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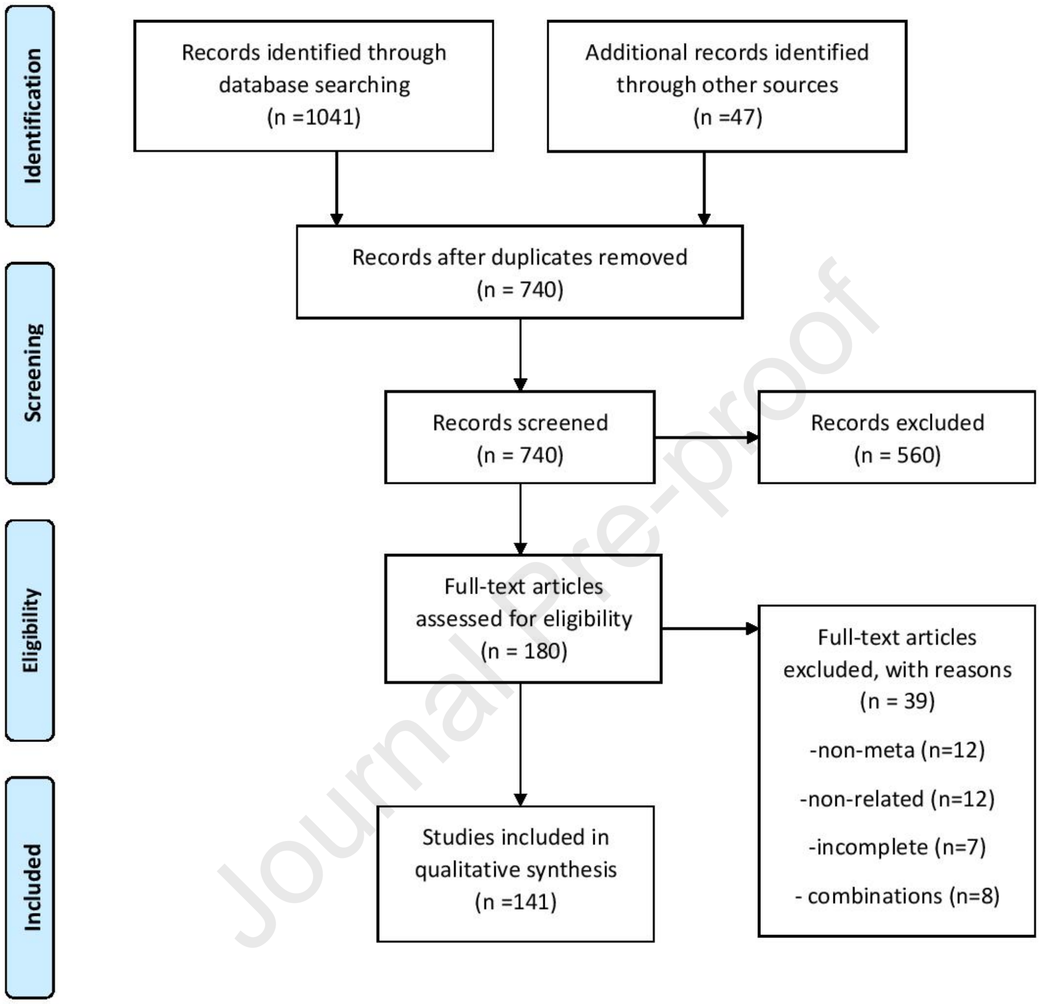

Figure 1. Flow diagram of study processes

Targeting dyslipidemia by herbal medicines: a systematic review of meta-analyses

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Abstract:

Ethnopharmacological relevance:

The worldwide increasing prevalence of dyslipidemia has become a global health concern. Various herbal remedies have been claimed to be effective for the treatment of dyslipidemia in traditional and folkloric medicine of different regions clinical trials have been conducted to investigate their efficacy. The aim of the current systematic review is to critically assess the meta-analyses of controlled trials (CT) evaluated herb medicines for dyslipidemia.

Materials and Methods:

Relevant studies from Web of Science, PubMed, Scopus, and Cochrane Library databases based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist until January 2021 have been searched. All meta-analyses which pooled studies on the effect of herbal medicines on lipid profile including total cholesterol (TC), triglyceride (TG), and low- or high- density lipoprotein cholesterol (LDL-C, HDL-C) were also included. Meta-analyses of *in vitro*, animal or observational studies were excluded.

Results:

The overall of 141 meta-analyses were revealed. Vegetable oils, phytosterols, tea, soy protein, nuts, and curcumin have been studied frequently among the herbal medicines. Among 13 meta-analyses on vegetable oils, the greater reduce of TC (18.95 mg/dl), LDL-C (16.24 mg/dl) and TG (13.69 mg/dl) were exhibited from sunflower oil. Furthermore, rice bran oil (6.65 mg/dl) increased HDL-C significantly. Phytosterols in 12 meta-analyses demonstrated significant improvements in reducing TC, LDL-C and TG as 16.4, 23.7, and 8.85 mg/dl, respectively, and rise in HDL-C as 10.6 mg/dl. The highest reduction in serum level of TC, LDL-C and TG was reported while intake *Green* tea; 27.57, 24.75, and 31.87 mg/dl, accordingly within 9 meta-analyses. Average improvement of lipid profiles by 6 meta-analyses on plant proteins were 23.2, 21.7, 15.06, and 1.55 mg/dl for TC, LDL-C, TG, and HDL-C, respectively. Among 11 meta-analyses on nuts, almond showed better and significant alleviations in TC (10.69 mg/dl), walnut in LDL-C (9.23 mg/dl), pistachio in TG (22.14mg/dl), and peanut in HDL-C (2.72 mg/dl). Overall, *Curcumin, Curcuminoid*, and *Turmeric* have resulted in the reduction of TC (25.13 mg/dl), LDL-C (39.83 mg/dl), TG (33.65 mg/dl), and an increase in the HDL-C (4.31 mg/dl).

Conclusion:

The current systematic review shed light on the use of herbal medicines for the management of dyslipidemia. However, more well-conducted CTs are required to determine effective doses of herbal medicines.

Keywords: *Herbal Medicine, Plant, Phytochemical, Lipid profile, Triglyceride, Cholesterol*

1. Introduction

Dyslipidemia (DLP) is defined as an elevation in the level of total cholesterol (TC), triglyceride (TG), or low-density lipoprotein cholesterol (LDL-C) and decreased level of high-density lipoprotein cholesterol (HDL-C) (Heshmat-Ghahdarijani et al., 2020). Simultaneous increment of health problems led into the attraction of global attention. Atherosclerosis, cardiovascular complications, pancreas disorders, and fatty liver are avowed as the concurrent disease with DLP (Zhang et al., 2020). Likewise, DLP is associated with metabolic syndrome (Mets) and its components such as obesity and diabetes (Tabatabaei-Malazy et al., 2015). Cardiovascular disease (CVD) accounts for about 30% of the overall deaths in 2010 and an estimated annual deaths of 25 million by 2030; moreover, altered lipid profile plays a significant role in progression or regression of CVD (Khorshidi et al., 2020). As stated in previous studies, more than 60% patients with early coronary artery disease (CAD) symptoms struggle with DLP and 10% decline in TC reduces 15% of CAD, the importance of lipid profile supervise becomes prominent (Ding et al., 2020).

Diverse approaches are recommended to manage DLP; such as lifestyle modifications, diet intervention, and pharmacotherapy options (Shekarchizadeh-Esfahani et al., 2020). The more efforts do for the management of DLP, the less beneficial results the patients receive (Zhang et al., 2020). Despite the worldwide use of lipid-lowering agents, their long-term efficacy is still questionable (Shekarchizadeh-Esfahani et al., 2020). Lipid-lowering medications are associated with various adverse effects such as myopathy, impaired liver function, neuropathy and declined mental status (Tóth et al., 2020); also increased risk of diabetes has been reported to be associated with the use of lipid-lowering medications (Yuan et al., 2019). Therefore, considering alternative therapies with lower adverse effects and cheaper choices is reasonable.

Herbal remedies used in traditional and folkloric medicine of different regions provide a worthwhile source for discovering and introducing new drugs (Bahramsoltani and Rahimi, 2020; Bahramsoltani et al., 2019; Ebrahimi et al., 2019). Recently, tremendous increase of the patients and physicians desire to manage lipid profile with natural extracts has been noticed (Sahebkar et al., 2016b; Tabatabaei-Malazy et al., 2016). A vast number of studies performed on the efficacy and safety of natural products, showed auspicious changes in the lipid profile and thus, reduction of the risk of CVD (Sahebkar et al., 2016b). Contrarily, a number of studies showed fewer positive effects on this matter or reported adverse effects of herbs, as containing active biologic components (Posadzki et al., 2013).

The aim of the present systematic review is to critically assess the meta-analysis studies conducted on the efficacy of herbal medicines trials in dyslipidemia.

2. Methods

2.1. Data sources

Based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Liberati et al., 2009) and Supplementary 1, we comprehensively searched Web of Science, PubMed, Scopus, and Cochrane Library databases. Data until January 2021 from English language literature, systematic review and meta-analysis studies, were conducted to assess the effect of herbal medicines on lipid profiles. The search terms were “Herbal Medicine”, “Plant”, “Phytotherapy”, "Medicine, Traditional", “Dyslipidemia”, “lipid”, “Hyperlipidemia”, “metabolic syndrome”, and “Cardiovascular”. Search strategy is presented as appendix, Table S1. After evaluation of the title and abstract of all recorded studies, and deletion of unrelated or duplicated publications, reference lists of remained studies were manually searched in order to not missing related studies.

2.2. Eligibility criteria and study selection

The inclusion criteria for current study were;

1. Meta-analyses of controlled trials (CTs) conducted to assess the effect of herbal medicines on lipid profiles; TC, LDL-C, HDL-C, and TG in human without limitation in age, sex, or health status.
2. Publications with English language full text .

The exclusion criteria were:

1. Meta-analyses of CTs conducted to assess the effect of combinations of herbal medicines together or conventional treatments on lipid profiles.
2. Meta-analyses of in vitro, animal or observational studies.

2.3. Data extraction and Quality assessment

The following data were extracted from various studies: authors' names, publication year, number and type of included studies in meta-analysis, participants’ characteristics (total sample size, age, sex, and underlying disorder), type, dose, and duration of intervention, significant main outcomes, and recommended effective dose. Plant names have been checked with www.theplantlist.org.

Assessment of Multiple Systematic Reviews (AMSTAR) tool was used to evaluate the quality of methodology of included studies (Supplementary file) (Shea et al., 2007) The AMSTAR scores were categorized as high quality (score of 8-11), medium quality (score of 4-7), and low quality (score of ≤3), Table S2.

All of above process were independently assessed by two authors and any discrepancy was resolved through discussion with third author.

3. Results

The overall of 141 studies met the inclusion criteria and were included in the study. Details of search study process are presented in Figure 1. Then, based on studied herbal medicines, they have been categorized into the 7 following distinct groups: (1) polyphenolic compounds, (2) nuts, (3) phytosterols, (4) vegetable oils, (5) plant proteins, (6) tea and coffee, and (7) other herbal medicines.

The characteristics of the selected studies are shown in Tables 1 to 7. Due to the diversity of herbs investigated by Payab et al., this meta-analysis was divided into two records in the survey table (Payab et al., 2020). In summary, 142 records from 141 systematic reviews with meta-analysis were included comprising effect of herbal medicines on lipid profiles of a population ranged from 6 to 10983 subjects, both genders, and aged 14-89 years old. Some underlying health status of participants was healthy, MetS, type 2 diabetes mellitus (T2DM), dyslipidemia, obesity, and hypertension (HTN). From 3 to 124 trials were investigated among included studies. The majority of included studies (98%) met the quality requirements (AMSTAR score≥8).

3.1. Polyphenolic compounds

Thirty meta-analyses were evaluated the effects of various polyphenolic compounds including curcumin in 7 meta-analyses (Jalali et al., 2020b; Azhdari et al., 2019; Simental-Mendía et al., 2019; Yuan et al., 2019; Wei et al., 2019; Qin et al., 2017; Sahebkar et al., 2014), cocoa products (in 5 studies: Lin etal., 2016; Hoope et al., 2012; Shrime et al., 2011; Tokede et al., 2011; Jia et al. 2010), isoflavones (in 7 studies: Kanadys et al., 2020; Soltanipour et al., 2019; Luis et al., 2018; Simental-Mendia et al., 2018; Taku et al., 2007; Reynolds et al., 2006; Zhan et al., 2005), flavonoids (in 3 studies: Tabrizi et al., 2020; Sahebkar 2017; Hooper et al., 2008) resveratrol (in 5 studies: Asgary et al., 2019; Elgebaly et al., 2017; Zhang et al., 2016a; Sahebkar et al., 2015; Sahebkar, 2013), hesperidin or anthocyanins or grape polyphenols each in one study (Mohammadi et al., 2019b; Daneshzad et al., 2019; Ghaedi et al., 2019). The sample size of these studies ranged from 156 to 6557, and aged 18 - 85 years old. Dose ranges were 6.3-2110 mg/d for cocoa, 45-6000 mg/d for curcumin, 500-1500 mg/d for flavonoids, 292-800 mg/d for hesperidine, 33.8-160 mg/d for isoflavones, 30-3000 mg/d for quercetin, 31.45-1050 mg/d for anthocyanins, and 8-3000 mg/d for resveratrol. The minimum (min) duration of intervention was 2 hours for quercetin (Tabrizi et al., 2020) and the maximum (max) was 96 weeks for anthocyanins (Daneshzad et al. 2019). Except hesperidin, other flavonoids reported positive effects for the improvement of dyslipidemia; also significant improvements of TC were reported to range from 3.9 to 37.9 mg/dl, as the result flavonoids use, in particular soy protein (Taku et al., 2007; Tabrizi et al., 2020). The improvement range of LDL-C was from 2.71 to 39.83 mg/dl in use of cocoa and curcumin, respectively (Hooper et al., 2012; jalali et al., 2020b); however, a meta-analysis on resveratrol showed significant elevation by 18.17 mg/dl (Zhang et al., 2016a). Improvements of HDL-C as the result of soy protein isoflavone and anthocyanins consumption was also reported from 0.77 to 7.40 mg/dl (Reynolds et al., 2006; Daneshzad et al., 2019), and these figures for TG were from 6.26 to 33.65 mg/dl when taken soy protein isoflavone and curcumin (Reynolds et al., 2006; Azhdari et al., 2019). The defined effective doses of the mentioned herbal medicines were reported to be more than 600 mg/d of cocoa for better and significant reduce of TG, however, the required dose of cocoa for alleviation of TC, LDL-C, and HDL-C was reported to be less than 260 mg/d. Effective dose of curcumin for improvement of TC, LDL-C, and HDL-C was ranged from 330 to 1795 mg/d, whilst it was from 1000 to 1795 mg/d for TG. Isoflavones in dose of 40 mg/d and quercetin in dose of ≥500 mg/d demonstrated the greater improvement than their lower doses. Reported effective dose of anthocyanins was >300 mg/d for reducing LDL-C and increasing HDL-C when used more than 12 weeks (Daneshzad et al., 2019). Details have been demonstrated in Table 1.

