frontiers in Pharmacology

SYSTEMATIC REVIEW
published: 14 February 2022
doi: 10.3389/fphar.2022.822678

Citrus Extract as a Perspective for the Control of Dyslipidemia: A Systematic Review With Meta-Analysis From Animal Models to Human Studies

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Specialty section:
This article was submitted to Gastrointestinal and Hepatic Pharmacology, a section of the journal Frontiers in Pharmacology

Received: *26 November 2021*
Accepted: *10 January 2022*
Published: *14 February 2022*

Citation:
Carvalho BMR, Nascimento LC, Nascimento JC, Gonçalves VSS, Ziegelmann PK, Tavares DS and Guimarães AG (2022) Citrus *Extract as a Perspective for the Control of Dyslipidemia: A Systematic Review With Meta-Analysis From Animal Models to Human Studies. Front. Pharmacol. 13:822678. doi: 10.3389/fphar.2022.822678*

This study aims to obtain scientific evidence on the use of *Citrus* to control dyslipidemia. The surveys were carried out in 2020 and updated in March 2021, in the PubMed, Scopus, LILACS, and SciELO databases, using the following descriptors: *Citrus*, dyslipidemias, hypercholesterolemia, hyperlipidemias, lipoproteins, and cholesterol. The risk of bias was assessed according to the Cochrane methodology for clinical trials and ARRIVE for preclinical trials. A meta-analysis was performed using the application of R software. A total of 958 articles were identified and 26 studies demonstrating the effectiveness of the *Citrus* genus in controlling dyslipidemia were selected, of which 25 were included in the meta-analysis. The effects of *Citrus* products on dyslipidemia appear consistently robust, acting to reduce total cholesterol, LDL, and triglycerides, in addition to increasing HDL. These effects are associated with the composition of the extracts, extremely rich in antioxidant, as flavonoids, and that act on biochemical targets involved in lipogenesis and beta-oxidation. The risk of bias over all of the included studies was considered critically low to moderate. The meta-analysis demonstrated results favorable to control dyslipidemia by *Citrus* products. On the other hand, high heterogeneity values were identified, weakening the evidence presented. From this study, one can suggest that *Citrus* species extracts are potential candidates for dyslipidemia control, but more studies are needed to increase the strength of this occurrence.

Keywords: dyslipidemia, citrus, hyperlipidemia, flavonoids, cholesterol

Systematic Review Registration: [https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019121238], identifier [PROSPERO 2019 CRD42019121238].

INTRODUCTION

Dyslipidemia has high rates of occurrence in the world population (Pirillo et al., 2021), being closely related to obesity, metabolic syndrome (Mach et al., 2020), atherosclerosis (Wiggins et al., 2019),

coronary heart disease (Zhao et al., 2021), increased susceptibility to cancer (Khan et al., 2021), and more recently increased mortality and severity of COVID-19 (Atmosudigdo et al., 2021). This disorder is characterized by changes in the lipid profile, including an increase in total serum cholesterol, low-density lipoprotein (LDL-c), and triglycerides, as well as a decrease in high-density lipoprotein (HDL-c) rates in the blood (Fruchart et al., 2008). The relationships between these markers have been used as indicators of insulin resistance and metabolic disorders (Sowndarya et al., 2021), in addition to atherosclerosis and coronary heart disease (Abid et al., 2021). However, inflammation markers such as us-CRP (high serum sensitivity C-reactive protein) can also be considered important indicators to estimate the severity and risk of coronary artery disease (Patil et al., 2020). Although there are therapeutic options for the treatment of dyslipidemias, these are not fully effective, due to non-adherence to treatment by various factors such as adverse effects, intolerance, regimen complexity, and imperceptible benefits, besides the need to combine drugs to improve the clinical condition (Schulz, 2006; Ingersgaard et al., 2020). On the other hand, lipid-lowering drugs are still inaccessible to the majority of the population in low-income countries (Pirillo et al., 2021), making the search for new strategies to control dyslipidemia necessary.

In this sense, searching for new treatment strategies for this important health problem is necessary. In this perspective, several plants and natural products have been studied regarding their effects on dyslipidemia control (Ballard et al., 2019; Adel Mehraban et al., 2021); among them, the species of the genus *Citrus* (Lamiquiz-Moneo et al., 2020) stand out. Belonging to the Rutaceae family, the genus *Citrus* is widely distributed in tropical and subtropical regions (Manuel et al., 2020) and contains several substances with biological and nutritional potential, such as fibers (e.g., pectin), vitamins, and bioactive compounds, with emphasis on the flavonoids (Alam et al., 2013; Rafiq et al., 2018). Naringin, naringenin, nobiletin, narirutin, and hesperidin correspond to the most frequently found flavonoids. They have pronounced antioxidant and anti-inflammatory activities (Tripoli et al., 2007; Craft et al., 2012), in addition to being effective in controlling metabolic syndromes, lipid changes, and obesity (Geleijnse et al., 1999; Lee et al., 2001; Gattuso et al., 2007; Alam et al., 2013; Sahebkar, 2017; Ballard et al., 2019).

Thus, this review sought to compile the scientific findings that demonstrate the effect of *Citrus* extracts on the control of serum lipid levels, measuring the size of the effect through meta-analysis.

MATERIAL AND METHODS

Focused Question

The question to be answered was established from the bibliographic survey "Are species of the genus *Citrus* effective in reducing dyslipidemia?" conducted through four steps: (Pirillo et al., 2021) identification of the use of the *Citrus* species, (Mach et al., 2020) identification of the pathology to be applied (dyslipidemia), (Wiggins et al., 2019) definition of the types of studies included (preclinical and clinical), and (Zhao et al., 2021) definition of the target outcome to be analyzed, which is the lipid profile, building the PICOS strategy (patient or pathology, intervention, control, other outcomes, and the type of study). PICOS is highlighted as follows: P: dyslipidemia; I: species of the genera *Citrus* (extract); C: untreated or placebo-treated and hyperlipidemia-induced group; O: blood lipid levels; and S: preclinical or clinical studies.

Review Writing and Registration of Protocols

The writing of this systematic review was based on the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Page et al., 2021) tool. In addition, the instrument that guides how the experimental studies should be analyzed was ARRIVE (Animal Research: Reporting of *In Vivo* Experiments) guidelines (Kilkenny et al., 2010). The protocol for this review was registered in the International Prospective Register of Systematic Reviews (Prospero) database and registered on the website https://www.crd.york.ac.uk/prospero/, through approved registry No. CRD42019121238.

Literature Search

The search was carried out through search strategies in the LILACS, PubMed, SciELO, and Scopus databases in 2019 and updated in March 2021. The terms used to compose the search in the databases were defined from consultations with MeSH and DeCS descriptors. Thus, the following search strategy was structured: "*CITRUS*" AND "Lipoproteins" OR "Cholesterol" OR "Epicholesterol" OR "Dyslipidemias" OR "Dyslipoproteinemia" OR "Hypercholesterolemia" OR "High Cholesterol Levels" OR "Hyperlipidemias" OR "Lipidemia," described in detail in **Supplementary Table S1**.

Study Selection and Eligibility Criteria

After excluding duplicate records, titles, abstracts, and full texts were independently analyzed by two researchers in order to determine the study's eligibility for inclusion in the review. The inclusion criteria were preclinical studies or randomized clinical trials that include the use of *Citrus* species to assess the effect on the lipid profile. In this review, were excluded reviews, case studies, case reports, and studies that did not assess the action on the lipid profile, which included the use of juices from *Citrus* species and their action on the lipid profile, or the association of *Citrus* species with another compound that could modify the lipid profile, as well as studies that used compounds isolated from *Citrus* species to target hyperlipidemia. To assess the agreement among researchers, the statistical test of the Kappa coefficient (K) was applied.

Data Extraction and Risk of Bias Assessment

Two independent reviewers extracted data from the included studies. The data from preclinical studies were as follows: *Citrus* species, type of extract and part of the plant, composition,

hyperlipidemia induction model, evaluation methods, treatment, animal species, and results (all results that were in mg/dL were converted to mmol/L using the OnlineConversion.com electronic calculator according to the type of cholesterol). The data from clinical studies were as follows: *Citrus* species, type of extract and part of the plant, composition, study design/location, sample, criteria for inclusion and exclusion of participants, pathologies, treatment, and results (all results that were in mmol/L were converted to mg/dL using the OnlineConversion.com electronic calculator according to the type of cholesterol). All the outcomes of the experiments carried out in the articles were extracted for descriptive and inferential analyses.

Through ARRIVE, we apply the following: precise and concise description of the content of the article in the title, abstract, explanation of the methodological approach of the introduction, general and specific objectives, ethical nature of care and use of animals, study design regarding the number of animals per group, experimental procedures, information about animals such as sex, size, weight, and age, housing and breeding, sample size, statistical methods, description of results and their interpretation, and study funding.

All clinical studies included in this research were approved for methodological quality in the risk checklist of Cochrane randomized for controlled trials (Cochrane Training, 2019). Items such as generation of random sequence, concealment of allocation, certification of participants and professionals, as well as of evaluators, incomplete and selective outcomes, or whether the study presents any other problem or fraud were used. The studies considered as having the highest methodological quality were those related to randomization, blinding, and complete outcomes.

Meta-Analysis

The studies selected for the meta-analysis had the following outcomes analyzed: total cholesterol, LDL, HDL, and triglyceride levels, including the baseline and post-treatment data from both the control and treatment groups for both preclinical and clinical studies. In addition to the primary outcomes, to improve the understanding of the effects observed in preclinical studies, the studies were separated into the following subgroups: route of administration of the extract, type of animal, type of extract, and parts of the plant used.

For the quantitative analysis of the articles, the studies selected presented the value of the sample n, mean, deviation, or standard error for the serum levels of total cholesterol, LDL, HDL, and/or triglycerides of the treatment and control groups. All data were tabulated in Excel and later analyzed using the application of R software. The heterogeneity of the studies was measured using Cochran's Q test, using the I^2 statistic, which was considered as heterogeneous when the p value was less than 0.05. The heterogeneity between the studies was defined using the I^2 statistic, which was considered with an unimportant (I^2 < 25%), moderate (25% < I^2 < 75%), or high degree of heterogeneity (I^2 > 75%) (Higgins and Thompson, 2002). For heterogeneous studies (I^2 > 75%), the following subgroup analyses were performed: route of administration, type of animal, parts of the plant used in the extract, type of fruit, and type of extract. In addition, we performed a sensitivity analysis, sequentially removing the individual studies to determine whether any single study affected the overall effect estimate.

RESULTS

Study Selection and Study Characteristics

During the search process, 958 articles were obtained: 169 from PubMed, 762 from SciVerse Scopus, 12 from SciELO, and 15 from LILACS. After analyzing the titles, 598 duplicate articles were removed. After excluding the repeated articles, 360 titles were screened for analysis according to the inclusion criteria, from which 329 studies were excluded for not inducing hyperlipidemia in an animal model or for not having dyslipidemia installed in the case of clinical studies. In addition, studies with isolated compounds of the *Citrus* species or without evaluation of total cholesterol, LDL-C, HDL-C, or triglycerides were also excluded.

