TRADITIONAL AND INTEGRATIVE MEDICINE

Trad Integr Med, Volume 9, Issue 3, Summer 2024

Review

# Unveiling the Metabolic Effects of *Ganoderma lucidum* in Humans: A Systematic Review and Meta-Analysis

**Steven Alvianto, Nicolas Daniel Widjanarko*, Stevan Kristian Lionardi, Erlangga Saputra Arifin**

*Faculty of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, North Jakarta, Indonesia*

**Received:** 12 Mar 2024 **Revised:** 21 May 2024 **Accepted:** 22 May 2024

## Abstract

Ganoderma is a mushroom renowned for its medical attributes, encompassing hepatoprotective, hypocholesterolemic, antioxidant, anti-inflammatory, hypoglycemic, and immunomodulatory activities. This study aimed to evaluate the effect of *Ganoderma lucidum* supplementation on metabolic profile in adult populations. Articles were retrieved from MEDLINE, ScienceDirect, ProQuest, and Google Scholar databases until the year 2023. Inclusion criteria were all published trials examining the effect of *G. lucidum* supplementation on metabolic profile in adult populations. The quality assessment and meta-analysis was performed. A total of 13 studies (two in populations with metabolic syndrome, two in type 2 diabetes mellitus, one in fibromyalgia patients, six in healthy populations, and two patients with coronary arterial disease) were included in this study, and seven studies met the eligibility criteria for meta-analysis. *G. lucidum* was mostly administered as capsules. There were no significant differences among outcomes in between group comparisons of high-density lipoprotein, low-density lipoprotein, total cholesterol, and fasting plasma glucose in the metabolic syndrome population (p value=1.00, 0.90, 0.78, and 0.33, respectively). Within group comparisons among the healthy population, only serum glutamic-pyruvic transaminase (p=0.03) and total cholesterol (p<0.0001) exhibited significant changes. In conclusion, we observed significant reductions in serum glutamic pyruvic transaminase and total cholesterol levels among healthy individuals following *G. lucidum* supplementation. However, despite promising preliminary findings, greater sample numbers with a more diverse demographic studies are required to fully understand and uncover any capabilities of *G. lucidum* in a therapeutic role.

**Keywords:** *Ganoderma lucidum*; Lingzhi; Reishi; Metabolic profiles

**http://doi.org/10.18502/tim.v9i3.16536**

**Citation:** Alvianto S, Widjanarko ND, Lionardi SK, Arifin ES. **Unveiling the Metabolic Effects of *Ganoderma lucidum* in Humans: A Systematic Review and Meta-Analysis.** Trad Integr Med 2024;9(3):318-338. http://doi.org/10.18502/tim.v9i3.16536

*Corresponding Author: Nicolas Daniel Widjanarko
Faculty of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, North Jakarta, Indonesia
Email: nicolaswidjanarko310@gmail.com

Copyright © 2024 Tehran University of Medical Sciences. Published by Tehran University of Medical Sciences.This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International license (https://creativecommons.org/licenses/by-nc/4.0/). Noncommercial uses of the work are permitted, provided the original work is properly cited.

## Introduction

Various mushrooms have been utilized in traditional medicine, predominantly in Asian regions, for more than 4000 years, owing to their claimed therapeutic attributes [1]. Ganoderma, with the scientific name of *Ganoderma lucidum* and as a member of the *Ganodermataceae* fungal family, is a widely recognized medicinal mushroom with longstanding historical usage [2]. It was known as "God's herb" in ancient China and "10,000-year" mushroom among Japanese people, which was believed to prolong life, enhance the youthful spirit, and sustain or preserve vitality [2]. However, it has been employed among diverse taxonomic designations in various nations, such as China ("Lingzhi"), Japan ("Reishi" or "Mannentake"), and Korea ("Yeongji") [1,2].

Ganoderma is renowned for its medicinal attributes rather than nutritional content, being classified as a non-edible mushroom in its raw state owing to its polyphore [1]. Encompassing a plethora of diverse bioactive constituents with therapeutic efficacy, it has garnered considerable attention among researchers [3]. The triterpenoids and polysaccharides derived from *G. lucidum* have been documented to exhibit a diverse range of pharmacological effects [3]. These effects encompass cytotoxic, hepatoprotective, antihypertensive, hypocholesterolemic, antihistaminic, antioxidant, antimicrobial, anti-inflammatory, hypoglycemic, antiallergic, neuroprotective, antitumor, immunomodulatory, and antiangiogenic activities [1,3].

Metabolic states play a pivotal role in determining individuals' health, as poorly regulated metabolic profiles have been highly associated with many diseases, including metabolic-associated fatty liver disease (MAFLD), diabetes, cardiovascular, and cerebrovascular disease (CVD) [4-6]. Therefore, modifying these metabolic alterations are crucial in reducing the risk of metabolic associated complications, along with its morbidity and mortality. Ganoderma have shown a metabolic shift ability both in endogenous and exogenous processes through its active compounds [7].

Emerging evidence from animal studies showed that *G. lucidum* has benefits in improving lipid parameters, such as triglyceride (TG), total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and very low-density lipoprotein (VLDL), on a dosage-dependent manner [8]. While on human studies, a review by Klupp et al., 2015 does not support the use of *G. lucidum* for cardiovascular risk factor therapy, specifically in individuals with type 2 diabetes mellitus (T2DM) [9]. *Ganoderma lucidum* has also shown to be relatively safe and no serious adverse events have been reported. The most common mild symptomatic reported adverse events being dry mouth, sore throat, and nausea.[10] Therefore, due to increasing interest in utilizing *G. lucidum* as an adjunctive therapy to ameliorate metabolic profiles, the evident of research gap in advanced clinical trials on *G. lucidum*, the existence of conflicting findings associated with *G. lucidum*, and the absence of a comprehensive systematic review or meta-analysis, this study was designed to evaluate the beneficial effects of *G. lucidum* on metabolic profiles among humans with various medical conditions.

## Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 statement was used as a guideline to design and conduct this systematic review and meta-analysis [11].

### *Registration of the review protocol*

The protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO) on November 3rd, 2023 with the following registration number: CRD420234735XX. To ensuring the blind review, we hide the last two numbers of PROSPERO registration.

### *Variable of interest*

This study aimed to evaluate the beneficial effects of *G. lucidum* on metabolic profile in human subjects among various medical conditions.

### *Eligibility criteria*

#### Type of studies

This systematic review included all published and unpublished trials, examining the effect of *G. lucidum* supplementation on metabolic profile in adult populations. Conversely, studies falling under the categories of reviews, cross-sectional, cohort studies, case reports, case series, conference abstracts, book sections, commentaries/editorials, and papers entailing non-human subjects were excluded.

#### Participants

All patients aged ≥18 years old are included in this study, and further divided into either healthy or having some medical condition, namely Metabolic Syndrome (MetS), T2DM, Fibromyalgia (FM), or Coronary Artery Disease (CAD). There were no limitations for gender and races. Patients who are pregnant or breastfeeding, consuming anticoagulants or immunosuppressants, taking *G. lucidum* before the study period, or allergic to Lingzhi products were excluded from the study.

#### Outcome of interest

The outcome of interest was the altered value of metabolic profiles, namely glycemic, lipid, blood pressure, and liver function parameters, measured by fasting plasma glucose (FPG), Homeostatic Model Assessment

for Insulin Resistance (HOMA-IR), 2-hour postprandial glucose (2h-PPG), HbA1c, TG, TC, LDL, HDL, Serum Glutamic Oxaloacetic Transaminase (SGOT), and Serum Glutamate Pyruvate Transaminase (SGPT).

### *Search strategy and study selection*

A literature search was carried out from November 5th to 28th 2023 on electronic databases including MEDLINE, EBSCO-Host, Science Direct, ProQuest, and Google Scholar to retrieve eligible studies. This was performed by four independent authors using a PICOTS-SD and specified search strategy. Detailed information is available in tables 1 and 2 of the supplementary materials.

All studies obtained were exported into the Zotero reference manager software, and then checked for duplication, followed by titles and abstracts screening. The assessment was performed separately by the authors and studies were excluded when the title and/or abstract were not appropriate for this review. The selected papers were reviewed in full-text assessment using the aforementioned eligibility criteria. The differences observed were settled among the review team members.

### *Data collection process*

The included studies were analyzed and the following data were extracted: first author, publication year, country of origin, study design, sample sizes, age, gender, population, inclusion and exclusion criteria, *G. lucidum* administration protocol, duration of follow-up, as well as the concerned outcomes.

### *Summary measures*

All of the lipid, glycemic, and other parameters were measured and reported as numerical (continuous) data. The data were presented in mean ± standard deviation for normally distributed data, or median (interquartile range) for non-normally distributed data. On the contrary, adverse events were identified and reported as proportional data. The p value was also included for each item to show the significance of results, with less than 0.05 was considered significant.

Regarding the missing changes from baseline to the end of the study period in some reported outcomes, we calculated it using a dependent t-test to determine the value from each *G. lucidum* (GL) and control groups. We converted values from studies that did not report in a form of mean and standard deviation using the formula proposed by Wan et al., 2014 [11] and Luo et al., 2018 [13]. The aforementioned formula requires data of sample size (N), lower quartile (Q1), middle quartile (Median/Q2), and upper quartile (Q3), which can be extracted from each original study.

### *Quality assessment in the cumulative evidence*

To determine the level of confidence in cumulative evidence, the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) method was described. Numerous study factors, including study limitations, consistency, directness, imprecision, and reporting bias, were taken into account while making the decision. The results of the evidence were very low, low, moderate, and high.

Each study categorized as RCT was evaluated using Cochrane Risk of Bias Tool (RoB) [14], while quasi-experimental studies were assessed with the Joanna Briggs Institute (JBI) Critical Appraisal tools for Systematic Reviews [15].

The ROB tool comprised of seven domains, namely (a) Random Sequence Generation, (b) Allocation Concealment, (c) Blinding of Participants and Personnel, (d) Blinding of Outcome Assessment, (e) Incomplete Outcome Data, (f) Selective Reporting, and (g) Other Source of Bias. The JBI Critical Appraisal tools consisted of 10 domains, namely: (1) the causal relationship between variables, (2) similarity of participants in comparisons, (3) similarity of other treatments apart from intervention of interest, (4) presence of control group, (5) multiple measurements of the outcome, (6) completeness of follow-up, (7) same outcome measurements for all patients, (8) reliability of outcome measurement, and (9) appropriateness of statistical analysis. The overall risk of bias was considered as low, high, and some concerns from each domain. Based on the degree of bias present, the overall quality of each trial was divided into three categories: (1) low risk of bias (across all domains), (2) high risk of bias (across multiple domains or some worries), and (3) some concerns (across at least one domain). Four authors separately evaluated each article, and any discrepancies were then addressed among the whole review team until agreement was reached.

