

Methodological insights into intervention and outcomes in randomised controlled trials of herbal medicine for obesity: a scoping review

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Abstract

Background: With rising obesity rates worldwide, clinical trials focused on identifying effective treatments are increasing. While guidelines exist for pharmaceutical drugs targeting obesity, there are none for herbal medicine clinical trials for anti-obesity. Both industries refer to the same guidelines for clinical trials.

Objectives: This scoping review aimed to gather information from herbal medicine anti-obesity randomised controlled trials (RCTs), analyse the methodologies and assess their alignment with international guidelines.

Eligibility criteria: This review included RCTs of participants of all ages with obesity utilising herbal medicine with any comparators and focusing on various outcome measures.

Sources of evidence: Only published journal articles were included.

Charting methods: Articles were extracted from MEDLINE, CENTRAL and EMBASE using predetermined keywords. Relevant data, such as the study characteristics, types of herbal interventions and controls, treatment durations, outcome measures and safety monitoring methods were recorded in a table format for comparative analysis.

Results: We included 99 RCTs that showed participant sample sizes ranging from 8 to 182, ages 18 to 80 years and body mass indexes (BMIs) between 25 and 49.9 kg/m². Herbal interventions used single herbs ($n=57$) and mixtures ($n=42$), given for 14 days to 56 weeks. Studies implementing diet modifications include restricted calorie diets ($n=35$), food-portion controlled diets ($n=7$) and fixed calorie diets ($n=7$). Of the 28 studies implementing exercise, most were of moderate intensity ($n=22$). All studies collected BMI and weight as primary outcomes. Body fat composition was measured in over 50% of studies using a body analyser ($n=57$). Waist, hip and abdominal circumferences were infrequently measured. Radiological tools used include dual-energy X-ray absorptiometry ($n=16$), computed tomography scans ($n=10$) and ultrasound ($n=2$). Safety monitoring methods were reported in most studies ($n=76$).

Conclusion: In conclusion, almost 50% of the studies adhered to international pharmaceutical clinical trial guidelines, addressing dietary, lifestyle, physical activity and cardiovascular risk factors. Nonetheless, more herbal anti-obesity studies need to consider the assessment of weight maintenance.

Ther Adv Chronic Dis

2025, Vol. 16: 1–44

DOI: 10.1177/
20406223241310206

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Plain language summary

Clinical trials of herbal medicine for obesity: a scoping review of methodologies

The global rise in obesity has increased the focus on clinical trials to identify effective treatments. While guidelines such as the USFDA Guidance for Industry Developing Products for Weight Management (2007) and the EMA Guideline on Clinical Evaluation of Medicinal Products Used in Weight Management (2017) exist, they have not been updated recently, and specific guidelines for herbal medicine are lacking. Consequently, both industries often refer to the same guidelines. Our review aimed to gather and analyse data from randomised controlled trials (RCTs) involving herbal medicine for anti-obesity treatment. We examined how these trials are conducted, their adherence to international guidelines, and identified specific challenges and limitations. The review included 99 studies, with sample sizes ranging from 8 to 182, ages 18 to 80 years, and BMIs between 25 and 49.9 kg/m². Nearly 50% of the RCTs adhered to international pharmaceutical guidelines, but significant gaps remain, particularly regarding study duration, lifestyle modifications and safety monitoring. These findings highlight the need for specific guidelines for herbal medicine trials.

Keywords: herbal medicine, methodology, obesity, overweight, scoping review

Received: 23 August 2024; revised manuscript accepted: 9 December 2024.

Introduction

Globally, obesity is a rising health crisis. Obesity is one of the most prevalent non-communicable diseases, causing a multitude of health challenges. In the United States of America (USA), the prevalence of obesity has escalated from 30.5% in 2000 to 41.9% in 2020.¹ An increase in obesity prevalence is also seen locally in Malaysia. The National Health and Morbidity Survey (NHMS) reports of 2015 and 2019 estimated that the prevalence of overweight adults was 30.0% and 30.4%, whereas obesity prevalence was 17.7% and 19.7%, respectively.² Increased risk of many serious diseases, including cardiovascular diseases, stroke, diabetes mellitus, hypertension, dyslipidaemia, chronic kidney disease, respiratory dysfunction, osteoarthritis and certain cancers are associated with the growing obesity epidemic and sedentary lifestyle.³ Obesity has also been identified as an independent risk factor for severe COVID-19, intensive care unit admissions and deaths.^{4,5}

Overweight and obesity are influenced by a combination of risk factors, including individual dietary, exercise, behavioural and lifestyle choices, in addition to individual genetics, environment and

metabolic risk factors.⁶ A review by Swinburn et al.⁷ reported that poor dietary habits and inadequate physical activity are contributing factors to the development of obesity. Dietary fibre (non-starch polysaccharides) and physical exercise were found to be substantially protective against obesity, while sedentary lifestyles and high intakes of high-energy food which are deficient in micronutrients were risk factors for obesity.⁷ Another review discussed that sedentary lifestyle, in addition to decreasing energy expenditure, is also associated with an increased risk of cardiometabolic diseases, independent of physical activity levels.⁸ A questionnaire-based study by Junne et al.⁹ found that specific obesity-related psychological and social factors, such as dissatisfaction with body figure and social insecurity, can lead to stress. Prolonged stress affects metabolism, causes negative emotions and hormonal imbalances, which can then promote binge eating, a heightened appetite and cravings for unhealthy foods.⁹

In response to the escalating prevalence of obesity, there has been a surge in clinical trials aiming to identify effective interventions. These trials utilise a wide range of approaches to address the

complex nature of obesity. For instance, there are anti-obesity trials with behavioural approaches,^{10–12} pharmacological approaches,^{13–15} dietary approaches,^{16–18} and others. In anti-obesity human trials, a comprehensive approach is usually recommended. This begins with a thorough history taking, anthropometry measurements, physical examination and necessary laboratory tests. This initial assessment is critical for evaluating the severity of obesity and related health issues. Following that, setting realistic weight loss goals is crucial. The main principle of obesity treatment is lifestyle modification which includes adopting a hypocaloric or normocaloric diet, increasing physical activity and in some cases, undergoing cognitive behavioural therapy. Non-invasive treatment methods that could be beneficial include pharmacotherapy, vaccines, gut microbiota modulation and gene therapy. That said, obesity management could differ among individuals, and a tailored approach needs to be adopted.¹⁹

Historically, pharmacological management of obesity has been associated notoriously with serious adverse effects. The infamous anti-obesity drug, Sibutramine, which was withdrawn in 2010, was associated with an increased risk of heart attacks and strokes in patients with cardiovascular disease history.²⁰ The same goes for several other banned anti-obesity drugs such as ephedra,²¹ rimonabant and dinitrophenol, which have been associated with negative cardiovascular, pulmonary and metabolic effects.²²

Concerned with the risk of harm associated with pharmacological anti-obesity drugs, there is growing interest in developing herbal and complementary medicines with the perception that natural remedies could potentially offer a safer alternative, though this remains to be proven. Herbal medicine has been used for centuries to prevent and treat various diseases, and many studies have reported their efficacies in obesity treatment.²³ Herbal medicine is defined by the World Health Organization (WHO) as ‘herbs, herbal materials, herbal preparations and finished herbal products, that contain parts of plants, other plant materials or combinations thereof as active ingredients’.²⁴ Among the potential anti-obesity benefits that may be offered by herbal medicine include mechanisms like thermogenesis, inhibiting pancreatic lipase activity, reducing food intake and increasing lipolysis.²⁵ Secondary metabolites commonly

found in medicinal plants, such as flavonoids and saponins, can trigger physiological changes (i.e. upregulating glutathione and superoxide dismutase production and inhibiting cell growth), offering potential therapeutic benefits for metabolic disorders and obesity treatment.²⁶

Medicinal products (conventional and herbal medicine) with weight loss claims should be tested rigorously in clinical trials to prove their efficacy and safety in humans. The European Medicines Agency (EMA)²⁷ and United States Food and Drug Administration (US FDA)²⁸ have laid out guidelines for the industries to conduct clinical trials for medicinal products on obesity, outlining some recommended requirements to facilitate drug development. These guidelines are used universally for all interventions. Despite the standard recommendations for obesity trials, it is common for individual clinical trials to be conducted uniquely as there is no one-size-fits-all methodology. Anti-obesity clinical trials often have the additional consideration of incorporating adjunct therapies such as lifestyle modifications. A long study duration with additional follow-ups conducted at least 6 months after treatment cessation is also often recommended to reflect good and sustainable efficacy. These requirements can be challenging to be met by both investigators and participants of clinical trials, consequently leading to high drop-out rates, or loss to follow-up.²⁹

Although there are some similarities between herbal medicine and conventional medicine trials, there are also additional requirements. For example, in herbal medicine interventional trials, the quality of the herbal interventions is an important consideration.^{30,31} In addition, compared to conventional medicines or synthetic small molecules, which often have specific pharmacological targets, herbal medicine, rich in phytoconstituents, is often reported to have pleiotropic effects, modulating multiple pathways simultaneously.³² In some cases, the principles of treatment of obesity may differ between traditional medicine philosophies and modern medicine approaches. For instance, traditional Chinese medicine addresses diseases in an integrated manner, targeting multiple interactions in a biological system, and is personalised according to the individual. Modern medicine, on the other hand, comprises well-defined chemical compounds that are designed to

target specific molecular pathways or biological processes, with their direct effects well-understood and predictable.³³ In view of the known differences between herbal medicine and conventional medicine, given that current anti-obesity guidelines for clinical trials are catered generally to conventional drug development, there is a significant research gap in understanding how herbal medicine trials have been conducted. Therefore, we conducted this scoping review to collate literature of clinical trials investigating the anti-obesity effects of herbal medicines to gain insights towards the landscape of methodologies used in such trials and explore the associated challenges as well as limitations unique to herbal trials.

Methods

This review was conducted according to the York Framework of scoping studies by Arksey and O'Malley,³⁴ refined by Levac et al.³⁵ This framework serves as a guide for a standardised and systematic approach in conducting scoping studies to address new or broad research questions of complex or heterogeneous nature. All five stages of the scoping review, namely, (1) identification of research question(s), (2) identification of relevant studies, (3) selection of studies, (4) data charting and (5) collation, summarisation and reporting of findings, were undertaken.³⁶ We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure relevant items for the scoping review were included. The PRISMA Scoping Review checklist is provided in Supplemental Material 1.

Identification of research questions

This review was conducted based on the primary research question 'What are the methodologies used for herbal medicine randomised controlled trials (RCTs) for the management of obesity?'

Secondary research questions include the following:

1. What are the commonly collected measurements to assess anti-obesity effects of herbal medicines in RCTs and how were they measured?

2. What are the common laboratory tests carried out to assess the efficacy of intervention in reducing obesity?
3. What adjunct therapies are commonly used in the trials?
4. How was the safety monitoring carried out?
5. Were herbal trials performed differently from those as recommended in guidelines for interventional anti-obesity RCTs? If so, how are they different?

Identification of relevant studies

Inclusion and exclusion criteria. Only English-language publications were included. There was no year limit on publications. Review papers and book sections were excluded. All searches were performed and matched by two independent investigators. Search results were managed using bibliographic software (EndNote X9), and duplicates were removed. The following population, intervention, comparison, outcome and study design (PICOS) framework was used to identify relevant articles:

Participants. Participants included individuals of all ages who are obese or overweight, with or without comorbidities. Overweight was defined as a body mass index (BMI) ranging from 25 to $<30 \text{ kg/m}^2$, while obesity was defined as $\text{BMI} \geq 30 \text{ kg/m}^2$.³⁷

Interventions. Herbal medicine is defined by the WHO²⁴ as the main intervention. This review included herbal medicines in the form of a single herb or herbal mixture in any formulation.

Comparators. Studies with any comparators were included.

Outcome. The outcomes of our review focused on parameters of methodologies, mainly:

1. anthropometric measurements (e.g. BMI, waist and hip circumference and body fat composition)
2. objective measurement tools of efficacy (e.g. weighing scales, measuring tapes, bio-electrical impedance analysis, dual-energy X-ray absorptiometry (DEXA))
3. subjective measurement tools of efficacy (e.g. questionnaires to evaluate the

participant's quality of life, stress response, eating habits and other factors related to obesity)

4. laboratory parameters (e.g. biochemical or hormone tests related to obesity)
5. behavioural interventions (e.g. diet regimen and physical activities)
6. multi-disciplinary team approach (e.g. involvement of dietitian or allied healthcare professionals)
7. use of concomitant herbs, drugs or supplements
8. parameters for safety monitoring (e.g. clinical examination, clinical bedside tests such as vital signs measurement and electrocardiography, biochemical tests and adverse event self-reporting).

Study design. RCTs were included.

Search strategy. A systematic search was conducted by two independent investigators for published literature with predetermined keywords. Three electronic databases (MEDLINE via PubMed, CENTRAL via Cochrane Library, Embase via Ovid) were searched from their inception until March 2023. The search was constructed around the keyword search terms 'obesity or overweight', 'weight loss' and 'herbal medicine'. These were adapted for each database as necessary. The complete search strategy for the databases is shown in Supplemental Material 2.

Selection of studies

The articles from each database were then imported into the Endnote (Version X9, Clarivate Analytics, Philadelphia, 2013) reference manager for deduplication. After deduplication, the remaining articles were transferred to an Excel document for title and abstract screening. This screening was conducted by five pairs of investigators independently and cross-checked afterwards. In cases of disagreements, a third investigator was consulted. Studies were selected based on the inclusion and exclusion criteria with reference to the research questions and PICOS elements mentioned. Studies that appeared to meet the inclusion criteria subsequently undergo screening of the full text. Full-text article screening was conducted by four pairs of investigators independently and cross-checked afterwards. Following full-text screening, two investigators

assessed the overall studies included again before proceeding with data extraction.

