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Targeting obesity management through gut microbiota modulation by herbal products: A systematic review

Hanieh-Sadat Ejtahed[a], Ahmad-Reza Soroush[a], Seyed-Davar Siadat[b], Zahra Hoseini-Tavassol[b], Bagher Larijani[c], Shirin Hasani-Ranjbar[a,*]

[a] Obesity and Eating Habits Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran
[b] Department of Mycobacteriology and Pulmonary Research, Microbiology Research Center, Pasteur Institute of Iran, Tehran, Iran
[c] Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

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ABSTRACT

Objectives: The gut dysbiosis has been implicated as a mediator to obesity and its manipulation could be an appropriate approach to sustainable weight loss. In this systematic review, our primary objective was to assess the potential manipulation of gut microbiota by herbal products in obesity.

Materials and methods: We did a comprehensive search in PubMed, Web of Science, Scopus and Cochrane databases for all clinical trials and animal studies exploring the effects of various herbal products on gut microbiota composition in obesity documented up to May 2017.

Results: Our initial search yielded 2766 articles. After screening abstracts and full texts, 68 articles were included (55 animal studies and 13 clinical trials). The studies differed in their methodologies, type of interventions and intervention lengths. The weight loss was only reported in 23% of trials and in 64% of animal studies. An increasing tendency in *Bifidobacterium* species and butyrate-producing bacteria such as Faecalibacterium prausnitzii were observed after consuming non-digestible carbohydrates, although these changes did not always correlate with weight loss. Supplementation with high concentration of polyphenols reduced body weight gain in animal studies and inhibited growth of detrimental species such as *Clostridia* and *Enterobacteria* while the growth of Lactic acid bacteria and *Akkermansia muciniphila* is enriched.

Conclusions: Alteration of gut microbiota after interventions has been affected by the baseline composition of gut microbiota. This systematic review shows that consumption of herbal products might have beneficial effects on restoring healthy gut microbiome besides body fat reduction.

1. Introduction

The worldwide epidemic of obesity and its related metabolic complications has become a major challenge for public health and has imposed a heavy financial burden on society. [1,2] Excessive adiposity is associated with insulin resistance and chronic inflammation. [3,4] Therefore, as one of the leading causes of mortality, obesity significantly enhances the risk of many chronic diseases, including diabetes, cardiovascular diseases, hypertension, cancer, osteoarthritis and psychological diseases. [2,5]

The rapid increase in obesity prevalence over the past few decades can be partly explained by changes in lifestyles and dietary patterns.[6] However, the major mediators in the development of obesity are still investigating. Nowadays, the gut microbiota, microorganisms which inhabit the human intestine, has been implicated in the etiology of chronic diseases including obesity.[7,8] Indeed, it has a role as a mediator to diet-induced obesity.[9] Humans as supraorganisms consist of both human cells and microbial cells, including the gut microbiota. Interactions among the host, the microbiota and the environment influence the human health.[7,8] Although identification of the exact species involved in weight management is not yet possible and remains to be determined, the causative role for the endotoxin-producing bacteria in the development of obesity has been demonstrated.[7] Impaired gut barrier function in obesity increases uptake of endotoxin and

Abbreviations: LPS, lipopolysaccharides; GLP-1, glucagon-like peptide 1; PYY, peptide YY; FIAF, fasting-induced adipose factor; LPL, lipoprotein lipase; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCTs, randomized clinical trials; qPCR, quantitative polymerase chain reaction; FISH, fluorescence in situ hybridization; DGGE, denaturing gradient gel electrophoresis; OTU, operational taxonomic units

* Corresponding author at: Endocrinology and Metabolism Research Institute, 5th Floor, Shariati Hospital, North Kargar Ave., Tehran, 14114, Iran.
E-mail addresses: sh_hasani@sina.tums.ac.ir, shirinhasanir@yahoo.com (S. Hasani-Ranjbar).

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lipopolysaccharides (LPS) and eventually systemic inflammation.[8] Short chain fatty acids, which produced from fermentation of indigestible dietary compounds by intestinal bacteria play a critical role in regulating release of satiety hormones, including glucagon-like peptide 1 (GLP-1), peptide YY (PYY) and leptin and expression of fasting-induced adipose factor (FIAF).[7,8,10] FIAF has an inhibitory effect on lipoprotein lipase (LPL) activity and triglyceride accumulation in adipose tissue.[8,10] It seems that gut microbiota manipulation could be an appropriate approach to sustainable weight loss.[11]

Herbal products as prebiotics could be a good candidate for modulating gut microbiota.[12] The anti-obesity effects of medicinal plants via increasing energy expenditure, appetite suppression, inhibition of lipase activity, inhibition of food absorption, and regulation of adipocyte differentiation and lipid metabolism have been documented so far.[12–17] However, the effects of herbal products on gut microbiota in obesity should be investigated more. This systematic review was conducted to assess the effect of herbal products supplementation on any related parameters of gut microbiota in obesity.

2. Material and methods

2.1. Search strategy and study selection

A literature search of PubMed, Web of Science, Scopus and the Cochrane Central Register of Clinical Trials was conducted for entire clinical trials and animal studies exploring the effects of various herbal products on gut microbiota composition in obesity up to May 2017. There was no restriction regarding publication date or language. The search was conducted by two separate investigators. Moreover, the reference lists of the key reviews in the area were screened for any additional relevant studies. The search strategy is shown in Table 1.

After combining the search results of different databases, duplicates were removed. Two investigators screened the titles and abstracts of articles, independently. Then, the full texts of potentially eligible studies were reviewed. Disagreements and uncertainty between the two investigators were resolved by discussion, and studies were included if they assessed the effect of herbal products supplementation on any related parameters of gut microbiota among obese patients and animals. In Vitro studies, case studies, case series, cross-sectional, study protocols, literature reviews, and studies which did not include intestinal microbiota assessment were excluded from the systematic review. All kinds of herbs, vegetables, fruits, herbal extracts, oligosaccharides, fiber and antioxidants derived from herbs were included in this review. Studies with multiple intervention components (combination of probiotics and prebiotics or combination of prebiotics and vitamins and minerals) which the independent effects of prebiotics on gut microbiota were not assessed were excluded from the study. Studies which conducted on normal-weight subjects, patients with gastrointestinal disorders or patients who had undergone bariatric surgeries were excluded. Studies comparing herbal products with placebo or no supplementation were included. This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[18]

2.2. Data extraction

The following information was extracted from included studies: first author's name, publication year, study design, sample size, duration of supplementation, demographic characteristics of participants, types of prebiotics and the daily dose, methods of gut microbiota evaluation and evaluated outcomes. The primary outcome was gut microbiota assessment and the secondary outcome included anthropometric indices. Relevant data were extracted from studies by two separate investigators.

2.3. Quality assessment

Delphi checklist was used to assess the quality of included clinical trials and SYRCLE's risk of bias tool was used to evaluate the quality of included animal studies.[19,20] The quality assessment of included studies was done by two separate investigators and consensus-based discussion.

