Review Article

Effect of *Ganoderma lucidum* on serum lipid profiles: A systematic review and meta-analysis on animal studies

Maryam Aref[1], Mehri Khoshhali[2], Pouria Ghasemi[3], Shaghayegh Adeli[4], Motahar Heidari-Beni[1], Roya Kelishadi[2]

[1]Department of Nutrition, Child Growth and Development Research Center, Research Institute for Primordial Prevention of Non-Communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran, [2]Department of Pediatrics, Child Growth and Development Research Center, Research Institute for Primordial Prevention of Non-Communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran, [3]Department of Pediatrics, Isfahan University of Medical Sciences, Isfahan, Iran, [4]Department of Biochemistry and Diet Therapy, Faculty of Nutrition and Food Sciences, Tabriz University of Medical Sciences, Tabriz, Iran

Background: *Ganoderma lucidum* (*G. lucidum*) is one of the most popular edible mushrooms in the world which has various pharmacological components. Recently, some animal studies have investigated the lipid-lowering effects of *G. lucidum* and have shown contradictory results. This study aims to systematically review the effects of *G. lucidum* on lipid parameters in animal studies. **Materials and Methods:** A systematic search was conducted in the Medline database (PubMed), Scopus, Web of Science, Cochrane Library, and Google Scholar up to the end of January 2022. Only animal studies and all eligible randomized controlled trials (RCTs), including cluster RCTs and randomized crossover trials were included. The English language studies that assessed the effects of *G. lucidum* on lipid profiles including total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and very low-density lipoproteins (VLDL) were selected. **Results:** Among 358 studies, 49 articles were included in the systematic review and meta-analysis. *G. lucidum* consumption was associated with decreased levels of TG (standardized mean difference [SMD] = −1.52, 95% CI: −1.79, −1.24), TC (SMD = −1.51, 95% CI: −1.75, −1.27), LDL-C (SMD = −2.03, 95% CI: −2.37, −1.69) and VLDL (SMD =-1.06, 95% CI: −1.638, −0.482). Furthermore, *G. lucidum* consumption was associated with increased levels of HDL-C (SMD = 1.03, 95% CI: 0.73, 1.33). **Conclusion:** *G. lucidum* has favorable effects on TG, TC, LDL-C, HDL-C, and VLDL. Different doses of *G. lucidum* have various degrees of effectiveness on lipid profiles.

Key words: *Agaricales*, dyslipidemias, reishi

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INTRODUCTION

Lipid metabolism disorders can cause a variety of problems.[1] Hyperlipidemia, which is characterized by elevated levels of triglyceride (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C) and decreased levels of high-density lipoprotein cholesterol (HDL-C), has been considered an important globally public health problem.[2,3] Unhealthy dietary patterns with high-fat and high-calorie foods and drinks, gut microbiota disturbances, and genetic and environmental risk factors can lead to lipid profile abnormalities, atherosclerosis, and cardiovascular diseases.[4-7] There are various lipid-lowering drugs to prevent or treatment of subsequent diseases related to dyslipidemia.[8-11] Nowadays, using medicinal plants and traditional medicine have increased for prevention, promotion, and rehabilitation of noncommunicable diseases.[12] There are some functional foods such as some edible mushrooms with some bioactive compounds and antioxidant activities which could be considered as a nutritional strategy for preventing and treatment of hyperlipidemia. Edible mushrooms have

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Address for correspondence: Dr. Motahar Heidari-Beni, Department of Nutrition, Child Growth and Development Research Center, Research Institute for Primordial Prevention of Non-Communicable Disease, Hezarjerib St., Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: heidari.motahar@gmail.com, motahar.heidari@nutr.mui.ac.ir
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high amounts of fiber, protein, micronutrients, and low amounts of fat.[13-15]

Ganoderma lucidum (*G. lucidum*), known commercially as "Lingzhi" or "Reishi," is one of the most popular edible mushrooms in the world which has various pharmacological components such as triterpenoids, polysaccharides, peptides, ganoderic acids, steroids, and sterols.[16,17] It has been extensively used in traditional Chinese medicine that has a wide range of beneficial effects on improving different diseases including hepatitis, cancer, hypertension, hypercholesterolemia, diabetes, arthritis, and asthma. It has very low toxicity and without side effects.[18-21] Recently, some animal studies have investigated the lipid-lowering effects of *G. lucidum* and have shown contradictory results.[22] Some animal studies reported significant lipid-lowering effects of *G. lucidum*,[15,23] while others did not report any significant beneficial effects.[24]

Due to increasing interest in using *G. lucidum* as an adjunctive strategy for treatment dyslipidemia, the presence of inconsistent results of previous studies, insufficient human studies, and lack of comprehensive systematic review or meta-analysis, this study was designed to investigate the effects of *G. lucidum* on lipid parameters in animal studies with RCTs design.

MATERIALS AND METHODS

The current systematic review and meta-analysis study were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA) statement.[25] The protocol was registered on PROSPERO (ID: CRD42021225476)

Search strategy

A comprehensive literature search was conducted in Medline database (PubMed), Scopus, Web of Science, Cochrane Library, and Google Scholar up to the end of January 2022 using the following search terms ("*Ganoderma*" OR "*G. lucidum*") and ("blood lipid" OR "lipid profile" OR "blood cholesterol" OR "dyslipidemia" OR "hypercholesterolemia" OR "LDL-C" OR "LDL" OR "HDL-C" OR "HDL" OR "TC" OR "TG" OR "TG") The references of related review articles were checked to find undetected appropriate studies. The search strategy for each database is shown in Supplementary Table 1.

Inclusion criteria

Animal studies with randomized controlled trials (RCTs) design, including cluster RCTs and randomized cross-over trials, were included. The English language studies that assessed the effects of G. lucidum on lipid profiles including TC, TGs, HDL-C, or LDL-C were selected.

Excluded criteria

Observational studies, human or *in vitro* studies**,** duplicated articles, and studies with insufficient data were excluded from the study.

Data extraction

Two independent reviewers (MA and MHB) reviewed and screened the published papers based on title, abstract, and full text. Any disagreement related to eligible records was resolved by the third reviewer (RK).

If the article and data were not available, we emailed the corresponding author and requested to send the article. The following data were extracted from relevant studies: first author's name, year of publication, study design, study duration, species and sex, number of animal in each group, type of *G. lucidum*, dose of *G. lucidum* supplementation, and mean of levels of TG, TC, LDL-C, and HDL-C before and after the intervention.

Quality assessment

The quality of included studies was assessed using The Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies (CAMARADES) tool by two independent reviewers (MA, PGh). Any discrepancy was resolved by third reviewer (MHB). The scale consists of 10 questions. Supplementary Table 2 shows the quality assessment of included studies.

