterpenes and polysaccharides extracts, have undergone extensive testing for their antitumor properties. Various investigations have utilized various sources of *G. lucidum* and extraction methods to obtain the necessary components. The extraction procedure is required to purify the mushroom by removing extraneous components produced by the mushroom's natural growth, while preserving the essential bioactive components. Numerous methods of extraction have been devised in an effort to obtain extracts with higher yields and reduced costs.

In general, water-extract-alcohol precipitation procedures are used to extract the majority of polysaccharides. Solubility and extraction efficacy in water are dependent on the molecular weight of the polysaccharide and the temperature of the water, with lesser molecular weight and hotter water exhibiting greater efficiency (Srivastav *et al*., 2022). However, this method has a number of drawbacks, including low yields, a lengthy extraction period, and a high extraction temperature; as a result, new technologies are being developed to address these issues. Recently, novel technologies utilising ultrasonic, microwave, and enzymatic techniques have been devised to increase extraction yield in less time.

It has been documented that extracting triterpenes with ethanol is the simplest way to maintain their activity and scale up their production. Triterpenes are typically extracted using organic solvents like methanol, ethanol, chloroform, or ether, followed by a variety of separation techniques. Currently, ultrasonic techniques are used to increase the rate of triterpene extraction by disrupting the complex structure within the cells.

There are, however, a paucity of studies comparing the efficacy of the individual bioactive components extracted using various methods. However, Lu *et al.* (2004) examined the ethanol and water extracts from the fruiting bodies and spores of *G. lucidum* using the MTT (3-(4,

Table 1: Comparison of water and ethanol extracts from *G. lucidum* fruiting bodies and spores

***Ganoderma lucidum* Extract**	**Cell Line***	**24 h IC_{50} (µg/ml)**
Fruiting Body Ethanol Extract	HUC-PC	326
Fruiting Body Water Extract	HUC-PC	1000
Spore Ethanol Extract	HUC-PC	520
Spore Water Extract	HUC-PC	363
Fruiting Body Ethanol Extract	MTC-11	129.4
Fruiting Body Water Extract	MTC-11	510
Spore Ethanol Extract	MTC-11	275.7
Spore Water Extract	MTC-11	366.4

***HUC-PC:** human uroepithelial cell line; **MTC-11:** Low-grade bladder cancer cell line

5-dimethylthiazolyl-2) - 2, 5 -diphenyltetrazolium bromide) cell proliferation assay, and the IC_{50}s are listed in Table 1.

Tong *et al.* (2009) compared the cytotoxic activity induced by *G. lucidum* fruiting body extracts obtained via hot water and methanol extraction techniques. J_{558} (Balb/C murine Myeloma) cells exhibited a two-fold increase in cytotoxic activity as a result of methanol extraction, according to the results.

This indicates that the organic solvent has a greater cytotoxic effect on cancer cells than the water extraction method. The primary active ingredient extracted from organic solvent is triterpene, while the primary active ingredient extracted from water is polysaccharide (Das *et al.,* 2014). This indicates that triterpenes might be more cytotoxic than polysaccharides. However, comparative investigations with additional cell lines are required to confirm these findings (Das *et al.,* 2015).

Ganoderma lucidum in Combination with other Cancer Treatments:

Radiation therapy is frequently used in the treatment of cancer to disrupt the DNA of tumour cells, inhibit proliferation, and induce apoptosis (Das *et al*., 2019). Radiation therapy's primary adverse effect is DNA injury to the neighboring healthy tissues. Therefore, protecting non-cancerous tissues from radiation is essential for minimizing adverse effects.

Recent cytoprotective agents capable of protecting normal tissues from radiation injury have a number of undesirable and severe adverse effects that limit their therapeutic applications. It has been demonstrated; however, that *G. lucidum* has radio protective effects on normal cells and enhances the recovery of cellular immune competence following gamma–irradiation.

