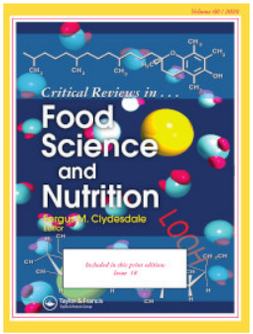

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REVIEW

Effect of bergamot on lipid profile in humans: A systematic review

Itziar Lamiquiz-Moneo[a], Jaume Giné-González[a], Sonsoles Alisente, Ana M. Bea[a], Sofía Pérez-Calahorra[a], Victoria Marco-Benedí[a], Lucía Baila-Rueda[a], Estíbaliz Jarauta[a], Ana Cenarro[a], Fernando Civeira[a,b], and Rocío Mateo-Gallego[a,c]

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ABSTRACT

Dyslipidemia is a well-established modifiable cardiovascular risk. Although statins can reduce LDLc by 50–60%, less than 20% of patients with high risk of CVD achieve LDL targets. The aim of this systematic review is to evaluate the effect of the nutraceutical, bergamot (*Citrus bergamia*), on lipid parameters in humans. PubMed, Embase, Cochrane Library, and Google Scholar databases were searched for interventional and observational studies investigating the effect of bergamot on lipid profile in humans. This systematic review retrieved a total of 442 studies of which 12 articles fulfilled the eligibility criteria and were included in the qualitative synthesis. Based on data, 75% of studies showed a significant decrease in total cholesterol, triglycerides and LDLc. The decrease in total cholesterol varied from 12.3% to 31.3%, from 7.6% to 40.8% in LDLc and from 11.5% to 39.5% in triglycerides. Eight trials reported HDLc increase after intervention with bergamot. Overall, a dose-dependent and possible synergistic effect when administering with statins can be deducted from these trials. It is essential to point out that studies had heterogeneous designs and scientific quality of studies was quite limited. Promising findings reveal an alternative therapeutic option in dyslipidemia management with bergamot supplementation, especially in subjects with statins intolerance.

KEYWORDS

Bergamot; *Citrus bergamia*; LDL cholesterol; total cholesterol; triglycerides

Introduction

Dyslipidemia is a well-established modifiable cardiovascular risk factor and its treatment is an essential aim in the prevention of cardiovascular diseases (CVD), which represent the leading cause of death and use of health service in developed countries (Bea et al. 2017). Current guidelines highlights lifestyle intervention as a key issue in the management of patients with hyperlipidemia, but it is often scarce to control the lipid profile (Grundy et al. 2018). Current lipid-lowering therapies, mainly statins with or without ezetimibe, can reduce LDL cholesterol by 50–60% and they are proven to reduce primary and secondary cardiovascular endpoints (Masana et al. 2017). However, less than 20% of patients with high risk of CVD achieve LDL targets and up to 60% of patients refer to some statin intolerance or side effects related to this treatment (Masana et al. 2017; Zhang et al. 2013). This constitutes the main reason for statin discontinuation and poor adherence to treatment that remains a significant problem in dyslipidemia management (Banach et al. 2016). The increasing need to find a nonpharmacological alternative, in particular for patients with moderate hypercholesterolemia, low cardiovascular risk or intolerance to traditional pharmacological treatment, has led to test many phytochemicals as nutraceuticals that have shown lipid-lowering properties (Johnston et al. 2017). Nutraceuticals are food components that may be used as therapeutic agents due to their beneficial effects on health (Kalra 2003).

Recent studies have shown that Bergamot (*Citrus bergamia*) juice and its flavonoids were able to reduce serum levels of lipids, even improving atherosclerosis through modulating enzymatic activities, antioxidation, antiinflammatory mechanisms and inhibition of monocyte activation and proliferation (Ferlazzo et al. 2016; Benavente-García and Castillo 2008; Ferlazzo et al. 2015; Li et al. 2016). Bergamot is an endemic plant growing in the Calabrian region of Southern Italy with a unique profile of flavonoids and glycosides present in its juice and albedo, such as neoeriocitrin, neohesperidin, naringin, rutin, neodesmin, rhoifolin and poncirin (Gliozzi et al. 2013). Bergamot differs from other citrus fruits, not only for the nutritional composition, but also for the particularly high content of flavonoids (Nogata et al. 2006; Dugo et al. 2005). Some of these flavonoids, such as naringin and its aglycone naringenin, have already been shown to have an antiatherogenic effect on animal models, while neoeriocitrin and rutin have been found to inhibit LDL oxidation (Yu et al. 2005). Besides, bergamot juice is rich in 3-hidroxy-3-methylglutaryl neohesperidosides

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of hesperetin (brutieridine) and naringenin (melitidine) with the ability to inhibit HMG-CoA reductase (Di Donna et al. 2009). These compounds are likely to contribute to the substantial hypolipidemic effects that bergamot juice has demonstrated in several animal studies (Mollace et al. 2008; Miceli et al. 2007). However, to date, there are few human studies that have evaluated the effect of bergamot in adults with dyslipidemia. Thus, the aim of this systematic review is to evaluate the effect of bergamot, as isolated component or as part of a nutraceutical product, in lipid profile (total cholesterol, LDL cholesterol, triglycerides, and HDL cholesterol) in humans.

Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews (Liberati et al. 2009). Prisma checklist is available in Supplemental Table 1.