Statistical analysis

The mean changes in lipid profiles before and after the administration of *G. lucidum* between groups of treatment and control were extracted from included studies. The effect size of standardized mean difference (SMD) was calculated by dividing the mean difference of lipid profiles between treatment and control groups by its standard deviation. The potential heterogeneity across studies was assessed using Cochran's Q-test and expressed using the I^2 index. A random-effects model was used to estimate the SMDs. Subgroup analyses based on disease status (hyperlipidemic, diabetic, and healthy animals), dose of *G. lucidum* (<75, 75–150, 150–300, > =300 mg/kg), and gender of animals (male, female, and both) were performed to seek the sources of heterogeneity. In addition, meta-regression was used for assessing continuous variables including dose of *G. lucidum*, mean age, treatment duration, sample size, and year of publication of studies, to find the possible source of heterogeneity. The sensitivity analyses were performed by excluding one or several studies at a time to gauge the robustness of our results. Publication bias was evaluated by Funnel plot and Egger's test. All statistical analyses were conducted using the software STATA 12.0 (STATA Corp, College Station, Texas, USA).

RESULTS

Study selection

The flow diagram for the process of study selection is shown in Figure 1. The initial search recognized 358 articles and 226 of them remained after excluding duplicates. After screening the title and abstracts, 127 articles were excluded, and 99 articles remained for further assessment. The full texts of the remaining studies were reviewed carefully by two researchers. Any discrepancy was resolved by the third reviewer. Finally, 49 articles were included in the systematic review and meta-analysis. Characteristics of included studies are shown in Supplementary Table 2. Quality assessment of included studies is shown in Supplementary Table 3.

Influence of *Ganoderma lucidum* on lipid profiles

Table 1 shows estimated pooled SMD and 95% CI for the influence of *G. lucidum* on TG, TC, LDL-C, HDL-C, and very low-density lipoproteins (VLDL) between treatment and control groups. *G. lucidum* consumption was associated with decreased levels of TG, TC, LDL-C, and VLDL and was associated with increased levels of HDL-C. The pooled SMD was estimated negative and significant for TG (SMD = −1.52, 95% CI:-1.79, −1.24), TC (SMD = −1.51, 95% CI: −1.75, −1.27), LDL-C (SMD = −2.03, 95% CI: −2.37, −1.69) and VLDL (SMD = −1.06, 95% CI: −1.638, −0.482). Furthermore, the pooled SMD was estimated positive and significant for HDL-C (SMD = 1.03, 95% CI: 0.73, 1.33).

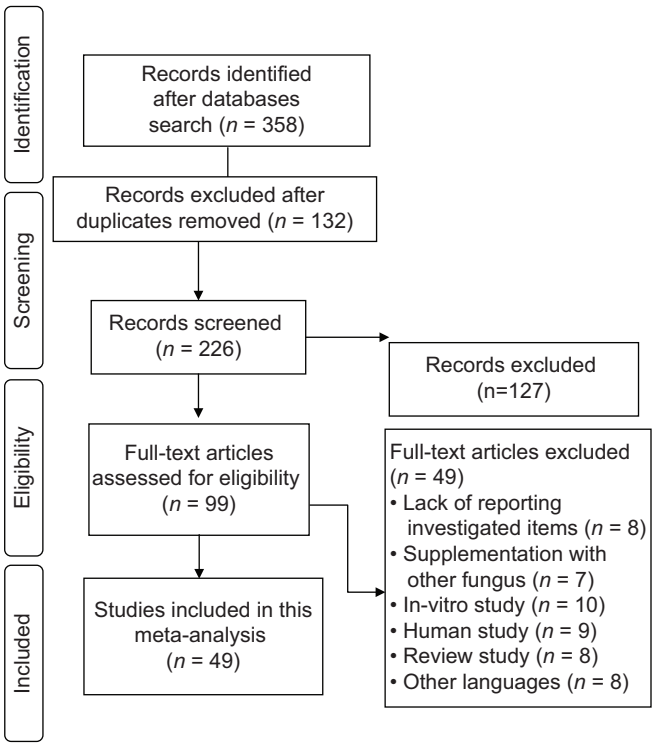

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart of study selection process

For all lipid profiles, funnel plots were asymmetry [Supplementary Figures 1-5], and Egger's tests were significant ($P < 0.001$). Therefore, there was publication bias among these studies. Trim and fill analysis was conducted. Only for TG levels, 3 studies were filled to adjust publication bias. The pooled SMD based on filled meta-analysis was estimated negative and significant (SMD = −1.57, 95% CI: −1.86, −1.28) but for other lipids, no study was filled. Hence, the publication bias had a non-significant effect on the results. The heterogeneity between studies was more than 80% for all lipid profiles except VLDL (I^2 = 66.40%). Therefore, the subgroup analysis and meta-regression were used to explore the potential sources of heterogeneity. Results of subgroup meta-analysis according to disease status, dose of *G. lucidum,* and gender are presented in Tables 2-4. The pooled SMD showed *G. lucidum* was associated with decreased levels of TG, cholesterol, and LDL in hyperlipidemic and diabetic rats. The highest degree of effectiveness of *G. lucidum* was shown for LDL-C levels (SMD = −2.49, 95% CI: −3.01, −1.98) in diabetic rats. The pooled SMD showed *G. lucidum* was associated with increased levels of HDL-C levels in hyperlipidemic and diabetic rats. In healthy rats, the pooled SMD was negative and significant for TC and LDL-C. However, there was evidence of heterogeneity between the included studies. The heterogeneity between studies was more than 60% ($P < 0.05$).

The highest degree of effectiveness of *G. lucidum* was with doses >300 mg/kg (SMD = −2.22, 95% CI: −3.01, −1.43) on TG levels, 150–300 mg/kg (SMD = −1.87, 95% CI: −2.56, −1.19) and 75–150 mg/kg (SMD = −2.90, 95% CI: −3.68,

Table 1: Estimated pooled standardized mean difference and 95% confidence interval for the influence of *Ganoderma* on lipid profiles

Lipid profiles (mg/dL)	Number of study	Pooled SMD (95% CI)	*P**	I^2 (%)	*P***	Egger	*P****	Number of filled studies	Pooled SMD (95% CI)
TG	45	−1.52 (−1.79–−1.24)	<0.001	83.80	<0.001	−4.73	<0.001	3	−1.57 (−1.86–−1.28)
TC	43	−1.51 (−1.75–−1.27)	<0.001	80.60	<0.001	−15.93	<0.001	0	-
LDL	41	−2.03 (−2.37–−1.69)	<0.001	84.60	<0.001	−13.67	<0.001	0	-
HDL	46	1.03 (0.73–1.33)	<0.001	83.20	<0.001	7.04	<0.001	0	-
VLDL	6	−1.06 (−1.638–−0.482)	<0.001	66.40	<0.001	−4.3	0.002	0	-

*P-value of pooled SMD, **P-value of Cochran's Q-test, ***P-value of egger test. TG: Triglycerides, TC: Total cholesterol, LDL: Low-density lipoprotein cholesterol, HDL: High-density lipoprotein cholesterol, VLDL: Very LDL, SMD: Standardized mean difference, CI: Confidence interval