3.2. Nuts

This group contains Brazil nut, cashew, peanut, almond, pistachio, walnut, hazelnut, macadamia, pecan, and other nuts on dyslipidemia via 11 meta-analyses (Hou et al., 2020; Jalali et al., 2020a; Jafari Azad et al., 2020; Liu et al., 2020; Lee-Bravatti et al., 2019; Guasch-

Ferré et al., 2018; Musa-veloso et al., 2016; Del Gobbo et al., 2015; Blanco Mejia et al., 2014; Banel et al., 2009; Phung et al., 2009). Beside healthy subjects, some suffered from DM, HTN, obesity, and MetS. Sample sizes ranged from 142 to 2582, aged 15 to 86 years old of both genders. All of the studies had high quality. Overall dose range was from 5 (for Brazil nut) to 168 g/d (for almond) (Hou et al., 2002; Phung et al., 2009). Intervention duration ranged from 2 weeks for almond to 108 weeks for walnut (Musa-veloso et al., 2016; Banel et al., 2009). In control of dyslipidemia components, except cashew and peanut (Jalali et al., 2020a; Jafari Azad et al., 2020) other nuts significantly reduced TC from 5.02 to 24.7 mg/dl (Liu et al., 2020; Del Gobbo et al., 2015). Reduction in LDL-C by nuts was ranged between 3.48 and 24.8 mg/dl (Liu et al., 2019; Del Gobbo et al., 2015). Peanut increased HDL-C by 2.72 mg/dl (Jafari Azad et al., 2020) just in use of more than 12 weeks, almond decreased HDL-C by 1.26 mg/dl (Lee-Bravatti et al., 2019) and other nuts didn't have significant effect on HDL-C. The positive effects of Brazil nut, pistachio, walnut, almond and most of the tree nuts on improvement of TG was from 4.69 to 22.2 mg/dl (Hou et al., 2020; Liu et al., 2020; Del Gobbo et al., 2015; Blanco Mejia et al., 2014; Guasch-Ferre et al., 2018); on the contrary, cashew and peanut didn't change it significantly (Jalali et al., 2020a; Jafari Azad et al., 2020). Details are shown in Table 2.

3.3. Phytosterols

This group included 12 meta-analyses that pooled the effects of phytosterols and stanols on lipid profiles (Soto-Mendez et al., 2019; Rocha et al., 2016; Ras et al., 2014; Amir Shaghaghi et al., 2013; Demonty et al., 2013; Musa-veloso et al., 2011; Talati et al., 2010; Demonty et al., 2009; Wu et al., 2009; AbuMweis et al., 2008; Seppo et al., 2007; Chen et al., 2005). Number of subjects ranged from 199 to 9635, aged 12.6 to 71 years old, among both genders and suffering from MetS, obesity, PCOS, DM, and hypercholesterolemia. Consumption doses ranged from 0.3 to 9 g/d (Ras et al., 2014; Musa-veloso et al., 2011; Demonty et al., 2009; AbuMweis et al., 2008; Chen et al., 2005) with 3 to 85 weeks of the intervention's duration, the significant reduction in TC was reported to be from 7.7 to 16.4 mg/dl (Chen et al., 2005; Rocha et al., 2016). However, 10 studies showed significant changes in LDL-C from 10.44 to 23.7 mg/dl (Musa-veloso et al., 2011; Chen et al., 2005), another study also showed significant change in HDL-C by 10.6 mg/dl (Chen et al., 2005), and 3 studies showed significant change in TG from 7.9 to 8.85 mg/dl (Rocha et al., 2016; Wu et al., 2009). Four studies reported effective dose for reduction of LDL-C ranged from 0.6 to 2.15 g/d (Soto-Mendez et al., 2019; Ras et al., 2014; Musa-veloso et al., 2011; Demonty et al., 2009) and 1 meta-analysis reported 2 g/d of phytosterols/stanols as the effective dose to improve TC, LDL-C and TG (Wu et al., 2009). Details are shown in Table 3.

3.4. Vegetable oils

Thirteen meta-analyses were included in this group that assessed the effect of vegetable oils on dyslipidemia consisting canola oil, primrose oil, coconut oil, olive oil, palm olein, argan oil, and rice bran oil (Amiri et al., 2020; Khorshidi et al., 2020; Neelakantan et al., 2020; Teng et al., 2020; Ghobadi et al., 2019a; Ghobadi et al., 2019b; Voon et al., 2019; Schwingshackl et al., 2018, Ursoniu et al., 2018; Jolfaie et al., 2016; Hohmann et al., 2015; Sun et al., 2015; Fattore et al., 2014). Participants were 292 to 2002 subjects who were healthy or suffered from MetS, HLP, CVD, non-alcoholic fatty liver disease (NAFLD), and HTN, aged 16 to 91 years old, from both genders. The dose of intervention was varied from 1 to 105 g/d (Khorshidi et al., 2020; Hooper et al., 2012) or from 17 to 76 ml/d (Ursoniu et al., 2018; Hohmann et al., 2015) or from 2% to 34% of total energy/d (Neelakantan et al., 2020; Voon et al., 2019). The duration of intervention was ranged from 2 to 104 weeks. Canola oil, olive oil, argan oil, rice bran oil, palm oil, and other oils play role in reduction of TC by 6.72 to 18.95 mg/dl (Ghobadi et al., 2019a; Schwingshackl et al., 2018). Despite the 10 reported studies, lowering effects of oils in LDL-C by range of 0.37 to 16.24 mg/d in use of coconut oil and sunflower oil (Teng et al., 2020; Schwingshackl et al., 2018), 2 studies reported increasing effects of coconut oil on LDL-C by maximum 10.47 to 11.98 by palm oil (Neelakantan et al., 2020; Sun et al., 2015). Significant changes in HDL-C ranged from 0.33 to 6.65 mg/dl in the use of coconut oil and rice bran oil (Teng et al., 2020; Jolfaie et al., 2016) and for TG ranged from 3.54 to 13.69 in use of sunflower oil and argan oil (Schwingshackl et al., 2018;Ursoniu et al., 2018). However, there are only 3 meta-analyses which reported the effective dose including 15% of total daily energy intake in use of canola oil for reducing TC and LDL-C (Amiri et al., 2020), 20-30% of total required daily energy in use of palm oil for improvement of LDL-C and HDL-C (Sun et al., 2015), and ≤4 g/d of primrose oil for reducing TG and increasing HDL-C (Khorshidi et al., 2020). Details are shown in Table 4.

3.5. Plant proteins

From 6 meta-analyses considering the effects of plant proteins on dyslipidemia, most of the studies (4 studies) were investigated the effect of soy protein (Mejia et al., 2019; Anderson and Bush, 2011; Harland and Haffner, 2008; Anderson et al., 1995). Although some of the subjects were healthy and normocholesterolemic, others suffered from DM, MetS, hyperlipidemia (HLP), and obesity. Sample sizes ranged from 1562 to 10983, aged 18 to 89 years old from both genders. The quality of studies was high. Consumed dose ranges were from 4.5 to 93 g/d (Mejia et al., 2019) for the duration of 3 to 208 weeks. In almost all of the studies, significant decrease of TC and LDL-C was ranged from 6.41 to 23.2 mg/dl (Mejia et al., 2019; Anderson et al., 1995) and 4.76 to 21.7 mg/dl (Mejia et al., 2019; Anderson et al., 1995), respectively. HDL-C improvement was reported in 3 meta-analyses ranged from 1.16 to 1.55 (Zhao et al., 2020; Anderson and Bush, 2011). Five studies announced remarkable lowering effects of plant proteins, including soy protein, on TG by range of 4.92 to 15.06 mg/dl (Tokede et al., 2015; Anderson and Bush, 2011). Effective dose of soy protein in the reduction of TC, TG, and LDL-C was recorded 15-30 g/d; while dose of >80 mg/d of soy protein was required to significantly improve all components of lipid profiles (Zhan and Ho, 2005). Details are shown in Table 5.

3.6. Tea and coffee

To evaluate the effect of tea and coffee on dyslipidemia, 9 meta-analyses have been studied. Studies were categorized into 2 different subgroups: coffee (1 study) (Ding et al., 2020), and tea (8 studies) (Asbaghi et al., 2020a; Payab et al., 2020; Mansour-Ghanaei et al., 2018; Li et al., 2016; Zhao et al., 2015; Onakpoya et al., 2014; Hartley et al., 2013; Zheng et al., 2011). Along with healthy subjects, patients with MetS, obesity, NAFLD, DM, CVD, and HTN were participated in these studies. The age of the participants ranged from 6 to 75 years old, and participants were from both genders. Administered dose was ranged from 0.1 to 10 g/d for 2 to 96 weeks. Although 2 studies didn't report significant changes in TC (Li et al., 2016; Zhao et al., 2015), reduction range in other studies varied from 0.42 to 27.57 mg/dl by green tea (Payab et al., 2020; Mansour-Ghanaei et al., 2018). Two studies reported no significant change in LDL-C level (Asbaghi et al., 2020a; Li et al., 2016); but others declared significant reduction ranged from 0.21 to 24.75 mg/dl in use of green tea (Payab et al., 2020; Hartley et al., 2013). Notable changes in HDL-C just were reported in just 1 study by 1.33 mg/dl in coffee (Morvaridi et al., 2020). On the control of TG, 3 meta-analyses reported significant improvement after using green tea or coffee from 12.79 to 31.87 mg/dl (Asbaghi et al., 2020a; Mansour-Ghanaei et al., 2018). Effective reported doses were <500 mg/d for reducing TG by coffee, and ≥800 mg/d by green tea (Morvaridi et al., 2020; Asbaghi et al., 2020a), <800 mg/d for reducing TC by green tea (Asbaghi et al., 2020a), >400 mg/d for increasing HDL-C by coffee (Morvaridi et al., 2020), and 0.625 to 6 g/d for improving all components of lipid profiles by green tea (Zheng et al., 2011; Payab et al., 2020). Details are shown in Table 6.

3.7. Other herbal medicines

The remaining 60 meta-analyses have been categorized as "other herbal medicines" group, as they contained lower number of herbal medicines. This group was included pooled effect of avocado, berberis, cinnamon, cumin, *fenugreek*, garlic, ginger, ginseng, grape, sour tea, pomegranate, saffron, cayenne pepper, cardamom, purslane, aronia, rhus, tulsi, Artichoke, white mulberry , *Spirulina*, and other herbs (Mahmassani et al., 2018; Peou et al., 2016; Pourmasoumi et al., 2020; Hadi et al., 2019a; Zhang et al., 2019; Ju et al., 2018; Phimarn et al., 2017; Huang et al., 2016; Lan et al., 2015; Dong et al., 2013; Heydarpour et al., 2020; Ainehchi et al., 2019; Allen et al., 2013; Jafarnejad et al., 2018; Askarpour et al., 2020; Heshmat-Ghahdarijani et al., 2020; Khodamoradi et al., 2020; Gong et al., 2016; Shabani et al., 2019; Sun et al., 2018; Ried et al., 2013; Silagy et al., 1994; Maharlouei et al., 2019; Pourmasoumi et al., 2018; Jafarnejad et al., 2017; Mazidi et al., 2016; Ziaei et al., 2020; Hernandez-Garcia et al., 2019; Gui et al., 2016; Asbaghi et al., 2020b; Feringa et al., 2011; Bule et al., 2020; Najafpour Boushehri et al., 2020; Zhang et al., 2020; Aziz et al., 2013; Jandari et al., 2020; Sahebkar et al., 2016a; Taherifard et al., 2020; Asbaghi et al., 2019; Pourmasoumi et al., 2019; Rahmani et al., 2019a; ; Sahebkar et al., 2016c; Hallajzadeh et al., 2020; Jang et al., 2020; Payab et al., 2020; Shekarchizadeh-Esfahani et al., 2020; Hadi et al., 2019b; Lee et al., 2019; Rahmani et al., 2019b; Akbari-Fakhrabadi et al., 2018; Mohammadi et al., 2019a; Jamshidi et al., 2018; Sahebkar et al., 2018; Teoh et al., 2018; ; Sawangjit et al., 2017; Daryabeygi-Khotbehsara et al., 2017; Serban et al., 2016; Zhang et al., 2016b; Onakpoya et al., 2015; Cheng et al., 2013). Along with healthy subjects, the underlying disorders of participants were DM, HLP, obesity, NAFLD, CAD, MetS, chronic kidney disease (CKD), and HTN. Beneficial effects on TC ranged from 2.3 mg/dl by ginseng to 50.50 mg/dl by *cissus quadrangularis* (Hernandez-Garcia et al, 2019; Sawangjit et al., 2017). Based on the studies which reported significant improvements of LDL-C level, the minimum change 0.85 mg/dl by black seed and the maximum change 48.72 mg/dl by fenugreek (Payab et al., 2020; Heshmat-Ghahdarijani et al., 2020). Most of studies showed elevation in HDL-C ranged from 0.77 mg/dl in berberine to 27.07 mg/dl in fenugreek (Dong et al., 2013; Heshmat-Ghahdarijani et al., 2020). Reported improvement in TG level was from 1.63 mg/dl in ginger to 94.77 mg/dl in fenugreek (Mazidi et al., 2016; Heshmat-Ghahdarijani et al., 2020). Fourteen studies reported absolute effective dose on lipid profiles, on TC by used 30 mg/d crocin or 2 g/d ginger (Taherifard et al., 2020; Pormasoumi et al., 2018a), on LDL-C by 300 mg/d aronia or by >1500 mg/d ginseng and purslane (Rahmani et al., 2019a; Ziaei et al., 2020; Hadi et al., 2019b), on HDL-C by 30 mg/d saffron or <1500 mg/d ginseng (Asbaghi et al., 2019; Ziaei et al., 2020), and on TG by 300 mg/d aronia or <2 g/d ginger (Rahmani et al., 2019a; Pormasoumi et al., 2018a). Details are shown in Table 7.