Search strategy and study selection

A systematic search of the relevant literature was performed with the use of PubMed, Embase, Cochrane Library, and Google Scholar in order to identify interventional studies investigating the effect of bergamot on lipid profile in humans. If available, we also included systematic reviews, meta-analysis and clinical guidelines. References of included studies and reviews were manually checked for additional studies. The structured search strategies used the combination of bergamot and different outcomes related to lipid profile: [Bergamot OR Citrus bergamia OR Nutraceuticals] AND [Cholesterol OR Dyslipidemia OR Hyperlipidemia OR Cardiovascular disease OR Cardiovascular risk OR Lipids OR Lipoprotein OR Low-density lipoprotein OR High-density lipoprotein OR Lipid-lowering drugs OR Triglycerides]. Articles retrieved were then included or excluded based on the following criteria. Inclusion criteria included: (a) articles published in a peer-reviewed journal; (b) cross-sectional, cohort, and interventional studies; (c) studies conducted in both children and adults; (d) studies conducted in healthy humans, or those with metabolic impairment (overweight, obese, hypercholesterolemic, prehypertensive, hypertensive, or with type 2 diabetes) or any other disease. Exclusion criteria involved: (a) case studies; (b) letters, commentaries, conference papers, narrative reviews; (c) studies not conducted in humans. The search was limited to literature presented in English.

Outcome measures

Outcomes of interest were changes in total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides.

Quality measures

The quality of each included trial was assessed based on the previously validated methodology developed by Kmet et al. (2004). The methodology was derived from a checklist for assessing the quality of quantitative studies, which included the following criteria: (1) Question, objective sufficiently described?; (2) Study design evident and appropriate?; (3) Method of subject, comparison group selection or source of information, input variables described and appropriate?; (4) Subject and comparison group (if applicable) characteristics sufficiently described?; (5) If interventional and random allocation was possible, was it reported?; (6) If interventional and blinding of investigators was possible, was it reported?; (7) If interventional and blinding of subjects was possible, was it reported?; (8) Outcome and (if applicable) exposure measure(s) well defined and robust to measurement, misclassification bias? Means of assessment reported?; (9) Sample size appropriate?; (10) Analytic methods described, justified and appropriate?; (11) Some estimate of variance is reported for the main results?; (12) Controlling for confounding?; (13) Results reported in sufficient detail?; (14) Conclusion supported by the results?. Each question can be answered with "yes," "partial," "no," or "not applicable." Scoring process was done according to the following formula: ((number of "yes" x2) + (number of "partial" x1)/(total possible sum (28) – (number of "not applicable" x2)). The score ranged from 0 to 1; thus, the closer the value is to 1, the higher is the quality of the trial. Quality assessment of each trial was performed by three different researches (ILM, JGG and RMG). Two researchers performed the quality checklist of each trial; if a discordance was found (difference mean score more than 0.1 points), a third review by the remaining researcher was performed.

Results

Study selection

The systematic search retrieved a total of 442 studies of which 361 were identified in PubMed and 61 in Cochrane, Google Scholar and Embase. After removing 18 duplicated articles, we screened 404 manuscripts of which 293 were excluded because of they did not meet the requirement of eligibility criteria. We made full-text review of 118, excluding 106 articles for different reasons: most excluded articles did not include bergamot as active principle within the intervention, they were *in vitro* studies or developed in animal models ($n = 90$), they were reviews ($n = 15$) and we were unable to access to one full-text manuscript ($n = 1$). Finally, 12 articles (10 intervention studies and 2 observational studies) fulfilled the eligibility criteria and were included in qualitative synthesis (Figure 1).

Participants and main study characteristics

A detailed description of the included studies can be found in Table 1. The 12 studies included a total of 870 adults' participants (aged 27–77 years). There was quite heterogeneity in clinical characteristics of populations. In summary, two trials recruited subjects with overweight or obesity and other cardiovascular risk factors (Dahlberg et al. 2017) or metabolic syndrome (Di Folco et al. 2018), four trials included subjects with mixed hyperlipidemia (Gliozzi et al.

Table 1. Summary of trials.