Table 2: Subgroup meta-analysis of pooled standardized mean difference and 95% confidence interval for the influence of *Ganoderma* on lipid profiles by disease status

lipid profiles (mg/dL)	Number of studies	Pooled SMD (95% CI)	*P**	I^2 (%)	*P***
TG					
Hyperlipidemic	13	−1.86 (−2.42−−1.31)	<0.001	81.40	<0.001
Diabetic	30	−2.04 (−2.46−−1.63)	<0.001	83.90	<0.001
Healthy	12	−0.31 (−0.63-0.01)	0.059	67.50	<0.001
TC					
Hyperlipidemic	13	−1.91 (−2.44−−1.37)	<0.001	81.40	<0.001
Diabetic	29	−1.82 (−2.19−−1.44)	<0.001	81.40	<0.001
Healthy	11	−0.69 (−1.03−−0.35)	<0.001	70.40	<0.001
LDL					
Hyperlipidemic	13	−2.16 (−2.79−−1.53)	<0.001	85.10	<0.001
Diabetic	20	−2.49 (−3.01−−1.98)	<0.001	84.50	<0.001
Healthy	8	−0.74 (−1.27−−0.21)	0.006	74.50	<0.001
HDL					
Hyperlipidemic	11	1.41 (0.68-2.13)	<0.001	88.40	<0.001
Diabetic	21	1.27 (0.89-1.66)	<0.001	79.90	<0.001
Healthy	7	0.06 (−0.40-0.52)	0.791	71.40	<0.001
VLDL					
Healthy	3	−0.72 (−1.52-0.08)	0.078	64.30	0.024

**P*-value of pooled SMD, ***P*-value of Cochran's *Q*-test. TG: Triglycerides, TC: Total cholesterol, LDL: Low-density lipoprotein cholesterol, HDL: High-density lipoprotein cholesterol, VLDL: Very LDL, SMD: Standardized mean difference, CI: Confidence interval

Table 3: Subgroup meta-analysis of pooled standardized mean difference and 95% confidence interval for the influence of *Ganoderma* on lipid profiles by dose of *Ganoderma*

	Number of studies	Pooled SMD (95% CI)	*P**	I^2 (%)	*P***
TG (mg/dL)					
<75 mg/kg	21	−1.03 (−1.41−−0.64)	<0.001	67.60	<0.001
75-150 mg/kg	24	−1.70 (−2.23−−1.17)	<0.001	82.50	<0.001
150-300 mg/kg	21	−1.89 (−2.65−−1.13)	<0.001	88.30	<0.001
>300 mg/kg	12	−2.22 (−3.01−−1.43)	<0.001	88.90	<0.001
TC (mg/dL)					
<75 mg/kg	21	−1.34 (−1.70−−0.98)	<0.001	61.70	<0.001
75-150 mg/kg	23	−1.80 (−2.30−−1.31)	<0.001	79.50	<0.001
150-300 mg/kg	20	−1.87 (−2.56−−1.19)	<0.001	86.30	<0.001
>300 mg/kg	11	−1.86 (−2.55−−1.16)	<0.001	86.80	<0.001
LDL (mg/dL)					
<75 mg/kg	15	−1.72 (−2.32−−1.12)	<0.001	80.20	<0.001
75-150 mg/kg	16	−2.90 (−3.68−−2.12)	<0.001	85.00	<0.001
150-300 mg/kg	13	−1.89 (−2.63−−1.14)	<0.001	84.90	<0.001
>300 mg/kg	9	−2.86 (−3.86−−1.85)	<0.001	89.00	<0.001
HDL (mg/dL)					
<75 mg/kg	15	0.45 (−0.15-1.05)	0.14	83.50	<0.001
75-150 mg/kg	16	1.26 (0.69-1.83)	<0.001	81.80	<0.001
150-300 mg/kg	13	0.87 (0.22-1.52)	0.009	83.60	<0.001
>300 mg/kg	9	1.92 (1.02-2.81)	<0.001	88.20	<0.001
VLDL (mg/dL)					
75-150 mg/kg	3	−0.78 (−1.42−−0.13)	0.018	16.40	0.31
150-300 mg/kg	3	−1.58 (−3.09−−0.07)	0.041	84.50	<0.001

**P*-value of pooled SMD, ***P*-value of Cochran's *Q*-test. TG: Triglycerides, TC: Total cholesterol, LDL: Low-density lipoprotein cholesterol, HDL: High-density lipoprotein cholesterol, VLDL: Very LDL, SMD: Standardized mean difference, CI: Confidence interval

−2.12) on LDL-C levels, >300 mg/kg (SMD = 1.92, 95% CI: 1.02, 2.81) and 150–300 mg/kg (SMD = −1.58, 95% CI: −3.09, −0.07) on VLDL levels. Furthermore, *G. lucidum* had the highest degree of effectiveness on LDL-C levels in male rats (SMD = −2.27, 95% CI: −2.66, −1.89). However, there was evidence of heterogeneity between the included studies ($P < 0.05$).

Results of meta-regression showed that there was a positive and significant association between mean age and duration

of studies with pooled SMD of LDL-C and explain more than 83% of the heterogeneity between studies. Furthermore, the mean age and year of publication of studies contributed to the heterogeneity between studies related to HDL-C and VLDL levels, respectively [Table 5].

DISCUSSION

The present meta-analysis study investigated the effects of *G. lucidum* on lipid parameters in animal models. According to our findings, *G. lucidum* has lowering effects on TG, TC, LDL-C, HDL-C, and VLDL levels. Different doses of *G. lucidum* have various degrees of effectiveness on lipid profiles.

Some mechanisms were suggested related to the effect of *G. lucidum* on lipid profiles. *G. lucidum* inhibits cholesterol synthesis in T9A4 hepatocytes and decreases cholesterol levels. *G. lucidum* reduces the activity of 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase.[26]

G. lucidum influences the expression of some enzymes related to lipids including fatty acid synthase (FAS), acyl-CoA synthetase-1 (ACS1), fatty acid binding protein-4 (FABP4), and fatty acid transport protein-1 (FATP1).[27]

Studies on mice showed that *G. lucidum* extract could inhibit the increase of cholesterol and LDL levels by the reduction of AMP-activated protein kinase (AMPK) and acetyl-CoA carboxylase (ACC) phosphorylation in the liver.[28]

G. lucidum reduces the expression of sterol regulatory element-binding transcription factor 1 (SREBP1c), FAS, and ACC through a farnesoid X receptor and small heterodimer partner (FXR-SHP)-dependent mechanism and finally inhibits fatty acid synthesis and lipid droplets accumulation and the content of TG in the liver cell.[29]

Effect of *Ganoderma lucidum* on high-density lipoprotein cholesterol levels

Our results showed the beneficial effects of *G. lucidum* on HDL-C levels. However, some studies did not show any significant effect of *G. lucidum* on all lipid profiles[30-33] or only on HDL-C levels.[23,34-39] It seems that *G. lucidum* do not have significant effects on HDL-C levels in low doses and its effect becomes significant by increasing its dose.[40] Hence, it can be concluded that the method of purification is effective. There are different ways to use the active ingredient of *G. lucidum*. A traditional method of using *G. lucidum* is infusion with water and its powder. To achieve the maximum effect in this method, the cell walls must be completely destroyed during grinding. The most common method of purification is the use of ethanol and methanol. The use of different methods of consumption and purification, lack of knowledge about the dosage, and different quality of the consumed substance are the reasons of different results of studies.[41] It should be noted that in several articles, the use of *G. lucidum*, either in powder or purified form did not have significant adverse effects.[42,43]

