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学位（博士）論文

Arctium lappa Lam. and Its Related Lignans Improve Hyperglycemia and Dyslipidemia in Diabetic Rodent Models: A Systematic Review and Meta-Analysis

ゴボウ（*Arctium lappa* Lam.）抽出物とその関連リグナン投与が

糖尿病モデル動物の高血糖および脂質異常症を改善する：

システマティックレビューとメタアナリシス

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nutraceuticals

MDPI

Review

Arctium lappa Lam. and Its Related Lignans Improve Hyperglycemia and Dyslipidemia in Diabetic Rodent Models: A Systematic Review and Meta-Analysis

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Abstract: Research on nutraceuticals has focused on reducing the onset, progression, and significant consequences of diabetes mellitus. *Arctium lappa* Lam. is a great source of plant fibers and polyphenols that have anti-disease benefits, including those for diabetes mellitus. This study sought to determine the impact of *Arctium lappa* Lam. extracts and its associated lignans on diabetic hyperglycemia and dyslipidemia by conducting meta-analyses of the available research using diabetic rodents. English-language peer-reviewed articles were searched by PubMed and Embase up until 10 August 2022. Included were studies comparing the blood glucose and/or lipid levels of diabetic rodents given either extracts of *Arctium lappa* Lam. and its related lignans or vehicles. Blood glucose levels were reported in 16 studies involving 168 diabetic mice or rats treated with *Arctium lappa* Lam. and 168 diabetic controls. The pooled effect size was −1.42 [95% CI: −1.84 to −1.00] with significant heterogeneity. Type of diabetic model was found to be the prominent covariate that explained, at least partially, the heterogeneity. Moreover, diabetic rodents treated with *Arctium lappa* Lam. showed a notable improvement in their hypertriglyceridemia and hypercholesterolemia.

Keywords: *Arctium lappa* Lam.; meta-analysis; nutraceuticals; diabetes mellitus; dyslipidemia

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1. Introduction

The term "nutraceutical" is a coined word derived from "nutrition" and "pharmaceutical" and was first introduced in 1898 by the Foundation for Innovation in Medicine (New York, NY, USA) [1,2]. A nutraceutical is defined as any substance that is considered a food or part of a food and provides health and medical advantages for the prevention and treatment of certain diseases, including diabetes mellitus (DM) [2].

Arctium lappa Lam. (*A. lappa*), also referred to as burdock, is a perennial plant belonging to the family Asteraceae and is originally grown in the north of the Eurasian continent. *A. lappa* is popular as a vegetable and medical plant particularly in China, Taiwan, and Japan [3–5]. For example, *A. lappa* roots and fruits have been reported for their anti-inflammatory, hepatoprotective, and free radical scavenging activities in several pharmacological studies [6,7]. The leaves can be applied to the affected areas when treating tooth/gum diseases caused by microorganisms in the oral cavity [8]. Plants, in general, contain a broad range of bioactive compounds. The main active compounds extracted from *A. lappa* are lignans (arctigenin and arctiin), caffeoylquinic acid derivation (chlorogenic acid, caffeic acid, and cynarine), and flavonoids (quercetin, luteolin) [3,9]. Arctigenin and its glucoside, arctiin, are characteristic lignans in *A. lappa.* Fructus Arctii, dried *A. lappa* fruits and seeds, are particularly rich in these lignans. Biological and pharmacological functions reported for the lignans include activities against inflammation, cancer, and DM [3]. Chlorogenic acid, a caffeoylquinic acid derivative, is a major component of coffee and has been reported for its anti-obesity and anti-diabetic effects [10,11]. Quercetin, a

flavonoid, is abundant in vegetables such as onions and has effects against osteoporosis, DM, and cardiovascular diseases [12].

DM is a chronic metabolic disorder that involves elevated blood glucose (BG) levels. Patients with DM are unable to produce insulin in the pancreas and/or are resistant to insulin action [13]. The prevalence of DM has increased dramatically worldwide. The International Diabetes Federation estimated that DM affects about 537 million individuals in 2021 and that this number will rise to 783 million by 2045. Moreover, dyslipidemia is common in DM, which is characterized by increased triglyceride (TG) and total cholesterol (TC) and decreased high-density lipoprotein cholesterol (HDL-C) levels. Diabetic dyslipidemia is a major risk factor for ischemic cardiovascular diseases and their associated death, particularly among elderly DM patients [13].

Numerous pieces of evidence have suggested that *A. lappa* or its associated lignans may have beneficial effects on glucose and lipid metabolism both in vitro and in vivo [14–20]. However, few clinical studies on *A. lappa* and DM written in English have been reported to this day [21–24]. Thus, this study aims to investigate effects of *A. lappa* extracts and its associated lignans on diabetic hyperglycemia and dyslipidemia using a meta-analysis of the currently available evidence in rodent DM models.

2. Materials and Methods

2.1. Data Sources and Search Strategies

A comprehensive literature search through the databases Embase and PubMed was carried out using words ("fructus arctii" or "arctii fructus" or burdock or "*arctium lappa*" or arctigenin) and (glucose or diabetes or "insulin resistance" or insulin) up to 10 August 2022. Additionally, to ensure that no pertinent publications had been overlooked, the reference lists of the extracted publications were carefully examined manually.

2.2. Inclusion and Exclusion Criteria

Peer-reviewed manuscripts written in English were eligible for inclusion if they met the following criteria: (i) studies used diabetic rats/mice treated by either *A. lappa* extracts and its related lignans (arctigenin, arctiin, and arctigenic acid) or vehicles for 3 days and longer; (ii) at the experimental endpoint, they measured BG, TG, TC, or HDL-C levels of the treated DM animals. Excluded were studies which were not written in English, letters, editorials, review articles, conference abstracts, duplicates, or those that did not present BG or lipid values. Unpublished research was excluded. The PRISMA guidelines were strictly followed throughout the study (Table S1) [25,26].

2.3. Data Extraction and Quality Assessment

Titles and abstracts of the retrieved manuscripts were examined for eligible studies, which were next screened by a full-text evaluation. Two authors independently gathered data using a predesigned data extraction form; collected data were part of *A. lappa*, dose and treatment period, BG and/or lipid (TG, TC, and HDL-C) levels, weight or age at a baseline, sex, and type of rodent DM model. The Cochrane Collaboration "Risk of Bias" tool was used for assessing studies' quality [27]. Two authors independently examined the Risk of Bias for every quality factor in each criterion and gave it a score of "low", "medium", "high", "not clear", or "not applicable (N/A)" based on how it was described in every acquired publication. Disagreements during each stage were resolved through fair discussion.

