Ganoderma lucidum

Ganoderma lucidum is a potent immune system regulator, promising anti-cancer agent, and stress reducer. This mushroom is frequently used in traditional Chinese medicine.

Our evidence-based analysis features 227 unique references to scientific papers.

- History
-

Research analysis by Kamal Patel and verified by the Examine.com Research Team. Last updated on Jun 14, 2018.

Summary of Ganoderma lucidum

Primary Information, Benefits, Effects, and Important Facts

Ganoderma lucidum, commonly known as the lingzi mushroom, is frequently used in traditional Chinese medicine. Its popularity extends to Japanese and Korean medicine, and it has been making its way west.

Ganoderma lucidum has anti-oxidative effects when supplemented. It also has a therapeutic effect on insulin resistance, reduces the risk of prostate cancer, and can help treat a variety of conditions associated with metabolic syndrome.

The lingzi mushroom is well known for its anti-cancer effects. It is able to activate natural killer cells, increasing their activity and the body's ability to fight tumors. Supplementing *Ganoderma lucidum* reduces the chances of metastasis, which is when cancer spreads to another part of the body.

Ganoderma lucidum has a variety of mechanisms, but they are focused on moderating the immune system. The lingzi mushroom is able to reduce immune system activity when the system is overstimulated, and bolster the immune system when it is weakened. In general, *Ganoderma lucidum* increases the amount of active immune system cells.

Though further research is needed to confirm these effects, *Ganoderma lucidum* shows promise for a wide variety of cancer-related therapies. It has been shown to be an effective adjunct therapy, which means it improves health when taken alongside other medications, for breast cancer, hepatitis, fatigue syndrome, and prostate cancer. There are not many promising supplements with anti-cancer properties available over-the-counter but *Ganoderma lucidum* appears to be one of them.

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Things to Know

Also Known As

Reishi, Lingzhi, Yeongji, Mannamtake, 10, 000 years mushroom, Mushroom of Immortality, Antlered Reishi, Rokkaku-Reishi, Ganoderma spores

Things to Note

- Ganoderma has a large amount of bioactive molecules, and there is no single 'one' molecule in this mushroom that can be said to be the main bioactive
- Polysaccharide compounds (carbohydrates and fiber) tend to be found in the water-soluble fragment, or the hot-water extracts; triterpenoids are found in ethanolic extracts as they are fat soluble
- Polysaccharides, or water-soluble extracts, do not need to be taken with food; it would be prudent to take any ethanolic extract with food however
- Some effects, such as improving sleep and decreasing symptoms of chronic fatigue syndrome, are not acute; sleep improvements are seen after 3 days whereas aid in chronic fatigue may take more than 4 weeks

Is used for

- Allergies and Immunity

Also used for

- Antioxidant and Anti-inflammatory
- Mood

Is a form of

- Food or Food Product

Caution Notice

If you suffer from an autoimmune disease (a disease in which your own immune system causes dysfunction in the body) do **not** use Ganoderma Lucidum; increasing the potency of your immune system is a bad idea if your immune system is attacking you

Do not use Ganoderma Lucidum if on immunosuppressant therapy in accordance with an autoimmune disease, it is possible Ganoderma Lucidum could negate or hinder the immunosuppressant therapy

Talk to your MD or Chemotherapist if you decide you want to use Ganoderma Lucidum as an adjunct therapy

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How to Take

Recommended dosage, active amounts, other details

The standard dose of *Ganoderma lucidum* depends on the form of the supplement.

A general *Ganoderma lucidum* extract does not separate the triterpenoids and the polysaccharides present in the mushroom, which make up the ethanolic and water-soluble extracts, respectively. The standard dose for the basic extract is 1.44g – 5.2g. The most popular dose is 5.2g, taken in three doses of 1,800mg.

The standard dosage for the ethanolic extract is 6mg.

The water-soluble extract should be dosed similarly to the basic extract.

The basic extract is essentially dehydrated mushroom powder, which makes it about 10 times as potent as the actual mushroom. This means that 5g of extract is similar to about 50g of whole mushroom.

Human Effect Matrix

The **Human Effect Matrix** looks at human studies (it excludes animal and *in vitro* studies) to tell you what effects ganoderma lucidum has on your body, and how strong these effects are.

Grade	Level of Evidence
	Robust research conducted with repeated double-blind clinical trials
	Multiple studies where at least two are double-blind and placebo controlled
	Single double-blind study or multiple cohort studies
	Uncontrolled or observational studies only

Grade		Level of Evidence		
Level of Evidence ?	**Outcome**	**Magnitude of effect ?**	**Consistency of research results ?**	**Notes**
	Subjective Well-Being	Minor	**Very High** See all 3 studies	Subjective well being increases in disease states where other symptoms (seen as adverse) are decreased; an inherent increase of well being is uncertain.
	HDL-C	Notable	**Moderate** See 2 studies	There may be an increase in HDL-C in persons with hyperlipidemia that doesn't occur in otherwise healthy adults, but this is not certain due to lack of evidence. The degree of increase was fairly str... See more
	Anxiety	Minor	- See study	Some possible anti-anxiety effects secondary to reducing symptoms of cancer related fatigue
	CD3 Lymphocytes	Minor	- See study	Reishi appears to directly stimulate production of CD3+ T-cells at a dosage of 5,000mg of the water soluble polysaccharides in otherwise healthy athletes
	CD4 Lymphocytes	Minor	- See study	The decrease in the CD4:CD8 ratio seen with altitude training is attenuated with 2,500-5,000mg of the water soluble polysaccharides
	Colorectal Cancer	Minor	- See study	There appears to be a suppressive effect of reishi ingestion of colorectal adenocarcinomas with prolonged ingestion
	Depression	Minor	- See study	Depression as a symptom of cancer-related fatigue was reduced, may not hold inherent antidepressive effects
	Fatigue	Minor	**Very High** See 2 studies	A decrease in fatigue has been noted, but secondary to disease states characterized by fatigue. Usage of Reishi to reduce fatigue outright or to aid exercise is unexplored
	Immunity	Minor	- See all 4 studies	There appears to be proliferative effects on T-lymphocytes and natural killer cells and no significant

Grade			Level of Evidence	
				alteration in a CD4:CD8 lymphocytic ratio following ingestion of Ganoderma polysaccharides.
	Symptoms of Neurasthenia	Minor	- See study	Appears to slightly reduce the symptoms of neurasthenia, although this needs to be replicated
	Symptoms of the Lower Urinary Tract	Minor	**Very High** See 2 studies	Total symptoms scores (IPSS) appear to be decreased following ingestion of the ethanolic extract of reishi, although not to a remarkable degree (peak urine flow and residual urine seem unaffected)
	TNF-Alpha	Minor	**Very High** See 2 studies	A reduction in TNF-alpha levels have been noted in persons with elevated baseline TNF-alpha levels
	Triglycerides	Minor	**Moderate** See 2 studies	There may be a small decrease in triglycerides (8% or so) in unhealthy persons, but this has not been observed in otherwise healthy individuals
	Adrenaline	-	- See study	No significant influence on serum adrenaline
	Anti-Oxidant Enzyme Profile	-	**Very High** See 2 studies	No significant influences on superoxide dismutase or glutathione peroxidase are noted with ganoderma polysaccharide ingestion
	Blood Flow	-	- See study	No significant influence on blood flow noted with reishi ingestion
	Blood Pressure	-	- See study	No significant influence on blood pressure noted with reishi
	C-Reactive Protein	-	- See study	No significant interactions with C-reactive protein have been detected
	DNA Damage	-	- See study	DNA damage in lymphocytes of volunteers given the polysaccharides appear unchanged
	Dopamine	-	- See study	No significant influence on serum dopamine
	General Oxidation	-	**Very High** See 2 studies	No significant alterations in whole-body oxidation are apparent
	LDL-C	-	- See study	No significant reducing effects on LDL cholesterol have been noted with ganoderma supplementation