The mice were treated with gamma-irradiation to the entire body, followed by the administration of 400 mg/day/kg of *G. lucidum* (Chen *et al.* 2008). This was compared to radiation-treated mice alone as well as radiation-treated mice given Krestin, a polysaccharide isolated from the basidiomycetes of *Coriolus versicolor*. After 28 days, irradiated rodents treated with *G. lucidum* had the greatest relative thymus weight along with an increase in CD4 and CD8 splenocytes and leukocyte counts. This demonstrated that *G. lucidum* is more effective than *Coriolus versicolor* extracts at promoting the recovery of cellular immunocompetence following gamma–irradiation.

Another study by Pillai *et al.* (2016) demonstrated that *G. lucidum* prevents radiation-induced DNA damage. Radioprotective effects on Swiss albino mice exposed to gamma radiation and treated with *G. lucidum* fruiting body extracts

were evaluated. The results demonstrated that administration of *G. lucidum* extract protected plasmid DNA by 90% and prevented lipid peroxidation by 98%. We can conclude from this analysis that *G. lucidum* protects DNA from radiation-induced single-strand breaks and possesses significant radio-protective activity.

Cisplatin, the first clinical cancer chemotherapeutic agent pertaining to the class of anti-cancer medications containing platinum, is commonly used to treat a variety of malignancies. However, its benefits are nullified by renal impairment with a decline in glomerular filtration, a common cisplatin adverse effect. This nephrotoxicity has been attributed to a weakened anti-oxidant defence in the kidneys. Since it has been demonstrated that *G. lucidum* possesses anti-oxidant properties *in vitro*, a study was conducted to examine the prevention of cisplatin-induced nephrotoxicity. Mice of the Swiss albino strain were given fruiting-body extracts of *G. lucidum* (250 and 500 mg/kg body weight) orally one hour before receiving a high dose injection of cisplatin (a level commonly used in clinical settings and found to cause nephrotoxicity and cytotoxicity). Nephrotoxicity was measured by determining serum creatinine and urea levels and renal anti-oxidant status, and the results demonstrated a significant reduction in elevated serum creatinine and urea levels. Following treatment with cisplatin, renal anti-oxidant defence system (such as superoxide dismutase, catalase, glutathione peroxidase activities, and reduced glutathione) levels were restored to normal and cisplatin therapeutic effects were maintained.

These studies demonstrate that *G. lucidum* aides in the reduction of toxicities caused by popular cancer treatment methods and could therefore play a significant role in combination cancer therapy.

Conclusion

Ganoderma lucidum has been used for centuries for a variety of pharmacological benefits, including immuno-modulating, anti-inflammatory, anti-cancer, anti-diabetic, anti-oxidative, and radical-scavenging, and anti-aging effects. However, it has only been in the last two decades that scientific evidence has emerged to support some of these claims. *G. lucidum* derives its potency primarily from the triterpenes and polysaccharides that compose its fruiting body, mycelium, and spores. Multiple human and murine cancer cell lines have revealed its anti-cancer properties. However, the mechanisms underlying *G. lucidum's* anticancer effects on cancer cells remain unclear. This review identifies five putative anti-cancer mechanisms associated with triterpenes and three for polysaccharides.

Triterpenes have been shown to induce cell cycle arrest at the G_1 phase by inhibiting Cyclin D1 and at the G_2 phase by inhibiting PKC activity. Additionally, it induced apoptosis in cancer cell lines via mitochondria-dependent pathways followed by caspase cascade activation. Triterpenes also inhibited tumour metastasis by modulating MMP and IL-8 and by inhibiting the release of inflammatory cytokines by macrophage cells. Finally, it was discovered that triterpenes function as antioxidants by scavenging free radicals and boosting inherent anti-oxidant enzymes.