2.4. Data Synthesis and Analysis

Mean ± standard deviation (SD) was used to present continuous variables. The corresponding SD was calculated by multiplying by the square root of the sample size for studies that reported standard error of the mean (SE). When studies provided BG or lipid levels in mmol/L, those values were converted to mg/dL as previously described [28]. When more than one measure of BG and lipid levels was reported in a study, the values at

the treatment dose that showed the most significant difference in BG levels between the groups and after the longest treatment period were chosen and used in the meta-analyses. As chemically induced DM rodents, studies in which animals were treated with either streptozotocin (STZ) or alloxan were included.

A standardized mean difference (Hedges' g) transformation was chosen for calculating the associated statistics; those included mean effect size and 95% confidence intervals (CI) of every study, the overall effect size, and publication bias. Data are presented as g [95% CI] hereafter. A random-effects model was selected, since it is more conservative and better accounts for between-study variability. I^2 statistics were used to evaluate heterogeneity, with a value of $\geq$50% being considered as evidence of substantial heterogeneity [29].

Subgroup and meta-regression analyses were conducted by type of DM model (chemically induced by STZ or alloxan; genetic by db/db, ob/ob, KKAy mice, or Goto Kakizaki (GK) rats; diet-induced by high fat diet (HFD), high fat and high sugar diet (HFSD), or sucrose in drinking water), type of blood sample (serum, plasma, and whole blood), sex (males, females, or both), and treatment dose and duration to examine their influence to the overall estimates. To assess the robustness of the calculated summary effect sizes, sensitivity analysis was conducted by removing one study at a time and repeating the primary meta-analyses. Funnel plots with Duval and Tweedie's Trim and Fill analysis evaluated publication bias (random-effects model). Comprehensive Meta-Analysis 3.0 (Biostat Inc., Englewood, NJ, USA) and STATA16 (Stata Corp, College Station, TX, USA) software were used for statistical analyses.

3. Results

3.1. Search Results

Figure 1 shows the flowchart of our literature search. The search found 244 articles (165 by Embase and 79 by PubMed). After removing the duplicates and reviews by titles, 97 articles were moved to an abstract assessment and then 29 for a full-text evaluation. The articles that reported neither BG nor lipid levels of DM rodents given *A. lappa* or arctigenin-related compounds were further excluded. Thus, the following meta-analyses included 17 studies out of 16 articles.

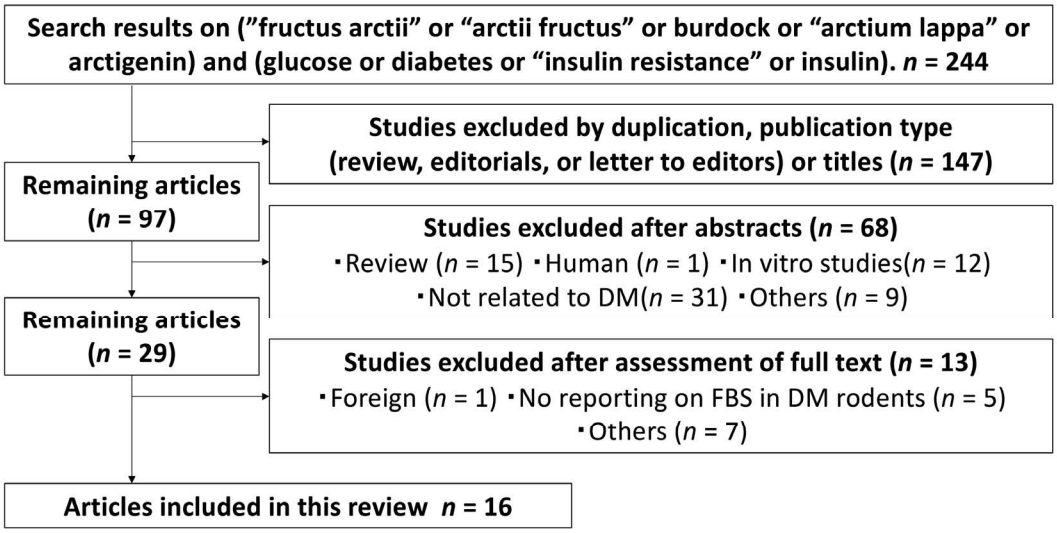

Figure 1. Flowchart of literature search and extraction process.

3.2. Study Characteristics and Quality Assessment

Table 1 summarizes basal characteristics of each included study. The sample sizes in those studies ranged from 12 to 40. Animals were given extracts isolated from roots in seven studies and Fructus Arctii in five, and with *A. lappa*-related lignans including arctigenin, arctigenic acid, and arctiin in five studies. Chemically (STZ or alloxan) induced

DM rodent models were used in 10 (8 in rats and 2 in mice), genetically obese and/or diabetic rodents (db/db, ob/ob, KKAy mice, and GK rats) were in 5 (2 in rats and 3 in mice), and diet-induced diabetes in 2 studies. Males, females, and both sexes were utilized in 12, 2, and 3 studies, respectively. Table S2 displays the quality assessment of every study. The overall study quality was considered to be fair, and the bias risk was rated as low to medium.

Table 1. Characteristics of included studies for the meta-analysis.