After this design, 31 articles remained, the full texts of which were analyzed, thus yielding 27 articles that were finally included in the qualitative synthesis (**Figure 1**; **Tables 1–3**). Of these, 22 studies were preclinical trials (Vinson et al., 1998; Bok et al., 1999; Terpstra et al., 2002; Zulkhairi et al., 2010; Ding et al., 2012; Kang et al., 2012; Raasmaja et al., 2013; Lu et al., 2013; Kim et al., 2013; Muhtadi et al., 2015; Dinesh and Hegde, 2016; Shin et al., 2016; Ashraf et al., 2017; Fayek et al., 2017; Chou et al., 2018; Feksa et al., 2018; Mir et al., 2019; Sato et al., 2019; Hase-Tamaru et al., 2019; Ling et al., 2020; Ke et al., 2020; Lee et al., 2020), 3 were exclusively clinical studies (Gorinstein et al., 2007; Toth et al., 2015; Cai et al., 2017) and 1 study contained preclinical and clinical protocols (Mollace et al., 2011) (**Figure 1**). For the quantitative synthesis, 25 articles (Vinson et al., 1998; Bok et al., 1999; Gorinstein et al., 2007; Zulkhairi et al., 2010; Mollace et al., 2011; Ding et al., 2012; Kang et al., 2012; Terpstra et al., 2012; Kim et al., 2013; Lu et al., 2013; Raasmaja et al., 2013; Muhtadi et al., 2015; Dinesh and Hegde, 2016; Shin et al., 2016; Ashraf et al., 2017; Cai et al., 2017; Fayek et al., 2017; Chou et al., 2018; Feksa et al., 2018; Hase-Tamaru et al., 2019; Mir et al., 2019; Sato et al., 2019; Ke et al., 2020; Lee et al., 2020; Ling et al., 2020) were selected. The level of agreement among the reviewers was 0.470, being considered as moderate.

Tables 2 and **3** show the general characteristics and results of the preclinical studies, arranged in the chronological order of publication. **Table 4** present the experimental conditions and results of clinical trials also arranged in the chronological order.

The selected articles were published between 1998 and 2020, with a predominance of the number of publications in 2013 (n = 3), 2017 (n = 3), 2019 (n = 3), and 2020 (n = 3). These studies were conducted mainly in China (n = 6; 23.0%) and Korea (n = 5; 19.2%) followed by Italy (n = 2; 7.6%) and Japan (n = 2; 7.6%), in addition to other countries in which only 1 study was found as described in **Tables 1–3**.

In the 26 selected articles, 15 different species of *Citrus* were studied in a dyslipidemia model: *C. reticulata* (n = 4; 15.3%), *C. bergamia* (n = 3; 11.5%), *C. sinensis* (n = 3; 13.6%),

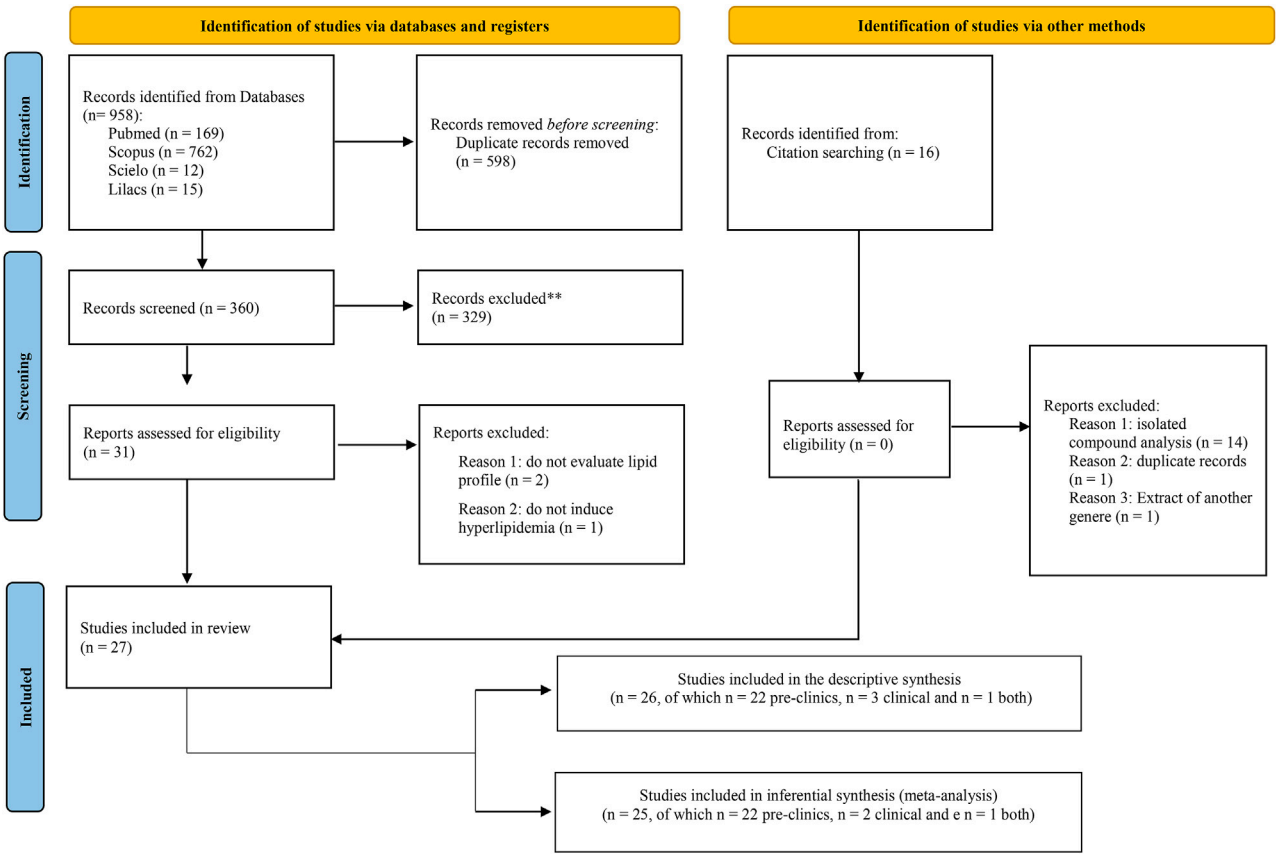

FIGURE 1 | Flowchart of the studies included in the qualitative and quantitative synthesis.

C. junos Tanaka (n = 2; 9.1%), *C. grandis* (L.) Osbeck also called *C. maxima* (n = 3; 11.5%), *C. paradise* also known as grapefruit (n = 2; 7.6%), *C. unshiu* (n = 2; 7.6%), *C. sunki* Hort. Ex Tanaka (n = 1; 3.8%), *C. aurantium* (n = 1; 3.8%), *C. mitis* (n = 1; 3.8%), *C. limon* (n = 1; 3.8%), *C. aurantiifolia* (n = 1; 3.8%), *C. ichangensis* (n = 1; 3.8%), *Poncirus trifoliata* x *Citrus sinensis* (n = 1; 3.8%), and *C. changshan-huyou* (n = 1; 3.8%). Among the *Citrus* species used in the preclinical studies, there was a predominance of six hybrid species in eight studies, followed by three orange species in eight studies and three types of lemons in four publications and tangerine species in four articles. In the clinical studies, on the other hand, there is a predominance of orange-based bergamot products (*C. bergamia*; n = 3 studies) and a study with supplements containing grapefruit (*C. paradise*).

\From these species, hydroalcoholic extracts or organic fractions (n = 20; 86.9%), aqueous extract (n = 1; 4.3%), and processed fruits (n = 3; 13.0%) were used, which were incorporated to the diet (n = 14; 60.8%) or administered orally by gavage (n = 9; 40.9%). In the clinical trials as a whole, supplementation with encapsulated dry extract was used or inclusion in the diet. In addition, 21 studies (80.7%) evaluated the chemical composition of the extracts, with a predominance of compounds belonging to the class of flavonoids, such as naringin, hesperidin, neoeriocitrin, neohesperidin, nobiletin, tangeretin, and naringenin (**Figure 2**).

As observed in **Table 1**, the method of inducing hyperlipidemia in the preclinical studies was by cholesterol-rich diet or cafeteria-type diet, conducted with rats (n = 12; 52.1%), mice (n = 8; 34.7%), and hamsters (n = 3; 13.0%). Among the randomized clinical trials (**Table 3**), the clinical conditions of the participants were in their entirety dyslipidemia (n = 4; 100%), associated or not with coronary disease (n = 1, 25%), and hypertension and glucose intolerance (n = 1; 25%). In the preclinical and clinical studies, the outcomes evaluated were the levels of total cholesterol (TC, n = 18; 100%), HDL (n = 14; 77.7%), LDL (n = 12; 66.7%), VLDL (n = 2; 13.3%), IDL (n = 1; 5.5%), and triglycerides (TG, n = 17; 94.4%).

From the analysis of the preclinical and clinical studies (**Tables 2–4**), it was found that the *Citrus* species were able to significantly alter the lipid profile in the 26 (100%) studies, decreasing serum total cholesterol (n = 25; 96.1%), LDL (n = 14; 53.8%), triglycerides (n = 17; 65.3%), and VLDL (n = 2; 7.6%) and increasing HDL (n = 4; 15.3%). In the liver, *Citrus* also reduced TC and TG (n = 6; 23.0%), lipid accumulation (n = 5; 19.2%), and weight (n = 2; 7.6%). These effects were accompanied by the maintenance (n = 1; 3.8%) of glutamic-oxaloacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT), and alkaline phosphatase (ALP) serum levels or the

TABLE 1 | Detailed description of the preclinical studies of the effect of *Citrus* extract on hyperlipidemia included in the systematic review.

References, country	Extract, plant part, and species	Composition	Model	Evaluated parameters	Treatment protocol	Animal (n/group)
Vinson et al., 1998 (Vinson et al., 1998)	Hydroalcoholic extract of whole dried ripe fruits *C. aurantium*	25.7% ascorbic acid 9.9% flavonoids (quercetin, hesperidin, naringenin, and myricetin)	Hamster fed on a high-cholesterol diet	LDL, VLDL HDL, TC, TG, foam cell injury	Feed containing 3% of the extract or 4% of the extract associated with ascorbic acid	Male Golden Syrian
EUA		31.2% protein 3.2% ash 30% carbohydrates		in the aorta artery lipid peroxidation	(57 mmol/kg diet) daily, for 4 or 10 weeks	Hamsters (n = 10)
Bok et al., 1999 (Bok et al., 1999)	Hydroalcoholic extract of the peel *C. reticulata*	2.7 g of protein 1.8 g of fat	Rats fed on a high-cholesterol diet	Plasmatic and hepatic TC, TG, HDL, LDL AI[a], fecal neutral sterols, HMGR, and ACAT activities in liver tissue	16.7 g/100 g of diet for 6 weeks	Male Sprague Dawley rats (n = 10)
Korea		1.0 g of ash 20 g of fructose 16.5 g of glucose 8.6 g of sucrose 0.6 g of hesperidin 0.03 g of naringin and 9.67 g of other sugars				
Terpstra et al., 2002 (Terpstra et al., 2002)	Peels or waste stream material of *C. limon*	-	Hamster fed on a high-cholesterol diet	BW, FI, and liver weight TC of plasma and liver Plasmatic TG, LDL, HDL, VLDL bile acids, and fecal sterols	Diets containing 3% of cellulose or lemon peels or the waste stream of the lemon pectin extraction for 8 weeks	Male hybrid F_1B Golden Syrian Hamster (n = 14)
Mollace et al., 2011 (Mollace et al., 2011)	Polyphenolic fraction of *C. bergamia* Risso & Poiteau peeled-off fruits	Neoeriocitrin (77,700 ppm), naringin (63,011 ppm), neohesperidin (72,056 ppm), melitidine (15,606 ppm), and brutieridine (33,202 ppm)	High-cholesterol diet-induced hyperlipemia	BW, TC, LDL, HDL TG and glucose Neutral sterols and fecal bile acids	10 or 20 mg/kg daily (p.o.) for 30 days	Male Wistar Rats (n = 10)
Zulkhairi et al., (Zulkhairi et al., 2010)	Aqueous extract (5% and 10%) of dried whole fruits *C. mitis*	Phenolic compounds	Rats fed on a high-cholesterol diet	BW, TC, HDL, LDL, TG, AI[b], sdLDL[c] Scavenging activity of DPPH radicals, reducing power, lipid peroxidation (*in vitro*)	5 mg/kg of extract at 5% and 10% daily (p.o.) for 10 weeks	Male Sprague Dawley rats (n = 6)
Ding et al., 2012 (Ding et al., 2012)	Hydroalcoholic extract of *C. ichangensis* peel	Naringin, hesperidin, poncirin, neoeriocitrin narirutin, neohesperidin, naringenin, nobiletin, and tangeretin	High-fat diet-induced Obese	BWG, FI TC, TG, LDL, HDL, and glucose Fecal and hepatic TC and TG; size of EWAT; mRNA expression of PPARγ, LXR, and them target genes in liver tissue	Diet supplemented with 1% of extract, for 8 weeks	Female C57BL/6 mice (n = 7)
Kang et al., 2012 (Kang et al., 2012)	Hydroalcoholic extract of *C sunki* peel	Tangeretin (55.13 mg/g) Nobiletin (38.83 mg/g)	High-fat diet-induced Obese	BWG, FI TC, TG, GPT, GOT, and LDH, EPAT weight, liver fat; p-AMPK, p-ACC, and adiponectin mRNA expression in EAT.	150 mg/kg/day of extract (p.o.) for 70 days	Male C57BL/6 mice (n = 10)

(Continued on following page)

TABLE 1 | (*Continued*) Detailed description of the preclinical studies of the effect of *Citrus* extract on hyperlipidemia included in the systematic review.