First author, year of publication (reference)	*N*	Participants	Male, *n* (%)	Age, years	Study design	Intervention dose, mg/day (number of subjects)	Duration (days)	Total cholesterol, (mg/dL)		LDL cholesterol, (mg/dL)		Triglycerides, (mg/dL)		Quality checklist score[b]
								Baseline	Final	Baseline	Final	Baseline	Final	
Bruno A, 2017 (Bruno, Pandolfo, Crucitti, Cacciola, et al. 2017)	28	Subjects in treatment with SGAs (clozapine, olanzapine, quetiapine, risperidone and paliperidone)	15 (53.5%)	45.8 ± 11.7	Prospective, single-arm, open-label, randomization not applicable	BPF 500 mg	60	203 ± 33.0	206 ± 23.8	125 ± 26.9	126 ± 20.1	109 ± 51.9	121 ± 64.8	0.74
Bruno A, 2017 (Bruno, Pandolfo, Crucitti, Maisano, et al. 2017)	15	Subjects in treatment with SGAs (clozapine, olanzapine, quetiapine, risperidone and paliperidone)	9 (60.0%)	44.5 ± 9.1	Prospective, single-arm, open-label, randomization not applicable	BPF 1000 mg	30	204 ± 31.9	204 ± 38.4	121 ± 26.8	125 ± 24.8	199 ± 90.6	183 ± 59.6	0.47
Dahlberg et al. (2017)	32	Subjects with overweight or obesity and at least two cardiovascular risk factors (waist circumference 89–156 cm in women and > 102 cm in men; LDLc > 130 mg/dL; triglycerides > 150 mg/dL; HDLc 29–81 mg/dL In women and 26-49 mg/dL in men; glucose > 100 mg/dL; Hb1Ac 4.8–7%; HOMA-IR: 0.5–5.8)	10 (31.3%)	27–64	Prospective, two-arm, open-label, randomized	Low glycemic load Mediterranean diet (17) Low glycemic load Mediterranean diet + nutraceutical supplementation including soy, pea, whey proteins, phytosterols, antioxidants, probiotics, fish oil, berberine and bergamot fruit extract (500 mg) (15)	91	215 (186–277) 220 (147–340)	198 (172–256)* 182 (121–281)*	142 (107–195) 149 (71–239)	128 (96.0–175)* 121 (57.8–220)*	162 (77–284) 184 (96–332)	112 (53.4- 197)* 90.5 (47.2–163)*	0.83
Cai et al. (2017)	98	Subjects with mixed hyperlipidemia (LDLc > 175 mg/dL, triglycerides > 149 mg/dL, total cholesterol > 220 mg/dL)	28 (28.6%)	65.2 ± 9.1	Prospective, two-arm, double-blind, randomized	Placebo (50) Bergamot extract (500 mg), plant esters and orange oil (820 mg), vitamin C (50mg), vitamin B (20 mg), vitamin B12 (2000 mcg) and folic acid (800 mcg) (48)	84	218 ± 29 211 ± 38.3	210 ± 29.8 199 ± 37.9	134 ± 28 131 ± 35.2	132 ± 24.0 121 ± 29**	168 ± 47 190 ± 70.9	170 ± 117 160 ± 80.5	0.94
Di Folco et al. (2018)	80	Subjects with overweight and metabolic syndrome	37 (46.3%)	45 ± 5	Prospective, two-arm, open-label, randomized	Low-calorie Mediterranean diet (40) Low-calorie Mediterranean diet + 200 mg bergamot juice dry extract, 120 mg phytosterols, 80 mg artichoke leaf extract and 20 mg vitamin C (40)	180	228 ± 14 224 ± 33	221 ± 15 190 ± 30*	141 ± 12 145 ± 35	138 ± 10 113 ± 26*	189 ± 9 195 ± 63	179 ± 10 149 ± 45*	0.64
Izzo et al. (2017)	41	Women with breast cancer under aromatase inhibitors treatment	0 (0%)	59 ± 12	Prospective, single-arm, open-label, randomized not applicable	Nutraceutical composed of bergamot, phytosterols, artichoke and vitamin C (not specified dose) (41)	180	247 ± 6.1	210 ± 5.3*	164 ± 6.4	116 ± 5.0*	183 ± 7.3	162 ± 6.8*	0.27
Babish et al. (2016)	11	Subjects with moderate dyslipidemia (LDLc between 150 and 350 mg/dL,	3 (27.3%)	38–65	Prospective, single-arm, open-label, randomized not applicable	BFE 500 mg and 200 mg phytocomplex blend (11) Subgroup analysis in subjects with HbA1c > 5.4% and HOMA-IR >2	84	260 (213–271) 245 (191–286)	228 (197–266)* 218 (187–268)*	169 (141–198) 162 (123–220)	143 (112–199)* 141 (112–199)*	180 (127–359) 187 (118–473)	207 (86-260) 144 (86-260)*	0.36

(*continued*)

Table 1. Continued.

First author, year of publication (reference)	*N*	Participants	Male, *n* (%)	Age, years	Study design	Intervention dose, mg/day (number of subjects)	Duration (days)	Total cholesterol, (mg/dL)		LDL cholesterol, (mg/dL)		Triglycerides, (mg/dL)		Quality checklist score[b]
								Baseline	Final	Baseline	Final	Baseline	Final	
		triglycerides between 150 and 400 mg/dL)				or elevated triglycerides (8)								
Campolongo et al. (2016)	64	Subjects with previous ischemic heart disease	37 (57.8%)	63 ± 13.5	Prospective, two-arm, single-blind, randomized	Simvastatin 40 mg (32) Simvastatin 20 mg + nutraceutical composed of bergamot (400 mg), phytosterols, artichoke and vitamin C (32)	90	17717 172 ± 21	162 ± 13* 151 ± 16*	107 ± 9 103 ± 7	92 ± 5* 85 ± 5*	131 ± 10 139 ± 13	118 ± 8* 122 ± 9*	0.63
Toth et al. (2015)	80	Subjects with hypercholesterolemia (LDLc between 160 and 190 mg/dL)	42 (52.5%)	55 ± 13	Prospective, single-arm, open-label, randomized not applicable	Bergamot-derived extract (Bergamit®) 150 mg of flavonoids (80)	180	257 ± 15	223 ± 41*	176 ± 8.00	144 ± 37*	162 ± 54.0	136 ± 79*	0.64
Gliozzi et al. (2014)	107	Subjects with nonalcoholic fatty liver disease and metabolic syndrome	64 (59.8%)	56 ± 12	Prospective, single-arm, open-label, randomized[a]	BPF 1300 mg (64)	120	245 ± 8.3	182 ± 7.1*	162 ± 4.3	101 ± 1.8*	232 ± 5.1	160 ± 4.8*	0.46
Gliozzi et al. (2013)	77	Subjects with mixed hypercholesterolemia (LDLc > 160 mg/dL and triglycerides levels > 225 mg/dL)	–	–	Prospective, multiple-arm, open-label, randomized	Placebo (15) Rosuvastatin 10 mg (16) Rosuvastatin 20 mg (16) BPF 1000 mg (15) BPF 1000 mg + rosuvastatin 10 (15)	30	278 ± 4 278 ± 4 278 ± 4 278 ± 4 278 ± 4	275 ± 4 195 ± 3** 174 ± 4** 191 ± 5** 172 ± 3**	191 ± 3 191 ± 3 191 ± 3 191 ± 3 191 ± 3	190 ± 2 115 ± 4** 87 ± 3** 113 ± 4** 90 ± 4**	238 ± 5 238 ± 5 238 ± 5 238 ± 5 238 ± 5	235 ± 5 200 ± 4** 202 ± 5** 165 ± 3** 152 ± 5**	0.54
Mollace et al. (2011)	237	Subjects with mixed hyperlipidemia	–	–	Prospective, multiple-arm, double-blind, randomized.	BPF 500 mg (69) BPF 1000 mg (70) Placebo (60) BPF 1500 mg + 1600 kcal/day diet (32)	30 60	–21.8 ± 1.40** –29.4 ± 1.30 –0.10 ± 0.30 –25.0 ± 1.60**		–24.1 ± 1.5** –36.0 ± 1.4*** –1.1 ± 0.5 –27.6 ± 0.5**		–30.5 ± 3.2** –39.5 ± 3.0 0.05 ± 0.55 Not described		0.44