3. Results

Overall, we identified 2766 articles in databases and hand searches. Titles and abstracts of 2044 articles were screened after removing the duplicates. 1971 articles were excluded for being review (n = 139) and irrelevant to the main topic (n = 1832). Out of 73 remained full texts, studies with no relevant outcomes were omitted (n = 5), and finally 55 animal studies and 13 clinical trials were included in the systematic review (n = 68). Two clinical trial articles were the results of same research which were published in two parts.[21,22] A detailed flowchart showing the process of study selection is presented in Fig. 1. The characteristics of the 68 included studies are summarized in Tables 2 and 3 categorizing studies based on herbs, herbal extracts and bioactive ingredients. It should be noted that many of the herbal extracts are used in traditional Chinese medicine.

Trials were published between 2006 and 2017 with high frequency in 2013 and 2016 (3 studies in each year). Human studies had different designs; six of them were double-blind randomized clinical trials (RCTs) (four with parallel assignments and two with cross-over design), two were single-blind RCTs, one was RCT and three were quasi-experiments (single-group assessment). The sample size of the trials varied between 7 and 53. Geographically, 5 (41.7%) of the trials were conducted in

Table 1
Search Strategy.

Search components	Search keywords
Component 1: Herbal products	("Herbal Medicine"[Mesh] OR Herbalism[TIAB] OR "Plants, Medicinal"[Mesh] OR ((Herb*[tiab] OR Plant*[tiab]) AND (Intervention* [tiab] OR treat[tiab] OR TREATMENT[TIAB] OR Therap*[tiab] OR "therapy" [Subheading] OR medicin*[tiab] OR Healing[TIAB] OR Pharmaceutical [TIAB])) OR "Phytotherapy"[Mesh] OR "Phytotherapy" [TIAB] OR "Naturopathy"[Mesh] OR Naturopath*[TIAB] OR "Drugs, Chinese Herbal"[Mesh] OR ((Chinese[TIAB] OR Drug* [TIAB]) AND Plant[TIAB]) OR "Medicine, Traditional"[Mesh] OR (Folk[TIAB] AND (Remed*[TIAB] OR medicine[TIAB])) OR (Indigenous[TIAB] AND Medicine[TIAB]) OR Ethnomedicine [TIAB] OR (Medicine[TIAB] AND Traditional[TIAB]) OR "Ethnopharmacology"[Mesh] OR "Ethnopharmacology" [TIAB] OR "Ethnobotany"[Mesh] OR "Ethnobotany"[TIAB] OR "Plant Extracts"[Mesh] OR "Prebiotics"[Mesh] OR PREBIOTIC*[TIAB] OR (Plant*[TIAB] AND Extract*[TIAB]))
AND	AND
Component 2: gut microbiota	((gut[TIAB] OR Colon*[TIAB] OR "Gastrointestinal Tract"[Mesh:NoExp] OR (Gastrointestin* [TIAB] AND Tract*[TIAB]) OR "GI Tract" [TIAB] OR "GI Tracts" [TIAB] OR (Digestive*[TIAB] AND Tract*) OR Intestin* [TIAB] OR "Intestines"[Mesh] OR "Feces"[Mesh] OR "Feces"[TIAB] OR fecal[TIAB] OR faecal[TIAB]) AND (microbiota[TIAB] OR MICROBE[TIAB] OR MICROBES[TIAB] OR microbial[TIAB] OR "Microbiota"[Mesh] OR microflora[TIAB] OR bacteria*[TIAB] OR microbiome[TIAB] OR microorganism*[TIAB] OR "dysbiosis"[Title/Abstract] OR "Dysbiosis"[Mesh]))
AND	AND
Component 3: obesity	(obes*[tiab] OR Overweight[tiab] OR "OveR weight"[TIAB] OR weight[tiab]OR "Overweight"[Mesh] OR "Body Fat Distribution"[Mesh] OR "Body Weight"[Mesh] OR "Adiposity"[Mesh] OR ADIPOS*[TIAB] OR (FAT[TIAB] AND (MASS[TIAB] OR BODY)))

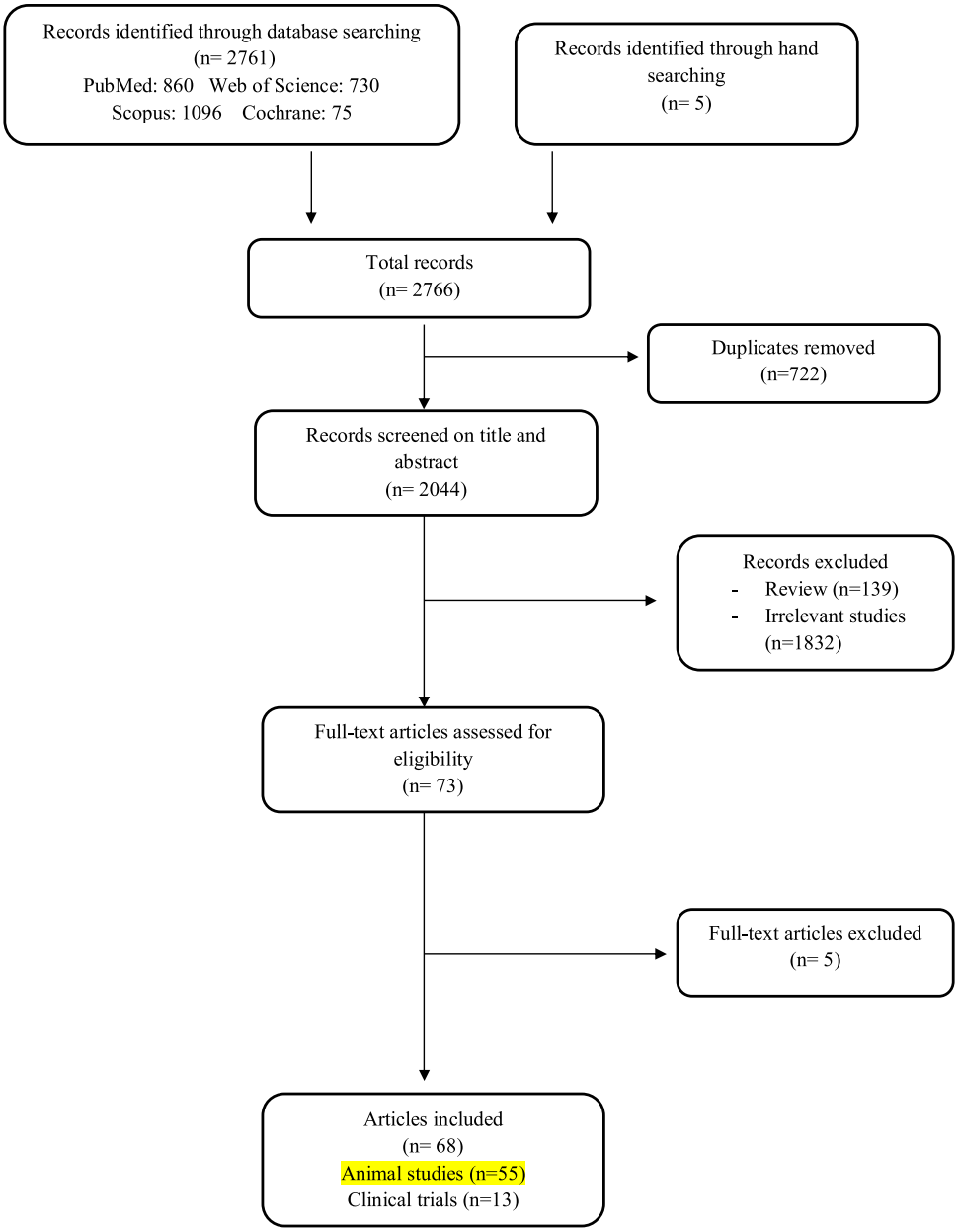

Fig. 1. Flow diagram of the systematic literature search.