Grade		Level of Evidence	
	Lipid Peroxidation	-	**Very High** See 2 studies	No significant changes in lipid peroxidation biomarkers (such as MDA) are present following ingestion of Reishi
	Liver Enzymes	-	- See study	No significant influence on liver enzymes has been noted in toxicological testing with ganoderma
	Prostate Hypertrophy	-	**Very High** See 2 studies	At an oral dose that can reduce symptoms of prostatic hyperplasia, there is no apparent effect on prostatic hypertrophy
	Prostate Specific Antigen	-	**Very High** See 2 studies	The ethanolic extract has failed to alter serum levels of PSA
	Testosterone	-	- See study	No significant influence on testosterone levels following ingestion of Reishi
	Total Cholesterol	-	- See study	No significant alterations in total cholesterol observed with reishi ingestion
	Uric Acid	-	- See study	No changes in serum uric acid seem apparent
	Weight	-	- See study	No significant alterations in body weight seen with ganoderma ingestion
	Natural Killer Cell Activity	Notable	- See study	Up to a 50% increase in NK cell activity relative to control has been noted with reishi, and this may be independent of a basic stimulatory action (which would lead into possible supplement combinations)
	Proteinuria	Minor	- See study	A decrease in urinary protein has been noted, indicative of kidney protective effects

Scientific Research

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1Sources and Composition

1.1. Sources

The mushroom *Ganoderma Lucidum* holds a place in a variety of Asian traditional medicine; it is most well known as Reishi, the name given to the mushroom by practitioners of Japanese medicine. In Traditional Chinese Medicine it is known as Lingzhi, and Korean medicine refers to it as Yeongji; in Taiwan it is sometimes referred to as *Ling-Chih*.[1] Other complimenting names given to Ganderma Lucidum include *The 10,000 year Mushroom* (Japanese), and the *Mushroom of Immortality* (Chinese).[2][3] The praise it receives is in part due to its bioactive effects, but may also be affected by the modes of distribution in the past (where, due to its rarity, only nobility or the privileged could afford it).[4][2] According to the year 2000 edition of the State Pharmacopoeia of the People's Republic of China (an official compendium of drugs), Ganoderma Lucidum "acts to replenish Qi, ease the mind, and relieve cough and asthma, and it is recommended for dizziness, insomnia, palpitation, and shortness of breath".[2]

Traditional usage of Ganoderma Lucidum extends to as anti-cancer and anti-tumor, anti-microbial, anti-fungal, and anti-viral (specifically against herpes and HIV), as well as anti-inflammatory or immunomodulatory. Pro-longevity claims have also been made.[2]

Traditionally known as the God of Fungi, although associations with nobility may have raised it to undeserved god-like status. Used for almost everything and said to work for everything; tends to be more focused on immunity, sickness, and cancer

1.2. Comparison of Lingzhi sources

In the Chinese Pharmacopoeia (v.2000) both Ganoderma *Lucidum* (Red Lingzhi) and *Sinensis* (Purple Zingzhi) are listed as *Lingzhi*[5][6] Despite both being referred to as *Lingzhi* in Chinese medicine, these two species have some shared and differing properties. The term *Ling Zhi* can extend to more mushrooms, and ancient Chinese texts (*ShenNong Ben Cao Jing* and from the Qui/Han Dynasty and *Ben Cao Gang Mu* from the Ming Dynasty, the latter of which is considered the first pharmacopoeia[7]) indicated up to 6 types of *Ling Zhi*. The possible other

Ganoderma mushrooms implicated here are *atrum*, *luteum*, *tsugae*, *tropicum*, *tenue*, *applantum*, *asutrale*, and *capense*; all other 250+ strains of Ganoderma known worldwide currently were not known during the era in China *Ling Zhi* was used as medicine. Ganoderma Lucidum is seen as the 'most medicinal' *Ling Zhi*, and is the strain that permeates into Korean and Japanese (Kampo) medicine.[3]

They (in reference to the two main strains, Purple and Red Lingzhi) differ in levels of the bioactive *ergosterol* and some triterpenoids[8] and the genetic influence of triterpenoids on monocytes (immune cells) shares about 26% similarity between species at best;[5] polysaccharide content does not differ as significantly.[9] In assessing their influences on the genome, it was demonstrated that 90% ethanolic extracts of the two respective mushrooms differnetially influence immunity.[5] When investigating genetic cross-over between the species, the similarities are relatively diverse with genes involved in cell development (21%), negative regulation of cellular process (16%), cellular protein metabolic process (16%), signal transduction (14%), and transcription (14%). Of the top 20 activity genes between the two species, they are most involved in immunomodulation and notable genes are the upregulation of IL-1B, IL-8, CLEC4E, BIRC3 and ADAMDEC1 with downregulation of Glycoprotein A33 and several genes with unknown actions.[5]

Beyond species, different locations that grow Ganoderma Lucidum can markedly differ in quantities of bioactives.[10] At least one study investigating over-the-counter Reishi products noted that out of 11 randomly selected products, the triterpenoids ranged from indeterminate to 7.8% and polysaccharides from 1.1-5.8%, the differences was attributed to differences in production method (with water soluble extracts possessing less triterpenoids) and growth conditions.[3] One study growin Reishi noted somewhat similar levels of triterpenoids overall, but the specific triterpenoids fluctuated wildy between samples.[11]

The triterpenoid (ethanolic extract) of these two species (Lucidum and Sinensis) markedly differs in their biological effects, but neither species is inactive in any way; the polysaccharides have more similarities between the two. There is also moderate to large differences between crops of Ganoderma Lucidum

1.3. Composition

Mushrooms in general tend to be 90% water or so, which makes a basic mushroom 'extract' dehydrated mushroom powder (and thus 1g extract, if unspecified, may be about as potent as 10g of the mushroom). Beyond that, they tend to be a good source of protein (10-40% of the non-water weight) carbohydrates (3-28%), fiber (3-32%) and then trace Essential Vitamins or Minerals.[12][3] Ganoderma is on the high end for fiber, low end for carbohydrate, moderate to high end for protein and has a relatively low ash (mineral) content.[13] Beyond the basics, Ganoderma Lucidum possesses unique bioactive molecules including:

- A variety of Bioactive polysaccharides[14][15][16][17] that tend to be the components that interact with the immune system[18] and are subdivided into β-1,3-glucans and polysaccharide peptides like peptidoglycan.

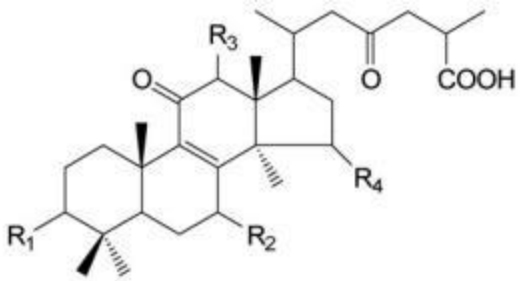
- Water-soluble Polysaccharide Peptides, or carbs with amino acids in the structure. They include GLPS peptide (GLPP),[19][6] GLPG,[20] GLIS,[21] PGY,[22] and F3[23]
- β-1,3-Glucans (subset of polysaccharides) sometimes called 'Curdlan' [24] and some other Glucan molecules[25]
- Over 120 triterpenoid compounds[26][27] which can be separated into those with a carboxylic side chain (Ganoderma Acids) and those without (Ganoderma alcohols). Some are referred to as *lucidenic acids*[28][29]
- Nucleotide bases (thymine, uridine, inosine, guanosine, adenosine) the sum of all ranging from 303-1217mcg/g (in the mushroom cap) and 22-334mcg/g in the stem.[30]
- Some bioactive proteins, such as LZ-8 (Lingzhi-8)[31] and Ganodermin[32]
- A 114kDa hexameric lectin, a glycoprotein with 9.3% sugar[33]
- A reversible and highly specific competitive alpha-glucosidase inhibitor known as SKG-3 with an IC_{50} value of 4.6mcg/mL[34]
- Ergostane sterols[35] and ergosterol, known as pro-vitamin D2[36]
- C19 fatty acids (nonadecenoic acid and cis-9-nonadecenoic acid)[37][38]
- Riboflavin
- Vitamin C
- Copper and Zinc[39]
- Selenium at up to 72mcg/g dry weight (best estimate of wet weight is 7.2ug/g) and can biotransform selenium into selenium-containing proteins[40][41]
- Germanium (the ion, not to be confused with *Geranium*) at up to 489mcg/g[42]

There is also a large Chitin content in the Ganoderma Lucidum mushroom, which is indigestible (and for the most part, not bioactive) and makes the mushroom tough to chew.[3] The mushroom is hazel/red in color, which is due to the polysaccharide content.