References, country	Extract, plant part, and species	Composition	Model	Evaluated parameters	Treatment protocol	Animal (n/group)
Korea		Hesperidin (17.11 mg/g)		In mature 3T3-L1 adipocytes: LKB1, AMPK, ACC, PKA, and HSL phosphorylation, CPT-1a gene expression, and glycerol release		
		Rutin (17.02 mg/g) Sinensetin (4.23 mg/g)				
Raasmaja et al., 2013 (Raasmaja et al., 2013)	Hydroalcoholic extract of *C. grandis* (L.) Osbeck whole fruits	Naringin at 19%	High-fat diet-induced	BWG, FI	300, 600, or 1,200 mg/kg (p.o.) daily	Female
Finland			Obese	TG, TC, HDL, glucose, insulin, ghrelin, GLP-1 PYY, leptin, and amylin in plasma	for 12 weeks	Zucker Rats (n = 10)
Lu et al.,	Hydroalcoholic extract of *Citrange* (*Poncirus trifoliata* x *C. sinensis*) peel or flesh and seed	Bark extract	High-fat diet-induced obese	BWG, FI, ipGTT, blood glucose, serum TG, TC, LDL and HDL, hepatic TG and TC	Diet supplemented with 1% w/w of peel extract	Female
2013 (Lu et al., 2013)		Neoeriocitrin (14.5 mg/g), naringin (8.12 mg/g), neohesperidin (21.1 mg/g), and poncirin (14.1 mg/g)		Fecal TC and TG, histological analysis	or 1% w/w of flesh and seed	C57BL/6 mice (n = 6)
China		Seed extract Poncirin (4.85 mg/g) Neohesperidin (1.87 mg/g) Naringin (0.87 mg/g)		of liver tissue mRNA levels of PPARγ, LXR, and their target genes in liver tissue	extract, daily for 8 weeks	
Kim et al.,	Hydroalcoholic extract of *C. junos* Tanaka peel	Hesperidin (36.3 mg/100 g)	High-fat diet-induced obese	BWG, FI	Diet supplemented with 1% and 5% of extract	Male
2013 (Kim et al., 2013)		Naringin (11.6 mg/100 g)		TC, TG, glucose, insulin, leptin, resistin, GOT, GPT, histological analysis of liver tissue	for 9 weeks	C57BL/6 J mice (n = 8)
Korea		Rutin (2.7 mg/100 g)		AMPK phosphorylation in muscle tissue		
		Quercetin (1.7 mg/100 g) and tangeretin (0.7 mg/100 g)		AMPK and PPARγ activation in C2C12 and HEK293 cells, respectively		
Muhtadi et al., 2015 (Muhtadi et al., 2015)	Hydroalcoholic extract of *C. sinensis* fruit peel	-	High-fat diet-induced hypercholesterolemia	TC; glucose in rats	125, 250, and 500 mg/kg (p.o.), daily for 2 weeks	Male
Indonesia				induced by alloxan monohydrate	After 4-week diet	Wistar rats (n = 5)
Dinesh and Hegde, 2016 (Dinesh and Hegde, 2016)	Hydroalcoholic extract of *C. maxim*a leaves	Flavonoids, alkaloids, carbohydrates, glycosides, saponins, and tannins	Cafeteria diet and Olanzapine-induced obesity	BWG, FI	200 and 400 mg/kg (p.o.), daily for 4 weeks	Female
India				TC, TG, HDL, LDL, VLDL, GOT, GPT, glucose Liver weight and TG		Wistar rats (n = 6)
Shin et al.,	Hydroalcoholic extract of *C. junos* Tanaka peel	-	Mice fed on a high-cholesterol diet	BWG, FI	Diet supplemented with 1% and 5% of the extract	Male
2016 (Shin et al., 2016)				TG, TC, HDL, GOT, GPT, ALP, histological analysis	for 10 weeks	C57BL/6 J mice (n = 8)
Korea				of liver tissue		

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TABLE 1 | (*Continued*) Detailed description of the preclinical studies of the effect of *Citrus* extract on hyperlipidemia included in the systematic review.

References, country	Extract, plant part, and species	Composition	Model	Evaluated parameters	Treatment protocol	Animal (n/group)
				Expression of PPARα, FAS, and HMGR in liver tissue Lipid accumulation and expression of p-AMPK, p-ACC, PPARα, CPT-1, and HMGR in HepG2 cells		
Ashraf et al., 2017 (Ashraf et al., 2017) Pakistan	Hydroalcoholic extract of *C. sinensis* peel	-	Rats fed on high-glucose or cholesterol-rich diet	BWG, FI TG, TC, LDL, HDL, glucose, insulin	Diet supplemented with 10% *Citrus* peel powder (functional) and 5% peel extract (nutraceutical), for 8 weeks	Male Sprague Dawley rats (n = 6)
Fayek et al., 2017 (Fayek et al., 2017) Egypt	Methanolic extract, hexanic extract, aqueous homogenate of *C. reticulata* (Mandarin), *C. sinensis* (sweet orange), *C. paradise* (white grapefruit), or *C. aurantiifolia* (lime) fruit peels	Nobiletin (%) in hexanic extracts Mandarin (10.14%) Sweet orange (3.6%) White grapefruit (0.9%) Lime (0.0045%) Pectin (%) in peel powder Sweet orange (21.33%) Lime (19.7%) While grapefruit (11.66%) Mandarin (9.14%)	Hypercholesterolemia induced by diet rich in cholesterol and bile salts	TC TG and glucose	0.1 ml of the corresponding extract (p.o.) for 8 weeks	Male Wistar rats (n = 6)
Chou et al., 2018 (Chou et al., 2018) China	Methanolic extract of *C. reticulata*	Narirutin (4.52 ± 0.31 mg/g), hesperidin (9.14 ± 0.32 mg/g), nobiletin (2.54 ± 0.07 mg/g) Tangeretin (1.67 ± 0.05 mg/g)	High-fat diet-induced obese	AST, ALT, triglyceride, total cholesterol, glucose, insulin, HOMA-IR	1% of the corresponding extract for 11 weeks	Male C57BL/6 J mice (n = 8)
Feksa et al., 2018 (Feksa et al., 2018) Brazil	Hydroalcoholic extract of leaves of *C. maxima*	Gallic acid, catechin, caffeic acid, epicatechin, rutin and isoquercetin, and the major compounds were caffeic acid (3.71 mg/g) and catechin (3.65 mg/g	High-fat diet and fructose	Blood count, AST, ALT, triglyceride, total cholesterol, LDL, HDL, glucose, urea, creatinine,	50 mg/kg	Male Wistar rats (n =
Mir et al., 2019 (Mir et al., 2019) Algeria	Hydroalcoholic extract of *C. latifolia*	-	Hypercholesterolemia induced by diet rich in cholesterol	triglyceride, and total cholesterol	1% of the corresponding extract for 4 weeks	Male Wistar rats (n = 10)
Sato et al., 2019 (Sato et al., 2019) Japan	*C. tumida* peel powder	Calorie (275 kcal), moisture (2.9 g), protein (7.4 g), fat (2.7 g), ash (4.9 g), carbohydrate (82.1 g), sugar (28.4 g), fiber (53.7 g), galacturonic acid (12.2 g), and sodium (4.3 mg)	High-fat diet	AST, ALT, triglyceride, total cholesterol, HDL-C, creatinine, albumin, calcium, and LDH	*C. tumida* peel powder 5% (w/w)	Male C57BL/6 J mice (n = 8)
Tamaru et al., 2019 (Hase-Tamaru et al., 2019) Japan	*C. unshiu* MARC lyophilized and powdered	76.1 g carbohydrate, 7.6 g crude protein, 0.7 g crude fat, 2.7 g ash, 12.9 g moisture, 40.9 g total fiber, 6.6 g total pectin, 14.4 g hesperidin, and 3.0 g narirutin	High-fat diet	Total cholesterol, triglycerides, free fatty acids, glucose, insulin, and leptin	2.5% 5.0%, or 10.0%	Sprague Dawley (SD) rats (n = 7)
Lee et al., 2020 (Lee et al., 2020) Korea	*C. unshiu*: dried extract (CPEW) and lyophilized (CPEF)	Hesperidin, narirutin, and synephrine	High-fat diet	AST, ALT, triglyceride, total cholesterol, and LDL-C	CPEW: 50 mg/kg; 100 mg/kg CPEF: 50 mg/kg; 100 mg/kg	Male SD rats (n = 8)
Ling et al., 2020 (Ling et al., 2020)	*C. changshan-huyou*	Naringin, narirutin, and neohesperidin	High-fat diet		PTFC: 25 mg/kg; 50 mg/kg; 100 mg/kg	

(Continued on following page)

TABLE 1 | (*Continued*) Detailed description of the preclinical studies of the effect of *Citrus* extract on hyperlipidemia included in the systematic review.

References, country	Extract, plant part, and species	Composition	Model	Evaluated parameters	Treatment protocol	Animal (n/group)
China				AST, ALT, triglyceride, total cholesterol, LDL-C, and HDL-C		Golden hamsters (n = 12)
Ke et al., 2020 (Ke et al., 2020) China	*C. reticulata* Blanco	Nobiletin (98.34 mg/g), heptamethoxyflavone (44.26 mg/g), tangeretin (26.20 mg/g), and isosinensetin (26.14 mg/g)	High-fat diet	Triglyceride, total cholesterol, LDL-C, and HDL-C	0.2 and 0.5% JZE	C57BL/6 J mice (n = 8)

glutamic p.o., intragastric gavage; TC, total cholesterol; TG, triglycerides; LDL, low-density lipoprotein; HDL, high-density lipoprotein; VLDL, very low-density lipoprotein; LDH, lactate dehydrogenase; GOT, -oxaloacetic transaminase; GPT, glutamic-pyruvic transaminase; EWAT, epididymal white adipose tissue; PPARγ, peroxisome proliferator-activated receptor γ; FAS, fatty acid synthase; ACO, acyl-CoA oxidase; LXRα, liver X receptor α; LXRβ, liver X receptor β; AMPK, AMP-activated protein kinase; ACC, acetyl-CoA carboxylase; PKA, cAMP-dependent protein kinase; HSL, hormone-sensitive lipase. GLP-1, glucagon-like peptide-1; PYY, pancreatic peptide YY; BWG, body weight gain; FI, food intake; ipGTT, intraperitoneal glucose tolerance test; ALP, alkaline phosphatase; FAS, fatty acid synthase receptor; CPT-1, carnitine palmitoyl transferase-1; HMGR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; EPAT, epididymal and perirenal adipose tissue; EAT, epididymal adipose tissue.