Asia and 7 (58.3%) in Europe.

Two third of the studies were conducted on women and the rest of studies had no gender limit. The ages of the included subjects varied between 18 and 70 years old. The duration of the trials varied from 3 to 12 weeks. Type of interventions and methodology of microbiota analysis were highly variable among the trials. In all of the trials, changes of gut microbiota composition were assessed as an outcome.

Different techniques including cultivation (1 study), quantitative polymerase chain reaction (qPCR) (2 studies), fluorescence in situ hybridization (FISH) (3 studies), combination of denaturing gradient gel electrophoresis (DGGE) and qPCR (2 studies), 16S rRNA sequencing (3 studies) and metagenomic analysis (1 study) were used to assess the intestinal microbiome in trials.

The interventions varied and included fruit (n = 1), herbal and fruit extracts (n = 4), thylakoids (n = 1), and different kinds of fibers (n = 6) (very long chain inulin, glucomannan, mucilage, galactooligosaccharide, inulin-type fructans, arabinoxylans).[21–33] The herbal products had diverse effects on microbial phylum in gut microbiota, although most of the trials showed an increase in the *Actinobacteria* phylum, as *Bifidobacterium* spp. enriched after intervention in 7 studies.[21,22,24–26,29,32,33] Interventions exerted inconsistent impacts on *Firmicutes* and *Bacteroidetes* abundances. *Firmicutes* was decreased after the intake of *Schisandra chinensis* or *Rehmannia glutinosa* extracts,[26,33] although this phylum showed no changes after Bofutsushosan and Arabinoxylan intakes.[28,30] On the other hand, an increase in *Firmicutes* was observed after inulin-type fructans consumption.[21,22] Alteration of *Bacteroidetes* was also inconsistent after various interventions.[21,22,26,28,30,33]

Lactobacillus genus was increased after the intake of very long chain inulin, glucomannan and fructans.[21,22,24,25] The abundance of *Bacteroides*, *Prevotella*, *Faecalibacterium* and *Clostridium* genera showed contradictory results.[21–25,31–33] Manipulation of gut microbiota with the use of mucilage and *Schisandra chinensis* extract resulted in depletion of *Ruminococcus* abundance.[23,33] An increase in *Akkermansia* genus was observed after *Schisandra chinensis* extract intake.[33] Two clinical trials reported no impact on gut microbiome following interventions[28,30] and

Table 2
Characteristics of the included clinical trials investigating the effects of herbal products on gut microbiota in obesity.

Study(year)	Country	Study design	Quality score (Delphi)	Population sex and age (y)	Mean BMI (kg/m^2)	Sample size (n)	Intervention group	Control group	Duration	Methods of microbiota analysis	Results (Intervention vs control after supplementation)
Herbs, vegetables, fruits											
Chen et al. (2006)	Taiwan	Single-blind, before and after study	4/9	Healthy adults, aged 21–54 y, 7 females, 1 male, Mean of BMI: 24.8 ± 1.4	24.8 ± 1.4	8	Konjac glucomannan powder, 4.5 g/d, three gelatin capsules (n = 8)	Corn starch as placebo, 4.5 g/d, three gelatin capsules (n = 8)	21 days	Fluorescence in situ hybridisation (FISH)	↑ Total bacteria, ↑ Bifidobacteria, ↑ Lactobacilli, ↓ Clostridia
Costabile et al. (2010)	Germany	Double-blind, placebo-controlled, cross-over trial	6/9	Healthy adults, aged 20–42 y, eighteen females, fourteen males, BMI: 20-30	–	31	Very-long-chain inulin extracted from globe artichoke (Cynara scolymus), 10 g/d (n = 31)	Maltodextrin, 10 g/d (n = 31)	Two 3-week study periods, separated by a 3-week washout period	Fluorescence in situ hybridisation (FISH)	↔ Total bacteria, ↑ Bifidoacterium, ↑ Lactobacilli–enterococci, ↑ Atopobium, ↓ Bacteroides–Prevotella, ↔ Escherichia coli
Mitsou et al. (2011)	Greece	Randomized controlled clinical trial	4/9	Healthy premenopausal women, aged 19-45 y, BMI: 24-30	27	31	-Banana, 2 medium (240 g/d) (n = 12) - Banana-flavoured drink, 2 cup/d (n = 9)	2 cup of water (n = 10)	60 days	Cultivation (plate count techniques)	↑ Bifidobacteria in banana group
Brahe et al. (2015)	Denmark	Single-blind paralleled randomized controlled clinical trial	6/9	Obese postmenopausal women, aged 40-70 y, BMI: 30-45, WC > 80 cm	Flaxseed:35.2 ± 4.5, Probiotic:34.2 ± 3.1, Placebo:34.3 ± 3.8	53	flaxseed mucilage, 10 g/d (n = 19)	Lactobacillus paracasei F19, 9·4 × 10^{10} colony-forming units (n = 18) Placebo (n = 16)	6 weeks	Quantitative metagenomic analysis	↓ Faecalibacterium genus, ↓ Ruminococcus Lactaris, ↑ Clostridium genus, ↑ Bilophila wadsworthia, ↑ Parabacteroides merdae, ↑ Parabacteroides johnsonii
Herbal Extracts											
Kim et al. (2014)	Korea	Before and after study	2/9	Obese women, aged 40-65 y, BMI≥25	30.2 ± 3.3	7	Ephedra sinica extracts, 4 g/d (n = 7)	–	2 months	16S rRNA gene based pyrosequencing	↓ Weight, BMI, body fat percentage Alteration of gut microbiota varied between subjects due to the differences of gut microbiota before intake.
Lee et al. (2014)	Korea	Double-blind randomized placebo-controlled clinical trial	7/9	Female subjects aged 19-65, BMI > 25 and WC > 85	Intervention:28.3 ± 1.3 Control:28.5 ± 1.7	50	Bofutsushosan (herbal extracts contained 18 components),6 g/d + 2 probiotic capsules (n = 25)	Bofutsushosan (herbal extracts contained 18 components),6 g/d + 2 placebo capsules (n = 25)	8 weeks	Quantitative polymerase chain reaction	↓ Weight, BMI, WC, fat mass, body fat percentage after herbal supplementation. No changes in gut bacteria in herbal group. ↑ B. breve, B. lactis, L. rhamnosus, L. plantarum, Gram negative bacteria in probiotic group.
Han et al. (2015)	Korea	Before and after study	3/9	Obese women, aged 40-65 y, BMI > 25	27.8 ± 1.9	12	Steamed extract of *Rehmannia glutinosa* Libosch, 8 g/d (n = 12)	–	8 weeks	16S rRNA gene based pyrosequencing	↓ WC ↓ Firmicutes, ↓ Bacteroidetes, ↑ Actinobacteria, ↓ Blautia, ↑ Bifidobacterium, ↓ Eubacterium

(*continued on next page*)

Table 2 (*continued*)

