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Herbal medicines for suppressing appetite: A systematic review of randomized clinical trials

Monirsadat Sahebkar- Khorasani[a], Lida Jarahi[b], Holger Cramer[c], Mohammad Safarian[d,e], Hamideh Naghedi-Baghdar[a], Roshanak Salari[f], Pardis Behravanrad[g], Hoda Azizi[h,*]

[a] School of Persian and Complementary Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[b] Department of Community Medicine, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[c] Department of Internal and Integrative Medicine, Kliniken Essen-Mitte, Faculty of Medicine, University of Duisburg-Essen, Essen, Germany
[d] Metabolic Syndrome Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[e] Department of Nutrition, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[f] Department of Pharmaceutical Sciences in Persian Medicine, School of Persian and Complementary Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[g] Student of Veterinary Medicine, Islamic Azad University, Science and Research Branch, Tehran, Iran
[h] Department of Chinese and Complementary Medicine, School of Persian and Complementary Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

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ABSTRACT

The suppression of appetite with herbal medicines has become very popular in recent years. We conducted this systematic review to evaluate the recent scientific evidence regarding herbal medicines that are used to suppress appetite. We retrieved clinical trials from PubMed, Cochrane Central Register of Controlled Trials, Web of Science, Scientific Information Database, and IranMedex from January 1, 2013 to April 24, 2018. English and Persian language randomized clinical trials that used herbal medicines to suppress appetite in healthy or obese or overweight individuals were included. Risk of bias was assessed using Cochrane methodology. Out of 591 articles, 22 trials with 973 participants were included. One study on the Meratrim formulation which contained the Sphaeranthus indicus flower heads extract and Garcinia mangostana fruit, revealed longer-term evidence; while 6 studies on Ilex paraguariensis, Spinacia oleracea, Phaseolus vulgaris, Secale cereale, Sorghum bicolor and Plantago showed short-term evidence for suppressing appetite. No serious adverse events were reported. Despite some methodological concerns in the included studies, there is promising evidence for suppressing appetite with herbal medicines that needs to be confirmed in long-term clinical trials with adequate sample size and higher methodological quality with more attention to safety, effective dose and side effects.

1. Introduction

Overweight and obesity are defined as an abnormal or excess fat accumulation that compromises health. Body mass index (BMI) values of 29.9 or higher and 24.9 or higher are considered as obesity and overweight, respectively.[1] The prevalence of obesity has significantly increased in recent decades and is currently one of the most important global health problems.[2]

The prevalence of obesity was about 20% or more in several countries in the USA, Micronesia and Polynesia, the Middle East, North Africa and the Caribbean.[3] Increasing global obesity has a major impact on health and quality of life. The Global Burden of Disease Study and the World Health Organization have recently confirmed that obesity is actually one of the main causes of illness, disability and death in many parts of the world In particular, obesity is a major contributor to the global incidence of type 2 diabetes mellitus, cardiovascular disease, cancer, osteoarthritis, work disability and sleep apnea.[4]

The great burden of obesity affects many health outcomes (such as quality of life, disability, mortality) and results in increased use of health services.Findings show that costs grow curvilinearly with increasing body mass index, particularly in obese people. Empirical evidence has undeniably shown that obesity has a negative impact on individuals, health care systems, employers, and the entire economy.[2]

The standard treatment of obesity is lifestyle modification based on reducing calorie intake and increasing energy expenditure. Medicinal and surgical therapies also help in some cases but they have several complications. Considering the reversibility of the results after standard treatment and the complications of medicinal therapy and surgery,

Abbreviations: BMI, body mass index; VAS, visual analogue scale; RCT, randomized controlled trial

* Corresponding author at: School of Persian and Complementary Medicine, Pardis University Campus, Azadi Square, Mashhad, 9177948564, Iran.
E-mail address: azizih@mums.ac.ir (H. Azizi).

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many patients seek complementary therapies such as herbs to reduce appetite and weight. The anti-obesity effects of medicinal herbs were studied in the previous systematic reviews.[5–19] However, there is only one systematic review on the effects of herbs in weight loss through reducing appetite by 2013.[20,21]

There are various mechanisms through which molecules found in herbal medicines may suppress appetite; such as increased leptin sensitivity, adrenergic receptor modulation, cannabinoid receptor inhibition, bulking effect in stomach.[22–24]

The present study aimed at providing information and evaluating the methodological quality of RCTs on herbs which reduce appetite regardless of losing weight; their efficacy and safety, and the mechanism of action from 2013 to date; since studies prior to 2013 had been reviewed by the Astell and colleagues.[20,21] We reviewed RCTs from 2013 to date and compared our results with Astell's. Therefore, the purpose of this study is to systematically review the randomized clinical trials of appetite suppressant herbal medicines in healthy, obese or overweight individuals.

2. Methods

We followed the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines and the Cochrane recommendations in conducting and reporting this systematic review.[25,26] The present research team applied a systematic search to evaluate randomized clinical trials that used herbal medicines to reduce appetite in healthy, obese or overweight individuals. In this systematic review, we did a qualitative analysis because it was not possible to do the meta-analysis due to the heterogeneity of the data.

2.1. Eligibility Criteria

Randomized clinical trials in which healthy, obese or overweight individuals without any underlying disease used herbal medicines to reduce appetite.

2.2. Inclusion criteria

1 Healthy or overweight or obese individuals according to the definition of World Health Organization, of any age and sex were eligible.
2 Randomized controlled trials and randomized crossover trials using single herbs or combination of herbs were eligible.
3 Experimental interventions using any kind of herbal medicines, either single herbs or a combination of herbs, without any restrictions on formulation, preparation method and form (capsule, granule, tablet, extract or injection) were considered. Herbal medicine was defined as a product of the botanical source, whether it is a plant or a part of a plant such as seed, leaf, air organ, root, and other parts.[27] No restrictions were imposed on dosage including frequency, dose, intensity, and duration.
4 Comparators including placebo, medicines and food were included.
5 Studies measuring outcomes regarding appetite, satiation, food intake and appetite-related hormones were eligible. Outcomes included appetite, hunger, desire to eat, satiety based on Visual Analogue Scales (VAS) or other validated instruments, energy intake, appetite-related hormones and side effects.
6 English and Persian language articles were eligible.