Authors (Year)	Parts or Compounds	Animal Models (Doses of STZ or Alloxan)	Study No. (+/−)	Weight or Age at a Baseline	Sex	Diet	Sample Type for BG/Lipids	Measured Data
Chen et al. (2020) [14]	roots	Rats, STZ (120 mg/kgBW)	10/10	NS	Males	HFSD	Whole blood/serum	BG, TG, TC, and HDL-C
Zhang et al. (2020) [30]	Fructus Arctii	Rats, STZ (60 mg/kgBW)	8/8	100~120 g	Males	HFSD	Whole blood/ND	BG
Vengerovskii et al. (2019) [15]	roots	Rats, STZ (30 mg/kgBW)	10/10	200~220 g	Males	HFD	Whole blood/serum	BG, TG, TC, and HDL-C
Li et al. (2019) [16]	roots	Rats, STZ (120 mg/kgBW)	8/8	NS	Males	HFSD	Whole blood/plasma	BG, TG, TC, and HDL-C
Zhang et al. (2019) [31]	arctigenin	db/db mice	10/10	6 wks	Males	Control	Whole blood/ND	BG
Gao et al. (2018) [32]	Fructus Arctii	KKAy mice	10/10	9 wks	Males	HFD	Whole blood/plasma	BG, TG, TC, and HDL-C
Ahangarpour et al. (2017) [17]	roots	Mice, STZ (50 mg/kgBW)	10/10	30~35 g	Males	Control	Whole blood/serum	BG, TG, TC, and HDL-C
Bok et al. (2017) [33]	roots	Mice, diet-induced	8/8	NS	Both	HFD	Serum/ND	BG
Ahangarpour et al. (2016) [18]	roots	Rats, diet-induced	8/8	150~250 g	Females	Control + sucrose in water	ND/serum	TG, TC, and HDL-C
Naeimeh et al. (2015) [34]	roots	Rats, alloxan (160 mg/kgBW)	6/6	NS	Males	NS	Whole blood/ND	BG
Xu et al. (2015) [35]	arctigenin acid	GK rats	10/10	9 wks	Males	HFD	Whole blood/serum	BG, TG, TC, and HDL-C
Xu et al. (2014) [19]	Fructus Arctii	GK rats	10/10	9 wks	Males	HFD	Whole blood/serum	BG, TG, TC, and HDL-C
Ma et al. (2013) [36]	arctiin	Rats, STZ (65 mg/kgBW)	10/10	180~200 g	Males	Control	Whole blood/ND	BG
Lu et al. (2012) [37]	arctiin	Rats, STZ (30 mg/kgBW)	20/20	160~180 g	Males	HFSD	Serum/ND	BG
Huang et al. (2012) [38]	arctigenin	ob/ob mice	8/8	6~7 wks	Females	NS	Whole blood/serum	BG, TG, and TC
Xu et al. (2008) (1) [39]	Fructus Arctii	Mice, alloxan (90 mg/kgBW)	20/20	6 wks or 20 ± 2 g	Both	Control	Whole blood/NS	BG
Xu et al. (2008) (2) [39]	Fructus Arctii	Rats, alloxan (50 mg/kgBW)	10/10	6 wks or 120 ± 10 g	Both	Control + fat emulsion	Whole blood/serum	BG, TG, TC, and HDL-C

STZ: streptozotocin, BW: body weight, +/−: treatment/no treatment with *A. lappa*, wks: weeks, Control: control diet, NS: not specified, ND: no data.

3.3. A. lappa Reduces BG Levels in DM Rodent Models

3.3.1. Forest Plot Analysis

A total of 16 studies from 15 publications enrolling 168 DM rodents administered with extracts of *A. lappa* or its related lignans and 168 DM controls with vehicles reported their BG levels and were included in the meta-analysis (Figure 2). Ten studies displayed that administration of *A. lappa* and its related lignans markedly reduces BG levels of DM rodents; six had no impacts. A random-effects model was used to combine all those studies. The results showed that BG levels of DM rodents significantly decreased by administration of extracts of *A. lappa* or arctigenin-related compounds (−1.42 [−1.84, −1.00]; I^2 = 67.02%, p = 0.00) (Figure 2). The stability of results was next evaluated using sensitivity analysis. All re-pooled summary estimates were similar to the primary estimates; they ranged from −1.50 [−1.92, −1.08] to −1.30 [−1.65, −0.94].

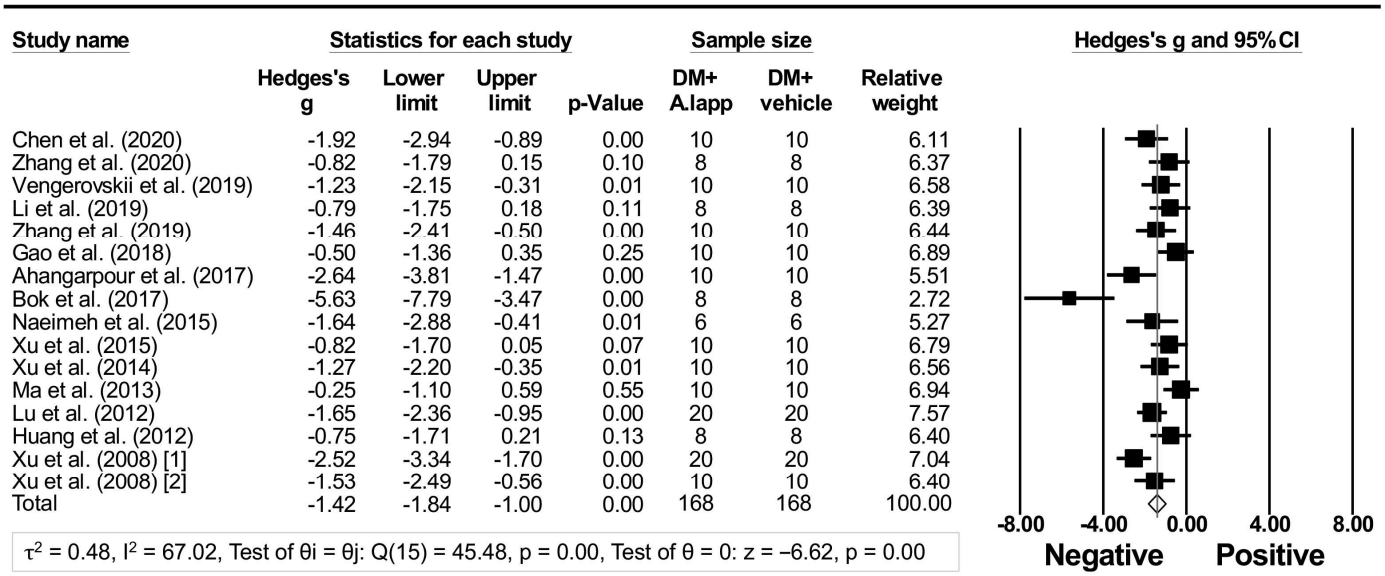

Figure 2. Meta-analysis of Hedges' g of BG levels in DM rodents administered with either *A. lappa* extracts and arctigenin-related compounds or vehicles. A red line indicates the pooled effect size. CI, confidence interval.

3.3.2. Subgroup and Meta-Regression Analyses

Subgroup analyses were next performed to determine categorical moderators that could influence the between-study heterogeneity. DM rodent models and sex were found to be significant moderators (p = 0.001 and 0.02, respectively). Sample type seemed to modify the effect of *A. lappa* (p = 0.04) on diabetic hyperglycemia. Type of rodent and part of *A. lappa* were not prominent covariates (p = 0.13 and 0.16, respectively) (Table 2).