Summary of the effects is represented as Table 8.

4. Discussion

This systematic review showed evidence-based data on impacts of herbal medicines including soy protein, nuts, phytosterols, vegetable oils, green tea and curcumin in the management of the dyslipidemia.

Although previous studies noted lipid-lowering agents such as statins and fibrates as the only available pharmacological interventions to control dyslipidemia (Hadi et al., 2019a) in case of failure of the lifestyle modifications (Shekarchizadeh-Esfahani et al., 2020), recent studies declared the harmful complications and side effects of oral lipid-modifying medications, for instance on muscles and liver (Hadi et al., 2019a). By the year 2018, the American College of Cardiology (ACC) and the American Heart Association (AHA) compiled a guideline in order to control the LDL-C impairment, recommending adults to modify their diet by adding nutraceutical substances (Liu et al., 2020), but the competent plants supposed to be advantageous in management of dyslipidemia and their absolute effective dose, still remained ambiguous that indicates the necessity of assessment and summarization of studies performed to evaluate the impact of herbs on dyslipidemia (Tabatabaei-Malazy et al., 2018). This study is the first to explore the existing meta-analyses considering this lack of evidence.

One hundred and forty-one meta-analyses met the inclusion criteria which most of them gained high score in the quality assessment. Among studies that reported reduction in TC, the most impressive herbal medicines were *Cissus quadrangularis* L., tree nuts, phytosterols, sunflower oil, plant protein, green tea, and garlic. In LDL-C reduction, the most powerful herbal medicines were curcumin, tree nuts, phytosterols, sunflower oil, plant protein, green tea, and fenugreek. The beneficial effects of quercetin, peanut, phytosterols, plant protein, coffee, and fenugreek in elevation of HDL-C were prominent. In control of TG, flavonoids, pistachio, phytosterols, sunflower oil, plant protein, green tea, and blackseed demonstrated remarkable effects. On the other hand, meta-analyses revealed the increment effect of coconut oil, palm oil, resveratrol on LDL-C, and cranberry on TG and reducing effect of *Hibiscus sabdariffa* and resveratrol on HDL-C. Totally, the most potent herbs on TC, LDL-C, HDL-C, and TG were *Cissus quadrangularis* L. (50.50 mg/dl), fenugreek (48.72 mg/dl), quercetin (37.9 mg/dl), and blackseed (147.9 mg/dl), respectively.

Cissus quadrangularis L. was the most effective herbal medicine in TC lowering. In addition to the flavonoids, it contains phytosterols, resveratrol, and other components accounting for its function (Sawangjit et al., 2018). In gastrointestinal tract (GIT), phytosterols oppose with cholesterols to absorb and inhibit intestinal cells to uptake cholesterol and by which stimulate them to excrete into the stool (Han et al., 2016). *Cissus quadrangularis* L. plays a significant role in lipid metabolism through accumulation inhibition of lipids while adipocytes are differentiating, declines the adipogenesis and lipogenesis by affecting gene expression and adipocyte-related protein production (Lee et al., 2018). On the other hand, studies on resveratrol supplements revealed no significant impacts on TC, LDL-C, HDL-C, and TG. Causes led to this neutral or reverse effect are as follows: (1) The dose range in studies was 8 to 3000 mg/d that may be inadequate to alter lipid profile that does not reach sufficient plasma level (sahebkar, 2013). (2) Oral intake of resveratrol and its first passage from liver, metabolizes it into glucuronil conjugates and sulfate and decreases its bioavailability; in spite of its adequate absorption. (3) Enterohepatic pathway excretes resveratrol and its substances into the stool (Sahebkar et al., 2015; Sahebkar, 2013).

Different effects of garlic on lipid profile, depends mainly on the dose, preparation, way of consumption, and design of the study that affects the bioavailability of garlic metabolites (Shabani et al., 2019; Ried et al., 2013). These components decline the TG and LDL-C plasma level and excrete them into the feces by following mechanisms: elevation of prostaglandin in adipocytes, increment in bile acid discharge, altering level of enzymes involved in oxidation of cholesterols, etc. Also, it reduces both cholesterol absorption and synthesis by inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase and squalene monooxygenase that play role in cholesterol synthesis (Shabani et al., 2019; Sun et al., 2018).

Trigonella foenum-graceum L., also known as fenugreek, is a plant that its leaves and seeds are full of soluble fibers, aminoacids, ascorbic acid, saponin, nicotinic acid, flavonoids, etc. which is used in diet of diabetic patients widely (Heshmat-Ghahdarijani et al., 2020; Khodamoradi et al., 2020). Fenugreek is also favored for its lipid-modifying activity. 4-hydroxyisoleucine, is a novel amino acid that is expected to play the main role in inhibiting TG production in collaboration with its phenolic content and saponin (Heshmat-Ghahdarijani et al., 2020). In addition, fenugreek declines uptake of cholesterols, reduces plasma level of lipids, and facilitates cholesterol extrude by stimulating bile acid secretion and prevention of bile salt absorption (Askarpour et al., 2020).

Among herbal medications with positive effects on the HDL-C level, quercetin reported better and more significant outcomes. Quercetin is a flavonoid subtype, mainly used as its antioxidant and anti-inflammatory effects. The lipid-modifying effects of quercetin may be ascribed to its capability of reducing the excess of insulin and androgens (Tabrizi et al., 2020). Also, quercetin enhances bile acid evacuation and cholesterol defecation and declines TG and very low- density lipoprotein cholesterol (VLDL-C) by impeding TG biosynthesis. It should be noted that the difference of effectiveness of quercetin may depend on the genotype distinction of hosts, almost in variations of E3 and E4 in the APOE genes (Sahebkar, 2015).

Due to the lipid-lowering, anti-hypertensive, anti-diabetic, antioxidative, and other biological effects of black seed (*Nigella sativa* L.), it is well-known and widely used; especially among overweight patients suffering from MetS or DM. Black seed contains polyunsaturated fatty acids (PUFA), flavonoids, saponins, alkaloids, etc. that are expected to be responsible for its therapeutic effects (Hallajzadeh et al., 2020; Daryabeygi-Khotbehsara et al., 2017). These phytochemicals diminish VLDL-C, and apo-B100, and boost excretion of TG by influencing lipoprotein lipase and metabolism of fatty acids. Also, through inhibiting of the cholesterols absorption, disrupting cholesterols and TG biosynthesis, removing LDL-C from blood by hepatocytes via upregulating LDL receptors and promoting bile acid secretion, they subtract plasma level of lipids (Hallajzadeh et al., 2020; Payab et al., 2020). Black seed acts as a lipid-modifying herb by affecting the gene that governs HMG-CoA reductase and PPAR gamma that manage cholesterols and TG composition and catabolism, too (Daryabeygi-Khotbehsara et al., 2017; Sahebkar et al., 2106). However, 4 meta-analyses performed on the effect of black seed on dyslipidemia, 3 studies expressed no significant change in HDL-C. Although some studies have attributed it to the consumption dose of ineffective studies, our study revealed the dose range of effective studies and ineffective studies were the same.

In addition to resveratrol, meta-analyses conducted on palm oil and coconut oil showed rising effect on LDL-C, considering their saturated fat supply. Despite polyphenol content of coconut oil presents anti-inflammatory and anti-diabetic effects, studies suggest that due to the elevating effect of these oils, it is better not to use them in preparing foods and they should be replaced with polyunsaturated fats (Neelakantan et al., 2020). Disturbance in cholesterol excretion, apolipoprotein metabolism, and lipoprotein synthesis, may lead to these undesirable effects, decreasing HDL-C and increasing LDL-C (Sun et al., 2015).

Cranberry (*Vaccinium macrocarpon* Aiton) is consumed due to various purposes such as the management of infections, cancers, and CVD. The phenolic content makes it a good choice as an antioxidant substance. The only meta-analysis accomplished on assessment of the lipid-lowering effect of cranberry showed enhancing effects of cranberry on TG. Nevertheless, the exact mechanism of this result is ambiguous, this study infers that clinical trials on cranberry were designed amiss, so that results are not trustworthy. Although the effects on other contents of lipid profile were not significant, this change was remarkable in population under 50 years old. A part of favorable effects of cranberry on lipid profile depends on the activity of HDL-C, as by decreasing HDL-C through aging process, adequate distribution of cholesterols and metabolism of LDL-C are disturbed (Pourmasoumi et al., 2020).

Hibiscus Sabdariffa L. (sour tea) improves lipid profile by its polyphenol, anthocyanins, flavonoid, etc. contents. Polyphenols enhance uptake of cholesterols by macrophages, with the assistance of the upregulation of hepatocyte LDL-C receptors, reduce plasma level of cholesterols, and decline cholesterol and TG biosynthesis by means of genes. Although, hibiscus sabdariffa reduces TC and LDL-C, unexpectedly, it declines the HDL-C serum level too. It may be induced by different genotypes that play role in lipid metabolism (Zhang et al., 2020). Sour tea controls the production of cholesterols and TG by restricting HMG-CoA reductase and stirring discharge of hormones that play role in cholesterol metabolism (Najafpour Boushehri et al., 2020). These controversial results may be due to the insufficient dosage used in clinical trials or the incorrect identification of *hibiscus sabdariffa* L. in methodology of the study (Najafpour Boushehri et al., 2020; Aziz et al., 2013).

Strengths and limitations

This study faced some strengths and limitations. The first strength point is the critical evaluation of all meta-analyses conducted on CTs of herbal medicines for treatment of dyslipidemia. And, the second strength is its high quality status which stemmed from utilization of high quality meta-analyses. Thereby, this study can provide a valuable data for researcher in future studies and for clinicians in treatment of dyslipidemia. Although this research has been done based on the PRISMA flow diagram, but it has not been registered in PROSPERO, or in similar databases. This study affords a scarce data on description of the relationship between herbs and lipid profile. However, the second limitation was the lack of enough data on the effective dose of some herbal medicines for improvement of lipid profiles.

5. Conclusion

The current systematic review shed light on the use of herbal medicines for the management of dyslipidemia. The most powerful effects reported in use of *Cissus quadrangularis* L., tree nuts, phytosterols, sunflower oil, plant protein, green tea, and garlic for TC, curcumin, tree nuts, phytosterols, sunflower oil, plant protein, green tea, and fenugreek for LDL-C, quercetin, peanut, phytosterols, plant protein (soy, lupin, pea, legume, pinto proteins), coffee, and fenugreek for HDL-C, and flavonoids, pistachio, phytosterols, sunflower oil, plant protein, green tea, and blackseed for TG. Regardless of proposed mechanisms to control and treat dyslipidemia by herbal medicines, it was observed discrepancy between the results in the same interventions which could be partly attributed to differences in characteristics of studied population, duration, type and dose of intervention. However, more well-conducted trials are required to clear effective dose of used plant-derived in the meta-analysis.

List of Abbreviations

CT	controlled trials
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
TC	total cholesterol
TG	triglyceride
LDL-C	low- density lipoprotein cholesterol
HDL-C	high- density lipoprotein cholesterol
DLP	Dyslipidemia
Mets	metabolic syndrome
CVD	Cardiovascular disease
CAD	coronary artery disease
AMSTAR	Assessment of Multiple Systematic Reviews
T2DM	type 2 diabetes mellitus
NAFLD	non-alcoholic fatty liver disease
HLP	hyperlipidemia
ACC	American College of Cardiology
AHA	American Heart Association
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
VLDL-C	Very low- density lipoprotein cholesterol
APOE	Apolipoprotein E
PUFA	polyunsaturated fatty acids

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Conflict of interest
All authors declare any conflict of study.

Author Contribution
OTM and RR designed the study and interpreted data. MSAM and OTM extracted data and wrote draft of the manuscript. OTM and RR equally interpreted data and revised

manuscript. MD, PK, and BL helped in quality assessment and revised some sections. All authors read and approved the final manuscript .

Ethics approval and consent to participate

Not applicable .

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Legend Figure :

Fig. 1 Flow diagram of the study selection process

Legend Tables :

Table 1 Characteristics of meta-analyses investigating the effects of polyphenolic compounds on dyslipidemia

Table 2 Characteristics of meta-analyses investigating the effects of nuts on dyslipidemia

Table 3 Characteristics of meta-analyses investigating the effects of phytosterols on dyslipidemia

Table 4 Characteristics of meta-analyses investigating the effects of vegetable oils on dyslipidemia

Table 5 Characteristics of meta-analyses investigating the effects of plant proteins on dyslipidemia

Table 6 Characteristics of meta-analyses investigating the effects of tea and coffee on dyslipidemia

Table 7 Characteristics of meta-analyses investigating the effects of other herbal medicines on dyslipidemia

Table 8 Summary of the effects of herbal medicines on dyslipidemia

Supplementary:

Supplementary 1: PRISMA 2020 checklist

Table S1. Search strategy in PubMed database

Table S2. AMSTAR tool

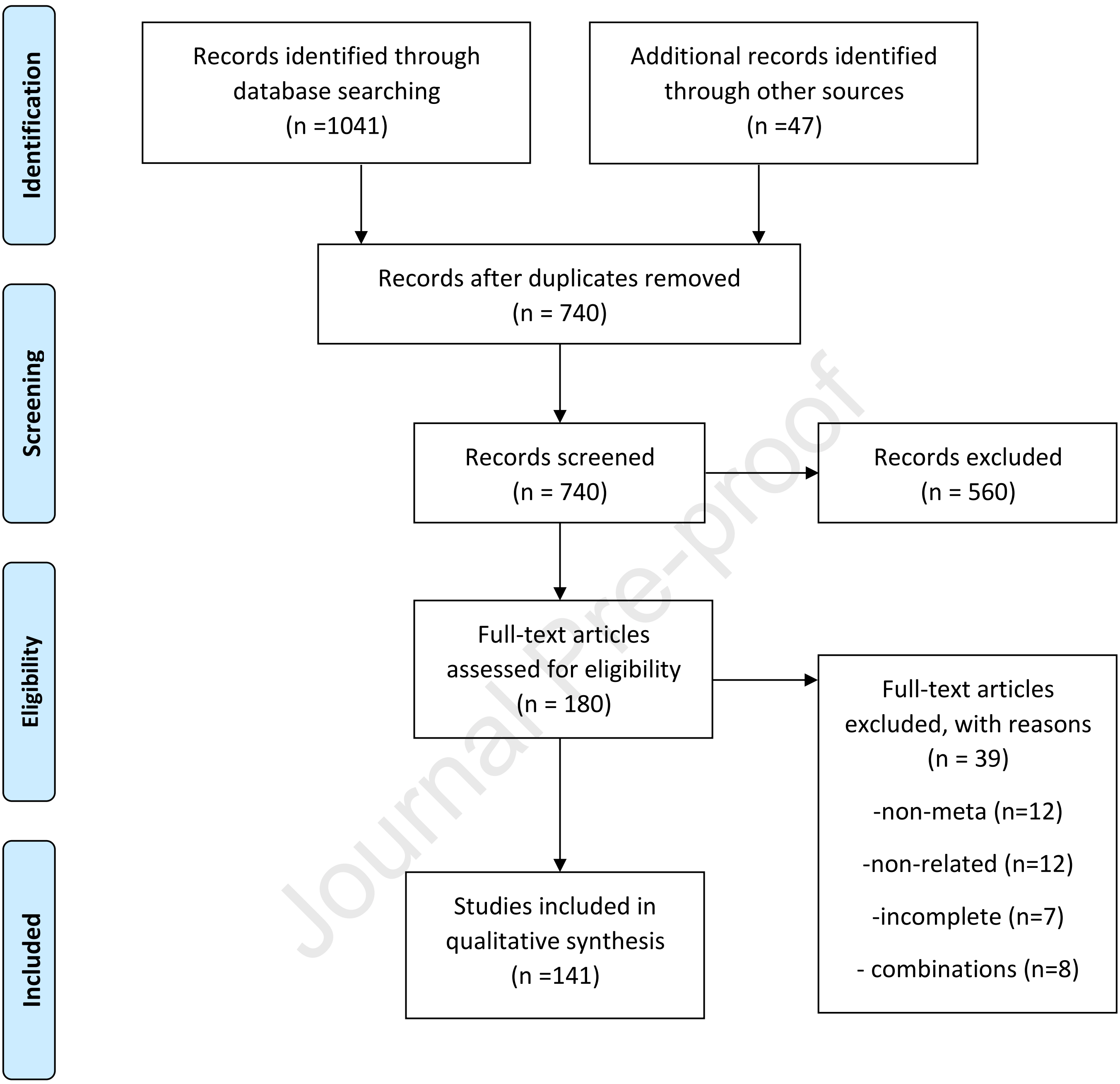

Figure 1. PRISMA Flow diagram of study processes

Table 1. Characteristics of meta-analyses investigating the effects of polyphenolic compounds on dyslipidemia

Subgroup	Study	Herbal medicine/ Control	meta-analyzed studies (n)/ disorders	Participants			Intervention		Significant main outcome	Effective dose	Quality assessment in meta-analysis	AMSTAR score
				Sample size (n)	Age (yr)	Sex	Dose/ Frequency	Duration (w)				
Anthocyanins	Daneshzad et al. (2019)	Anthocyanins (supplement from unspecified source) / placebo	19/ NR	742	NR	Both	31.45-1050 mg/d	1-96	↓ LDL-C: (-10.67, 95% CI: -14.97, -6.37), ↑ HDL-C: (7.40, 95% CI: 6.04, 8.75).	>300 mg/d for >12w	yes	10
Cocoa (bean of *Theobroma cacao* L.)	Lin et al. (2016)	Cocoa flavanol/placebo	19/healthy, DM, obese, CVD	1131	27-71	both	166-2110 mg/d	2-52	↓ TG: (-8.85, 95%CI: -14.17,-3.54), ↑ HDL-C: (2.32,95%CI: 0.77, 3.48), no significant change in TC, LDL-C	≥600 mg/d for TG, <600 mg/d for HDL-C	yes	10
	Hooper et al. (2012)	chocolate, cocoa, flavan-3 oil/ low	42/ HTN, T2DM, others	1297	18-76	both	6.3-105 g/d	2-18	↓ LDL-C: (-2.71, 95% CI: -5.03,	NR	yes	10

		dose diet							0.00), ↑ HDL-C (1.16, 95% CI: 0.00, 2.32).			
	Shrime et al. (2011)	Cocoa/placebo, white chocolate, skim milk	24/DM, CVD, hyperlipidemia	1109	18-69.7	NR	26.7-1080 mg/d	2-18	↓ LDL-C: (-3.09, 95%CI: -0.15, -5.8), ↑ HDL-C: (1.93, 95%CI, 0.12, 3.48), no significant change in TC, TG.	500 mg/d	yes	9
	Tokede et al. (2011)	Cocoa products, dark chocholate /placebo, white chocholate, cocoa butter	10/overweight, healthy, HTN	320	18-80	both	20-105 g/d	2-12	↓ TC (-6.23, 95%CI: -11.60,-0.85), ↓ LDL-C: (-5.90, 95%CI: -10.47,-1.32), no significant change in TG, HDL-C	NR	yes	9
	Jia et al. (2010)	Cocoa/placebo, non-cocoa	8/healthy, DM, HTN	215	NR	both	30-963 mg/d	2-18 (short term)	↓ LDL-C: (-5.87, 95% CI: -11.13,-0.61), marginally ↓sig in TC, no	<260 mg/d for TC, LDL-C	yes	9

									significant change in HDL-C.			
curcumin	Jalali et al. (2020b)	Curcumin (supplement from unspecified source) / placebo	9/ NAFLD	588	41.8-46.64	Both	50-1500 mg/d	8-12	↓ TC: (-25.13, 95% CI: -40.6, -9.28), ↓ LDL-C:(-39.83, 95% CI: -75.02, -4.25). No significant change in TG, HDL-C.	NR	yes	10
	Azhdari et al. (2019)	Curcumin (supplement from unspecified source) / placebo, non-active agents	7 / MetS	503	38-59	Both	800-2400 mg/d	4-12	↓ TG: (−33.65, 95% CI: −51.27, −16.03), ↑ HDL-C: (4.31, 95% CI: 1.50, 7.11).	NR	yes	11
	Simental-Mendía et al. (2019)	Curcuminoids (supplement from unspecified source)/ placebo	20/ HLP, T2DM, health, others	1427	25-76	both	45-6000 mg/d	1-24	↓ TG: (-21.36, 95% CI: -32.18, -10.53), ↑ HDL-C: (1.42, 95% CI: 0.03, 2.81). No	NR	yes	8

									significant change in LDL-C, TC			
	Wei et al. (2019)	Curcumin (suppleme nt from unspecifie d source)/ placebo	4/NAFLD	229	31-70	both	500-3000 mg/d	8-24	↓ LDL-C: (-27.02, 95%CI: -52.30,-1.74), ↓ TG: (-33.20, 95%CI:-42.30, -24.09), no significant change in TC, HDL-C.	NR	yes	9
	Yuan et al. (2019)	Turmeric, curcuminoi d (suppleme nt from unspecifie d source)/ NR	14/ Mets, NAFLD, T2DM, others	1142	18-70	NR	66.3-1795 mg/d	4-24	↓ TG: (-19.1, 95%CI: -31.7,-6.46), ↓ TC: (-11.4, 95%CI: -17.1,-5.74), ↓ LDL-C: (-9.83, 95%CI: -15.9,-3.74), ↑ HDL-C: (1.9, 95%CI:	330-1795 mg/d for TC,LDL-C, HDL-C, 1000-1795 mg/d for TG	yes	8

									0.31, 3.49)			
	Qin et al. (2017)	Turmeric, curcumin (supplement from unspecified source)/ placebo	7/ T2DM, MetS, others	649	35-73	Both	70-1890 mg/d curcuminoids, 2.4 g/d turmeric	4-24	↓ LDL-C: (-13.14, 95% CI: -20.49, -5.8), ↓ TG:(-18.95, 95%CI:-32.68, -5.22), ↓ TC in MetS patients (-36.12, 95% CI: -49.85, -22.39).	NR	yes	10
	Sahebkar et al. (2014)	Curcumin (supplement from unspecified source)/ placebo, statin, vit E	5/ ACS, T2DM, others	223	24-81	both	45-4000 mg/d	1-24	No significant change in lipid profiles.	NR	yes	9
Flavonoids	Tabrizi et al. (2020)	Quercetin (supplement from unspecified source) / placebo	16/ obese, T2DM, HLP, others	1575	35-72	NR	31.12-3000 mg/d	2h-12w	↓ TC: (-37.9, 95%CI: -57.23, -18.95), ↓ LDL-C:(-34.03,	NR	yes	10

									95%CI:-52.2, -15.85), No significant change in TG, HDL-C			
	Sahebkar (2017)	Quercetin (suppleme nt from unspecifie d source)/ placebo	5/ obese, hyper TG, T2DM, HTN, healthy	442	44-62	both	30-730 mg/d	2-10	↓ TC (3.57, 95% CI: 0.21, 6.92), ↓TG: (-24.54, 95%CI: -33.09, -15.99). No significant change in LDL-C, HDL-C	≥ 500 mg/d ≥4w for TC, TG	yes	9
	Hooper et al. (2008)	Flavonoids (derived from onion, broccoli, etc.)/NR	102/NR	6557	NR	NR	NR	Mean: 4.75	↓ LDL-C: by soy protein (-7.35, 95%CI: -9.28,-5.41), green tea (-8.89, 95%CI: -13.15,-4.64). No significant change in HDL-C	NR	Yes	9
Hesperidin	Mohammadi et al. (2019b)	Hesperidin (suppleme	10 / obese, T2DM,	577	18-81	Both	292-800 mg/d	3-12	No significant change in	NR	yes	11

		nt from unspecified source)/ placebo	MetS, MI, HLP						lipid profiles.			
Isoflavones	Kanadys et al. (2020)	Red clover (flower of *Trifolium pratense* L.) isoflavones /placebo	10/ pri-menopause	910	40-85	Female	33.8-160 mg/d	12-48	↓ TC: (-11.21, 95% CI: -20.49, -13.92), no sig change in TG, LDL-C, HDL-C	NR	yes	10
	Soltanipour et al. (2019)	Soy (bean of *Glycine max* (L.) Merr.) protein, isoflavone / placebo	16/obese, T2DM, others	471	42-89	Both	Soy protein 0.8-50 g/d, isoflavone 32-165 mg/d	4-208	↓ TC: (-18.17, 95% CI: -27.84, -8.12).	NR	yes	11
	Luis et al. (2018)	Red clover (flower of *Trifolium pretense* L.) isoflavones / placebo	12/ perimenopause, postmenopause	1284	47-62	Female	40-160 mg/d	4-72	↓ TC: (-12.34, 95% CI: -18.21, -6.48), ↓ LDL-C:(-10.61, 95%CI:-15.51, -5.72), ↓ TG:(-10.18, 95%CI: 16.23, -4.13), ↑HDL-	40 mg/d	yes	11

									C: (1.60, 95% CI: 0.17, 3.03).			
	Simental-Mendia et al. (2018)	Soy (bean of *Glycine max* (L.) Merr.) isoflavone / placebo	10 / T2DM, HLP, HTN, menopause	973	6-80	both	40 mg - 25.6 g/d	5-48	↓ TC: (-7.38, 95% CI: -13.84, -0.92), ↓ LDL-C:(-6.25, 95%CI:-12.39, -0.10). No significant changes in HDL-C, TG	NR	yes	9
	Taku et al. (2007)	Soy (bean of *Glycine max* (L.) Merr.) protein, isoflavono n/ non soy, dairy, animal protein	11/normo-hypercholes terolemic	780	26.3-62.7	both	1.64-317.9 mg/d isoflavon e, 25-133 g/d soy	4-13.3	↓ TC: (-3.9, 95%CI: -6.6, -0.8), ↓ LDL-C: (-5.0, 95%CI: -7.7,-2.7), no significant change in TG, HDL-C.	NR	yes	9
	Reynolds et al. (2006)	Soy (bean of *Glycine max* (L.) Merr.)	41/normo-hypercholes terolemic	1756	22-67	both	Soy protein: 20-106.2 g/d,	3-52	↓ TC: (-5.26, 95%CI: -7.14, -3.38),	NR	yes	9

		protein, isoflavone/ placebo					isoflavone: 3-192.4 mg/d		↓ LDL-C: (-4.25, 95%CI: -6.00,-2.50), ↓ TG: (-6.26, 95%CI: -9.14, -3.38), ↑ HDL-C: (0.77, 95%CI: 0.20, 1.34).			
	Zhan and Ho (2005)	Soy (bean of *Glycine max* (L.) Merr.) protein isoflavone / placebo	23/ HLP	1381	NR	both	3-185 mg/d	3-26	↓ TC: (-8.51, 95% CI: -11.21, -6.19), ↓ LDL-C:(-8.12, 95% CI: -11.6, -5.03), ↓ TG:(-9.74, 95% CI: -14.17, -4.43), ↑ HDL-C (1.55, 95% CI: 0.00, 2.71).	> 80 mg/d	NR	9
	Asgary et al. (2019)	Resveratrol (supplement from unspecifie	10 / MetS	396	20 - 75	NR	100 - 3000 mg/d	4-12	no significant change in TG, TC, HDL-C	NR	yes	10

		d source)/ placebo										
Resveratrol	Elgebaly et al. (2017)	Resveratrol (supplement from unspecified source)/ placebo	4/ NAFLD, overweight, obese	158	32-58	both	300-3000 mg/d	8-24	No significant change in lipid profiles	NR	yes	9
	Zhang et al. (2016a)	Resveratrol (supplement from unspecified source)/placebo	4/NAFLD	156	32-60	both	300-3000 mg/d	8-25.7	↓ TC: (18.95,95%CI: 6.96, 30.93), ↑ LDL-C: (18.17,95%CI: 8.12, 28.61). no significant change in HDL-C.	NR	yes	9
	Sahebkar et al. (2015)	Resveratrol (supplement from unspecified source)/ placebo	10/ smoker, T2DM, HLP, HTN, CHD	600	29-75	both	8-1500 mg/d	4-26	↓ HDL-C (-4.18, 95%CI: -6.54,-1.82). No significant change in other lipids.	NR	yes	9
	Sahebkar (2013)	Resveratrol (derived from grape, etc.)/	7/ MetS, obese, others	282	28-73	Both	8-1500 mg/d	4-24	No significant change in lipid profile	NR	yes	10

		placebo										
	Ghaedi et al. (2019)	Grape (berry of *Vitis vinifera* L.) polyphenols/ placebo	48 / healthy, HLP, CKD, MetS, others	2346	25-79	Both	90-2000 mg/d	2-48	↓ TC (-6.20, 95%CI: -9.20,-3.19), ↓ LDL-C (-4.96, 95% CI: -7.59, -2.33), ↓ TG (-7.64, 95%CI: 12.12, -3.16). no significant change in HDL-C	≤500 mg/d, ≤8w for TC, TG, LDL-C	yes	10

Legend: n, number; yr, year; w, week; NR, not reported; ↓ indicates significant reduction (p value <0.05); ↑ indicates significant elevation (p value <0.05); TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; DM, diabetes mellitus; CVD, cardiovascular disease; HTN, hypertension; T2DM, type-2 diabetes mellitus; NAFLD, non-alcoholic fatty liver disease; MetS, metabolic syndrome; HLP, hyperlipidemia; hyper TG, hypertriglyceridemia; MI, myocardial infarction; CHD, congestive heart disease; CKD, chronic kidney disease.