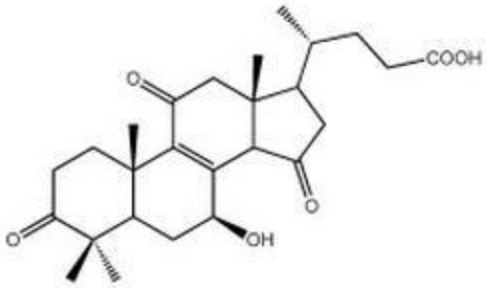
Polysaccharides (the carb and fiber content), Peptidoglycans (carbs with amino acids branching off of them), and Triterpenoids (fat-soluble molecules with a structure similar to cholester) are the main reasons for the activity of Ganoderma Lucidum. Other molecules, like the C19 fatty acids, may also play a role but are less studied. The mushroom is pretty to look at and pretty hard to chew

1.4. Structure and Properties

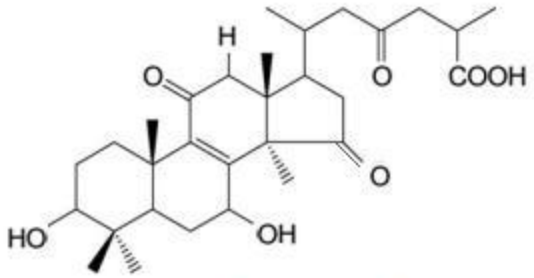
The main bioactives of Ganoderma Lucidum tend to be seen as the triterpenoid component (broken down into Ganodermic acids, Ganodermic Alcohols, and Lucidenic Acids) and the polysaccharide content.



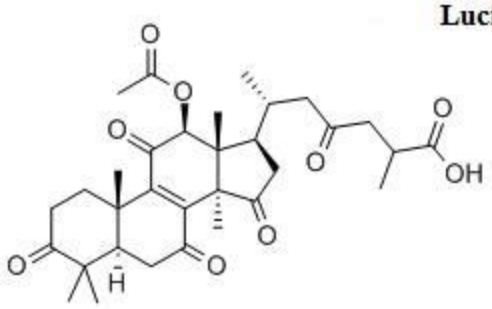
Ganoderic Acid (Backbone)



Lucidenic Acid (A)

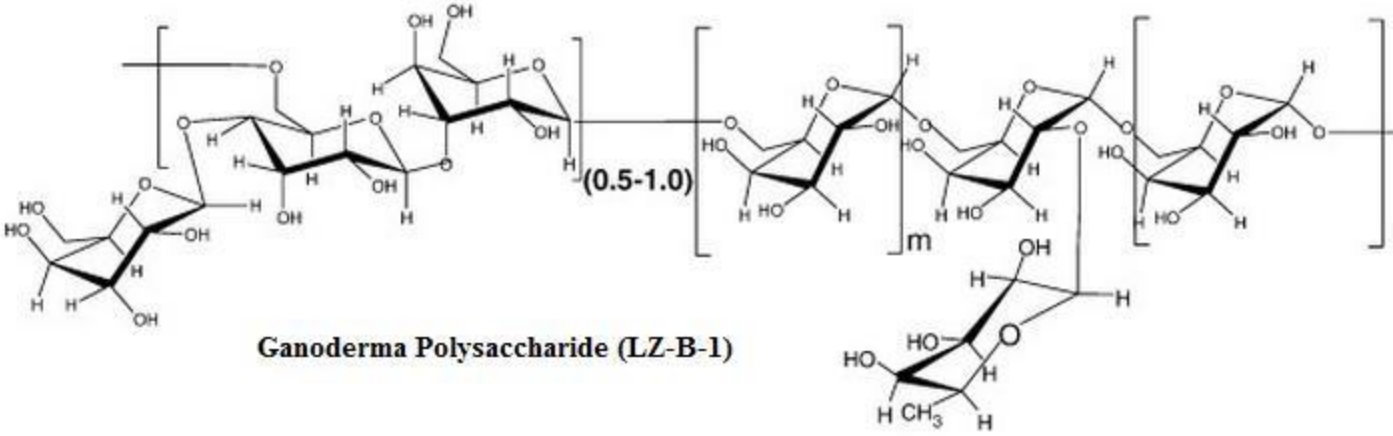


Ganoderic Acid B



Ganoderic Acid F

(Modified from: Wang XM, et al. HPLC determination of four triterpenoids in rat urine after oral administration o total triterpenoids from Ganoderma lucidum. J Pharm Biomed Anal. (2007) and 'Lucidenic acids-rich extract from antlered form of Ganoderma lucidum enhances TNFα induction in THP-1 monocytic cells possibly via its modulation of MAP kinases p38 and JNK' Volume 408, Issue 1, 29 April 2011)



Ganoderma Polysaccharide (LZ-B-1)

(Modified from: Ye L, et al. NMR characterization for polysaccharide moiety of a glycopeptide. Fitoterapia. (201

In regards to the differentiation between Ganoderma Acids and Alcohols (the triterpenoid compounds), acidic fractions appear to favor acid accrual and neutral fractions the alcohol fragment.[43] Triterpenoids appear to be hydrophobic, and are present in ethanolic or chrorophyll extractions; the polysaccharides are water-soluble and are the main bioactive in any Ganoderma water-soluble extract.

2Different forms of Ganoderma Lucidum

2.1. The Actual Mushroom

Traditional usage of the mushroom for its medicinal properties was in the range of 25-100g of the fruiting body (mushroom head) daily and a course of 'treatment' is 1-3 months.[44][45] The fruiting body contains a large amount of chitin, and is generally seen as touch to chew; the polysaccharides in Ganoderma Lucidum give the mushroom a reddish/hazel hue.

By weight, the fruiting body of the mushroom is about 0.5% polysaccharides.[45]

2.2. Water-soluble Extract

The water-soluble extract tends to be catered towards the polysaccharide content.

One patented blend, Ganopoly, is an extraction process yielding 98.8% content of polysaccharides by weight with no measurable triterpenoids; capsules contain 600mg total weight and 25% polysaccharides, and the recommended daily dose of 5,200mg is bioequivalent to 81g whole mushrooms based on polysaccharide content.[45]

2.3. Ethanolic Extract

The ethanolic extract of Ganoderma Lucidum tends to be catered towards the triterpenoid content, contributing little to no polysaccharides.

2.4. Antlered

The antlered form of Ganoderma (*Ganoderma Lucidum* AF; *rokkaku-reishi*) is the same species of Ganoderma Lucidum but varies in appearance, looking more like antlers than the standard mushroom.[46] It is rarely found in nature (although recently has been cultivated to higher levels), but consists of mostly the same bioactive compounds in regular Ganoderma Lucidum.[47][48] Although polysaccharide content is roughly similar at 40.1% of dry weight,[46] Triterpenoid compounds such as lucidenic acid, however, are higher in the antlered version[49][46] The specific amount of triterpene structures in the Antlered version range from 5875.8+/-80mcg/g and 7034.2+/-274.8mcg/g, whereas regular Ganoderma ranges from 2443.1+/-45.6mcg/g to 4441.2+/-328.4mcg/g; the lowest and highest recorded values being 140% and 58% higher in the Antlered version, respectively.[11]

Same as standard Ganoderma Lucidum, except with a higher triterpenoid content. Completely irrelevant if you are using a hot-water extract, but possibly beneficial to use the antlered version if consuming the entire mushroom or an ethanolic extract

2.5. Mycelium

The mycelium of a mushroom is a branching vegetable network that is seen as a growth of the mushroom, but not the stem nor the cap. Ganoderma Mycelium appears to contain many of the same bioactives that the fruiting body (cap) does,[50] and polysaccharides from the Mycelia have been used to similar efficacy as the fruiting body.[51][52][53]

A cheaper way to sell Ganoderma polysaccharides, and isn't completely inactive; can be useful for the frugal