### *Synthesis of results and statistical analysis*

Review Manager (RevMan; Cochrane Collaboration) version 5.4 was used to extract and pool the data for quantitative synthesis [16]. For the analysis, all patients were classified into two groups to obtain the difference between the intervention (*G. lucidum*) and control (placebo). Statistical analyses were carried out for between-group comparison using totals and subtotals with a 95% CI.

Some studies reported primary outcomes using different evaluation or calculation methods; hence, meta-analyses were conducted with a random effects model. This model presupposed that the treatment impact would be distributed over certain populations and offered each study a more equal weighting. Moreover, it enabled extrapolation to a larger sample of the population in cases when new studies were subsequently performed. The combined effect measures from an individual intervention were compared by the inverse

variance method for numerical (continuous) data. The Standardized Mean Differences (SMDs) were used as the most appropriate effect size for continuous data. Heterogeneity across trials was assessed using the $I^2$ statistic. An $I^2$ value less than 25% was considered subtle, 26% - 50% showed low, 51% - 75% signified moderate, and more than 75% implied high heterogeneity [16]. When heterogeneity was present, possible causes were investigated through sensitivity analyses.

## Results

### *Study selection*

The study selection process and the results obtained were summarized in a flowchart as shown in Figure 1. A total of 258 relevant studies were identified using the search strategy. According to the selection criteria, 210 were obtained after the duplicate removal, and 31 were extracted after the title and abstract screening. Those studies were further identified for full-text screening based on the selection criteria. Consequently, 18 studies were not relevant to the criteria, among which seven were *in vivo* (animal) studies, three were laboratory (*in vitro*) studies, four were systematic or literature reviews, two were irrelevant to the subject matter, and one did not have access to the full-text. Finally, thirteen studies were incorporated in the systematic review, and seven meeting eligibility criteria for data extraction were used in meta-analysis. Despite an in-depth literature search has been carried out, no unpublished studies meeting the inclusion criteria were identified. This absence did not affect the conclusions and also minimized the potential of qualitative publication bias.

### *Characteristics of the included studies*

The inclusion criteria were met by a total of 13 studies, including two in MetS population [21, 22], two in T2DM subjects [18,20], one in FM patient [30], six in healthy volunteer [24–29], and two suffered from CAD [19,23]. The total participants were 138, 117, 64, 134, and 133 in each group, respectively, with relatively similar male to female ratios, except for Babamiri et al. [24], Sarikaputhi et al. [29], and Pazzi et al. [30] with predominantly female respondents. The characteristics of the included studies, including first author, publication year, country of origin, design, sample sizes, age and gender, popu-

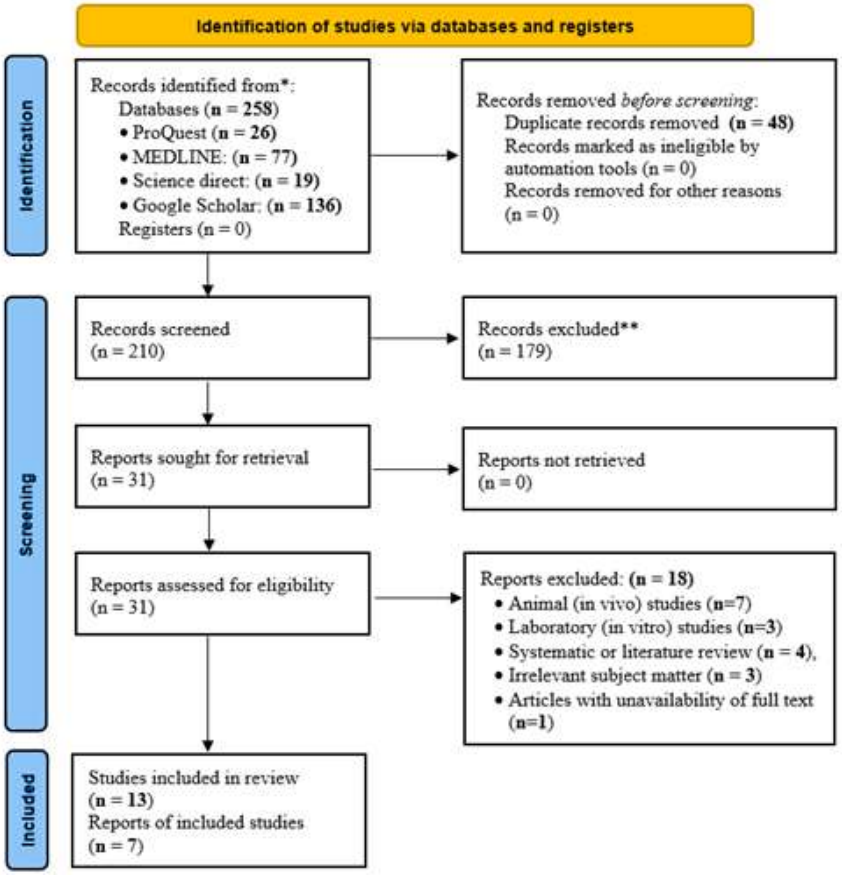


**Figure 1.** PRISMA 2020 Flow Diagram of Included Studies.

lation characteristics, inclusion/exclusion criteria of participants, GL mushrooms and placebo administration protocol, duration of treatment/follow-up, metabolic parameter outcome, and therapy-related adverse events were extracted and reported in table 1. The included studies were ten RCTs and three quasi-experimental studies. The mean ages of the population range from 35.2 ± 10.4 [25] to 61.8 ± 2.4 [20] years old in the intervention (GL group), and 35.2 ± 10.4 [25] to 57.1 ± 8.3 [22] years old in the control group. Among the 13 studies, one was conducted in Australia, one in Spain, five were in China (including two in Hong Kong and one in Taiwan), one in Thailand, one in Iran, one in Indonesia, and three studies do not provide any information regarding their country of origin. The follow-up duration of treatment in each study was varied, with 12 – 24 weeks in MetS, 12 weeks in T2DM, 6 weeks in FM, 10 days – 6 months in healthy, and 12 weeks in CAD populations. The supplementation of GL was mostly administered as capsules in nine studies, followed by one study used GL extract powder dissolved in water [30], one study utilized spray-dried Lingzhi mushroom extract powder [29], one study employed a fermented liquid contain the GL extract [28], and one study applied the extract of *G. lucidum* active compound without further information regarding their preparation [23].

### *Quality assessment*

Among the nine studies evaluated using ROB, six had some risk of bias concerns, and three had low risk of bias. Concurrently, three quasi-experimental studies all exhibited low risk of bias. In line with Cochrane's recommendations, the Robvis tool was used to summarize the bias risk (Table 2.A and 2.B), rated as "low", "some concerns", "high" and "critical" risk of bias across various domains.

### *Final results*

A total of seven included studies in the quantitative synthesis showed various results in between and within group comparisons. Table 4.A shows the differences of metabolic parameters between GL and control group after the treatment period (between group comparison). Meanwhile, table 4.B showed the changes of metabolic parameters between before and after treatment from GL group (within group comparison).

### *Meta-analysis results*

The quantitative synthesis results for between group comparisons of HDL, LDL, TC, and FPG are shown in figure 2.A, whereas the results for within group comparisons of HDL, LDL, TC, TG, FPG, SGOT, and SGPT are displayed in figure 2.B. Based on the results, there were no significant differences among outcomes in between group comparison (p= 1.00, 0.90, 0.78, and 0.33, respectively), and only two outcomes, TC and SGPT, exhibited significant changes in within group comparisons ($p<0.00001$ and $p=0.02$, respectively). Nevertheless, all outcomes in between group comparisons demonstrated a very low heterogeneity ($I^2 = 0\%$), compared with only five outcomes (LDL, TC, TG, FPG, SGOT) considered as homogenous ($I^2 = 0\%$), followed by SGPT ($I^2 = 34\%$) and HDL ($I^2 = 50\%$) in within group comparisons.

## Discussion

Numerous studies have demonstrated the advantageous impact of *G. lucidum* on a variety of metabolic parameters *in vivo* [8]. Furthermore, human trials have been conducted to evaluate the cardioprotective effects of *G. lucidum* [9]. Based on our systematic review and meta-analysis, we discovered that *G. lucidum* also exhibits favorable effects on metabolic parameters in humans afflicted with diverse conditions, mainly due to its hypolipidemic, hypoglycemic, hypotensive, and hepatoprotective effects.

In clinical trials on human volunteers, extracts obtained from *G. lucidum* involved the processing of raw mushrooms through a sequential method, encompassing boiling, filtering, dissolving, drying, and fermenting [20]. Following this series of procedures, the processed materials underwent concentration and micro-milling techniques, resulting in the final product being either in powdered form, encapsulated, formed into tablets, or prepared as a liquid formulation [20,29,30]. Sarikaputhi et al. [29] included additional components, such as brix sugar, which functions as a sweetening agent that may potentially impede absorption through the gastrointestinal tract. Consequently, it is advisable to administer the consumption of this preparation on an empty stomach whenever feasible [31]. Klupp et al. [22] integrated *Cordyceps sinensis*, a well-regarded mushroom with effects analogous to those of *G. lucidum*, with the objective of augmenting the potency of *G. lucidum*. Upon further research, there is no adverse effects associated among both substances.

Prior recommendations suggest a minimum dosage of 6 to 12 grams of *G. lucidum* extract on a daily basis [32]. This aligns with findings by Gao et al. [33], who reported that oral administration of 5,400 mg per day over a 12-week period significantly augments immune responses in individuals with advanced-stage cancers. While a universally-accepted recommended dosage for Lingzhi does not exist, reported dosages vary within the range of 1,500 mg to 9 grams [18] per day to achieve therapeutic benefits. It is pertinent to note that during a fasting state, *G. lucidum* can be discerned in the plasma within a span of 5 to 10 minutes subsequent to oral administration, achieving its maximum concentration ($T_{max}$) nearly 30 minutes with a short elimination half-life less than 40 minutes [31].