Table 2. Characteristics of meta-analyses investigating the effects of nuts on dyslipidemia

Study	Herbal medicine/ Control	meta-analyzed studies (n)/ disorders	Participants			Intervention		Significant main outcome	Effective dose	Quality assessment in meta-analysis	AMSTAR score
			Sample size (n)	Age (yr)	Sex	Dose/ Frequency	Duration (w)				
Hou et al. (2020)	Brazil nut (nut of *Bertholletia excelsa* Bonpl.)/ NR	6/ NR	178	15-80	Both	5-20 g/d	6-16	↓ TG: (-8.23, 95%CI: -15.09,-1.38), ↓ TC: (-14.31, 95% CI: -23.38, -5.24), ↓ LDL-C: (-9.27, 95%CI: -13.48,-5.06). No significant change in HDL-C	NR	Yes	10
Jalali et al. (2020a)	Cashew (nut of *Anacardium occidentale* L.)/NR	3/MetS, healthy, DM	392	45-56.8	NR	30-42 g/d	4-12	No significant change in lipid profiles.	NR	yes	11
Jafari Azad et al. (2020)	Peanut (nut of *Arachis hypogaea* L.)	13/ healthy, obese, T2DM, HTN	800	18-75	both	<10-88 g/d	4-24	↑ HDL-C (2.72, 95% CI: 1.10, 4.35).	>12 w	yes	11

	/ placebo, others							No significant change in other lipid profiles.			
Liu et al. (2020)	Pistachio (nut of *Pistacia vera* L.), walnut (nut of *Juglans regia* L.), hazelnut (nut of *Corylus maxima* Mill.), cashew (nut of *Anacardium occidentale* L.), almond (nut of *Prunus dulcis* (Mill.) D.A.Webb)/habitual diet	34/normo-hyperlipidemic	1677	22.1-66	both	NR	24	↓ TG first choice by Walnut: (−18.6, 95%CI: −31, −7.08), then by Pistachio:(-22.14, 95%CI: -38.09, -6.2), ↓ LDL-C first choice by Walnut: (−3.48, 95%CI: −4.64, −2.70), then by Pistachio:(-6.57, 95%CI: -10.82, -2.32), then by almond:(-4.64, 95%CI: -8.89, -0.38), ↓ TC	NR	yes	11

								first choice by Pistachio:(-9.66, 95%CI: −15.08, −4.25), then by Walnut:(-5.02, 95%CI: -6.18, -4.25), no significant change for HDL-C.			
Lee-Bravatti et al. (2019)	Almond (nut of *Prunus dulcis* (Mill.) D.A.Webb)/diet without almond	15/healthy, overweight, hyperlipidemia	534	24-64	both	25-75	4-16	↓ TC: (−10.69, 95%CI: −16.75, −4.63), ↓LDL-C: (−5.83, 95%CI: −9.91, −1.75), ↓ HDL-C: (−1.26, 95%CI: −2.47, −0.05), no sig change in TG.	Both ≤, >42.5g/d for ≤6w for TC, ≤42.5 g/d for ≤6w for LDL-C	yes	9

Guasch-Ferré et al. (2018)	Walnut (nut of *Juglans regia* L.)/nut free, western type, habitual diet	26/healthy, overweight, DM	1059	22-75	both	15-56 g/d	4-108	↓ TC: (−6.99, 95%CI: −9.39, −4.58), ↓ LDL-C: (−5.51, 95%CI: −7.72, −3.29), ↓ TG (−4.69, 95%CI: −8.93, −0.45). no significant change in HDL-C.	Both <, ≥28 g/d for <, ≥8w for TC, LDL-C, ≥28 g/d for ≥8w for TG	yes	11
Musa-veloso et al. (2016)	Almond (nut of *Prunus dulcis* (Mill.) D.A.Webb)/no nut, olive oil, canola oil	18/ healthy, DM, hypercholesterolemic	1697	18-70	both	20-113 g/d	2-72	↓ TC: (-5.80, 95%CI: -9.28, -2.71), ↓ LDL-C: (-4.64, 95%CI: -7.73, -1.93), ↓ TG:	≥45 g/d for <12w	yes	9

								(-6.20, 95%CI: -11.52, -0.18), no significant change in HDL-C.			
Del Gobbo et al. (2015)	Tree nuts (walnut (nut of *Juglans regia* L.), almond (nut of *Prunus dulcis* (Mill.) D.A.Webb), macadamia (nut of *Macadamia integrifolia* Var. integrifolia Maiden & Betche), pistachio (nut of *Pistacia vera* L.), hazelnut (nut of *Corylus maxima* Mill.), pecan (nut of *Carya illinoinensis*	61/T2DM, healthy, obese	2582	35-64	both	15-100 g/d	3-26	<u>Total nut*:</u> ↓ TC: (-24.7, 95% CI: -25.3, -24.0, ↓ LDL-C: (-24.8: 95% CI: -25.5, -24.2), ↓ TG: (-22.2: 95%CI: -23.8, -20.5), no sig change in HDL-C.	Per one serving /d (28.4 g/d): ↓TC: (-4.66, 95%CI: -5.29, -4.03)	yes	10

	(Wangenh.) K.Koch), cashew (nut of *Anacardium occidentale* L.)/ habitual diet, low fat										
Blanco Mejia et al. (2014)	Different tree nuts/ diet advice, supplement, others	45/ HTN, MetS, others	2142	17-78	Both	28-85.5 g/d	4-24	↓ TG: (−5.31, 95% CI: −7.97, -2.65). No significant change in HDL-C	NR	Yes	10
Banel et al. (2009)	Walnut (nut of *Juglans regia* L.)/low fat	13/healthy, overweight, MetS	365	20-75	both	30-108 g/d	4-24	↓ TC: (-10.29, 95%CI: -14.76, -5.83), ↓ LDL-C: (-9.23, 95%CI: -13.10, -5.36), no significant change in TG, HDL-C.	NR	yes	8

Phung et al. (2009)	Almond (nut of *Prunus dulcis* (Mill.) D.A.Webb)/usual diet, low fat or high fat diet	5/DM, normo-hyperlipidemic	142	18-86	both	25-168 g/d	4	↓ TC: (-6.95, 95%CI: -13.12, -0.77), ↓ LDL-C: (-5.79, 95%CI: –11.2, 0.00), no significant change in TG, HDL-C.	NR	yes	9

Legend: n, number; **yr**, year; **w**, week; **NR**, not reported; ↓ indicates significant reduction (p value <0.05); ↑ indicates significant elevation (p value <0.05); **TC**, total cholesterol; **LDL-C**, low-density lipoprotein cholesterol; **HDL-C**, high-density lipoprotein cholesterol; **TG**, triglyceride; **MetS**, metabolic syndrome; **DM**, diabetes mellitus; **T2DM**, type-2 diabetes mellitus; **HTN**, hypertension.

Table 3. Characteristics of meta-analyses investigating the effects of phytosterols on dyslipidemia

Subgroup	Study	Herbal medicine/ Control	meta-analyzed studies (n)/ disorders	Participants			Intervention		Significant main outcome	Effective dose	Quality assessment in meta-analysis	AMSTAR score
				Sample size (n)	Age (yr)	Sex	Dose/ Frequency	Duration (w)				
phytosterols	Soto-Mendez et al. (2019)	phytosterol-fortified dairy (milk, etc. fortified with unspecified source)/placebo	31/normo-hypercholesterolemia	2449	22.3-65	both	0.7-4 g/d	3-12	↓ LDL-C in Total dairy: (-13.92, 95% CI: -15.86, -11.99), by milk: -14.31 (95% CI: −18.18, −10.05), by yogurt: −12.76 (95% CI: −15.47, −10.05), Cheese: −17.02 (95% CI: −22.04, −12.37),	>3g/d	yes	11

									butter: −16.63 (95%CI: -19.72, -13.53), no significant change for TC.			
	Rocha et al. (2016)	Phytosterol (orange, etc. fortified with unspecified source)/placebo	20/ MetS, hypercholesterolemic, obesity	1308	42.5-66.0	both	1.4-4.0 g/d	3-17.2	↓ LDL-C: -14.3 (95%CI: -17.3, -11.3), ↓ TC (-16.4, 95% CI: -20.1, -12.8), ↓ TG: (-7.9, 95% CI: -12.7, -3.1). no significant change in HDL-C	NR	NR	9

	Ras et al. (2014)	Plant sterols, stanols (margarine, etc. fortified with unspecified source)/	124/ normo-hypercholes terolemic	9635	NR	NR	0.3-9 g/d	NR	↓ dose dependent LDL-C: mean 6-12%	0.6-3.3 g/d	yes	9
	Amir Shaghaghi et al. (2013)	Sterols, Stanols (from commercial brands such as Phytocell, etc.)/ placebo	8/ NR	263	36-62	Both	1-3 g/d	4-6	↓ LDL-C (11.98, 95% CI: -15.08, -9.28).	NR	Yes	8
	Demonty et al. (2013)	Plant sterols (margarine, etc. fortified with unspecified source)/pla cebo	12/ normo-hypercholes terolemic	935	33-68	both	0.8-2.5 g/d	3-4	↓ TG: 6% (95%CI: -10.7,-1.2), no significant change in HDL-C	NR	yes	8
	Musa-veloso et al. (2011)	Stanols and sterols (margarine, etc. fortified	114/ NR	9239	22.7-66	both	Sterols 0.19-9 g/d, Stanols	3-45	↓ LDL-C (-10.44, 95% CI,	2 g/d	NR	8

		with unspecified source)/ placebo					0.8 -8.8 g/d		-18.17, -2.70)			
	Talati et al. (2010)	plant sterols (margarine, etc. fortified with unspecified source)/ plant stanols	14/ normo-hypercholes terolemic	531	NR	NR	0.625-3.25 gr/d	3-16	No significant change in lipid profiles	NR	yes	9
	Demonty et al. (2009)	Plant sterols (orange juice, etc. fortified with unspecified source)/placebo	84/ normo-hypercholes terolemic	6805	22.7-66	both	0.7-9 g/d	3-26	↓ LDL-C:(-13.14, 95% CI: -13.92, -11.98)	2.15 g/d	yes	8
	Wu et al. (2009)	Phytosterols, stanols (yoghurt, etc. fortified with unspecified source)/ NR	20/ HLP	1273	20-70	NR	0.45-3.2 g/d	3-52	↓ TC (-13.92, 95% CI: -17.78, -10.05), ↓ LDL-C	2 g/d	Yes	10

									(-13.53, 95% CI: -18.17, -8.50), ↓ TG (-8.85, 95% CI: -14.17, -2.65)			
	AbuMweis et al. (2008)	Plant sterols, stanols (orange juice, etc. fortified with unspecified source) /placebo	59/ normo-hypercholesterolemic	4500	29-66	both	0.3-9 g/d	3-52	↓ LDL-C: (-11.98, 95% CI: -13.53, -10.44)	NR	yes	9
	Seppo et al. (2007)	Plant stanols (milk, etc. fortified with unspecific source)/placebo	4/hypercholesterolemic	199	25-65	both	0.9-1.3 g/d	3-5	↓ TC : (-3.8%, CI95%: -6.0, -1.7%), ↓ LDL-C : (-4.9% 95%CI:	NR	NR	7

									-7.8, -1.8%), non change in HDL-C, TG			
	Chen et al. (2005)	sterol and stanol sters, policosanol (margarine, etc. fortified with unspecified source)/ placebo	23,29/ T2DM, HLP, others	1662 in sterol and stanol, 2934 in policosanol	NR	NR	2-9 g/d sterol and stanol sters, 5-40 mg/d policosanol	4-52 for sterol and stanol sters, 4-104 w for policosanol	for sterol and stanol: ↓ TC: (-7.7, 95%CI: -2.8,-19.5), ↓ LDL-C: (-11.0, 95%CI: -4.6,-24.3). No significant change in HDL-C, TG. For policosanol ↓ TC (-16.2, 95% CI: -8.8, -28.8), ↓LDL-C:	NR	yes	8

									(-23.7, 95% CI: -12.6, -42.1), ↑ HDL-C: (10.6, 95% CI: -3.3, 33.9). No significant change in TG.			

Legend: n, number; **yr**, year; **w**, week; **NR**, not reported; ↓ indicates significant reduction (p value <0.05); ↑ indicates significant elevation (p value <0.05); **TC**, total cholesterol; **LDL-C**, low-density lipoprotein cholesterol; **HDL-C**, high-density lipoprotein cholesterol; **TG**, triglyceride; MetS, metabolic syndrome; **HLP**, hyperlipidemia; **T2DM**, type-2 diabetes mellitus.