2.3. Exclusion Criterion

1 Studies which used interventions such as acupuncture and moxibustion along with herbal medicine were excluded.

2.4. Literature search

We searched PubMed, Cochrane Central Registry, Web of Science, Scientific Information Database and IranMedex from January 1, 2013 to April 24, 2018 for English and Persian language human studies. Keywords that were used alone or in combination included: Appetite Regulation, Appetite Depressants, Appetite control, Satiety, Fullness, Antiappetite, Suppressing appetite, Appetite regulator, satiation, Neural control of appetite, Appetite Suppressant hormone, Appetite control, Hunger, Obesity, Overweight, Plant Extracts, Medicinal Plant, Herbs, Botany, Pharmacognosy, Phytotherapy, Naturopathy, Plants Medicinal, Herbal Drugs, Herbal Medicine, Herbal Remedy, Herbal Preparations, Herbal Product, Herbal Supplement, Natural supplement, Chinese Herbal Medicine, Traditional Medicine, Unani Medicine, Complementary Medicine, and Alternative Medicine. The complete search strategy for PubMed is presented in the supplement. The reference lists of identified original articles or reviews were also searched manually to retrieve additional articles. The literature search and study selection were done by two reviewers individually (HA, MSK); and controversial cases were re-examined for inclusion to achieve consensus. Extracted data included time, place and name of the author, methodology, the name of the herb, details of the intervention, such as the dosage and pharmaceutical form used, type of the control group, the duration of the intervention, characteristics and the number of participants, and the results were extracted based on the outcomes.

2.5. Risk of Bias

Risk of bias was evaluated using the Cochrane Tool for risk of bias assessment.[26] Risk of bias was evaluated by a reviewer and cross checked by a second reviewer. Any disagreement between the two authors was solved by discussing and seeking resources and no disagreement between the two reviewers remained.

Risk of bias was investigated in 8 areas: allocation concealment, random sequence generation, blinding of the participants, blinding of the treating physician, blinding of outcome assessment, incomplete outcome data reporting and selective reporting.

3. Results

The flowchart of the systematic review showing the selection of studies is shown in Fig. 1. A total of 541 articles were found by electronic and 50 by manual method in the initial search. After removing the duplicates and articles in languages other than English or Persian, 545 records remained. Among them, 472 records were excluded because they were not trials or they were out of the search time period. After carefully reviewing the remained 73 full texts, 51full-texts excluded. The 22 remaining articles were included based on the predefined criteria. Table 1 presents the basic characteristics of the included studies, and Table 2 summarizes the key points of the methodology and results of those studies.

3.1. Study design

We reviewed 22 clinical trials involving 973 participants. Both genders were included in 10 studies; in 11 studies, only women were included; and in one study, only men were included. These RCTs reported random allocation of healthy, overweight or obese participants regarding appetite with herbal medicine, placebo, diet or food.

3.2. Participants

The participants were from the United States, Australia, the Netherlands, the United Kingdom, Kuwait, Greece, Sweden, Italy, Canada, India, and Iran. The participants were aged between 18–75 years. The participants' body mass index was between 18.5 kg /m^2 and

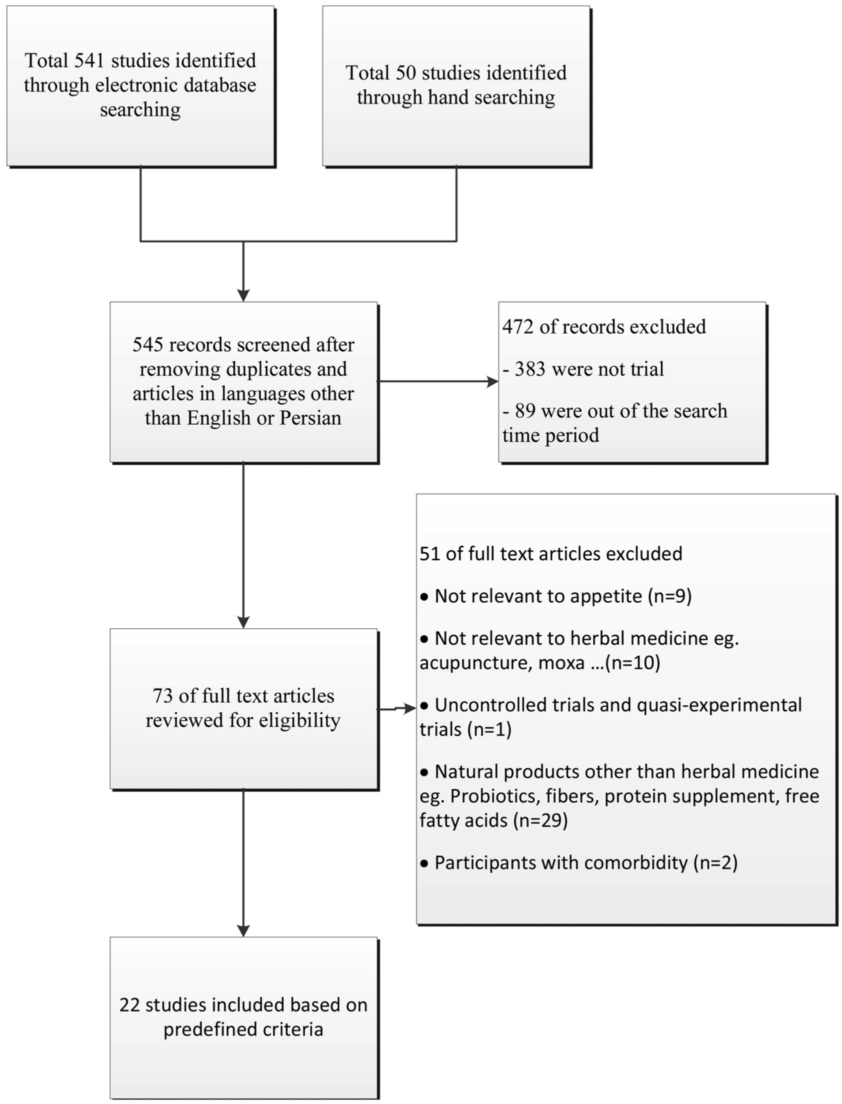

Fig. 1. Systematic review flowchart.

38 kg /m^2.