[a]*The duration of the experiment is not explicitly informed in the article. AI, atherogenic index.*

[b]*[(TC-HDL)/HDL].*

[c]*(LDL/HDL); sdLDL, small dense LDL, particle size.*

[d]*(TG/HDL).*

reduction of GOT, GPT (n = 2; 7.6%), and lactate dehydrogenase (LDH) (n = 1; 3.8%).

In addition, some *Citrus* products also reduced body weight gain (BWG; n = 7; 26.9%), food intake (FI; n = 1; 3.8%), and lipid accumulation in adipose tissue or cells (n = 3; 11.5%). In human, a study also demonstrated their effect on the reduction of waist circumference (WC), waist-to-hip ratio (WHR), and body mass index (BMI). Taken together, these effects can reduce the risk of atherosclerosis as shown in three studies (16.6%). However, its effects on the lipid excretion are still controversial, since two studies (11.0%) demonstrate increased excretion, two studies (11.0%) did not identify changes, and only one study (5.5%) found a reduction in excretion (**Table 3**). In parallel, some authors investigated the effect of *Citrus*-based products on glucose and their effects on blood glucose reduction (n = 8; 44.4%), insulin increase (n = 2; 11.0%), and glucose uptake in the cell (n = 1; 5.5%).

In addition, several targets involved in the energy and nutrient metabolism have been studied. As can be seen in **Table 3**, some species of *Citrus* demonstrated effects on peroxisome proliferator-activated receptor γ (PPARγ) and peroxisome proliferator-activated receptor α (PPARα), downmodulating fatty acid synthase (FAS), acyl-CoA oxidase (ACO), uncoupling protein 2 (UCP2), and adipocyte fatty-acid-binding protein (aP2), besides upregulating CD36 and acetyl-CoA carboxylase (ACC). They can also act on liver X receptor (LXR), reducing lipoprotein lipase (LPL), apolipoprotein E (ApoE), and cholesterol 7α-hydroxylase (CYP7A1) and increasing ATP-binding cassette transporter G1 (ABCG1) and ATP-binding cassette transporter A1 (ABCA1).

The adiponectin signaling pathway also can be involved in the lipid control. In fact, some *Citrus* products were able to increase adiponectin; stimulate the phosphorylation of LKB1, AMP-activated protein kinase (AMPK), ACC, and carnitine palmitoyl transferase-1 (CPT-1); and reduce HMGR and ACAT activities. Their effects on lipolysis were also observed by the upmodulation of cAMP-dependent protein kinase (PKA) and hormone-sensitive lipase (HSL), with increase in glycerol. Besides adiponectin, *Citrus* seems to act reducing other adipocytokines, as leptin and resistin, which regulate the appetite and glucose metabolism and have been associated with insulin resistance. Their effects were also observed in the hormones involved with satiety and hunger control, as leptin, glucagon-like peptide-1 (GLP-1), and ghrelin. Finally, the antioxidant potential of *Citrus* has also been demonstrated, which can offer benefits in reducing lipid oxidation and in the development of atheromatous plaques.

Methodological Quality/Risk of Bias

The 23 preclinical studies, using the criteria provided by the ARRIVE guidelines, were analyzed for methodological quality. The studies showed a percentage of adequacy varying between 50 and 92% (83.82 ± 10.77%), with a greater weakness in the quality of the methodological description of the studies (**Supplementary Table S2**).

As for the clinical studies included in this research and evaluated by the Cochrane list (**Figure 3**), all of them had blinding outcome evaluators and incomplete outcomes. In addition, 50% of the articles presented low risk of uncertain bias regarding the criteria of generating a random sequence, concealment of allocation, blinding of the participants, reporting of the selective outcome, and other sources of bias (conflict of interest, based on the source of funding for the study and method of determination of the sample size).

Meta-Analysis

For the meta-analysis, the preclinical studies measured the level of total cholesterol [n = 23; 100%; I^2 = 99.1% (98.9%; 99.2%)], triglycerides [n = 20; 87%; I^2 = 99.4% (99.3%; 99.5%)], LDL [n = 12; 52.2%; I^2 = 99.1% (98.9%; 99.3%)], and HDL [n = 14; 60.9%; I^2 = 93.4% (90.6%; 95.4%)]. As for the clinical studies, three clinical trials with 92, 98, and 237 participants were included in the

TABLE 2 | Outcomes of the preclinical studies included in this systematic review.

Reference	Experimental group (mmol/L)	Control group (mmol/L)	Summary of results
Vinson et al., (Vinson et al., 1998)	Baseline: TC: 5.84; HDL: 3.31; TG: 25.1	Baseline: TC: 10.3; HDL: 2.84; TG: 41.6	↓TC and TG
	10 weeks: TC: 6.88; HDL: 1.68; TG: 27.1	10 weeks: TC: 15.1; HDL: 1.48; TG: 55.9	↓ lipid peroxidation
			↓ atherosclerosis signals (↓ area and density of foam cells), without changing BW
Bok et al. (Bok et al., 1999)	Baseline	Baseline:	↓ plasma TC
	6 weeks: TC: 2.44; HDL: 0.61; TG: 1.22	6 weeks: TC: 3.8; HDL: 0.57; TG: 1.12	↓ hepatic TC and TG, without changing HDL, TG, and LDL plasmatic
			↓AI and cholesterol excretion
			↓ HMGR and ACAT activities
Terpstra et al. (Terpstra et al., 2002)	Baseline:	Baseline:	↓ plasma and liver TC, ↓ VLDL + LDL being more effective in ↓VLDL, without changing HDL, ↑ excretion of fecal neutral sterols and bile acids
	8 weeks (lemon peel): TC: 3.51	8 weeks (cellulose): TC: 4.21	without changing BW, FI, and liver weight
	8 weeks (waste stream): TC: 3.44		
Mollace et al. (Mollace et al., 2011)	Baseline:	Baseline:	↓TC, LDL, and TG, without changing BW, HDL and glucose
	30 days (10 mg): TC: 5.95; LDL: 4.49; HDL: 0.58; TG: 2.75	30 days: TC: 8.19; LDL: 6.04; HDL: 0.53; TG: 2.74	↑ fecal neutral sterols and bile acids
	30 days (20 mg): TC: 5.00; LDL: 3.90; HDL: 0.65; TG: 2.74		
Zulkhairi et al. (Zulkhairi et al., 2010)	Baseline (5%)	Baseline: TC: 1.75; LDL: 0.45; HDL: 0.85; TG: 0.54	↓ TC, LDL, TG
	TC: 1.73; LDL: 0.45; HDL: 1.34; TG: 0.76	4 weeks	↑ HDL
	Baseline (10%)	TC: 2.13; LDL: 0.93; HDL: 0.89; TG: 0.79	↓AI and sdLDL
	TC: 1.68; LDL: 0.49; HDL: 1.27; TG: 0.74		Antioxidant activity, without changing BW
	4 weeks (5%)		
	TC: 1.28; LDL: 0.27; HDL: 1.39; TG: 0.63		
	4 weeks (10%)		
	TC: 1.06; LDL: 0.23; HDL: 1.54; TG: 0.53		
Ding et al. (Ding et al., 2012)	Baseline:	Baseline:	↓ BWG
	8 weeks	8 weeks	↓TC and LDL plasmatic
	TC: 2.27; LDL: 0.35; HDL: 2.32; TG: 0.70	TC: 2.65; LDL: 0.46; HDL: 1.95; TG: 0.70	↓ hepatic TC, TG, glucose, and adipocyte size, without changing
			Plasmatic FI, HDL, and TG and
			fecal TC and TG
			↓ expression of PPARγ (↓FAS, ACO, and UCP2 and ↑ CD36) ↓ LXR α and β (↓ ApoE, CYP7A1, LPL, and ↑ABCA1)
Kang et al. (Kang et al., 2012)	Baseline:	Baseline:	↓ BWG without changing in FI
	70 days	70 days: TC: 4.63; TG: 1.56	↓ TC, TG, LDH, GOT, and GPT
	TC: 3.81; TG: 0.94		↓ weight and cell size of EPAT
			↓ liver fat
			↑ p-AMPK, p-ACC, p-LKB1, and adiponectin
			↑ glycerol release
			↑ p-PKA and p-HSL
Raasmaja et al. (Raasmaja et al., 2013)	Baseline (300 mg/kg)	Baseline	Tendency to ↓ TC, glucose, and TG and ↑ HDL
	TC: 3.72; HDL: 1.42; TG: 8.34	TC: 3.56; HDL: 1.67; TG: 7.31	↓ GLP-1 and reversing the ↓ of ghrelin, without changing BWG, FI
	Baseline (600 mg/kg)	12 weeks	PYY, leptin, insulin, and amylin
	TC: 3.13; HDL: 1.70; TG: 6.27	TC: 4.13; HDL: 0.52; TG: 15.76	
	Baseline (1,200 mg/kg)		
	TC: 3.59; HDL: 1.53; TG: 8.11		
	12 weeks (300 mg/kg)		
	TC: 4.23; HDL: 0.44; TG: 16.68		
	12 weeks (600 mg/kg)		
	TC: 3.62; HDL: 0.80; TG: 12.57		
	12 weeks (1,200 mg/kg)		
	TC: 4.36; HDL: 0.80; TG: 17.42		
Lu et al. (Lu et al., 2013)	Baseline	Baseline	↓ BWG

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TABLE 2 | (*Continued*) Outcomes of the preclinical studies included in this systematic review.