Data charting

Data extraction was performed by four pairs of investigators. The characteristics of each study were extracted, including study details (author, year of publication, country, study design, trial registry number, ethics approval, study phase, primary and secondary objectives, sample size, drop-out rate, power of study and informed consent), participants (age, sex, inclusion criteria, exclusion criteria, recruitment sites or intervention delivery setting), intervention (type, dose, frequency, duration, route of administration, voucher specimen, qualitative or quantitative tests and any use of concomitant herbs, drugs or supplement), behavioural interventions (diet regimen and physical activities) and outcome measurements (primary and secondary parameters, physical measurements, radiological estimation measurements, biochemical measurements, questionnaires, other methods for determining obesity parameters). We also extracted data on the involvement of dietitians or allied healthcare professionals, compliance monitoring methods and safety monitoring (reporting of adverse events or other related investigations).

Collation, summarisation and reporting of findings

We performed a descriptive numerical analysis using the extracted data details. Subsequently, a comparative analysis was undertaken to assess the methodologies employed in the included studies. This comparison was based on established obesity clinical trial guidelines, specifically the USFDA Guidance for Industry Developing Products for Weight Management (2007)²⁸ and the EMA Guideline on Clinical Evaluation of Medicinal Products Used in Weight Management (2016).²⁷

Results

Study selection

A total of 1367 records were identified from online databases. Prior to the abstract screening, 105 duplicate records were removed, resulting in 1262 studies being screened. Of these, 114

full-text studies were assessed for eligibility, and 99 studies were included for analysis. Our primary focus is on the methodologies of the trials rather than their findings. The study selection process is presented in the PRISMA flowchart shown in Figure 1.

Characteristics of included studies

Study characteristics. The study designs of the included articles were all RCTs of herbal-related interventions for obesity. The sample size included in the study ranged from 8 to 182 participants and were mainly from the age range of 18–80 years. There were no participants aged younger than 18 years in the studies found. The BMI range of all the studies was from 25 to 49.9 kg/m². The participants were either healthy patients with obesity (*n* = 81 studies) or with comorbidities (*n* = 18

studies) including hyperlipidaemia, metabolic syndrome, type 2 diabetes mellitus and schizophrenia. The types of intervention used were all herbal medicine as defined by the WHO.²⁴ The recruitment locations for different studies varied and included virtual recruitment through social media platforms or marketing (*n* = 13), as well as recruitment sites such as medical and research centres (*n* = 46), public health clinics (*n* = 3) and other public facilities (*n* = 3). Some studies did not mention their recruitment sites (*n* = 34). Additionally, studies were categorised based on whether they were conducted at a single centre or involved multiple centres. This diversity in recruitment strategies and study settings contributes to the overall understanding of the recruitment landscape in the reviewed studies. In several studies (*n* = 6), a run-in period was implemented prior to study commencement. The duration of the run-in

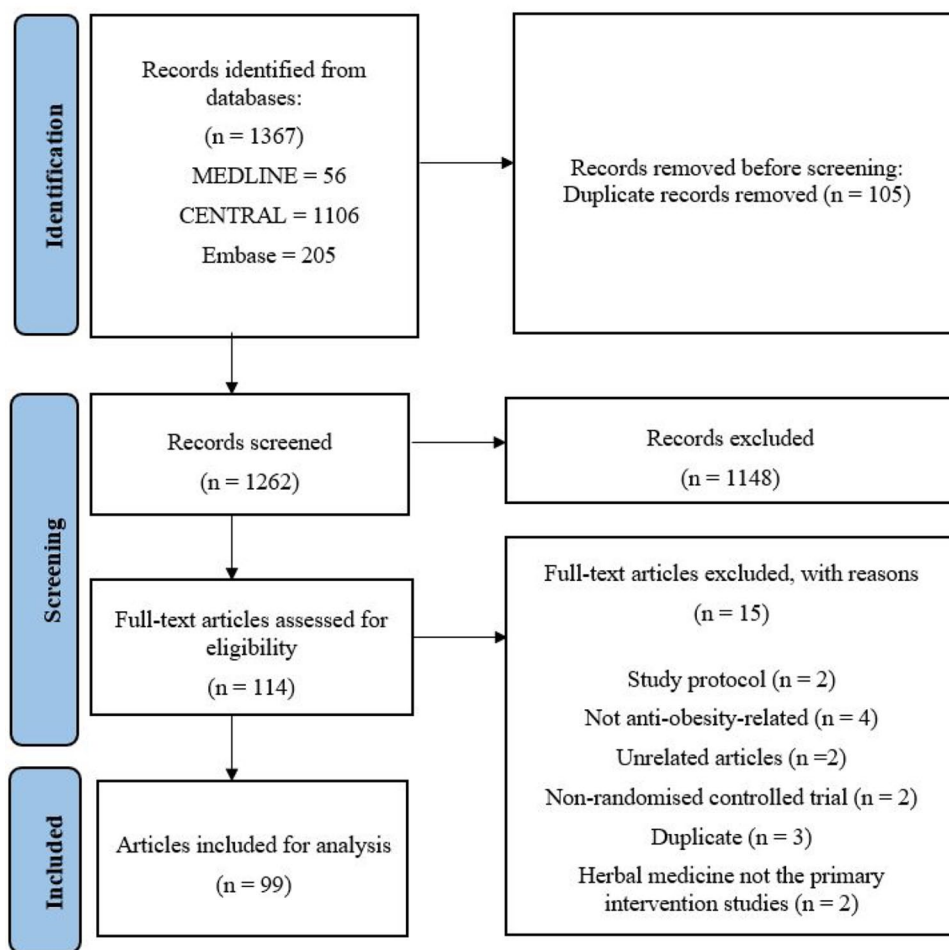


Figure 1. PRISMA flowchart of included studies. PRISMA, preferred reporting items for systematic reviews and meta-analyses.

was from 3 days to 2 weeks. A summary table of the characteristics of the included studies is shown in Supplemental Material 3.

Countries included RCTs. The USA had the highest number of herbal medicine anti-obesity RCTs ($n=18$), followed by Korea ($n=12$), Iran ($n=11$), India ($n=9$), Japan ($n=6$), Italy ($n=5$), Cameroon ($n=4$), Australia ($n=4$), Brazil ($n=3$), Taiwan ($n=3$), China ($n=3$), Pakistan ($n=2$), Germany ($n=2$), Canada ($n=2$), Poland ($n=2$) and France ($n=2$). The remaining countries, namely Mexico, Thailand, Romania, Spain, Denmark, Iraq, Russia, Armenia, Syria, Netherlands and Argentina, had one study each. Figure 2 shows the worldwide distribution of anti-obesity RCTs involving herbal medicines.

Herbal intervention, daily dosage, duration

We categorised the herbal interventions into single herbs ($n=57$) and mixtures ($n=42$). The treatment duration varies from as short as 14 days to as long as 56 weeks. The most studied herbs in obesity RCTs are *Ephedra sinica* as a mixture

($n=9$), *Camellia sinensis* as a single herb ($n=5$) and in mixture ($n=4$). Only one study utilised an injectable form for administering the herbal medicine, whereas the others ($n=96$) used oral formulations in various forms such as tablets, capsules, gel, powder, granules, decoction, oral spray, syrup, seeds, cereal, confection or served as a beverage. Two studies did not provide information about the type of formulation used. Details of the herbal interventions included RCTs were presented in Table 1.

Lifestyle modifications

For adjunct treatments, we categorized the included studies into the following groups: (1) without lifestyle modifications, (2) diet only, (3) exercise only and (4) both diet and exercise implementation. The distribution of studies across these categories is shown in Figure 3. The majority of studies incorporated dietary modifications, with restricted calorie diet being the most frequently implemented ($n=35$), followed by a food-portion controlled diet ($n=7$) and fixed calorie diet ($n=7$). Additionally, 23 studies adopted a

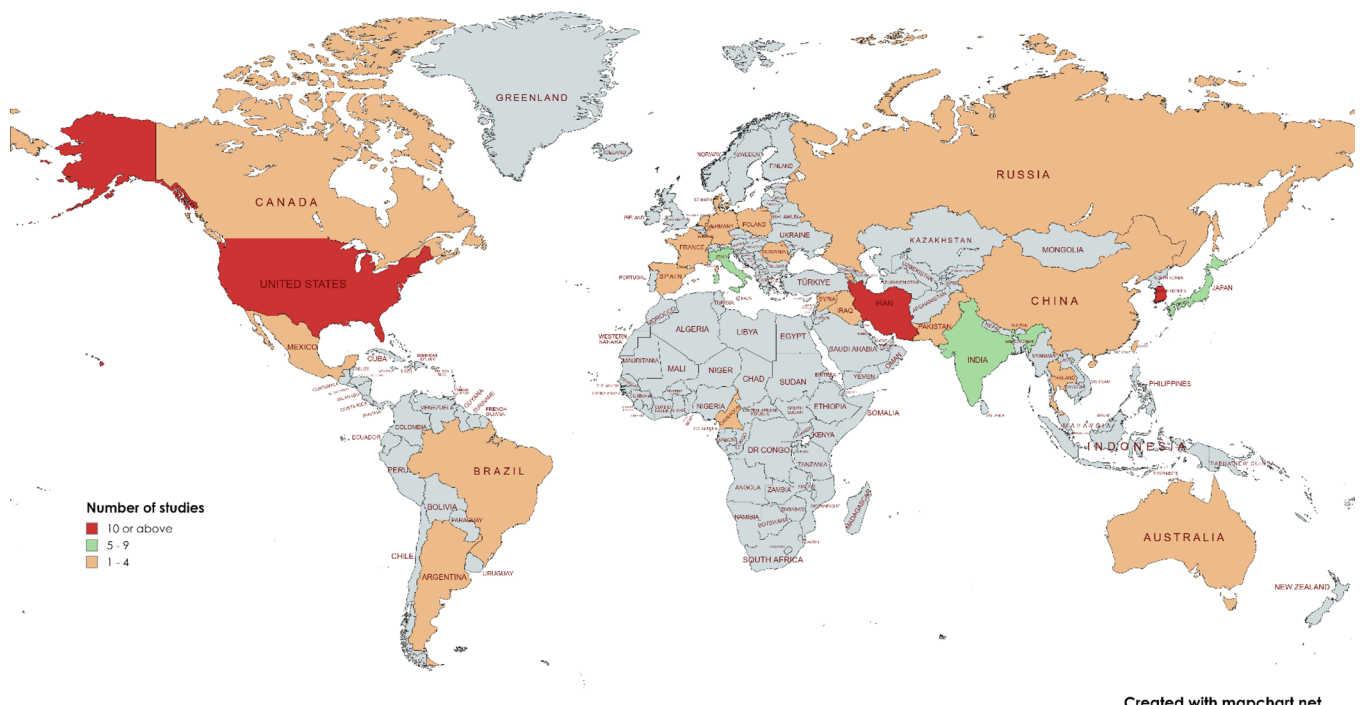


Figure 2. Geographical demographics of included RCTs. RCT, randomised controlled trials.

Table 1. Herbal intervention details of included RCTs.

No.	Study Location	Single herb/mixtures	Herbal intervention (daily dose; duration)	Formulation	Comparator
1	Fernandes (2023) ³⁸ Brazil	Single herb	<i>Amorphophallus konjac</i> tubers gummies 500 mg, 14 days	Confectionery	Golden flaxseed meal gummies
2	Ain (2022) ³⁹ India	Mixture	Jawarish Falafali 10 g; <i>Piper nigrum</i> mature dried fruit 200 g, <i>P. nigrum</i> dried fruit without pericarp 200 g, <i>P. longum</i> mature dried fruits 200 g, <i>Commiphora opobalsamum</i> (L) Engl. stem 10 g, <i>Cinnamomum cassia</i> bark, 10 g, <i>Apium graveolens</i> seeds 10 g, <i>Asarum europaeum</i> root 10 g, <i>Zingiber officinale</i> rhizome 10 g, <i>Apis mellifera</i> nectar 1.95 kg; 90 days	Gel	Atorvastatin 20 mg/day
3	Cortez-Navarrete (2022) ⁴⁰ Mexico	Single herb	<i>Momordica charantia</i> 2000 mg; 12 weeks	Capsule	Placebo (calcined magnesia)
4	Lee (2022) ⁴¹ Taiwan	Single herb	<i>Cassia obtusifolia</i> seed powder 3000 mg; 36 weeks	Powder	Placebo (0.3 g Cassia seed powder and 2.7 g starch)
5	Liu (2022) ⁴² China	Mixture	Hedan tablets 4.38 g; <i>Folium Nelumbinis</i> , <i>Radix Salviae Miltiorrhizae</i> , <i>Fructus Crataegi</i> , <i>Folium Sennae</i> and <i>Fructus Psoraleae</i> ; Dose not reported; 24 weeks	Tablet	Placebo (starch)
6	Rao (2022) ⁴³ Australia	Single herb	ActivAMP® <i>Gynostemma pentaphyllum</i> 450 mg; 16 weeks	Capsule	Placebo (maltodextrin)
7	Aoe (2021) ⁴⁴ Japan	Single herb	<i>Laminaria japonica</i> boiled kelp powder: Alginate 3279 mg; 8 weeks	Tablet	Placebo
8	Gherbon (2021) ⁴⁵ Romania	Single herb	<i>Aloe ferox</i> crystallised juice 920 mg; 3 months (2-week treatment, 2-week break, repeated 3 times)	Capsule	Placebo
9	Hancke (2021) ⁴⁶ USA	Mixture	CitruSlim: <i>Bergamote Citrus bergamia</i> Risso (fruit) extract and <i>Adapticort Eurycoma longifolia</i> (root) extract; (1) 1200 mg CitruSlim-HD, (2) 600 mg CitruSlim-LD; 112 days	Capsule	Placebo (methyl crystalline cellulose)
10	Lin (2021) ⁴⁷ Taiwan	Single herb	<i>Citrus reticulata</i> extract 20 ml; 6 weeks	Beverage	Placebo (water)
11	Hosseini (2020) ⁴⁸ Iran	Single herb	Green tea 500 mg; catechin 300 mg; 8 weeks	Tablet	Placebo (starch)

(Continued)

Table 1. (Continued)