BPF denotes: Bergamot-derived polyphenolic fraction; BFE: Bergamot orange fruit extract; HbA1c: Glycated hemoglobin; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; SGAs: Second-generation antipsychotics.

[a]Gliozzi et al. randomized 107 patients in two groups: one receiving placebo and second receiving BPF 1300 mg/day, however they did not show any results of control group and they did not compare any parameter between placebo and intervention group.

[b]The Quality checklist score was calculated according to the following formula: ((number of "yes" x2) + (number of "partial" x1)/(total possible sum (28) – (number of "not applicable" x2)).

*Significance with $p < 0.05$ comparing baseline and final values within each treatment group.

**Significance with $p < 0.05$ comparing placebo and BPF group after intervention.

***Significance with $p < 0.05$ between BPF 500 mg and BPF 1000 mg group after intervention.

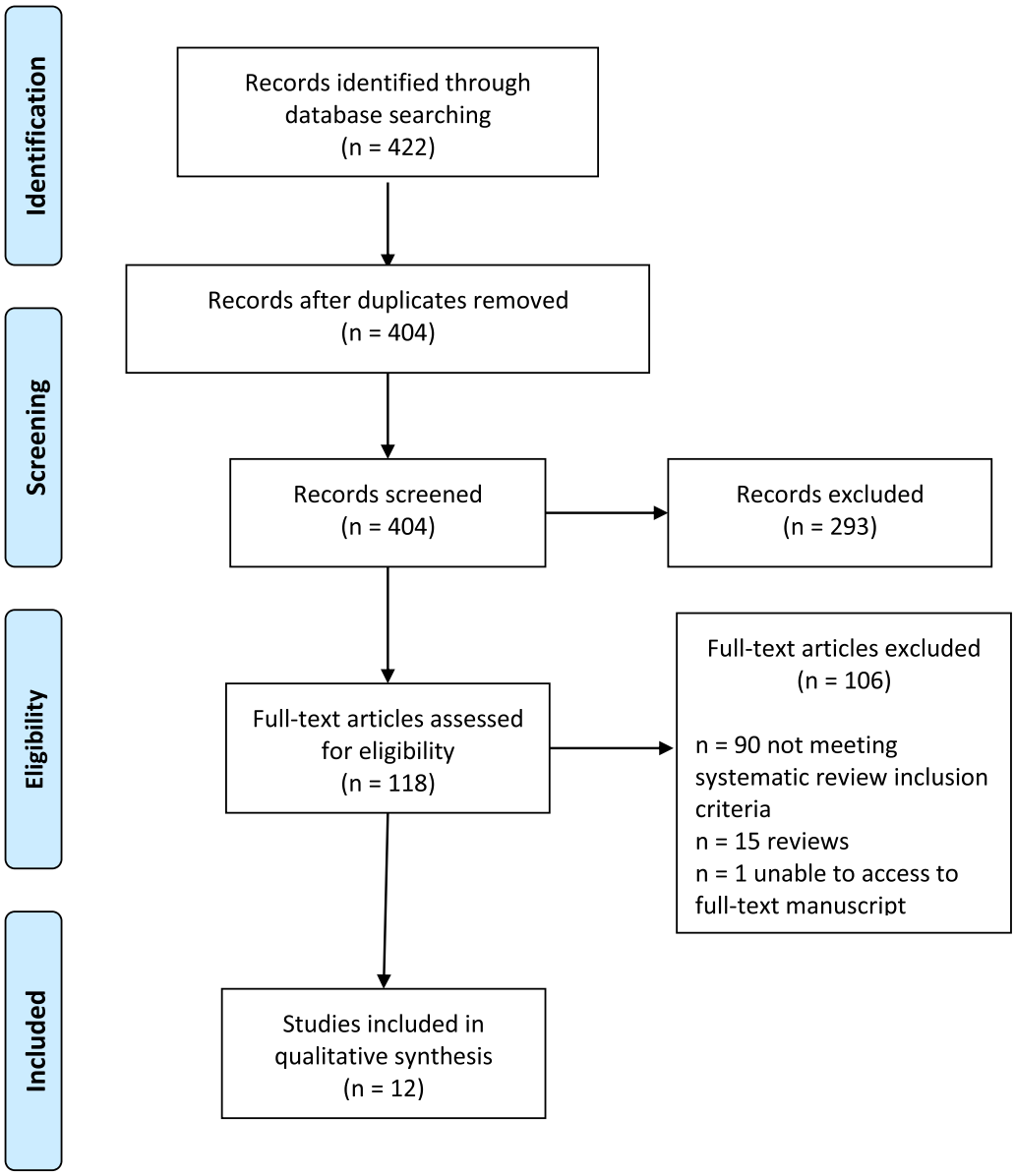

Figure 1. Flow chart of the study selection.