Effect of *Ganoderma lucidum* on total cholesterol levels

Six studies reported no significant association between *G. lucidum* consumption and TC levels.[30,31,33,37,44,45] However, some studies showed significant beneficial effects of *G. lucidum* on TC levels.[34-36]

The reason for the contradiction between the results of the studies can be due to the following reasons. Rats do not have a gall bladder, so the access of the liver to unmodified cholesterol is limited as part of secreted substances to the intestine through bile and bile salt. In addition, high-fat diet

Table 4: Subgroup meta-analysis of pooled standardized mean difference and 95% confidence interval for influence of *Ganoderma* lucidum on lipid profiles by gender of rats

lipid profiles (mg/dL)	Number of studies	Pooled SMD (95% CI)	*P**	I^2 (%)	*P***
TG					
Male	40	−1.67 (−1.98−−1.35)	<0.001	82.90	<0.001
Female	6	−0.10 (−0.65-0.45)	0.733	75.30	<0.001
TC					
Male	38	−1.76 (−2.07−−1.46)	<0.001	81.70	<0.001
Female	5	−0.37 (−0.70−−0.03)	0.033	46.60	0.018
LDL					
Male	32	−2.27 (−2.66−−1.89)	<0.001	85.60	<0.001
Female	4	−0.56 (−1.12-0.00)	0.051	52.50	0.04
HDL					
Male	16	1.16 (0.84-1.49)	<0.001	83.30	<0.001
Female	3	−0.03 (−0.89-0.84)	0.954	81.60	<0.001
VLDL					
Male	3	−1.02 (−1.72−−0.33)	0.004	69.70	<0.001

*P-value of pooled SMD, **P-value of Cochran's Q-test. TG: Triglycerides, TC: Total cholesterol, LDL: Low-density lipoprotein cholesterol, HDL: High-density lipoprotein cholesterol, VLDL: Very LDL, SMD: Standardized mean difference, CI: Confidence interval

Table 5: Results of meta-regression analysis for lipid profiles

	β (SE)	*P*	I^2 (%)
TG (mg/dL)			
Dose (mg/kg)	−0.001 (0.001)	0.55	83.98
Sample size	−0.02 (0.05)	0.666	83.71
Year	0.01 (0.05)	0.769	83.90
Age mean (weeks)	0.07 (0.05)	0.184	81.56
Duration of intervention (weeks)	−0.01 (0.05)	0.873	83.56
TC (mg/dL)			
Dose	−0.0003 (0.001)	0.764	80.94
Sample size	0.07 (0.04)	0.084	80.17
Year	0.01 (0.04)	0.766	80.72
Age mean (weeks)	0.06 (0.04)	0.106	76.27
Duration of intervention (weeks)	0.06 (0.04)	0.13	80.78
LDL (mg/dL)			
Dose (mg/kg)	−0.0002 (0.001)	0.865	84.81
Sample size	−0.02 (0.06)	0.715	84.53
Year	0.01 (0.07)	0.841	84.76
Age mean (weeks)	0.13 (0.05)	0.014	83.39
Duration of intervention (weeks)	0.14 (0.07)	0.038	84.76
HDL (mg/dL)			
Does (mg/kg)	0.002 (0.001)	0.173	84.11
Sample size	0.03 (0.04)	0.438	82.73
Year	0.003 (0.05)	0.948	83.30
Age mean (weeks)	−0.12 (0.06)	0.046	86.04
Duration of intervention (weeks)	−0.08 (0.05)	0.111	83.28
VLDL (mg/dL)			
Dose (mg/kg)	−0.01 (0.01)	0.22	72.05
Sample size	0.11 (0.07)	0.128	62.46
Year	0.16 (0.06)	0.026	46.64
Age mean (weeks)	−2.27 (0.89)	0.062	7.62
Duration of intervention (weeks)	−0.07 (0.11)	0.511	64.42

TG: Triglycerides, TC: Total cholesterol, LDL: Low-density lipoprotein cholesterol, HDL: High-density lipoprotein cholesterol, VLDL: Very LDL, SE: Standard error

was used in several studies which neutralized the effect of *G. lucidum*.[30]

Effect of *Ganoderma lucidum* on low-density lipoprotein cholesterol levels

Several studies showed the beneficial effects of *G. lucidum* on LDL-C levels. Four studies reported that *G. lucidum* had a non-significant effect on LDL-C along with other lipid profile components.[30,31,44,46]

Different purification methods, dosage and duration of G.lucidum consumption lead to various results in studies. 4 weeks' intervention with *G. lucidum* reduced LDL-C by 44% while 8 weeks of intervention reduced LDL-C by 54%.[47]

Effect of *Ganoderma lucidum* on very low-density lipoproteins levels

Among the studies, only three studies investigated VLDL, one of which explicitly reported a significant effect of *G. lucidum* on VLDL levels[38] and another reported a significant effect only for mycelium products not fruitbody products of *G. lucidum*.[48] The third study showed that *G. lucidum* reduced the levels of VLDL. However, results were not significant.[37] The fruit body and mycelium product had hypoglycemic and hypolipidemic effects. However, it has a synergistic effect when taken together.[48]

Due to the limited number of studies, it is not possible to confidently comment on the effectiveness of *G. lucidum* and its mechanism on VLDL levels. It requires additional studies.

Effect of *Ganoderma lucidum* on triglyceride levels

Several studies showed *G. lucidum* consumption had a significant effect on TG levels.[34,35] Non-significant effect was reported in eight studies.[31-33,37,44,46,48,49] In seven of them non-significant effects were reported for other lipid profile components and in one study[49] it was reported only for TG levels.

In various studies, the intervention was done on healthy or unhealthy animals, but most of them reported the beneficial effects of *G. lucidum* on TG levels.

CONCLUSION

Meta-analysis of animal studies showed that *G. lucidum* had beneficial effects on lipid profiles. However, there are still many uncertainties about its mechanism and effects on metabolism. It is suggested that due to the absence of significant side effects regarding this type of mushroom and its beneficial effects, it can be used for the prevention or even treatment of abnormal lipid profiles.

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Conflicts of interest

There are no conflicts of interest.