3.3. Interventions

Among the 22 included trials, 17 used single herb and 5 trials used the combination of several herbs. A total of 17 different herbs were used individually or in combination, including psyllium, puer tea, green tea, coffee, Spinacia oleracea, Phaseolus vulgaris, grain Secale cereale, Meratrim product containing Sphaeranthus indicus flower heads and Garcinia mangostana fruit, Caralluma fimbriata, Zingiber officinale, purple Daucus carota, Plectranthus barbatus, Sorghum bicolor, vinegar, Capsicum oleoresin, Ilex paraguariensis and pea. The duration of treatment varied from once to 12 months.

3.4. Outcomes

The reported outcomes were appetite, hunger, desire to eat, fullness, satiety, and food intake based on VAS. In 11 studies, appetite-related hormones were measured; in only 3 studies, hormonal changes were significant, which included Phaseolus vulgaris, Secale cereale and Sorghum bicolor in the short term. An increase in peptide YY (PYY) was observed with Phaseolus vulgaris, Secale cereale and Sorghum bicolor; increase of nesfatin with Secale cereale; reduction of ghrelin with Phaseolus vulgaris; increase in glucagon-like peptide-1 (GLP1) with Secale cereale and Sorghum bicolor and increase in glucagon-like peptide-2 (GLP2) was reported with Phaseolus vulgaris.

Out of ten articles related to 9 effective herbal medicines, 2 articles reported that no adverse events occurred with Sorghum bicolor and Ilex paraguariensis. Only 5 reported any safety-related data; two articles

Table 1
The basic Characteristics of the included studies.

Number of studies	Publication period	Study design		Participants		
		Randomized clinical trial-Parallel	Randomized clinical trial- cross over	Number	Age	Body Mass Index
22	2013-2017	11	11	973	18 to 75 years	18.5 – 38 kg /m^2

Table 2
Summary of the key points of the included studies on herbal medicines for appetite control.

First author Year	Study design	Samples	Duration	Interventions	Outcomes related to appetite
Astell et al [20,21]	Randomized, double blind placebo controlled clinical trial	33 adults aged 29-59 years; BMI > 25 kg/m^2, or a waist circumference > 94 cm (male), > 80 cm (female)	12 weeks	**Caralluma fimbriata extract** and placebo, 500 mg capsules twice daily (1 g/day). + diet + exercise	No significant difference between two groups in total energy intake and appetite sensations (hunger, desire to eat, fullness, palatability, meal weight) pre and post ingestion.
Nilsson et al [28]	Randomized crossover design	16 healthy volunteers (10 women and 6 men) aged 23.8 ± 0.7; mean BMI 22.5 ± 0.6 kg/m2	single dose; 2 daily trials separated by one week	An evening meal of brown beans, or white wheat bread (WWB)	An evening meal of brown beans, in comparison with WWB, increased satiety hormones (PYY 51%, $p < 0.001$), suppressed hunger hormones (ghrelin -14%, $p < 0.05$), and hunger sensations (-15%, $p = 0.05$), and increased GLP-2 concentrations (8.4%, $p < 0.05$) at a subsequent standardized breakfast.
Wright et al [29]	Randomized, double-blind, placebo-controlled trial	16 males aged 53.1 ± 7.6 years; mean BMI 32.8 ± 4.6 kg/m^2	4 weeks	**Dried purple carrot** compared with placebo.	No significant changes in body mass, body composition, appetite, dietary intake, at the dose and length of intervention used in this trial.
Harrold et al [30]	Double blind, placebo-controlled, cross-over	58 normal to slightly overweight healthy **women**, aged 18–65, BMI 18.5-29.9 kg/m2	One time	**Yerbe Maté, Guarana and Damiana** (YGD) 3 tablets and inulin-based soluble fermentable fibre (SFF) (5 g in 100 ml water); YGD and water (100 ml); SFF and placebo (3 tablets) ; water and placebo 15 min before meals. A standard fixed-load breakfast (496 kcal), no diet restriction for lunch	Significant reductions in food intake and energy intake were observed when YGD was present (59.5 g, 16.3%; 112.4 kcal, 17.3%) and when SFF was present (31.9 g, 9.1%; 80 kcal, 11.7%) compared with conditions where products were absent. The lowest intake (gram and kcal) and significant reductions in AUC hunger and AUC desire to eat were in the YGD + SFF condition.
Gavrieli et al [31]	Randomized, cross-over design	33 (16 normal-weight, 17 overweight/obese) healthy and habitual coffee drinkers (≥1 cup of coffee/day).	3 daily trials	A standard breakfast along with 200 ml of either **coffee** with 3 or 6 mg caffeine/kg body weight, or water. No diet restriction	A significant difference for energy intake of the ad libitum meal ($P = 0.05$) and of the whole day ($P = 0.02$) only in overweight/obese individuals. Specifically, Coffee 6 resulted in a reduced energy intake during the ad libitum meal compared with Coffee 3 ($P = 0.03$) and in the total day compared with both water ($P = 0.04$) and Coffee 3 ($P = 0.008$). No effect was observed for the appetite feelings.
Spadafranca et al [32]	Randomized, double-blind, placebo-controlled study	12 volunteers (female and male) aged 20–26; normal weight, BMI 19·7–23·5 kg/m^2, body fat 11·5–31·5 %	Two different days	A mixed standardized meal consisting of a sandwich of white bread, ham, oil and tomato plus a 100 mg tablet of **Phaseolus vulgaris** (PVE) or a 100 mg tablet of placebo ingested immediately before the meal.	In the first 2 h, plasma ghrelin decreased similarly in both groups but did not rebound as in placebo thereafter ($P = 0·04$). Correspondingly, satiety sensation in the third hour was significantly reduced in the placebo but not in the PVE condition. PVE induced a lower desire to eat than placebo ($P = 0·02$) over the 3 h.
Montelius 2014	Single-blinded, single-centered, randomized and placebo-controlled	38 healthy non-smoking women aged 40–65 years; BMI 25 – 33	12 weeks	**Green-plant membranes** (5 g) or placebo, once daily before breakfast + diet	No significant differences in GLP-1 and ghrelin concentrations in day 1 and 90. All VAS-ratings for sensation of hunger, satiety, urge for specific foods and food intake were influenced by time ($p < 0.001$) in day 1. There was also an effect of treatment on the ratings for the urge for sweet and chocolate (sweet; $p < 0.05$ and chocolate; $p < 0.05$). The ratings of hunger, satiety, and urge for a high carbohydrate snack or salt were not different between the treated and the control groups.