2.6. Spores

Ganoderma Lucidum spores (*Reishi Houshi*) possesses a much higher content of triterpenoids on a weight basis when compared to standard Ganoderma Lucidum, but is insignificantly different or less than the antlered form of Ganoderma.[11] Whereas the total content of triterpenes in 6 strains of standard Ganoderma ranged from 2443.1+/-45.6mcg/g to 4441.2+/-328.4mcg/g, the spores averaged at 5549.2+/-317.3mcg/g (24% higher than the largest recorded Ganoderma strain). The antlered version of Ganoderma (*Rokkaku-Reishi*) averaged between 5875.8+/-80mcg/g and 7034.2+/-274.8mcg/g (all numbers dry weight).[11]

2.7. Jisheng Injections

Jisheng injections are injections of Ganoderma Lucidum that have been reported to aid in sleep and increase appetite for up to 2 weeks after administration.[54]

3Molecular Targets

3.1. Toll Like Receptors

Toll-Like Receptor 4 (TLR4) is a receptor that is highly expressed on cells in the immune system, such as dendritic cells[55] and macrophages;[56] polysaccharides from Ganoderma Lucidum appear to be a ligand for this receptor and activate it[56][57] which activates other pro-inflammatory proteins such as NF-kB (nuclear receptor) and TNF-α (cytokine). These effects are related to the polysaccharide and peptidoglycan content of Ganoderma Lucidum.[58]

When looking at the activation of NF-kB (correlates well with TLR4 activation in cells expressing TLR4), it appears to be activated when the pro-inflammatory stimuli LPS is not present[59][5] yet suppressed when LPS is coincubated;[60] this suggests that Ganoderma polysaccharides are a receptor modulator.

These same trends are seen with TNF-α (consequence of NF-kB activation, among other things) where Ganoderma Lucidum suppresses the increase of TNF-α induced by LPS[60] associated with less phosphorylation of Akt (Ser473)[61] and less IkB degradation and NF-kB activity.[62] When there is no proinflammatory stimuli, Ganoderma Lucidum polysaccharides reliably increase TNF-a in animal models[63][64] and isolate human cells[65][66] secondary to macrophage activation.[67] One human study on persons with breast cancer noted an improvement in immunomodulation as it pertains to cancer in response to 3g Ganoderma spores daily, suggesting the above works in humans.[68]

Ganoderma Lucidum polysaccharides appear to be a TLR4 receptor modulator, and using Lipopolysaccharide (LPS) as a proinflammatory reference Ganoderma can increase inflammation when there is no inflammatory stimuli present and attenuate inflammation when

there is a stimuli present. NF-kB activation and TNF-α levels follow this same pattern, and Ganoderma appears to be a context dependent pro and anti-inflammatory (immune system modulator)

The cytokine known as Matrix metallopeptidase 9 (MMP9) is normally induced by TNF-α,[69] yet does not occur with Ganoderma-induced TNF-α;[62] a compound in Ganoderma appears to interfere with MMP9 mRNA and protein content by interfering with the promotor in the nucleus;[62] this may be related to the triterpenoids[70][71][72] and at least one peptidoglycan.[62] Another cytokine, MCP-1, is suppressed by the water soluble extract (usually polysaccharides) yet induced by the ethanolic extract (triterpenoids).[73]

Some triterpenoids (usually in ethanolic extracts) may also have immunomodulatory properties as they have been noted ot upregulate IL-2, IL-4, and IL-8 *in vitro*[73] while inhibiting NF-kB activation via AP-1[72] which is due to ERK phosphorylation; MEK inhibitors are synergistic in this regard with Ganoderma triterpenoids.[71]

Ganoderma may disregulate the connections between inflammation and the carcinogenic consequences of inflammation, but more research is required to assess practical relevance of this (as many compounds in Ganoderma act in different manners)

4Pharmacology

4.1. Serum

After oral administration of a blend of Reishi (13.5% polysaccharides, 6% triterpenoids) at 500mg/kg bodyweight in rats and another blend (13.4% triterpenoids) at 500mg/kg bodyweight in rats show a T_{max} of around 90 minutes for Ganoderic Acid A, F, and H[74] which were similar to a previous study measuring these triterpenoids.[75] Peaks were seen quite rapidly, with a few triterpenoids appearing in plasma in relatively high quantities in under 20 minutes after ingestion.[74][75]

5Neurology

5.1. Cholinergic Neurotransmission

Numerous (18) triterpenoids from Ganoderma Lucidum have been shown to possess acetylcholinesterase inhibitory actions with an IC_{50} value ranging from 9.40μM to 31.03μM, potency favoring those with an *n*-butyl ester side chain.[76]

Some triterpenoids have shown acetylcholinesterase inhibition when tested *in vitro*; the practical relevance of this to oral supplementation is currently not known

5.2. Neurogenesis

Triterpenoids from Ganoderma Lucidum appear to be able to act as NGF and BDNF mimetics, and enhance neuronal survival *in vitro*.[77] However, Ganoderma polysaccharides have been shown *in vitro* to induce MAPK activation and neuronal differentiation in rat neurons and prevent NGF-induced apoptosis.[78]

5.3. Neurooxidation

Ganoderma Lucidum has been implicated in reducing neuronal loss induced by kainic-acid excitotoxicity[79] and has been demonstrated to reduce dopaminergic losses secondary to its anti-inflammatory effects on microglia, as coincubation of LPS (pro-inflammatory agent) and Ganoderma can reduce the harmful effects of LPS on microglia and dopaminergic neurons.[80][81]

5.4. Fatigue

One large study has been conducted on Ganoderma Lucidum and 'Neurasthenia', which is a term that has its diagnostic criteria to 'Chronic Fatigue Syndrome' (despite neurasthenia not being a commonly used term in the West).[45] Neurasthenia is a functional diagnosis of at least two of the following symptoms: muscular aches and pains, dizziness, headaches, sleep disturbance, inability to relax, irritability, and dyspepsia[82] and varies between affecting 0.5-2.4% of tested populations.[83][84][85]

The study found that in a sample of 132 persons with diagnosed neurasthenia (as assessed by the criteria mentioned before from the ICD-10) given Ganopoly (Ganoderma Polysaccharide at 25% by weight) at 5,400mg daily, bioequivalent to 81g of the mushroom, found that after 2 months of supplementation that there were significant improvements in measured parameters overall with more persons reporting 'significant improvement' and less reporting 'regression' of well-being.[45] Improvements in fatigue and well-being were both noted with no significant side-effects, although a pilot study done by the same research group ntoed that 4 weeks usage was insufficient in alleviating symptoms; suggesting chronic usage is needed.[45]

Mechanism as to why Ganoderma aids in fatigue syndrome is unknown, but apparently it does

5.5. Sedation and Sleep

Ganoderma Lucidum has traditionally been used as a tranquilizing agent (An-Shen effect) for treatment of restlessness and insomnia.[86] 80mg/kg intra-gastric dosing of Ganoderma polysaccharide for 5 days in rats was able to induce a hypnotic effect, and works synergistically with TNF-α (half the dose of Reishi, plus 12.5mg/kg TNF-α, was as effective as 80mg/kg; a TNF-α antibody abolished the effects of Reishi).[86] There was no effect on day 1 and 2 of supplementation, but total and non-REM sleep as well as TNF-α concentrations in the serum (31%), hypothalamus (37%), and dorsal raphe (31%) from 3 days onwards.[86] Beyond being synergistic with TNF-α, Ganoderma water extract has been demonstrated to enhance barbituate-induced sleep, and increased delta-wave activity by non-barbituate mediated means[87][88] in a dose dependent manner.[54] Ganoderma may, at least in part, be a benzodiazepine receptor agonist.[87]

In regards to general locomotor activity (moving around), moderate doses (80mg/kg) in rats do not inherently reduce spontaneous activity after a single dose but appear to reduce spontaneous activity after 3 days of supplementation.[87] Chronic usage appears to be more effective than acute usage,[89] although injections of Ganoderma (Jisheng injections) can induce reductions quite acutely.[54]

Ganoderma Lucidum appears to be a sedative, able to induce relaxation and sleep while reducing spontaneous movement during waking; might be good to pair with other compounds (Valerian or Melatonin?) as it does not inherently increase REM sleep time (instead increasing overall sleep time and reducing sleep latency, the time it takes to fall asleep)