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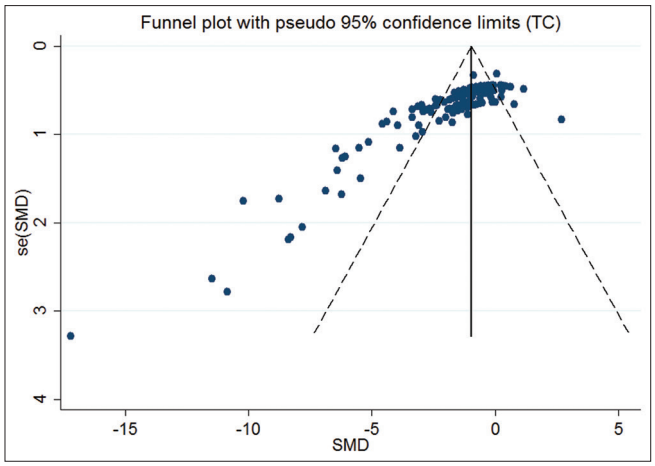
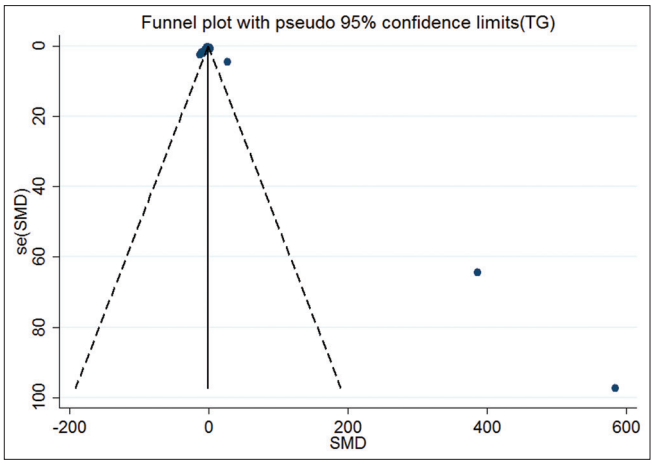
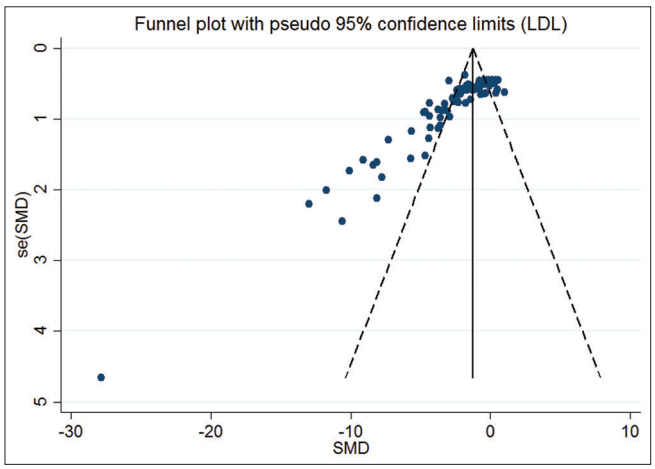


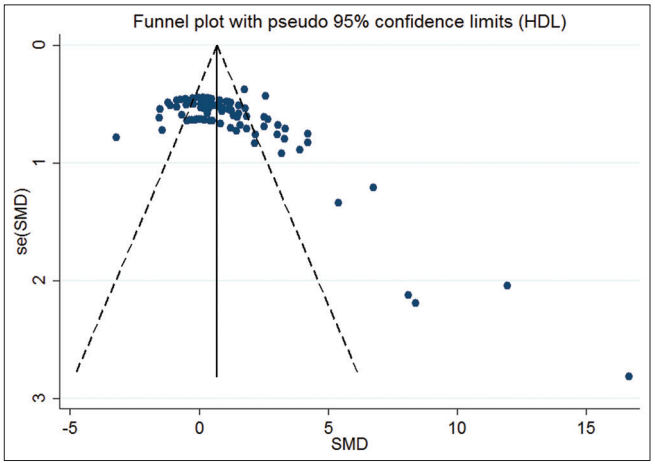
Supplementary Figure 1: Funnel plot of the effect of *Ganoderma* on total cholesterol. TC: Total cholesterol



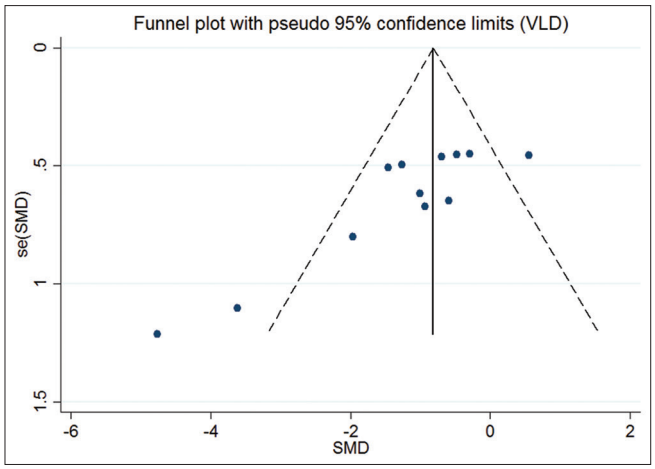
Supplementary Figure 2: Funnel plot of the effect of *Ganoderma* on triglyceride. TG: Triglyceride



Supplementary Figure 3: Funnel plot of the effect of *Ganoderma* on low-density lipoprotein cholesterol. LDL: Low-density lipoprotein



Supplementary Figure 4: Funnel plot of the effect of *Ganoderma* on high-density lipoprotein cholesterol. HDL: High-density lipoprotein



Supplementary Figure 5: Funnel plot of the effect of *Ganoderma* on very low-density lipoproteins. VLDL: Very low-density lipoproteins

Supplementary Table 1: Search strategy for each database

Database	Search strategy
PubMed	#1 “Ganoderma“ [MeSH Terms] OR “G.lucidum” [ti, ab] OR “ Ganoderma lucidum“ [ti, ab] #2 “blood lipid“ [ti, ab] OR “lipid profile”[ti, ab] OR “blood cholesterol”[ti, ab] OR “dyslipidemia”[MeSH Terms] OR “hypercholesterolemia”[MeSH Terms] OR “low-density lipoprotein cholesterol”[ti, ab] OR “ Cholesterol, LDL”[MeSH Terms] OR “LDL”[ti, ab] OR “high-density lipoprotein cholesterol”[ti, ab] OR “ Cholesterol, HDL”[MeSH Terms] OR “HDL”[ti, ab] OR “total cholesterol”[ti, ab] OR “triglycerides”[MeSH Terms] OR “TG”[ti, ab] #1 AND #2
Scopus	#1 “Ganoderma” [ti, ab, kw] OR “G.lucidum” [ti, ab, kw] OR “ Ganoderma lucidum” [ti, ab, kw] #2 “lipid profile”[ti, ab, kw] OR “blood cholesterol”[ti, ab, kw] OR “dyslipidemia”[ti, ab, kw] OR “hypercholesterolemia”[ti, ab, kw] OR “low-density lipoprotein cholesterol”[ti, ab, kw] OR “LDL”[ti, ab, kw] OR “high-density lipoprotein cholesterol”[ti, ab, kw] OR “HDL”[ti, ab, kw] OR “total cholesterol”[ti, ab, kw] OR “triglycerides”[ti, ab, kw] OR “TG”[ti, ab, kw] #1 AND #2
Cochrane library	#1 “Ganoderma” [ti, ab, kw] OR “G.lucidum” [ti, ab, kw] OR “ Ganoderma lucidum” [ti, ab, kw] #2 “lipid profile”[ti, ab, kw] OR “blood cholesterol”[ti, ab, kw] OR “dyslipidemia”[ti, ab, kw] OR “hypercholesterolemia”[ti, ab, kw] OR “low-density lipoprotein cholesterol”[ti, ab, kw] OR “high-density lipoprotein cholesterol”[ti, ab, kw] OR “total cholesterol”[ti, ab, kw] OR “triglycerides”[ti, ab, kw] #1 AND #2
Web of Science	#1 “Ganoderma” [topic] OR “G.lucidum” [topic] OR “Ganoderma lucidum” [topic] #2 “lipid profile”[topic] OR “blood cholesterol”[topic] OR “dyslipidemia”[topic] OR “hypercholesterolemia”[topic] OR “low-density lipoprotein cholesterol”[topic] OR “high-density lipoprotein cholesterol”[topic] OR “total cholesterol”[topic] OR “triglycerides”[topic] #1 AND #2
Google Scholar	((“Ganoderma” OR “G.lucidum” OR” Ganoderma lucidum”) AND (“lipid profile” OR “blood cholesterol”OR “dyslipidemia” OR “hypercholesterolemia” OR “low-density lipoprotein cholesterol” OR “high-density lipoprotein cholesterol” OR “total cholesterol” OR “triglycerides”))