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Table 2 (*continued*)

First author Year	Study design	Samples	Duration	Interventions	Outcomes related to appetite
Darzi et al[33]?	Randomized crossover balanced design	Study 1 (n = 16) healthy, young, normal weight unrestrained eaters Study 2 (n = 14)	2 occasions separated by at least 2 days	Study 1: supplying vinegar within both palatable and unpalatable drinks + mixed breakfast in comparison to a non-vinegar control Study 2: a modified sham feeding study (taste only without ingestion) comparing vinegar to a non-vinegar control following a milkshake preload.	In Study 1, ingestion of vinegar significantly reduced quantitative ($P = 0.022$) and subjective measures of appetite (fullness $p < 0.0001$; hunger $p = 0.045$; Prospective food consumption $p = 0.036$) which were accompanied by significantly higher nausea ratings, with unpalatable treatment having the greatest effect. Significant correlations between palatability ratings and appetite measures were found. In Study 2, orosensory stimulation with vinegar did not influence subsequent subjective or quantitative measures of appetite compared with control.
Lambert et al[34]	Double blind, placebo controlled, parallel group	60 overweight and obese adults (9 M/41 F) aged 18-70; BMI 25-38 kg/m^2	12 weeks	Isocaloric doses of placebo or pea fiber (15 g/d) biscuits	no significant difference between pea fiber and placebo in food intake and VAS hunger/satiety scores.
Alkhatib et al[35]	Double-blind crossover repeated measures controlled design	12 healthy recreationally active adults (5 females and 7 males) aged 24 ± 3.8 ; BMI 22.5 ± 3.85 kg/m^2; body fat percentage 21.3 ± 9.6 %	Three days within two weeks period	1.5 g (3 × capsules) placebo (PL) or a commercially available multi-ingredient product (Shred-Matrix®), containing Green Tea Extract, Yerba Maté, Guarana Seed Extract, Anhydrous caffeine, Saw palmetto, Fo-Ti, Eleuthero root, Cayenne Chili pepper, and Yohimbine HCI + 30-min cycling exercise	Mood state and perception of hunger were not different between conditions, with no interaction effects. A trend was shown towards improved satiety in SHRED compared with PL, [$F(1, 11) = 3.58$, $p = 0.085$].
Rebello et al[36]	Double-blind randomized crossover study	60 overweight or obese (males and females) aged 18 -65	single dose; 2 daily trials	The **spinach extract** (5 g before lunch) or placebo in random order at least a week apart	The spinach extract reduced VAS ratings for hunger ($p < 0.01$) and longing for food over 2 hours ($p < 0.01$). There were no differences in energy intake at dinner, but males showed a trend toward decreased energy intake ($p = 0.08$).
Loftus et al[37]	Randomized, double blind placebo-controlled clinical study	41 overweight or obese participants (12 males and 29 females) aged 20–65; BMI > 25 m^2 or waist circumference > 94 cm (male) and > 80 cm (female)	12 weeks	250 mg of Coleus forskohlii extract or placebo twice daily for 12 weeks.	There were no significant differences in ghrelin, leptin, the satiety quotient, energy intake and appetite sensations.
Ebrahimzadeh Attari et al[38]	Randomized, double-blind, placebo-controlled trial	80 obese women aged 18-45 were genotyped for the -3826A > G and Trp64Arg polymorphisms of uncoupling protein 1 and ß3-adrenergic receptor genes respectively.	12 weeks	Ginger (two 1-g tablets per day) or placebo (corn starch)	Ginger supplementation resulted in a slight but not statistically significant decrease in total appetite score as compared with placebo group ($p = 0.066$), which were more pronounced in subjects with the AA genotype for uncoupling protein 1 and Trp64Trp genotype for ß3-adrenergic receptor gene
Dostal et al[39]	Randomized, double-blind, placebo-controlled	937 healthy postmenopausal women, stratified by catechol-O-methyltransferase (COMT) genotype. This study was conducted in a subset of 237 overweight and obese participants; BMI ≥ 25 kg/m^2	12 months	4 Green **Tea** Extract (GTE) capsules containing 1315 mg ± 116 total catechins per day or a placebo. No diet restriction	No significant changes in energy intake, leptin, ghrelin, adiponectin, or glucose concentrations at month 12 between groups.
van Avesaat et al [40]	Single-blind, randomized, placebo-controlled crossover	13 (7 women) aged 21.5 ± 0.6 ; BMI 22.8 ± 0.6 kg/m^2	once	Intra-duodenal infusion of either capsaicin or a placebo (physiologic saline) was performed with the use of a naso-duodenal catheter over a period of 30 min	Significant increase in satiety ($P < 0.05$) by intra-duodenal capsaicin infusion. Satiety scores had a positive correlation with all gastrointestinal symptoms. No differences in GLP-1 and PYY concentrations and gallbladder volumes between groups.

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Table 2 (*continued*)