6Cardiovascular Health

6.1. Blood Flow

In vitro studies on triterpenes from Ganoderma suggest that they possess fibrolynic and anti-platelet functions,[90][91] although when Reishi is ingested at 1.5g for 4 weeks there are no noticeable effects on blood flow and hemostasis.[92]

6.2. Cholesterol

After oral ingestion of 0.3g/kg Ganoderma extract in diabetic mice, hepatic and extra-hepatic expression of HMG-CoA reductase (target enzyme of statins) is unaffected[93] despite *in vitro* studies suggesting otherwise.[94] Alternatively, *in vitro* studies suggest cholesterol synthesis is inhibited at another step, inhibiting the *14alpha-demethylase* enzyme; cells treated with Ganoderma triterpenoids show increased levels of lanosterol and squalene and 25% reductions in cholesterol.[95][96] Ganoderma also possesses a non-competitive cholesterol esterase inhibitor, the enzyme that is required for dietary cholesterol to be absorbed.[97] Via inhibition of this enzyme, cholesterol uptake from the diet can be reduced,[98][99] increased fecal cholesterol has been noted in experimental animals fed Ganoderma Lucidum before.[94]

When tested *in vivo*, three separate studies on rats suggest that cholesterol levels can be reduced after consumption of Ganoderma polysaccharides; however, these studies were in models of type I diabetes.[100][101][102]

Ganoderma Lucidum may be able to reduce cholesterol, but whether this affects healthy persons and the mechanism(s) by which it is practically relevant need a bit more research

7Inflammation and Immunology

7.1. Interleukins

Reishi has been noted to increase IL-2 production in T cells (Specifically, $Foxp3^{+}CD4^{+}$ T cells) secondary to the CD18 receptor, which is activated when the reishi protein LZ-8 (1µg/mL) acts on the CD45 receptor.[103] An increase in IL-2 secretion from murine, jurkat, and human CD4+ T

cells has been noted with LZ-8 at 1μg/mL even without any antigen present.[104][105] This production of IL-2 depends on *phospholipase C* (PLC) activation and subsequent activation of calcium channels recruiting PKC alpha (PKCα) and theta (PKCθ)[104] which serve as intermediates in CD18 signalling in T cells, with MAPKs and ROS production both also playing intermediate roles.[104]

The LZ-8 immunomodulatory protein found in Reishi increases IL-2 secretion from $CD4^+$ T cells secondary to activating PLC and two PKC proteins

The increase in IL-2 that occurs with Reishi (from 1μg/mL LZ-8 acting on CD45) results in an increase in IL-10 secreted from T cells.[103]

The increase in IL-2 from the LZ-8 protein in Reishi also promotes an increase in IL-10

7.2. Natural Killer Cells

Natural Killer (NK) cells are an immune cell that exhibit cytotoxicity towards certain cells such as tumor cells and are a mechanism by which cancer therapy can be undergone vicariously through the immune system. In particular, when tumor cells attempt to metastasis (spread to other organs) the main mechanism by which they are destroyed are via the immune system;[106][107] NK cells tend to be seen as anti-metastatic.[108][109]

When looking at Human Interventions and NK-cells, both studies noted increases in NK cell activity although one was statistically insignificant[110] whereas the other noted a statistically relevant increase of 34.5 +/- 11.8%[111] associated with ingestion of Ganoderma polysaccharides. These effects have been reported in mice after administration of either Ganoderma polysaccharides[112] or select triterpenoids.[113]

May increase the overall count of Natural Killer cells in the immune system, although the two human studies that noted an inrease only had one returning statistically significant

It has been noted that Ganoderma can prevent fibrogenin-induced protection of tumor cells (where fibrin coagulates and forms a coat, preventing NK cells from acting on tumors[114]) by preventing fibrin from associating with cancer cells; indirectly enhancing NK-cell cytotoxicity.[115] Fibrin normally associates with $\alpha_v\beta_3$ and $\alpha_5\beta_1$ integrins on tumor cell surfaces, and Ganoderma can reduce this association to near control levels.[115] This same study noted that Ganoderma decreased lung metastasis in mice (after injection) via the polysaccharide component,[115] and Ganoderma can enhance cytotoxicity of tumors in 'evasive' tumors.[116]

May, independent of NK cell count, increase the cytotoxicity of NK cells on tumors by preventing fibrin formation on tumor cells. Fibrin protection on tumor cells may 'coat' them against NK cells, and Ganoderma can preserve the actions of NK cells by reducing this protective coat

7.3. Macrophages

Ganoderma water-extract (polsaccharides) have been shown to increase peritoneal macrophage phagocytosis *in vitro* and *in vivo*[117][118][6] as well as increase their size, activity, and induce pseudopodia.[119] Secondary to the 'activated' macrophages IL-1β, IL-6 and TNF-α production has been shown to be enhanced[119][6] alongside increased TNF-α mRNA at concentrations of 25-400ug/mL,[120] and mRNA transcrition of various interleukins.[119] At least the TNF-α production has been noted in peripheral mononuclear cells as well,[121]

The secretion of TNF-α (and some other cytokines) by isolated triterpenoids and beta-glucans appears to be synergsitic with pro-inflammatory LPS as both work on inducing activity of p38 MAPK while suppressing the c-JNK signalling pathway[122][47] although the opposite (suppression of TNF-α) has been reported in some studies.[60]

Consumption of 500mg/L (drinking water) in mice enhanced macrophage activation by by 340% relative to control and increase IL-1β and TNF-α secretion (theoretically) secondary to nitric oxide production in macrophages, and was able to increased phagocytosis rates.[117] Nitric Oxide production may be increased secondary to increased iNOS protein content in peritoneal macrophages.[123] These effects are also seen with 25-200mg/kg bodyweight isolated polysaccharide pepties (GLPP).

One study investigating the effects of polysaccharides on intracellular calcium noted that Ganoderma can induce cellular release of Ca^{2+} ions and also induce extracellular influx of Ca^{2+}.[6] It is hypothesized that these may be secondary to IP3 formation, or secondary to PKC activation which has been observed.[124][125] Alternate theories include TLR4 activation and the signalling cascade from that receptor, which some polsaccharides have been shown to act upon.[57][56]

Mechanistically, Macrophages appear to have their activity and phagocytic ability increase secondary to increase cytokine production (from nitric oxide signalling). What exactly causes this nitric oxide signalling is not completely hammered out yet, but may be through acting on TLR4 receptors

Polysaccharide peptides from Ganoderma at 100mg/kg oral ingestion have also been shown to protect macrophages from oxidative damage *in vivo* (mice) and prevent morphological changes to the mitochondria and endoplasmic reticulum as assessed by electron and light microscope.[126][6] It also demonstrated a rehabilitative effect, and 5 days of supplementation with the same dose mitochondrial membrane potential in macrophages (previously damaged by oxidative insult) was recovered.[6]

A protective effect may also exist for macrophages, which could possible extend to cardioprotection (preventing foam cell formation, could alleviate artherosclerotic buildup)

7.4. Dendritic Cells

On dendritic cells, Ganoderma polysaccharides can increase the expression of I-A/I-E and CDl1c on the cell surface as well as increase secretion of IL12p40 and IL23p19[127] as well as increase production of all four aforementioned proteins.[128] This study was conducted in cultured murine

bone marrow cells in the presence of LPS (Lipopolysaccharide) and suggests that Ganoderma polysaccharides (Gl-PS) can enhance the adaptive immune response. This study was corroborated by one showing that enhancement of dendritic cells enhanced Cytotoxic T-cell activity via (IFN)-γ and granzyme B pathways.[129] This enhancement of cytotoxic T-cell activity has been noted elsewhere, and is through TLR4 activation and NF-kB translocation; inhibiting either the receptor of the MAPK signalling cascade or NF-kB activation prevented the enhancement from occurring; showing that the effects of Ganoderma on active immunity are secondary to pro-inflammatory signalling.[55][130]

At least one study has noted that extracts produced by organic solvents (containing triterpenoids) do not influence dendritic cells[127] like the polysaccharides do.[23]