Reference	Experimental group (mmol/L)	Control group (mmol/L)	Summary of results
	8 weeks (peel) TC: 2.30; LDL: 0.36; HDL: 2.00; TG: 0.70 8 weeks (seed) TC: 2.43; LDL: 0.41; HDL: 1.87; TG: 0.74	8 weeks TC: 2.64; LDL: 0.41; HDL: 1.97; TG: 0.70	Improves glucose tolerance and insulin resistance ↓ serum glucose, TC, and LDL ↓ hepatic TC and TG, without changing FI, serum HDL, and fecal TC and TG ↓ PPARγ (↓ ap2, FAS); ↓ LXRβ (↓ LPL and ApoE and ↑ ABCG1) ↓ lipid accumulation in liver tissue
Kim et al. (Kim et al., 2013)	Baseline 9 weeks (1%) TC: 2.00; TG: 0.85 9 weeks (5%) TC: 1.91; TG: 0.76	Baseline: 9 weeks TC: 2.37; TG: 0.88	↓ BWG, glucose, TG, TC, insulin, leptin, and resistin ↑ glucose uptake ↓ liver tissue fat ↑ PPARγ and AMPK, without changing FI, GOT, and GPT
Muhtadi et al. (Muhtadi et al., 2015)	Baseline (125 mg/kg): TC: 4.31 Baseline (250 mg/kg): TC: 5.08 Baseline 500 (mg/kg): TC: 4.87 2 weeks (125 mg/kg): TC: 1.88 2 weeks (250 mg/kg): TC: 2.13 2 weeks (500 mg/kg): TC: 2.02	Baseline: TC: 3.77 2 weeks: TC: 3.27	↓ TC and glucose
Dinesh and Hegde (Dinesh and Hegde, 2016)	Baseline 4 weeks (200 mg/kg) TC: 79.76; LDL: 54.31; HDL: 40.68; TG: 104.3 4 weeks (400 mg/kg) TC: 75.77; LDL: 51.75; HDL: 43.22; TG: 98.05	Baseline: 4 weeks TC: 88.75; LDL: 74.71; HDL: 35.11; TG: 130.0	↓ BWG and FI ↓ TC, TG, LDL, and VLDL ↑ HDL ↓ GOT and GPT ↓ liver weight and TG ↓ glucose
Shin et al. (Shin et al., 2016)	Baseline: 10 weeks (1%) TC: 2.89; LDL: 1.81; HDL: 0.87 10 weeks (5%) TC: 2.96; LDL: 1.80; HDL: 0.80	Baseline: 10 weeks TC: 4.03; LDL: 3.03; HDL: 0.80	↓ BWG ↓ TC, LDL, GOT, GPT, ALP, without changing FI, HDL ↓ liver fat content and weight ↑ p-AMPK, p-ACC, PPARα, and CPT-1 expression ↓ FAS and HMGR expression ↓ lipid accumulation
Ashraf et al. (Ashraf et al., 2017)	Baseline (powder) TC: 3.34; HDL: 1.19; LDL: 1.67; TRI: 1.07 Baseline (extract) TC: 3.32; HDL: 1.21; LDL: 1.62; TRI: 1.05 8 weeks (powder) TC: 3.14; HDL: 1.21; LDL: 1.52; TRI: 1.01 8 weeks (extract) TC: 3.03; HDL: 1.24; LDL: 1.44; TRI: 0.97	Baseline TC: 3.30; HDL: 1.17; LDL: 1.63; TRI: 1.04 8 weeks TC: 3.81; HDL: 1.17; LDL: 1.85; TRI: 1.16	Tendency to ↓ BWG and FI ↓ TG, TC, and LDL ↑ HDL ↓ glucose and ↑ insulin
Fayek et al. (Fayek et al., 2017)	Baseline: Tangerine (alcoholic extract) TC: 2.00; TG: 0.78 Orange (alcoholic extract) TC: 3.25; TG: 0.94 Hybrid (alcoholic extract) TC: 3.95; TG: 0.85 Lime (alcoholic extract) TC: 5.47; TG: 0.51	Baseline: Diet TC: 3.92; TG: 2.66	Tendency to ↓ TC ↓ TG and glucose
Chou et al. (Chou et al., 2018)	Baseline: 11 weeks (1%) TC: 3.85; TG: 0.44	Baseline: 11 weeks (diet) TC: 4.68; TG: 0.85	Tendency to ↓ TC ↓ TG and insulin resistance
Feksa et al. (Feksa et al., 2018)	Baseline 45 days (50 mg/kg) TC: 2.12; TG: 2.84; HDL: 0.34; LDL: 0.61	Baseline: 45 days (diet): TC: 3.34; TG: 3.38; HDL: 0.47; LDL: 1.23	Tendency to ↓ TG, TC, and LDL
Mir et al. (Mir et al., 2019)	Baseline 4 weeks (1%)	Baseline: 4 weeks (diet)	Tendency to ↓ TG and TC

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TABLE 2 | (*Continued*) Outcomes of the preclinical studies included in this systematic review.

Reference	Experimental group (mmol/L)	Control group (mmol/L)	Summary of results
	TC: 3.8; TG: 0.9	TC: 5.9; TG: 1.8	
Sato et al. (Sato et al., 2019)	Baseline: 4 weeks (5%) TC: 3.31; TG: 0.28; HDL: 2.06	Baseline: 4 weeks (diet) TC: 4.39; TG: 0.41; HDL: 2.42	Tendency to ↓ TG and TC
Tamaru et al. (Hase-Tamaru et al., 2019)	Baseline: 4 weeks (2.5%) TC: 2.01; TG: 1.67 4 weeks (5%) TC: 2.22; TG: 1.63 4 weeks (10%) TC: 1.72; TG: 2.74	Baseline: 4 weeks (diet) TC: 2.27 TG: 2.00	Tendency to ↓ TG and TC ↓ free fatty acids, glucose, insulin, and leptin ↓ FAS, G6PDH in cytosol, and PAP in microsome
Lee et al. (Lee et al., 2020)	Baseline 8 weeks (CPEW 50 mg/kg): TC: 4.00; TG: 2.89; LDL: 2.58 8 weeks (CPEW 100 mg/kg): TC: 3.54; TG: 2.52; LDL: 2.27 8 weeks (CPEF 50 mg/kg): TC: 4.08; TG: 2.79; LDL: 2.56 8 weeks (CPEF 100 mg/kg): TC: 3.64; TG: 2.59; LDL: 2.37	Baseline: 8 weeks (diet): TC: 4.00; TG: 2.89; LDL: 2.58	Tendency to ↓ TG and TC
Ling et al. (Ling et al., 2020)	Baseline 4 weeks (25 mg/kg): TC: 32.00; TG: 10.20; HDL: 2.30; LDL: 11.41 4 weeks (50 mg/kg): TC: 22.30; TG: 5.30; HDL: 2.83; LDL: 9.83 4 weeks (100 mg/kg): TC: 21.70; TG: 5.30; HDL: 2.65; LDL: 8.67	Baseline: 4 weeks (diet) TC: 41.59; TG: 11.15; HDL: 4.95; LDL: 11.80	Tendency to ↓ TG, TC, and LDL-C
Ke et al. (Ke et al., 2020)	Baseline 4 weeks (0.2%): TC: 5.69; TG: 0.28; HDL: 4.10; LDL: 1.01 4 weeks (0.5%): TC: 5.04; TG: 0.28; HDL: 3.84; LDL: 0.81	Baseline: 4 weeks (diet) TC: 5.62; TG: 0.41; HDL: 4.20; LDL: 1.20	Tendency to ↓ TG, TC, and LDL-C

TC, total cholesterol; TG, triglycerides; LDL, low-density lipoprotein; HDL, high-density lipoprotein; VLDL, very low-density lipoprotein; BW, body weight; HMGR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; ACAT, acyl-CoA cholesterol acyltransferase; AI, atherogenic index; FI, food intake; BWG, body weight gain; PPARγ, peroxisome proliferator-activated receptor γ; FAS, fatty acid synthase; ACO, acyl-CoA oxidase; UCP2, uncoupling protein 2; CD36, cluster of differentiation 36; LXR, liver X receptor; ApoE, apolipoprotein E; CYP7A1, cholesterol 7α-hydroxylase; LPL, reducing lipoprotein lipase; ABCA1, ATP-binding cassette transporter A1; LDH, lactate dehydrogenase; GPT, glutamic-pyruvic transaminase; GOT, glutamic-oxaloacetic transaminase; AMPK, AMP-activated protein kinase; ACC, acetyl-CoA carboxylase; PKA; AMP-dependent protein kinase; HSL, hormone-sensitive lipase; PYY, pancreatic peptide YY; GLP-1, glucagon-like peptide-1; ABCG1, ATP-binding cassette transporter G1; ALP, alkaline phosphatase; CPT-1, carnitine palmitoyl transferase-1; G6PDH, glucose-6-phosphate dehydrogenase; PAP, phosphatidic acid phosphohydrolase in the microsome.

quantitative analyses, which were performed with patients with dyslipidemia and demonstrated the *Citrus* effects on the levels of total cholesterol [I^2 = 94.5% (87.3%; 97.6%)], triglycerides [I^2 = 95.6% (90.5%; 98.0%)], LDL [I^2 = 96.6% (93.0%; 98.4%)], and HDL [I^2 = 81.4% (42.2%; 94.0%)] (in both, n = 3; 100%).

The presentation of the forest graphs was distributed according to the results of the levels of total cholesterol, triglycerides, LDL, and HDL for preclinical and clinical studies. Through the global analysis of preclinical studies, a reduction of −1.08 mmol/L (95% CI: 1.23; −0.92; **Figure 4A**) was found in total cholesterol, equivalent to 41.76 mg/dL; a reduction of −0.50 mmol/L (95% CI: 0.69; −0.31; **Figure 4B**) was found in triglycerides, corresponding to 44.28 mg/dL; and a reduction of −0.71 mmol/L (95% CI: 0.97; −0.45; **Figure 4C**) was found in LDL, what represents 27.45 mg/dL. In addition, an increase of 0.11 mmol/L in the HDL levels was verified (95% CI: 0.05; 0.17; **Figure 4D**), equivalent to 4.25 mg/dL.

As illustrated in **Figure 5**, in the studies carried out on humans, the levels (mg/dL) of total cholesterol (MD = −42.03, 95% CI: 73.53; −10.52), triglycerides (MD = −62.41, 95% CI: 110.09; −14.73), and LDL (MD = −37.76, 95% CI: 69.45; −6.06) were reduced after treating patients with *Citrus* extracts. In addition, it was observed that these patients had increased HDL levels (MD = 5.85, 95% CI: 0.41; 11.28). Although a high heterogeneity has been observed (I^2 > 75%), the synthase of the results obtained with individual studies favors treatment to the control of serum lipids. After the analysis of subgroups, high heterogeneity was still verified and the sensitivity analysis did not change the result of the general analysis (data not shown).

DISCUSSION

This systematic review compiled data from 25 studies on the effects of *Citrus*-based products in the control of dyslipidemia. Based on the countries where the studies were carried out, most of them were developed in countries of Asia (such as Korea and China) and the European Union, in addition to United States and Egypt, which are among the biggest *Citrus* product makers in the world (FAS, 2018). In fact, countries that have greater production

TABLE 3 | Detailed description of the clinical studies of the effect of *Citrus* extract on hyperlipidemia included in the systematic review.

References/ country	Extract, plant part and species	Composition	Sample	Pathology	Parameters evaluated	Treatment protocol
Gorinstein et al., 2007 (Gorinstein et al., 2007) Israel	Fresh fruit peels of red grapefruit or blond grapefruit processed	Anthocyanins Red: 51.5 mg/100 g Blond: 49.3 mg/100 g Flavonoids (naringin) Red: 21.61 mg/100 g Blond: 19.53 mg/100 g Total fibers Red: 1.39 g/100 g Blond: 1.37 g/100 g	57 patients (39–72 years)	Hypertriglyceridemia and coronary disease	HR, BP, BW CT, LDL, HDL, TG, serum antioxidant activity by ABTS and TEAC	Daily supplementation with red or blond grapefruits associated with anti-atherosclerosis diet for 30 days (n = 19/group)
Mollace et al., 2011 (Mollace et al., 2011) Italy	Polyphenolic fraction of *C. bergamia* peeled-off fruits	Neoeriocitrin (77,700 ppm) Naringin (63,011 ppm) Neohesperidin (72,056 ppm) and melitidine (15,606 ppm) Brutieridine (33,202 ppm)	237 patients	Hyperlipemia associated or not with hyperglycaemia	TC, LDL, HDL, TG, reactive vasodilation	500 or 1,000 mg/day encapsulated with 50 mg ascorbic acid, for 30 days (n = 104–32/group)
Toth et al., 2016 (Toth et al., 2015) Italy	Bergavit® (Bergamot juice derived extract, *C. bergamia*)	150 mg of flavonoids 16% of neoeriocitrin 47% neohesperidin 37% naringin	80 individuals (42 men and 38 women)	Moderate hypercholesterolemia	TC, LDL, HDL, TG, VLDL, IDL, IMT, LDL size	150 mg/day for 6 months (n = 80)
Cai et al., 2017 (Cai et al., 2017) China	*C. bergamia* extract (CitriCholess®)	25% bioflavonoids, sterols and orange oil (820 mg/day), vitamin C (50 mg/day), vitamin B6 (20 mg/daily), B12 (2,000 μg/day), and folic acid (800 μg/day)	98 older people	Dyslipidemia and arterial hypertension and problems of glucose intolerance	TG, TC, LDL, HDL, glucose, BW, WC, HC, WHR, and BMI	500 mg/day for 12 weeks (n = 48–50/group)

Legend: TC, total cholesterol; TG, triglycerides; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TEAC, Trolox-equivalent antioxidant capacity; HR, heart rate; BP, blood pressure; BW, body weight; IMT, carotid intima-media thickness; BW, body weight (kg); WC, waist circumference (cm); HC, hip circumference (cm); WHR, waist-to-hip ratio; BMI, body mass index.

of natural resources tend to explore their products more from a commercial and scientific point of view.