2013; Mollace et al. 2011; Cai et al. 2017; Babish et al. 2016), one trial involved subjects with isolated hypercholesterolemia (Toth et al. 2015), one trial recruited participants with previous ischemic heart disease (Campolongo et al. 2016), two similar trials recruited subjects under second-generation antipsychotics (SGA) treatment (Bruno, Pandolfo, Crucitti, Cacciola, et al. 2017; Bruno, Pandolfo, Crucitti, Maisano, et al. 2017), and one trial included women with breast cancer and receiving aromatase inhibitors treatment (Izzo et al. 2017). Five studies had a single-arm intervention, while six of them showed double or multiple-arm designs by comparing different doses of bergamot, using a placebo or statin group as comparison arm. It is important to point out that one trial referred to have a randomized clinical trial design by comparing bergamot effect with placebo; however, authors did not report placebo group results and they only reached conclusions using changes in lipid profile after the intake of bergamot supplements (Gliozzi et al. 2014). Dietary intervention duration ranged from 1 month to 6 months and bergamot doses used in the different studies ranged from 150 mg/day in the study by Toth et al. (2015) to 1500 mg as the maximum dose in the study carried out by Mollace et al. (2011)

Quality of the studies

The overall quality score of the included studies is summarized in Table 1 and ranged from 0.27 to 0.96, with a mean score of 0.55. Detailed description of each issue assessment for each study is included in Supplemental Table 1. The greatest concerning issues were randomization of descriptions, blinding of investigators and subjects, sample size calculation, appropriate analytic methodology, and controlling for confounding factors. Among six studies including a randomized clinical trial design, only two described randomization process and carried out a blinded intervention. Among 12 included trials, only one included a sample size calculation and two of them partially described it. In

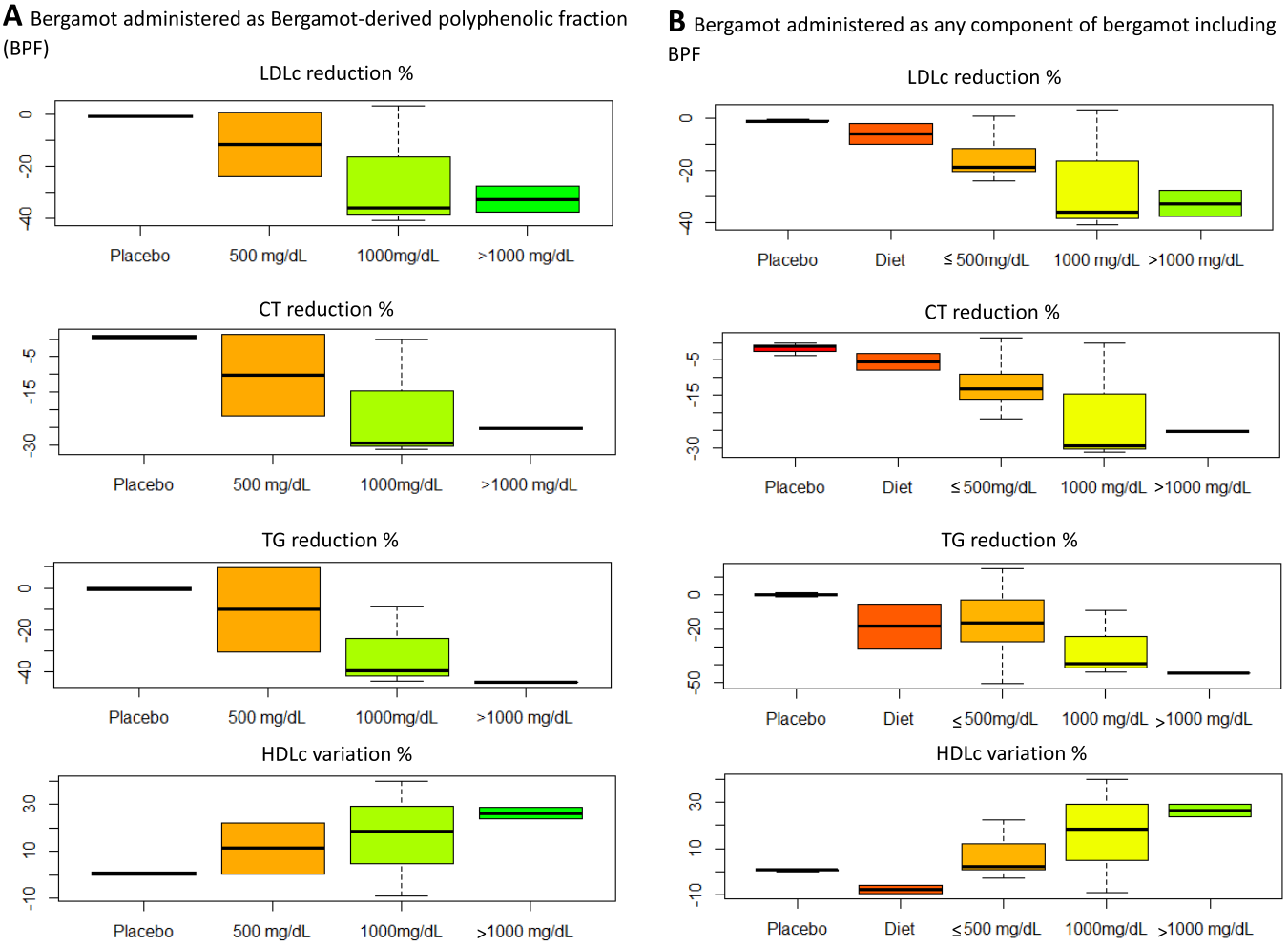

Figure 2. The effect of bergamot on lipid profile according to the type of bergamot component that was administered.

addition, eight of them did not use an appropriate statistical analysis or it was partially suitable and only one study made a statistical analysis taking into account the confounding factors; this is one of the main reasons why conclusions of most of the studies have been considered as partially or completely not supported by the results.