Meta-regression analysis was then conducted to find another covariate. DM models and sex were confirmed to be significant covariates, which explained approximately 54 (R^2 = 0.54) and 31% (R^2 = 0.31) of between-study variance, respectively. However, treatment period did not influence the variance. In the analysis of dose effect, we divided studies into two groups: extracts of *A. lappa* (roots and Fructus Arctii), and arctigenin-related compounds which include arctigenin, arctigenic acid, and arctiin. Extracts of *A. lappa* roots and Fructus Arctii contain various bioactive compounds, while when animals are treated with either arctigenin, arctiin, or arctigenic acid, its molar dose can be calculated. Daily doses (g/kg/day) and total doses of *A. lappa* extracts administered during the entire treatment period (g/kg) did not influence the variance of I^2 = 70.60 (Table 2, R^2 = 0.00). Daily doses (μmol/kg/day) and total doses of arctigenin-related compounds (mmol/kg) were identified as prominent moderators to influence approximately 28% (R^2 = 0.28) and 100% (R^2 = 1.00) of between-study variance of I^2 = 47.00, respectively (Table 2, Figure 3).

Collectively, the high heterogeneity among the 16 studies was, at least in part, caused by type of DM model and sex, and, apparently, sample type. However, the number of studies using serum is only two, and more studies are needed to make a certain conclusion. In the treatment with arctigenin-related compounds, daily and total molar doses of those compounds administered to DM rodents affected the between-study heterogeneity.

Table 2. Subgroup analyses of BG levels in DM animals.

Subgroups	Effect Size					Heterogeneity (I^2)	Test of Group Difference (p)
	Study No.	g		95% CI	p-Value		
DM rodent models							
chemical	10	−1.48	−1.89	−1.06	<0.001	60.98	0.001
diet	1	−5.63	−7.97	−3.28	<0.001	0.00	
genetic	5	−0.95	−1.53	−0.37	0.001	0.00	
Rodent type							
mice	6	−1.86	−2.57	−1.16	<0.001	83.64	0.13
rats	10	−1.18	−1.70	−0.66	<0.001	19.54	
Sample type							
whole blood	14	−1.27	−1.71	−0.83	<0.001	55.14	0.04
serum	2	−2.70	−4.00	−1.40	<0.001	91.49	
Sex							
male	12	−1.21	−1.64	−0.79	<0.001	43.22	0.02
females	1	−0.75	−2.23	0.74	0.32	0.00	
both	3	−2.59	−3.52	−1.65	<0.001	83.09	
Parts							
extracts	11	−1.64	−2.15	−1.12	<0.001	70.61	0.16
arctigenin-related compounds	5	−1.00	−1.71	−0.28	0.006	47.01	

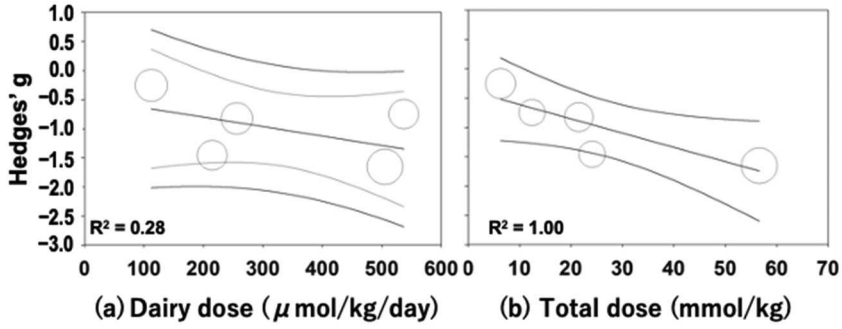

Figure 3. Meta-regression analyses for Hedges' g of BG levels and daily (μmol/kg/day) (**a**) or total doses (mmol/kg) (**b**) of arctigenin-related compounds. R^2 values explain how much daily or total doses of arctigenin-related lignans influence the heterogeneity among DM rodents treated with those compounds (I^2 = 47.01 in Table 2).

3.3.3. Forest Plot, Subgroup, and Meta-Regression Analyses in Chemically Induced DM Rodents

The type of DM rodent model was suggested to influence the between-study variables of BG levels given either *A. lappa* and its related lignans or vehicles in DM rodents; thus, the analyses were next performed separately in chemically, diet-induced, and genetic DM models. Table 2 shows that *A. lappa* administration significantly reduces BG levels in chemically induced DM rodents (−1.48 [−1.89, −1.06]; I^2 = 60.98%, $p < 0.001$). Subgroup and meta-regression analyses were next conducted as described above. The type of rodent (mice, n = 2; rats, n = 8) could affect the between-study variance (p = 0.002, R^2 = 0.8). Sex

(p = 0.19), type of blood sample (p = 0.81), part of *A. lappa* (p = 0.28), duration (R^2 = 0.00), and dose (R^2 = 0.00) were not prominent factors to explain the variance (Table S3).

In diet-induced or genetic DM rodents, *A. lappa* administration significantly improved BG levels (Table 2). No heterogeneity was found in genetic models. Collectively, the high heterogeneity in chemically induced DM rodents might be due, at least partially, to type of rodent. However, the number of studies using chemically induced DM mice (n = 2) and diet-induced DM models (n = 1) was quite low, and more studies are required to make a certain conclusion.

3.3.4. Assessment of Publication Bias

It was suggested that administration of *A. lappa* and its related lignans reduces BG levels of DM animals with substantial heterogeneity; therefore, publication bias was next assessed using a random-effects model. There was no significant publication bias in studies on BG levels of DM rodent models (Figure 4).

Figure 4. Funnel plots of standard error and Hedges' g of BG levels in DM rodents given either *A. lappa* and arctigenin-related compounds or vehicles. Open and closed diamonds indicate the imputed overall estimates before and after Duval and Tweedie's Trim and Fill adjustment, respectively.

3.4. A. lappa Improved Serum/Plasma Lipid Levels in DM Rodent Models

3.4.1. Forest Plot Analysis

A total of 10 studies using 98 DM rodents administered with *A. lappa* extracts or arctigenin-related compounds and 98 DM vehicle controls presented their serum/plasma TG and TC levels; 9 studies involving 84 DM rodents given *A. lappa* and 84 vehicle controls obtained HDL-C levels. Forest plot analysis exhibited that *A. lappa* or its related lignans significantly reduce TG (−1.45 [−2.25, −0.66]; I^2 = 83.11%, p = 0.00) and TC levels (−1.72 [−2.68, −0.75]; I^2 = 87.22%, p = 0.00) compared with vehicle in DM rodents (Figure 5). No significant effect was observed on HDL-C levels (0.39 [−1.08, 1.86]; I^2 = 92.97%, p = 0.60). The stability of results was then examined. When compared to the overall estimates, all re-pooled summary estimates remained similar; the results were from −1.62 [−2.49, −0.75] to −1.19 [−1.91, −0.46] for TG, from −1.99 [−3.06, −0.93] to −1.24 [−2.03, −0.45] for TC, and from −0.21 [−1.62, 1.21] to 1.12 [−0.19, 2.42] for HDL-C.

