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The effect of chamomile intake on lipid profile in patients with diabetes and related metabolic disorders. A systematic review and meta-analysis of randomized controlled trials

ABSTRACT

Background. The current study sought to provide a robust examination of the evidence for the efficacy of chamomile on lipid profile in diabetics.

Methods. PubMed, Scopus, Web of Science, and Cochrane Library were systematically searched to find randomized controlled trials (RCTs) assessing the impact of chamomile intake on lipid profile, up to 17 August 2020. To obtain weighted mean difference (WMD) and 95% confidence intervals (CIs), a random-effects model was applied. A random-effects meta-regression was ran to detect the potential source of inter-study heterogeneity. Publication bias was checked using Begg's and Egger's tests.

Results. Four trials, comprising 254 participants, were included to the meta-analysis. In comparison with controls, total cholesterol (TC) (WMD = –22.40, 95% CI = = [–37.85, –6.96], P = 0.004, I^2 = 59.1%) was significantly decreased in the groups receiving chamomile. In contrast, serum triglycerides (TG) (WMD = –17.47, 95% CI = [–44.44, 9.50], P = 0.20, I^2 = 74.3%), high density lipoproteins cholesterol (HDL-C) (WMD = 0.63, 95% CI = [–1.38, 2.64], P = 0.53, I^2 = 0.0%), and low density lipoprotein cholesterol (LDL-C) (WMD = –10.94, 95% CI = [–23.71, 1.81], P = 0.09, I^2 = 71.3%) were not significantly altered by chamomile consumption.

Conclusion. The present meta-analysis demonstrates that chamomile can elicit significant reductions in serum TC, but not TG, HDL-C and LDL-C in diabetics. Moreover, further large-scale and well-designed RCTs are required to confirm the veracity of these findings. (Clin Diabetol 2021; 10; 4: 375–381)

Key words: chamomile, lipid profile, diabetes, review, meta-analysis

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Background

Diabetes mellitus (DM) is a group of metabolic disorders characterized by high blood glucose level over a prolonged period [1, 2] and causes due to insufficient

insulin secretion or insulin resistance or both [3]. Nowadays, DM has become a global health problem all over the world, the number of diabetic patients was about 171 million in 2000 and is predicted to reach 366 million by 2030 [4]. Chronic diabetes leads to the several complications such as diabetic ketoacidosis (DKA), hyperosmolar coma, chronic kidney diseases (CKD), neuropathy and cardiovascular disorders, but the most common of them is hyperlipidemia [5–8]. It is suggested that poor glycemic control disrupts the function of fat metabolism enzymes [9] and stress oxidation increases the lipid oxidation that cause macrovascular and microvascular diseases [10]. Hence, health care systems is trying to find an urgent strategy to prevent diabetes all over the world. One of these strategies is to use medicines such as atorvastatin [11], that might have some ramifications including muscle cramps, diarrhea and memory loss [12]. Therefore, in cases who have statin intolerance, it is suggested to use traditional medicine to control diabetes risk factors [13, 14].

Chamomile, also termed "betmatricaria chamomillaor matricariarecutita", is one of the most popular herbal drinks in the world [15]. It is known for its wide range of therapeutics effects, such as anti-inflammatory, antioxidant, anticancer, antimicrobial, antidiabetics and sedative features [16]. The main components of chamomile are flavonoids, sesquiterpenes, coumarins and polyacetylenes, in addition to containing numerous other chemical constituents with pharmacological properties [17]. Those compounds recuperate the sensitivity of insulin, which in turn improves lipid profile through the following mechanisms. Lipoprotein lipase is an insulin sensitive enzyme, which is primarily responsible for triglyceride (TG) hydrolysis, so by improving insulin sensitivity, the function of this enzyme improves, and serum TG levels decrease. Another involved mechanism can be contributed to peroxisome proliferator-activated receptors (PPARs). PPARs, by acting as lipid sensors, are major metabolic regulators in the body and control every aspect of fatty acid metabolism. The expression of this gene decreases serum TG, increases high- density- lipoprotein-cholesterol (HDL-C) [18, 19]. Therefore, in the present study we sought to illuminate the effect of chamomile on the lipid profile in diabetics by conducting the first systematic review and meta-analysis of randomized controlled trials.