Change on lipid profile

Among five studies that administrated 500 mg of bergamot, four of them used bergamot as an isolated component and one of them used bergamot as part of a complex nutraceutical including soy, phytosterols or berberine, among others. Four out of five studies found a significant effect of bergamot on lipid profile while one of them did not describe significant differences after the intervention. This study was carried out by Bruno, Pandolfo, Crucitti, Cacciola, et al. (2017) who recruited 28 subjects under SGAs treatment receiving 500 mg/day of Bergamot-derived polyphenolic fraction (BPF) during 30 days. In contrast, Mollace et al. (2011) randomized 237 participants with combined hyperlipidemia to 500, 1000 mg/day of bergamot or placebo during 30 days, 69 subjects taking 500 mg/day of BPF obtained significant reductions of total cholesterol, LDL cholesterol and triglycerides with respect to the placebo group (−21.8 ± 1.40%, −24.1 ± 1.5%, −30.5 ± 3.2%, respectively). On the other hand, Dahlberg et al. (2017) randomized 32 subjects with overweight or obesity and at least two cardiovascular risk factors in two groups: a low glycemic load Mediterranean diet and the same intervention plus a nutraceutical including 500 mg/day of bergamot fruit extract, soy, berberine, and phytosterols, among other components. Authors found significant differences between baseline and final values in lipid profile in both study groups, although the change was greater in participants receiving the nutraceutical, who showed decreases of 17.3%, 18.8%, and 50.8% in total cholesterol, LDL cholesterol and triglycerides, respectively (Dahlberg et al. 2017). Cai et al. (2017) randomized 98 subjects with mixed hyperlipidemia to receive either a nutraceutical supplementation including 500 mg/day of bergamot extract, among others, or placebo for 84 days. They just found significant decreases in LDL cholesterol (7.63%) what was statistically significant compared to the placebo group ($p = 0.032$). Finally, Babish et al. (2016) recruited 11 subjects with moderate hypercholesterolemia who were supplemented with 500 mg of BPF and 200 mg of phytocomplex mixture each day. Participants showed significant decreases in total cholesterol (12.3%) and LDL cholesterol (15.4%) but not in triglycerides concentration. Subjects

with a baseline concentration of glycated hemoglobin (HbA1c) > 5.4%, HOMA-IR score > 2 or elevated triglycerides showed greater reductions in their lipid profile, especially in their triglyceride levels (Table 1).

Three studies used doses below 500 mg of bergamot extract, of which two used bergamot as part of a complex nutraceutical and one of them used bergamot as isolated active principle. All of them found statistically significant decreases both in total cholesterol, LDL cholesterol and triglycerides. Di Folco et al. (2018) recruited 80 subjects with overweight and metabolic syndrome, who were randomized to a low-calorie Mediterranean diet (control group) or the same intervention plus 200 mg/day of a dry extract of bergamot juice with 120 mg of phytosterols. Only the intervention group (supplemented with 200 mg/day of bergamot) showed significant reductions in total cholesterol (15.2%), LDL cholesterol (22.1%) and triglycerides (11.5%) concentration with respect to the baseline. Campolongo et al. (2016) randomized 64 subjects with previous ischemic heart disease in two groups: one of them was treated with 40 mg of simvastatin, and another group was treated with 20 mg of simvastatin plus nutraceutical including 400 mg/day of bergamot, phytosterols, artichoke and vitamin C. Both groups showed significant reductions in lipid profile suggesting an additive effect when adding the nutraceutical to lower doses of simvastatin. Finally, in a study conducted by Toth et al. (2015), 80 patients with hypercholesterolemia received 150 mg/day of flavonoids coming from bergamot during 180 days. Authors described similar reductions in total cholesterol (13.2%), LDL cholesterol (18.2%) and triglycerides (16.5%) than those reported by Di Folco et al. (2018) and Campolongo et al. (2016).

Three studies administered 1000 mg of bergamot as isolated principle active. Two of them found statistically significant improvement in lipid profile while one of them did not. This study was carried out by Bruno, Pandolfo, Crucitti, Maisano, et al. (2017) who prescribed 1000 mg/day of BPF for 30 days to 15 subjects under SGA treatment. In contrast, Gliozzi et al. (2013) showed that subjects with mixed hyperlipidemia receiving 1000 mg/day of BPF had similar reductions in total cholesterol (31.3%), LDL cholesterol (40.8%), and triglycerides (30.7%) than subjects under treatment with 10 mg/day of rosuvastatin. They also proved that participants treated with 1000 mg/day of BPF plus 10 mg of rosuvastatin showed the same improvement in lipid profile than subjects receiving 20 mg/day of rosuvastatin. This synergistic or additive effect was also described by Campolongo et al. who described a similar decrease in total cholesterol, LDL cholesterol and triglycerides in those participants receiving simvastatin 20 mg plus 400 mg/day (as part of a complex nutraceutical) than those taking simvastatin 40 mg. Finally, in previously described study carried out by Mollace et al. (2011), dyslipidemic participants taking 1000 mg/day of BPF had greater significant reductions in LDL cholesterol than those receiving 500 mg/day (−36.0 ± 1.4% vs. −24.1 ± 1.5%, respectively) or placebo group.