No.	Study Location	Single herb/ mixtures	Herbal intervention (daily dose; duration)	Formulation	Comparator
12	Abolghasemi (2020) ⁴⁹ Iran	Single herb	Zataria oxymel syrup: <i>Zataria multiflora</i> Boiss., sugar, vinegar, water; (1) 1500 mg ZM in 20 ml oxymel, (2) 3000 mg ZM in 20 ml oxymel. 12 weeks	Syrup	Oxymel
13	Cheon (2020) ⁵⁰ Korea	Mixture	Euiyin-tang 3300 mg; 1330 mg <i>Ephedra sinica</i> Stapf, 1330 mg <i>Angelica gigantis</i> Radix, 1330 mg <i>Atractylodis rhizoma</i> Alba, 3330 mg <i>Coicis Semen</i> , 1000 mg <i>Cinnamomi cortex</i> , 1000 mg <i>Paeonia lactiflora</i> , 670 mg <i>Glycyrrhiza uralensis</i> ; 12 weeks	Granule	Placebo (corn starch, lactose hydrate)
14	Riazurrehman (2020) ⁵¹ Pakistan	Mixture	Obesecure 1000 mg: <i>Caralluma fimbriata</i> dried extract, <i>Saussurea costus</i> roots, <i>Delphinium denudatum</i> roots, <i>Cassia fistula</i> dried legumes; 3 months	Capsule	Placebo (Plasicure)
15	Etemad (2019) ⁵² Iran	Single herb	200 mg strawberry extract; 14 days	Capsule	Placebo (not reported)
16	Heydari (2019) ⁵³ Iran	Single herb	1000 mg <i>Rhus coriaria</i> L. (Sumac) fruit; 6 weeks	Capsule	Placebo (white wheat flour)
17	Jeong (2019) ⁵⁴ Korea	Single herb	ONIRO 2700 mg: hydrolysed Jeju steamed onion 1012 mg; 12 weeks	Capsule	Placebo (baked barley powder, indigestible maltodextrin)
18	Leverrier (2019) ⁵⁵ Spain	Single herb	<i>Helianthus annuus</i> seed extract 500 mg; 12 weeks	Capsule	Placebo (maltodextrin)
19	Nishimura (2019) ⁵⁶ Japan	Single herb	Quercetin-rich onion powder 9000 mg; quercetin aglycone 60 mg; 12 weeks	Powder	Placebo (white onion powder)
20	Salunke (2019) ⁵⁷ India	Mixture	Trimad 500 mg: <i>Cyperus rotundus</i> tubers, <i>Embelia ribes</i> fruits and <i>Plumbago zeylanica</i> roots; Triphala 500 mg: <i>Terminalia chebula</i> , <i>T. bellirica</i> and <i>Phyllanthus emblica</i> fruits; (1) overweight: Trimad 2000 mg/Triphala 2000 mg, (2) obese: Trimad 3000 mg/Triphala 3000 mg; 3 months	Tablet	Placebo (dextrin)
21	Uebelhack (2019) ⁵⁸ Germany	Mixture	IQP-AE-103: <i>Abelmoschus esculentus</i> whole okra pods; High dose: 1980 mg, Low-dose: 990 mg; 12 weeks	Capsule	Placebo (standard excipients)
22	Dixit (2018) ⁵⁹ India	Mixture	LI85008F/Slimvance/Slendacor: <i>Moringa oleifera</i> 360 mg, <i>Murraya koenigii</i> 180 mg and <i>Curcuma longa</i> 60 mg); 16 weeks	Capsule	Placebo (maize starch and xylitol)
23	Gholaman (2018) ⁶⁰ Iran	Single herb	Fenugreek seeds 15 grams, mixed with yoghurt (100 g); 8 weeks	Seeds	Placebo (yoghurt with flavour)

(Continued)

Table 1. (Continued)

No.	Study Location	Single herb/mixtures	Herbal intervention (daily dose; duration)	Formulation	Comparator
24	Kakutani (2018) ⁶¹ Japan	Mixture	PapriX: paprika xanthophylls 9 mg; 12 weeks	Capsule	Placebo (vegetable oil and caramel colouring)
25	Kang (2018) ⁶² Korea	Mixture	Ob-X 1380 mg; <i>Morus alba</i> L. 612.6 mg, <i>Melissa officinalis</i> L. 614.4 mg, <i>Artemisia capillaris</i> 153 mg; 12 weeks	Capsule	Placebo (dextrin)
26	Yousefi (2018) ⁶³ Iran	Single herb	Spiruvit® <i>Spirulina platensis</i> 2000 mg; 12 weeks	Tablet	Placebo (starch and lactose monohydrate)
27	Cho (2017) ⁶⁴ Korea	Mixture	YY-312 (1800 mg) <i>Imperata cylindrica</i> Beauvois, <i>Citrus unshiu</i> Markovich, <i>Evodia officinalis</i> Dode [5:2:3]; cyclodextrin (600 mg); 12 weeks	Tablet	Not reported
28	Vuksan (2017) ⁶⁵ Canada	Single herb	Salba-chia <i>Salvia hispanica</i> L. 30 g/1000 kcal/day; 6 months	Chia seed-infused bread and chia seed powder	Placebo (oat bran)
29	Zeinalian (2017) ⁶⁶ Iran	Single herb	<i>Spirulina platensis</i> 1000 mg; 12 weeks	Tablet	Placebo (starch)
30	Chung (2016) ⁶⁷ Korea	Mixture	Qingxue Dan 900 mg; <i>Scutellaria baicalensis</i> GEORGI, <i>Coptis japonica</i> MAKINO, <i>Phellodendron amurense</i> RUPRECHT, <i>Gardenia jasminoides</i> ELLIS, <i>Rheum palmatum</i> L.; 8 weeks	Capsule	Placebo (phenylthiocarbamide, squid ink, herbal flavor, starch)
31	Jensen (2016) ⁶⁸ USA	Single herb	Puer tea extract 3000 mg; 20 weeks	Tea	Placebo (dextrin)
32	Kazemipoor (2016) ⁶⁹ Iran	Single herb	Caraway <i>Carum carvi</i> L. 30 ml; 90 days	Beverage	Placebo (edible caraway essence in drinking water (1% g/L))
33	Kudiganti (2016) ⁷⁰ India	Mixture	Meratrim: <i>Sphaeranthus indicus</i> flower heads extract 600 mg, <i>Garcinia mangostana</i> fruit rind 200 mg; 16 weeks	Capsule	Placebo (microcrystalline cellulose)
34	Lee (2016) ⁷¹ Korea	Single herb	<i>Glycine max./Chongja</i> No. 3: Anthocyanin rich-black soybean testa extracts; 2500 mg; 8 weeks	Capsule	Placebo (starch)
35	Morimoto-Kobayashi (2016) ⁷² Japan	Single herb	<i>Humulus lupulus</i> L. matured hop extracts; MHBA 35 mg; 350 ml; 12 weeks	Beverage	Placebo
36	Khazaal (2015) ⁷³ Iraq	Single herb	(1) Raspberry Ketones 500 mg pure ketones 500®; (2) L-carnitine 1000 mg; 12 weeks	Capsule	Placebo (without treatment)

(Continued)

Table 1. (Continued)

No.	Study Location	Single herb/ mixtures	Herbal intervention (daily dose; duration)	Formulation	Comparator
37	Kim (2015) ⁷⁴ Korea	Single herb	<i>Ilex paraguariensis</i> 3150 mg; 12 weeks	Capsule	Not reported
38	Taghizadeh (2015) ⁷⁵ Iran	Single herb	<i>Cumin cyminum</i> essential oil 300 mg; 8 weeks	Capsule	(1) Orlistat 120 mg (2) Placebo (not reported)
39	Toscano (2015) ⁷⁶ Brazil	Single herb	<i>Salvia hispanica</i> chia flour 35 g; 12 weeks	Dietary supplement	Placebo (wheat flour)
40	Bajerska (2015) ⁷⁷ Poland	Single herb	Green tea extract-enriched rye bread: (1) women: 280 g rye bread, 123.2 mg caffeine, 188.3 mg EGCG, (2) men: 360 g rye bread, 158.4 mg caffeine, 242.1 mg of EGCG; 12 weeks	Enriched rye bread	Rye bread
41	Zhou (2014) ⁷⁸ China	Mixture	XJGF 340 ml: rhubarb, coptis, semen cassia and citrus aurantium; Dose not reported; 24 weeks	Decoction	Low-dose XJGF (10% of decoction)
42	Astell (2013) ⁷⁹ Australia	Single herb	<i>C. fimbriata</i> 1000 mg; 12 weeks	Capsule	Placebo (maltodextrin)
43	Chang (2013) ⁸⁰ Taiwan	Single herb	Beta glucan-containing oat cereal 75 g; 12 weeks	Cereal	Placebo (not reported)
44	Grube (2013) ⁸¹ Germany	Single herb	Litramine IQP G-002AS <i>Opuntia ficus-indica</i> 3000 mg; 12 weeks	Tablet	Placebo (microcrystalline cellulose)
45	Kazemipoor (2013) ⁸² Iran	Single herb	Caraway <i>C. carvi</i> 30 ml; 3 months	Beverage	Placebo (edible caraway essence in drinking water [1% g/L])
46	Mostafa (2013) ⁸³ Syria	Single herb	<i>Zizyphus jujube</i> dried fruits powder Group 1: 5 g/day; Group 2: 15 g/day; Group 3: 30 g/day; 2 months	Powder	None
47	Rondanelli (2013) ⁸⁴ Italy	Mixture	A CBF1: <i>Camellia sinensis</i> decaffeinated dried extract, mixed with soya phospholipides 300 mg, Microencapsulated <i>Capsicum annum</i> oleoresin 15 mg, L-Carnitine 300 mg, <i>Fucus vesiculosus</i> dried extract 113 mg, <i>Allium sativa</i> dried extract 5 mg, Microencapsulated mint essential oil 5, <i>P. nigrum</i> dried extract 6 mg; 8 weeks	Capsule	Placebo (not reported)
48	Singh (2013) ⁸⁵ India	Mixture	(1) Shilajatu vati (<i>Asphaltum punjabinum</i>) 1000 mg; (2) Kutaki vati (<i>Picrorhiza kurroa</i>) 1000 mg; (3) Khadir Ghana vati (<i>Acacia catechu</i>) 500 mg; 3 months	Capsule	Placebo (wheat flour)
49	Cho (2013) ⁸⁶ Korea	Mixture	<i>Scutellariae radix</i> and <i>Platyocodi radix</i> 6.84 g in 150 ml; 2 months	Beverage	Placebo (oligosaccharide, berry flavour)

(Continued)

Table 1. (Continued)

No.	Study Location	Single herb/mixtures	Herbal intervention (daily dose; duration)	Formulation	Comparator
50	Stern (2013) ⁸⁷ USA	Mixture	<i>S. indicus</i> flower heads 600 mg, <i>G. mangostana</i> fruit rinds 200 mg; 8 weeks	Capsule	Not reported
51	Stern (2013) ⁸⁸ USA	Mixture	<i>S. indicus</i> flower heads 600 mg, <i>G. mangostana</i> fruit rinds 200 mg; 8 weeks	Capsule	Not reported
52	Park (2013) ⁸⁹ Korea	Mixture	Taeumjowi-tang T J001 7g: <i>Semen Coicis</i> 3.75g, <i>Semen Castaneaee</i> 3.75g, <i>Semen Raphani</i> 2.5g, <i>Schisandrae Fructus</i> 1.25g, <i>Liriopeis tuber</i> 1.25g, <i>Herba Ephedrae</i> 1.25g, <i>Radix platycodi</i> 1.25g and <i>Acori Tatarinowii Rhizoma</i> 1.25g; 12 weeks	Granules	Placebo
53	Tripthy (2013) ⁹⁰ India	Single herb	<i>G. cambogia</i> ; dose not reported; 4 months	Caplet	Not reported
54	Kamali (2012) ⁹¹ Iran	Mixture	Itrifal Saghir: <i>T. chebula</i> , <i>T. bellerica</i> , <i>P. emblica</i> 10 g/day; 3 months	Herbal confection	Not reported
55	Lenon (2012) ⁹² Australia	Mixture	RCM-104: <i>C. sinensis</i> 2400 mg (314 mg EGCG, 187 mg caffeine), <i>C. obtusifolia</i> , <i>Sophora Japonica</i> ; 12 weeks	Capsule	Placebo (herbal starch)
56	Rondanelli (2012) ⁹³ Italy	Mixture	Oral sprays containing 5- HTP from botanical extracts (10.24 mg of <i>Griffonia simplicifolia</i> , 11.7 mg of <i>Centella asiatica</i> L., 11.7 mg of <i>Taraxacum officinale</i> , 9.75 mg of <i>Cynara scolymus</i> , 4.55 mg of <i>Paulinia cupana</i> L. Mart, 39 µg of Alga klamathi); 3 oral sprays each time, 5 times per day; 4 weeks	Oral spray	Placebo (excipients)
57	Ross (2012) ⁹⁴ Cameroon	Single herb	<i>Cissus quadrangularis</i> formulation 1028 mg; <i>G. max</i> ; <i>C. sinensis</i> ; 8 weeks	Capsule	Placebo
58	Sengupta (2012) ⁹⁵ India	Mixture	LI85008F/Adipromin (M. oleifera 540 mg, M. koenigii 270 mg and C. longa 90 mg); 8 weeks	Capsule	Placebo
59	Sengupta (2012) ⁹⁶ India	Mixture	LI10903F/LOWAT: <i>P. betle</i> leaf extract 36 mg, <i>Dolichos biflorus</i> seed extract 540 mg; 8 weeks	Capsule	Placebo (microcrystalline cellulose, magnesium stearate)
60	Shin (2012) ⁹⁷ Korea	Single herb	<i>Ecklonia cava</i> polyphenols; (1) low dose: 72 mg-ECP/day; (2) high dose: 144 mg-ECP/day; 12 weeks	Beverage	Placebo (fructose, dextrin, sucralose, sodium chloride, citric acid, vitamin c, lemon flavour)

(Continued)

Table 1. (Continued)