Through the scientific analyses compiled, we can also verify that species of the genus *Citrus* have the potential to reduce the serum levels of total cholesterol (TC), triglycerides (TGs), LDL, and VLDL and increase HDL. Consequently, *Citrus*-based products reduced the body weight, lipid accumulation, and atherosclerosis risk by the modulation of proteins and genes involved in the lipid metabolism. Recently, a study with a standardized extract containing *Citrus sinensis* L. Osbeck associated with *Citrus limon* (Chiechio et al., 2021) also demonstrated an effect in controlling the levels of total cholesterol and triglycerides as well as glycemia, possibly due to its composition rich in anthocyanins, flavonoids, and hydroxycinnamic acids, reinstating the high potential of *Citrus* species in lipid control.

These effects were studied mainly in the animal models of dyslipidemia induced by cholesterol- or high-fat diets. In these protocols, lipids ingested are initially degraded by intestinal lipase and, in enterocytes, TGs are resynthesized and associated with cholesterol and lipoproteins (ApoB-48, ApoE, and ApoC-II), forming chylomicrons. These distributed fatty acids between tissues and their remnants are metabolized in the liver. In this organ, fatty acid and glucose activate metabolic pathways for energy synthesis and storage, so that excess citrate is converted by citrate lyase (ACLY) into acetyl-CoA, which by the action of acetyl-CoA carboxylase (ACC) forms malonyl-CoA. This metabolic intermediate is used by the cell to produce fatty acid through the action of the enzymes Stearoyl-CoA Desaturase-1 (SCD1) and fatty acid synthase (FAS), in addition to downregulating CPT-1, an important transporter of Acil-Coa into the mitochondria which enables its β-oxidation. These fatty acids give rise to triglyceride molecules. In addition, acetyl-CoA can participate in the synthetic pathway of cholesterol, forming HMG-CoA which is converted into mevalonic acid by HMGR. This originates the free cholesterol molecule, which can be

TABLE 4 | Outcomes of the clinical studies included in this systematic review.

Reference	Experimental group (mg/dL)	Control group (mg/dL)	Summary of results
Gorinstein et al. (Gorinstein et al., 2007)	Baseline: Red TC: 258.70 LDL: 193.73 HDL: 52.59 TG: 149.68 Blond TC: 283.06 LDL: 217.32 HDL: 50.27 TG: 193.97	Baseline: TC: 306.26 LDL: 243.23 HDL: 46.20 TG: 205.49	Red: ↓ TC, LDL, and TG Blond: ↓ LDL only Both: ↑ serum antioxidant activity, without change in HR, BP, BW, HDL
Mollace et al. (Mollace et al., 2011)	Baseline (500 mg) TC: 286.00 LDL: 184.96 HDL: 34.55 TG: 266.87 Baseline (1,000 mg) TC: 279.40 LDL: 189.70 HDL: 32.78 TG: 270.11 After 30 days (500 mg) TC: 211.42 LDL: 132.79 HDL: 40.53 TG: 180.18 After 30 days (1,000 mg) TC: 201.99 LDL: 125.34 HDL: 46.00 TG: 157.48	Treated with capsules containing 500 mg of maltodextrin and 50 mg of ascorbic acid Baseline TC: 275.67 LDL: 186.31 HDL: 34.59 TG: 275.62 TC: 279.40 LDL: 185.64 HDL: 35.05 TG: 275.71	↓ TC, TG, and LDL ↑ HDL ↓ glucose ↑ reactive vasodilation
Toth et al. (Toth et al., 2015)	Baseline TC: 224.28 LDL: 143.07 HDL: 54.13 TG: 132.86	Baseline: TC: 255.22 LDL: 177.88 HDL: 50.27 TG: 159.43	↓ TC, LDL, TG, and IMT ↑ HDL, IDL, and LDL size without changing VLDL
Cai et al. (Cai et al., 2017)	Baseline TC: 211.13 LDL: 131.09 HDL: 49.88 TG: 192.20 500 mg TC: 198.76 LDL: 121.03 HDL: 50.27 TG: 162.09	Baseline TC: 217.32; LDL: 138.43; HDL: 51.81; TG: 170.94 TC: 210.36 LDL: 132.63 HDL: 52.20; TG: 172.71	↓ LDL ↓ BW, WC, WHR, and BMI without changing TG, TC, HDL, glucose, HC

Legend: TC, total cholesterol; TG, triglycerides; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TEAC, Trolox-equivalent antioxidant capacity; HR, heart rate; BP, blood pressure; BW, body weight; IMT, carotid intima-media thickness; BW, body weight (kg); WC, waist circumference (cm); HC, hip circumference (cm); WHR, waist-to-hip ratio; BMI, body mass index.

esterified by acyl-CoA:cholesterol acyltransferase (ACAT) or converted into bile acids by CYP7A1. TG, free cholesterol, and cholesterol ester conjugate with lipoproteins (ApoE, ApoC-II, and ApoB-100) constituting the VLDL molecule (TGs > cholesterol). This lipoprotein distributes fatty acids to tissues by the action of lipoprotein lipase (LPL) and becomes IDL (TGs ≈ cholesterol, ApoB-100, ApoE) and later LDL (TGs, < cholesterol, ApoB-100). That way, high-lipid diets increase the plasmatic concentrations of TG, TC, VLDL, IDL, and LDL (DiNicolantonio and O'Keefe, 2018; Andreadou et al., 2020). These mechanisms can be observed in **Figure 6** (black lines).

Through this review, it was found that the effect of *Citrus*-based products on the release of adipocytokines and their signaling pathways has been studied. These molecules are produced by adipose tissue and control several metabolic pathways, in addition to affecting the state of hunger and

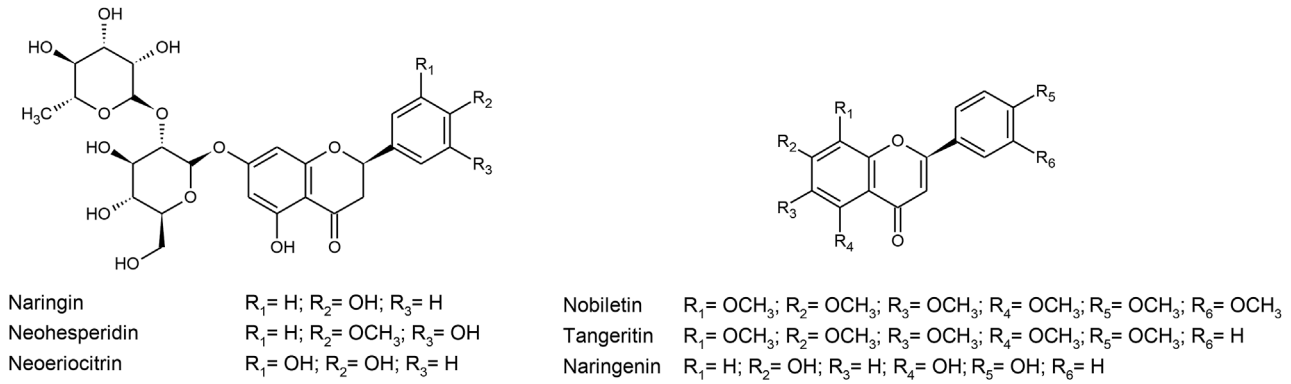

FIGURE 2 | Chemical structure of the main flavonoids found in *Citrus*.

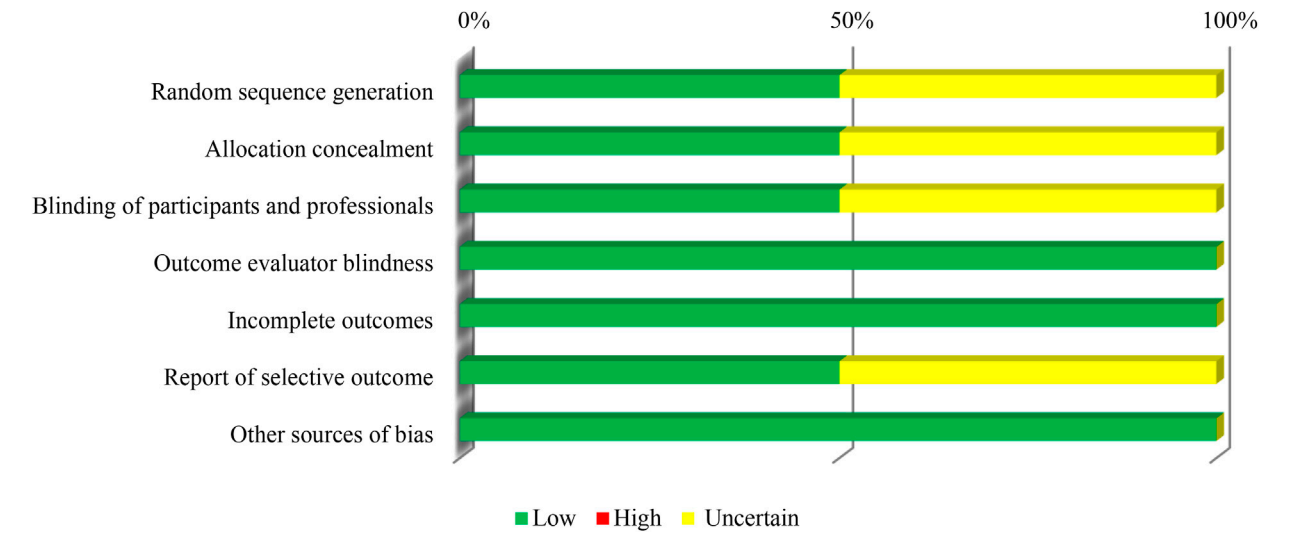

FIGURE 3 | Methodological quality of clinical trials included.

satiety and being related to the development of coronary diseases and metabolic disorders (Cao, 2014). *Citrus* products reduce adiponectin (Kang et al., 2012), whose action on specific receptors (AdipoR) increases the phosphorylation of LKB1 and AMPK (Kang et al., 2012; Shin et al., 2016). It negatively modulates ACC (Kang et al., 2012; Shin et al., 2016), reducing malonyl-Coa levels and, consequently, increasing CPT-1 (Shin et al., 2016); in addition, it decreases the HMGR activity (Bok et al., 1999; Shin et al., 2016) and modulates genes like LXR (Ding et al., 2012; Lu et al., 2013) and PPAR (Kim et al., 2013; Shin et al., 2016; Lu et al., 2018). Through these genes, *Citrus* regulates several protein targets involved in lipogenesis (FAS, aP2, ACC) (Ding et al., 2012; Lu et al., 2013; Shin et al., 2016), lipoprotein formation and metabolism (ApoE, LPL) (Ding et al., 2012; Lu et al., 2013), cholesterol metabolism (CYP7A1) (Ding et al., 2012), and cholesterol and lipid efflux (ABCG1 and ABCA1) (Ding et al., 2012; Lu et al., 2013). At the same time, its ability to stimulate the PKA-HSL pathway has also been observed (Kang et al., 2012), increasing the degradation of TG in glycerol and fatty acid, in addition to reducing the activity of ACAT (Bok et al., 1999), which contributes to the reduction of cholesterol ester levels. It is worth mentioning that bio-products based on *Citrus* help in glycemic control (Mollace et al., 2011; Ding et al., 2012; Kim et al., 2013; Lu et al., 2013; Raasmaja et al., 2013; Muhtadi et al., 2015; Dinesh and Hegde, 2016; Ashraf et al., 2017; Fayek et al., 2017), possibly by reducing resistin (Kim et al., 2013), an adipocytokine whose increase has been associated with insulin resistance, atherosclerosis, oxidative stress, and inflammation. All of these molecular events result in decreased lipogenesis and increased lipid oxidation, contributing to the control of the lipid profile (**Figure 6**).