Methods

The study is conducted based on the guidance of Cochrane Handbook [20] and the review protocol registered with PROSPERO (CRD42020213991).

Search strategy

Two researchers independently undertook the process of the systematic search in the online databases, PubMed, Scopus, Web of Science, and Cochrane Library, to detect relevant articles, published up to 17 August 2020, that assessed the efficacy of chamomile intake on lipid profile in adults. The search strategy was refined by consulting with an epidemiology expert and designed as a combination of the search terms shown in supplementary material. To augment the sensitivity of our search strategy, the wild-card term "*" was included and the reference lists of relevant articles or reviews and Google Scholar were hand-scanned. Any doubts were resolved through a discussion with the corresponding author.

Inclusion and exclusion criteria

Two independent reviewers assessed the detected studies against the following inclusion criteria: 1) randomized controlled trials (RCTs) with parallel design; and 2) studies that assessed the effects of chamomile on lipid profile (TC or/and TG or/and HDL-C or/and LDL-C) in diabetic patients. Studies were excluded if they were animal-designed, reviews, conference abstracts, editorials, observational-designed, book chapters, or brief reports and not randomized. In addition, papers that lacked any essential data, for example, non-extractable or unconvertable data, studies without a suitable control group, and trials with combined supplementation of clinical effective nutrients or/and medicines besides chamomile, which were not comparable between intervention and control group, were removed. If any disagreements arose, consensus was achieved through discussion with the corresponding author.

Data extraction

After selecting the eligible studies for the meta-analysis, two authors extracted the following data: first authors' last name, publication date, country, study design, participants' characteristics, a dosage of chamomile, control type, intervention duration, quality of trials, mean changes and standard deviations (SDs) for each outcomes in pre-treatment and post-treatment. In instances standard error (SE) or 95% confidence intervals (CIs) were reported instead of SD, the appropriate formulas were used to convert them to SD. If needed, e-mails were sent to the corresponding author of the related articles. The Cochrane Risk of Bias Tool [21] was used, by two independent reviewers, to qualify the included RCTs, and explore the potential risk of bias in the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other biases. "Low", "high" or "unclear" terms were used to score each item. RevMan V5.3 was executed to draw

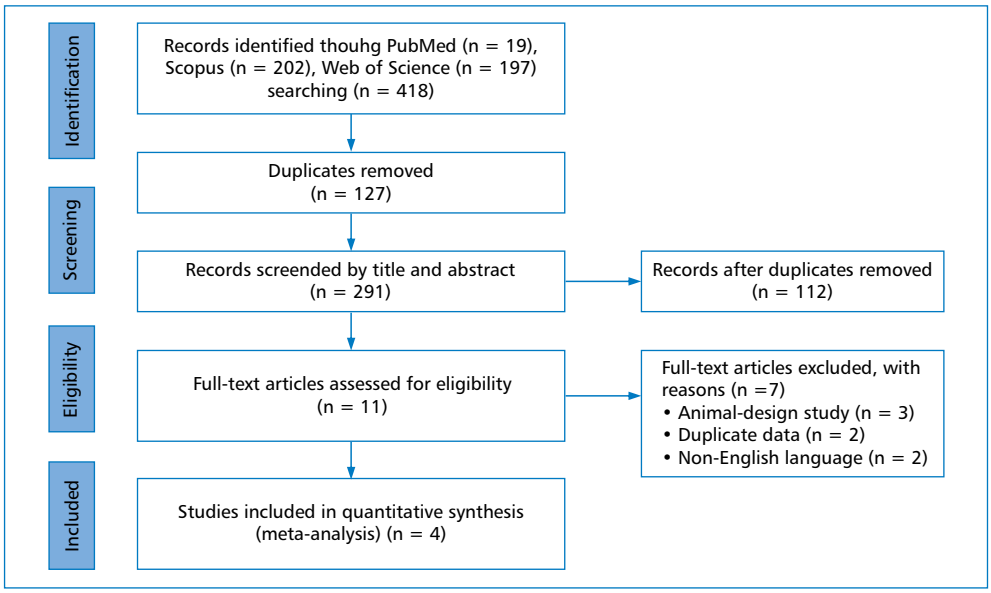

Figure 1. Flow diagram of the study selection process

any relevant graph. Corresponding author resolved any discrepancy between authors.