Study(year)	Country	Study design	Quality score (Delphi)	Population sex and age (y)	Mean BMI (kg/m^2)	Sample size (n)	Intervention group	Control group	Duration	Methods of microbiota analysis	Results (Intervention vs control after supplementation)
Song et al. (2015)	Korea	Double-blind randomized placebo-controlled clinical trial	6/9	Obese women, Mean of BMI: Intervention:34.9 ± 6.5 Control:37.0 ± 7.3	Intervention:29.9 ± 4.3 Control:28.8 ± 3.5	28	*Schisandra chinensis* fruit extract, 200 ml/d (n = 13)	Placebo, 200 ml/d (n = 15)	12 weeks	Denaturing gradient gel electrophoresis and quantitative polymerase chain reaction	↓ WC, ↓fat mass ↔ BMI ↓ Firmicutes, ↑Bacteroidetes, ↑ Bacteroides, ↑ Akkermansia, ↑ Roseburia, ↑ Prevotella, ↑Bifidoacterium, ↓ Ruminococcus
Dietary fibers											
Dewulf et al. (2013)*	Belgium	Double-blind, randomized, placebo-controlled, parallel trial	8/9	Obese women, aged 18-65 y, BMI > 30	Intervention:36.1 ± 4.1 Control:35.6 ± 4.3	30	Inulin-type fructans (inulin/oligofructose:50/50), 16 g/d (n = 15)	Maltodexterin, 16 g/d (n = 15)	3 months	Phylogenetic microarray, denaturing gradient gel electrophoresis (DGGE) and quantitative polymerase chain reaction	↔BMI, waist/hip ratio ↓ Fat mass ↓Total SCFA, acetate, propionate ↑ Firmicutes, Actinobacteria ↓Bacteroidetes, ↑Bacilli, Clostridium clusters IV and XVI ↑ Bifidoacterium, Faecalibacterium prausnitzii, Lactobacillus ↓ Bacteroides intestinalis, B vulgatus ↑Bifidobacterium longum, Bifidobacterium pseudocatenulatum, Bifidobacterium adolescentis
Vulevic et al. (2013)	United Kingdom	Double-blind, randomized, placebo-controlled, cross-over trial	6/9	Overweight adults, aged 18-65 y, 29 females, 16 males, BMI > 25	Male:30.7 ± 5.3 Female:32.1 ± 6.3	45	Galactooligosaccharide mixture, 5.5 g/d, Sachets	Maltodexterin, 5.5 g/d, Sachets	Two 12-week study periods, separated by a 4-week washout period	Fluorescence in situ hybridisation (FISH)	↔ Body weight ↑ Bifidobacteria, ↓Bacteroides, C. histolyticum, Desulfovibrio, Proteobacteria
Salden et al. (2017)	The Netherlands	Double-blind, randomized, placebo-controlled, parallel trial	8/9	Overweight and obese adults, aged 18-70 y, 22 females, 25 males, BMI:28-35	31.0 ± 2.4	47	-Arabinoxylans, 7.5 g/d, Sachets (n = 16) -Arabinoxylans, 15 g/d, Sachets (n = 17)	Maltodexterin, 15 g/d, Sachets (n = 14)	6 weeks	16S targeted DNA-based Illumina with MiSeq platform	↑Total SCFA, acetate, propionate, butyrate ↓ Fecal microbiota diversity ↔ Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria

(*continued on next page*)

Table 2 (*continued*)

Study(year)	Country	Study design	Quality score (Delphi)	Population sex and age (y)	Mean BMI (kg/m^2)	Sample size (n)	Intervention group	Control group	Duration	Methods of microbiota analysis	Results (Intervention vs control after supplementation)
Others											
Stenblom et al. (2016)	Sweden	Single-blinded, single-centered, randomized and placebo-controlled trial	5/9	Healthy women, aged 40-65 y, BMI: 25-33	Thylakoid:28.9 ± 2.2, Placebo:28.6 ± 2.3	34	green-plant membranes (thylakoids), 5 g/d + blueberry drink (50 ml blueberry soup + 208 g rapeseed oil) (n = 18)	blueberry drink (50 ml blueberry soup + 208 g rapeseed oil) (n = 16)	12 weeks	Quantitative polymerase chain reaction	↓ Body weight ↑ Total bacteria, ↑ Bacteriodes fragilis, ↔ Akkermansia muciniphilia, Clostridium coccoides group, Clostridium leptum subgroup, Enterobacteriaecae, Lactobacillus

*Results of two articles.

one trial showed that alterations of gut microbiota were dependent on the baseline richness and taxonomic microbial composition of the patients' intestinal microbiota.[27]

Short-chain fatty acid concentrations showed inconsistent results after interventions.[21,22,30] Mild weight loss was only reported in three trials and mean of reduced weight was below two kg,[27,28,31] while the remaining trials observed no impact on body weight. However, a decrease in body fat percentage was reported in four studies[21,22,27,28,33] and three studies revealed a waist circumference reduction.[26,28,33] Adverse effects were reported in six studies[21–23,25,27,33]; the most prevalent one was flatulence[21,23,25] and the remaining were changed bowel habits,[23,33] coughs,[33] headache, nausea and dyspepsia.[27] The quality score of included clinical trials was between two and eight from nine with a mean of six. Two-third of the studies had scored higher than four from nine, showing moderate quality.

Animal studies were published between 2003 and 2017. Most of them (54.4%) were conducted on mice, 40.3% were conducted on rats and 5.3% on hamsters. The duration of the interventions varied between 2 and 22 weeks. Like clinical trials, various techniques were used for microbiome analysis; which among these methods, qPCR and pyrosequencing were most used.

A variety of natural plants (herbs, fruits and vegetables) and their bioactive ingredients have been explored in animal studies; the effects of different types of dietary fibers and oligosaccharides (glucomannan, arabinoxylan, oligofructose, inulin, pectin, hydroxypropyl methylcellulose, resistant starch, and isomalto- oligosaccharides) and phytochemicals (polyphenols, berberine, lycopene, quercetin and epigallocatechin 3-O-methyl gallate) on gut microbiota in obese animals have been explored.[34–88] Weight loss and fat mass reduction were reported in 64% of animal studies.[34,38–44,47,48,51–53,55,60–63,66,67,70–72,75–81,83–86,88] On the phylum level, an increase was observed in *Bacteroidetes* and a decrease was reported in *Firmicutes* abundance in most of the studies.[46,55,61,64,67,69,73,76,80,81,83,84,88] Twelve studies explored the effects of fructo-oligosaccarides on microbiome which 50% of them reported weight reduction or decreasing in weight gain and fat accumulation in high fat diet feeding animals.[2,5,40,41,42,43,45,46,49,50,54] *Bifidobacterium*, *Lactobacillus* and *Akkermansia* were increased after the intake of fructo-oligosaccarides and the abundance of *Clostridium* spp. was decreased.[34,35,41,46,47,55,56,64,70,75,78] An increasing tendency in butyrate-producing bacteria such as *Faecalibacterium prausnitzii*, *Eubacterium*, and *Roseburia* species were observed after the intake of non-digestible carbohydrates.[56] The quality score of included animal experiments was between three and eight from ten, showing poor to moderate quality.