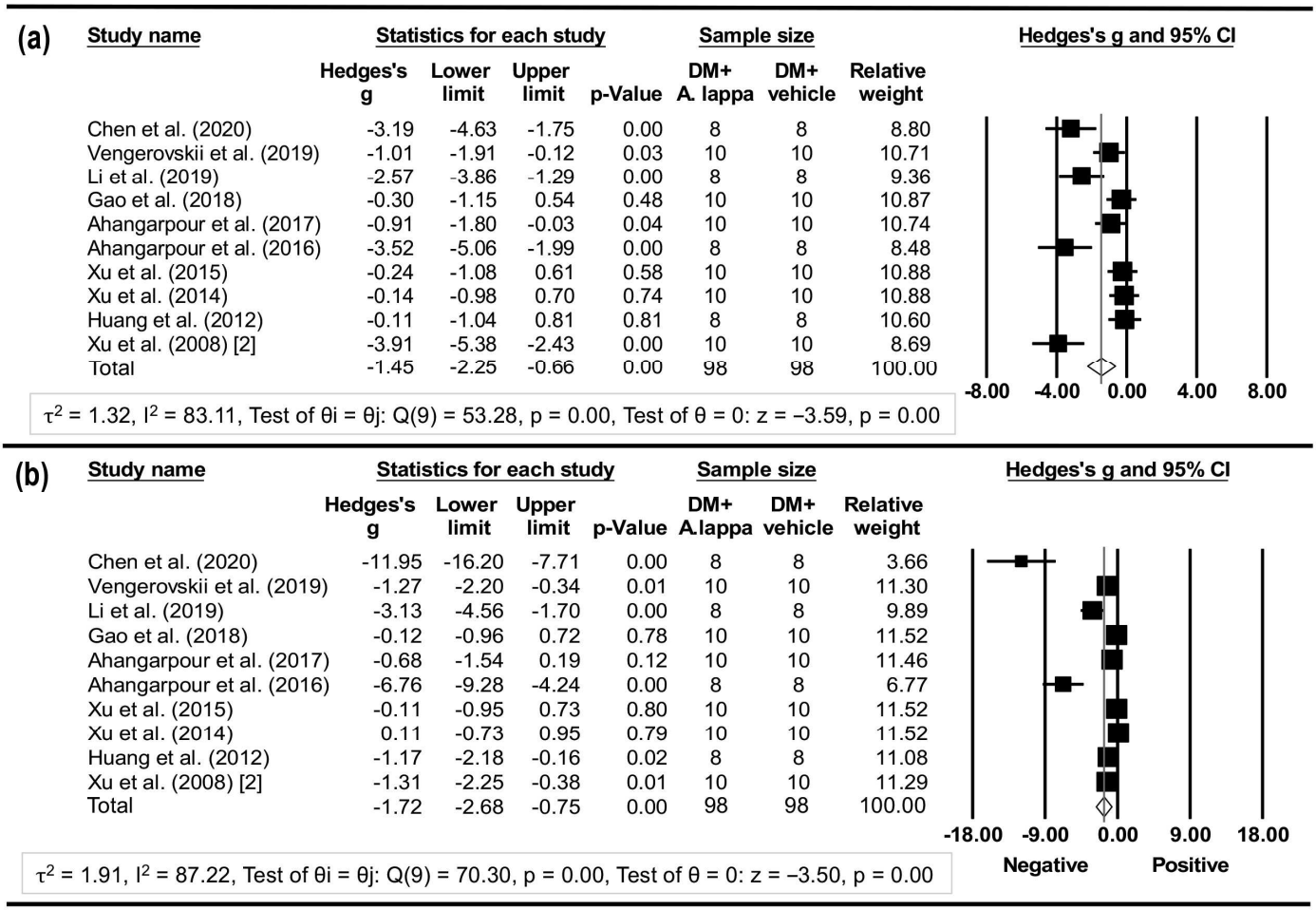

Figure 5. Meta-analysis of Hedges' g of serum/plasma TG (**a**) and TC (**b**) levels of DM rodents given either *A. lappa* extracts and arctigenin-related compounds or vehicles. A red line indicates the pooled effect size.

3.4.2. Subgroup and Meta-Regression Analyses

Subgroup and meta-regression analyses were then performed as described above. Results exhibited that type of DM model was a prominent moderator, which explained about 65% of between-study variance (R^2 = 0.65) for TG and 43% (R^2 = 0.43) for TC levels. Type of rodent (TG, p = 0.09; TC, p = 0.13) and sample (TG, p = 0.90; TC, p = 0.80), sex (TG, p = 0.12; TC, p = 0.38), part of *A. lappa* (TG, p = 0.09; TC, p = 0.24), and treatment period (R^2 = 0.00) were not significant covariates (Table 3). Collectively, type of DM rodent model was responsible, at least partially, for the high between-study heterogeneity in both diabetic hypertriglyceridemia and hypercholesterolemia.

Table 3. Subgroup analyses of serum/plasma TG and TC levels in DM rodents.

TG Levels							
Subgroups	**Effect Size**					**Heterogeneity (I^2)**	**Test of Group Difference (p)**
	Study No.	***g***		**95% CI**	***p*-Value**		
DM rodent models							
chemical	5	−2.10	−2.89	−1.30	<0.001	79.64	<0.001
diet	1	−3.52	−5.56	−1.49	0.001	0.00	
genetic	4	−0.20	−1.00	0.60	0.62	0.00	
Rodent type							
mice	3	−0.44	−1.84	0.95	0.53	0.00	0.09
rats	7	−1.93	−2.89	−0.97	<0.001	86.42	
Sample type							
plasma	2	−1.36	−3.25	0.53	0.16	88.03	0.90
serum	8	−1.50	−2.45	−0.54	0.002	84.42	
Sex							
male	7	−1.10	−1.96	−0.23	0.03	74.45	0.12
female	2	−1.60	−3.29	0.09	0.06	92.82	
both	1	−3.91	−6.44	−1.38	0.002	0.00	
Parts							
extracts	8	−1.80	−2.68	−0.92	<0.001	84.17	0.09
arctigenin-related compounds	2	−0.18	−1.86	1.50	0.84	0.00	
TC Levels							
Subgroups	**Effect Size**					**Heterogeneity (I^2)**	**Test of Group Difference (p)**
	Study No.	***g***		**95% CI**	***p*-Value**		
DM rodent models							
chemical	5	−2.10	−3.22	−0.99	<0.001	87.55	<0.001
diet	1	−6.76	−10.01	−3.52	<0.001	0.00	
genetic	4	−0.31	−1.42	0.81	0.59	26.35	
Rodent type							
mice	3	−0.65	−2.41	1.11	0.47	19.45	0.13
rats	7	−2.34	−3.60	−1.09	<0.001	90.90	
Sample type							
plasma	2	−1.53	−3.77	0.71	0.18	92.12	0.80
serum	8	−1.85	−3.02	−0.68	0.002	87.87	
Sex							
male	7	−1.46	−2.71	−0.21	0.02	87.20	0.38
female	2	−3.38	−5.83	−0.92	0.01	93.87	
both	1	−1.31	−4.45	1.82	0.41	0.00	
Parts							
extracts	8	−2.11	−3.27	−0.94	<0.001	89.47	0.24
arctigenin-related compounds	2	−0.63	−2.80	1.54	0.57	59.91	