No.	Study Location	Single herb/ mixtures	Herbal intervention (daily dose; duration)	Formulation	Comparator
61	Song (2012) ⁹⁸ Korea	Mixture	Herbal Ephedra and green tea Injection: 8 ml (0.064 g) administered. Herbal extract used. Two techniques used: 0.2 cc administered over 5 cm × 5 cm area (point by point technique). 0.01 cc administered per 1 cm × 1 cm area (nappage technique). Eight mesotherapy treatments in total. Treatments are conducted weekly. Phase I (weeks 1–4): Four treatments on the right thigh. Phase II (weeks 6–9): Four treatments on the left thigh. One-week interval (5th week) between phases as a wash-out period	Injection	Saline-treated
62	Amagase (2011) ⁹⁹ USA	Single herb	GoChi <i>Lycium barbarum</i> fruit juice; (1) Trial 1: 30 or 60- or 120-ml <i>L. barbarum</i> juice, once on the test day (2) Trial 2: <i>L. barbarum</i> juice 120 ml daily for 14 days	Beverage	Placebo (sucralose, artificial fruit flavor, citric acid and caramel colour in 30 ml of purified water)
63	Blom (2011) ¹⁰⁰ Netherlands	Single herb	<i>Hoodia gordonii</i> purified extract 2220 mg; 15 days	Beverage	Placebo
64	Kamiya (2011) ¹⁰¹ Japan	Single herb	<i>Puerariae thomsonii</i> flos extract: (1) Group I: 100 mg, (2) Group II: 200 mg, (3) Group III: 300 mg; 8 weeks	Tablet	The placebo (caramel)
65	Pal (2011) ¹⁰² Australia	Single herb	Metamucil: <i>Plantago ovata</i> Psyllium 12 g; 12 weeks	Fibre supplement	Placebo (breadcrumbs)
66	Aptekmann (2010) Brazil ¹⁰³	Single herb	Frozen concentrated orange juice (65° Brix) 500 ml; 90 days	Beverage	Control (untreated)
67	Basu (2010) ¹⁰⁴ USA	Single herb	(1) Green tea beverage: 440 mg EGCG, 4 cups/day; 8 weeks. (2) Green tea extracts: 460 mg EGCG, 2 capsules and 4 cups of water/day; 8 weeks	Beverage, capsule	Water
68	Chevassus (2010) ¹⁰⁵ France	Single herb	<i>Trigonella foenum-graecum</i> L. seed extract 1176 mg; 6 weeks	Tablet	Placebo (excipients)
69	Gout (2010) ¹⁰⁶ France	Single herb	<i>Crocus sativus</i> L. dried saffron stigma extract Satiereal 176.5 mg; 8 weeks	Capsule	Placebo (Microcrystalline cellulose)
70	Li (2010) ¹⁰⁷ USA	Single herb	Salted pistachios 53 g; 12 weeks	Seed	Salted pretzel
71	Wang (2010) ¹⁰⁸ China	Single herb	<i>C. sinensis</i> leaf tea; catechin/caffeine, (1) 458 mg/104 mg, (2) 468 mg/126 mg, (3) 886 mg/198 mg; 90 days	Tea	Placebo (green leaf, green powder perfume)

(Continued)

Table 1. (Continued)

No.	Study Location	Single herb/mixtures	Herbal intervention (daily dose; duration)	Formulation	Comparator
72	Belcaro (2009) ¹⁰⁹ Italy	Single herb	Glucacfect™ formulation 48g; low-fat soy flour 35.12 g, soy lecithin 600 mg; 8 weeks	Powder	Control (low-fat soy flour, corn-based starch)
73	Pierro (2009) ¹¹⁰ Italy	Single herb	Monoselect Camellia® 300 mg; GreenSelect® Phytosome green tea extract; 90 days	Tablet	Placebo (diet only)
74	Genta (2009) ¹¹¹ Argentina	Single herb	<i>Smalanthus sonchifolius</i> & Endl. yacon roots syrup: (1) Group 1: 0.29 g FOS/kg body weight/day; (2) Group 2: 0.14 g FOS/kg body weight/day; 120 days	Syrup	The syrup was prepared with the following additives (w/v): tartaric acid 2.5%, carboxymethylcellulose 1.8%, saccharine 2.5% and glycerine 10%
75	Ngondi (2009) ¹¹² Cameroon	Single herb	IGOB131 <i>Irvingia gabonensis</i> seed extract 300 mg; 10 weeks	Capsule	Placebo (maltodextrin)
76	Qidwai (2009) ¹¹³ Pakistan	Single herb	<i>Nigella sativa</i> seed 2000 mg; 6 weeks	Capsule	Placebo (calcium lactate)
77	Kim (2008) ¹¹⁴ Korea	Mixture	<i>Evodia rutaecarpa</i> 3000 mg, 7 mg evodiamine, rutaecarpine 0.66 mg; <i>E. sinica</i> 2000 mg, 31.52 mg pseudoephedrine; 8 weeks	Capsule	Placebo (corn starch)
78	Oben (2008) ¹¹⁵ Cameroon	Mixture	CQR-300 <i>Cissus quadrangularis</i> formula, IGOB131 <i>Irvingia gabonensis</i> seed extract; (1) 300 mg CQ, (2) 500 mg CQ-IG; 10 weeks	Capsule	Not reported
79	Kuriyan (2007) ¹¹⁶ India	Single herb	<i>C. fimbriata</i> 1000 mg; 60 days	Capsule	Placebo
80	Roberts (2007) ¹¹⁷ USA	Mixture	NT, a dietary herbal supplement: rhubarb, ginger, astragalus, red sage and turmeric, combined with GA; NT-GA combination, (1) 300 mg/1.2 g, (2) 600 mg/2.4 g; 24 weeks	Extract	Placebo
81	Roongpisuthipong (2007) ¹¹⁸ Thailand	Single herb	<i>G. atroviridis</i> fruit rind extract 1150 mg; 8 weeks	Powder	Not reported
82	Toromanyan (2007) ¹¹⁹ Armenia	Mixture	Slim339® <i>G. cambogia</i> 396 mg, <i>M. chamomilla</i> , <i>R. damascena</i> , <i>L. officinalis</i> and <i>C. odorata</i> ; 60 days	Tablet	Placebo (lactose, potato starch, <i>S. media</i>)
83	Abidov (2006) ¹²⁰ Russia	Single herb	Aralox: <i>Aralia mandshurica</i> 450 mg, <i>Engelhardtia chrysolepis</i> 450 mg; 15 weeks	Extract/hot reported.	Placebo

(Continued)

Table 1. (Continued)

No.	Study Location	Single herb/mixtures	Herbal intervention (daily dose; duration)	Formulation	Comparator
84	Dellalibera (2006) ¹²¹ Italy	Single herb	Sveto [®] decaffeinated green coffee extract 400 mg; 60 days	Capsule	Placebo (Maltodextrin)
85	Greenway (2006) ¹²² USA	Mixture	Pilot study I: <i>Citrus aurantium</i> (herbal phenylephrine); pantothenic acid, 40 mg; green tea leaf extract (95% polyphenols, 90% catechins, 45% EGCG), 200 mg; guarana extract (198 mg of caffeine), 550 mg; bitter orange (9 mg of synephrine), 150 mg; white willow bark extract (7.5 mg of salicin), 50 mg; ginger root, 10 mg; and proprietary charge thermoblend (L-tyrosine, L-carnitine and naringin), 375 mg; Twice a day; 8 weeks Pilot study II: Phenylephrine 60 mg; 8 weeks	Capsule	Placebo
86	Greenway (2006) ¹²³ USA	Mixture	Number 10: 40% rhubarb root and stem (<i>radix et rhizoma rhei</i>), 13.3% astragalus root (<i>Radix astragalii</i>), 13.3% red sage root (<i>Radix Salviae Miltiorrhizae</i>), 26%-27% turmeric (<i>rhizome curcumae longae</i>) and 6%-7% dried ginger (<i>rhizoma zingiberis officinalis</i>); Group 1: freeze-dried NT 6 g; Group 2: bed-dried NT 6 g; Group 3: freeze-dried NT 12 g. The dose was escalated over a 3-week period.	Capsule	Placebo
87	Hackman (2006) ¹²⁴ USA	Mixture	Dietary supplement: <i>G. cambogia</i> , <i>C. sinensis</i> green tea extract, <i>E. sinica</i> , <i>P. cupana</i> ; ephedra alkaloids 40 mg; caffeine 100 mg; high potency mixture of vitamins, minerals, omega-3 fatty acids; 9 months	Caplet	Placebo (cellulose tablet, small amount of lutein, corn oil capsule)
88	Opala (2006) ¹²⁵ Poland	Mixture	nutrifin [®] Tablet 1: Extracts of asparagus, green tea, black tea, guarana, yerba mate, kidney beans; Tablet 2: Extracts of kidney bean pods, <i>G. cambogia</i> and Chromium yeast; Dose not reported; 12 weeks	Tablet	Placebo
89	Ngondi (2005) ¹²⁶ Cameroon	Single herb	<i>Irvingia gabonensis</i> seed extract 3150 mg; 4 weeks	Capsule	Placebo (oat bran)
90	Coffey (2004) ¹²⁷ USA	Mixture	<i>E. sinica</i> 750 mg (25 mg ephedrine alkaloids), <i>Cola nitida</i> 250 mg (152 mg caffeine); Salix alba 600 mg; 12 weeks	Caplet	Not reported
91	Greenway (2004) ¹²⁸ USA	Mixture	Dietary supplement: <i>Cola nitida</i> , <i>E. sinica</i> ; caffeine 70 mg, ephedra 24 mg. Phase I: caffeine 70 mg, ephedra 24 mg; on 2 occasions 1 week apart, followed by a 1-week washout before phase II. Phase II: caffeine 210 mg, ephedra 72 mg; 3 months. Phase III: caffeine 210 mg, ephedra 72 mg; 3 months (original treatment group), 6 months (placebo convert to treatment group)	Capsule	Phase I: 2 placebo pills after 1 week post herbal products Phase II: placebo (2 pills) Phase III: placebo

(Continued)

Table 1. (Continued)

No.	Study Location	Single herb/mixtures	Herbal intervention (daily dose; duration)	Formulation	Comparator
92	Hioiki (2004) ¹²⁹ Japan	Mixture	Bofu-tsussho-san: <i>Ephedrae Herba</i> , <i>Glycyrrhizae Radix</i> , <i>Forsythiae Fructus</i> , <i>Schizonepetae Spica</i> ; 24 mg ephedrine, 280 mg caffeine; 24 weeks	Dry extract	Placebo
93	Udani (2004) ¹³⁰ USA	Single herb	Phase 2™ <i>Phaseolus vulgaris</i> extract 3000 mg; 8 weeks	Not reported	Not reported
94	Woodgate (2003) ¹³¹ Canada	Mixture	Dietary supplement 4185 mg: glucomannan, chitosan, fenugreek, <i>Gymnema sylvestre</i> , vitamin C; 6 weeks	Capsule	Placebo (rice flour)
95	Boozer (2002) ¹³² USA	Mixture	<i>E. sinica</i> , <i>Cola nitida</i> ; 90 mg ephedrine alkaloids, 192 mg caffeine; 6 months	Tablet	Placebo (cellulose, silica, alfalfa)
96	Andersen (2001) ¹³³ Denmark	Mixture	YGD each capsule: Yerbe Mate (<i>Ilex paraguayensis</i> leaves extract) 112 mg, Guarana (<i>P. cupana</i> seeds extract) 95 mg, Damiana (<i>Turnera diffusa</i> var. <i>aphrodisiaca</i> leaf extract) 36 mg; (1) 3 capsules, 10 days; (2) 3 capsules, 45 days; (3) 3 capsules, 12 months	Capsule	Placebo (lactose contents)
97	Boozer (2001) ¹³⁴ USA	Mixture	Metabolife-356 ^{1®} ; 72 mg ephedrine alkaloids, 240 mg caffeine; 8 weeks	Tablet	Placebo (inert ingredients)
98	Mattes (2000) ¹³⁵ USA	Single herb	Citrin® <i>G. cambogia</i> dried pericarp extract 2400 mg; 1200 mg HCA; 12 weeks	Caplet	Not reported
99	Heymsfield ¹³⁶ (1998) USA	Single herb	<i>G. cambogia</i> extract 3000 mg/day; 1500 mg/day HCA; 12 weeks	Caplet	Placebo (inert ingredients)

CBF1, combination of bioactive food ingredients; GA, gallic acid; RCTs, randomised controlled trials; XJXGF, Xin-Ju-Xiao-Gao-Fang; 5-HTP, 5-hydroxytryptophan.

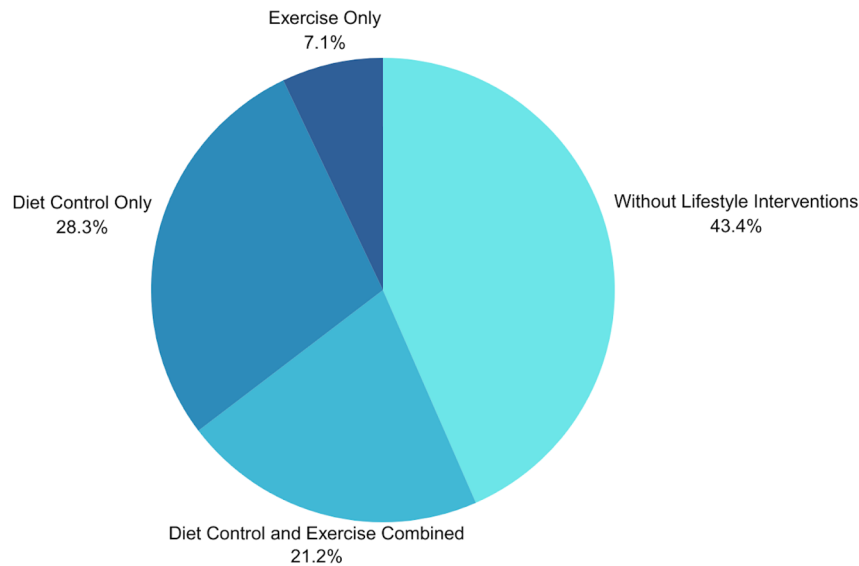


Figure 3. Lifestyle modifications in included studies.

multidisciplinary approach involving a dietitian, nutritionist, or exercise physiologist.^{43,58,59,62–65,73,74,77,86,93,102–105,107,112,117,122,123,126,128} Among studies incorporating exercise, two included RCTs used light intensity, 22 used moderate intensity, and four studies used a combination of moderate to vigorous intensity. Detailed information on lifestyle modifications in the included RCTs is shown in Table 2.