Only two studies used a dose of bergamot higher than 1000 mg/day and both found a significant effect of bergamot on lipid profile. Gliozzi et al. (2014) prescribed 1300 mg/day of BPF to 107 patients with nonalcoholic fatty liver disease and metabolic syndrome for 120 days. The intervention led to significant decreases in total cholesterol (25.7%), LDL cholesterol (37.7%) and triglycerides (31.0%). However, it is important to point out that results of placebo group are not included in the manuscript that may be essential to reach definitive conclusions according to study design. Finally, 32 subjects with mixed hyperlipidemia received 1500 mg of bergamot combined with hypocaloric diet (1600 kcal/day). This study reported that the reduction of total cholesterol and LDL cholesterol was lower in patients treated with 1000 mg of bergamot, although it was only a statistically significant reduction compared to the control-placebo group (Mollace et al. 2011).

It should be noted that one of the found articles did not explicitly indicate the bergamot dose used in the intervention. This study was conducted by Izzo et al. (2017) who recruited 41 women with breast cancer who were prescribed with a nutraceutical composed of bergamot, phytosterol and vitamins. Authors found significant reductions in total cholesterol, LDL cholesterol and triglycerides with respect to the baseline.

Figure 2 shows the effect of bergamot on lipid profile based on the type of component that was administered (A) BPF or (B) any component of bergamot including BPF, compared to placebo or diet intervention. Mean changes in each lipid parameter for every study were used to figure out the graphics. The figure shows a dose-dependent effect of bergamot with higher decreasing in total cholesterol, LDL cholesterol and triglycerides concentration when they received higher doses of BPF or with any other form of bergamot.

Among 12 studies included in the systematic review, eight trials reported significant increased effect in HDL cholesterol concentration after receiving bergamot in any form. The study carried out by Cai et al. (2017) did not find statistically significant differences. Even though, it is important to note that Babish et al. (2016), Bruno, Pandolfo, Crucitti, Cacciola, et al. (2017) and Dahlberg et al. (2017) showed light although significant decreases in HDL cholesterol concentration, that ranged from 1% to 6.5%.

Discussion

To our knowledge, this is the first systematic review aiming to explore the effect of bergamot in lipid profile in humans. We found 12 studies of which: 9 showed significant decrease of total cholesterol, triglycerides and LDL cholesterol; 1 only showed significant decrease in LDL cholesterol; and 2 did not find significant change in any lipid variable. Eight trials reported HDL cholesterol increase after intervention with bergamot in any form, while three studies described slight but significant decreases in HDL cholesterol concentration. A dose-dependent effect can be deduced from the studies but it should be confirmed with larger trials. However, it is

essential to point out that studies had quite heterogenous designs and scientific quality of the studies was quite limited. The first issue is crucial to reach conclusions since bergamot was provided in different forms: (a) isolated phytosterols of bergamot; (b) dry extract of whole bergamot juice; and (c) as part of a complex nutraceutical including other substances like phytosterols, artichoke or vitamin C. Thus, a solidly elucidation of whether bergamot has a significant effect on lipid profile in humans, which would be the optimal dose, and the mechanism responsible for this benefit, should still be clarified.

Statins are the main therapeutic approach in dyslipidemia management due to their solidly demonstrated cholesterol decreasing and cardiovascular protective effect (Stone et al. 2014; Baigent et al. 2005). However, some subjects show statin-intolerance especially at high doses (Rosenson et al. 2017; Serban et al. 2017). Inadequate lipid-lowering therapy and nonadherence to statin treatment are the main causes of failing to achieve LDL cholesterol targets (Guglielmi et al. 2017). Nutraceuticals can help to achieve lipid therapeutic goals and reduce cardiovascular residual risk. However, data about them are still limited. A recent position paper of International Lipid Expert Panel established that nutraceuticals could reach an LDL cholesterol reduction from <10% to 20%, although some of them or the combinations of different nutraceuticals could achieve greater reductions in LDL cholesterol(Banach et al. 2018). Our systematic review founded 12 trials exploring the effect of bergamot effect on lipid profile in humans; among them, 9 trials showed significant improvement in lipid parameters. The decrease in total cholesterol varied from 12.3% to 31.3%, from 7.63% to 40.8% in LDL cholesterol and from 11.5% to 39.5% in triglycerides. These improvements are similar to those reported when taking red yeast rice (15–25% decrease in LDL cholesterol), phytosterols (8–12%) or berberine (15–20%), among others (Banach et al. 2018).