3.4.3. Forest Plot, Subgroup, and Meta-Regression Analyses in Chemically Induced DM Rodents

The statistical analyses were next conducted separately in chemically and diet-induced and genetic DM models. Treatment of chemically induced DM rodents with *A. lappa* or its associated lignans markedly decreased both serum/plasma TG and TC levels (TG, −2.10 [−2.89, −1.30], I^2 = 79.64%, p = 0.00; TC, −2.10 [−3.22, −0.99], I^2 = 87.55%, p = 0.00) (Table 3). To examine significant factors which influenced the serum/plasma TG and TC levels of chemically induced DM models, subgroup and meta-regression analyses were then performed. Both daily and total doses of *A. lappa* extracts administered to chemically

induced DM animals were found to be significant covariates for TG, which explained approximately one-third of the between-study heterogeneity (daily dose, $R^2 = 0.29$; total dose, $R^2 = 0.31$) (Figure 6a,b). Moreover, treatment period was a prominent factor for TC, which affects the heterogeneity by 43% ($R^2 = 0.43$) (Figure 6c). Type of rodent (TG, $p = 0.25$; TC, $p = 0.24$), type of sample (TG, $p = 0.79$; TC, $p = 0.66$), and sex (TG, $p = 0.10$; TC, $p = 0.44$) were not significant covariates to contribute to the heterogeneity (Table S4).

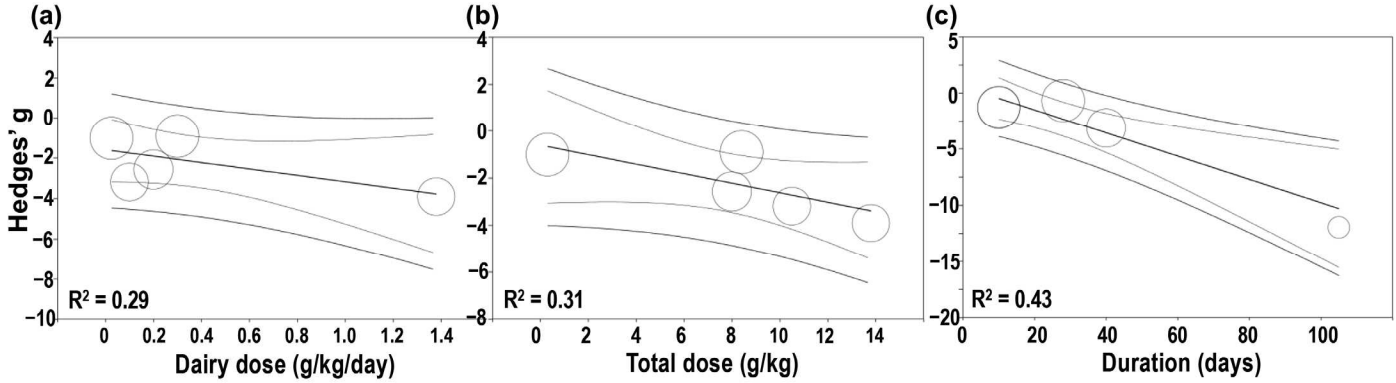

Figure 6. Meta-regression analyses for Hedges' g of serum/plasma TG levels and daily (g/kg/day) (**a**) and total doses (g/kg) (**b**) of *A. lappa* extracts in chemically induced DM models. That for Hedges' g of serum/plasma TC levels and duration (days) (**c**) in chemically induced DM models.

A single study showed that an administration of *A. lappa* significantly lowered serum/plasma TG and TC levels in a diet-induced DM model. In genetic DM rodents, there were no significant effects of *A. lappa* or its related lignans on serum/plasma TG and TC levels (Table 3). Collectively, the high heterogeneity found in chemically induced DM rodents might be due, at least partially, to doses of *A. lappa* extracts for TG and treatment duration for TC levels. Moreover, the number of studies using diet-induced DM models was quite low, and more studies are required for further assessment.

3.4.4. Assessment of Publication Bias

Publication bias was assessed separately for serum/plasma TG and TC levels of DM rodents as described above (Figure 7). Trim and Fill analysis found one imputed study each (closed circles) in both TG and TC levels, the adjusted values of which were −1.22 [−2.03, −0.42] and −2.10 [−3.20, −1.01], respectively. Taken together, publication bias was detected in the analyses; however, our finding that *A. lappa* or arctigenin-related compounds had significant impacts on lowering serum/plasma TG and TC levels of DM rodents stands even after the Trim and Fill adjustment.

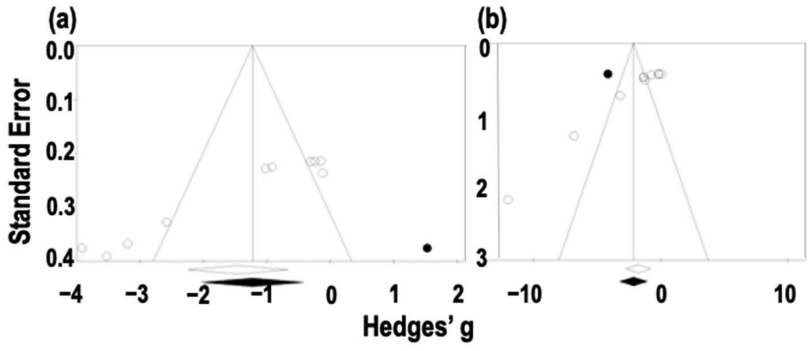

Figure 7. Funnel plots of standard error by Hedges' g of serum/plasma TG (**a**) and TC (**b**) levels of DM rodents given either *A. lappa* and its related lignans or vehicles. Open and closed diamonds represent imputed overall effect sizes before and after Trim and Fill adjustment, respectively. An imputed study was shown as a closed circle.