Measurement methods for obesity-related parameters

The measurement methods utilised in the included RCTs consisted of physical body measurements, radiological tools, laboratory tests and others. These measurements are used to assess the changes in patient's metabolic profile. All included RCTs ($n=99$) utilised both BMI and weight as their main outcome measurement. Over 50% of the studies measured body fat composition using a body analyser ($n=57$). Other anthropometry measurements such as waist circumference, hip circumference and abdominal circumference were not routinely measured.

As for the radiological tools used to assess obesity-related parameters, DEXA ($n=16$), Computed Tomography (CT scans) ($n=10$) and ultrasound ($n=2$) were used. The utilisation of radiological measurements, including DEXA,

CT scans and ultrasound, in the evaluation of obesity-related parameters provide more detailed information about the distribution and composition of body fat, as well as other related factors.

Majority 87% ($n=86$) of the studies utilised laboratory test for biosampling including blood and urine. These laboratory assessments include the lipid profile which is the most commonly used biochemical test to be conducted during anti-obesity study. Apart from that, the studies utilised hormone tests such as insulin, adiponectin, thyroid hormone, testosterone, cortisol and leptin; urinalysis; inflammatory markers such as C-reactive protein, interleukin 6 and plasma fibrinogen; oxidative stress markers such as lipid peroxidation levels, plasma antioxidant capacity, glutathione; and nutrition profile such as vitamin panels and glycoalbumin.

The methods of measurement of obesity-related parameters are shown in Table 3.

Approximately 47% ($n=46$) of the studies employed questionnaires to assess participants' dietary and nutritional intake, along with their appetite, mood and overall well-being. These include the Food Frequency Questionnaires, 3-day food records, 24-h dietary recalls, food history questionnaires, food compliance questionnaires, dietary composition analysis using

Table 2. Diet, exercise and combination adjunctive interventions.

Author (year)	Diet			Exercise		
	Restricted calorie diet	Fixed calorie diet	Food portion-controlled diet	Light intensity	Moderate intensity	Moderate to vigorous intensity
Cheon (2020) ⁵⁰ Leverrier (2019) ⁵⁵ Uebelhack (2019) ⁵⁸ Yousefi (2018) ⁶³ Cho (2017) ⁶⁴ Vuksan (2017) ⁶⁵ Kudiganti (2016) ⁷⁰ Khazaal (2015) ⁷³ Astell (2013) ⁷⁹ Chang (2013) ⁸⁰ Rondanelli (2012) ⁹³ Ross (2012) ⁹⁴ Li (2010) ¹⁰⁷ Pierro (2009) ¹¹⁰ Roberts (2007) ¹¹⁷ Roongpisuthipong (2007) ¹¹⁸ Abidov (2006) ¹²⁰ Dellalibera (2006) ¹²¹ Greenway (2006) ^{122,123} Ngondi (2005) ¹²⁶ Mattes (2000) ¹³⁵	✓					
Rondanelli (2013) ⁸⁴ Blom (2011) ¹⁰⁰ Kamiya (2011) ¹⁰¹ Chevassus (2010) ¹⁰⁵		✓				
Tripathy (2013) ⁹⁰ Udani (2004) ¹³⁰ Heymsfield (1998) ¹³⁶			✓			
Etemad (2019) ⁵² Bajerska (2015) ⁷⁷ Qidwai (2009) ¹¹³					✓	
Gholaman (2018) ⁶⁰ Kazemipoor (2016) ⁶⁹ Kazemipoor (2013) ⁸² Aptekmann (2010) ¹⁰³						✓
Hancke (2021) ⁴⁶ Hioki (2004) ¹²⁹	✓			✓		
Hosseini (2020) ⁴⁸ Heydari (2019) ⁵³ Boozer (2002) ¹³² Boozer (2001) ¹³⁴			✓		✓	
Dixit (2018) ⁵⁹ Kang (2018) ⁶² Grube (2013) ⁸¹ Park (2013) ⁸⁹ Sengupta (2012) ^{95,96} Genta (2009) ¹¹¹ Kim (2008) ¹¹⁴ Greenway (2006) ^{122,123} Greenway (2004) ¹²⁸ Amagase (2011) ⁹⁹ Belcaro (2009) ¹⁰⁹ Opala (2006) ¹²⁵	✓				✓	
Stern (2013) ⁸⁷ Stern (2013) ⁸⁸ Sengupta (2012) ^{95,96}		✓			✓	

Table 3. Methods of measurement of obesity-related parameters.

Author, year	Physical				Radiological				Laboratory tests		Other(s)	
	BMI	Weight	Waist circumference	Hip circumference	Abdominal circumference	Waist-hip ratio	Body fat composition	DEXA	CT scan	Ultrasound		Biochemical and lipid profile
Fernandes, 2023 ³⁸	✓	✓	✓	NR	NR	NR	NR	NR	NR	NR	✓	Oxidative stress parameters: lipid peroxidation levels, GSH, the non-protein thiol (PNSH), vitamin C levels
Ain, 2022 ³⁹	✓	✓	NR	NR	NR	NR	NR	NR	NR	NR	✓	ESR, urinalysis
Cortez-Navarrete, 2022 ⁴⁰	✓	✓	✓	NR	NR	NR	✓	NR	NR	NR	✓	
Lee, 2022 ⁴¹	✓	✓	✓	NR	NR	NR	NR	NR	NR	NR	✓	CRP, IL-6
Liu, 2022 ⁴²	✓	✓	NR	NR	NR	NR	NR	NR	NR	NR	✓	Adiponectin and insulin level, HOMA-IR
Rao, 2022 ⁴³	✓	✓	✓	✓	NR	NR	✓	✓	NR	NR	✓	
Aoe, 2021 ⁴⁴	✓	✓	NR	NR	NR	NR	✓	NR	NR	NR	✓	Serum thyroid hormone
Gherbon, 2021 ⁴⁵	✓	✓	NR	NR	✓	NR	NR	NR	NR	NR	✓	
Hancke, 2021 ⁴⁶	✓	✓	NR	NR	NR	✓	✓	✓	NR	NR	✓	HOMA-IR, serum testosterone and salivary cortisol level, adiponectin and leptin level, serum ghrelin level
Lin, 2021 ⁴⁷	✓	✓	✓	NR	NR	NR	✓	NR	NR	NR	✓	Insulin level
Hosseini, 2020 ⁴⁸	✓	✓	NR	NR	NR	NR	NR	NR	NR	NR	✓	
Abolghasemi, 2020 ⁴⁹	✓	✓	✓	✓	NR	NR	NR	NR	NR	NR	✓	HOMA, serum insulin level
Cheon, 2020 ⁵⁰	✓	✓	✓	✓	NR	NR	✓	NR	NR	NR	✓	CRP
Riazurrehman, 2020 ⁵¹	✓	✓	NR	NR	NR	NR	NR	NR	NR	NR	✓	Leptin level
Etemad, 2019 ⁵²	✓	✓	NR	NR	NR	NR	✓	NR	NR	NR	✓	Inflammatory markers, plasma fibrinogen
Heydari, 2019 ⁵³	✓	✓	✓	✓	NR	NR	✓	NR	NR	NR	✓	Insulin, leptin level

(Continued)

Table 3. (Continued)

Author, year	Physical			Radiological				Laboratory tests		Other(s)		
	BMI	Weight	Waist circumference	Hip circumference	Abdominal circumference	Waist-hip ratio	Body fat composition	DEXA	CT scan		Ultrasound	Biochemical and lipid profile
Jeong, 2019 ⁵⁴	✓	✓	✓	✓	Abdominal fat	✓	NR	✓	✓	NR	✓	CRP, adiponectin, leptin, thyroid hormone (T3, T4, TSH)
Leverrier, 2019 ⁵⁵	✓	✓	✓	NR	NR	NR	✓	NR	NR	NR	✓	
Nishimura, 2019 ⁵⁶	✓	✓	NR	NR	✓	NR	Abdominal fat	NR	✓	NR	✓	Oxidative stress – TBARS
Salunke, 2019 ⁵⁷	✓	✓	✓	✓	NR	✓	✓	NR	NR	NR	NR	
Uebelhack, 2019 ⁵⁸	✓	✓	✓	✓	NR	NR	✓	NR	NR	NR	✓	fat-soluble vitamins (A, D, E and K) levels) and urine analysis
Dixit, 2018 ⁵⁹	✓	✓	✓	✓	NR	NR	✓	✓	NR	NR	✓	Serum adiponectin and ghrelin level
Gholaman, 2018 ⁶⁰	✓	✓	NR	NR	NR	NR	✓	NR	NR	NR	✓	Insulin level, HOMA-IR
Kakutani, 2018 ⁶¹	✓	✓	NR	NR	NR	NR	✓	NR	✓	NR	✓	Adiponectin, leptin, glycoalbumin and urinalysis
Kang, 2018 ⁶²	✓	✓	✓	✓	NR	NR	✓	NR	✓	NR	✓	
Yousefi, 2018 ⁶³	✓	✓	✓	✓	NR	NR	NR	NR	NR	NR	✓	Hs-CRP, adiponectin level
Cho, 2017 ⁶⁴	✓	✓	✓	NR	NR	NR	✓	✓	NR	NR	✓	
Vuksan, 2017 ⁶⁵	✓	✓	✓	NR	NR	NR	✓	✓	NR	NR	✓	CRP, satiety hormone
Zeinalian, 2017 ⁶⁶	✓	✓	NR	NR	NR	NR	NR	NR	NR	NR	✓	
Chung, 2016 ⁶⁷	✓	✓	✓	✓	NR	NR	✓	✓	NR	NR	✓	HOMA-IR
Jensen, 2016 ⁶⁸	✓	✓	✓	✓	NR	NR	✓	✓	NR	NR	✓	CRP
Kazemipoor, 2016 ⁶⁹	✓	✓	✓	✓	NR	NR	NR	NR	NR	NR	✓	
Kudiganti, 2016 ⁷⁰	✓	✓	✓	✓	NR	NR	✓	✓	NR	NR	✓	Serum adiponectin, leptin, ghrelin, insulin hormone

(Continued)

Table 3. (Continued)

Author, year	Physical				Radiological				Laboratory tests		Other(s)	
	BMI	Weight	Waist circumference	Hip circumference	Abdominal circumference	Waist-hip ratio	Body fat composition	DEXA	CT scan	Ultrasound		Biochemical and lipid profile
Lee, 2016 ⁷¹	✓	✓	✓	✓	NR	✓	✓	✓	NR	NR	✓	Blood cytokines, urinalysis
Morimoto-Kobayashi, 2016 ⁷²	✓	✓	NR	NR	NR	NR	✓	NR	✓	NR	✓	
Khazaal, 2015 ⁷³	✓	✓	✓	NR	NR	NR	NR	NR	NR	NR	NR	Oxidative stress markers
Kim, 2015 ⁷⁴	✓	✓	✓	✓	NR	NR	✓	NR	✓	NR	✓	
Taghizadeh, 2015 ⁷⁵	✓	✓	NR	NR	NR	NR	NR	NR	NR	NR	✓	Thyroid hormone, plasma total antioxidant capacity, plasma total glutathione (GSH), HOMA-1R, HOMA-β, QUICKI
Tosciano, 2015 ⁷⁶	✓	✓	✓	NR	NR	NR	✓	NR	NR	NR	✓	
Bajarska, 2015 ⁷⁷	✓	✓	✓	NR	NR	NR	✓	NR	NR	NR	✓	Resting metabolic rate and respiratory quotient
Zhou, 2014 ⁷⁸	✓	✓	✓	✓	NR	NR	NR	NR	NR	NR	✓	HOMA-β and HOMA-1R, insulin action index
Astell, 2013 ⁷⁹	✓	✓	✓	✓	NR	✓	NR	NR	NR	NR	✓	
Chang, 2013 ⁸⁰	✓	✓	✓	✓	NR	✓	✓	NR	NR	✓ fatty liver score	✓	
Grube, 2013 ⁸¹	✓	✓	✓	NR	NR	NR	✓	NR	NR	NR	✓	
Kazemipoor, 2013 ⁸²	✓	✓	✓	✓	NR	NR	✓	NR	NR	NR	✓	Urine
Mostafa, 2013 ⁸³	✓	✓	✓	NR	NR	NR	NR	NR	NR	NR	✓	
Rondanelli, 2013 ⁸⁴	✓	✓	NR	NR	NR	NR	NR	✓	NR	NR	NR	GLP-1 and FFA analyses
Singh, 2013 ⁸⁵	✓	✓	✓	✓	NR	NR	NR	NR	NR	NR	NR	
Cho, 2013 ⁸⁶	✓	✓	✓	NR	NR	NR	✓	NR	NR	NR	✓	Urinalysis
Stern, 2013 ⁸⁷	✓	✓	✓	NR	NR	NR	NR	NR	NR	NR	✓	Serum adiponectin

(Continued)

Table 3. (Continued)