4. Discussion

Regarding the growing interest in weight management by gut microbiota manipulation, this systematic review was conducted to assess studies of herbal product interventions on gut microbiota in overweight and obese patients and animals. There were significant differences in types of herbal products, methodology, design, duration and outcomes among the included studies. Moreover, the baseline gut microbiota composition depends on race, age, sex and lifestyle and the microbial colonization process is modulated by several factors, including mode of delivery, dietary pattern, environment, and exposure to antibiotics. So the inter-individual variations of gut microbiota could have effects on the observed alteration of microbiota after interventions. Although long-term dietary patterns exert key impacts on the gut microbiota composition,[89] dietary interventions and supplementations have a rapid and powerful influence on gut microbiome too.

The important challenge in comparing the results of different studies was the diverse techniques which have been used for gut microbiota assessment with different ways of presenting microbiota composition for example differences in the assessed taxonomic level. Even in sequencing technique, differences in DNA extraction protocol,

Table 3
Characteristics of the included animal studies investigating the effects of herbal products on gut microbiota in obesity.

Study (year)	Quality score (SYRCLE)	Target species	Sample size (n)	Intervention group	Control group	Duration	Methods of microbiota analysis	Results (Intervention vs control after supplementation)
Herbs, vegetables, fruits								
Prestamo et al. (2003)	5/10	12-week-old female Wistar Hannover rats	20 in 2 equal groups	- Buckwheat diet (n = 10)	- Conventional diet (n = 10)	30 days	Cultivation	↓ body weight ↑ Lactic acid bacteria, Lactobacillus plantarum, Bifidobacterium, Bifidobacterium lactis ↓ Enterobacteria
Sembries et al. (2003)	7/10	Male Wistar rats weighing 177 ± 4 g	40 in 4 equal groups	- 5% apple pomace extraction juices colloids + enzymatic treatment (n = 10) - 5% apple pomace extraction juices colloids (n = 10) - Alcohol-insoluble substance (AIS) from apples (n = 10)	Control: diets without any apple dietary fibre (n = 10)	6 weeks	Cultivation and Fluorescence in situ hybridisation (FISH)	↓ Weight ↑ SCFA ↑ Total bacteria ↑ Eubacterium rectale cluster in caecum ↑ Bacteroides in caecum ↑ Bacteroidaceae in faeces
Kuda et al. (2004)	4/10	Male ICR mice	18 in 3 equal groups	- Red pepper powder, 2% (n = 6) - Garlic powder, 2% (n = 6)	- Control group, beef tallow-fed (n = 6)	4 weeks	Cultivation	↔ body weight ↓ bacteroidaceae, bifidobacteria, staphylococci in red pepper group
Marinangeli et al. (2011)	6/10	Two-week-old male Golden Syrian hamsters	55 in 3 groups	- Whole yellow pea flour,10% + hypercholesterolemic diet (n = 15) - Fractioned yellow pea flour,10% + hypercholesterolemic diet (n = 15)	- Corn starch,10% + hypercholesterolemic diet (n = 15)	28 days	PCR amplification and terminal restriction length polymorphism analysis	↔ body weight gain ↑clostridia in Whole yellow pea group ↑Bacilli and Lactobacillales in both yellow pea groups
Neyrinck et al. (2011)	6/10	Nine-week-old male C57b16/J mice	24 in 3 equal groups	- Wheat arabinoxylan, 10% + high fat diet (n = 8)	- High fat diet (n = 8) - Control diet (n = 8)	4 weeks	Quantitative PCR (qPCR) and denaturing gradient gel electrophoresis (DGGE)	↓ adipocyte size, adiposity, body weight gain ↑ Bacteroides-Prevotella, Roseburia, bifidobacteria, Bifidobacterium animalis lactis
Xie et al. (2011)	7/10	Four-week old male high-fat diet-fed C57BL/6 J mice	24 in 4 equal groups	- Berberine (200 mg/kg) + high-fat diet (n = 6) - Rhizoma coptidis (200 mg/kg) + high-fat diet (n = 6)	- Common chow diet-fed normal animals (Normal) (n = 6) - High-fat diet-fed controls (HFD) (n = 6)	6 weeks	Real-time PCR	↓ Body and visceral adipose weights in berberine and Rhizoma coptidis groups ↓ Firmicutes in berberine and Rhizoma coptidis groups ↓ Bacteroidetes in berberine and Rhizoma coptidis groups
Axling et al. (2012)	7/10	Eight-week-old female C57BL/6 JBomTac mice	84 in 4 equal groups	- Green tea powder 4% + high-fat diet (n = 21) - Green tea powder 4% + Lactobacillus plantarum, 10^{10} cfu/day + high-fat diet (n = 21) - Lactobacillus plantarum, 10^{10} cfu/day + high-fat diet (n = 21)	- high-fat diet (n = 21)	22 weeks	Cultivation and sequencing of the 16S rRNA genes and Quantitative PCR (qPCR)	↓ body weight gain and body fat content in green tea group ↑ Lactobacillus and diversity in green tea + L plantarum group ↑ Akkermansia and total bacteria in green tea + L plantarum group ↔ Enterobacteriaceae
Neyrink et al. (2012)	6/10	9-week-old male high fat diet-induced obese C57BL6/J mice	24 in 3 equal groups	- arabinoxylan oligosaccharides derived from wheat bran, 7.5% + % + high fat diet (n = 8)	- Control diet (n = 8) - High fat diet (n = 8)	8 weeks	Quantitative PCR (qPCR)	↓ Body weight gain, fat mass in arabinoxylan group ↑ Bifidobacteria in

(*continued on next page*)

Table 3 (*continued*)