4. Discussion

4.1. Main Findings

This meta-analysis summarized the evidence that treatment of DM rodent models with *A. lappa* or its related lignans significantly lowers BG, serum/plasma TG, and TC levels compared with vehicles. These associations were likely to be influenced by type of DM model. The analysis on TG and TC levels suggested publication bias; however, the significant beneficial effects of *A. lappa* on TG and TC levels remain observed even after the Trim and Fill adjustment.

4.2. Data Interpretation

4.2.1. Underlying Mechanisms by Which the Bioactive Compounds of *A. lappa* Combat DM

Research on *A. lappa* extracts and arctigenin-related compounds have unveiled several mechanistic insights by which they play a beneficial role in DM. *A. lappa* extracts contain several critical bioactive compounds, which include lignans (arctigenin and arctiin), caffeoylquinic acid derivatives (chlorogenic and caffeic acids and cynarine), flavonoids (quercetin and luteolin), sitosterol-β-D-glucopyranoside, and inulin [3,40].

(i) Inhibitory effects on α-glucosidase activities:

α-Glucosidase is a carbohydrate-hydrolase, which acts on the terminal bonds of glycogen and starch and hydrolyzes and releases a single α-glucose. Xu et al. demonstrated that extracts of Fructus Arctii inhibit α-glucosidase activity at similar levels to a known α-glucosidase inhibitor, acarbose [19]. Arctigenin, chlorogenic and caffeic acids, a glucoside derivative of quercetin, and sitosterol-β-D-glucopyranoside also showed inhibitory capacities on α-glucosidase [41–44].

(ii) Reduced glucagon expression and increased insulin secretion in pancreas:

Treatment of GK rats with total lignans isolated from Fructus Arctii decreased glucagon expression in the pancreas and increased insulin secretion [19]. One of the suggested mechanisms underlying the restored insulin levels was that the lignans stimulate GLP-1 release from the intestine and colon [19]. GLP-1 is a potent incretin hormone, which stimulates insulin secretion from β cells of the pancreas through two signaling pathways: PI3-K activation of ERK1/2, MAPK, or PKC, and cAMP/PKA-mediated translocation of duodenal homeobox-1 [45].

(iii) Enhanced glucose uptake in skeletal muscles:

Treatment of KKAy mice with total lignans isolated from Fructus Arctii inhibited PTP1B and activated the PI3-K/Akt signaling pathway to promote translocation of GLUT4 to the cell membrane and increase glucose uptake in the skeletal muscle [32]. Arctigenin was also reported to increase glucose uptake by the MAPK/ACC-1 signaling pathway in skeletal muscles [38]. Moreover, *A. lappa* root extracts rich in caffeoylquinic acid derivatives showed increased glucose uptake in L6 myocytes [46].

(iv) Suppression of gluconeogenesis and lipid synthesis in the liver:

Reduced glucagon expression in the pancreas mentioned in (ii) resulted in decreases in glucagon-mediated glycogenolysis, gluconeogenesis, and glucose outputs in the liver [47]. Further, treatment of primary hepatocytes with arctigenin stimulated phosphorylation of AMPK and ACC-1, suggesting inhibition of hepatic gluconeogenesis and lipid synthesis [38].

(v) Modulation of adiponectin levels:

Adiponectin is an adipokine, which regulates glucose levels and fatty acid oxidation and improves insulin resistance in mice and humans [48,49]. Treatment of 3T3-L1 adipocytes with total lignans from Fructus Arctii increased adiponectin levels, which then reversed insulin resistance through the AMPK-mediated signaling pathway [50].

(vi) Reduced glucose absorption from intestine:

This is considered to be mediated through the action of inulin in dietary fibers of *A. lappa* extracts [51].

Dyslipidemia is a primary risk factor for developing atherosclerosis and ischemic cardiovascular diseases [52]. This meta-analysis suggested that *A. lappa* extracts and arctigenin-related compounds improve lipid profiles in DM rodents. Several possible underlying mechanisms have been suggested; *A. lappa* root extracts inhibit HMG-CoA reductase activity and cholesterol absorption from the intestines [17]. Moreover, *A. lappa* polysaccharide was shown to modulate both AMPK/SREBP-1/SCD -1 and PKC/NFκB signaling pathways to reduce TG and cholesterol synthesis and inflammation in the liver [14,16]. Further, it was reported that chlorogenic acids improve dyslipidemia and that some flavonoids reduce lipid synthesis and its release from hepatocytes [53].

In the current meta-analysis, type of DM model was identified as a prominent covariate which influenced an effect of *A. lappa* or its related lignans on BG and serum/plasma TG and TC levels. Chemically induced DM models by STZ and alloxan are often used as insulin-dependent DM models caused by reduced insulin secretion from β cells of the pancreas [54,55]. Diet-induced or genetic DM models including ob/ob, db/db, and KKAy mice and GK rats are thought to be models for type 2 DM characterized by insulin resistance [56]. The severity and progress of DM might differ among DM rodent models. In fact, *A. lappa* administration exhibited no significant effect on serum/plasma lipid levels of genetic DM models in this analysis. Therefore, it is plausible that the impact of *A. lappa* might differ among patients with DM depending on the etiology and their dietary lifestyle in actual clinical settings.

Lastly, despite the above-mentioned positive effects of *A. lappa* and its associated lignans on glucose and lipid metabolism, it is also critical to note that several adverse effects caused by a prolonged use of *A. lappa* were reported in the literature. For instance, contact dermatitis occurred after applying a plaster or oil made of *A. lappa* root to a wound [57,58]. Long-term ingestion of *A. lappa* resulted in anaphylaxis in a Japanese case [59]. Therefore, caution should be always advised in application of *A. lappa* to humans.

4.2.2. Strength and Limitations

The inclusion of a comparatively large number of DM rodent models and the focus on the effects of *A. lappa* extracts and arctigenin-related compounds on their BG and lipid levels are the primary strengths of the meta-analysis. Various publication biases and cofounding factors were also systematically evaluated. There are also a few limitations to this meta-analysis. Firstly, although two electronic databases were utilized for a comprehensive literature search, there were only a small number of studies evaluating a role of *A. lappa* in diet-induced and genetic DM models. Additionally, the language restriction and exclusion of equivocal manuscripts could increase the risk of publication bias even further. Secondly, the meta-analyses revealed heterogeneity that the pre-specified variables could not fully explain. The robustness of our findings might be weakened by the heterogeneity. Thirdly, the outcomes could differ when additional studies include females or both sexes, because male rodents were used in the majority of the included studies.