Statistical analysis

Mean changes of the interested outcomes and the relevant SD were obtained by executing the following formulas, respectively: [mean-post − mean-baseline], SD = $\sqrt{([SD^2\text{-baseline} + SD^2\text{-post}] - [2r \times SD\text{-baseline} \times SD\text{-post}])}$, assuming correlation coefficient (r) as 0.5 [22], SD = SE/$\sqrt{n}$.

The meta-analysis was conducted using STATA software v13 (Stata Corp.). A random-effects model was applied to pool weighted mean differences (WMD) and corresponding 95% confidence intervals (CIs) [22]. The statistical heterogeneity among the studies was assessed using Cochrane Q test (I^2 statistic (high ≥ 50%, low < 50%) and p-value) [22]. In presence of high statistical heterogeneity among studies, random-effects meta-regression was done to investigate the potential sources. Sensitivity analysis was conducted to assess the impact of each study on the pooled results by removing one study, consecutively [22]. Potential publication bias was evaluated by applying Begg's and Egger's tests [22, 23]. A p-value < 0.05 was accepted as statistically significant.

Results

Systematic review

Figure 1 presents the search process; briefly, 418 references were identified through our systematic search, of which 127 were omitted as duplicates. The remaining papers were screened by title and abstract, resulting in the exclusion of another 280. Finally, 11 full-text articles were assessed for eligibility, and four RCTs were selected for meta-analysis [24–27].

Table 1 outlines demographic characteristics of the included studies, which were conducted in Iran and published between 2015– 2018. A total of 252 participants, aged between 24.38 and 55.33 years, were pooled in the meta-analysis. Moreover, the duration of the chamomile intervention was 4 [25], 8 [27], and 12 [24, 26] weeks, respectively. All of the included trials were graded as 'Good' in quality (Table 2).

Findings from meta-analysis

The results of the meta-analysis are shown in Table 3. Pooled effects of the included trials demonstrated that chamomile yielded a significant reduction in serum TC (WMD = –22.40, 95% CI = [–37.85, –6.96], P = 0.004, I^2 = 59.1%), in comparison with controls. In contrast, the meta-analysis indicated that chamomile intake did not cause a statistically significant change in the concentration of serum TG (WMD = –17.47, 95% CI = [–44.44, 9.50], P = 0.20, I^2 = 74.3%), HDL-C (WMD = 0.63, 95% CI = [–1.38, 2.64], p = 0.53, I^2 = 0.0%), and LDL-C (WMD = –10.94, 95% CI = [–23.71, 1.81], P = 0.09, I^2 = 71.3%).

Publication bias and sensitivity analysis

As shown in Table 3, none of the outcomes demonstrated a publication bias based on both Begg's and Egger's test. In addition, sensitivity analysis indicated that pooled results were not affected by removing any individual trial.

Table 1. Study characteristics of the included RCTs

First author	Publication year	Country	Population	Sample size	Mean age (year)	Dose (g/day)	Intervention type	Intervention duration (weeks)	Results
Rafraf et al.	2015	Iran	T2D	64	50.19	9	Water	8	↓TC, ↓TG, ↓LDL-C
Heidary et al.	2018	Iran	PCOS	80	24.38	1.11	Capsule	12	*
Kaseb et al.	2018	Iran	T2D	44	55.33	20	Water	4	↓TC, ↓LDL-C
Kermanian et al.	2018	Iran	Depressed T2D	64	51.95	7.5	Water	12	*

↓ A significant reduction; * No significant change observed; TC: total cholesterol; TG: triglycerides; LDL-C: low density lipoprotein-cholesterol; T2D: type 2 diabetes; PCOS: poly cystic ovary