Study (year)	Quality score (SYRCLE)	Target species	Sample size (n)	Intervention group	Control group	Duration	Methods of microbiota analysis	Results (Intervention vs control after supplementation)
								arabinoxylan group ↓ Lactobacilli in arabinoxylan group ↔ Bacteroides-Prevotella spp. in arabinoxylan group
Neyrinck et al. (2012)	5/10	Nine-week-old male Balb/c mice	18 in 3 equal groups	- Polyphenol-rich extract of pomegranate peel, 6 mg/d + high fat diet (n = 6)	- High fat diet (n = 6) - Control diet (n = 6)	4 weeks	Quantitative PCR (qPCR)	↔ body weight gain ↑ Bifidobacteria
Engevik et al. (2013)	3/10	Male mice	25 in 2 groups	- Galursan HF 7 K (oligosaccharide derivative of carrots), 2% (n = 11)	- Control group (n = 14)	2 weeks	Real-time PCR	↔ body weight ↔ total bacteria ↑ Proteobacteria ↔ Lactobacillus and Bifidobacterium
Yin et al. (2013)	6/10	Male high-fat diet-induced NAFLD Sprague–Dawley rats	26 in 4 groups	- Chinese herbal formula(*Qushi Huayu Fang*), high dose (0.93 g/100 g body weight)+ HFD diet (n = 7) - Chinese herbal formula(*Qushi Huayu Fang*), low dose (0.47 g/100 g body weight)+ HFD diet (n = 7)	- Control group, normal chow -fed (n = 5) - High-fat diet-fed controls (n = 7)	4 weeks	Polymerase chain reaction-denaturing gradient gel electrophoresis and bar-coded pyrosequencing of the V3 region of 16S rRNA genes	↓Body weight ↓Escherichia/Shigella ↑ Collinsella (short chain fatty acid producers)
Berger et al. (2014)	6/10	Four-week-old male C57BL/6 mice	100 in 10 equal groups	- barley products, 5 g/100 g dietary fiber + high fat diet (n = 10) - refined barley products, 5 g/100 g dietary fiber + high fat diet (n = 10) - rye products, 5 g/100 g dietary fiber + high fat diet (n = 10) - refined rye products, 5 g/100 g dietary fiber + high fat diet (n = 10) - soluble refined rye products, 5 g/100 g dietary fiber + high fat diet (n = 10) - oat products, 5 g/100 g dietary fiber + high fat diet (n = 10) - refined oat products, 5 g/100 g dietary fiber + high fat diet (n = 10)	- guar gum, 5 g/100 g dietary fiber + high fat diet (n = 10) - high fat diet (n = 10) - low fat diet (n = 10)	5 weeks	Quantitative real-time PCR (qPCR)	↔ body weight and fat mass ↔ C. leptum ↑ Bifidobacteria, propionic acid in soluble refined rye products group vs high fat fed control group ↑ Lactobacilli, propionic and butyric acid in oat groups vs high fat fed control group ↔ Enterobacteriaceae ↑ Akkermansia muciniphila in guar gum group vs high fat fed control group
Harmayani et al. (2014)	6/10	Eight-week-old male Wistar rats	32 in 4 equal groups	- Porang glucomannan (n = 8) - Commercial konjac glucomannan (n = 8) - Inulin (n = 8)	- Control: standard diet, cellulose (n = 8)	2 weeks	Cultivation	↑ body weight gain ↔ Lactobacillus and Bifidobacterium ↓ Escherichia coli
Hu et al. (2014)	6/10	Male 6-week-old Kunming mice	24 in 2 equal groups	- Plantago asiatica L. Polysaccharide, 0.4 g/kg body Weight (n = 12)	- Control (n = 12)	30 days	Denaturing gradient gel electrophoresis (DGGE) of V3 regions of bacterial 16S rDNA amplifications	↑ diversity ↑ Bacteroides sp., Eubacterium sp., butyrate-producing bacteria Butyrivibrio sp., Bifidobacterium bifidum, Lactobacillus fermentum, and Lactobacillus reuteri
Huang et al. (2014)	5/10	Male Golden Syrian hamsters	32 in 4 equal groups	- Pineapple peel water insoluble fiber-rich fraction, 2.5% (n = 8) - Pineapple peel water insoluble fiber-rich fraction, 5% (n = 8)	- Control group, 5% cellulose (n = 8)	30 days	Cultivation	↔ body weight ↑ Lactobacillus spp and Bifidobacterium spp in pineapple peel group

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Table 3 (*continued*)

Study (year)	Quality score (SYRCLE)	Target species	Sample size (n)	Intervention group	Control group	Duration	Methods of microbiota analysis	Results (Intervention vs control after supplementation)
				- Pineapple peel water insoluble fiber-rich fraction, 10% (n = 8)				↓ Clostridium perfringens in pineapple peel group
Murtaza et al. (2014)	6/10	High fat diet fed Swiss albino LACA mice	5 to 8 animals in each four groups	- Finger millet whole grain,10%+high fat diet - Finger millet bran, 10%+high fat diet	- normal diet (10% energy from fat) - high fat diet (45% energy from fat)	12 weeks	Quantitative PCR (qPCR)	↓ body weight gain in finger millet bran group ↑ Lactobacillus, bifidobacteria and Roseburia in both finger millet groups ↑Bacteroides-Prevotella in bran group ↓ Enterobacter in bran group ↓ Firmicutes in bran group ↑ Firmicutes in whole grain group
Noratto et al. (2014)	5/10	Male Zucker-Lepr^{fa}/Lepr + heterozygotes rats and lean Zucker-Lepr+ (Wild Type) rats	40 in 4 equal groups	- Peach juice (n = 10) - Plum juice (n = 10)	- Negative control: lean rats, control juice (n = 10) - Positive control: obese rats, control juice (n = 10)	11weeks	Real-time PCR and 454-pyrosequencing	↓body weight in plum group ↑acetate and propionate in obese control group ↔ butyrate ↔ bacterial diversity ↑ Bacteroidetes and Turicibacteraceae, Faecalibacterium, Lactobacillus in plum group ↑ Ruminococcaceae, Turicibacter in plum and peach groups ↔ Firmicutes/Bacteroidetes ratio
Wang et al. (2014)	6/10	Male high fat diet-induced obese Sprague-Dawley rats	48 in 6 equal groups	- UFL (250 mg/kg of Unfermented Flos Lonicera+HFD + 0.75 mg/kg of LPS) (n = 8) - FFL (250 mg/kg of Fermented Flos Lonicera+HFD + 0.75 mg/kg of LPS) (n = 8)	- Normal control (n = 8) - HFD control (high fat diet only) (n = 8) - LPS control (HFD + 0.75 mg/kg of LPS) (n = 8) - Colostrum control: Positive control (10% of colostrum+HFD + 0.75 mg/kg of LPS) (n = 8)	8 weeks	PCR-DGGE (Denaturing Gradient Gel Electrophoresis) and Real-time PCR	↓Body mass and abdominal adipose tissue weight in FFL and UFL groups ↓ Epididymal adipose tissue weight in FFL group ↑ Akkermansia muciniphila, ↑Bacteroidetes, ↑ Bacteroidetes/ Firmicutes ratio in FFL and UFL groups
Chen et al. (2015)	6/10	Eight-week-old male mice	50 in 5 equal groups	- Ginseng saponins, 500 mg/kg (n = 10) - Red ginseng saponins, 500 mg/kg (n = 10) - Notoginseng saponins, 500 mg/kg (n = 10) - Gynostemma pentaphyllum saponins, 500 mg/kg (n = 10)	- Standard diet (n = 10)	15 days	Real-time PCR	↔ body weight ↑ Bacteroides, Lactobacillus and Bifidobacterium ↑ Bacteroidetes/Firmicutes in notoginseng and Gynostemma pentaphyllum groups ↑ Faecalibacterium prausnitzii in Gynostemma pentaphyllum group ↑ Clostridium Cluster IV in red ginseng group
Kim et al. (2015)	6/10	Male Golden Syrian hamsters	30 in 3 equal groups	- Chardonnay Grape Seed Flour, 10%+high fat diet (n = 10) - Cabernet Sauvignon Grape Seed Flour, 10%+high fat diet (n = 10)	- Control: 5% microcrystalline cellulose + high fat diet (n = 10)	3 weeks	Real-time PCR	↓ weight ↓ total bacteria, Bifidobacterium spp., Lactobacillus spp., and

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Table 3 (*continued*)