Across the 13 studies considered, the mean treatment

**Table 1.** Characteristics of the included studies

| No. | Author, Publication Year, Country | Study Designs | Groups: Ganoderma Group Age (years) | Groups: Ganoderma Group Sex N (%) | Groups: Control Group Age (years) | Groups: Control Group Sex N (%) | Population Characteristics | GL Mushrooms and Control/Placebo Administration Protocol | Duration of treatment/ follow-up | Metabolic Parameter Outcome | Therapy-related Adverse Events |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Metabolic Syndrome (MetS) Subjects** | | | | | | | | | | | |
| 1 | Klupp et al., 2016, Australia [22]. | Multiple-blinded, randomized, placebo-controlled, parallel design clinical trial | 60.2 ± 10.0 | Male: 27 (50) Female: 27 (50) | 57.1 ± 8.3 | Male: 17 (57) Female: 13 (43) | • A total of 84 patients from Cardiac Health Institute (CHI), Sydney, Australia.<br>• Aged 18 years and older<br>• Having high fasting serum glucose (≥ 6.1 mmol/L)<br>• Having at least two additional metabolic syndrome diagnostic criteria (fasting serum triglycerides ≥ 1.7 mmol/L, blood pressure ≥ 130/85 mmHg, waist circumference > 102 or 88 cm, and HDL cholesterol < 1 or 1.3 mmol/L for men and women, respectively) | Three interventions: *Ganoderma lucidum, Ganoderma lucidum* plus *Cordyceps sinensis*, or placebo, all of which were made and packaged in accordance with Australian Good Manufacturing Practice and Therapeutic Goods Administration (TGA) standards. All participants took **eight capsules** (3 g of *Ganoderma lucidum*, with or without *Cordyceps sinensis*) **each day** (four in the morning and four at night), **orally** | 24 weeks (8 weeks of washout periods) | After controlling for baseline differences, combined Ganoderma lucidum **had no effect** ($p>0.05$) on any of the outcome measures (HbA1c and FPG; secondary: blood pressure, TG, TC, HDL and LDL cholesterol at 16 weeks compared to placebo | Common side effects did not make substantial discomfort among the participants. The most prevalent adverse event for all groups was an **infection or immune system disorder**, which was more commonly reported by individuals in the placebo group |
| 2 | Chu et al., 2012, Hong Kong [21]. | Randomized controlled, crossover trial | 56.0 ± 9.3 | Male: 13 (38.5) Female: 21 (62) | 53.2 ± 6.7 | Male: 10 (50) Female: 10 (50) | • A total of 54 outpatient clinic in teaching hospital (Prince of Wales Hospital, Hong Kong)<br>• Having prehypertension or stage 1 hypertension (as defined by JNC7; or being treated with antihypertensive medication)<br>• Having mild to moderate elevations in plasma total cholesterol (>= 6.0 mmol/L) and/or triglyceride (>=1.7 mmol/L and <=5.0 mmol/L) with or without lipid-lowering therapy<br>• Having T2DM with good management (HbA1c 8.5) | *G. lucidum* polysaccharide extract 1.44 g/day (360 mg/capsule) equals 13.2 g mushroom/day taken as 2 capsules twice daily | 12 weeks (4 weeks of placebo run and crossover) | • There were **no significant changes** in BMI, waist: hip ratio, or systolic and diastolic blood pressure<br>• During both treatment periods, plasma glucose and insulin levels **tended to rise**<br>• HOMA-IR **increased** somewhat following Lingzhi therapy<br>• Following Lingzhi therapy, TG fell by 8% and HDL **increased** by 24%<br>• LDL levels **increased** to a comparable extent after both treatments | • A total of **6** and **19** adverse events occurred in Lingzhi and placebo groups, respectively<br>• The most common reported side effects in the Lingzhi group are **headache** (50%), followed by **influenza** (16.6%) and **sore throat** (16.6%)<br>• The most common reported side effects in the placebo group are **chest discomfort** (21%), followed by **headache** (15.8%) and **sore throat** (15.8%) |
| **Type 2 Diabetes Mellitus (T2DM) Subjects** | | | | | | | | | | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Lingzhi mushroom was produced by the *Guo-Ren-Shun-Tian-Tang Pharmaceutical Company*, Nantou County Puli Town. The Food Industry Research and Development Institute (FIRDI) verified the strain. Raw mushrooms were decocted, concentrated, dried, and capsuled once quantity and quality were approved. Dosage: 1000 mg three times each day for 12 weeks | • A **statistically significant difference** between groups for 2-hour postprandial blood glucose in favor of placebo (WMD 0.7 mmol/L; 95% CI 0.29 to 1.11)<br>• A **statistically significant difference** between groups in plasma glucose under the curve at 4th hour of meal tolerance test favored *G. lucidum* (WMD -49.40 mg/dL/h; 95% CI -77.21 to -21.59) | 12 weeks | N/A |
| 3 | Wang et al., 2008 [20]. | Randomized controlled trial | 61.8 ± 2.4 | N/A | 58.6 ± 2.3 | N/A | • A total of 46 participants with T2DM<br>• Having an 8-week diet and activity plan and whose blood glucose level remained between 150 and 250 mg/dL | Ganopoly capsules each containing 600 mg extract of G lucidum, with 25% (w/w) crude polysaccharides, equivalent to 9 g of fruiting body of *G. lucidum* (provided by Encore International Co. Auckland, NZ). Dose: 5400 mg per day (9 capsules), dose adjusted within the first 4 weeks. 3 capsules taken orally, 3 times/day before meals for 12 weeks<br><br>The control group was given placebo (provided by Encore International, Auckland, NZ) | • Mean of HbA1c **reduced dramatically** from 8.4 to 7.6% after 12 weeks of therapy<br>• The mean PPG declined to 11.8 mmol/L by week 12, followed by a **significant difference** ($p< 0.05$) in PPG levels between groups<br>• At the most recent visit, there were **substantial differences** between the groups in fasting insulin, 2-hour postprandial insulin, fasting C-peptide, and 2-hour postprandial C-peptide. These changes were consistent | 12 weeks | N/A |
| 4 | Gao, 2004a [18]. | Randomized controlled trial | 57.2 ± 8.8 | N/A | 54.4 ± 8.1 | N/A | • A total of 71 patients with confirmed T2DM<br>• Age 18 years or above<br>• Body weight 90%-150% of desirable weight for sex, body frame and height.<br>• • FPG 8.9-16.7 mmol/L in sulfonylurea-naïve patients<br>• FPG < 10 mmol/L before washout in sulfonylurea-treated patients | | | | |
| **Fibromyalgia (FM) Subjects** | | | | | | | | | | |
| 5 | Pazzi et al., 2021, Spain [30]. | Randomized double-blind pilot trial | 55.92 ± 8.06 | Female: 64 (100%) | N/A | N/A | • A total of 64 fibromyalgia participants from Spanish FM associations<br>• Age 18 or older with a diagnosis of FM by a rheumatologist | Participants were given 3 g of micro-milled *Ganoderma lucidum* carpophores which are dissolved in water twice a day, at breakfast and dinner | There were **no significant changes** observed in glucose, triglycerides, cholesterol, systolic and diastolic blood pressure between pre- and post-treatment groups | 6 weeks | N/A |
| **Healthy Subjects** | | | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 6 | Wu et al., 2017, China [28]. | Quasi-experimental study | Single group (quasi)<br>Age: N/A<br>Female: 4 (50%)<br>Male: 4 (50%) | • A total of 8 healthy adults at Shandong University, China<br>• Age 20 or older with a BMI of 18.5–24.9 kg/m$^2$ | Participants were given 50 mL of *Ganoderma lucidum* mycelium-fermented liquid (GLFL) every day for one month. The administration was random in a day | 4 weeks | **No significant changes** were found in the amount of glucose, triglyceride, HDL, and total cholesterol between the pre- and post-treatment groups. However, there was a **slight decrease** in the LDL cholesterol | N/A |
| 7 | Sarikaputhi, 2021, Thailand [29]. | Quasi-experimental study | Single group (quasi)<br>Age: 35.19 ± 5.57<br>Female: 7 (87.5%)<br>Male: 1 (12.5%) | • A total of 8 healthy adults at Mae Fah Luang and Chulalong-korn University<br>• Aged 18–60 years old, having a glycated hemoglobin (HbA1c) < 7% | The fresh longan fruit pulp (PC Innova, Inc.) had been boiled in hot water with no extra ingredient. The spray-dried Lingzhi mushroom extract powder was then dissolved in 50% water. Final product comprised of one gram of Lingzhi extract and ninety-nine grams of longan juice<br>For a period of 12 weeks, each participant was required to consume 5 mL of longan and Lingzhi mushroom syrup every morning as a sweetener | 12 weeks | • **No significant difference** between the mean concentrations of FPG and HbA1c and the baseline was identified<br>• **No changes** were identified in the mean concentrations of SGOT and SGPT | No any significant adverse events were reported. |
| 8 | Galor et al., 2004a, China [25]. | Double-blind placebo-controlled crossover study | Single group (crossover)<br>Age: 35.2 ± 10.4<br>Male: 4 (40%)<br>Female: 6 (60%) | • A total of 10 healthy and normotensive people<br>• Patients with no history of chronic illness and who were not on any regular medication | Participants were given two capsules of Lingzhi each day (totaling 0.72 g, which is the equivalent of 6.6 g of fresh mushroom) or a placebo. On a non-selective basis, five participants began with placebo and five began with Lingzhi. Lingzhi or a placebo were taken with 200/400 ml of warm water | 10 days | • **No significant differences** were found on total cholesterol, LDL cholesterol, HDL cholesterol, LDL/HDL ratio, and triacylglycerol between Lingzhi and placebo groups | N/A |
| 9 | Galor et al, 2004b, China [26]. | Double-blind, crossover, placebo-controlled intervention study | Single group (crossover)<br>Age: 35 ± 10<br>Male: N/A<br>Female: N/A | • A total of 18 healthy Chinese adults<br>• Aged between 22 and 52 years<br>• Non-smokers | Participants were given four capsules of Lingzhi/d (1.44g Lingzhi extract/d equivalent to 13.2 g fresh mushroom/d), or four capsules placebo/d with 4-6 weeks washout period before participants crossed over onto other intervention | 4 weeks | • **No significant differences** were found on TC, HDL, LDL, TG in response to Lingzhi compared to placebo after 4 weeks, although a slight trends towards lower plasma lipids was demonstrated | N/A |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 10 | Chiu et al., 2017, Taiwan [27]. | Randomized, placebo-controlled crossover study | Single group (crossover)<br>Age: 40 – 54<br>Male: 11 (52.4)<br>Female: 10 (47.6) | | | | • A total of 21 healthy middle-aged volunteers at Chung Shan Medical University Hospital<br>• Healthy subjects with mild liver dysfunction (elevated SGOT and SGPT as well as fatty liver) | Each 225 mg GL capsule includes 7% triterpenoid-ganoderic acid (A, B, C, C5, C6, D, E, and G), 6% polysaccharide peptides, and trace elements. Placebo capsules are identical to GL capsules in appearance and contain 90% starch and 10% GL residues | 24 weeks | • There was a **reduction** in SGOT and SGPT levels in after treatment compared to before treatment groups, respectively, from baseline to three and six months | N/A |
| 11 | Babamiri et al., 2022, Iran [24]. | Randomized, placebo-controlled trial | 37.25 | Male: 10 (27.8) Female: 26 (72.2) | 42.52 ± 1.85 | Male: 8 (24.2) Female: 25 (75.6) | • A total of 69 patients with BMI of 25-29.9 kg/m$^2$ in Salahuddin Hospital, Iran | Three Capsule (each 220 mg whole powder and 30 mg pure aqueous extract of *G. lucidum*) for 6 weeks. Matching placebo (250 mg of wheat flour) was given for 6 weeks (42 consecutive days) | 6 weeks | • There were **significant changes** in TC<br>• There were **no significant changes** in FPG, LDL, HDL, TG, and Blood Pressure | No side effects were reported within 6 weeks of supplementation. |
| **Coronary Arterial Disease (CAD) Subjects** | | | | | | | | | | | |
| 12 | Sargowo et al., 2019, Indonesia [23]. | Randomized control perspective method with pre-test and post-test design | 59.26 ± 8.97 | N/A | 59.26 ± 8.97 | N/A | • 45 patients with STEMI and NSTEMI in Dr Saiful Anwar Malang Hospital, Indonesia | Participants was given an extract during a 3-month period, containing Polysaccharide Peptide extracted from bioactive compounds B-1,3 / 1,6-D-Glucan. Further information regarding the contents of extract was not explained, as well as the placebo materials | 12 weeks | • There were **significant changes** in Mean Systolic Blood Pressure | Five out of 50 patients underwent allergic reactions (itching and diarrhea), which then dropped out |
| 13 | Gao, 2004b [19]. | Double-blind, randomized, multicentered study | 54.2±9.8 | N/A | 55.4±11.1 | N/A | • A total of 88 patients with confirmed coronary heart disease (CHD)<br>• Men and women aged 18-75 years<br>• Confirmed coronary heart disease, after a comprehensive medical and physical examination comprising history, blood biochemistry and heart ultrasound scanning | Ganopoly capsules each containing 600 mg extract of *G. lucidum*, with 25% crude polysaccharides, equivalent to 9 g fruiting body of *G. lucidum* (provided by Encore International Co. Auckland, NZ). Dose: 5400 mg/day (9 capsules), dose adjusted within first 4 weeks. 3 capsules taken orally, 3 times per day before meals for 12 weeks. Control group receiving placebo (provided by Encore International, Auckland, NZ) | 12 weeks | • The blood pressure of the Ganopoly group **significantly decreased**<br>• In 22.5% of individuals receiving Ganopoly, the diastolic pressure dropped by ≥10 mmHg. After 12 weeks of therapy, the average blood pressure (systolic/diastolic, 142.5/96.4 mmHg) in this group **declined** to 135.1/92.8 mmHg<br>• After 12 weeks of Ganopoly treatment, serum cholesterol levels **declined dramatically** to baseline levels | N/A |