Polysaccharides have been shown to stimulate the production of macrophages, NK cells, and T-lymphocytes, thereby enhancing the immune response of the host. Similar to triterpenes, polysaccharides can act as an anti-oxidant by preventing ROS-induced oxidative damage and DNA strand breaks. In addition, it inhibits the proliferation of HUVEC and the secretion of angiogenic factors such as VEGF and TGF-β1 to prevent tumor-derived angiogenesis.

In conclusion, current data from *in vitro* and *in vivo* investigations suggest that *G. lucidum* may represent a feasible and promising approach for cancer prevention and cancer treatment. However, additional experimental, epidemiological, and clinical studies are required to identify other molecular targets; clarify the associations between *G. lucidum* consumption and cancer risks; and

determine the optimal dose, efficacy, and safety alone and in combination with chemotherapy/radiotherapy. In addition to its anticancer properties, *G. lucidum* has also been used to promote overall health and longevity. The anti-inflammatory and immune-stimulating effects described in this review may aid in the treatment of diseases such as arthritis, HIV, and Crohn's disease.

References

Cao QZ and Lin ZB. (2006) *Ganoderma lucidum* polysaccharides peptide inhibits the growth of vascular endothelial cell and the induction of VEGF in human lung cancer cell. Life Sci. 78(13): 1457-1463.

Chen NH, Liu JW and Zhong JJ. (2008) Ganoderic acid Me inhibits tumor invasion through down- regulating matrix metalloproteinases 2/9 gene expression. J Pharmacol Sci. 108(2): 212-216.

Chen NH, Liu JW and Zhong JJ. (2010) Ganoderic acid T inhibits tumor invasion *in vitro* and *in vivo* through inhibition of MMP expression. Pharmacol Rep. 62(1): 150-163.

Chien CA, Cheng JL, Chang WT, Tien MH, Tsao CM, Chang YH, Chang HY, Hsieh JF, Wong CH and Chen ST. (2004) Polysaccharides of *Ganoderma lucidum* alter cell immunophenotypic expression and enhance CD56(+) NK-cell cytotoxicity in cord blood. Bioorganic Med Chem. 12(21): 5603-5609.

Das P and Janahiraman V. (2019) Analytical study on heterocyclic anticancer compounds. Res Rev Int J Multidisciplinary 4(5): 172-175.

Das P and Srivastav AK. (2014) Phytochemical extraction and characterization of the leaves of *Andrographis paniculata* for its anti-bacterial, anti-oxidant, anti-pyretic and anti-diabetic activity. Int J Innov Res Sci Engineer Technol. 3(8): 15176-15184.

Das P and Srivastav AK. (2015) Phytochemical extraction and characterization of the leaves of *Aloe vera barbadensis* for its anti-bacterial and anti-oxidant activity. Int J Sci Res. 4(6): 658-661.

Das P and Srivastav AK. (2021) A study on molecular targeted approaches to cancer therapy and the role of chalcones in chemoprevention. European J Molec Clin Med. 8(3): 3254-3267.

Dudhgaonkar S, Thyagarajan A and Sliva D. (2009) Suppression of the inflammatory response by triterpenes isolated from the mushroom *Ganoderma lucidum*. Int Immunopharmacol. 9(11): 1272-1280.

Johnson GL and Lapadat R. (2002) Mitogen-activated protein kinase pathways mediated by ERK, JNK, and p38 protein kinases. Science 298(5600): 1911-1912.

Li CH, Chen PY, Chang UM, Kan LS, Fang WH, Tsai KS and Lin SB. (2005) Ganoderic acid X, a lanostanoid triterpene, inhibits topoisomerases and induces apoptosis of cancer cells. Life Sci. 77(3): 252-265.

Lu HM, Uesaka T, Katoh O, Kyo E and Watanabe H. (2001) Prevention of the development of preneoplastic lesions, aberrant crypt foci, by a water-soluble extract from cultured medium of *Ganoderma lucidum* (Rei-shi) mycelia in male F344 rats. Oncol Rep. 8(6): 1341-1345.