A dose-response effect could be deducted from the studies we have analyzed. Overall, higher decreases in total cholesterol, LDL cholesterol, and triglycerides were observed with higher bergamot doses when mean changes were calculated including the results of all trials (Figure 2). Although we found a linear association between bergamot dose and lipid profile improvement, there is a high variation in the lipid profile reduction within these studies. In this way, Cai et al. (2017) reported a decrease in LDL cholesterol of 7.63% when taking 500 mg/day dose of bergamot, while the same dose led to a decrease of 24.1% in the trial conducted by Mollace et al. (2011) On the other hand, the study carried out by Toth et al. (2015) included a low dose of 150 mg/day of flavonoids coming from bergamot and they found a 18.2% decrease in LDL cholesterol. Based on the other trials, a lower effect would had been expected if a linear dose-response would had existed. It is crucial to note that participants characteristics are quite different among trials and, most importantly, it results quite heterogeneous the way in which bergamot was administered. This could play an essential role in the findings observed. While Cai et al. (2017) studied the effect of a whole-bergamot extract (within a complex nutraceutical), Mollace et al. (2011) used BPF and Toth et al. (2015) provided isolated bergamot flavonoids. Animal and *in vitro* studies suggested that polyphenols, particularly, flavonoids, such as melitidin and brutieridinin combination with other flavonoid glycosides present in bergamot, are likely to be responsible for lipid-lowering effects of this fruit (Di Donna et al. 2014; Choe et al. 2001; Miceli et al. 2007). Thus, it would be vital to solidly establish which is the most effective way (in terms of lipid-lowering effect) of bergamot supplementation in humans including either isolation of certain flavonoids, whole polyphenols extraction or whole bergamot juice extract. Future studies should also focus on determining the exact dose that would reach the maximum benefit on lipid metabolism with no side effects and whether the effects could reach a plateau at a certain dose.

One of the main observations obtained of this systematic review is that adding bergamot to low-doses of statins led to a similar lipid profile improvement than could be reached with higher doses, suggesting a synergic effect between statins and bergamot. Despite findings are promising, only two studies included small sample number have explored this issue. Gliozzi et al. (2013) demonstrated that adding BPF to rosuvastatin 10 mg showed the same reduction in lipid parameters than the improvement achieved under rosuvastatin 20 mg treatment. Similar results were reported by Campolongo et al. (2016) who observed an equivalent reduction in LDL cholesterol when adding bergamot to simvastatin 20 mg with respect to those who received simvastatin 40 mg. High-risk or very-high-risk patients with partial statin intolerance (who can tolerate a dose of statin that is less than required based on their cardiovascular risk) could be benefited by this therapeutic option (Banach et al. 2018). Bergamot contains flavanones (including brutieridin, melitidin and HMG-neoeriocitrin) which have been demonstrated to inhibit 3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase like statins (Di Donna et al. 2014). Some authors have also proposed different mechanisms that may concur in lipid homeostasis regulation by flavonoids. These included the activation of situin-1, which in turns activate adenosine monophosphate-activated protein kinase (AMPK)-α by increasing fatty acid oxidation and decreasing VLDL synthesis through of hepatocyte nuclear factor 4 (HNF4) inhibition, sterol regulatory element-binding protein 1 (SREBP-1) regulation (Tsutsumi et al. 2014; Bruckbauer and Zemel 2014; Chang et al. 2013; Quesada et al. 2009) and the inhibition of the pancreatic cholesterol ester hydrolase and Acyl-CoA cholesterol acyltransferase, which increase the cholesterol fecal excretion (Musolino et al. 2017). Despite this is the most probable mechanism like bergamot, there are other mechanisms that have been proposed to be responsible for lipid-lowering effects of bergamot. Other potential mechanisms include increased gene transcription and increased membrane translocation of the LDL receptor, which could be mediated by proliferator-activated receptors gamma (PPAR-γ) activation (Farràs et al. 2013; Kumar et al. 1997). Although any study has specifically explored the effect of bergamot alone by comparing to its

combination with other nutraceutical components, a synergic effect of lipid-lowering nutraceuticals is deducted from published research. Those studies using low doses of bermagot together to other bioactive components have reached similar decreases than those using higher doses of bergamot alone. These findings point out a similar synergistic effect than the one described with statins by influencing on different lipid metabolic pathways.

It is essential to emphasized that quality assessment of trials revealed important issues which limit interpretation and conclusions that can be reached based on these trials. Among 12 studies identified through a systematic review process, only half of them used a randomization design and only two trials described how the randomization process was carried out. Most importantly, only one study took into consideration confounding factors in analyzing study data. Adjustment of lipid parameters change after intervention with bergamot by body weight or dietary changes, among others, is crucial to correct interpretation of results and establish firm conclusions. According to the study design, many trials carried out some statistical approaches that could be inappropriate according to study design. Limited methodology quality of trials is a cornerstone to establish definitive conclusions that should be considered when interpreting the results.

In conclusion, this is the first systematic review aiming to compile all studies that have explored the effect of bergamot on lipid profile in humans. Nine of 12 founded trials showed a significant decrease in total cholesterol, triglycerides and LDL cholesterol, while one study showed a significant decrease just in LDL cholesterol. Two trials did not find significant change in any variable. Eight trials reported HDL increase after intervention with bergamot in any form. Overall, a dose-dependent effect and a potential synergistic effect when administering with statins can be deducted from these trials. Possible synergistic effect could be explained because the mechanism of bergamot acts to different levels: inhibiting the HMG-CoA reductase, the pancreatic cholesterol ester hydrolase and Acyl-CoA cholesterol acyltransferase, which would produce lower cholesterol synthesis and higher cholesterol fecal excretion. Promising findings give away from an alternative therapeutic option in dyslipidemia management with bergamot supplementation, especially in patients with moderate hypercholesterolemia, low cardiovascular risk or intolerant to traditional pharmacological treatment. However, crucial issues are still remained to be clarified before a solid recommendation on this nutraceutical could be performed. These questions include the form in which most efficiently bergamot should be provided (BPF, certain flavonoids or whole bergamot juice extraction) and the optimal dose and its safety.

Supplementary information

Supplemental data for this article can be accessed on the publisher's website at [article DOI].

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