Author, year	Physical				Radiological				Laboratory tests		Other(s)	
	BMI	Weight	Waist circumference	Hip circumference	Abdominal circumference	Waist-hip ratio	Body fat composition	DEXA	CT scan	Ultrasound		Biochemical and lipid profile
Stern, 2013 ⁸⁸	✓	✓	✓	NR	NR	NR	NR	NR	NR	NR	✓	Serum adiponectin, cardiac assessment, urinalysis
Park, 2013 ⁸⁹	✓	✓	✓	✓	NR	✓	✓	NR	✓	NR	✓	CRP
Tripathy, 2013 ⁹⁰	✓	✓	NR	NR	NR	NR	NR	NR	NR	NR	NR	
Kamali, 2012 ⁹¹	✓	✓	✓	✓	NR	NR	NR	NR	NR	NR	✓	
Lenon, 2012 ⁹²	✓	✓	✓	✓	NR	NR	✓	NR	NR	NR	✓	Fasting insulin, HOMA-IR
Rondanelli, 2012 ⁹³	✓	✓	NR	NR	NR	NR	✓	NR	NR	NR	NR	24-h urinary 5-HIAA
Ross, 2012 ⁹⁴	✓	✓	✓	NR	NR	NR	✓	NR	NR	NR	✓	CRP
Sengupta, 2012 ⁹⁵	✓	✓	✓	✓	NR	NR	NR	NR	NR	NR	✓	Serum adiponectin, urinalysis
Sengupta, 2012 ⁹⁶	✓	✓	✓	✓	NR	NR	NR	NR	NR	NR	✓	Serum adiponectin and ghrelin
Shin, 2012 ⁹⁷	✓	✓	✓	✓	NR	NR	NR	NR	NR	NR	✓	
Song, 2012 ⁹⁸	✓	✓	NR	NR	NR	NR	NR	NR	✓	NR	NR	FFA assay
Amagase, 2011 ⁹⁹	✓	✓	✓	NR	NR	NR	NR	NR	NR	NR	NR	
Blom, 2011 ¹⁰⁰	✓	✓	NR	NR	NR	NR	NR	✓	NR	NR	✓	Urinalysis
Kamiya, 2011 ¹⁰¹	✓	✓	✓	✓	NR	NR	NR	NR	✓	NR	✓	Urinalysis
Pal, 2011 ¹⁰²	✓	✓	✓	✓	NR	NR	NR	✓	NR	NR	✓	Insulin level
Aptekmann, 2010 ¹⁰³	✓	✓	NR	NR	NR	NR	NR	NR	NR	NR	✓	Blood lactate
Basu, 2010 ¹⁰⁴	✓	✓	✓	NR	NR	NR	NR	NR	NR	NR	✓	NMR-based lipid particle size, Oxidative stress markers, free catechins
Chevassus, 2010 ¹⁰⁵	✓	✓	NR	NR	NR	NR	NR	NR	NR	NR	✓	Basal metabolic rate, Serum insulin, oxidative stress, antioxidant capacity

(Continued)

Table 3. (Continued)

Author, year	Physical				Radiological				Laboratory tests		Other(s)	
	BMI	Weight	Waist circumference	Hip circumference	Abdominal circumference	Waist-hip ratio	Body fat composition	DEXA	CT scan	Ultrasound		Biochemical and lipid profile
Gout, 2010 ¹⁰⁶	✓	✓	✓	✓	NR	NR	✓	NR	NR	NR	✓	Urinalysis
Li, 2010 ¹⁰⁷	✓	✓	NR	NR	NR	NR	NR	NR	NR	NR	✓	Insulin level
Wang, 2010 ¹⁰⁸	✓	✓	✓	✓	NR	NR	✓	NR	NR	NR	✓	
Belcaro, 2009 ¹⁰⁹	✓	✓	NR	NR	NR	NR	NR	NR	NR	NR	✓	
Pierro, 2009 ¹¹⁰	✓	✓	NR	NR	NR	NR	NR	NR	NR	NR	✓	Insulin, leptin, IGF-1, growth hormone, cortisol
Genta, 2009 ¹¹¹	✓	✓	✓	NR	NR	NR	NR	NR	NR	NR	✓	Serum insulin, HOMA-IR
Ngondi, 2009 ¹¹²	✓	✓	NR	NR	NR	✓	✓	NR	NR	NR	✓	Adiponectin, leptin, CRP
Qidwai, 2009 ¹¹³	✓	✓	✓	✓	NR	NR	NR	NR	NR	NR	✓	
Kim, 2008 ¹¹⁴	✓	✓	✓	✓	NR	✓	✓	NR	NR	NR	✓	Resting metabolic rate
Oben, 2008 ¹¹⁵	✓	✓	✓	NR	NR	NR	NR	NR	NR	NR	✓	
Kuriyan, 2007 ¹¹⁶	✓	✓	✓	✓	NR	NR	NR	NR	NR	NR	✓	
Roberts, 2007 ¹¹⁷	✓	✓	NR	NR	NR	NR	NR	NR	NR	NR	✓	
Roongpisuthipong, 2007 ¹¹⁸	✓	✓	✓	✓	NR	✓	✓	NR	NR	NR	✓	
Toromanyan, 2007 ¹¹⁹	✓	✓	NR	NR	NR	NR	NR	NR	NR	NR	✓	
Abidov, 2006 ¹²⁰	✓	✓	NR	NR	NR	NR	NR	NR	NR	NR	✓	Fatty acid, Adipocyte HSL activity, Perilipin content
Delalibera, 2006 ¹²¹	✓	✓	NR	NR	NR	NR	✓	NR	NR	NR	NR	
Greenway, 2006 ¹²²	✓	✓	✓	NR	NR	NR	NR	✓	NR	NR	✓	Urinalysis
Greenway, 2006 ¹²³	✓	✓	NR	NR	NR	NR	NR	NR	NR	NR	✓	Urinalysis
Hackman, 2006 ¹²⁴	✓	✓	NR	NR	NR	NR	✓	NR	NR	NR	✓	Urinalysis
Opala, 2006 ¹²⁵	✓	✓	✓	✓	NR	✓	✓	NR	NR	NR	✓	Fasting insulin
Ngondi, 2005 ¹²⁶	✓	✓	✓	✓	NR	NR	✓	NR	NR	NR	✓	

(Continued)

Table 3. (Continued)

Author, year	Physical				Radiological				Laboratory tests		Other(s)	
	BMI	Weight	Waist circumference	Hip circumference	Abdominal circumference	Waist-hip ratio	Body fat composition	DEXA	CT scan	Ultrasound		Biochemical and lipid profile
Coffey, 2004 ¹²⁷	✓	✓	✓	NR	NR	NR	✓	NR	NR	NR	✓	
Greenway, 2004 ¹²⁸	✓	✓	NR	NR	NR	NR	✓	✓	NR	NR	✓	TSH, urinalysis
Hicki, 2004 ¹²⁹	✓	✓	✓	✓	NR	NR	NR	NR	✓	NR	✓	Resting metabolic rate, insulin level, HOMA-IR
Udani, 2004 ¹³⁰	✓	✓	✓	✓	NR	NR	NR	NR	NR	NR	✓	Urinalysis
Woodgate, 2003 ¹³¹	✓	✓	✓	✓	NR	NR	NR	NR	NR	NR	NR	
Boozer, 2002 ¹³²	✓	✓	✓	✓	NR	NR	NR	NR	NR	NR	✓	TSH, Toxicologic urine screens
Andersen, 2001 ¹³³	✓	✓	NR	NR	NR	NR	NR	NR	NR	✓ to confirm gastric emptiness	NR	
Boozer, 2001 ¹³⁴	✓	✓	✓	✓	NR	NR	NR	NR	NR	NR	✓	TSH, urinalysis
Mattes, 2000 ¹³⁵	✓	✓	NR	NR	NR	NR	NR	NR	NR	NR	NR	
Heymsfield, 1998 ¹³⁶	✓	✓	NR	NR	NR	NR	NR	✓	NR	NR	NR	

BMI, body mass index; CT, computed tomography; DEXA, dual-energy x-ray absorptiometry; FFA, free fatty acid; GLP-1, glucagon-like peptide-1; GSH, glutathione; HIAA, 5-hydroxyindoleacetic acid; HOMA-IR, homeostatic model assessment of insulin resistance; HOMA-β, homeostatic model assessment of β-cell function; Hs-CRP, high-sensitivity C-reactive protein; HSL, hormone sensitive lipase; IGF, insulin-like growth factor; IL-6, interleukin 6; NMR, nuclear magnetic resonance; NR, not reported; TBARS, thiobarbituric acid reactive substances; TSH, thyroid stimulating hormone; QUICKI, quantitative insulin sensitivity check index.

specialised software, assessment of hunger and fullness, mood evaluations, quality of life (QOL) assessments, international physical activity questionnaires and metabolic equivalent scales. These tools record participants' food intake, dietary patterns and their adherence to study guidelines. Some of the questionnaires were internationally validated such as the Korean version of Eating Attitudes Test-26, Three-Factor Eating and the Obesity and Weight-Loss Quality of Life measure. The questionnaires utilised in the studies are shown in Table 4.

Power of study and sample size calculation

In our analysis of the included studies, it was found that 37 out of the total 99 studies achieved the final sample size based on their stated study power calculations and sample size justifications.^{39–42,44,59,60,64–66,75,87,100–105,117,127,135} Among these, 33 studies provided clear documentation of their power, significance level and effect size estimates. However, in four studies, the reporting on effect sizes was not sufficiently specified.^{99,101,108,135}

Compliance monitoring methods

Nine methods of compliance monitoring were reported in the included RCTs ($n=70$) categorised as follows, 'Patient diary' involved monitoring the pill counting, daily records of experimental tablet intake, food intake frequency records, physical activity records, 'Email communication' involved monitoring compliance through email in addition to site visits, 'Regular Telephone Calls' maintained protocol adherence through calls and messaging apps, 'Capsule Calendar' provided calendars for medication tracking, 'Measuring Cup and Containers' included measuring cups and containers for supplement measurement and compliance assessment, 'Follow-Up Visits' assessed compliance during scheduled visits, 'Direct Observation' confirmed supplement consumption through direct observation, 'Compliance Survey' assessed adherence during visits and 'Feedback and Strategies' provided feedback and strategies to enhance compliance. There were 29 studies that did not report on the compliance monitoring methods they undertook. The most used compliance monitoring method was patient diary recording ($n=28$). Details of the compliance monitoring methods and related studies are shown in Table 5.

Safety monitoring

Majority of the studies ($n=76$) either mentioned in their methods section or in their methodology or suggested through their results and discussion section that some safety monitoring was conducted. A handful of studies ($n=6$) did not mention safety monitoring or adverse events at all throughout the report. The safety monitoring methods include 'Adverse Event Recording' involving the documentation of adverse events, their severity, and relation to the intervention at follow-up visits, 'Laboratory Tests' including baseline and post-treatment measurements of haematological and biochemical parameters for safety assessment, 'Other Safety-Related Parameters' involving measurements like blood pressure, pulse rate and ECGs to assess safety and 'Assessment of Compliance and Adverse Events' evaluating adherence alongside adverse event monitoring, including the counting of unused study products. Details of the safety monitoring methods and related studies are shown in Table 6.

Methods of follow-up

Methods of follow-up reported in the included RCTs can be categorised into five major types based on the planned outcomes of interest that is measured at each visit. Firstly, 'In-Person on Site' visits involved participants physically visiting a specific location for various activities, including measurements, interviews and sample collections, often occurring at regular intervals. Secondly, 'In Person' visits included face-to-face interactions with participants, but the location (on-site or elsewhere) and specific activities were unspecified. Thirdly, 'In Person at Site and Phone Calls' encompassed study visits conducted both in person at a physical site and via phone calls, allowing for a combination of physical examinations and remote interactions. Additionally, 'Virtual Visits' were carried out virtually, eliminating the need for physical presence, though the activities involved were not specified. Lastly, 'Routine Health Checkup' visits provided participants with routine health assessments, with specific components remaining unspecified in the provided information. The most common follow up methods utilised was the 'In-Person on Site' ($n=74$). The follow-up methods and related studies are shown in Table 7.

Table 4. Questionnaires used in the RCTs.

Number of studies (n = 49)	Categories	Questionnaires
38	Appetite, sensory perceptions	(1) Hunger assessment: regular hunger intensities; (2) Gum consumption effects: assessment of the time of gum consumption, evaluation of adverse effects, measurement of hunger intensity, monitoring the amount of food consumed at meals; (3) Effects of the intervention on appetite and sensory aspects
43 79	Health-related quality of life	36-Item Short Form Survey
46 59	Health-related quality of life	POMS
50	Appetite, sensory perceptions; Health-related quality of life	KEAT-26, SRRS, SRI. KOQOL
54 56	Dietary and nutritional assessment	Food Frequency Questionnaires
55	Physical activity	IPAQ
58	Appetite, sensory perceptions, physical activity	Assessment of hunger and fullness using VAS, food cravings on a 5-point scale. IPAQ
63	Appetite, sensory perceptions, physical activity	MET Scales
65,75	Dietary and nutritional assessment	3-day dietary records
66	Physical activity	MET Scales
68, 84, 106, 117, 122, 123, 130	Appetite, sensory perceptions	Appetite, sensory perceptions questionnaires
69	Dietary and nutritional assessment, Appetite, sensory perceptions	Food Frequency Questionnaires Appetite, sensory perceptions questionnaires
70	Appetite, sensory perceptions, Health-related quality of life	Appetite, sensory perceptions questionnaires POMS
71	Dietary and nutritional assessment, Physical activity	3-day dietary records Global physical activity questionnaire
72	Dietary and nutritional assessment	Dietary composition analysis using a specialised software
76, 91, 118	Dietary and nutritional assessment	24-h dietary recalls
77	Dietary and nutritional assessment, Appetite, sensory perceptions	Food history questionnaires Three-factor eating questionnaire
87	Dietary and nutritional assessment, Physical activity	Food compliance questionnaires Exercise compliance questionnaires
88	Physical activity	Self-report questionnaire

(Continued)

Table 4. (Continued)

Number of studies (n=49)	Categories	Questionnaires
89	Appetite, sensory perceptions, Health-related quality of life	KEAT-26 and QSCC Obesity-related Quality of Life
92	Health-related quality of life	Validated WRSM and the OWLQOL Questionnaires
84	Appetite, sensory perceptions	Satiating effect: Haber score Severity of binge eating: Gormally BES Depressive symptom: A BDI-II
97	Dietary and nutritional assessment, Physical activity	Food Frequency Questionnaires IPAQ
98	Appetite, sensory perceptions	Satisfaction index
108	Dietary and nutritional assessment	3-days food records
112, 126, 131	Dietary and nutritional assessment	Dietary composition analysis using a specialised software
115	Appetite, sensory perceptions	Patients' subjective impressions of their well-being
116	Dietary and nutritional assessment, Appetite, sensory perceptions	Food Frequency Questionnaires Appetite, sensory perceptions questionnaires
119	Appetite, sensory perceptions	Abnormal eating behaviour using the standard SCOFF questionnaire
121	Physical activity	Self-evaluation of physical aspect
124	Dietary and nutritional assessment, Health-related quality of life, Physical activity	Food Frequency Questionnaires 36-Item Short Form Survey 7-Days Physical Activity Recalls
135	Appetite, sensory perceptions	Three-Factor Eating Questionnaire

BDI-II, Beck Depression Inventory; BES, Binge Eating Scale; IPAQ, International Physical Activity Questionnaire; KEAT-26, Korean version of Eating Attitudes Test-26; KOQOL, Korean Obesity-related Quality of Life; MET, Metabolic Equivalent; OWLQOL, Obesity & Weight-Loss Quality of Life measure; POMS, Profile of Mood Status; QSCC, Questionnaire for the Sasang Constitution Classification; SRI, Stress Response Inventory; SRRS, Social Readjustment Rating Scale; VAS, Visual Analogue Scales; WRSM, Weight-Related Symptom Measure.