Increasing expression and activity of Dendritic cells (which 'present' toxins to the killing immune cells) via inflammatory signalling can increase adaptive immunity, and theoretically could be used acutely to fight off sickness

7.5. T cells

Promotion of naive CD4+ T-cells into effector T-cells occurs under the influence of cytokines. There are four types of T-cell types; Th1, Th2, Th17, and Treg[131] and all are intimiately involved with the aforementioned dendritic (antigen-presenting protein, or APN) cells. Interestingly, Ganoderma beta-glucans can increase proliferation of immature CD4+ T-cells just as potently as LPS, a pro-inflammatory molecule.[127]

Ganoderma has been implicated in increase Th1 differentiation. Additionally, the third subset of T-cells (Th17) seems to be preferentially increased after polysaccharide ingestion *without inflammatory stimuli* via increasing IL-23p19 secretion by dendritic cells.[127] Conversely, incubation with LPS to induce pro-inflammatory signalling suppressed IL-23p19 production and favored IL-12p40 production, which was barely existent without LPS.[127] The increase in IL-23p19 production is mediated by beta-glucans in Ganoderma (and has been reported elsewhere[132]) and is via the ERK/MEK pathway; all the above effects have been seen *in vivo* after oral ingestion.[127]

An increase in Treg cell ($Foxp3^+$; a major class of T regulatory cells[133]) has been noted with the LZ-8 protein in Reishi, where 1μg/mL applied to CD4+ cells increased Treg expression 4 to 10-fold resulting in increased IL-2 and IL-10 secretion;[103] implanting these activated Treg cells into mice with intestinal inflammation show suppressive effects (seen with other Treg cell inducers such as lactobacillus reuteri).[103]

The stimulatory effect of Reishi appears to extend to T cells

There is a method of training for athletes known as "living high and training low" which involves training at or near sea level and training at a higher altitude, thought to achieve the benefits of hypoxic training[134] although it is associated with immunosuppression (related to NK cells and T cells).[135]

In football players subject to a hypoxic sleep condition (mimicking 2500m altitude) and training in normoxic conditions Reishi supplementation at 2.5-5g (water soluble polysaccharide extract) for 28 days noted that while the short-term immunosuppression (assessed by CD3+, CD4+, and CD8+ T-cell counts) was attenuated in control the CD3+ T-cells with 5g Reishi were stimulated past control and placebo levels.[136]

Alterations in CD3+ T-cells from hypoxic training appear to be fully normalized and a bit reversed with 5,000mg Reishi supplementation

7.6. B cells

Reishi polysaccharides (water-soluble fragments known as F3[137]) have been demonstrated to induce splenic B-cell differentiation and cause activation of B cells in mouse spleen cells,[138][57] and induce differentiation into IgM secreting cells (plasma cells).[139] The potency of the Reishi-induced induction of B-cell activity was similar to Lipopolysaccharide (LPS), a pro-inflammatory research standard.[139] In accordance with this observed differentiation, it induces activity of B lymphocyte-induced maturation protein-1 (Blimp-1) via activating TLR4 and/or TLR2 receptors (as inhibition of either alone did not alter results much, signifying a shared post-cytosolic pathway) and signalling through p38/MAPK.[139][140]

In mature B-cells (plasma cells), increased content was seen (assessed by increased CD138 detection after 3 days) and increased antibody secretion was noted.[139] Ig secretion appears to be mediated through JNK, NF-kB, and MEK-ERK1/2 as inhibition of any of these three reduces Ig secretion but not Blimp-1 induction.[140]

No significant effects on differentiation or activation were seen in human peripheral B-cells[140] yet an increase in IL-6, IL-8 and MIP-1α was seen, and no induction of TNFα from B-cells.[140]

8Skeletal Muscle and Physical Performance

8.1. Muscular Endurance

Ganoderma Lucidum at 500mg/kg bodyweight to rats undergoing a weighted forced swim test, Ganoderma Lucidum was actually associated with less time to exhaustion; perhaps secondary to its sedative effects.[141]

9Interactions with Hormones

9.1. Testosterone

Ganoderma Lucidum possesses 5-alpha reductase inhibitors, able to attenuate the conversion of testosterone to dihydrotestosterone (DHT). Out of a cluster (n=19) of medicinal mushrooms examined, Ganoderma appears to be the most effective.[142][143] The ethanolic extracts are more potent than the water-soluble extracts, and Ganoderols F[144] and B[145] appear to be the most bioactive molecules. The inhibition is concentration dependent.[146]

Ganoderols from Reishi appear to have inhibitory potential on 5-alpha reductase enzymes, and underlie how Reishi is one of the more potent tested medicinal mushrooms for its anti-androgenic effects

Beyond 5α reductase inhibition, triterpenoids such as Ganoderic acid DF can block the androgen receptor when their concentration is high (15uM) and prevent androgen-receptor activation by DHT.[146] Increasing DHT concentration does not appear to override the blockade, and once a certain threshold is passed Ganoderma exerts potent *in vitro* androgen receptor blocking.[146]

Increases in testosterone have been reported in mice, and are synergistic with 5α-reductase inhibitors (including finasteride).[147] After oral ingestion of 6mg ethanolic extract in older men, however, no significant effects were seen on circulating testosterone.[148]

In humans, does not appear to affect circulating testosterone levels. However, it possesses multiple mechanisms in how it can exert *anti*-androgenic activity and may reduce the effects of androgens independent of circulating testosterone levels. The one human study noted a nonsignificant decrease in PSA levels, a biomarker for androgen receptor activity

9.2. Estrogen

Ganoderma Lucidum has been shown *in vitro* to reduce expression of the estrogen receptor (alpha) in MCF-7 breast cancer cells.[149]

10Interactions with Glucose Metabolism

10.1. Absorption

Two compounds in Ganoderma Lucidum, a fragment known as SKG-3[34] and a triterpenoid called Ganosterol B[150] have both been demonstrated to inhibit the α-glucosidase enzyme, which breaks down dietary starches and disaccharides into glucose so the carbs can be absorbed.

10.2. Mechanisms

Aldose reductase is the first enzyme that reduces glucose into polyols (such as sorbitol), and its inhibition serves a therapeutic role in diabetes management, specifically diabetic retinopathy.[151] Reishi possesses aldose reductase activity, and appears to be one of the most potent mushrooms at doing so,[152] the ethanol extract has been shown *in vivo* to reduce polyol formation in the rat eye.[152] When looking at the IC_{50} values of Ganoderma acids (the more potent portion of the triterpenoids), 17 tested fragments have an IC_{50} value below 200uM whereas some are very potent at 22.8uM (ganoderic acid Df) and 43.8uM (ganoderic acid C2).[27] It appears the carboxyl group on the side-chain is critical for aldose reductase inhibition, and double bonds on C20-C22 as well as hydroxyl groups on C3,7,11, and 15 increase inhibition (this 'ideal' molecule is ganoderic acid C2).[27]

Aldose Reductase inhibition may underlie the ability of the ethanolic extract for alleviating some complications of diabetes

The first investigation on Reishi and diabetes came from a study injecting 100mg/kg bodyweight polysaccharides (Ganoderan A and B) into mice, which subsequently demonstrated a 50% reduction in blood glucose levels with some noticeable effect on blood glucose reduction for up to 24 hours after injection.[153] Ganoderan B was later reported to increase insulin secretion and modulate glucose metabolism in liver tissue.[154] A related polysaccharide, Ganoderan C, also possesses hypoglycemic action via increasing insulin.[155] Polysaccharides can act on pancreatic beta-cells (where insulin is producted) where they induce Ca^{2+} influx into beta-cells to induce insulin secretion.[156] Ganoderma polysaccharides also exert an anti-oxidative protective effect on pancraetic beta-cells, and can reduce apoptosis while modulating biomarkers of apoptosis such as Bax/Bcl-2.[157][100][158]

Polysaccharides, if reaching the pancreas, may stimulate insulin release and subsequently reduce blood glucose levels