5. Conclusions

This meta-analysis revealed that BG and serum/plasma TG and TC levels markedly decreased in diabetic rodent models administered with *A. lappa* and its associated lignans. However, the results from animal observations could not be immediately applicable to humans because of the physiological diversity between the species. For example, the lipoprotein profile of rodents is quite different from that of humans [60]. Mutations in the L-gulono-γ-lactone oxidase gene caused humans, but not rodents, loss of the capability to synthesize vitamin C [61–63]. It was also reported that rats have their specific subsystems for bile acid metabolism [63]. Therefore, those factors could modify an effect of *A. lappa* and its associated lignans on glucose and lipid metabolism differently in humans from rodents.

To the best of our knowledge, no clinical studies reported in English have been run to assess how *A. lappa* could modify glucose and lipid levels of patients with DM. Therefore, our current finding may encourage researchers to conduct subsequent clinical trials to examine the role of *A. lappa* in physiological regulation of glucose and lipid metabolism in individuals with DM or glucose intolerance. Finally, developing plant extracts such as *A. lappa* into natural nutraceuticals for the purpose of preventing, delaying the onset, or slowing the progression of DM will have a critical impact on the accelerating number of diabetic patients.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/nutraceuticals2040026/s1, Table S1: PRISMA checklist; Table S2: Risk of Bias; Table S3: Subgroup analyses of BG levels in chemically induced DM rodents; Table S4: Subgroup analyses of serum/plasma TG and TC levels in chemically induced DM rodents.

Author Contributions: S.W. and M.S. designed the research content, collected and reviewed literature, and analyzed the data; S.W., S.Y. and M.S. discussed the data; S.W. and M.S. wrote the paper. All authors have read and agreed to the published version of the manuscript.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1-2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	2
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	2, 3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	2
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	3
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	3

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	2, 3
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	3
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	3, 4
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	3, 4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	4, S2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	4-11
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	4-11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	4-11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	4-11
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12-13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Table S2. Risk of Bias

Authors (year)	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	Other possible bias
Chen et al. (2020)	Low (Sex, FBS matched, stated 'randomly')	N/A (Rats)	Not clear	Low	Low	None
Zhang et al. (2020)	Low (Sex, BW, FBS matched, stated 'randomly')	N/A (Rats)	Not clear	Low	Low	None
Vengerovskii et al. (2019)	Low (Sex, BW, FBS matched)	N/A (Rats)	Not clear	Low	Low	None
Li et al. (2019)	Low (Sex, FBS matched, stated 'randomly')	N/A (Rats)	Not clear	Low	Low	None
Zhang et al. (2019)	Low (Sex, age matched, stated 'randomly')	N/A (Mice)	Not clear	Low	Low	None
Gao et al. (2018)	Low (Sex, age matched)	N/A (Mice)	Not clear	Low	Low	None
Ahangarpour et al. (2017)	Low (Sex, BW, FBS matched, stated 'randomly')	N/A (Mice)	Not clear	Low	Low	None
Bok et al. (2017)	Medium (BW matched)	N/A (Mice)	Not clear	Low	Low	None
Ahangarpour et al. (2016)	Low (Sex, BW, FBS matched, stated 'randomly')	N/A (Rats)	Not clear	Low	Low	None
Naeimeh et al. (2015)	Low (Sex, FBS matched, stated 'randomly')	N/A (Rats)	Not clear	Low	Low	None
Xu et al. (2015)	Low (Sex, age, BW, FBS matched)	N/A (Rats)	Not clear	Low	Low	None
Xu et al. (2014)	Low (Sex, age, FBS matched)	N/A (Rats)	Not clear	Low	Low	None
Ma et al. (2013)	Low (Sex, BW, FBS matched)	N/A (Rats)	Not clear	Low	Low	None
Lu et al. (2012)	Low (Sex, BW, FBS matched, stated 'randomly')	N/A (Rats)	Not clear	Low	Low	None
Huang et al. (2012)	Low (Sex, age, BW, FBS matched)	N/A (Mice)	Not clear	Low	Low	None
Xu et al. (2008)	Low (Age, BW, FBS matched, stated 'randomly')	N/A (Mice, Rats)	Not clear	Low	Low	None

N/A: not applicable

Table S3. Subgroup analyses of BG levels in chemically induced DM rodents.

Subgroups	Effect size					Heterogeneity (I^2)	Test of Group difference (p)
	Study No.	*g*	95% CI		p-value		
Rodent type							
mice	2	-2.57	-3.34	-1.79	<0.001	0.00	0.002
rats	8	-1.21	-1.59	-0.83	<0.001	33.24	
Sample type							
whole blood	9	-1.46	-2.01	-0.91	<0.001	64.82	0.81
serum	1	-1.65	-3.15	-0.16	0.03	0.00	
Sex							
male	8	-1.32	-1.83	-0.82	<0.001	55.03	0.19
both	2	-2.06	-3.03	-1.08	<0.001	58.05	
Parts							
extracts	8	-1.63	-2.17	-1.08	<0.001	50.08	0.28
arctigenin-related compounds	2	-0.99	-1.99	0.01	0.05	83.90	

Table S4. Subgroup analyses of serum/plasma TG and TC levels in chemically induced DM rodents.

(a) TG levels

Subgroups	Effect size					Heterogeneity (I^2)	Test of Group difference (p)
	Study No.	*g*	95% CI		p-value		
Rodent type							
mice	1	-0.91	-3.45	1.63	0.48	0.00	0.25
rats	4	-2.59	-3.94	-1.24	<0.001	78.62	
Sample type							
plasma	1	-2.57	-5.38	0.23	0.07	0.00	0.79
serum	4	-2.14	-3.52	-0.76	0.002	83.35	
Sex							
male	4	-1.80	-2.83	-0.76	0.001	72.14	0.10
both	1	-3.91	-6.19	-1.63	0.001	0.00	

(b) TC levels

Subgroups	Effect size					Heterogeneity (I^2)	Test of Group difference (p)
	Study No.	*g*	95% CI		p-value		
Rodent type							
mice	1	-0.68	-4.44	3.08	0.72	0.00	0.24
rats	4	-3.23	-5.28	-1.17	0.002	89.14	
Sample type							
plasma	1	-3.13	-6.49	0.23	0.07	0.00	0.66
serum	4	-2.28	-4.01	-0.55	0.01	88.52	
Sex							
male	4	-3.11	-5.26	-0.95	0.01	90.63	0.44
both	1	-1.31	-5.30	2.67	0.52	0.00	