First author Year	Study design	Samples	Duration	Interventions	Outcomes related to appetite
Sandberg et al [41]	Randomized cross-over design	19 healthy volunteers (9 men and 10 women) aged 25.6 ± 3.5; BMI 21.9 ± 1.87 kg/m2	3 consecutive days	Whole grain rye kernel test bread (RKB) or white wheat flour based bread (WWB) as late evening meals	Increase in PYY (0–120 min, $P < 0.001$), GLP-1 (0–90 min, $P < 0.05$), improve in subjective appetite ratings ($P < 0.05$), by RKB compared with WWB. A trend towards increased concentrations of p-nesfatin-1 at fasting after a RKB evening meal compared with WWB ($P = 0.095$). No significant difference in p-ghrelin fasting concentrations and p-GLP-2.
Kudiganti et al [42]	Randomized, double-blind, placebo-controlled	57 participants; BMI 28.3 kg/m^2	16 weeks	Meratrim or placebo capsules twice daily +Diet +Exercise	Significant decrease in VAS appetite by Meratrim compared with placebo ($p < 0.001$). No statistically significant changes in adiponectin, leptin, ghrelin or insulin levels.
Stefoska-Needham et al [43]	Randomized, cross-over trial	40 healthy subjects aged 18-50 years; BMI 20-31 kg/m^2	4 separate occasions with a minimum 3 days between visits	White, red, or brown sorghum biscuits (50 gr) or a wheat control	Significantly lower subjective satiety ratings after consuming wheat compared with sorghum biscuits. Incremental area under the plasma concentration-time curve of postprandial GLP-1, GIP and in males, PYY, were significantly higher ($p = 0.018$, $p = 0.031$, $p = 0.036$, respectively) for sorghum breakfasts compared with wheat. No significant difference in energy intake at a subsequent meal did between groups.
Jensen et al [44]	Randomized, double-blind, placebo-controlled	59 overweight or mildly obese men and premenopausal women (female: male ratio of 2:1) aged 35–75; BMI 25–35 kg/m2	20 weeks	**Puer tea** extract (PTE) (3 g/day) or placebo	A transient reduction in appetite in PTE group compared with placebo ($P < 0.1$).
Brum et al [45]	Randomized, double-blind, placebo-controlled cross-over design	study 1: 28 Men and women study 2: 40 Men and women; 18.5 < BMI < 32 kg/m2	2-treatment, 3-period cross-over; 4-5 days of washout between periods	Study 1: 3.4 g, 6.8 g, and 10.2 g of **psyllium** taken before breakfast and lunch for 3 days. Study 2: 6.8 g taken before breakfast and lunch on Days 1 and 2 and before breakfast on Day 3. + an energy restricted breakfast for 3 days	Study 1: Significant mean reductions in hunger and desire to eat, and increased fullness between meals in all 3 groups compared with placebo; with both higher doses better than placebo or 3.4 g. The 6.8 g dose provided more consistent ($p \leq 0.013$) satiety benefits versus placebo. Study 2: Significant decrease in hunger ($p \leq 0.004$), desire to eat, and increase in fullness for 6.8 g psyllium compared with placebo.
Alkhatib and Atcheson[46]	Double-blind repeated-measures crossover placebo-controlled design	12 healthy active females	3 sessions separated by at least 3 days within a two-week period	Yerba Mate (YM) capsules or placebo (PLC) (4 × 500 mg capsules) Participants rested for 120 min before performing a 30-min cycling exercise corresponding to individuals' crossover point intensity.	Significantly different decrease in VAS scores for hunger, prospective eating, and desire to eat between groups ($p < 0.05$).
Stefoska-Needham et al. [47]	Double-blinded, parallel, randomized controlled trial	60 subjects (46 females and 14 males) aged 18–65 years; BMI 25–35 kg/m^2	12 weeks	Red sorghum or white wheat (control) group	No significant differences for feelings of hunger/fullness.

Abbreviations: VAS, Visual Analogue Scale; BMI, Body Mass Index.

Table 3
Risk of bias assessment.

Trial name	Random sequence generation	Allocation concealment	Blinding (study patient)	Blinding (treating physician)	Blinding (clinical outcome assessment)	Incomplete outcome data addressed	Free of selective repo rting	Free of other bias
Astell et al [20],[21]	+	+	+	+	–	+	+	+
Nilsson et al [28]	+	**Unclear**	–	–	–	+	+	–
Wright et al [29]	**Unclear**	**Unclear**	+	+	–	+	+	–
Harrold et al [30]	+	**Unclear**	+	–	–	+	+	+
Gavrieli et al [31]	+	**Unclear**	–	–	–	+	+	–
Spadafranca et al [32]	**Unclear**	**Unclear**	+	+	–	+	+	+
Montelius 2014	+	**Unclear**	+	–	–	+	+	+
Darzi et al [33]	+	**Unclear**	–	–	–	+	+	+
Lambert et al [34]	+	+	+	+	–	+	+	–
Alkhatib et al [35]	**Unclear**	**Unclear**	+	+	–	+	+	–
Rebello et al [36]	+	**Unclear**	+	+	–	+	+	+
Loftus et al [37]	+	+	+	+	–	+	+	+
Ebrahimzadeh Attari et al [38]	+	**Unclear**	+	+	–	+	+	+
Dostal et al [39]	+	+	+	+	–	+	+	+
van Avesaat et al [40]	+	**Unclear**	+	–	–	+	+	–
Sandberg et al [41]	+	**Unclear**	–	–	–	+	+	–
Kudiganti et al [42]	+	+	+	+	–	+	+	+
Stefoska-Needham et al [43]	**Unclear**	**Unclear**	+	+	–	+	+	+
Jensen et al [44]	**Unclear**	**Unclear**	+	+	–	+	+	–
Brum et al [45]	**Unclear**	**Unclear**	+	+	–	+	+	+
Alkhatib and Atcheson[46]	**Unclear**	**Unclear**	+	+	–	+	+	+
Stefoska-Needham et al [47]	+	**Unclear**	+	+	–	+	+	–

reported digestive disorders associated with Capsicum oleoresin and psyllium, one article reported the occurrence of headache associated with Spinacia oleracea extract, 2 articles reported nausea associated with Capsicum oleoresin and vinegar, and one article reported 9 minor adverse events with Meratrim. Headache and gastrointestinal (GI) symptoms reported by Meratrim and Psyllium were similar with placebo.

3.5. Risk of bias within studies

The risk of bias for each trial was evaluated using the Cochrane Collaboration Tool (21). The results are summarized in Table 3. All 22 studies included in this review were described as randomized trials but random sequence generation was unclear in 7 studies. Allocation concealment was unclear in 17 trials. Blinding of patients was done in 18 studies and blinding of physicians was properly done in 15 studies; while blinding of outcome assessment was not described in none of the studies. Fifteen out of 22 articles were described as double-blinded (patient and physician).