Abbreviations: SGOT: serum glutamic oxaloacetic transaminase, SGPT: serum glutamate pyruvate transaminase, TC: total cholesterol, TG: triglyceride, LDL: low-density lipoprotein, HDL: high-density lipoprotein, FPG: fasting plasma glucose, Hba1c: glycosylated hemoglobin, BMI: body mass index, HOMA-IR: homeostatic model assessment for insulin resistance, STEMI: ST-elevation myocardial infarction, NSTEMI: non-ST-elevation myocardial infarction, WMD: weighted mean difference

**Table 2. A.** Results of quality assessment in RCT studies using RoB tools

| No. | First author, Year of publication, Country | Domain 1: Random sequence generation (selection bias) | Domain 2: Allocation concealment (selection bias) | Domain 3: Blinding of participants and personnel (performance bias) | Domain 4: Blinding of outcome assessment (detection bias) | Domain 5: Incomplete outcome data (attrition bias) | Domain 6: Selective reporting (reporting bias) | Domain 7: Other bias | Overall Risk of Bias |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Gao, 2004a [17]. | Unclear risk | Unclear risk | Unclear risk | Unclear risk | Unclear risk | High risk | Low risk | Some concerns |
| 2 | Gao, 2004b [18]. | Unclear risk | Unclear risk | Unclear risk | Unclear risk | Unclear risk | High risk | Low risk | Some concerns |
| 3 | Wang et al., 2008 [19]. | Unclear risk | Unclear risk | Unclear risk | Unclear risk | Unclear risk | Unclear risk | Low risk | Some concerns |
| 4 | Chu et al., 2012, Hong Kong [20]. | Low risk | Unclear risk | Low risk | Unclear risk | Low risk | Low risk | Low risk | Some concerns |
| 5 | Klupp et al., 2016, Australia [21]. | Low risk | Low risk | Low risk | Unclear risk | Low risk | Low risk | Low risk | Low risk |
| 6 | Sargowo et al., 2019, Indonesia [22]. | Low risk | Low risk | No Information | No Information | Low risk | Low risk | Low risk | Some concerns |
| 7 | Babamiri et al., 2022, Iran [23]. | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| 8 | Galor et al., 2004a, China [24]. | Unclear risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Some concerns |
| 9 | Galor et al, 2004b, China [25]. | Unclear risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Some concerns |
| 10 | Chiu et al., 2017, China [26]. | Low risk | Low risk | Low risk | Unclear risk | Low risk | Low risk | Low risk | Low risk |

duration is 80 days with approximately 11 weeks. Although there has been no information pertaining to the minimum treatment duration yet. However, an inclination towards better outcomes is observed with extended treatment periods. There are five cohorts comprising healthy subjects, while the remaining seven studies are among subjects with MetS, T2DM, CAD, and FM. This underscores a transition in focus from a predominantly supplemental perspective directed at healthy subjects to a more prospective therapeutic orientation.

## *G. lucidum in T2DM subjects*

*G. lucidum* has a therapeutic effect against T2DM by altering glycemic profiles through several mechanisms. It could exert hypoglycemic effects by inhibiting the enzyme α-glucosidase similar to the acarbose. Furthermore, this herbal medicine could inhibit Protein tyrosine phosphatase 1B (PTP1B) which leads to an increase in insulin sensitivity, similar to the effect of metformin [10].

A total of two studies were conducted with the inclusion of T2DM patients. Two parameters were reported in both studies, namely HbA1c and 2hPPG. Study conducted by Wang et al. [20] showed a significant difference of 2hPPG (MD 0.70; 95% CI: 0.29, 1.11) in between-group analysis involving GL and placebo post-intervention; However, no difference was found in the HbA1c value (MD -0.60; 95% CI: -1.34, 0.14). Gao et al. [19] study differs by analyzing the within-group comparison at baseline and post-intervention, in which both parameters (HbA1c and 2hPPG) display a significant difference ($p<0.05$) in the GL group. There is a dosage discrepancy between these two studies that may affect the overall results. The acceptable or appropriate dosage of *G. lucidum* is yet to be agreed on. These results correlate with a previous *in vivo* study conducted by Sarker et al. [34] which also found a significant decrease in the level of HbA1c and 2hPPG in rats treated with *G. lucidum*. It is noteworthy to mention that both studies have some concerns regarding the risk of bias, and specifically, Gao et al. [19] exhibited a high risk in the selective reporting domain. Nevertheless, past review by Klupp et al. [9] did not support the use of *G. lucidum* in T2DM patients.

**Table 2.B.** Results of study quality assessment in quasi-experimental studies using Joanna Briggs Institute (JBI) tool

| No | Author, year, country | The causal relationship between variables | Similarity of participants in comparisons | Similarity of other treatments apart from intervention of interest | Presence of control group | Multiple measurements of the outcome | Complete-ness of follow-up | Same outcome measurements for all patients | Reliability of outcome measurement | Appropriateness of statistical analysis | Overall Results |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. | Wu et al., 2017 [27]. | Yes | Yes | Unclear | No | Yes | Yes | Yes | Yes | Yes | Low risk |
| 2. | Sarikaputhi et al., 2021, Thailand [28]. | Yes | Yes | Unclear | No | Yes | Yes | Yes | Yes | Yes | Low risk |
| 3. | Pazzi et al., 2021 [29]. | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Low risk |

The level of confidence in cumulative evidence for between and within group comparison using GRADE assessment were shown in tables 3.A and 3.B, respectively.

**Table 3.A.** GRADE assessment in the cumulative evidence for metabolic parameter changes in *G. lucidum* versus placebo groups after treatment periods (between group comparison) among metabolic syndrome subjects

| | | Quality Assessment | | | | | | Summary findings | |
|---|---|---|---|---|---|---|---|---|---|
| Outcome | Number of studies | Risk of Bias 2 (ROB 2) | Inconsistency | Indirect-ness | Imprecision | Publication bias | Overall quality of evidence | MD total | 95% CI (upper, lower) |
| HDL | 2 RCT | Not Serious | Serious | Not Serious | Serious | Not Serious* | Moderate | 0.00 | (-0.13, 0.13) |
| LDL | 2 RCT | Not Serious | Serious | Not Serious | Serious | Not Serious* | Moderate | 0.03 | (-0.46, 0.52) |
| TC | 2 RCT | Not Serious | Serious | Not Serious | Serious | Not Serious* | Moderate | -0.07 | (-0.57, 0.43) |
| FPG | 2 RCT | Not Serious | Not Serious | Not Serious | Serious | Not Serious* | Moderate | -0.06 | (-0.18, 0.06) |

There was no substantial heterogeneity among included studies (the results of $I^2$ test were 0%).
* Publication bias was assessed qualitatively, and no unpublished studies were found in the literature search, thus not affecting the publication bias.

**Table 3.B.** GRADE assessment in the cumulative evidence for metabolic parameter changes before and after treatment of *G. lucidum* (within group comparison) among healthy individuals

| | | Quality Assessment | | | | | | Summary findings | |
|---|---|---|---|---|---|---|---|---|---|
| Outcome | Number of studies | Risk of Bias 2 (ROB 2) or Joanna Briggs Institute (JBI) tool | Inconsistency | Indirectness | Imprecision | Publication bias | Overall quality of evidence | MD total | 95% CI (lower, upper) |
| HDL | 1 Quasi, 2 RCT | Not Serious | Serious* | Not Serious | Serious | Not Serious** | Moderate | -1.84 | (-6.42, 2.74) |
| LDL | 1 Quasi, 2 RCT | Not Serious | Not Serious | Not Serious | Serious | Not Serious** | Moderate | 0.35 | (-0.73, 1.42) |
| TC | 1 Quasi, 2 RCT | Not Serious | Not Serious | Not Serious | Serious | Not Serious** | Moderate | 6.16 | (4.67, 7.66) |
| TG | 1 Quasi, 2 RCT | Not Serious | Serious | Not Serious | Serious | Not Serious** | Moderate | 1.65 | (-0.47, 3.76) |
| FPG | 2 Quasi | Not Serious | Serious | Not Serious | Serious | Not Serious | Moderate | 0.99 | (-2.06, 4.04) |
| SGOT | 1 Quasi, 2 RCT | Not Serious | Serious | Not Serious | Serious | Not Serious | Moderate | 0.57 | (-1.76, 2.91) |
| SGPT | 1 Quasi, 2 RCT | Not Serious | Not Serious* | Not Serious | Serious | Not Serious | Moderate | 3.77 | (0.42, 7.11) |

* There was no substantial heterogeneity among included studies (the results of $I^2$ test were 50% for HDL, 34% for SGPT which marked as low heterogeneity).
** Publication bias was assessed qualitatively, and no unpublished studies were found in the literature search, thus not affecting the publication bias.