Table 5. Compliance monitoring methods used in included RCTs.

No.	Compliance monitoring methods	Details	Number of studies (n=70)
1	Patient diary	Monitoring the pill counting, daily records of experimental tablet intake, food intake frequency records, physical activity records.	3, 5, 9, 12, 15, 21, 23–25, 33, 39, 40, 59, 63, 77, 86, 93, 102, 103, 104, 105, 107, 111, 116, 121, 125, 127
2	Email communication	Monitoring compliance through email in addition to site visits.	2
3	Regular telephone calls	Maintained protocol adherence through calls and messaging apps.	11, 14, 42, 73
4	Capsule calendar	Provided calendars for medication tracking.	3, 63

(Continued)

Table 5. (Continued)

No.	Compliance monitoring methods	Details	Number of studies (n = 70)
5	Measuring cup and containers	Included measuring cups and containers for supplement measurement and compliance assessment.	13, 42, 58, 121
6	Follow-up visits	Assessed compliance during scheduled visits.	1, 2, 4, 6–8, 10, 18–20, 26, 27, 46, 47, 49, 53, 64, 66, 69, 70–74
7	Direct observation	Confirmed supplement consumption through direct observation.	42, 75, 79
8	Compliance survey	Assessed adherence during visits.	28, 30, 31, 81, 82, 89
9	Feedback and strategies	Provided feedback and strategies to enhance compliance.	29, 121

RCT, randomised controlled trials.

Guideline recommendations

We extracted pertinent guideline recommendations from the USFDA Guidance for Industry Developing Products for Weight Management (2007)²⁸ and the EMA Guideline on Clinical Evaluation of Medicinal Products Used in Weight Management (2017)²⁷ to align with anti-obesity clinical trial standards. The details on the guideline points with RCTs that adhere to them are shown in Table 8.

In conducting anti-obesity trials, specific methodological aspects of both guidelines are essential to ensure compliance with regulatory standards and align with scientific best practices. Both guidelines emphasise that trials should have a minimum duration of 12 months to adequately assess the long-term effects on weight management and associated comorbidities. The primary endpoint should be body weight loss, aiming for at least a 5% reduction from baseline to demonstrate efficacy. Additionally, secondary outcomes should include improvements in comorbidities such as cardiovascular risk and diabetes, QOL and waist circumference measurements. Safety and tolerability are crucial components of these trials, requiring careful monitoring of safety outcomes, including dose adjustments and any adverse effects. Lastly, the selection of participants should focus on individuals with a baseline

BMI of at least 27 kg/m², particularly those with obesity-related health risks, to ensure the study population reflects the target demographic for potential treatments.^{27,28}

Based on the guideline aspects, the comparative analysis showed that most studies (n = 83) had a study duration of 0–6 months, while only six studies were carried out between 6 and 12 months, and just two exceeded 12 months. Majority studies had primary endpoint of weight loss (n = 80) with two of the studies also having an aim of 5% weight reduction from baseline. There were also studies that account for cardiovascular risk reduction in conjunction with the weight loss herbal intervention (n = 49). Safety monitoring was reported in most studies (n = 93).

Discussion

In our review, we identified 99 studies meeting our inclusion criteria, primarily involving individuals aged 18–80 years, with BMIs between 25 and 49.9 kg/m². Herbal interventions were diverse, comprising single herbs and mixtures, with durations spanning from 14 days to 56 weeks. Diet modifications were implemented through various approaches, including restricted calorie diets, food-portion controlled diets and fixed calorie diets. Exercise, often at moderate intensity, was

commonly integrated with the interventions. BMI and weight were the primary outcomes across all studies, while body fat composition was measured in over 50% of studies using various methods such as body analysers and radiological tools. Interestingly, there were no interventional anti-obesity RCTs on herbal medicine conducted for participants aged younger than 18 years in our included studies, indicating a gap in research despite the rising cases of childhood obesity. This suggests that herbal medicine trials have not yet been globally recognised as an alternative therapy for combating obesity. However, survey studies have shown that adolescents aged 12–18 do in fact take herbal medicines for weight loss.¹³⁷ Research on the underage is challenging due to the requirement of parental consent and the risk of litigation. Hence, lifestyle changes are often advocated first before any medical intervention.

Some of the RCTs implemented a run-in period prior to the commencement of their studies. The purpose is to identify and exclude participants who may not adhere to the study protocol or have a high risk of dropping out. The run-in phase of clinical trials can double as a washout period to gradually discontinue prior medications to prevent sudden cessation effects and clear previous treatments from patients' systems before introducing new interventions. Some of the trials integrated this approach, ensuring any lingering effects are eliminated before administering the herbal treatment.^{46,58,81,101,108} These strategies enhance the validity and safety of study outcomes, especially for those with multiple medication regimens. Leahey *et al.*¹³⁸ assessed the predictive value of behavioural run-in data, encompassing food diary completion, questionnaire responses and staff interviews, on intervention adherence, trial retention and outcomes in a behavioural weight loss trial. Using run-in information, researchers categorised participants as having high, moderate, or low adherence and then randomised those with predicted high or moderate adherence. Results indicated that predicted high adherers exhibited better intervention adherence, as evident from session attendance and record completion, and achieved more favourable outcomes, particularly in terms of weight loss. However, run-in data did not predict trial retention. This suggests that run-in assessments

effectively identify participants likely to adhere to intervention protocols, bolstering behavioural efficacy trial validity.

Adherence to medication is crucial, but adherence to follow-up is equally significant and is most commonly measured by the follow-up rate. A systematic review reported that the pooled odds ratio (OR) for improved follow-up rate in the group receiving Short Message Service (SMS) reminders compared with the control group was 1.76 (95% CI (1.37, 2.26); $p < 0.01$), while the pooled OR for enhancing the follow-up rate in the group with telephone reminder compared to the control group was 2.09 (95% CI (1.85, 2.36); $p < 0.01$). Although telephone reminders demonstrated a greater probability than SMS reminders in improving the follow-up rate, the authors argued that cell phone SMS interventions could be more practical and easier to adapt to various settings.¹³⁹ Among the included studies in this review, a majority of the herbal medicine anti-obesity studies did not report on the adherence rate, but those that did ($n = 30$) reported up to 70%–100% adherence rate. In our study, of the five studies that utilised email communication⁴³ and regular telephone calls,^{63,66,113,123} only three reported adherence rates exceeding 87.5%, indicating a satisfactory level of adherence.^{63,66,113} Hence, at this point in time, the exact methods to improve adherence to herbal trials are still unclear.

Clinical counselling that emphasises dietary change stands out as a key strategy in addressing adult obesity.¹⁴⁰ Dietitians and nutritionists are healthcare experts specialising in weight management, play a pivotal role in delivering this form of treatment.¹⁴¹ Participants who received intervention from dietitians achieved an extra weight loss of 1.03 kg (95% CI (-1.40, -0.66); $p < 0.0001$) and a BMI reduction of 0.43 kg/m² (95% CI (-0.59, -0.26); $p < 0.0001$) compared to those who received usual care.¹⁴² In this review, studies utilising these allied healthcare professionals ($n = 23$) however did not consistently report lower dropout rates overall. The drop-out rates ranged from 0 to 39%, whereby the drop-outs for seven studies ranged 0%–9%,^{59,72,86,92,104,121,125} six studies ranged 10%–19%,^{58,74,102,103,111,122} seven studies ranged 20%–29%,^{43,63,65,77,101,106,127} and three studies ranged 30%–39%.^{62,64,116}

In accordance with the USFDA (Guidance for Industry Developing Products for Weight Management 2007) and EMA (EMA Guideline on Clinical Evaluation of Medicinal Products Used in Weight Management 2017) guidelines, patient selection often considers a lower baseline BMI, especially for individuals with weight-related risk factors (e.g. $\geq 27 \text{ kg/m}^2$). While interventions may contribute to improvements in cardiovascular health, they cannot be attributed to reducing blood pressure, glucose levels, heart rate, etc., apart from the targeted claim of weight loss. The guidelines recommend a study duration of 12 months to comprehensively assess the impact on weight development and obesity-related comorbidities. Our study conducted a comparative analysis between methodologies employed in herbal RCTs and the guidelines for developing products for weight management. This comparison allows an assessment of how the methods prescribed in clinical trial guidelines align with those implemented in real-life studies. Notably, the primary efficacy endpoint in most studies is body weight loss, with limited consideration for weight maintenance over 6 months to 1 year, as suggested by the guidelines. Few studies reported on certain secondary efficacy endpoints, such as sleep apnoea, joint pain, urinary incontinence, impaired fertility, depression, anxiety and functional limitations. One study included patients with schizophrenia.⁴¹ In adding a comparative context with guidelines, both the USFDA and EMA recommend anthropometric measurements, with BMI and weight being the most utilised. Although the guidelines advise the implementation of diet and physical activity in anti-obesity studies, only 21 studies incorporated these lifestyle modifications alongside herbal interventions. A significant portion of the included studies ($n=43$) did not implement lifestyle modifications, requiring participants to maintain their current lifestyle. This may be due to the apparent

difficulty in administering and monitoring compliance with lifestyle interventions alongside herbal interventions. Conducting anti-obesity RCTs poses challenges, as most of these included studies planned for participants to maintain their preexisting lifestyle to avoid additional confounding factors influencing body weight. This is contrary to the guidelines that recommend the implementation of lifestyle modifications alongside the tested interventions. We were unable to extract three suggestions outlined in the guidelines, including 'meaningful dose reduction/withdrawal from concomitant medication', 'selection of patients who have failed at least one trial of weight-reducing diet', and the 'inclusion of various demographic, ethnic and racial groups where obesity prevalence is high'. These data were not reported in the trial publications across the included studies.

In our review, 93 out of 99 studies reported safety monitoring of the participants, revealing a strong awareness of this crucial aspect. However, we would expect a 100% reporting rate for such a critical aspect. Safety reporting is a mandatory requirement in RCTs, particularly in pharmaceutical trials, as emphasised by the CONSORT checklist (2010).³⁰ However, in herbal medicine or natural product clinical trials, the emphasis on safety reporting is sometimes overlooked in comparison to efficacy reporting. This discrepancy may stem partly from regulatory differences, such as those observed in Malaysia's regulations concerning herbal and traditional medicines. Marketed products in this category may face less stringent approval processes compared to pharmaceuticals, potentially posing challenges in monitoring safety and quality. Limited consumer awareness of the risks associated with herbal medicine further compounds this issue.¹⁴³ Fortunately, there is growing recognition of the importance of safety reporting in herbal

Table 6. Safety monitoring methods used in the RCTs.

No.	Safety monitoring methods	Description	Number of studies (<i>n</i> = 99) (%)	Studies
1	Adverse event recording	Involved the documentation of adverse events, their severity and relation to the intervention at follow-up visits.	<i>n</i> = 71 (71.72)	1–6, 8–10, 15, 16, 18–20, 22–28, 32–34, 36, 39, 41–43, 46, 49, 58, 59, 62, 63, 65, 69–73, 77, 79, 81, 86, 92, 101, 103, 104, 106, 111, 116, 121, 122, 124–135
2	Laboratory tests	Included baseline and post-treatment measurements of haematological and biochemical parameters for safety assessment.	<i>n</i> = 75 (75.76)	2–14, 17–21, 23–33, 35, 37, 39, 40–43, 46, 49, 58, 59, 62, 63, 65, 69–73, 77, 79, 81, 86, 92, 101, 103, 104, 106, 111, 116, 121, 122
3	Other safety-related parameters	Involved measurements like blood pressure, pulse rate and ECGs to assess safety.	<i>n</i> = 35 (35.35)	3, 5–10, 15, 17–20, 27, 28, 39–43, 46, 49, 58, 59, 62, 63, 65, 69–73, 77, 79, 81, 86, 92, 101, 103, 104, 106, 111, 116, 121, 122
4	Assessment of compliance and adverse events	Evaluated adherence alongside adverse event monitoring, including the counting of unused study products.	<i>n</i> = 4 (4.04)	53, 59, 64, 104
5	No reporting of safety monitoring	Did not mention on safety data or monitoring methods in the methodology	<i>n</i> = 6 (6.06)	38, 46, 50, 54, 75, 144

ECGs, electrocardiogram; RCTs, randomised controlled trials.

Table 7. Follow-up methods used in the RCTs.