Table 2. The results of the quality assessment using Cochrane Collaboration Tool

Study	Sequence generation	Allocation concealment	Blinding	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Overall quality
Rafraf et al.	+	+	+	?	+	+	Good
Heidary et al.	+	+	+	?	+	+	Good
Kaseb et al.	+	+	+	?	+	+	Good
Kermanian et al.	+	+	+	?	+	+	Good

+ low risk; − high risk; ? unclear

Meta-regression

The meta-regression analysis was conducted based on the age of participants, dose of chamomile, and intervention duration, to discern the possible sources of statistical heterogeneity across studies; however, we were unable to detect the potential sources (Table 3).

Discussion

To the best of our knowledge, the present study is the first comprehensive meta-analysis evaluating the effects of chamomile on lipid profile. In line with evidence from Aljubouri *et al.* [28] and Al-Bayati [29], the present meta-analysis showed that TC was significantly ameliorated following chamomile consumption, but did not yield a statistically meaningful change in the concentration of serum TG, HDL-C, and LDL-C. The impact of chamomile extract on the serum lipid profile in diabetic animals has been already investigated [30, 31]. For instance, Najla *et al.* [32] indicated that alterations in the serum levels of HDL-C, TG, TC, and LDL-C were substantially different from those in the control groups, following chamomile extract administration in diabetic rats. In addition, chamomile tea consumption in patients with T2DM yielded a substantial reduction in serum TG, TC, and LDL-C levels after 8 weeks of treatment [27], and similar impacts in obese mice were reported [33]. It has been suggested that the antihyperlipidemic activity of chamomile may be due to its potential properties including the high concentration essential oil [34], the presence of chlorogenic acid in the chamomile flowers [35, 36], modulation of peroxisome proliferator-activated receptor (PPARs) [37], as well as its antioxidant action [38, 39]. Regarding PCOS, chamomile improves lipid oxidation via decreasing LDL-C and TG, and increasing serum HDL-C through its phytoestrogen compounds [24].

PPARα ligands [40] and PPARα activation have been demonstrated to up-regulate genes expression that participate in lipoprotein and lipid metabolism, in addition to oxidation of fatty acids in the skeletal muscle [41]. Indeed, in Weidner *et al.* [33], this putative role was explored, and the results indicated that ethanolic *Matricaria chamomilla L.* flowers extract mediated gene expression of PPARα target genes.

Table 3. The summary of meta-analysis, publication bias, sensitivity analysis and meta-regression analysis

Outcome	Study	WMD (95% CI) (random-effects)	Overall p	Heterogeneity (I^2/p)	Publication bias (p)		Sensitivity analysis (WMD [95% CI])	Meta-regression (random-effects)		
					Begg test	Egger test		Age [year] (p)	Dose [g] (p)	Duration [week] (p)
TC	Rafraf *et al.*	–21.31 (–30.13, –12.48)	0.004	59.1%/0.08	0.6	0.92	–23.5 (–57.63, 10.62)	0.53	0.30	0.27
	Kaseb *et al.*	–40.99 (-63.12, –18.85)					–17.11 (–30.40, –3.82)			
	Kermanian *et al.*	–6.16 (–27.86, 15.54)					–28.42 (–46.95, –9.89)			
	Pooled estimate	–22.40 (–37.85, –6.96)					–22.4 (–37.84, –6.96)			
TG	Rafraf *et al.*	–45.74 (–61.60, –29.87)	0.20	74.3%/0.009	1	0.19	–3.83 (–21.97, 14.31)	0.64	0.96	0.79
	Heidary *et al.*	–1.86 (–27.02, 23.30)					–23.43 (–54.46, 7.59)			
	Kaseb *et al.*	–5.72 (–37.51, 26.07)					–20.67 (–54.34, 13.00)			
	Kermanian *et al.*	–6.48 (–52.65, 39.69)					-19.51 (–51.38, 12.36)			
	Pooled estimate	–17.47 (–44.44, 9.50)					–17.47 (–44.44, 9.50)			
HDL-L	Rafraf *et al.*	0.16 (–2.49, 2.81)	0.53	0.0%/0.58	0.49	0.59	1.27 (–1.82, 4.37)	—	—	—
	Heidary *et al.*	1.17 (–3.18, 5.52)					0.48 (–1.78, 2.75)			
	Kaseb *et al.*	4.40 (–1.97, 10.77)					0.21 (–1.90, 2.33)			
	Kermanian *et al.*	–1.38 (–7.48, 4.72)					0.87 (–1.25, 3.01)			
	Pooled estimate	0.63 (–1.38, 2.64)					0.63 (–1.38, 2.64)			
LDL-C	Rafraf *et al.*	–11.80 (–20.17, –3.42)	0.09	71.3%/0.01	0.49	0.56	–12.59 (–34.35, 9.16)	0.47	0.10	0.09
	Heidary *et al.*	–1.27 (–11.59, 9.05)					–16.08 (–34.59, 2.43)			
	Kaseb *et al.*	–44.25 (–70.26, –18.23)					–6.13 (–13.94, 1.67)			
	Kermanian *et al.*	–0.68 (–18.57, 17.21)					–14.49 (–30.57, 1.57)			
	Pooled estimate	–10.94 (–23.71, 1.81)					–10.94 (–23.71, 1.81)			