3.6. Herbal intervention effective on appetite in longer-term

3.6.1. The capsule containing Meratrim product compared with placebo for 16 weeks

In an RCT conducted by Kudiganti et al in 2016, a product called Meratrim was studied over a period of 16 weeks and had positive effects on appetite in the intervention group compared with the placebo. Prescribed Meratrim capsules contained the Sphaeranthus indicus flower heads extract and Garcinia mangostana fruit that were compared to placebo capsules containing excipients. Among participants, 24 were men and 36 were women. The method of calculating sample size was based on a previous study and the randomization method was block randomization. The randomization process was described in detail. The method of blinding patients was described in this double-blinded study. No serious complications were observed after the use of meratrim, but 7 patients in the intervention group and 9 in the placebo showed minor gastrointestinal complications including increased gastric acidity, dyspepsia, nausea and gastritis. Given that these complications were common in both groups, they are most likely not attributable to the intervention. In this study, the mechanism of the effect of meratrim on weight loss was mentioned as inhibiting the lipidogenesis and lipid degradation through beta oxidation. Meratrim increased adiponectin, although it did not significantly differ from placebo. Meratrim did not make a significant difference in leptin and ghrelin, although it reduced hunger and resulted in satiation.[42]

3.7. Herbal interventions effective on appetite in the short term

3.7.1. Yerba mate compared with placebo: three clinical trials

In the present systematic review, three RCTs in which Ilex paraguariensis was used as ingredient in the studied product, met the inclusion criteria. Two of them showed meaningful positive effect on appetite, including Harold 2013 and Alkhatib and Atcheson[46] studies. In the study by Harold et al, the effect of a tablet contained Ilex paraguariensis (Yerba mate), Paullinia cupana (Guarana), and Turnera diffusa (Damiana) was compared with inulin fiber and placebo, also with synergistic formulation and fiber in women participants. [30] Ilex paraguayensis A. St.-Hil.is a genus of Aquifoliaceae family, Species *I. paraguariensis* and is known as Yerba mate. Paullinia cupana is a genus of the Sapindaceae family and is known as Guarana. Turnera diffusa is a genus of the Passifloraceae family and is known as Damiana. No adverse events have been reported following the use of the combination drug. The sample size calculation was done based on a prior unpublished study. The randomization and blinding processes were described in detail and the placebo content was listed but the allocation concealment was unclear. In this study, the caffeine content of Ilex paraguariensis was mentioned as a mechanism to reduce the energy intake and increase in energy expenditure. Compared to two other RCTs, the Harold study had a higher sample size, but the given drug was a combination. In the study by Alkhatib and Atcheson[46] the Ilex paraguariensis was used as a single herb. So, it shows the effects of Ilex paraguariensis on appetite specifically. The 2017 Alkhatib et al study showed a significant decrease in the rate of hunger and prospective eating and desire to eat following the administration of 2-grams Ilex paraguariensis capsule compared with placebo.[46] In a study by the same author in 2015, a multi-ingredient product containing Ilex paraguariensis did not have a significant effect on the appetite-related outcomes.[35]

3.7.2. Spinach Extract compared with placebo: two clinical trials

Spinacia oleracea L. is a genus of Amaranthaceae family, species *S. oleracea* and is known as Spinach. In a cross-over study by Rebello et al in 2015, a single dose of spinach extract significantly reduced the appetite-related outcomes compared with placebo. In this study, men showed a better response in reducing energy intake than women. One patient who showed serious headache was excluded from the study. This study showed that the addition of 5 g of condensed thylakoid extract from Spinacia oleracea in a single dose increased satiation 2 h after consumption.[36] However, in the long term study conducted by Montelius in 2014, there was no effect on the level of subjective appetite and the amount of GLP1 and ghrelin hormones after 90 days.[48] Spinach extract contains condensed thylakoid derived from Spinacia oleracea leaves chloroplast. In this article, it is suggested that the spinach extract can reduce appetite by interfering with lipids, slowing down the absorption of fat, releasing the satiation hormones such as cholecystokinin, and reduction of hunger hormones such as ghrelin.

3.7.3. Brown beans meal compared with wheat bread

Phaseolus vulgaris L. is a genus of Fabaceae family, Species *P. vulgaris* and is known as kidney bean. A study by Nilsson et al studied the effect of a meal consisted of Swedish brown beans (Phaseolus vulgaris var. nanus) in comparison with wheat bread at the dinner meal on appetite and regulating hormones in the next breakfast meal as a short-term cross-over randomized trial. This study showed a significant increase in the satiation hormones and a significant decrease in hunger hormones and the feeling of hunger with Phaseolus vulgaris in short term compared with wheat bread.[28] In this study, the biochemical properties of the intervention and control were fully described. The method of randomization, the basis and formula for calculating sample size and gender distribution were described, although the blinding process was not done. No drop was reported and no adverse events described.

3.7.4. Phaseolus vulgaris extract compared with placebo

A short-term study by Spadafranca et al compared the effect of 100 g of Phaseolus Vulgaris extract with placebo, taken immediately before meal. Phaseolus vulgaris tablets reduced eating desire compared with placebo and suppressed ghrelin secretion.[32]

This paper suggested that Phaseolus vulgaris extract delayed gastric emptying through carbohydrate hydrolysis. Thus, the modulation of the ghrelin hormone secretion can be mediated through the mechanism performed by cholecystokinin and Glucagon-like peptide. Also, the inhibition of alpha amylase, which regulates the secretion of ghrelin through the central nervous system, is another mechanism by which Phaseolus vulgaris might reduce the desire to eat.[32,49]

3.7.5. Whole grain rye kernel test bread compared with white wheat flour based bread

Secale cereale L. is a genus of Poaceae family, species *S. cereale* and is known as Rye. Whole grain rye kernel test bread reduced the subjective appetite and increased satiation hormones significantly compared to wheat bread in a randomized trial by Sandberg et al. In this study, the randomization was done using the Excel Random Formula. The base and formula for sample size calculation, and the gender distribution were mentioned. The biochemical characteristics of the Secale cereal and control were described. None of the subjects dropped out and no complication was reported for rye. In this paper, the improvement of glycemic regulation and increase in gut hormones involved in metabolism and appetite adjustment are suggested as the action mechanism of rye.[41]

3.7.6. Sorghum biscuits compared with wheat biscuits: two clinical trials

Sorghum bicolor (L.) Moench is a genus of Poaceae family, species *S. bicolor* and is known as Sorghum. The effects of Sorghum bicolor on appetite and appetite-related hormones were studied in two short and long term studies. In the short-term randomized crossover study by Stefoska et al, biscuits containing Sorghum (white, brown, red) were compared with wheat flour biscuits. The satiation feeling was decreased in the wheat flour group. The levels of satiety hormones were significantly increased in the Sorghum groups compared to wheat, but the energy intake did not differ significantly.[43] The long term 12-week study by same author demonstrated no meaningful effect for red Sorghum compared with placebo.[47]