Table 4. Characteristics of meta-analyses investigating the effects of vegetable oils on dyslipidemia

Study	Herbal medicine/ Control	meta-analyzed studies (n)/ disorders	Participants			Intervention		Significant Main outcome	Effective dose	Quality assessment in meta-analysis	AMSTAR score
			Sample size (n)	Age (yr)	Sex	Dose/ Frequency	Duration (w)				
Amiri et al. (2020)	Canola oil (seed of *Brassica napus* L.)/ other edible oils	42 / healthy, HLP, T2DM, MetS, others	2002	22-67	both	NR	2-24	↓ TC (-10.44, 95% CI: -14.69,-6.57), ↓ LDL-C (-8.89, 95% CI: -12.76,-5.41). No significant change in TG, HDL-C.	~15% of total caloric intake	yes	11
Khorshidi et al. (2020)	Primrose oil (seed of *Primula vulgaris* Huds.)/ placebo	6/ healthy, PCOS, others	6-60	20-53	both	1-27.8 g/d	6-17	No significant change in TC, TG, LDL-C, HDL-C.	≤4 g/d for TG, HDL-C	yes	11
Neelakantan et al. (2020)	Coconut oil (fruit of *Cocos nucifera* L.)/ soybean oil, olive oil,	16/ healthy, HLP, others	730	20-60	both	2-25 % total energy/d	3-104	↑ LDL-C: (10.47, 95% CI: 3.01, 17.94), ↑ HDL-C (4.00, 95%CI: 2.26, 5.73).	NR	yes	9

	others										
Teng et al. (2020)	Coconut oil (fruit of *Cocos nucifera* L.)/ other vegetable oils, animal oils	18/obese, hyperlipidemic, CVD, normolipidemic	1016	18-79	both	NR	4-24	↑ HDL-C vs. plant oil: (0.57, 95%cI: 0.40, 0.74), ↑ HDL-c vs. animal oil: (0.33, 95%cI: 0.01, 0.65), ↑ LDL-C vs. plant oil: (0.26, 95%cI: 0.09, 0.43), ↓ LDL-C vs. animal oil: (-0.37, 95%cI: -0.69, -0.05), no significant change in TG.	NR	yes	9
Ghobadi et al. (2019a)	Olive oil (fruit of *Olea europaea* L.) / rapeseed oil, sunflower oil, other plant oils	27 / healthy, HLP, MetS, NAFLD, others	1089	16-91	both	15-25 ml/d, 20-60 g/d	3-24	↓ TC (−6.72, 95% CI: −2.8, −10.6), ↓ LDL-C (−4.2, 95% CI: −1.4, −7.01), ↓ TG (−4.31, 95% CI: −0.5, −8.12), ↑ HDL-C (1.37, 95% CI: 0.4,	NR	yes	11

								2.36).			
Ghobadi et al. (2019b)	Canola oil (seed of *Brassica napus* L.)/ sunflower oil, olive oil, others	27 / healthy, T2DM, NAFLD, others	1359	22-65	both	12-50 g/d	3- 25.7	↓ TC (-7.24, 95% CI: -12.1,-2.7), ↓ LDL-C (-6.4, 95% CI: -10.8,-2.0). No significant change in HDL-C, TG.	NR	yes	11
Voon et al. (2019)	Palm olein (fruit of *Elaeis guineensis* Jacq.)/other oils: canola, coconut, olive	9/healthy	1075	18-64	both	27-34% energy	4-12	No significant change in lipid profiles	NR	yes	10
Schwingshackl et al. (2018)	Oils (safflower (seed of *Carthamus tinctorius* L.), sunflower (seed of *Helianthus annuus* L.),	54/ healthy	NR	22-84	NR	NR	3-27	↓ LDL-C sun flower (**-16.24, 95% CI: −25.14, −6.96**), rapeseed (**−13.92, 95% CI: −20.11, −8.12**), flaxseed (**−14.31, 95%**	NR	Yes	9

	rapeseed (seed of *Brassica napus* L.), hempseed (seed of *Cannabis sativa* L.), flaxseed (seed of *Linum usitatissimum* L.), corn (fruit of *Zea mays* L.), olive (fruit of *Olea europaea* L.), soybean (bean of *Glycine max* (L.) Merr.), palm (fruit of *Elaeis guineensis* Jacq.), and coconut oil (fruit of *Cocos nucifera* L.) / butter							**CI: −23.2, −5.03**), corn (**−12.76, 95% CI: −17.4, −8.12**), olive (**−9.67, 95% CI: −13.92, −5.8**), soybean (**-11.21, 95% CI: −15.08, −6.96**), palm (**−9.28, 95% CI: −13.92, −4.64**), coconut (**−8.89, 95% CI: −15.47, −2.71**), ↓ TG by palm (**−5.31, 95% CI: −8.86, −0.89**), soybean (**−5.31, 95% CI: −7.09, −2.66**), sunflower (**−3.54, 95% CI: −7.09, −0.89**), ↓ TC by sun flower (**−18.95, 95% CI: −27.46, −10.44**), rapeseed (**−16.63, 95% CI: −22.82, −10.44**),			

								flaxseed (**−12.76, 95% CI: −22.43, −3.09**), corn (**−14.31, 95% CI: −18.95, −9.67**), olive (**−10.83, 95% CI: −14.70, −6.57**), soybean (**−12.76, 95% CI: −17.02, −8.51**), palm (**−9.67, 95% CI: −13.92, −5.03**), coconut (**−6.96, 95% CI: −13.15, −0.77**), ↑ HDL-C by coconut (**1.55, 95% CI: 0.39, 3.09**).			
Ursoniu et al. (2018)	Argan oil (nut of *Argania spinosa* (L.) Skeels) / placebo	5 / hemodialysis, HLP, T2DM, healthy	292	20 - 66	both	17-30 ml/d	3-4	↓ TC (−16.85, 95% CI: −25.10, −8.60), ↓ LDL-C (−11.67, 95% CI: −17.32, −11.6), ↓ TG (−13.69, 95% CI: −25.80, −1.58), ↑ HDL-C (4.14, 95% CI:	NR	yes	9

								0.86, 7.41)			
Jolfaie et al. (2016)	Rice bran oil (chaff of *Oryza sativa* L.)/ soybean oils or others	11 / HLP, healthy	9-60	34-61	both	18-35g/d	3-13	↓ LDL-C (-6.91, 95% CI: -10.24, -3.57), ↓ TC (-12.65, 95% CI: -18.04, -7.27), ↑ HDL-C only in men (6.65, 95% CI: 2.38, 10.92), all above changes in<30 usage, No significant change in TG, VLDL-C	NR	yes	9
Hohmann et al. (2015)	Virgin Olive oil (fruit of *Olea europaea* L.)/refined olive oil	8/ healthy, HTN, others	355	26-69.9	Both	25-76 ml/d	3-12	No significant change in lipid profiles	NR	Yes	9
Sun et al. (2015)	Palm oil (fruit of *Elaeis guineensis* Jacq.)/vegetable oils (olive, sunflower, canola,	30/NR	764	16-66	Both	NR	2-16	↑ TC (13.53, 95% CI: 8.89, 18.17), ↑ LDL-C (11.98, 95% CI: 7.73, 16.24), ↑ HDL-C (0.77, 95% CI: 0.38,	Intake: 20 to <30% energy	yes	11

	soybean)							1.54), not change in TG			
Fattore et al. (2014)	Palm oil (fruit of *Elaeis guineensis* Jacq.)/ peanut oil. Sunflower oil, others	51/ HLP, healthy, others	1526	16-70	both	NR	2-16	↓ TC (-14.15, 95% CI: -4.11,-24.19), ↓ LDL-C (-10.83, 95% CI: -0.91,-20.75), ↑ HDL-C (3.73, 95% CI: 1.43, 6.03). No significant change in TG	NR	NR	9

Legend: n, number; **yr**, year; **w**, week; **NR**, not reported; **↓** indicates significant reduction (p value <0.05); **↑** indicates significant elevation (p value <0.05); **TC**, total cholesterol; **LDL-C**, low-density lipoprotein cholesterol; **HDL-C**, high-density lipoprotein cholesterol; **TG**, triglyceride; **HLP**, hyperlipidemia; **T2DM**, type-2 diabetes mellitus; **MetS**, metabolic syndrome; **PCOS**, polycystic ovary syndrome; **CVD**, cardiovascular disease; **NAFLD**, non-alcoholic fatty liver disease; **HTN**, hypertension.

Table 5. Characteristics of meta-analyses investigating the effects of plant proteins on dyslipidemia

Subgroup	Study	Herbal medicine/ Control	meta-analyzed studies (n)/ disorders	Participants			Intervention		Significant main outcome	Effective dose	Quality assessment in meta-analysis	AMSTAR score
				Sample size (n)	Age (yr)	Sex	Dose/ Frequency	Duration (w)				
Soy protein (been of *Glycine max* (L.) Merr.)	Mejia et al. (2019)	Soy protein/ placebo, milk, others	43/postmenopausal, hypercholestrolemic	2607	20-73	both	4.5-93 g/d	4-20	↓ TC: (-6.41, 95% CI: −9.30, −3.52), ↓ LDL-C:(-4.76, 95%CI: -6.71, -2.80).	NR	yes	8
	Anderson and Bush (2011)	Soy protein/non soy diets	43 (20 parallel, 23 crossover studies)/MetS, hypercholesterolemic, DM	3796	NR	both	11.3-62 g/d	4-13	↓ LDL-C: (-8.89, 95%CI: -10.83, -6.96) in parallel studies, ↓ LDL-C: (-6.19, 95%CI: -8.51,	15-30 g/d	yes	11

									-4.25) in crossover studies, Net ↓sig TGs: (-15.06, 95%CI: -22.14, -7.09), net ↑ HDL-C: (1.55, 95%CI: 0.39, 2.71).			
	Harland and Haffner (2008)	Soya protein/ placebo	30/NR	2913	27-67	both	15-40 g/d	4-52	↓ TC: (-8.51, 95%CI: −5.41, −11.21), ↓ LDL-C: (-8.89, 95%CI: −6.19, −11.99), ↓ TG: (-7.09, 95%CI: −0.35,	25g/d	yes	10

									−14.17), no significant change in HDL-C.			
	Anderson et al. (1995)	Soy protein/ control diet	38/ HLP, others	3-127	NR	Both	Mean: 47 g/d	NR	↓ TC: (-23.2, 95% CI: -13.5, -32.9), ↓ LDL-C: (-21.7, 95% CI: -11.2, -31.7), ↓ TG: (-13.3, 95% CI: -0.3, -25.7). No significant change in HDL-C	NR	NR	6
	Zhao et al. (2020)	Plant protein (derived from soybean, etc.)/animal protein	32/NR	1562	18-80	both	NR	4-24	↓ TC (-7.34, 95%CI:-10.05, -4.64),	NR	yes	10

Other Plant proteins									↓ TG: (-6.2, 95%CI: -11.51, -1.77), ↓ LDL-C: (-7.34, 95%CI: -10.05, -5.02), ↑ HDL-C: (1.16, 95%CI: 0.38, 2.32).			
	Li et al. (2017)	Plant protein (derived from soybean, etc.)/animal protein	112/T2DM, HTN, healthy, others	10983	44-59	Both	22-50 g/d	3-208	↓ LDL-C (− 6.18, 95% CI: −7.73, -4.64), ↓ non-HDL-C (-6.96, 95%CI, -8.50,-5.41)	NR	Yes	10

Legend: n, number; **yr**, year; **w**, week; **NR**, not reported; ↓ indicates significant reduction (p value <0.05); ↑ indicates significant elevation (p value <0.05); **TC**, total cholesterol; **LDL-C**, low-density lipoprotein cholesterol; **HDL-C**, high-density lipoprotein cholesterol; **TG**, triglyceride; **MetS**, metabolic syndrome; **DM**, diabetes mellitus; **HLP**, hyperlipidemia; **HTN**, hypertension.

Table 6. Characteristics of meta-analyses investigating the effects of tea and coffee on dyslipidemia

Subgroup	Study	Herbal medicine/ Control	meta-analyzed studies (n)/ disorders	Participants			Intervention		Significant main outcome	Effective dose	Quality assessment	AMSTAR score
				Sample size (n)	Age (yr)	Sex	Dose/ Frequency	Duration (w)				
Coffee (bean of *Coffea arabica* L.)	Morvaridi et al. (2020)	Green coffee/ placebo	27/ healthy, with any disorder	992	18-70	both	100-6000 mg/d	2-24	↓ TG (-9.28, 95% CI: -14.93, -3.63), ↑ HDL-C (1.33, 95%CI: 0.08, 3.072.5). No significant change in TC, LDL-C	<500 mg/d , >4 w for TG, >400 mg/d, ≤4w for HDL-C	yes	10
Tea (leaf of *Camellia sinensis* (L.) Kuntze)	Asbaghi et al. (2020a)	Green tea/ placebo	7/ T2DM	512	50-65	both	0.4-10 g/d	4-16	↓ TG (-12.79, 95% CI: -24.74, -0.84), ↓ TC (-14.25, 95% CI: -23.70, -4.80). No significant change in	>8w and ≥800 mg/d for TG, >8w and <800 mg/d for TC	yes	10

									LDL-C, HDL-C			
	Payab et al. (2020)	Green tea/NR	16/NR	NR	NR	NR	Green tea 300-6000 mg/d, catechin 150-1200 mg/d	8-12	↓ TC (−0.42, 95% CI: −0.76, −0.09), ↓ LDL-C (−0.21, 95% CI: −0.39, −0.03), No significant change in TG, HDL-C.	green tea 6000 mg/d for lipid profiles	yes	10
	Mansour-Ghanaei et al. (2018)	Green tea / placebo, diet+ exercise	6 / NAFLD, NASH	265	26-60	both	500-1080 mg/d	12-25 w	↓ TG (-31.87, 95% CI: -40.62, -23.12), ↓ TC (−27.57, 95% CI: -36.17, -18.98), ↓ LDL-C (-14.15, 95% CI: -23.69, -4.60). No significant changes in	NR	yes	10

									HDL-C.			
	Li et al. (2016)	Tea, tea extract/ water, placebo, others	10/ T2DM	608	20-64.9	NR	150 mg/d - 15 g/d	4-16	No significant change in lipid profiles	NR	Yes	11
	Zhao et al. (2015)	Black tea/placebo	10/healthy, CVD, hypercholesterolemic	411	NR	both	NR	3-12	↓ LDL-C: -4.64 (95%CI: -8.99, -0.30), no sig change in TC, HDL-C	NR	yes	11
	Onakpoya et al. (2014)	Green tea/ placebo, lactose, others	20/ healthy, HTN	1536	6-71	both	250-2034 mg/d	2-24	↓ TC (-5.02, 95% CI: -7.73, -2.70), ↓ LDL-C (-7.34, 95% CI: -11.6, -3.48). No significant Change in HDL-C, TG	NR	yes	10

	Hartley et al. (2013)	Black tea, green tea/placebo	11/healthy, high risk CVD	821	25-75	both	Varied: 1-3 capsule daily, two tablets TDS	12-96	<u>Black tea:</u> ↓ LDL-C: -16.62 (95% CI: -21.65, -11.98). <u>Green tea:</u> ↓ TC: -23.97, (95% CI: -29.77, -17.78), ↓ LDL-C: -24.75, (95% CI: -29.77, -20.11), Both tea: ↓ LDL-C: -18.56, (95% CI: -23.59, -13.53).	NR	yes	11
	Zheng et al. (2011)	Green tea/ placebo, no intervention	14/healthy, overweight, CVD	1136	16-73	both	150-2500 mg/d	4-12	↓ TC: (-7.20 95%CI:	Both < , ≥625 mg/d, ≥12 w for TC, LDL-	yes	10

									-28.19, -26.21), ↓ LDL-C: (-2.19 95%CI: -23.16, -21.21), no significant change in HDL-C.	C, <12w by above doses just for LDL-C		

Legend: n, number; **yr**, year; **w**, week; **NR**, not reported; ↓ indicates significant reduction (p value <0.05); ↑ indicates significant elevation (p value <0.05); **TC**, total cholesterol; **LDL-C**, low-density lipoprotein cholesterol; **HDL-C**, high-density lipoprotein cholesterol; **TG**, triglyceride; **T2DM**, type-2 diabetes mellitus; **NAFLD**, non-alcoholic fatty liver disease; **NASH**, non-alcoholic steatohepatitis; **CVD**, cardiovascular disease; **HTN**, hypertension; **TDS**, 3 times a day.