Ganoderma also appears to possess a proteoglycan (polysaccharide with amino acids) PTP1B competitive inhibitor, dubbed Fudan-Yueyang-Ganoderma Lucidum, possessing an IC_{50} value of 5.12+/-0.05 μg/mL.[159][160] This proteoglycan, called FYGL for short, contains 77+/-3% polysaccharide and 16.8+/-0.9% protein, and possesses a certain extraction process mentioned here.[159] Oral administration of FYGL can decreased blood glucose in type 1 diabetic mice, as well as both reducing serum insulin and increasing insulin sensitivity.[160] At oral doses of 50 and 150mg/kg bodyweight in mice over 4 weeks, improvements in glucose and insulin sensitivity are observed and the higher dose is comparable to 300mg/kg Metformin.[159] These effects have been observed in Type II diabetes as well, increasing the insulin sensitivity of skeletal muscle.[101] No toxicity of this particular extract was seen at up to 6g/kg daily.[159]

A proteoglycan from Ganoderma appears to act as a PTP1B inhibitor, and may prolong signalling through its receptor (which would reduce the rate of which the receptor desensitizes to insulin); it is moderately potent and has *in vivo* support for efficacy, but its IC_{50} value is weaker than other compounds such as ursolic acid or berberine

In diabetic mice, reductions in blood glucose have been seen and attributed to reduced hepatic expression of phosphoenolpyruvate carboxykinase (PEPCK) after 0.3g/kg oral ingestion for 4 weeks.[93] In vitro, activation of AMPK and increased glucose uptake have been noted with Reishi in fat cells as well.[161] Reductions in blood glucose after ingestion of 400mg/kg Ganoderma polysaccharides are roughly as potent as 30mg/kg Berberine, a potent hypoglycemic.[162]

Can reduce expression of PEPCK, and thus endogenous production of glucose in the liver; it is not as potent as Berberine, used as a reference compound

The Farnesoid X Receptor (FXR), a nuclear transcription activator, is induced by five triterpenpoids from the ethanolic fragment of Ganoderma Lucidum; ergosterol peroxide , lucidumol A, ganoderic acid TR, ganodermanontriol, and ganoderiol F.[163] General Lucidum

extracts at 100ug/mL were able to induce FXR to 150% the level of the active control, CDCA (Chenodeoxycholic acid), whereas the 5 isolated triterpenoids at 10uM were similar in potency to CDCA at 25uM (with ganodermanontriol causing the highest increase, and erogsterol peroxide having the lowest EC_{50} of 0.85uM).[163] As the FXR monomer can activate GLUT4 vesicles,[164] this mechanism of action may play a role in the anti-diabetic effects of Ganoderma.

May activate FXR, which has potential relations to glucose uptake in cells

10.3. Interventions

These effects have once been replicated in humans with hypertension (130/85 or above) or dyslipidemia, consuming 1.44g Ganoderma Lucidum extract (equivalent to 13.2g fresh mushroom) daily for 12 weeks found insignificant improvements in insulin sensitivity and fasting glucose.[165] Another trial[166] on 71 type II diabetic adults given 1800mg thrice daily Ganopoly (Ganoderma Polysaccharide, 5200mg daily) for 12 weeks was able to decrease HbA1c from 8.4% to 7.6%, and reduced postprandial blood glucose from 13.6mmol/L to 11.8mmol/L.

Oral ingestion of Ganoderma at 50 and 250mg/kg bodyweight was able to accelerate wound healing in a model of animal diabetes, which tend to have suppressed wound healing rates.[167] The mechanisms appear to be, in part, due to presveratrion of mitochondrial function and anti-oxidant enzymes.[167]

Via the ability of triterpenoids to inhibit the aldose reductase enzyme, Ganoderma Lucidum is being investigated for its usage in diabetic management to control production of polyols through aldose reductase and preserve retinal function in type II diabetics.

In diabetic mice, Ganoderma polysaccharides have been shown to reduce morphological damage to kidney tissue and exert a protective effect on kidney tissue.[168] This protective effect may extend to the pancreas[158] and has once been implicated in rats to reduce progression of type 1 diabetes via modulating the immune response, although the study has not been replicated.[169]

Shows potential to aid in wound healing, eye health, and kidney harm induced from Diabetes type II; either secondary to reducing blood glucose or via separate mechanisms (anti-inflammatory, aldose reductase)

11Hepatology (The Liver)

11.1. Protective effects

Ganoderma Lucidum appears to have general protective effects on the liver, and has shown efficacy in protecting the liver from mineral (cadmium) toxicity,[170] D-galactosamine,[171] carbon tetrachloride,[172] benzo(a)pyrene,[173] Mycobacterium bovis infection,[174] and general oxidative stress.[175] Therapeutic effects have been seen in regards to fibrosis by thioacetamide,[176] hepatic tumor cells,[177][178]

11.2. Viral infections

Ganoderma appears to possess anti-viral effects, and *in vitro* has been shown to inhibit the replication of the Hepatitis B virus in incubated liver cells.[179] It shows possible synergism when prepared with the root of the herbal *Sophorae flavescentis*, or *Ku shen*.[180] When investigaing these effects in humans, a blinded multicenter study of 90 persons with chronic hepatitis B infection and elevated AST levels given Ganoderma polysaccharides was shown to be able to reduce the amount of viral DNA and circulating antigen, but only significantly affected 25% of subjects in the experimental group[181] demonstrating potency but a lack of reliability in treating hepatitis B.

12Interactions with other Organ Systems

12.1. Prostate

The triterpenoids in Ganoderma possess 5α-reductase inhibitory potential, inhibiting the conversion of testosterone into dihydrotestosterone (DHT)[182] and a triterpenoid concentrated ethanolic extract (10-50mg/kg) in rats can reduce the effects testosterone has on prostate growth with a potency between B-sitosterol (stronger than) and Finasteride (weaker than).[147] While the water extract had an IC_{50} of 0.29mg/mL, the ethanol extract was found to have an IC_{50} of 0.01mg/mL in inhibiting testosterone-induced prostatic growth *in vitro* (Finasteride had an IC_{50} of 1.06mcg/mL).[147] A complete recovery of urine flow (impeded during prostatic hypertrophy) was seen with 50mg/kg bodyweight, although beyond that there was no significant difference between the doses of 20 or 50mg/kg in rats[147] and this increase in urine flow rate has been seen after 6mg ethanolic extract in men with slight-to-moderate lower urinary tract symptoms.[148] Effects in these studies kicked in 2-4 weeks after the beginning of ingestion.

May reduce prostatic size secondary to anti-androgenic effects, and increase urinary flow rate in instances of benign prostatic hyperplasia

13Ganoderma and Cancer

13.1. Popularity and Usage

Ganoderma appears to be a highly popular anti-cancer herb in the China area, as a survey of 4,149 survivors of breast cancer noted that 58.8% used Ganoderma on their own volition; it was positively associated with social well being and negatively associated with physical well being, and quite weakly associated on both accounts.[183] At least in leukocytes, Ganoderma Lucudium was found to upregulate 603 genes while suppressing the activity of 26.[5]

In the year of 2002, global production of Ganoderma Lucidum was estimated at 4700 tons; with 3800 tons being made in China.[184]

People like this mushroom for rehabilitative cancer treatment. No indication whether this is due to social renown or efficacy however

13.2. General Cytotoxicity Overview

Ganoderma Lucidum has been demonstrated to induce apoptosis (cell death) in a remarkably wide amount of cells. It has been demonstrated to show **in vitro** efficacy in:

- Murine Leukemia cells (L1210)[185]
- Human Leukemia HL-60[178][186][187]
- Other human Leukemia cell lines Blin-1, U937, K562, Nalm-6, and RPMI8226[188][187]
- Lung Carcinoma cells[189][190] with regard to the PG line[191][192]
- Small cell lung carcinoma NCI-H69 and Multidrug resistant strain VPA[193]
- Mouse reticulocyte sarcinoma L-II[194]
- Murine sarcoma Meth-A[185]
- Murine S180[194][195]
- Human liver cancer cells (hepatoma) PLC/PRF/5, HepG2, HepG3, Huh-7 and SMMC7721[66][196][196][177][190]
- Breast cancer cell lines MDA-MB-123,[72] MCF-7,[149] T-47D,[195] and MT-1[197][198]
- Prostate cell line PC-3[199][200]
- Human Cervix tumor HeLa[190][188]
- Bladder (low-grade) cell line MTC-11[201]
- Uroepithelial cancer cell HUC-PC[202]
- Colon cancer cell lines HT-29[203] and SW480[204]