Supplementary Table 2: Characteristics of included studies

Study reference year	Animal model	Dose of Ganoderma	Duration	Sex	Sample size	Lipid profile	Result
Adeyi A, 2021	Rats	26 mg/kg 44 mg/kg 70 mg/kg	2 weeks	Male	30	TG, TC, HDL, LDL	Ganoderma (70 mg/kg body weight) showed, anti-dyslipidemia effects (TG, CHOL, LDL levels reduced dose dependently) were markedly (P<0.05) in a rat model of metabolic syndrome
Bach E, 2018	Wistar rats	1.00 mg/kg	4 weeks	Male	20	TG, TC	Biochemical analysis also showed an effect of a decrease of total CHOL, triglycerides
Chen M, 2019	Rats	400 mg/kg	4 weeks	Male	16	TG, TC, HDL, LDL	Ganoderma treatment reduced the levels of serum TC, TG, LDL, in T2DM rats. These results were consistent with a previous GLP administration which reduced serum TC, TG, LDL, levels, in HFD-induced obesity mice
Elhussainy E, 2016	Rats	50 mg/kg 100 mg/kg	8 weeks	Male	40	TG, TC, HDL, LDL	Treatment Ganoderma with low dose in diabetic rats significantly decrease the levels of serum TC, TG, LDL (P<0.01), and significantly increase the levels of HDL (P<0.05) compared to untreated diabetic rats. While with high dose in diabetic rats significantly decrease the levels of serum TC, TG, LDL (P<0.001), and significantly increase the levels of HDL (P<0.001) compared to STZ-induced diabetic rats
Eroglu H, 2018	Wistar rats	60 mg/kg 120 mg/kg 180 mg/kg	3 weeks	Male	60	TG, TC, HDL, LDL	With the diabetic rats, the dose of 60, 120 and 180 mg/kg of Ganoderma effected in the increase of total TC, TG, VLDL, HDL levels, although it was not a significant change (P>0.05), instead, we observed a statistically significant decrease of LDL level (P<0.05)
Guo W, 2020	Mice	15 mg/kg 75 mg/kg	8 weeks	Male	40	TG, TC, HDL, LDL	Supplementation with GA markedly reduced serum TG, TC and LDL levels in HFD-fed mice (P<0.05) but did not significantly increase the serum HDL-C level
Guo W, 2018	Wistar rats	150 mg/kg	8 weeks	Male	20	TG, TC, HDL, LDL	Oral administration of GL95 markedly alleviated the dyslipidemia through decreasing the levels of serum TG, TC and LDL, and inhibiting hepatic lipid accumulation and steatosis. Consumption for 8 weeks significantly elevated the serum HDL level compared with the HFD and Sym groups (P<0.05)
Heriansyah T, 2015	Wistar rats	50 mg/kg 150 mg/kg 300 mg/kg	12 weeks	Male/ female	35	TG, TC	*G. lucidum* PsP is beneficial in lowering the levels of lipid profiles TG and TC
Hu R, 2018	Wistar rats	150 mg/kg	8 weeks	Male	32	TG, TC, HDL, LDL	The investigation of serum TG, TC, LDL, levels demonstrated that GL55 significantly improved these parameters compared with the HFD group
Li F, 2011	Mice	50 mg/kg 150 mg/kg	4 weeks	Male	32	TG, TC, HDL, LDL	Supplementation resulted in lowering the TC, TG and LDL levels with elevation of HDL levels
Meng G, 2011	Rats	200 mg/kg 400 mg/kg 800 mg/kg	16 weeks	Male/ female	40	TG, TC	GLP decrease TC and TG in high-fat fed/STZ diabetic rats. In the DC group, TC and TG were increased compared with the NC group. After treatment, TC and TG in the GLP-M or GLP-H group were reversed to the value that was significantly lower than that in DC group
Oluba M,2010	Wistar rats	100 mg/kg 200 mg/kg	4 weeks	Male	60	TG, TC, HDL, LDL, VLDL	It is observed that the extract produced a significant decrease in serum TG, TC, VLDL and LDL- in normal rats and STZ-diabetic rats. In addition, serum HDL was significantly increased in STZ-diabetic rats given 200 mg/kg of the extract at the end of the 4th week

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Supplementary Table 2: Contd...