Study (year)	Quality score (SYRCLE)	Target species	Sample size (n)	Intervention group	Control group	Duration	Methods of microbiota analysis	Results (Intervention vs control after supplementation)
								Firmicutes in Chardonnay group ↑ Bacteroides fragilis in Chardonnay group ↓ Firmicutes/Bacteroidetes in Chardonnay group ↓ Enterobacteriaceae, Proteobacteria in Cabernet Sauvignon group
Shi et al. (2015)	7/10	Obese male C57BL/6 mice induced by a high-fat diet(60% fat), 8-weeks-old	24 in 3 equal groups	MDG-1, water-soluble β-d-fructan extracted from the roots of Ophiopogon japonicas, 300 mg/kg by oral gavage + high fat diet (n = 8)	- Obese control:Normal saline + high fat diet (n = 8) - Lean control:Normal saline + low-calorie diet (n = 8)	12 weeks	Pyrosequencing	↓ ratio of Firmicutes/ Bacteroidetes ↑ Bacteroidetes ↓ Firmicutes
Shi et al. (2015)	–	8 week-old male diet-induced obese C57BL/6 J mice	60 in 5 equal groups	- Low-dose MDG-1 (water-soluble fructan polysaccharide from Ophiopogon Japonicas): 75 mg/kg (n = 12) - Medial-dose MDG-1: 150 mg/kg (n = 12) - High-dose MDG-1: 300 mg/kg (n = 12)	- Diet induced obese model (n = 12) - Normal control (n = 12)	12 weeks	Denaturing gradient gel electrophoresis and cultivation	↑ Taiwan Lactobacillus and Lactobacillus murinus ↑ diversity
Wang et al. (2015)	8/10	Male Sprague-Dawley rats weighing 180–220 g	48 in 6 equal groups	- URAM: 250 mg/kg of Rhizoma Atractylodis Macrocephalae + HFD + 0.75 mg/kg of LPS (n = 8) - FRAM: 250 mg/kg of Fermented Rhizoma Atractylodis Macrocephalae +HFD + 0.75 mg/kg of LPS (n = 8)	- Normal (n = 8) - HFD control: high fat diet only (n = 8) - LPS control: HFD + 0.75 mg/kg of LPS (n = 8) - Colostrum control: 10% colostrums + HFD + 0.75 mg/kg of LPS (n = 8)	8 weeks	Denaturing gradient gel electrophoresis and quantitative real-time PCR (qRT-PCR)	↓ Weights of body and abdominal fat tissue in URAM and FRAM groups ↓ Adipose tissue fat in FRAM group ↑ Bifidobacterium spp. and Akkermansia spp. and Bacteriodetes/Firmicutes ratio in URAM and FRAM groups ↑ Bacteriodetes and Lactobacillus spp. in FRAM group
Ansari et al. (2016)	6/10	Male C57BL/6 J mice	24 in 4 equal groups	- Chowiseungcheng-tang (CST, 12 different herbs), 700 mg/kg/day + high fat diet (n = 6) - Orlistat, 10 mg/kg/day + high fat diet (n = 6)	- High fat diet (60%:fat) (n = 6) - Normal diet (15.8%:fat) (n = 6)	12 weeks	Quantitative Real-Time PCR	↓ body weight, adipose tissue weight ↑ Bacteroidetes in both CST and orlistat groups ↓ Firmicutes in CST group ↔ Akkermansia, Bacteroides, Lactobacillus, Prevotella in both groups ↑ Bifidobacterium, Roseburia, Ruminococcus in CST group
Bai et al. (2016)	5/10	Male Sprague-Dawley rats	32 in 4 equal groups	- Bitter melon powder, 300 mg/kg/day + high fat diet (n = 8) - Pioglitazone, 10 mg/kg/day + high fat diet (n = 8)	- High fat diet (n = 8) - Normal diet (n = 8)	8 weeks	16S rRNA sequencing (MiSeq platform)	↓ body weight gain, adiposity ↑ Microbial diversity ↓ Proteobacteria ↔ Bacteroidetes and Firmicutes ↓ Desulfovibrionaceae, Enterobacteriaceae ↑ Odoribacteriaceae ↑ Allobaculum, Butyricimonas, Faecalibacterium,

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Table 3 (*continued*)

Study (year)	Quality score (SYRCLE)	Target species	Sample size (n)	Intervention group	Control group	Duration	Methods of microbiota analysis	Results (Intervention vs control after supplementation)
Cheng et al. (2016)	6/10	Six-weeks-old male C57BL/6 J mice	60 in 4 equal groups	- High phenolic Rutgers Scarlet Lettuce (RSL), 6.4% wt/wt + very high fat diet (60%:fat) (n = 15) - Green Lettuce (GL), 6.4% wt/wt + very high fat diet (60%:fat) (n = 15)	- Very high fat diet (n = 15) - Low fat diet (10%:fat) (n = 15)	13 weeks	16S rDNA gene sequencing	odoribacter ↓ Escherichia ↔ body weight gain and fat mass in RSL and GL groups ↓ Firmicutes/Bacteroidetes in RSL group ↔ Verrucomicrobia, Proteobacteria, Actinobacteria and Tenericutes in RSL group ↑ Lachnospiraceae family in RSL and GL groups ↑ Peptococcaceae family, Roseburia spp. and Ruminococcus spp. in RSL group ↑ Coprococcus, Blautia, Moryella spp. and Clostridium spp. in GL group
Hussain et al. (2016)	7/10	Six-weeks-old male high fat diet-induced obese C57BL/6 J mice	28 in 4 equal groups	- Daesiho-tang (DSHT: eight medicinal herbs), 700 mg/kg/day + high fat diet (n = 7) - Orlistat, 10 mg/kg/day + high fat diet (n = 7)	- High fat diet (60%:fat) (n = 7) - Control diet (12.7%:fat) (n = 7)	12 weeks	Quantitative Real-Time PCR	↓ body weight gain, total body fat and intestinal fat in DSHT and orlistat groups ↑ Bacteroidetes, Bifidobacteria, Akkermansia, Bacteroides, Roseburia, Prevotella, Lactobacillus and Ruminococcus in DSHT and orlistat groups ↓ Firmicutes in DSHT and orlistat groups ↓ Firmicutes/Bacteroidetes in DSHT and orlistat groups
Jiang et al. (2016)	7/10	Male Sprague Dawley rats	24 in 3 equal groups	- Apple-derived pectin, 5% wt/wt + high fat diet (n = 8)	- Control: standard chow diet (n = 8) - High fat diet (n = 8)	6 weeks	16S rRNA pyrosequencing (MiSeq platform)	↓ weight gain and fat accumulation in pectin group ↓ Firmicutes ↑ Bacteroidetes ↔ Proteobacteria ↓ Bacilli, Gammaproteobacteria ↑ Bacteroidia, Deltaproteobacteria ↑ Bacteroides ↓ Lactococcus ↓ Clostridium ruminantium
Li et al. (2016)	7/10	Eight-week-old female C57BL/6 J mice	135 in 9 equal groups	- Bamboo shoot fiber, 10%+ high fat diet (n = 15) - 7 different dietary fiber groups, 10%+ high fat diet (n = 15 for each group)	- Low fat control diet (n = 15)	6 weeks	16S rRNA sequencing (MiSeq/ HiSeq platforms)	↓ weight gain, fat mass development ↑ microbial diversity ↑ Bacteroidetes ↓ Verrucomicrobia ↔ Firmicutes ↓ Akkermansia ↑ Bacteroides, Bilophila, Prevotella