At least *in vitro* (not in a living creature), various mixtures of Ganoderma Lucidum appear to be able to induce tumor cell death. This seemingly broad and non-specific anti-cancer mechanism of action is not limited to one bioactive molecule. Triterpenoids (Ganoderic acids and alcohols, as well as Lucidenic acids) polysaccharides (regular, and selenium containing ones) and peptidoglycans have all been implicated

In regards to mouse studies, injections of the water-soluble polysaccharide (GL-1) can inhibit 95-98% of transplanted sarcoma 180 tumors in mice.[205] And similar results have been reported on S180 cells with injected glycoproteins at 50mg/kg bodyweight with 88% inhibition rates and full regression in a third of test animals.[206] These effects have been noted with low dose injections of 2mg/kg bodyweight with lower potency (74%) with 30% of animals showing complete regression, and daily *oral* administration had a lesser potency of 45-63% inhibition, and was seen in two trials feeding rats oral water-soluble Reishi extract.[3] Finally, oral administration of 2.5% Ganoderma Lucidum to the diet of mice resulted in inhibition of S180 tumor carrying mice as well as mammary tumors (MM-46).[48]

In regards to the prostate, a herbal blend containing Reishi (called TBS-101) was able to suppress PC-3 tumor growth when both the cancer cell line and the supplement were administered to mice.[200] Reductions in testosterone-induced tumor growth has also been attributed to the triterpenoid fragment of Ganoderma, which appears to be secondary to its ability to act as a 5 alpha reductase inhibitor.[207][145]

Lung adenoma formation has been reduced after 9 week oral administration of Ganoderma Lucidum Mycelium[208] and the triterpenoid fragment has been shown to be protective in mice

injected with Lewis lung cancer cells.[209][113] Injections of basic water extracts also show efficacy in protecting the body from lung cancer.[210]

Reductions of count and size of hepatoma (HepG2) liver tumors up to 99% have been noted in rats after oral administration for 68 days of an (obscenely) high oral dose of 800mg/kg lucidenic acid, a triterpenoid unique to Ganoderma Lucidum.[177]

For colon cancers, preloading of a hot water extract can reduce the development of aberrant crypt foci and precancerous lesions in rats[211][212]

Mouse studies appear to be mimicking the anti-cancer effects seen in vitro, and a good deal of them are done in a rehabilitative/therapeutic manner as well. Only problem appears to be studies randomly using different fragments of Ganoderma Lucidum, which makes there surprisingly little replication done amongst the large amount of animal studies

13.3. Angiogenesis

Inhibiting angiogenesis is seen as a therapeutic mechanisms of chemotherapy, as reducing the creation of blood vessels to tumors can cut off their nutrient and blood supply to induce apoptosis (cell death).

In the presence of polysaccharides (F3) from Ganoderma, less signals of angiogensis (VEGFR-3 and CD105) were seen despite being in the presence of angiogenic growth factors, while downregulating angiogenesis *in vitro*.[213] The peptidoglycan content also may contribute towards inhibiting angiogenesis alongside polysaccharides.[214]

Reduction in angiogenesis have been noted *in vivo*, but was confounded with the addition of Genistein; a soy isoflavone.[215]

13.4. Human Interventions

One recent human intervention noted that Ganoderma water-soluble extract (1.5g daily, about 14g of fresh mushrooms) consumed by persons with colorectal adenomas was able to reverse an increase in adenomas in control (0.66+/-0.1) to a decrease in the Ganoderma group (-0.42+/-0.1).[216] Average size of adenomas also decreased with Ganoderma, while increasing in the control group.[216] Another study shows preliminary evidence that doses of 5.4g daily for 12 weeks have no significant adverse effects in advanced colon cancer,[110] and this dose and timing has been replicated with no significant adverse effects in advanced stage cancer patients.[111]

One study in lung cancer patients given a blend of Reishi known as Ganopoly (Polysaccharides) found increases in T cells, NK cells, and CD4/CD8 after treatment, and reported back 65% of patients having greater well-being.[217]

Surprisingly little human studies on people with cancer. The colon cancer study looks incredibly promising, but the latter two studies use the same protocol and dosage yet come up with slightly different conclusions. More replication and trials will be needed

14Interactions with Aesthetics

14.1. Skin

Ganoderma Lucidum appears to be able to inhibit the tyrosinase enzyme with an IC_{50} of 0.32mg/mL;[218] inhibition of this enzyme, which is the rate-limiting step in melanin synthesis, is seen as a skin-lightening property.

15Nutrient-Nutrient Interactions

15.1. Soy Isoflavones

Soy Isoflavones, particularily Genistein, has been created using Ganoderma as a fermentation vessel; Ganoderma expresses beta-glucosidase, which can cleave the glycosides of the soy isoflavones into their active aglycones. The supplement is then capsulated at up to 18% soy isoflavones (genistein at 10%, daidzein and glycetin at 6% and 2%) and 60% Ganoderma polysaccharides. This combination has been reported in one case study to cause complete regression of prostate cancer over 44 days of supplementation, decreasing prostate specific antigen (PSA) from 19.7ng/mL to 4.2ng/mL.[219]

In a larger scale study[220] using 5g of the above supplement daily (900mg total isoflavones, 3g polysaccharides) this case study was not replicated, and only 1 patient out of 52 had significant reduction of prostate specific antigen (PSA) of 61% over 6 months. 35 patients continued progression of prostate cancer while 8 were stable and 9 regressed slightly between 3-19% reductions.[220] The patient with a 61% reduction was the only one noting a significant reduction in serum testosterone after 3 months, dropping from 3.3ng/mL to 1.94ng/mL whereas other persons experiencing minor regression merely fluctuated randomly.

This supplement has been reported to (for lack of a better term, despite being inaccurate) *cure* prostate cancer, but attempted replication suggests it was rare. There appears to be some *thing* with some people that makes them respond to this combination supplement more, and that *thing* is currently unknown but may be related to reductions in testosterone

15.2. Vitamin C

It has been reported that Ganoderma Lucidum, in large doses of 5-10g daily, may cause loose stools; it has similarly been reported that superloading Vitamin C in the range of 6-12g can alleviate these loose stools.[44][7]

15.3. Select Antibiotics

Ganoderma Lucidum extract has been shown *in vitro* to be synergistic with cephazolin.[221]

16Safety and Toxicology

16.1. Acute studies

In rats, oral doses of 5g/kg bodyweight water-soluble Ganoderma Extract is not associated with any abnormal effects or toxic symptoms.[102]

16.2. General

After consumption of 1.44g Reishi extract (equivalent to 13.2g fresh mushroom) for 28 days was not associated with any toxicological signs of blood, liver, or cardiac parameters.[222] A non-significant beneficial trend was noted in this study for cardiac parameters (Triglycerides, HDL-C, LDL-C).[222]

16.3. In Cancer therapy

16.4. Case Studies

Two case studies associate powdered Ganoderma with hepatotoxic effects.[223] The subject was a 47 year old women with schizophrenia using lithium, perphenazine, and trihexyphenidil and who had been using traditionally boiled Lingzhi slices for several years with no effects, but developed hepatitis after 2 months of taking a 400mg powdered capsule.[223] There was necrosis of the liver cells (+70%) noted, and this is not observed with any of her other medications.[223] The other case study[224] was in a 78 year old chinese woman using felodipine for 2 years and had reported usage of Ganoderma via boiling the mushroom (traditional preparation) for up to a year, but switching to a new powdered formulation in the previous 4 weeks who suffered from signs of lethary and anorexia.[224] Neither case study was able to demonstrate causation.

The fact that both case studies had boiled Ganoderma Lucidum for a year or more prior to switching to capsules suggests that Ganoderma is not to blame *per se*, but not enough evidence exists to rule anything out

Scientific Support & Reference Citations

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(Common misspellings for Ganoderma lucidum include Rayshi, rayshe, rieshi, lingshi, linshi, lingze, ganderma, ganoderm, lucidem, lucidim, lucedum)

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