Study reference year	Animal model	Dose of Ganoderma	Duration	Sex	Sample size	Lipid profile	Result
Pan D, 2014	Mice	75 mg/kg 250 mg/kg 450 mg/kg	8 weeks	Male	60	TG, TC, HDL, LDL	TG and TC were significantly decreased by 47.8% (P<0.01) and 41.0% (P<0.01) for high dose, compared with those for the control. Furthermore, the serum LDL levels for both middle and high-dosage of FYGL treated mice were significantly (P<0.01) lower than those for control group, whereas the serum HDL level for those nutritional supplement-treated groups were higher (P<0.01) than that for control group
Pan R, 2021	Mice	100 mg/kg 400 mg/kg	8 weeks	Male	24	TG, TC, HDL, LDL	The concentration of TC, TG, LDL in the wildtype (P<0.001), GLP (P<0.01) and MET groups (P<0.01) were significantly lower compared with the model control group. Additionally, the concentration of HDL in the serum of mice in the wildtype (P<0.001), GLP (P<0.001 or P<0.05) and MET groups (P<0.01) was significantly higher compared with the model control group
Sargowo D, 2015	Rats	50 mg/kg 150 mg/kg 300 mg/kg	5 weeks	Male	25	TG, TC, HDL, LDL	PsP treatment decreased CHOL total level [Tabel 1] and increased HDL level significantly (P=0.04 and P=0.002 respectively) at PsP dose 50, 150, 300 mg/kg BW, but there is no correlation with LDL and triglyceride level (P=0.129 and P=0.340)
Sargowo D, 2017	Wistar rats	50 mg/kg 150 mg/kg 300 mg/kg	12 weeks	Male/ female	35	TG, TC, HDL, LDL	The administration of *G. lucidum* PsP to diabetic model rats provided a significant difference in lowering foam cell (P=0.017; CI 95%). It also gave significant difference between levels of each lipid components (TC, TG, LDL and HDL) in at least two treatment groups (P=0.010; CI 95%)
Sarker M, 2015	Rats	200 mg/kg 400 mg/kg 600 mg/kg 800 mg/kg	7 days	Male	55	TG, TC, HDL, LDL	With GLPEE (800 mg/kg) significantly reduced TC (P<0.001), TG (P<0.001) and LDL (P<0.001) levels, HDL level was significantly increased (P<0.01) compared to diabetic control rats. Similarly, GL-ME significantly reduced TC, TG and LDL and increased HDL levels compared to untreated diabetic rats. Overall, the effect of GL-PEE was comparatively better than of GL ME
Seto S, 2009	Mice	0.03 g/kg 0.3 g/kg	4 weeks	Female		TG, TC, HDL, LDL	There was no apparent difference in TG levels measured between + db/+ m and + db/+ db mice (P>0.05), and *G. lucidum* consumption failed to alter the TG. In contrast, there was a higher level of TC and LDL (and a lower level of HDL in + db/+ db mice, compared to + db/+ m mice. *G. lucidum* consumption failed to modify TC, HDL and LDL levels measured in + db/+ m mice. In + db/+ db mice, *G. lucidum* (0.3 g/kg) reduced the LDL-CHOL level and the atherogenic index TC/LDL, compared to controls (P<0.05)
Sharma P, 2019	Mice	50 mg/kg 100 mg/kg 200 mg/kg 500 mg/kg 1000 mg/kg	1 weeks 90 days	Male/ female	100	TG, TC	CR-induced elevated levels of TC, TG were dose dependently reduced with GLAQ and effects were better in comparison to positive control (gallic acid). But with extract treatment the levels of TG, and TC were normalized to control levels

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Supplementary Table 2: Contd...

Study reference year	Animal model	Dose of Ganoderma	Duration	Sex	Sample size	Lipid profile	Result
Tong C, 2008	Rats	0.1%	6 months	Male	24	TG, TC, HDL, LDL	Supplementation of the feed with *G. lucidum* (0.1%) in rats decreased the TC, TG and LDL level significantly ($P<0.05$) while further increased the plasma concentration of HDL. In the case of rats fed with diet containing a mixture of 1% CHOL and 0.1% of Ganoderma, the lipid profile showed much higher readings ($P<0.05$) compared to the chol group. This seemed to indicate the possible hypocholesterolemic effect of *G. lucidum* in reducing the deposition of CHOL on the wall of the blood vessels
Tseng H, 2018	Mouse	150 mg/kg 300 mg/kg	12 weeks	Male		TG, TC, LDL	Ganoderma had beneficial effects on lipid profiles
Wang F, 2015	Rats	1 g/day	4 weeks	Male	24	TG, TC, HDL, LDL	Following the therapeutic treatment of GLSP, the blood TG fell significantly by 49.0% and TC reduced by 17.8%, respectively, as compared to the nontreatment group. This study found that *G. lucidum* intervention could significantly enhance level HDL by 48.6% ($P<0.01$) compared to the model control. It is interesting to note that there was no significant difference in HDL between normal group and GLSP intervention group ($P=0.6850$)
Wang C, 2012	Mice	75 mg/kg 225 mg/kg	4 weeks	Male		TG, TC, HDL, LDL	TG, TC, LDL and HDL levels were significantly decreased by 52.8% ($P<0·01$), 65.9% ($P<0·001$), 75.2% ($P<0·001$) and 41.7% ($P<0·05$), respectively, in db/db diabetic mice treated with a high dose of FYGL, compared with those for the diabetic control, and the potency of FYGL was dose-dependent
Wihastuti T, 2016	Wistar strain	300 mg/kg/h 600 mg/kg/h 1200 mg/kg/h	90 days	Male/ female	80	TG, TC, HDL, LDL	The examination showed not significant at the lipid profile (TC, TG, HDL, and LDL) and leukocytes
Chen, 2008	Weanling piglets	0 (control), 50, 100 and 150 mg/kg feed	2 and 4 weeks	-	72	TG, TC	Ganoderma had not significant beneficial effects on lipid profiles
Hikino H, 1989	Mice	100 mg/kg	5 h	Male	-	TG, TC	Ganoderma had not significant beneficial effects on lipid profiles
Huang, 2020	SD rats	1% or 3% freeze-dried *G. lucidum*	5 weeks	Male	48	-	TBARS, a marker for lipid peroxidation, were reduced
Lai P, 2020	Japanese white rabbits	6, 24, 96 mg/kg *G. lucidum* spore (EEG)	4, 8 and 14 weeks	Male	54	TG, TC, LDL-C, HDL-C	Significantly reduced serum TG, TC and LDL-CHOL levels. Serum TC/HDL-CHOL values of rabbits were significantly lower
Li lu, 2019	Kunming mice	25, 50, and 100 mg/kg/day	4 weeks	Male	48	-	MDA content significantly decreased it suggest that Ganoderma atrum PSG can significantly alleviate STZ-induced lipid peroxidation in the pancreas of diabetic animals
Li NH, 2020	C57BL/KsJ-db/ db mice and wild-type C57BL6/J mice	100, 400 mg/kg/day	8 weeks	Male	24+6	TC, TG, LDL-C, HDL-C	Lipid profiles significantly upregulated in db/db mice
Liang Z, 2018	C57BL/6 mice	200, 400 mg/kg/day	12 weeks	Male	100	TC, TG, LDL-C, HDL-C	Effectively increased HDL-C levels and decreased TG, TC and LDL-C levels in the serum
Liu Y, 2019	SD rats	0.4 g/kg/BW	5 weeks	Male	60	TC, TG, LDL-C, HDL-C	TC, TG and LDL-C levels of the intervention groups were significantly lower and HDL-C is significantly higher
LIU Y, 2015	Chinese Holstein cows	33, 67, 100 g/cow/day	60 days	Female	40	TC, TG	TG contents were significantly different between control and the experimental groups but TC was not significantly different between the experimental groups and control

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Supplementary Table 2: Contd...