However, some results seem contradictory, such as the effect of *Citrus* in reduction of the mRNA levels of PPARγ target genes, including ACO and UCP2 in the liver tissue (Ding et al., 2012).

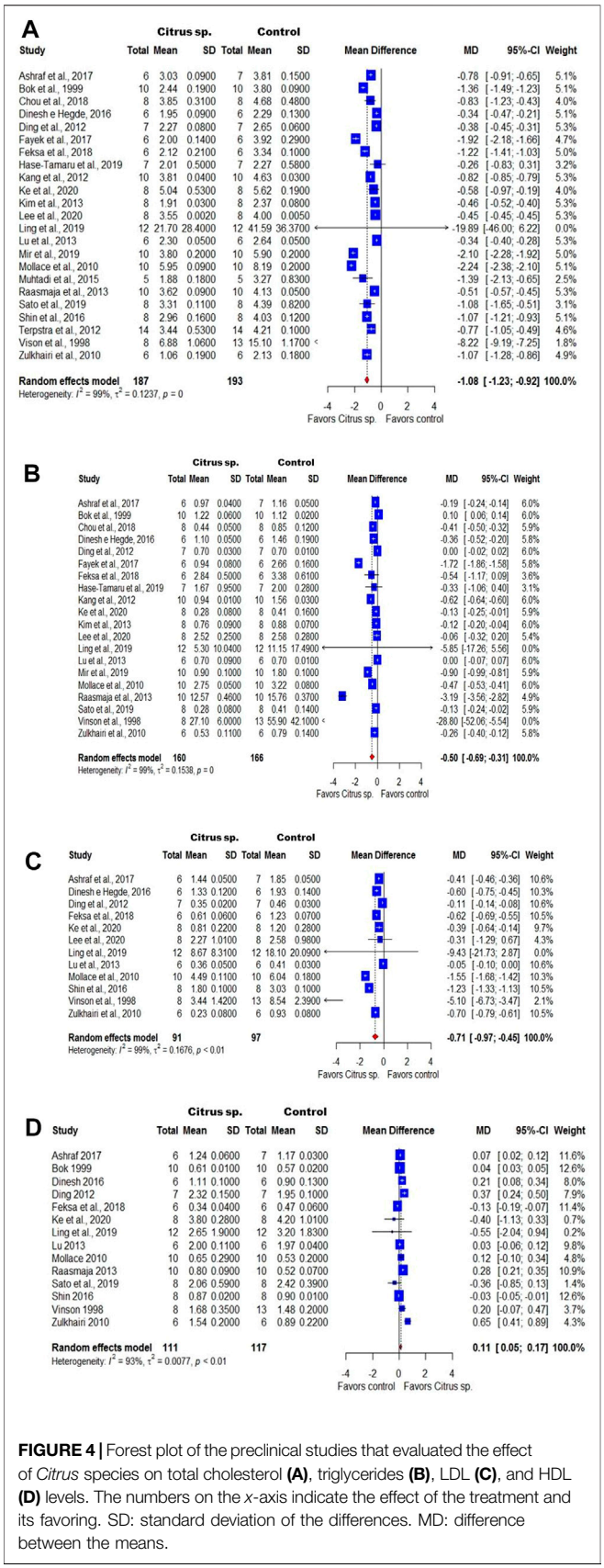

FIGURE 4 | Forest plot of the preclinical studies that evaluated the effect of *Citrus* species on total cholesterol **(A)**, triglycerides **(B)**, LDL **(C)**, and HDL **(D)** levels. The numbers on the *x*-axis indicate the effect of the treatment and its favoring. SD: standard deviation of the differences. MD: difference between the means.

ACO is the first enzyme of peroxisomal β-oxidation which will reduce the accumulation of lipids in the liver and promote its excretion (Ferdinandusse et al., 2007). On the other hand, UCP2 is an uncoupling protein which acts as a carrier of protons present in the inner membrane of mitochondria and contributes to thermogenesis, being a positive factor for the prevention of obesity (Brand and Esteves, 2005). Thus, upregulation of these mRNAs would contribute to the observed outcomes. However, the absence of baseline conditions for these targets makes it difficult to understand these data, so further studies are needed to elucidate this mechanism.

Similarly, *Citrus* seems to increase CD36 (Ding et al., 2012), the fatty acid translocase protein that facilitates the transport of fatty acids, the hepatic uptake of fatty acids, and the accumulation of fat and has a high affinity for binding with the oxidized LDL molecule, increasing the inflammatory activity and being a main condition for the development of atherosclerosis and thrombosis (Pepino et al., 2014). However, the correlation with the observed outcomes also needs to be further investigated, since the experimental conditions of the study do not allow a thorough analysis of this target in the experimental model used, as well as in the primary outcome studied.

It is also worth noting that some studies have shown that *Citrus* can help control hunger promoting the modulation of ghrelin. Known as "Hunger Hormone," this peptide is produced by endocrine cells present in the stomach and acts in the control of hunger, adiposity, and glucose- and energy-homeostasis, among other functions (Pradhan et al., 2013). More over, *Citrus* also downregulates leptin and GLP-1 levels, which are involved with satiety control. Leptin, a hormone produced by adipose tissue, plays an important role in the control of energy homeostasis, the excess and resistance of which are associated with obesity, leading to failures in the signaling mechanisms associated with decreased nutrition and body weight control (Pan and Myers, 2018). On the other hand, glucagon-like peptide 1 (GLP-1) is a gut hormone that promotes satiety; potentiates insulin release and suppression of glucagon release in response to nutrient intake; and decreases postprandial plasma levels of glucose (Andersen et al., 2018). Thus, the effects observed for *Citrus* in the reduction of GLP-1 may be related to overnight fasting or long-term regulation of eating and energy metabolism, requiring further investigation.

The notations are as follows: ABCA1: ATP-binding cassette transporter A1; ABCG1: ATP-binding cassette transporter G1; ACAT: acyl-CoA:cholesterol acyltransferase; ACC: acetyl-CoA carboxylase; ACLY: citrate lyase; ACO: acyl-CoA oxidase; AdipoR: adiponectin receptor; AMPK: AMP-activated protein kinase; aP2: adipocyte fatty-acid-binding protein; ApoB-100: apolipoprotein B-100; ApoC-II: apolipoprotein C2; ApoE: apolipoprotein E; CD36: cluster of differentiation 36; CPT-1: carnitine palmitoyl transferase-1; CYP7A1: cholesterol 7α-hydroxylase; FAS: fatty acid synthase; GLUT 4: glucose transporter 4; HMGR: 3-hydroxy-3-methylglutaryl-coenzyme A reductase; HSL:

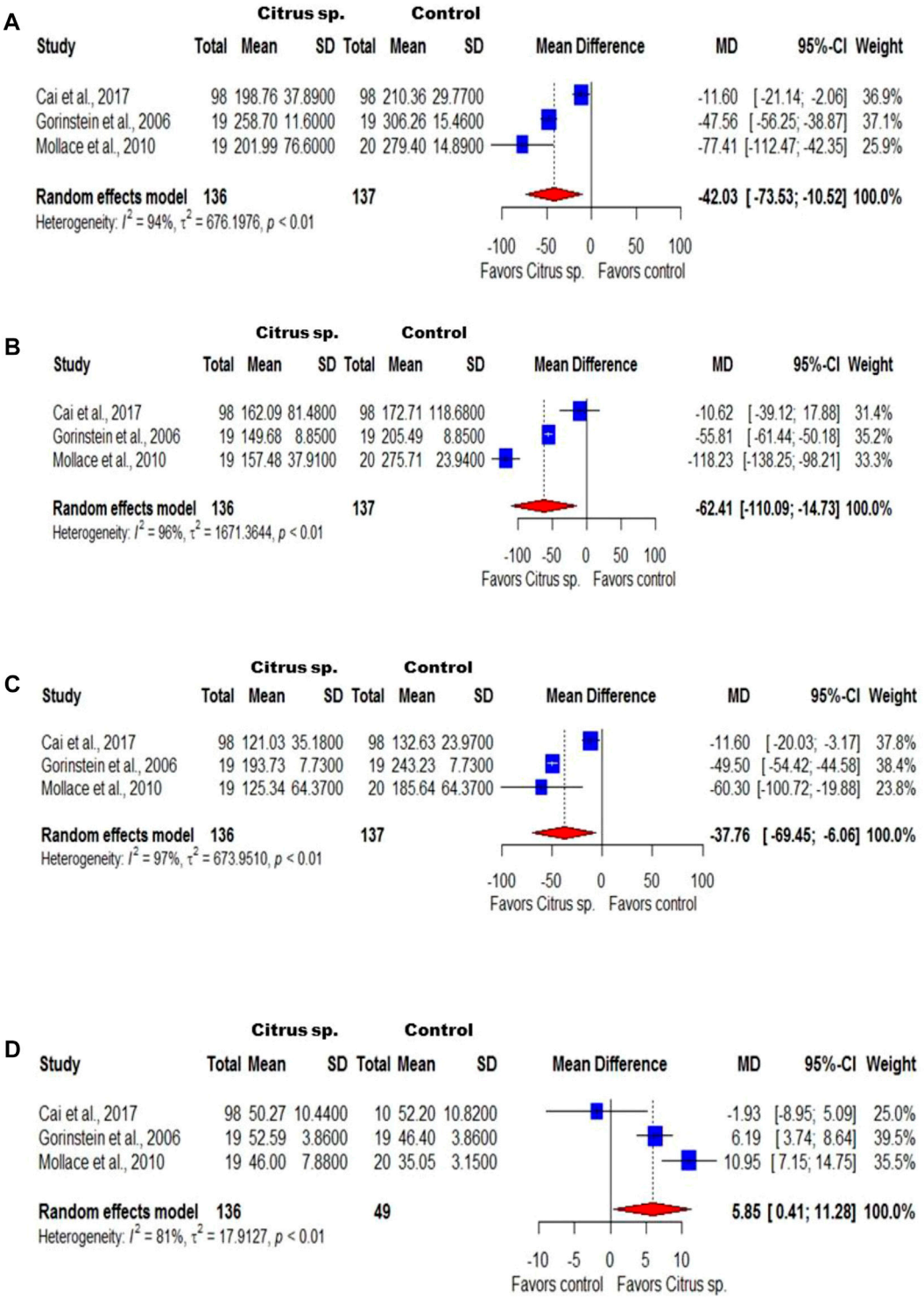

FIGURE 5 | Forest plot of the clinical studies that evaluated the effect of *Citrus* species on total cholesterol **(A)**, triglyceride **(B)**, LDL **(C)**, and HDL **(D)** levels. The numbers on the *x*-axis indicate the effect of the treatment and its favoring. SD: standard deviation of the differences. MD: difference between the means.