No.	Follow-up methods	Description	Number of studies (<i>n</i> = 95)
1	'In-Person on Site' visits	Involved participants physically visiting a specific location for various activities, including measurements, interviews and sample collections, often occurring at regular intervals.	3–7, 10–22, 25–32, 34, 35, 37, 40–42, 46, 49, 59, 62, 63, 65, 66, 69–71, 73, 77, 92, 101, 102–104, 111, 116, 121, 122, 127, 133, 135
2	'In Person' visits	Included face-to-face interactions with participants, but the location (on-site or elsewhere) and specific activities were unspecified.	8, 9, 23, 24, 33, 38, 43, 58, 63, 74, 96, 99, 106, 125, 143
3	'In Person at Site and Phone Calls'	Encompassed study visits conducted both in person at a physical site and via phone calls, allowing for a combination of physical examinations and remote interactions.	2, 39, 53, 73
4	Virtual visits	Visits carried out virtually, eliminating the need for physical presence, though the activities involved were not specified.	4
5	'Routine Health Checkup' visits	Provided participants with routine health assessments, with specific components remaining unspecified in the provided information.	36

RCT, randomised controlled trials.

Table 8. Guideline recommendations for clinical trials in weight management product development.

Guideline items	Primary and secondary efficacy endpoints				Additional documented effect				Patient selection	Additional intervention		Safety monitoring		
	Weight loss at least 5% of baseline	Central Adiposity	WC	Weight maintenance	CVS risk reduction	Weight reduction helps with comorbidities	QOL	DEXA scan (to prove primary reduction in fat content)		Type 2 DM	Lifestyle modification programmes	Adverse event assessment	ECG at baseline and 6 months	Neuropsychiatry safety (include patients with mild depression)
USFDA	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
EMA	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Studies														
Fernandes, 2023 ³⁸	✓		✓											
Ain, 2022 ³⁹					✓						✓			
Cortez-Navarrete, 2022 ⁴⁰	✓	✓	✓	✓							✓	✓		
Lee, 2022 ⁴¹			✓								✓			
Liu, 2022 ⁴²	✓				✓						✓			
Rao, 2022 ⁴³	✓		✓				✓	✓			✓			
Aoe, 2021 ⁴⁴		✓									✓			
Gherbon, 2021 ⁴⁵	✓	✓	✓		✓						✓			
Hancke, 2021 ⁴⁶	✓	✓	✓				✓	✓		✓	✓		✓	
Lin, 2021 ⁴⁷	✓		✓					✓						
Hosseini, 2020 ⁴⁸	✓								✓					
Abolghasemi, 2020 ⁴⁹	✓	✓	✓		✓						✓			
Cheon, 2020 ⁵⁰	✓	✓	✓		✓		✓			✓	✓		✓	
Riazurrehman, 2020 ⁵¹	✓										✓			
Etemad, 2019 ⁵²	✓	✓	✓		✓					✓	✓			
Heydari, 2019 ⁵³	✓		✓						✓		✓			
Jeong, 2019 ⁵⁴	✓	✓	✓		✓		✓				✓			
Leverrier, 2019 ⁵⁵	✓	✓	✓						✓		✓		✓	
Nishimura, 2019 ⁵⁶	✓	✓	✓								✓		✓	
Salunke, 2019 ⁵⁷	✓	✓	✓								✓		✓	

(Continued)

Table 8. (Continued)

Guideline items	Primary and secondary efficacy endpoints					Additional documented effect				Patient selection	Additional intervention		Safety monitoring	
	Weight loss at least 5% of baseline	Weight loss at least 5% of baseline	Central Adiposity	WC	Weight maintenance	CVS risk reduction	Weight reduction helps with comorbidities	QOL	DEXA scan (to prove primary reduction in fat content)		Type 2 DM	Lifestyle modification programmes	Adverse event assessment	ECG at baseline and 6 months
Uebelhack, 2019 ⁵⁸	✓			✓							✓	✓	✓	
Dixit, 2018 ⁵⁹	✓		✓	✓				✓			✓	✓	✓	
Gholaman, 2018 ⁶⁰		✓	✓			✓				✓				
Kakutani, 2018 ⁶¹			✓											
Kang, 2018 ⁶²		✓	✓	✓						✓	✓	✓	✓	
Yousefi, 2018 ⁶³	✓			✓						✓				
Cho, 2017 ⁶⁴	✓		✓	✓					✓		✓	✓	✓	
Vuksan, 2017 ⁶⁵	✓		✓	✓	✓	✓			✓	✓				
Zeinalian, 2017 ⁶⁶	✓		✓	✓										
Chung, 2016 ⁶⁷	✓		✓	✓		✓			✓			✓	✓	
Jensen, 2016 ⁶⁸	✓		✓	✓		✓			✓			✓	✓	
Kazemipoor, 2016 ⁶⁹	✓		✓	✓						✓				
Kudiganti, 2016 ⁷⁰	✓		✓	✓				✓	✓	✓		✓	✓	
Lee 2016 ⁷¹	✓		✓	✓					✓			✓	✓	
Morimoto-Kobayashi, 2016 ⁷²		✓	✓									✓	✓	
Khazaal, 2015 ⁷³	✓		✓	✓						✓	✓	✓	✓	
Kim, 2015 ⁷⁴		✓	✓	✓								✓	✓	
Taghizadeh, 2015 ⁷⁵	✓													
Toscano, 2015 ⁷⁶	✓		✓	✓								✓	✓	
Bajarska, 2015 ⁷⁷				✓	✓					✓				
Zhou, 2014 ⁷⁸	✓		✓	✓								✓	✓	
Astell, 2013 ⁷⁹		✓	✓	✓		✓		✓		✓	✓	✓	✓	
Chang, 2013 ⁸⁰	✓		✓	✓						✓	✓	✓	✓	

(Continued)

Table 8. (Continued)

Guideline items	Primary and secondary efficacy endpoints				Additional documented effect				Patient selection	Additional intervention		Safety monitoring	
	Weight loss at least 5% of baseline	Central Adiposity	WC	Weight maintenance	CVS risk reduction	Weight reduction helps with comorbidities	QOL	DEXA scan (to prove primary reduction in fat content)		Type 2 DM	Lifestyle modification programmes	Adverse event assessment	ECG at baseline and 6 months
Grube, 2013 ⁸¹	✓		✓							✓			✓
Kazemipoor, 2013 ⁸²	✓	✓								✓			✓
Mostafa, 2013 ⁸³			✓		✓	✓							
Rondanelli, 2013 ⁸⁴					✓		✓			✓			
Singh, 2013 ⁸⁵	✓		✓										
Cho, 2013 ⁸⁶	✓		✓								✓		
Stern, 2013 ⁸⁷	✓		✓						✓				
Stern 2013 ⁸⁷	✓		✓						✓				
Park, 2013 ⁸⁹	✓	✓	✓		✓				✓				✓
Tripathy, 2013 ⁹⁰	✓		✓					✓		✓			
Kamali, 2012 ⁹¹	✓		✓		✓						✓		✓
Lenon, 2012 ⁹²	✓		✓		✓			✓			✓		✓
Rondanelli, 2012 ⁹³			✓					✓		✓			✓
Ross, 2012 ⁹⁴	✓	✓	✓		✓					✓			
Sengupta, 2012 ⁹⁵	✓		✓		✓					✓			
Sengupta, 2012 ⁹⁶	✓		✓							✓			✓
Shin, 2012 ⁹⁷	✓		✓					✓					
Song, 2012 ⁹⁸	✓				✓						✓		
Amagase, 2011 ⁹⁹				✓						✓			
Blom, 2011 ¹⁰⁰	✓	✓			✓			✓		✓			✓
Kamiya, 2011 ¹⁰¹		✓	✓		✓					✓			✓
Pai, 2011 ¹⁰²		✓	✓		✓			✓					✓
Aptekmann, 2010 ¹⁰³		✓								✓			
Basu, 2010 ¹⁰⁴	✓		✓		✓								✓

(Continued)

Table 8. (Continued)

Guideline items	Primary and secondary efficacy endpoints				Additional documented effect				Patient selection	Additional intervention		Safety monitoring	
	Weight loss at least 5% of baseline	Central Adiposity	WC	Weight maintenance	CVS risk reduction	Weight reduction helps with comorbidities	QOL	DEXA scan (to prove primary reduction in fat content)		Type 2 DM	Lifestyle modification programmes	Adverse event assessment	ECG at baseline and 6 months
Chevassus, 2010 ¹⁰⁵	✓				✓					✓			✓
Gout, 2010 ¹⁰⁶	✓		✓				✓						✓
Li, 2010 ¹⁰⁷	✓				✓					✓			
Wang, 2010 ¹⁰⁸		✓	✓		✓		✓						
Belcaro, 2009 ¹⁰⁹	✓				✓			✓					
Pierro, 2009 ¹¹⁰	✓				✓					✓			
Genta, 2009 ¹¹¹	✓		✓		✓					✓			✓
Ngondi, 2009 ¹¹²	✓				✓								✓
Qidwai, 2009 ¹¹³	✓		✓		✓					✓			✓
Kim, 2008 ¹¹⁴	✓		✓		✓					✓			✓
Oben, 2008 ¹¹⁵	✓		✓		✓								✓
Kuriyan, 2007 ¹¹⁶	✓		✓		✓								✓
Roberts 2007 ¹¹⁷	✓				✓					✓			✓
Roongpisuthipong, 2007 ¹¹⁸	✓		✓		✓					✓			✓
Toromanyan, 2007 ¹¹⁹	✓				✓								✓
Abidov, 2006 ¹²⁰	✓				✓					✓			✓
DeLalibera, 2006 ¹²¹	✓				✓					✓			✓
Greenway, 2006 ¹²²			✓		✓		✓			✓			✓
Greenway, 2006 ¹²³	✓				✓					✓			✓
Hackman, 2006 ¹²⁴	✓				✓					✓			✓
Opala, 2006 ¹²⁵	✓		✓										
Ngondi, 2005 ¹²⁶	✓		✓		✓					✓			✓
Coffey, 2004 ¹²⁷	✓		✓		✓								✓

(Continued)

Table 8. (Continued)

Guideline items	Primary and secondary efficacy endpoints				Additional documented effect				Patient selection	Additional intervention		Safety monitoring	
	Weight loss at least 5% of baseline	Central Adiposity	WC	Weight maintenance	CVS risk reduction	Weight reduction helps with comorbidities	QOL	DEXA scan (to prove primary reduction in fat content)		Type 2 DM	Lifestyle modification programmes	Adverse event assessment	EGC at baseline and 6 months
Greenway, 2004 ¹²⁸	✓				✓			✓		✓	✓	✓	
Hicki, 2004 ¹²⁹	✓	✓	✓	✓	✓				✓	✓	✓		
Udani, 2004 ¹³⁰	✓		✓	✓	✓					✓			
Woodgate, 2003 ¹³¹	✓	✓	✓	✓							✓		
Boozer, 2002 ¹³²	✓		✓	✓						✓	✓	✓	
Andersen, 2001 ¹³³	✓			✓							✓		
Boozer, 2001 ¹³⁴	✓		✓	✓						✓	✓	✓	
Mattes, 2000 ¹³⁵	✓							✓		✓			
Heymsfield, 1998 ¹³⁶	✓							✓		✓			

CVS, cardiovascular system; DEXA, dual-energy X-ray absorptiometry; DM, diabetes mellitus; ECG, electrocardiogram; QOL, quality of life; WC, waist circumference

interventions. Specific clinical trial guidelines, such as the CONSORT Extension for Chinese Medicine Formulas 2017³¹ and the Guideline for Herbal Medicine Research 2023,¹⁴⁴ underscore the importance of prioritising safety in herbal medicine clinical research.

This scoping review has certain limitations that should be considered when interpreting its findings. Only studies published in English were included due to resource constraints. We did not exclude pilot studies or those with less than 6 months of follow-up, a decision made to ensure a comprehensive overview of the available literature. Due to the inadequate reporting of the sexes analysed in the included trials, we also could not conclude the numbers of recruited genders. Lastly, our assessment of included studies is based on reported information in published literature only. There may be instances where quality indicators were addressed in a trial but not reported, influenced by factors such as word count restrictions, editorial decisions and investigators' perceptions of importance. We utilised clinical study guidelines for weight management products, as there are currently no standard international guidelines for conducting RCTs specifically focusing on herbal medicine in anti-obesity interventions. These guidelines are based on drafts from the USFDA and the EMA, last updated in 2007 and 2017, respectively. Although not recently updated, these guidelines serve as a foundational reference for comparing the methods commonly employed in weight management trials. This review did not assess the included RCTs against the CONSORT guidelines, as the primary scope was to evaluate the methodology in relation to the two regulatory guidelines. However, future studies can consider including an assessment based on CONSORT guidelines to provide a more comprehensive evaluation of the included RCTs.

Conducting RCTs for anti-obesity interventions is challenging, given the multitude of factors to consider. These include various parameters such as weight loss measures, evidence of fat reduction, sustained weight maintenance, lowered cardiovascular risks, among others. Additionally, the ideal requirement for long-term clinical trials to establish both efficacy and sustainability adds to the complexity. Despite the difficulties, developing effective weight-loss products can bring significant benefits, particularly in marketing, if the trials show positive results across various indicators.

Companies that can manage these challenges may set themselves apart by creating reliable, evidence-based products, which is something not commonly achieved due to the inherent complexity of conducting such comprehensive trials.

In conclusion, approximately half of the RCTs assessing the anti-obesity efficacy of herbal medicine interventions adhere to international guidelines, incorporating considerations for diet control, lifestyle, physical activity and the assessment of cardiovascular risk factors. In addition to efficacy, adherence to recommendations for safety monitoring and reporting should also be emphasised. There is a need for more herbal anti-obesity RCTs to evaluate weight maintenance among participants.

Declarations

Ethics approval and consent to participate

An ethics statement and consent for participation was not required because this study is based exclusively on published literature. This review was registered and approved by the National Medical Research Register with the approval number NMRR ID-23-00928-AYO.

Consent for publication

Not applicable.

Author contributions

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Acknowledgements

The authors gratefully acknowledge the Director General of Health Malaysia, Deputy Director General of Health Malaysia (Research and Technical Support), Director of Institute for Medical Research and the Head of Herbal Medicine Research Centre for their authorisation and permission for the publication of this article.

Funding

The authors received no financial support for the research, authorship and/or publication of this article.

Competing interests

The authors declare that there is no conflict of interest.


Availability of data and materials


A data availability statement is not applicable as this scoping review is based exclusively on published literature.


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Supplemental material

Supplemental material for this article is available online.

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