**Table 4.A.** Results for Changes of Metabolic Profiles (TC, HDL, LDL, and FPG) in *G. lucidum* versus Placebo Groups After Treatment Periods (Between Group Comparison) in MetS Population.

| | | **High Density Lipoprotein (HDL)** | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | **Intervention** | | | **Control** | | | | |
| **No** | **Author, Year** | MD changes | SD changes | Participants | MD changes | SD changes | Participants | **MD changes between group** | **p value** |
| 1 | Chu 2012. | 0.15 | 4.303 | 13 | 0.02 | 1.957 | 10 | 0.13* | 0,93 |
| 2 | Klupp 2016 | 1.2 | 0.4 | 54 | 1.2 | 0.2 | 30 | 0.00 | 1.00 |
| | | **Low Density Lipoprotein (LDL)** | | | | | | | |
| | | **Intervention** | | | **Control** | | | | |
| **No** | **Author, Year** | MD changes | SD changes | Participants | MD changes | SD changes | Participants | **MD changes between group** | **p value** |
| 1 | Chu 2012 | 0.36 | 0.67 | 13 | 0.40 | 0.74 | 10 | -0.04 | 0.89 |
| 2 | Klupp 2016 | 0.1 | 2.828 | 54 | -0.1 | 1.414 | 30 | 0.2 | 0.72 |
| | | **Total Cholesterol (TC)** | | | | | | | |
| | | **Intervention** | | | **Control** | | | | |
| **No** | **Author, Year** | MD changes | SD changes | Participants | MD changes | SD changes | Participants | **MD changes between group** | **p value** |
| 1 | Chu 2012 | 6.5 | 1.1 | 13 | 6.5 | 1.2 | 10 | 0.0 | 1.00 |
| 2 | Klupp 2016 | 5 | 1.5 | 54 | 5.1 | 1.2 | 30 | - 0.1 | 0.75 |
| | | **Fasting Plasma Glucose (FPG)** | | | | | | | |
| | | **Intervention** | | | **Control** | | | | |
| **No** | **Author, Year** | MD changes | SD changes | Participants | MD changes | SD changes | Participants | **MD changes between group** | **p value** |
| 1 | Chu 2012 | 0.11 | 5.319 | 13 | 0.16 | 0.37 | 10 | -0.05 | 0.80 |
| 2 | Klupp 2016 | 0.07 | 0.4243 | 54 | 0.13 | 0.1414 | 30 | -0.06 | 0.46 |

**Table 4.B.** Results for Metabolic Parameters (TC, HDL, LDL, TG, and FPG) Before and After Treatment of *G. Lucidum* (Within Group Comparison) among Healthy Subjects.

| No | Author, Year | Low Density Lipoprotein (LDL) | | | | | |
|---|---|---|---|---|---|---|---|
| | | Pretreatment | | Posttreatment | | Participants | p value |
| | | Mean | SD | Mean | SD | | |
| 1 | Galor 2004b | 106.7 | 37.76 | 100.2 | 32.66 | 18 | 0.58 |
| 2 | Wu 2017 | 42.12 | 13.14 | 34.74 | 12.6 | 8 | 0.27 |
| 3 | Babamiri 2022 | 84.28 | 3.31 | 84 | 3.31 | 72 | 0.61 |
| **No** | **Author, Year** | **High Density Lipoprotein (HDL)** | | | | | |
| | | **Pretreatment** | | **Posttreatment** | | **Participants** | **p value** |
| | | Mean | SD | Mean | SD | | |
| 1 | Galor 2004b | 57.2 | 16.54 | 54.9 | 13.15 | 18 | 0.65 |
| 2 | Wu 2017 | 28.8 | 6.84 | 27.36 | 8.1 | 8 | 0.70 |
| 3 | Babamiri 2022 | 39.72 | 0.76 | 43.97 | 2.99 | 72 | <0.01 |
| **No** | **Author, Year** | **Total Cholesterol (TC)** | | | | | |
| | | **Pretreatment** | | **Posttreatment** | | **Participants** | **p value** |
| | | Mean | SD | Mean | SD | | |
| 1 | Galor 2004b | 183.7 | 42.85 | 166.7 | 19.51 | 18 | 0.13 |
| 2 | Wu 2017 | 71.71 | 14.96 | 70.27 | 15.68 | 8 | 0.85 |
| 3 | Babamiri 2022 | 149.33 | 3.71 | 143.17 | 5.35 | 72 | <0.01 |
| **No** | **Author, Year** | **Triglyceride (TG)** | | | | | |
| | | **Pretreatment** | | **Posttreatment** | | **Participants** | **p value** |
| | | Mean | SD | Mean | SD | | |
| 1 | Galor 2004b | 83.26 | 37.59 | 75.28 | 33.81 | 18 | 0.50 |
| 2 | Wu 2017 | 76.2 | 37.2 | 77.9 | 24.8 | 8 | 0.91 |
| 3 | Babamiri 2022 | 125.83 | 6.58 | 124.22 | 6.46 | 72 | 0.14 |
| **No** | **Author, Year** | **Fasting Plasma Glucose (FPG)** | | | | | |
| | | **Pretreatment** | | **Posttreatment** | | **Participants** | **p value** |
| | | Mean | SD | Mean | SD | | |
| 1 | Wu 2017 | 89.91 | 5.05 | 87.93 | 2.70 | 8 | 0.34 |
| 2 | Sarikaphuti 2021 | 101.43 | 6.19 | 101.86 | 2.97 | 8 | 0.86 |
| **No** | **Author, Year** | **Serum Glutamic Oxaloacetic Transaminase (SGOT)** | | | | | |
| | | **Pretreatment** | | **Posttreatment** | | **Participants** | **p value** |
| | | Mean | SD | Mean | SD | | |
| 1 | Galor 2004b | 21.9 | 8.4 | 32.8 | 11.79 | 18 | 0.58 |
| 2 | Chiu 2017 | 20.65 | 4.37 | 19.85 | 4.63 | 21 | 0.57 |
| 3 | Sarikaphuti 2021 | 18.88 | 6.62 | 17.38 | 5.97 | 8 | 0.64 |
| **No** | **Author, Year** | **Serum Glutamate Pyruvate Transaminase (SGPT)** | | | | | |
| | | **Pretreatment** | | **Posttreatment** | | **Participants** | **p value** |
| | | Mean | SD | Mean | SD | | |
| 1 | Galor 2004b | 19.3 | 10.86 | 18.4 | 8.4 | 18 | 0.78 |
| 2 | Chiu 2017 | 22.58 | 5.13 | 16.85 | 3.46 | 21 | <0.01 |
| 3 | Sarikaputhi 2021 | 22.63 | 7.29 | 21.25 | 5.36 | 8 | 0.67 |

## *G. lucidum in MetS subjects*

A quantitative analysis performed in two studies involving MetS patients reached the conclusion of *G. lucidum* had no significant impact on HDL, LDL, TC, and FPG, along with a subtle heterogeneity ($I^2$ = 0%). In addition, the majority of the results display a non-significant MDs ($p>0.05$) from baseline to post-intervention value in the GL and placebo group. Overall parameters (glycemic and lipid profiles) also tend to be stable or increase slightly. Only Chu et al. [21] reported a significant difference in the between-group and within-group analysis for TG ($p=0.003$) and LDL ($p<0.02$) values, respectively. Adverse events were considered mild, with headaches, fatigue, and unspecified infections (influenza and diarrhea) being the most common.

There are various plausible explanations regarding the insignificant results in the quantitative analysis. Chu et al. [21] employs a crossover design, which has the potential to influence the results due to the possibility of a carryover effect [35]. Additionally, Klupp et al.'s study [22] analyzed the GL group in conjunction with *C. sinensis*, which has its own metabolic effect [36,37]. Therefore, the true consequences following *G. lucidum* administration cannot be distinguished.

## *G. lucidum in CAD subjects*

Antihypertensive effects of *G. lucidum* are obtained through its ACE-inhibitory properties [38]. This is

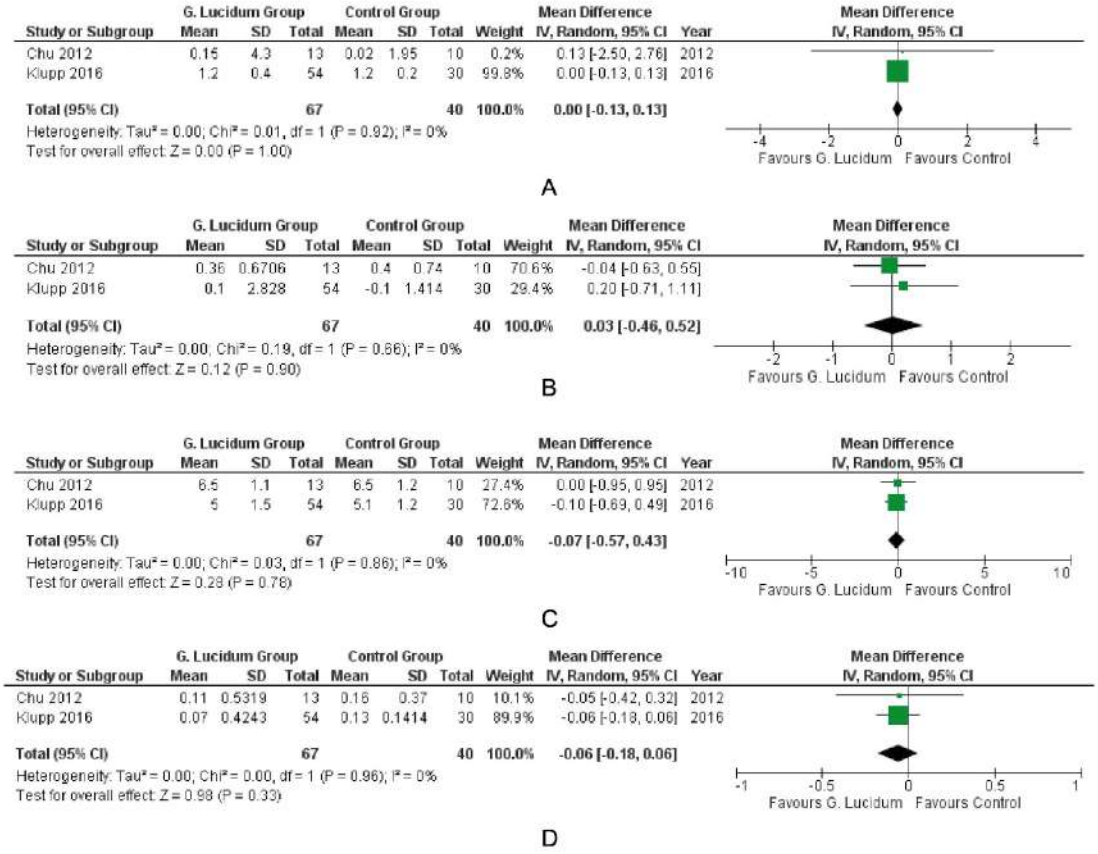


**Figure 2. A.** Meta-Analysis Results [Forest Plot] for Changes in Metabolic Parameters in *G. lucidum* versus placebo groups after treatment periods (between group comparison) among metabolic syndrome subjects; **A**: High-Density Lipoprotein (HDL), **B**: Low-Density Lipoprotein (LDL), **C**: Total Cholesterol (TC), and **D**: Fasting Plasma Glucose (FPG).