Table 7. Characteristics of meta-analyses investigating the effects of other herbal medicines on dyslipidemia

subgroup	Study	Herbal medicine/ Control	meta-analyzed studies (n)/ disorders	Participants			Intervention		Significant main outcome	Effective dose	Quality assessment in meta-analysis	AMSTAR score
				Sample size (n)	Age (yr)	Sex	Dose/ Frequency	Duration (w)				
Avocado (fruit of *Persea americana* Mill.)	Mahmassani et al. (2018)	Avocado/ low fat diet, diet without Avocado	18/healthy, DM	481	18-24	both	135-500 g/d	0.02-24	↑ HDL-C: (2.84, 95%CI: 0.18, 5.49), no sig change in TC, TG, LDL-C.	NR	yes	9
	Peou et al. (2016)	Avocado substitute, added to diet/regular diet	10/healthy, dyslipidemia, overweight	229	NR	NR	136-500 g/d	1-12	↓ TC: (-18.80, 95%CI, -24.56, -13.05), ↓ LDL-C: (-16.50 95%CI, -22.91, -10.10), ↓ TG: (-27.20, 95%CI,	NR	yes	9

									-44.41, -29.99), no significant change in HDL-C.			
Berberine	Zhang et al. (2019)	Berberine (from unspecified source)/ placebo, statin	11/ T2DM, CAD, carotid plaque	1386	25-82	NR	0.3-1 g/d	4-96	↓ TG vs. statins (-32.77, 95% CI: -58.46, -6.2), ↓ TGs vs. placebo (-71.74, 95% CI: -142.6, -1.77), ↓ TC vs. placebo (-32.09, 95% CI: -37.51, -27.07), ↓ LDL-C vs. placebo (-23.2, 95% CI: -27.84, -18.95), ↑ HDL-C vs. placebo (3.09, 95%	NR	yes	9

									CI: 14.69, 5.8), no significant change in TC, LDL-C, HDL-C vs. statins			
	Ju et al. (2018)	Berberine (from unspecified source)/ placebo	16/ T2DM, CAD, others	2147	31-83	Both	600-1500 mg/d	8-96	↓ TC (-18.17, 95% CI: -24.74, -11.98), ↓ LDL-C (-14.69, 95% CI: -20.49, -8.50), ↓TG (-24.8, 95%CI: -40.74, -8.85), ↑ HDL-C (3.09, 95%CI: 1.16, 4.64)	NR	Yes	10
	Lan et al. (2015)	Berberine (from unspecified	6/ DM, HLP	623	NR	NR	0.6-2.7 g/d	8-17	↓ TC (-25.52, 95%	NR	Yes	9

		source) ±lifestyle/ placebo, lifestyle							CI: -39.44, -11.98), ↓ TG (-34.54, 95% CI: -52.26, -16.83), ↓ LDL-C (-25.13, 95%CI: -79, -21.65), ↑ HDL-C (2.7, 95% CI: 1.54, 0.38)			
	Dong et al. (2013)	Berberine (from unspecified source)/ placebo, others	11/ T2DM, HLP, others	874	NR	NR	0.5-1.5 g/d	8-52	↓ TC (– 23.59, 95% CI: -32.09, -15.08), ↓ TG (- 44.29, 95% CI: -61.12, -27.46),	NR	Yes	11

									↓ LDL-C (-25.13, 95% CI: -29.39, -20.88), ↑ HDL-C (1.93, 95%CI: 0.77, 3.48)			
Berries	Pourmasoumi et al. (2020)	Cranberry (berry of *Vaccinium macrocarpon* Aiton) / placebo	10/ MetS, healthy, T2DM, others	496	27-62	both	Juice 240-750 ml/d, capsule 240-1500 mg/d	2-17.1	↑ TG by juice (7.82, 95% CI: 0.28, 15.35), No significant change in other lipid profiles.	NR	Yes	10
	Hadi et al. (2019a)	Barberry (berry of *Berberis vulgaris* L.)/ placebo	5/ MetS, NAFLD, T2DM	339	39-56	both	3-5 g/d fruit, 600-750 mg/d extract, 200 ml/d	6-12	↓ TC: (-23.58, 95% CI: -31.00, -16.16), ↓ TG: (-29.16, 95% CI: -42.91,	NR	yes	11

									-15.41), ↓ LDL-C: (-13.75, 95% CI: -19.31, -8.20), No significant change in HDL-C.			
	Rahmani et al. (2019a)	Chokeberry (berry of *Aronia arbutifolia* (L.) Pers.) / placebo	7 /Met S, healthy, HTN, others	286	16-66	both	100-500 ml or mg/d	4-24	↑ HDL-C (1.48, 95% CI: 1.29, 1.68), ↓ TC (−7.18, 95% CI: −13.90, −0.46), ↓ LDL-C (−5.84, 95% CI: −6.91, −4.77).	300 mg/d for TG, <10w for TC, LDL-C	yes	10
	Phimarn et al. (2017)	White mulberry (berry of *Morus alba* L.)/ placebo	13/healthy, DM, DLP	436	NR	NR	3-1200 mg/d	0.3-25.7	No significant change in lipid profiles	NA	yes	9
	Huang et al. (2016)	Berries (berry of cranberry,	22/ healthy, T2DM, others	1251	21.5-65.5	both	NR	2-24	↓ LDL-C: (-8.12, 95% CI: -13.15,	NR	yes	9

		etc.)/ placebo							-2.71). No significant change in TC, TG, HDL-C.			
Black seed (seed of *Nigella sativa* L.)	Hallajzadeh et al. (2020)	Black seed / placebo	50/ HTN, T2DM, others	3679	26-72	both	0.2-3 g/d Extract, 1.5-5 ml/d oil	2-48	↓TC: (-16.80, 95% CI: −21.04, -12.55), ↓ TG: (-15.73, 95% CI: −20.77, -10.69), ↓ LDL-C: (-18.45, 95% CI: −22.44, -14.94), ↑ HDL-C: (1.93, 95% CI: 1.23, 2.64)	NR	yes	11
	Payab et al. (2020)	Black seed/ NR	4/NR	NR	NR	NR	1500-3000 mg/d	6-8	↓TG (-1.67, 95%CI: −2.54, −0.79), ↓ LDL-C (−0.85,	1000 mg/d	yes	10

									95%CI: −1.7, −0.03). no significant change in TC, HDL-C			
	Daryabeygi-Khotbehsara et al. (2017)	Black seed/ metformin, atorvastatin, placebo	7/ T2DM	505	47-56	NR	0.5 -2 g/d powder, 1-5 ml/d oil	8-48	↓ TC (-22.99, 95% CI: -32.16, -13.83), ↓ LDL-C (-22.38, 95% CI: -33.60, -11.15), ↓ TG by oil(-14.8, 95%CI: -23.1, -6.5). No significant change HDL-C	NR	yes	10
	Sahebkar et al. (2016a)	Black seed/ placebo	17/ MetS, HTN, others	1185	29-59	both	Powder 1-8 g/d, Oil 5 ml/d, Oil 1-3	4-12	↓TC (-15.65, 95%CI: −24.67, −6.63), ↓	NR	yes	8

							g/d		LDL-C (14.10, 95%CI: −19.32, −8.88), ↓TG (−20.64,95% CI: −30.29, −11.00). No significant change in HDL-C			
Cinnamon (bark of *Cinnamomum verum* J.Presl)	Heydarpour et al. (2020)	cinnamon/ placebo	5/ PCOS, obese	448	26-31	female	336-1500 mg/d	6-24	↓ LDL-C (-14.33, 95% CI: -19.87, -8.80), ↓ TC (-12.10, 95% CI: -18.21, -5.98), ↓ TG (-13.05, 95% CI: -24.11, -1.99), ↑ HDL-C (3.20, 95% CI: 1.74,	NR	yes	10

									4.65).			
	Ainehchi et al. (2019)	Cinnamon, alone, mixture/ placebo	13/PCOS	668	12.6-42	Fem ale	1-3 g/d	8-48	↓ TC : (-14.60, 95% CI: -22.93, -6.26), ↓ LDL-C: (-16.58, 95% CI: -23.91, -9.24), ↓ TG: (-17.97, 95% CI: -30.51, -5.43). no significant change for HDL-C.	NR	yes	11
	Allen et al. (2013)	cinnamon/ placebo	10/ T2DM	543	42-71	both	0.12-6 g/d	4-18	↓ TC: (-15.60, 95% CI: -29.76, -1.44), ↓ LDL-C: (–9.42, 95%CI: -17.21,	NR	NR	8

									-1.63), ↓ TG: (−29.59, 95%CI: -48.27, -10.91), ↑ HDL-C; (1.66, 95%CI: 1.09, 2.24).			
Cumin (seed of *Cuminum cyminum* L.)	Hadi et al. (2018)	Cumin / food, placebo	6 / T2DM, NASH, obese	376	37-47	both	25mg-3g/d	8-24	↓ TC (−10.90, 95%, CI: −21.39, −0.42), ↓ LDL-C (−6.94, 95% CI: −11.53, −2.35), ↑ HDL-C (3.35, 95% CI:1.58, 5.12), no significant changes in TG	NR	yes	11
	Jafarnejad et al. (2018)	Cumin/ placebo	7/ T2DM, overweight	412	18-60	both	25-5000 mg/d	8-24	↓ TG: (-21.23, 95%CI: −37.64,	NR	yes	9

									−4.82), ↑ HDL-C: (4.16, 95% CI: 3.30, 5.01). No significant change in TC, LDL-C.			
Fenugreek (seed of *Trigonella foenum-graecum* L.)	Askarpour et al. (2020)	Fenugreek / placebo	12/ T2DM, HLP, healthy	560	22-70	Both	Powder 5 -100 g/d, hydro-alcoholic extract 0.588-1.176 g/d	2-162	↓ TC: (-9.37, 95% CI: -15.42, -3.32), ↓ TG: (-13.78, 95% CI: -26.64, -0.92), ↓ LDL-C: (-6.59, 95% CI: -13.04, -0.14), ↑ HDL-C: (3.501, 95% CI: 1.31, 5.69).	>10g/d for >8w	yes	10
	Heshmat-Ghahdarij	Fenugreek seed,	15/ healthy,	672	18-80	Both	NR	2h-3y	↓ TC: (−43.7, 95%	NR	yes	9

	ani et al. (2020)	leaves, others/ placebo, uncontrolled	T2DM, HLP						CI: −72.7, -14.30), ↓ LDL-C: (-48.72, 95%CI: -80.82, -16.62), ↓ TG: (-94.77, 95%CI: -161.2, -29.23), ↑ HDL-C: (27.07, 95%CI: 2.70, 51.82)			
	Khodamoradi et al. (2020)	Fenugreek (powder, hydroalcohol)/ placebo	14/ T2DM, obese, healthy, others	20-154	25-50	both	0.5-30 g/d	1-25.7	↓ TC (-9.13, 95% CI: -13.83, -4.43), ↓ LDL-C (-11.11, 95% CI: -20.32,	NR	yes	11

									-1.90). No significant change in TG, HDL-C.			
	Gong et al. (2016)	Fenugreek/ diet modulation , exercise, others	10/ T2DM, prediabetes	1173	30-72	NR	1-100 g/d	1-144	↓ TC (-11.6, 95% CI: -21.65, -1.16). No significant change in TG, LDL-C, HDL-C	NR	Yes	9
Garlic (bulb of *Allium sativum* L.)	Shabani et. al (2019)	Garlic / placebo	33/ HLP, T2DM	1273	20-71	both	0.5-20 g/d	0.28 – 25.7	↓ TC: (-16.87, 95% CI: −21.01, −12.73), ↓ LDL-C: (-9.65, 95% CI: −15.07, −4.23), ↓ TG: (-12.44, 95% CI: −18.19, −6.69), ↑ HDL-C:	NR	Yes	10

									(3.19, 95% CI: 1.85, 4.53)			
	Sun et al. (2018)	Garlic/ placebo	14/ NR	1093	33-63	both	0.3-20 g/d	4-40	↓ TC: (-48.72, 95% CI: –71.93, -25.52), ↓ LDL-C: (-41.38, 95% CI: -64.58, -18.17), ↑ HDL-C: (19.33, 95% CI: 2.32, 36.35). No significant change in TG	NR	Yes	8
	Ried et al. (2013)	Garlic/ placebo	39/ HLP, CAD, others	2298	20-60	NR	600-5600 mg/d powder, 9-18 mg/d oil, 1000-7200 mg/d extract, 4-10 g/d	2-48	↓ TC: (-15.25, 95% CI: -20.72, -9.78), ↓ LDL-C: (-6.41, 95% CI: -11.77,	NR	Yes	9

							raw		-1.05), ↑ HDL-C: (1.49, 95% CI: 0.19, 2.79). No significant change in TG.			
	Silagy et al. (1994)	Garlic/ placebo	16/ CHD, HLP	952	NR	both	0.6-10 g/d	4-40	↓ TC: (-29.77, 95% CI: -25.13, -34.41), ↓ TG: (27.46, 95% CI: -12.4, -43.4). No significant change in HDL-C	600-900 mg/d	Yes	7
Ginger (rhizome of *Zingiber officinale* Roscoe)	Maharlouei et al. (2019)	Ginger / placebo	14/ obese, T2DM, others	473	18-60	both	500-3000 mg/d	2-12	↑ HDL-C: (15.46, 95% CI: 3.86, 27.07). No significant change in TG, TC, LDL-C	< 1000 mg/d all effects	yes	11