Study reference year	Animal model	Dose of Ganoderma	Duration	Sex	Sample size	Lipid profile	Result
Majagi, 2009	Rats of Wistar strain	146, 243 mg/kg	24 h	Male	30	TG, TC, HDL, LDL, VLDL	Mycelium product significantly ($P<0.05$, $P<0.01$) raised the HDL and significantly ($P<0.01$) lowered TC, LDL, TG and VLDL. But fruit body product has no significant effect on TG and VLDL
Menses, 2016	C57BL/6 mice	GL low dose (0.5%)/ GL high dose (1.0%)	43 days	Male	56	TC, TG, LDL-C	The addition of GL extracts to the diet significantly reduced serum TC and TG. The reduction in TC was accompanied by a decrease in the LDL-C concentration
Rubel R, 2010	Swiss mice	Basal chow was supplemented with 85, 50, or 10% of *G. lucidum* CG 144 dried spawn	12 weeks	Female	54	TG, TC, HDL, LDL, VLDL	Except TC *G. lucidum* is significantly effective on lipid profiles
Sakib H, 2018	Wistar rats	100 mg/kg BW/day	28 days	Male	42	TC, TG, HDL-C, LDL-C	CF+GL significantly decrease TG but no significant effect on TC, HDL-C, LDL-C
Wihastuti, 2019	Wistar rats	50 mg/kg BW, 150 mg/kg BW, and 300 mg/kg BW	30 days	-	25	TG, TC	Significantly decrease TG and TC
Xiao, 2018	C57BL/6 mice and C57BL/6 db/db mice	50 mg/kg/day	6 weeks	Male	24	TC, TG, HDL-C, LDL-C	Significant effect on TC, HDL-C, LDL-C and no significant effect on TG level
Xiao H, 2020	SD rats	0.05, 5 mg/kg rLZ-8	12 weeks	Male	32	TC, TG	An increase in serum levels of TC, TG and HbA1c in STZ model group was observed
Xu Y, 2019	Kunming mice	50, 100, 200 mg/kg body weight	30 days	Male	70	TC, TG, HDL-C, LDL-C	Significantly effects on TC, TG, HDL-C, LDL-C
Yang BK-2002	SD rats	100 mg/kg BW	4 weeks	Male	32	TC, TG, LDL-C	Significantly effects on TC, TG, LDL-C
Yang BK, 2004	SD rats	100 mg/kg BW	2 weeks	Male	32	TC, TG, LDL-C	Significantly effects on TC, TG, LDL-C
Yang Q, 2010	Wistar rats	100, 200, or 300 mg/kg	40 days	-	40	TC, TG	Oral administration of the polysaccharides extract for 40 days resulted in a dose-dependent significant reduction of the levels of fasting blood glucose, TC and TG
Yang Z, 2017	WT C57BL/6 mice and obese C57BL/6 (ob/ob) mice	150, 300, 400 mg/kg	4 weeks	Male	10+50	Lipid (pg/mL)	Serum lipid level was reduced significantly after treatment with FYGL for 4 weeks
Zheng J, 2012	SD rats	200 mg/(kg BW)	8 weeks	Male	50	TC, TG	Significantly effects on TC, TG
Zhong, 2018	ob/ob mice on a C57BL6/J genetic background and C57BL6/J wild-type littermates	100 mg/kg/day	4 weeks	Male	-	TC, TG, HDL-C, LDL-C	Significant effect on TC, HDL-C, LDL-C and TG
Zhu J, 2018	Mice	25 or 50 mg/kg/day GAA	6 weeks	-	48	TC, TG, HDL-C, LDL-C	The serum TC, TG, LDL-C were largely reduced. HDL-C was markedly increased in GAA
Zhu K, 2013	Wistar rats	200 mg/kg BW and 400 mg/kg BW	4 weeks	Male	60	TC, TG, HDL-C, LDL-C	Administration of PSG-1 for 4 weeks to type 2 diabetic rats resulted in significant diminution of elevated TC, TG and LDL-C levels. Treatment with PSG-1 at 400 mg/kg BW showed a higher reduction of TC, TG and LDL-C levels in un-treated diabetic rats than PSG-1 at 200 mg/kg BW and 1, 1-dimethylbiguanide hydrochloride. Moreover, treatment of the diabetic rats with PSG-1 produced a significant increase in HDL-C levels

CHOL: Cholesterol, GAA: Ganoderic acid A, WT: Wild type, SD: Sprague-Dawley, PSG: Polysaccharide, TG: Triglycerides, TC: Total CHOL, LDL: Low-density lipoprotein CHOL, HDL: High-density lipoprotein CHOL, VLDL: Very LDL, EEG: Ethanol extract, HbA1C: Hemoglobin A1c, *G. lucidum: Ganoderma lucidum*, HFD: High-fat diet, T2DM: Type 2 diabetes mellitus, GLP: Glucagon-like peptide 1, GA: Glycated albumin, PsP: Polysaccharide peptide, DC: Diabetic control, NC: Normal control, BW: Body weight, CI: Confidence interval, GLSP: *G. lucidum* spore powder, GL: Glycemic load, CF: Carbofuran, TBARS: Thiobarbituric acid-reactive substance, MDA: Malondialdehyde, STZ: Streptozocin, GLPEE: Ganoderma lucidum Petroleum ether extract, GL-ME: Ganoderma lucidum Methanol extract, GLAQ: Aqueous extract of Ganoderma lucidum, FYGL: Fudan-Yueyang-Ganoderma lucidum, MET: Melbine

Supplementary Table 3: Quality assessment of included studies

Author, year	1	2	3	4	5	6	7	8	9	10
Adeyi A, 2021	Yes	Yes	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No
Bach E, 2018	Yes	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No
Chen M, 2019	Yes	Yes	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No
Elhussainy E, 2016	Yes	Yes	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No
Eroglu H, 2018	Yes	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No
Guo W, 2020	Yes	Yes	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No
Guo W, 2018	Yes	Yes	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No
Heriansyah T, 2015	Yes	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No
Hu R, 2018	Yes	Yes	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No
Li F, 2011	Yes	Yes	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No
Meng G, 2011	Yes	Yes	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No
Oluba M, 2010	Yes	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No
Pan D, 2014	Yes	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	No
Pan R, 2021	Yes	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No
Sargowo D, 2015	Yes	Yes	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No
Sargowo D, 2017	Yes	Yes	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No
Sarker M, 2015	Yes	Yes	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No
Seto S, 2009	Yes	Yes	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No
Sharma P, 2019	Yes	Yes	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No
Tong C, 2008	Yes	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No
Tseng H, 2018	Yes	Yes	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No
Wang F, 2015	Yes	Yes	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No
Wang C, 2012	Yes	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No
Wihastuti T, 2016	Yes	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No
Chen, 2008	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	No
Hikino H, 1989	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No
Huang, 2020	Yes	Yes	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No
Lai P, 2020	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	No
Li lu, 2019	Yes	Yes	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No
Li NH, 2020	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	No
Liang Z, 2018	Yes	Yes	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No
Liu Y , 2019	Yes	Yes	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No
LIU Y, 2015	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	No
Majagi, 2009	Yes	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Yes	No
Menses, 2016	Yes	Yes	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Yes	No
Rubel R , 2010	Yes	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No
Sakib H, 2018	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	No
Wihastuti, 2019	Yes	Yes	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No
Xiao, 2018	Yes	Yes	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No
Xiao H, 2020	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	No
Xu Y, 2019	Yes	Yes	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No
Yang BK, 2002	Yes	No	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Yes	No
Yang BK, 2004	Yes	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Yes	No
Yang Q, 2010	Yes	Yes	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No
Yang Z, 2017	Yes	Yes	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No
Zheng J, 2012	Yes	Yes	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Yes	No
Zhong, 2018	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	No
Zhu J, 2018	Yes	Yes	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No
Zhu K, 2013	Yes	Yes	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No