Lu QY, Jin YS, Zhang QF, Zhang ZF, Heber D, Go VLW, Li FP and Rao JY. (2004) *Ganoderma lucidum* extracts inhibit growth and induce actin polymerization in bladder cancer cells *in vitro*. Cancer Lett. 216(1): 9-20.

Pillai TG, Savi VP, Maurya DK, Nair CKK and Janardhanan KK. (2006) Prevention of radiation- induced damages by aqueous extract of *Ganoderma lucidum* occurring in southern parts of India. Curr Sci. 91(3): 341-344.

Smina TP, De S, Devasagayam TP, Adhikari S and Janardhanan KK. (2011) *Ganoderma lucidum* total triterpenes prevent radiation-induced DNA damage and apoptosis in splenic lymphocytes in vitro. Mutat Res. 726(2): 188-194.

Srivastav AK and Das P. (2014) Phytochemical extraction and characterization of roots of *Withania somnifera* for its anti-bacterial, anti-oxidant, anti-inflammation and analgesic activity. Int J Innov Res Develop. 3(7): 22-33.

Srivastav AK and Das P. (2015) Phytochemical extraction and characterization of *Acorus calamus*, *Moringa oliefera*, *Cucurbita maxima*, *Hibiscus rosa sinensis* and *Chrysanthemum leucanthemum* for their anti-bacterial and anti-oxidant activity. Int J Pharmaceut Res Bio-Sci. 4(3): 356-377.

Srivastav AK and Janahiraman V. (2019) Microbial synthesis of hyaluronan and its biomedical applications. Int J Sci Res Rev. 8(5): 852-863.

Srivastav AK and Suriyakala PC. (2021) Chemical mutants enable the photoresponsive synthesis of hyaluronic acid from *Streptococcus equi.* Nat Volatiles Essent Oils 8(3): 371-381.

Srivastav AK and Suriyakala PC. (2022) Hyaluronic acid generated by *Streptococcus zooepidemicus* is recovered utilising PEG-citrate aqueous two phase systems. J Pharmaceut Negative Results 13(1): 100-108.

Srivastav AK and Suriyakala PC. (2023) Biotechnological production and purification of hyaluronic acid from

Streptococcus zooepidemicus. J Pharmaceut Negative Results 14(2): 78-83.

Stanley G, Harvey K, Slivova V, Jiang J and Sliva D. (2005) *Ganoderma lucidum* suppresses angiogenesis through the inhibition of secretion of VEGF and TGF-beta1 from prostate cancer cells. Biochem Biophys Res Communications 330(1): 46-52.

Tang W, Liu JW, Zhao WM, Wei DZ and Zhong JJ. (2006) Ganoderic acid T from *Ganoderma lucidum* mycelia induces mitochondria mediated apoptosis in lung cancer cells. Life Sci. 80(3): 205-211.

Tong CC, Choong YK, Umar NaB, Noordin MM and Mohamed S. (2009) Cytotoxic activity induced by crude extracts of *Ganoderma lucidum* (W. Curt.: Fr.) P. Karst. on mouse myeloma cancer cell-line. World J Microbiol Biotechnol. 25(4): 687-695.

Wang YY, Khoo KH, Chen ST, Lin CC, Wong CH and Lin CH. (2002) Studies on the immuno-modulating and antitumor activities of *Ganoderma lucidum* (Reishi) polysaccharides: Functional and proteomic analyses of a fucose-containing glycoprotein fraction responsible for the activities. Bioorganic Med Chem. 10(4): 1057-1062.

Yue QX, Cao ZW, Guan SH, Liu XH, Tao L, Wu WY, Li YX, Yang PY, Liu X and Guo DA. (2018) Proteomics characterization of the cytotoxicity mechanism of ganoderic acid D and computer-automated estimation of the possible drug target network. Mol Cell Proteomics 7(5): 949-961.