further proven by isolating several proteins from *G. lucidum* mycelia which are highly potent ACE-inhibitors [39]. Blood pressure was one of the main measurements in studies involving CAD patients. Sargowo et al. [23] analyzing between-group comparisons concluded a significant difference in the mean systolic blood pressure between the GL and placebo groups (p=0.046). Different research conducted by Gao et al. [19] in CAD patients also demonstrated a significant decline in blood pressure between the pre- and post-intervention (within-group analysis) values in GL groups. Gao et al. [19] also reported a significant decrease of the TC in the GL compared to the placebo groups. In contrast, two separate studies by Klupp et al. [22] and Chu et al. [21] with MetS populations revealed an insignificant difference in blood pressure between the GL and placebo groups after intervention. A study conducted by Farský et al. [40] unveiled that individuals with MetS frequently develop a resistant form of hypertension that proves challenging to alleviate.

## *G. lucidum in FM subjects*

In FM patients, Pazzi et al [30]. reported no significant differences in within-group comparisons for glucose, and in both groups comparison for cholesterol and triglycerides. This might be due to the low dosages of active chemicals employed in the study, which used only 6 grams of the entire *G. lucidum* carpophore, as opposed to the amount of active ingredient concentration in the extracts used in previous studies [41]. Furthermore, the amount of *G. lucidum* compound taken per day was considerably low (3 g), as compared to other studies by Galor et al. (6.6 g) [25], Gao et al. (9 g) [18], and Chu et al. (13.2 g) [21].

Following oral treatment, Ganoderma active components were seen in the plasma as early as 5–10 min, and they achieved their $T_{max}$ in around 30 min [31]. Nevertheless, despite the high dose of Lingzhi preparation, the AUC values were low, thus indicating a low oral bioavailability of these compounds (reported at only 10%). This may not be due to poor absorption from the gastrointestinal tract, but rather to their extensive first-pass metabolism in the liver combined with intestinal bacteria's partial conversion of some triterpenes to their metabolites [42]. Hence, this encourages a higher bioavailability of *G. lucidum* may rely on its dose-cumulative effect. Therefore, although

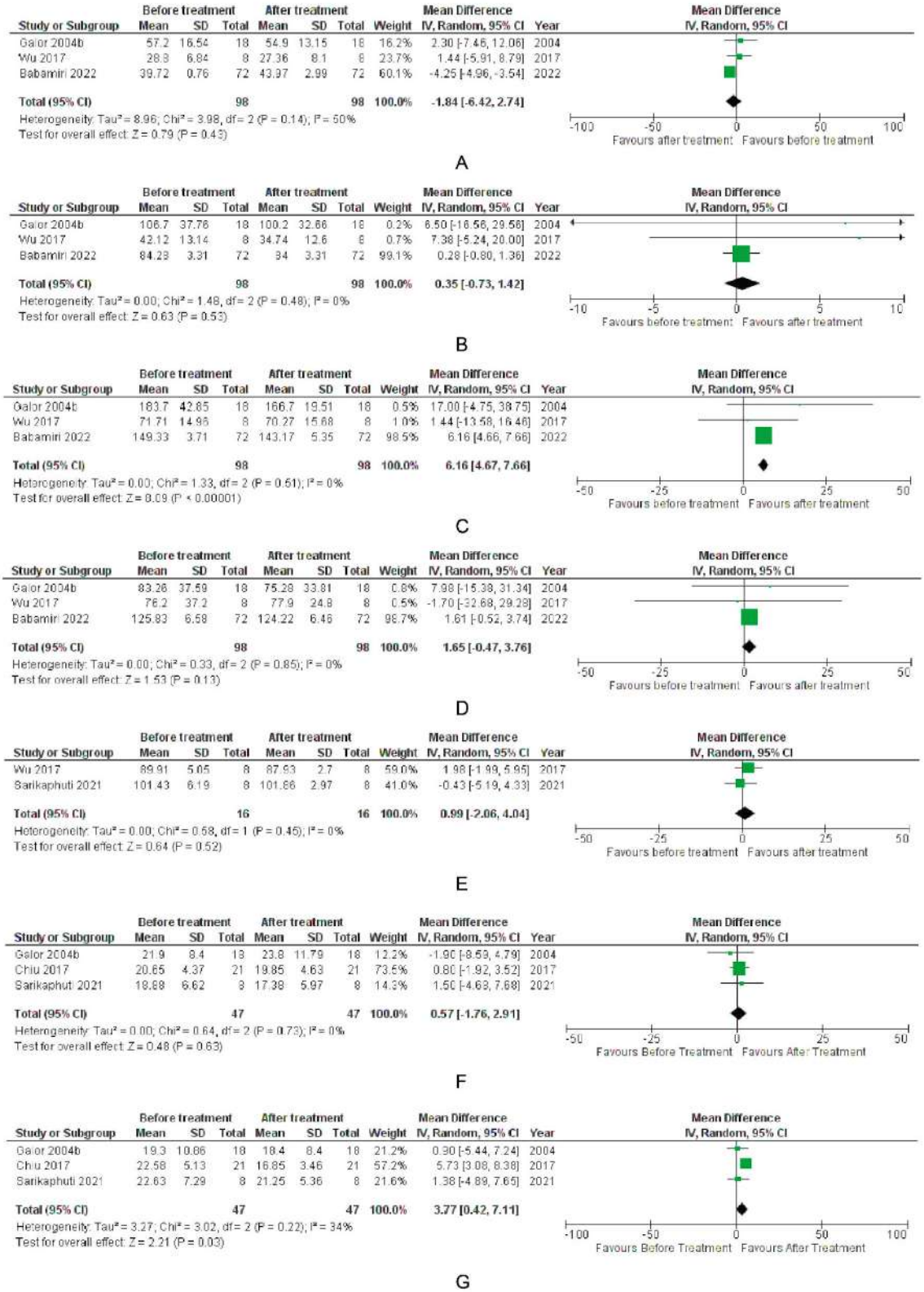


**Figure 2. B.** Meta-analysis results [forest plot] for metabolic parameters before and after treatment of *G. lucidum* (within group comparison) among healthy individuals; **A**: High-Density Lipoprotein (HDL), **B**: Low-Density Lipoprotein (LDL), **C**: Total Cholesterol (TC), **D**: Triglyceride, and **E**: Fasting Plasma Glucose (FPG), **F**: Serum Glutamic Oxaloacetic Transaminase (SGOT), **G**: Serum Glutamate Pyruvate Transaminase (SGPT).

Pazzi et al [30]. had shorter duration of treatment (6 weeks) compared to Galor et al. [25] (10 days), the significant effect was seen in Galor et al., suggesting that higher bioavailability may result from higher doses rather than a longer duration of treatment.

## *G. lucidum in Healthy Population*

*G. lucidum* showed a significant impact towards TC and SGPT reduction in healthy population ($p<0.00001$ and 0.03, respectively). These trends were followed by a substantial effect size for both outcomes (MD = 6.16 (4.67 – 7.66) and 3.77 (0.42 – 7.11), respectively) and a subsequent low heterogeneity ($I^2 = 0\%$ and 34%, respectively). However, overall results from five distinct studies involving healthy subjects indicated no significant difference across all metabolic parameters, with the exception of TC observed in Babamiri et al. [24], and hepatic enzyme markers (SGOT, SGPT) in Chiu et al [27]. This phenomenon may arise from relatively normal baseline values of these markers, thus *G. lucidum* only affects small changes on a previously-normal metabolic parameters.

*G. lucidum* may influence cholesterol synthesis at the rate-limiting 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase) step, which catalyzes the rate-limiting step in lanosterol-cholesterol conversion [43]. *G. lucidum*'s cholesterol-lowering capabilities have also been proven in a number of *in vitro* and *ex vivo* experiments [10]. In T9A4 hepatocytes, organic fractions containing oxygenated lanosterol derivatives hindered cholesterol production. In animal models, TG was likely reduced following *G. lucidum* due to decreased D1 TG levels in the GL groups compared to controls. As a result, plasma VLDL cholesterol secretion may be reduced, either by directly inhibiting LDL secretion or through VLDL-LDL conversion. The decreases in LDL and HDL found with *G. lucidum* are consistent with those using higher statin dosages [43].

Some beneficial effects of *G. lucidum* towards hepatic function were shown in a significant reduction of SGPT enzymes (figure 2.B (G), $p=0.02$, $I^2=36\%$). This finding supported that *G. lucidum* supplementation resulted in 4.52 higher SGPT depletion compared to control groups (95%Cl: 0.70–8.34). The mechanisms of *G. lucidum's* hepatoprotective effects include radical-scavenging behavior, hepatocellular calcium maintenance, hepatic enzyme modulation, homeostasis, and immunomodulation [44]. A hyperbranched proteoglycan (a combination of lipophilic protein and hydrophilic polysaccharide) isolated from *G. lucidum*, called Fudan-Yueyang *G. lucidum* (FYGL), suppresses steatosis in HepG2 hepatocytes which is produced by palmitic acid (PA). FYGL lowers TC and TG levels in these cells by increasing the activity of the enzymes' acetyl-CoA carboxylase (ACC) and AMP-activated protein kinase (AMPK), which suppresses the expression of fatty acid synthase [45]. Furthermore, our findings are also similar to a study in animal model, which demonstrated that *G. lucidum* extract significantly decreased the levels of SGPT in a carbon tetrachloride-induced liver injury in mice [46].