In addition, the chamomile plant sterols have been shown to promote the catabolism of lipids in mice cells. Ultimately, it appears that chamomile can reduce and regulate the absorption of cholesterol, whilst its' hydroalcoholic chamomile extract contains ascorbic acid which also reduces the cholesterol content [42]. It has been shown that phytoestrogens can control the homeostasis of cholesterol by increasing the secretion of fecal bile acid, changing the synthesis of bile acids, and raising the liver cholesterol secretion [43]. Furthermore, phytosterols lead to reduced LDL cholesterol and TG levels through interfering with the cholesterol absorption [24].

Several evidences also showed that chamomile ameliorated oxidative stress and improved antioxidant defense system because of its antioxidants agents such as apigenin, luteolin and quercetin. It also has been shown that chamomile had a potential role in augmenting the antioxidant enzymes, including superoxide dismutase (SOD) and catalase (CAT), that catalyzes the dismutation of the superoxide radical into ordinary molecular like oxygen and hydrogen peroxide [44]. Since antioxidants play an important role in protecting unsaturated fatty acids against reactive oxygen species, they improve lipid profile by reducing lipid peroxidation [45]. In this view, it seems that chamomile might have a potential role in improving lipid profile abnormality.

While reports of allergies from chamomile, such as bronchial constriction and skin rashes, have been reported; most people can use this herb without any complication, and reports tend to be scarce. It is necessary to mention that chamomile tea should not be consumed by pregnant individuals, as it can stimulate uterine contractions; whilst it also has a blood-diluting effect, and thus, people who use anticoagulant drugs should not use it [46]. Studies on the use of chamomile to improve lipid profile in humans are limited, and despite the tentative positive findings in the present study related to TC further human studies are needed for better discern of the biologic effects of chamomile.

Strengths and limitations

To our knowledge, this study is the first meta-analysis to have comprehensively evaluated the effects of chamomile on lipid profile. However, like any other study, the current meta-analysis has some limitations that should be noted. First, a limited number of published RCTs in the field could affect the between-study heterogeneity [47]. Second, although we conducted a meta-regression, we could not detect the potential source of heterogeneity. Third, although we did not restrict our search strategy to regions, only articles emanating from Iran were found, and thus, the findings cannot be generalized to other nations. Fourth, the participants were not restricted to any specific disease, so, further consideration of disease-specific processes and contraindications must be taken. Finally, in some cases, when we requested more details about patients' characteristics and relevant information from corresponding authors, we did not receive an appropriate response.

Conclusion

The present meta-analysis demonstrates that chamomile can elicit significant reductions in serum TC, but not TG, HDL-C and LDL-C. Further long term RCTs are needed in the field, with a particular focus on other cultures, doses, and diseases.

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Conflict of interest

None.

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