	Pourmasoumi et al. (2018)	Ginger/ corn, wheat flour, others	12/ obese, T2DM, others	586	24-57	both	0.5-4 g/d	4.28-12.85	↓ TG: (-17.59, 95% CI: -29.32, -5.87), ↓ LDL-C: (-4.90, 95% CI: -22.30, -6.17). No significant change in TC, HDL-C.	≤2 g/day	yes	11
	Jafarnejad et al. (2017)	Ginger/ placebo	9/ T2DM, HLP	609	35-55	NR	0.5-3 g/d	4-12	↓ TG: (-8.84, 95% CI: -11.95, -5.73), ↓ TC: (-4.42, 95% CI: -8.70, -0.13), ↑ HDL-C: (2.87, 95%CI: 0.88, 4.86).	NR	yes	9
	Mazidi et al. (2016)	Ginger/ placebo	9/DM, obese	479	19-79	both	1-3 g/d	8-12	↑ HDL-C: (1.16, 95%CI: 0.52, 1.08),	NR	yes	11

									↓ TG: (-1.63, 95%CI: -3.10, -0.17).			
Ginseng (root of *Panax quinquefolius* L.)	Ziaei et al. (2020)	Ginseng / placebo	27/ T2DM, healthy, MetS, others	1839	21-64	both	0.5-20 g/d	3-32	No significant change in lipid profiles, but ↓TC, TG, LDL-C in sub-group analysis	>1500 mg/d, ≥12w for TC, TG, >1500 mg/d for LDL-C, <1500 mg/d for HDL-C	yes	10
	Hernandez-Garcia et al. (2019)	Ginseng/ placebo	18/ MetS, healthy, others	1045	18-73	Both	0.2-20 g/d	2-12	↓ TC: (-2.3, 95%CI: -3.79, -0.8), ↓ LDL–C: (-1.47, 95%CI: -1.90, -1.05), No	NR	Yes	9

									significant change in HDL-C, TG.			
	Gui et al. (2016)	Ginseng/ placebo	8/ T2DM, obese, others	390	34-74	both	0.96-8 g/d	4-20	↓ TC: (-37.51, 95% CI: -59.55, -15.47), ↓ TG: (-59.34, 95% CI: -84.15, -34.54), ↓ LDL-C: (-28.23, 95%CI: -49.5, -7.35). No significant change in HDL-C	NR	yes	10
Grape seed (seed of *Vitis vinifera* L.)	Asbaghi et al. (2020b)	Grape seed/ placebo	15/ healthy, HTN, MetS, CVD, others	9-50	14-72	both	100-2000 mg/d	4-25	↓ TC: (−6.03, 95% CI: −9.71, −2.35), ↓ LDL-C: (−4.97, 95% CI: −8.37, −1.57), ↓	NR	yes	10

									TG: (−6.55, 95% CI: −9.28, −3.83). No sig, change in HDL-C.			
	Feringa et al. (2011)	Grape seed/diet, lifestyle modification	9/healthy, DM, MetS	390	18-70	both	150-2000 mg/d	2-24	No significant changes in lipid profiles	NR	yes	10
Sour tea (leaf of *Hibiscus sabdariffa* L.)	Bule et al. (2020)	Sour tea/ placebo	8/ MetS, T2DM	492	14-53	both	0.03-10 g/d	0.85-12.85	↓ LDL-C (−7.84, 95% CI: −14.33, −1.35). No significant change in TC, HDL-C, TG.	NR	yes	9
	Najafpour Boushehri et al. (2020)	Sour tea/ placebo	7/ MetS, HTN, healthy, others	362	Mean: 4418-65	both	100-1350 mg/d	4-12.8	No significant change in lipid profiles	NR	yes	9
	Zhang et al. (2020)	sour tea/ placebo, others	9/ T2DM, MetS, others	503	NR	NR	0.1-9 g/d	2-12	↓ TC (−14.66, 95% CI: −18.22,	NR	yes	10

									−11.10), ↓ LDL-C (−9.46, 95% CI: −14.93, −3.99), ↓ HDL-C (−1.93, 95% CI: −2.73, −1.14). No significant change in TG			
	Aziz et al. (2013)	Sour tea. / placebo, black tea, diet	6/ MetS, HTN, others	474	NR	NR	30-6000 mg/d	4-12	No significant change in lipid profiles.	NR	yes	10
Pomegranate (fruit of *Punica granatum* L.)	Jandari et al. (2020)	Pomegranate juice, seed oil, others / water, placebo	7/ T2DM	350	39-62	both	Juice 200-250 ml/d, seed oil 2-3 g/d	6-12	No significant change in lipid profiles	NR	yes	9
	Sahebkar et al. (2016c)	Pomegranate / placebo	12 / HTN, HLP, obese, healthy	545	22-80	both	NR	1.5-48	No significant change in lipid profiles	NR	yes	8
Saffron (flower of	Taherifard et al.	Crocin/	8 / healthy, MetS, CAD,	442	18-60	both	30-100	4-12	↓ TC	≥30 mg for FBS,	Yes	10

***Crocus sativus* L.)**	(2020)	placebo	others				mg/d		(-4.64, 95% CI: -8.19, -1.09). No significant change in other lipids	<12w, ≥30 mg for TC		
	Asbaghi et al. (2019)	Saffron/ placebo	6 / T2DM, MetS, CAD, others	291	35-64	both	30 – 1000 mg/d	4-12	↓ TG: (-8.93, 95% CI: -16.49, -1.37), ↓ TC: (-5.72, 95%CI: -11.10, -0.34), ↑ HDL-C: (2.7, 95% CI: 0.22, 5.18). No significant change in LDL-C.	Equal 30 mg/d for HDL-C	yes	9

	Pourmasoumi et al. (2019)	Saffron, crocin/placebo, non-active agents	11 / T2DM, MetS, CAD, others	622	31-67	both	5-353 mg/d	4-12.8	No significant change in lipid profiles	NR	yes	10
	Rahmani et al. (2019b)	Saffron, crocin / placebo	14 / T2DM, MetS, healthy, others	794	27-57	NR	5-1000 mg/d	1-12	↓ TC (−6.36, 95% CI: −10.58, −2.18), ↓ TG (−5.37, 95% CI: −10.25, −0.48), ↑ HDL-C (0.91, 95% CI: −0.13, 1.96). No significant change in LDL-C	NR	yes	9
Others	Jang et al. (2020)	Pepper (seed of *Capsicum annuum* L.) / placebo	5/ healthy, obese, others	115	18-74	both	1.35-34.5 g/d	4-12	↓ LDL-C: (-15.08, 95% CI: -27.84, -2.71). change in TC, HDL-C, TGs.	NR	yes	11
	Shekarchizadeh-	Cardamom (seed of	5/ T2DM, IHD, NAFLD,	361	45-60	both	3 g/d	8-12	↓ TG (−20.55,	NR	yes	10

	Esfahani et al. (2020)	*Elettaria cardamomum* (L.) Maton)/ placebo	others						95% CI: −32.48, −8.63). No significant change in other lipid profiles			
	Hadi et al. (2019b)	Purslane (leaf of *Portulaca oleracea* L.) / placebo, others	6 / T2DM, NAFLD, MetS	352	39-64	both	powder 7.5-10 g/d, capsule 0.06-0.18 mg/d	5-16	↓ TG (−19.16, 95% CI: −38.17, −0.15). No significant change in TC, LDL-C, HDL-C	>1.5 g/day For TC, TG, LDL-C	yes	11
	Lee et al. (2019)	Dika nut (seed of *Irvingia gabonensis* (Aubry-Lecomte ex O'Rorke) Baill.)/ placebo	5/ MetS, obese, others	214	19-60	both	300-1050 mg/d	4-13	↓ TC: (-24.01, 95% CI: -37.53, -10.50) ↓ LDL-C: (-27.08, 95% CI: -38.12, -16.05), ↓ TG:	NR	yes	10

									(-11.76, 95% CI: -23.82, 0.30), ↑ HDL-C: (10.16, 95% CI: 6.84, 13.49).			
	Mohammadi et al. (2019a)	Silymarin (flower of *Silybum marianum* (L.) Gaertn.)/ placebo	7 / T2DM	370	45-62	both	200-600 mg/d	6-48	↓ LDL-C (-23.55, 95% CI: -42.58, -4.53), ↑ HDL-C (7.06, 95% CI: 2.20, 11.92). No significant changes in TC, TGs	NR	yes	10
	Akbari-Fakhrabadi et al. (2018)	Sumac (flower of *Rhus Coriaria* L.) / placebo	4 / HLP, T2DM	223	14-45	both	1-3 g/d	4-12	No significant change in lipid profiles	NA	yes	8
	Jamshidi et al. (2018)	Holy basil (leaf of *Ocimum tenuiflorum* L.)/ sucrose,	6 / healthy, T2DM, MetS, obese	269	17-65	both	300 mg-2.5 g/d	4-12	No significant changes in lipid profiles	NR	yes	10

		water, no active agent										
	Sahebkar et al. (2018)	Artichoke (flower bud of *Cynara scolymus* L.)/ placebo	9 / HLP, T2DM, NASH, HTN, others	702	17-62	Both	500-2700 mg/d	5-12	↓ TC (-17.6, 95%CI: -22.0, -13.3), ↓ LDL-C (-14.9, 95%CI: -20.4, -9.5), ↓ TG(-9.2, 95%CI: -16.2,-2.1). No significant change in HDL-C	NR	yes	9
	Teoh et al. (2018)	Chia seed (seed of *Salvia hispanica* L.)/placebo , oat, inulin	14/DM, MetS	526	18-75	both	4-50 g/d	0.14-24	No significant change in lipid profiles	NR	yes	9

	Sawangjit et al. (2017)	Veld grape (whole of *Cissus quadrangularis* L.)/ placebo, flavonoid	9/bone fracture, obese, hemorrhoid	1108	12-70	both	500-1500 mg/d	1-10	↓ LDL-C: (-14.43, 95%CI:-20.06, -8.80), ↓ TG:(-37.50, 95%CI:-48.71, -26.29), ↓ TC: (-50.50, 95%CI:-70.97, -30.04).	NR	yes	11
	Serban et al. (2016)	Spirulina (whole of *Arthrospira platensis*)/ placebo	7/ T2DM, IHD, others	522	2-60	Both	1-10 g/d	8-48	↓ TC: (-46.76, 95% CI: - 67.31, -26.22), ↓ LDL-C: (-41.32, 95% CI: -60.62, -22.03), ↓ TG: (-44.23, 95% CI: -50.22, -38.24), ↑ HDL-C (6.06, 95% CI: 2.37,	NR	yes	10

									9.76)			
	Zhang et al. (2016b)	Aloe vera (leaf of *Aloe barbadensis*.)/placebo	5/DM, prediabetes	415	NR	both	1-2.8 g/d	6-12	↓ TC: (-16.94, 95% CI: -23.39, -10.50), ↓ TG: (-43.92, 95% CI: -66.33, -21.51), ↓ LDL-C: (-13.30, 95% CI: -17.19, -9.41), ↑ HDL-C: (2.67, 95%CI: 0.11, 5.23).	NR	yes	9
	Onakpoya et al. (2015)	cactus pear (fruit of *Opuntia ficus-indica* (L.) Mill.)/ placebo, nopal	4/obese, MetS, prediabetes	314	20-60	NR	NR	8-96	↓ TC: (-4.77, 95%CI: -9.23, -0.3), no significant change in other lipids	NR	yes	10
	Cheng et	Milkvetch	16/ placebo,	977	43-75	both	20-250	4-40	↓ TG:	NR	yes	10

	al. (2013)	(flower of *Astragalus propinquus* Schischkin) / placebo, others	others				ml/d Decoction 1.5-6 g/d capsule		(-31.89, 95% CI: -53.14, -10.63). No significant change in TC.			

Legend: n, number; **yr**, year; **w**, week; **NR**, not reported; **↓** indicates significant reduction (p value <0.05); **↑** indicates significant elevation (p value <0.05); **TC**, total cholesterol; **LDL-C**, low-density lipoprotein cholesterol; **HDL-C**, high-density lipoprotein cholesterol; **TG**, triglyceride; **DM**, diabetes mellitus; **MetS**, metabolic syndrome; **T2DM**, type-2 diabetes mellitus; **NAFLD**, non-alcoholic fatty liver disease; **CAD**, coronary artery disease; **DLP**, dyslipidemia; **HLP**, hyperlipidemia; **PCOS**, polycystic ovary syndrome; **NASH**, non-alcoholic steatohepatitis; **CHD**, congestive heart disease; **HTN**, hypertension; **CVD**, cardiovascular disease; **IHD**, ischemic heart disease.

Table 8. Summary of effects

Group	Effect	TC	LDL-C	HDL-C	TG
polyphenolic compounds	Increasing	-	1*	12	-
	Decreasing	16	17	1	11
	Neutral	10	8	17	13
nuts	Increasing	-	-	1	-
	Decreasing	8	8	1	6
	Neutral	2	2	9	5
Phytosterols	Increasing	-	-	1	-
	Decreasing	4	10	-	3
	Neutral	2	1	5	3
Vegetable oils	Increasing	1	3	8	-
	Decreasing	7	8	-	3
	Neutral	3	2	5	8
Plant proteins	Increasing	-	-	2	-
	Decreasing	4	6	-	4
	Neutral	-	-	2	-
Tea and coffee	Increasing	-	-	1	-
	Decreasing	6	6	-	3
	Neutral	3	3	7	3
Other herbal medicines	Increasing	-	-	25	1
	Decreasing	37	36	1	34
	Neutral	22	20	35	24

*** number of studies with this effect**

Legend: TC, total cholesterol; **LDL-C**, low-density lipoprotein cholesterol; **HDL-C**, high-density lipoprotein cholesterol; **TG**, triglyceride