hormone-sensitive lipase; IDL: intermediate low-density lipoprotein; LDL: low-density lipoprotein; LKB1: liver kinase B1; LPL: lipoprotein lipase; LXR: liver X receptor; p-ACC: phosphorylated acetyl-CoA carboxylase; PKA: cAMP-dependent protein kinase; PPAR: peroxisome proliferator-activated receptor; SCD1: Stearoyl-CoA

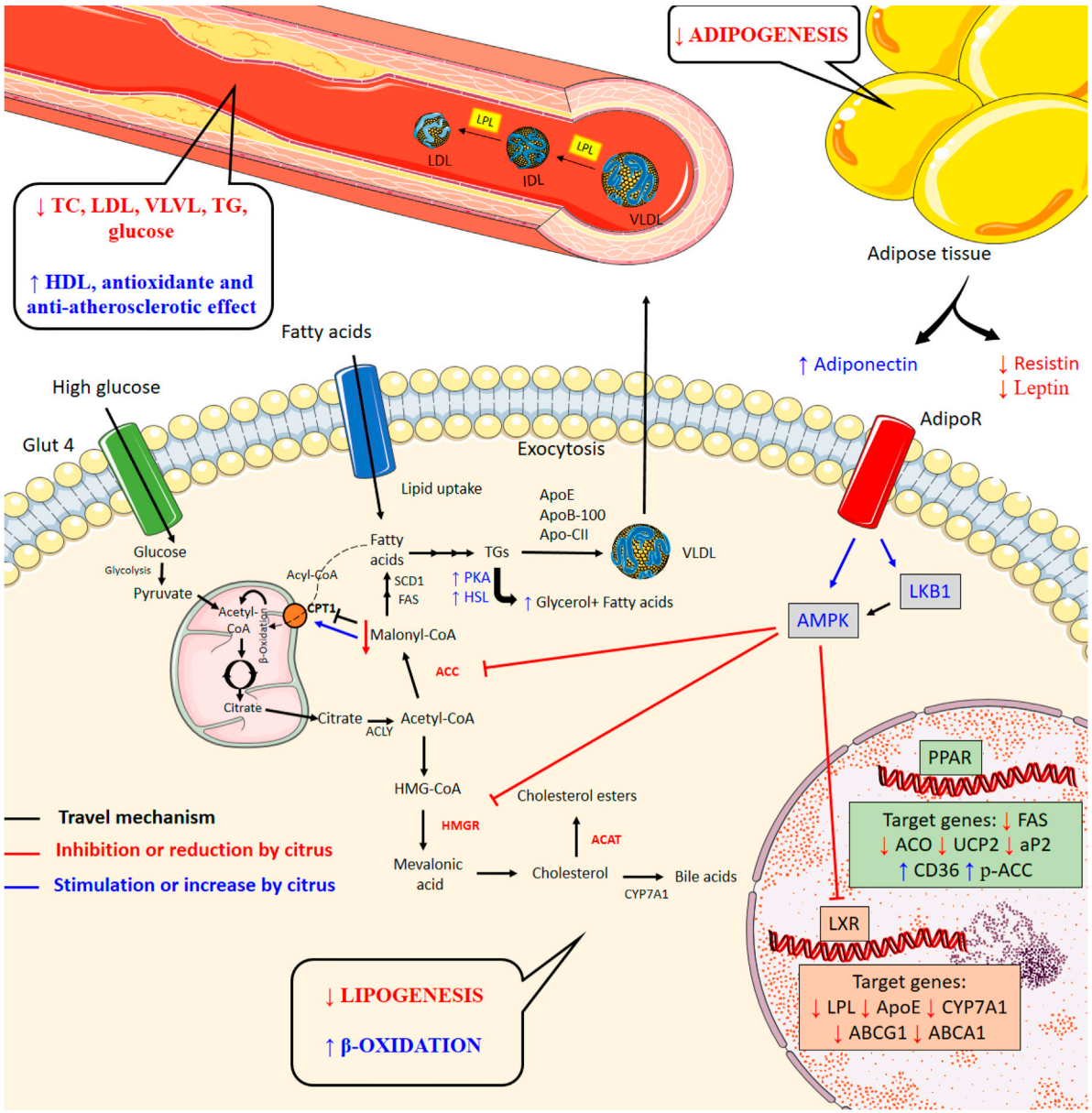

FIGURE 6 | Biochemical and tissue changes caused by diets high in fat and calories (black lines) and mechanisms of action of *Citrus* products upon metabolic disorders associated with hyperlipidemia (blue lines indicate activation and red lines indicate inhibition).

Desaturase-1; TC: total cholesterol; TGs: triglycerides; UCP2: uncoupling protein 2; VLDL: very low-density lipoprotein.

The effects of *Citrus* bioproducts on the lipid profile may be related to the presence of bioactive compounds, with emphasis on the flavonoids, such as naringin, hesperidin, neohesperidin, neoeriocitrin, nobiletin, tangeretin, and naringenin as compiled in this review. In fact, these compounds are believed to play a very significant role in reducing the levels of total cholesterol, triglycerides, and LDL (Mulvihill and Huff, 2012; Assini et al., 2013; Kou et al., 2017; Zeka et al., 2017). Several studies have shown that naringin reduces the HMGR activity more potently than does vitamin E (Choi et al., 2001; Lee et al., 2001), as well as decreasing the action of ACAT (Kim et al., 2006), which contributed to hypocholesterolemic action and higher excretion of fecal sterols (Jeon et al., 2004). Similarly, hesperidin reduces plasma cholesterol in hypercholesterolemic rats by decreasing ACAT and HMGR (Lee et al., 1999; Lee et al., 2012) besides changing the expressions of genes encoding PPARs and the LDL receptor (Akiyama et al., 2009). A recent study demonstrated that neohesperidin is also able to regulate the lipid metabolism *in vivo* and *in vitro via* FGF21 and AMPK/SIRT1/PGC-1α signaling axis (Wu et al., 2017). Furthermore, the non-glycoside *Citrus* flavonoid, naringenin, stimulates the hepatic fatty acid oxidation *via* PPARγ and prevents lipogenesis in both the liver and the muscle, reducing the serum lipid levels (Mulvihill et al., 2009).

In this review, we also observed that the *Citrus* products act by reducing the atherogenic index or tissue manifestations associated with atherosclerosis (Vinson et al., 1998; Bok et al., 1999; Zulkhairi et al., 2010). In fact, the polyphenolic compounds and flavonoids found in the *Citrus* species have antioxidant (Vinson et al., 1998; Gorinstein et al., 2007; Zulkhairi et al., 2010; Craft et al., 2012) and anti-inflammatory properties, in addition to their ability to decrease LDL levels, inhibiting the formation of atherosclerotic plaques (Tripoli et al., 2007; Assini et al., 2013; Onakpoya et al., 2017). Naringin, for example, reduces plaque progression once it decreases non-high-density lipoprotein cholesterol concentrations and biomarkers of endothelial dysfunction and inhibits the expression of ICAM-1 in endothelial cells, preventing immune cell adhesion and infiltration in the vascular wall (Choe et al., 2001; Chanet et al., 2012).

Confirming the results of the systematic review, the meta-analysis of preclinical studies indicated that *Citrus* products reduce the total cholesterol, triglycerides, and LDL levels by −41.76, −44.28, and −27.45 mg/dL, respectively, while increasing the HDL levels by 4.25 mg/dL. Similar results were observed in the clinical studies, in which the *Citrus* species induce a reduction in the total cholesterol, triglycerides, and LDL levels by −42.03, −62.41, and −37.76 mg/dL, respectively, whereas the HDL levels increased by an average of 5.85 mg/dL.

In the meta-analysis published by Onakpoyaa et al. (2015) (Onakpoya et al., 2017), performed with two clinical trials about the effect of grapefruits on the lipid profile, significant effects were observed only for the increase in HDL, without TC and LDL changes. More recently, a meta-analysis published by Kou et al. (2017) showed that the sizes of effect measures for LDL and total cholesterol presented significant results in the group of patients treated with *Citrus* juice, without considerable changes in HDL and TG levels. The divergence between the results presented in our meta-analysis compared to those previously published is justified by the broader scope of our question, as well as the inclusion of more recent studies, which have confirmed the contribution of *Citrus*-based products in the control of blood lipids.

Through the analysis of the risk of bias, it can be observed that the preclinical studies have a satisfactory average score, with some limitations in the methodological description of the studies and the results. Similarly, clinical studies had limitations in reporting or methodology in terms of blinding, allocation, randomization, and reporting of results. The use of tools to assess the risk of bias in the studies included in the systematic reviews has been widely well supported by groups such as SYRCLE (Hooijmans et al., 2014), ARRIVE (Kilkenny et al., 2010), and Cochrane (Cochrane Training, 2019), since the credibility of the results and the strength of the evidence depend on the methodological criteria of the studies (Busch et al., 2020).

Thus, although the results obtained are favorable to the treatment with *Citrus* extracts, the methodological limitations and high heterogeneity of the studies included in the meta-analysis weaken the evidence about the real benefits of this intervention. In addition, the studies do not provide information on effective dose, bioavailability, efficacy, and safety. These parameters are required to propel the use of these promising therapeutic agents into the clinical area. For this reason, further studies are needed to strengthen the evidence of the effects of *Citrus* on dyslipidemia.

This systematic review presents as limitations the low evidence found due to the high variability of the studies and variation of the methodological protocols of the articles. Among them, we can mention the differences in the induction of dyslipidemia, routes of administration, and types of extracts, besides the absence of baseline serum levels of lipids for comparison after the induction and inconclusive report. Finally, as in our review, of the 25 studies included in the meta-analysis, only 3 presented results in humans; we chose not to use the GRADE system. For this reason, we believe that further clinical studies are needed to provide sufficient scientific support to measure the effectiveness of *Citrus* effects on dyslipidemia.

CONCLUSION

From the compilations of the studies, one can suggest that the *Citrus* extract has a potential effect in dyslipidemia control, both in the preclinical studies and clinical trials. These effects can be associated with the presence of bioactive compounds, as flavonoids, which act synergistically through several pathways, causing inhibition of lipogenesis and activating β-oxidation. However, due to the high heterogeneity of the reposted findings, further studies are needed to increase the strength of clinical evidence of the action of *Citrus* extracts on the control of dyslipidemia and increase the strength of that evidence.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**; further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

Ideation and preparation of the review: BC and AG; search and selection of studies: BC and LN; third evaluation for discrepancy analysis: AG; qualitative data extraction: BC, LN, and JN; quantitative data extraction: BC and VG; meta-analysis: BC, VG, and PZ; writing and finalizing the review: BC, DT, and AG.

FUNDING

The authors acknowledge grants from the Foundation for Support of Research and Technological Innovation of the State of Sergipe (*Fundação de Apoio à Pesquisa e Inovação Tecnológica do Estado de Sergipe: FAPITEC/SE*, EDITAL CAPES/FAPITEC/SE N° 10/2016 – PROMOB 1995/2017), National Council for Scientific and Technological Development (*Conselho Nacional de Desenvolvimento Científico e Tecnológico: CNPq*/Brazil), Coordination for the Improvement of Personnel Higher Education (*Coordenação de Aperfeiçoamento de Pessoal de Nível Superior: CAPES*/Brazil), and Federal University of Sergipe.

ACKNOWLEDGMENTS

We are grateful for the support given by Patrícia K. Ziegelmann in the elaboration of the meta-analysis and to teacher Abilio Borghi for the assistance with English language review.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.822678/full#supplementary-material

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