## *Heterogeneity analysis*

Although the heterogeneity results in between group comparison exhibited an $I^2$ results of 0%, in within group comparison, the results ranged from 0% to 50%. Two outcomes, HDL and SGPT, displayed an $I^2$ results of 50% ($p=<0.14$) and 34% ($p=0.22$), respectively. These variations may result from different clinical, methodological, or statistical perspectives.

The differences of participants in healthy population could lead to higher heterogeneity. The number of participants ranged from 5 to 72 years old, with unequivocal male to female ratios found in one study [24]. Study by Wu et al. [39], also did not mention the age of participants. On the other hand, ethnicity might also play a role in evaluating the effects of *G. lucidum*, considering that the study population originated from different regions, including China, Thailand, Taiwan, and Iran. The variations among *G. lucidum* administration protocols included the content, preparation, dose, frequency, and duration of *G. lucidum* are another source of heterogeneity. Most of the included studies using the extract of *G. lucidum*, but there is no detailed information of which part of *G. lucidum* was taken; only study Wu et al. [39], mentioned the mycelium origin.

Almost all included studies used *G. lucidum* only, except for one study by Sarikaputhi et al. [29], which also utilized a longan fruit pulp as the sweetener. Longan fruit is well known for its antioxidant and immunomodulatory properties, but there is limited evidence demonstrating its effect on metabolic profiles.

## *Strengths and limitations of study*

To best of our knowledge, this is the first comprehensive systematic review and meta-analysis to evaluate the beneficial effects of *G. lucidum* on metabolic profiles across diverse human populations, encompassing subjects with MetS, T2DM, FM, CAD, and healthy adults. However, several limitations warrant further investigation. The included studies exhibited significant variability in terms of sample size, participant age and ethnicity, *G. lucidum* administration protocols and follow-up duration; thus, raising concerns about potential bias. Therefore, additional robust studies are required to solidify the current findings and draw more conclusive inferences about *G. lucidum*'s therapeutic potential.

## *Future direction*

While this review explored the impact of *G. lucidum*

on metabolic profiles through quantitative analysis for MetS and healthy participants, data limitations restricted assessment to qualitative analysis for other medical conditions. This necessitates further robust clinical trials with substantial sample sizes, employing rigorous methodologies including blinding, randomization, multicenter approaches, along with a broader demographic scope, to achieve a more profound understanding of *G. lucidum*'s potential therapeutic role.

## Conclusion

Our review found that SGPT and TC were considered to be significantly reduced following *G. lucidum* supplementation in healthy adults. However, although some preliminary results from interventional studies show promise, overall data remains inconclusive. Further research is crucial to clarify *G. lucidum*'s potential benefits in this area.

## Conflict of Interests and Funding

The authors declare that they have no conflicts of interest. This study did not receive any specific grant or funding from any agencies or sponsors.

## Acknowledgements

The authors are grateful to all colleagues from Atma Jaya Catholic University of Indonesia for all the support and contributions provided.

# Supplementary

**Table 1.** PICOTS-SD

| PICO elements | Operational Definition |
|---|---|
| Patients | Subjects aged ≥18 years old with further divided into either healthy or having some medical condition, namely Metabolic Syndrome (MetS), Type 2 Diabetes Mellitus (T2DM), Fibromyalgia (FM), or Coronary Artery Disease (CAD). No limitations for gender and races. |
| Intervention | MetS subjects:<br>Supplementation of *G. lucidum* (intervention group).<br><br>Healthy subjects:<br>Baseline values before *G. lucidum* supplementation (pre-intervention group) |
| Comparator | MetS subjects:<br>Placebo (control group).<br><br>Healthy subjects:<br>Values after *G. lucidum* supplementation (post-intervention group) |
| Outcomes | ● Glycemic parameter<br>o Fasting plasma glucose (FPG).<br>o Homeostatic Model Assessment for Insulin Resistance (HOMA-IR)<br>o Two hour postprandial glucose (2h-PPG),<br>o Hemoglobin A1c (HbA1c)<br>● Lipid parameter<br>o Total Cholesterol (TC)<br>o High density lipoprotein cholesterol (HDL-C)<br>o Low density lipoprotein cholesterol (LDL-C)<br>o Triglycerides (TG)<br>● Liver function parameters<br>o Serum Glutamic Oxaloacetic Transaminase (SGOT)<br>o Serum Glutamate Piruvate Transaminase (SGPT)<br>● Blood pressure (systolic and diastolic values). |
| Time | Not restricted |
| Setting | Subjects visiting medical facility |
| Study Design | Interventional study (randomized controlled trial (RCT), quasi-experimental study, multiple-arm study) |

**Notes**. PICOTS-SD: participant, intervention, comparator, outcomes, time, setting, study design.

**Table 2.A.** Search Terms and Strategy: Pubmed/MEDLINE

| Search Number | Query | Filter | Results |
|---|---|---|---|
| 1 | (("Reishi"[Mesh]) OR "Ganoderma"[Mesh]) OR "Ganoderma lingzhi" [Supplementary Concept] | Randomized Controlled Trial, Clinical Trial, Full Text | 33 |
| 2 | (((((("Metabolic Syndrome"[Mesh]) OR "Metabolic Diseases"[Mesh]) OR "Diabetes Mellitus, Type 2"[Mesh]) OR "Dyslipidemias"[Mesh]) OR "Fibromyalgia"[Mesh]) OR "Coronary Artery Disease"[Mesh] | Randomized Controlled Trial, Clinical Trial, Full Text | 59,985 |
| 3 | ("Blood Glucose"[Mesh]) OR "Glycated Hemoglobin"[Mesh] | Randomized Controlled Trial, Clinical Trial, Full Text | 22,898 |
| 4 | ((("Cholesterol"[Mesh]) OR "Cholesterol, LDL"[Mesh]) OR "Cholesterol, HDL"[Mesh]) OR "Triglycerides"[Mesh] | Randomized Controlled Trial, Clinical Trial, Full Text | 14,320 |
| 5 | ("Aspartate Aminotransferases"[Mesh]) OR "Transaminases"[Mesh] | Randomized Controlled Trial, Clinical Trial, Full Text | 2,680 |
| 6 | ("Blood Pressure"[Mesh]) OR "Arterial Pressure"[Mesh] | Randomized Controlled Trial, Clinical Trial, Full Text | 30,615 |
| 7 | #3 OR #4 OR #5 OR #6 | Randomized Controlled Trial, Clinical Trial, Full Text | 63,920 |
| 8 | #1 AND #2 AND #7 | Randomized Controlled Trial, Clinical Trial, Full Text | 77 |

**Table 2.B.** Search Terms and Strategy: ProQuest

| Search Number | Query | Filter | Results |
|---|---|---|---|
| 1 | (((“Reishi”) OR “Lingzhi”) OR "Ganoderma lucidum") | Scholarly Journals, Full text, Article type | 1,127 |
| 2 | (((((“Metabolic Syndrome") OR "Metabolic Diseases") OR "Diabetes Mellitus, Type 2") OR "Dyslipidemias") OR "Fibromyalgia") OR "Coronary Artery Disease") | Scholarly Journals, Full text, Article type | 2,349 |
| 3 | ((((“Fasting plasma glucose”) OR “Homeostatic Model Assessment for Insulin Resistance”) OR “Two hour postprandial glucose”) OR “Hemoglobin A1c”) | Scholarly Journals, Full text, Article type | 1,781 |
| 4 | ((((“Total Cholesterol”) OR “High density lipoprotein cholesterol”) OR “Low density lipoprotein cholesterol”) OR “Triglycerides”) | Scholarly Journals, Full text, Article type | 1,843 |
| 5 | ((“Serum Glutamic Oxaloacetic Transaminase”) OR “Serum Glutamate Piruvate Transaminase”) | Scholarly Journals, Full text, Article type | 919 |
| 6 | ((“Blood pressure”) OR “Arterial Pressure") | Scholarly Journals, Full text, Article type | 1,283 |
| 7 | #3 OR #4 OR #5 OR #6 | Scholarly Journals, Full text, Article type | 519 |
| 8 | #1 AND #2 AND #7 | Scholarly Journals, Full text, Article type | 26 |

**Table 2.C.** Search Terms and Strategy: Science Direct

| Search Number | Query | Filter | Results |
|---|---|---|---|
| 1 | (((“Reishi”) OR “Lingzhi”) OR "Ganoderma lucidum") | Research articles, Open access and Open archive, Medicine and Dentistry | 576 |
| 2 | (((((“Metabolic Syndrome") OR "Metabolic Diseases") OR "Diabetes Mellitus, Type 2") OR "Dyslipidemias") OR "Fibromyalgia") OR "Coronary Artery Disease") | Research articles, Open access and Open archive, Medicine and Dentistry | 1,315 |
| 3 | ((((“Fasting plasma glucose”) OR “Homeostatic Model Assessment for Insulin Resistance”) OR “Two hour postprandial glucose”) OR “Hemoglobin A1c”) | Research articles, Open access and Open archive, Medicine and Dentistry | 2,072 |
| 4 | ((((“Total Cholesterol”) OR “High density lipoprotein cholesterol”) OR “Low density lipoprotein cholesterol”) OR “Triglycerides”) | Research articles, Open access and Open archive, Medicine and Dentistry | 1,876 |
| 5 | ((“Serum Glutamic Oxaloacetic Transaminase”) OR “Serum Glutamate Piruvate Transaminase”) | Research articles, Open access and Open archive, Medicine and Dentistry | 892 |
| 6 | ((“Blood pressure”) OR “Arterial Pressure") | Research articles, Open access and Open archive, Medicine and Dentistry | 1,451 |
| 7 | #3 OR #4 OR #5 OR #6 | Research articles, Open access and Open archive, Medicine and Dentistry | 322 |
| 8 | #1 AND #2 AND #7 | Research articles, Open access and Open archive, Medicine and Dentistry | 19 |

**Table 2.D.** Search Terms and Strategy: Google Scholar

| Search Number | Query | Filter | Results |
|---|---|---|---|
| 1 | (((“Reishi”) OR “Lingzhi”) OR "Ganoderma lucidum") | Full text | 3,577 |
| 2 | (((((“Metabolic Syndrome") OR "Metabolic Diseases") OR "Diabetes Mellitus, Type 2") OR "Dyslipidemias") OR "Fibromyalgia") OR "Coronary Artery Disease") | Full text | 21,690 |
| 3 | ((((“Fasting plasma glucose”) OR “Homeostatic Model Assessment for Insulin Resistance”) OR “Two hour postprandial glucose”) OR “Hemoglobin A1c”) | Full text | 24,923 |
| 4 | ((((“Total Cholesterol”) OR “High density lipoprotein cholesterol”) OR “Low density lipoprotein cholesterol”) OR “Triglycerides”) | Full text | 19,760 |
| 5 | ((“Serum Glutamic Oxaloacetic Transaminase”) OR “Serum Glutamate Piruvate Transaminase”) | Full text | 20,516 |
| 6 | ((“Blood pressure”) OR “Arterial Pressure") | Full text | 33,652 |
| 7 | #3 OR #4 OR #5 OR #6 | Full text | 8,218 |
| 8 | #1 AND #2 AND #7 | Full text | 136 |

## References


[1] Oke MA, Afolabi FJ, Oyeleke OO, Kilani TA, Adeosun AR, et al. Ganoderma lucidum: Unutilized natural medicine and promising future solution to emerging diseases in Africa. Front Pharmacol [Internet]. 2022;13:952027

[2] El Sheikha AF. Nutritional profile and health benefits of Ganoderma lucidum "Lingzhi, Reishi, or Mannentake" as functional foods: current scenario and future perspectives. Foods 2022;11:1030.