In the short-term study, the biochemical characteristics of intervention and control were described; the basis and method of sample size calculation and the blinding process were expressed and the randomization was performed, but the randomization protocol was not described in detail. There was no drop in this study and no adverse event was detected. The gender distribution was described. The action mechanism of Sorghum was attributed to its fiber content in this study. Foods rich in fiber cause a delay in gastric emptying and enhance the feeling of satiation due to bulking, delay in gastric emptying, increasing the viscosity of the intestinal components. Both the wheat and Sorghum contain fiber and the main difference between them is probably in the total fiber and soluble fiber, which is suggested to be investigated in subsequent studies with higher doses. Also, Sorghum has a higher level of total polyphenol compared with wheat. Dietary polyphenols play a role in controlling and regulating appetite-related hormones.[47,50]

3.7.7. Psyllium compared with placebo

Plantago ovata Forssk. is a genus of Plantaginaceae family, species *P. ovata* and is known as blond psyllium. Psyllium was studied in a short term cross-over randomized study by Brown et al in 2016. Three doses of psyllium, 3.4 g, 6.8 and 10.2 resulted in a significant reduction in hunger and desire to eat and increase in the feeling of fullness between meals compared with placebo, and showed a more stable effect with the 6.8 g dose. [45] The biochemical characteristics of Psyllium and control were described and safety evaluation was done. Although this study was described as randomized and double-blinded, the details of the randomization protocol were not stated. The description of patients and study personnel's blinding was described in the article text, but there was no explanation for blinding of outcome assessment. The basis and method of sample size calculation, the drop rate, and the adverse events were mentioned. The adverse events were the same by 6.8-grams psyllium and placebo. They mainly included gastrointestinal disturbances, nausea, vomiting, and mild headache. In this paper, several mechanisms by which gel forming fibers such as psyllium cause satiation have been mentioned. One could be the delay in the degradation and nutrient absorption in the small intestine that results in sustained delivery of nutrients, and the delivery of nutrients to the distal ileum by stimulating the subsequent feedback mechanisms such as ileal brake phenomenon reduces appetite. The proposed mechanisms also include the role of gut hormones and the central nervous system.[45]

3.7.8. Beverage containing vinegar compared with vinegar-free beverage/ the vinegar taste

In a cross-over randomized study conducted by Darzi et al beverage containing vinegar was used in comparison with vinegar-free beverage and in the next stage, taste of vinegar was compared with the control group. The vinegar used was Tesco White Wine Vinegar, which contained 6% acetic acid. Vinegar significantly reduced quantitative appetite, but this effect was mainly due to low digestive tolerance and nausea. The study concluded that taking vinegar to suppress appetite is not recommended.[33] In this study, the biochemical characteristics of intervention and control were described; gender distribution was described; randomization was performed using the website (http://www.randomizer.org), and the basis and method of sample size calculation was described. The sample size seemed sufficient but blinding has not been possible in this study.

3.7.9. Infusion of Capsaicin into duodenum compared with placebo

Capsicum L. is a genus of Solanaceae family and is known as pepper. In a single-blinded cross-over randomized study conducted by van Avesaat, infusion of Capsicum oleoresin - an ethanol-based plant extract that contained 8.39% pure capsaicin- into duodenum significantly increased satiety compared to placebo, while satiation-related hormones did not significantly change. Increase in satiation was positively correlated with gastro-intestinal complications of Capsicum oleoresin including pain, burning, nausea and flatulence. Therefore, it seems that the effect of Capsicum oleoresin on the induction of satiation is due to the gastrointestinal discomfort.[40] In this study, the biochemical characteristics of intervention and placebo -normal saline- were described. The basis and method of sample size calculation was described and randomization was done via randomizer.org. There was one drop-out in the study due to discomfort caused by Capsicum oleoresin.

3.8. Herbal interventions not effective on appetite

3.8.1. Ginger rhizomes tablet compared with placebo for 12 weeks

Zingiber officinale Roscoe is a plant of Zingiberaceae family, species *Z. officinale* and known as garden ginger. In a double blinded study by Ebrahimzadeh Attari et al in 2015 on female participants, a slight but not statistically significant decrease in total appetite score was observed by Zingiber officinale tablets compared with placebo tablets contained corn starch after 12 weeks. The genotypic assessment showed that the appetite reduction effect of ginger was stronger in women with AA genotype. The total appetite score calculated by adding VAS scores in 5 domains of appetite changed from 29.3 ± 5.27–23.29 ± 5.3 by ginger, and 26.3 ± 9.34–23.09 ± 10.17 by placebo at week 8 ($p = 0.028$). However, the difference did not remain significant at the end of week 12 between groups. No specific adverse events were reported in this study. Randomization was done using random numbers table. Two mechanisms were mentioned for appetite reduction by ginger in this study; the modulation effect of ginger on 5-hydroxytryptamine and its receptors, and the digestive gastro-stimulant effect which increases gastrointestinal secretion and peristalsis and reduces the food transit time.[38]

3.8.2. Pea fiber biscuit compared with placebo

Pisum sativum L. is a genus of Fabaceae family, species *P. sativum* and known as garden pea. In a double-blinded study by Lambert, pea fiber and placebo had the same effects on VAS hunger/satiety scores.[34]

3.8.3. Caralluma fimbriata extract capsules compared with placebo

Caralluma adscendens (Roxb.) R.Br. or Caralluma fimbriata Wall. is a genus of Apocynaceae family, species *C. adscendens*. A double-blinded randomized clinical trial, conducted by Astell et al[20,21] on 33 participants, revealed similar effect of the capsule containing Caralluma Fimbriata extract and placebo in terms of desire to eat, hunger and total energy intake within 12 weeks[20,21].