[3] Park HJ. Current uses of mushrooms in cancer treatment and their anticancer mechanisms. Int J Mol Sci 2022;23:10502.

[4] Takahara M, Katakami N, Hayashino Y, Nishimura R, Suzuki H, et al. Different impacts of metabolic profiles on future risk of cardiovascular disease between diabetes with and without established cardiovascular disease: the Japan diabetes complication and its prevention prospective study 7 (JDCP study 7). Acta Diabetol 2022;59:57-65.

[5] Swarup S, Goyal A, Grigorova Y, Zeltser R. Metabolic Syndrome. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2024 Jan 11]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK459248/

[6] Heeren J, Scheja L. Metabolic-associated fatty liver disease and lipoprotein metabolism. Mol Metab 2021;50:101238.

[7] Boh B, Berovic M, Zhang J, Zhi-Bin L. Ganoderma lucidum and its pharmaceutically active compounds. Biotechnol Annu Rev 2007;13:265-301.

[8] Aref M, Khoshhali M, Ghasemi P, Adeli S, Heidari-Beni M, et al. Effect of Ganoderma lucidum on serum lipid profiles: A systematic review and meta-analysis on animal studies. J Res Med Sci 2023;28:70.

[9] Klupp NL, Chang D, Hawke F, Kiat H, Cao H, et al. Ganoderma lucidum mushroom for the treatment of cardiovascular risk factors. Cochrane Database Syst Rev 2015;2015:CD007259.

[10] Chan SW, Tomlinson B, Chan P, Lam CWK. The beneficial effects of Ganoderma lucidum on cardiovascular and metabolic disease risk. Pharm Biol 2021;59:1159-1169.

[11] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Syst Rev 2021;10:89.

[12] Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 2014;14:135.

[13] Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. Stat Methods Med Res 2018;27:1785-1805.

[14] Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.

[15] Kolaski K, Logan LR, Ioannidis JPA. Guidance to best tools and practices for systematic reviews. Jbi Evid Synth 2023;21:1699.

[16] Tantry TP, Karanth H, Shetty PK, Kadam D. Self-learning software tools for data analysis in meta-analysis. Korean J Anesthesiol 2021;74:459-461.

[17] Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557.

[18] Gao Y, Lan J, Dai X, Ye J, Zhou S. A Phase I/II Study of Ling Zhi Mushroom Ganoderma lucidum (W.Curt.:Fr.)Lloyd (Aphyllophoromycetideae) extract in patients with type ii diabetes mellitus. Int J Med Mushrooms 2004;6:.

[19] Gao Y, Chen G, Dai X, Ye J, Zhou S. A Phase I/II Study of Ling Zhi Mushroom *Ganoderma lucidum* (W.Curt.:Fr.) Lloyd (Aphyllophoromycetideae) Extract in Patients with Coronary Heart Disease. Int J Med Mushrooms 2004;6.

[20] Wang CW, Tschen JSM, Sheu WHH. Ganoderma lucidum on metabolic control in type 2 diabetes subjects - A double blinded placebo control study. J Intern Med Taiwan 2008;19:54-60.

[21] Chu TTW, Benzie IFF, Lam CWK, Fok BSP, Lee KKC, et al. Study of potential cardioprotective effects of Ganoderma lucidum (Lingzhi): results of a controlled human intervention trial. Br J Nutr 2012;107:1017-1027.

[22] Klupp NL, Kiat H, Bensoussan A, Steiner GZ, Chang DH. A double-blind, randomised, placebo-controlled trial of Ganoderma lucidum for the treatment of cardiovascular risk factors of metabolic syndrome. Sci Rep 2016;6:29540.

[23] Sargowo D, Purwanto EF, Nugroho FW, Kamila PA, Irawan D, et al. The role of polysaccharide peptides of miselia Ganoderma lucidum extracts on IL-1, IL-6, HSCRP and no in dislipidemic patients with or without hypertension in STEMI and NSTEMI patients. AIP Conf Proc 2019;2108:020027.

[24] Babamiri S, Mojani Qomi MS, Shiehmorteza M. The Efficacy of Ganoderma lucidum in Overweight Individuals: A Randomized Placebo-controlled trial. Mediterr J Nutr Metab 2022;15:263-271.

[25] Wachtel-Galor S, Szeto YT, Tomlinson B, Benzie IFF. Ganoderma lucidum ('Lingzhi'); acute and short-term biomarker response to supplementation. Int J Food Sci Nutr 2004;55:75-83.

[26] Wachtel-Galor S, Tomlinson B, Benzie IFF. Ganoderma lucidum ("Lingzhi"), a Chinese medicinal mushroom: biomarker responses in a controlled human supplementation study. Br J Nutr 2004;91:263-269.

[27] Chiu HF, Fu HY, Lu YY, Han YC, Shen YC, et al. Triterpenoids and polysaccharide peptides-enriched Ganoderma lucidum: a randomized, double-blind placebo-controlled crossover study of its antioxidation and hepatoprotective efficacy in healthy volunteers. Pharm Biol 2017;55:1041-1046.

[28] Wu Q, Zhang H, Wang PG, Chen M. Evaluation of the efficacy and safety of Ganoderma lucidum mycelium-fermented liquid on gut microbiota and its impact on cardiovascular risk factors in human. RSC Adv 2017;7:45093-45100.

[29] Sarikaphuti A, Napavichayanun S, Thaipitakwong T, Roskhrua P, Aramwit P. Longan syrup with lingzhi mushroom extract: Evaluation of safety and efficacy on immune and inflammatory modulation in healthy adults. Agric Nat Resour 2021;55:579-588.

[30] Pazzi F, Adsuar JC, Domínguez-Muñoz FJ, García-Gordillo MÁ, Gusi N, et al. Effects of Ganoderma lucidum and Ceratonia siliqua on blood glucose, lipid profile, and body composition in women with fibromyalgia. Nutr Hosp 2021;38:139-145.

[31] Teekachunhatean S, Sadja S, Ampasavate C, Chiranthanut N, Rojanasthien N, et al. Pharmacokinetics of ganoderic acids A and F after oral administration of Ling Zhi Preparation in healthy male volunteers. Evid-Based Complement Altern Med 2012;2012:780892.

[32] Wachtel-Galor S, Yuen J, Buswell JA, Benzie IFF. Ganoderma lucidum (Lingzhi or Reishi): A Medicinal Mushroom. In: Benzie IFF, Wachtel-Galor S, editors. Herbal Medicine: Biomolecular and Clinical Aspects [Internet]. 2nd ed. Boca Raton (FL): CRC Press/Taylor & Francis; 2011 [cited 2024 Jan 11]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK92757/

[33] Gao Y, Zhou S, Jiang W, Huang M, Dai X. Effects of ganopoly (a Ganoderma lucidum polysaccharide extract) on the immune

functions in advanced-stage cancer patients. Immunol Invest 2003;32:201-215.
[34] Sarker MMR. Antihyperglycemic, insulin-sensitivity and anti-hyperlipidemic potential of Ganoderma lucidum, a dietary mushroom, on alloxan- and glucocorticoid-induced diabetic Long-Evans rats. Funct Foods Health Dis 2015;5:450.
[35] Lim CY, In J. Considerations for crossover design in clinical study. Korean J Anesthesiol 2021;74:293-299.
[36] Li Y, Talbot CL, Chandravanshi B, Ksiazek A, Sood A, et al. Cordyceps inhibits ceramide biosynthesis and improves insulin resistance and hepatic steatosis. Sci Rep 2022;12:7273.
[37] Cao C, Yang S, Zhou Z. The potential application of Cordyceps in metabolic-related disorders. Phytother Res 2020;34:295-305.
[38] Mohamad Ansor N, Abdullah N, Aminudin N. Anti-angiotensin converting enzyme (ACE) proteins from mycelia of Ganoderma lucidum (Curtis) P. Karst. BMC Complement Altern Med 2013;13:256.
[39] Wu Q, Li Y, Peng K, Wang XL, Ding Z, et al. Isolation and characterization of three antihypertension peptides from the mycelia of Ganoderma Lucidum (Agaricomycetes). J Agric Food Chem 2019;67:8149-8159.
[40] Farský Š, Strišková A, Borčin M. Hypertension treatment in patients with metabolic syndrome and/or type 2 diabetes mellitus: analysis of the therapy effectivity and the therapeutic inertia in outpatient study. Cardiol Res Pract 2018;2018:e8387613.
[41] Hijikata Y, Yamada S. Effect of Ganoderma lucidum on postherpetic neuralgia. Am J Chin Med 1998;26:375-381.
[42] Zhang Q, Zuo F, Nakamura N, Ma CM, Hattori M. Metabolism and pharmacokinetics in rats of ganoderiol F, a highly cytotoxic and antitumor triterpene from Ganoderma lucidum. J Nat Med 2009;63:304-310.
[43] Berger A, Rein D, Kratky E, Monnard I, Hajjaj H, et al. Cholesterol-lowering properties of Ganoderma lucidum in vitro, ex vivo, and in hamsters and minipigs. Lipids Health Dis 2004;3:2.
[44] Ahmad MF, Ahmad FA, Zeyaullah Md, Alsayegh AA, Mahmood SE, et al. Ganoderma lucidum: novel insight into hepatoprotective potential with mechanisms of action. Nutrients 2023;15:1874.
[45] Zhong D, Xie Z, Huang B, Zhu S, Wang G, et al. Ganoderma Lucidum polysaccharide peptide alleviates hepatoteatosis via modulating bile acid metabolism dependent on FXR-SHP/FGF. Cell Physiol Biochem 2018;49:1163-1179.
[46] Susilo RJK, Winarni D, Husen SA, Hayaza S, Punnapayak H, et al. Hepatoprotective effect of crude polysaccharides extracted from Ganoderma lucidum against carbon tetrachloride-induced liver injury in mice. Vet World 2019;12:1987-1991.