3.8.4. Coleus forskohlii extract capsule compared with placebo

Plectranthus barbatus Andrews is a genus of Lamiaceae family, species *P. barbatus* and known as forskohlii. In a randomized, double-blinded clinical trial performed by Loftus et al., Coleus forskohlii extract capsule and placebo had the same effects on appetite, satiety, ghrelin and leptin during the 12-week period.[37]

3.8.5. Dried purple carrot compared with placebo

Daucus carota L. is a genus of Apiaceae family, species *D. carota* and known as wild carrot. In the double-blinded clinical trial conducted by Wright et al- the QUENCH trial, dried purple carrot did not have a significant effect on appetite and dietary intake compared with placebo.[29]

3.8.6. Tea / coffee compared with placebo

Camellia sinensis (L.) Kuntze is a genus of Theaceae family, species C. sinensis and known as tea. Teas are brewed from the leaves of Camellia sinensis. Various types of tea are categorized based on the degree of fermentation during manufacturing: nonfermented (green) tea, partially fermented (oolong) tea, fully fermented (black) tea, and postfermented tea (Puer). Coffee is a brewed drink prepared from roasted coffee beans, the seeds of berries from certain Coffea species. Coffea arabica L. is a genus of Rubiaceae family, species *C. Arabica* known as Arabian Coffee. Three studies were conducted on Puer tea, green tea and coffee. The decrease in appetite with Puer tea was not significant in comparison with placebo.[44] Green tea did not show a significant effect on appetite, ghrelin, leptin and adiponectin hormones in a long term 12 months study.[39] Coffee produced a significant decrease in energy intake, but there was no significant reduction in appetite.[31]

4. Discussion

The results of the clinical trials suggest 9 herbal medicines with a promising potential for outcomes related to appetite, of which, one showed appetite suppression effects in the longer term, and 8 in the short term. The herbal medicine that showed more prolonged effects (16 weeks) was the Meratrim formulation. The plants that suppressed appetite in the short term included psyllium, Ilex paraguariensis, Spinacia oleracea extract, Phaseolus vulgaris, Secale cereale, Sorghum bicolor, vinegar, and Capsicum oleoresin. Vinegar and Capsicum oleoresin are not recommended because they caused nausea and digestive complications.

In eleven studies, hormones related to appetite were measured. Among them only 3 herbal medicines induced significant hormonal changes. They include Phaseolus vulgaris, Secale cereal and Sorghum bicolor in short term.

The findings of our review are comparable to the systematic review of Astell et al [20,21]. In comparison, our study introduces more effective herbs to reduce appetite. Astell and colleagues explored plants affecting appetite with a goal to losing weight over a period of at least two weeks, only in obese and overweight people, from the beginning to December 2012; while we included all trials that examined appetite reduction regardless of weight loss and study duration from 2013 until 2018. One of our findings regarding Caralluma fimbriata is in contrast with the review of Astell et al. The systematic review of Astell et al suggested that Caralluma fimbriata was an effective herb on appetite whilst our systematic review conclude that it does not have a significant effect on appetite according to a clinical trial performed by the same author in 2013.

The strength of our review is the good coverage of all effective herbs on appetite, both in long and short term. Indeed, the current systematic review introduces herbal medicines that have shown positive results in the short term, especially those that have caused hormonal changes, including Phaseolus vulgaris, Secale cereal and Sorghum bicolor. We suggest that those plants could be investigated in future studies in the long term.

To the best of our knowledge, this is the first systematic review that reviews all appetite reducing herbs regardless of weight loss. Our review also had some limitations; one was limitation of language to English and Persian. So, we lost valuable articles in languages other than English and Persian.

In the studies examined in this systematic review, different mechanisms for controlling appetite were proposed. Herbs such as psyilium, rye and Sorghum increase the sense of satiety and reduce appetite due to high fiber content, through delayed absorption of food in the small intestine, delay in delivery of food to distal ileum, and stimulating gut hormones. Ginger can reduce appetite through two methods, modulating effect on 5-hydroxytryptamine, and the digesting stimulates effect. The mechanism of Spinacia oleracea on reducing appetite refers to its effect on satiety hormones such as cholecystokinin and hunger hormones such as ghrelin. Phaseolus vulgaris may inhibit appetite by increasing PYY, reducing ghrelin and GLP2.

The studies reviewed in this systematic review had some methodological shortcomings that reduce their quality and limit the judgment about the effectiveness of them. Some of them are reviewed below. The biochemical properties of the studied herbal medicines were not well described in some studies. Among studies with meaningful effect on appetite, three studies were conducted on female subjects only. This fact limits the generalizability of those studies to the entire community. The sample size of the studies was between 12 and 237. It should be noted that inadequate sample size, i.e. without an adequate sample size calculation, can make it difficult to assess the effectiveness of the herbal medicines in suppressing appetite. There seems to be insufficient attention to reporting adverse events in some of the investigated studies. Among effective interventions, there was no adverse event reporting in 3articles; 2 articles mentioned the absence of any adverse event; and in one article each headache or nausea, and in 2 articles gastrointestinal disorders were reported. There was not much drop-out in the studies, which may be due to the short duration of most of the reviewed studies. Other methodological shortcomings include the lack of clarity in the expression of the random sequence generation and allocation concealment in 7 and 17 papers respectively; also, the lack of explanation about the basis and method of calculating the sample size in some papers.

Suppressing appetite may also be considered as an anti-aging intervention to extend longevity and prevent chronic diseases by mimicking the effects of caloric restriction (CR) - The most effective known anti-aging intervention. Moreover, many compounds isolated from plants prolong lifespan and prevent age-related diseases by modulating the same cellular and physiological pathways as CR.[51,52]

Recent studies have revolutionized the treatment of obesity. Neurohormonal pathways, which are in fact a network of neurotransmitters between the gut and the brain, and the hypothalamus, are responsible for regulating signals that receive food and homeostasis of the energy.

Hormones such as ghrelin, glucagon like peptide 1 (GLP-1) peptide YY (PYY), pancreatic polypeptide (PP), cholecystokinin (CCK) secreted by an endocrine organ gut, have an intense impact on energy balance and maintenance of homeostasis by inducing satiety and meal termination [53].

In this systematic review, 5 short-term studies and 6 long-term hormonal evaluation studies were performed. Therefore, in order to a more accurate assessment of the herbal medicines that were suggested as appetite suppressants in the short term by this review, we suggest the design of future clinical trials should be double-blinded, consistent with CONSORT guideline, and long-term with adequate doses and hormonal assessment in addition to the subjective evaluation of appetite.

5. Conclusion

Despite some methodological flaws in the reviewed studies on herbal medicines affecting appetite, some of them suggest promising results including Meratrim formulation which contained the Sphaeranthus indicus flower heads extract and Garcinia mangostana fruit in the long term; and Ilex paraguariensis, Spinacia oleracea, Phaseolus vulgaris, Secale cereale, Sorghum bicolor and psyllium in short-term; besides hormonal changes by Phaseolus vulgaris, Secale cereal and Sorghum bicolor. The demonstration of their effectiveness requires the design of long-term clinical trials with adequate sample size and higher methodological quality, with more attention to efficacy, effective dosage and side effects in future.

Conflict of interests

None.

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