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Study (year)	Quality score (SYRCLE)	Target species	Sample size (n)	Intervention group	Control group	Duration	Methods of microbiota analysis	Results (Intervention vs control after supplementation)
Ojo et al. (2016)	7/10	Six-weeks-old male C57BL/6 J mice	60 in 4 equal groups	- Mango, 1% wt/wt + high fat diet (60%:fat) (n = 15) - Mango, 10% wt/wt + high fat diet (60%:fat) (n = 15)	- High fat diet (60%:fat) (n = 15) - Control diet (10%:fat) (n = 15)	12 weeks	16S rDNA gene sequencing	↑ body weight in 10% mango group ↑ Acetic and butyric acids in 10% mango group ↑ Bifidobacteria, Akkermansia, Adlercreutzia and Ruminococcus in 10% mango group ↓Bacteroides and Parabacteroides in 10% mango group
Moran-Ramos et al. (2017)	5/10	Male diet-induced obese Sprague-Dawley rats	38 in 4 groups	- Nopal cladodes (Opuntia ficus indica, cactus plant), 4% of dietary fiber + high fat diet (n = 14) - Nopal cladodes (Opuntia ficus indica, cactus plant), 4% of dietary fiber + normal fat diet (n = 5)	- Normal fat diet (3.8 kcal/g energy, fat:10%) (n = 5) - High fat diet (4.6 kcal/g energy, fat:46%) (n = 14)	6 weeks	16S rRNA sequencing (MiSeq platform)	↔ body weight gain ↓ adiposity ↑ Microbial diversity ↑ acetate, propionate, isobutyrate, isovalerate, and valerate ↑ Deferibacteres and Bacteroidetes ↓ Firmicutes ↑ Mucillispirum
Herbal Extracts								
Anhe et al. (2014)	6/10	Eight-week-old male C57BL/6 J mice	36 in 3 equal groups	- Cranberry extract, 200 mg/kg + high fat/ high sucrose diet (n = 12)	- high fat/high sucrose diet (n = 12) - normal chow diet (n = 12)	8 weeks	pyrosequencing of the 16S rRNA genes	↓ weight gain, visceral obesity, liver weight, and triglyceride accumulation in cranberry extract group ↑ Akkermansia in cranberry extract group
Romo-Vaquero et al. (2014)	6/10	Lean (fa/+) and obese (fa/fa) female Zucker rats	24 in 4 groups	- Rosemary extract rich in carnosic acid (40%), 0.5% w/w, lean rats (n = 7) - Rosemary extract rich in carnosic acid (40%), 0.5% w/w, obese rats (n = 5)	- Standard diet, lean rats (n = 7) - Standard diet, obese rats (n = 5)	64 days	Quantitative PCR (qPCR)	↓ weight gain in rosemary extract group ↔ energy consumption ↑ SCFA in obese rats in rosemary extract group ↓ SCFA in lean rats in rosemary extract group ↓ total bacteria, Lactobacillus/Leuconostoc/ Pediococcus in both rosemary groups ↑ B. coccoides, Bacteroides/ Prevotella in both rosemary groups ↑ Bifidobacterium in lean rosemary goup ↓ C. leptum in lean rosemary goup
Sun et al. (2014)	_	Male fructose-fed abdominal obese rats	5 groups	- Chicory extract, large dose - Chicory extract, small dose - Fenofibrate	- Normal group - Model group	_	Real-time PCR	↓ waist circumference ↓ E coli, Lactobacillus ↑ Bifidobacteria
Tinkov et al. (2014)	4/10	High-fat-fed Female 2-month-old Wistar rats	32 in 4 equal groups	Plantago maxima leaves water extract (n = 8)	- High-fat diet + pure water (n = 8) - Standard diet + pure water (n = 8) - Standard diet + Plantago extract (n = 8)	3 months	Cultivation	↓ body mass and adipose tissue, ↓ BMI, ↓ adipocyte area Prevent increase in Gram-

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Table 3 (*continued*)

Study (year)	Quality score (SYRCLE)	Target species	Sample size (n)	Intervention group	Control group	Duration	Methods of microbiota analysis	Results (Intervention vs control after supplementation)
								positive bacteria in jejunum and colon, ↓ Gram-negative bacteria in colon
Wicks et al. (2014)	3/10	60% fat diet-induced obese C57BL/6 J mice	20 in 4 equal groups	- Artemisia santafolia extracts (n = 5) - Artemisia scoparia extract (n = 5) - Artemisia dracunculus extract (n = 5)	- Control (n = 5)	4 weeks	Pyrosequencing of 16S rDNA hypervariable regions	↑Bacteroidetes:Firmicutes ratio in mucosal samples ↔ Bacteroidetes:Firmicutes ratio in luminal samples ↔ Diversity
Chang et al. (2015)	8/10	Eight-week-old male C57BL/6NCrlBltw mice	5 to 7 animals in each six groups	- water extract of Ganoderma lucidum mycelium(WEGL) 2%, 100 µl + high-fat diet (n = 7) - WEGL 4%, 100 µl + high-fat diet (n = 7) - WEGL 8%, 100 µl + high-fat diet (n = 7)	- water, 100 µl + standard chow diet (n = 7) - water, 100 µl + high-fat diet (n = 7) - WEGL 8%, 100 µl + standard chow diet (n = 7)	2 months	pyrosequencing of the V3-V5 regions of 16S rRNA genes and Quantitative real-time PCR (qPCR)	↓ weight gain and fat accumulation in WEGL groups in a dose-dependent manner ↓ Firmicutes to Bacteroidetes ratio, Proteobacteria in 4% and 8% WEGL groups ↓ Mucispirilum shaedleri, Escherichia fergusonii (Proteobacteria), Enterococcus spp., Lactococcus lactis, Clostridium lactatifermentans (Clostridium XIVb) and Oscillibacter valericigenes in 8% WEGL group ↑ Parabacteroides goldsteinii, Bacteroides spp., Anaerotruncus colihominis, Roseburia hominis, Clostridium methylpentosum (Clostridium IV), Clostridium XIVa and XVIII and Eubacterium coprostanoligenes in 8% WEGL group
Xie et al. (2015)	6/10	Male Sprague Dawley rats (220 ± 20 g)	50 in 5 equal groups	- Ligustrum robustum aqueous extract, 2.5 mg/kg/d + high fat diet (n = 10) - Ligustrum robustum aqueous extract, 5 mg/kg/d + high fat diet (n = 10) - Ligustrum robustum aqueous extract, 10 mg/kg/d + high fat diet (n = 10)	- High fat diet (n = 10) - Control diet (n = 10)	6 weeks	Cultivation and quantitative PCR (qPCR)	↔ food intake ↓ body weight gain ↑ Lactobacilli ↓ Entrococci ↓ Firmicutes/Bacteroidetes ratio ↓Bifidobacteria ↓Clostridium perfringens
Dietary fibers								
Dewulf et al. (2011)	5/10	10-week-old male C57BL6/J mice	24 in 3 equal groups	- Inulin-type fructans, 0.2 g/d + high fat diet (n = 8)	- High fat diet (n = 8) - Standard diet (n = 8)	4 weeks	Quantitative PCR (qPCR) and denaturing gradient gel electrophoresis (DGGE)	↓ Body weight gain, fat mass in prebiotic group ↑ Bifidobacteria in prebiotic group ↓ Roseburia, Clostridium cluster XIVa
Everard et al. (2011)	5/10	Six-week-old *ob/ob* C57BL/6 mice ten-week-old C57BL/6 J mice		- Oligofructose, 0.3 g/d + control diet in *ob/ob* mice (n = 10)	- Control diet in *ob/ob* mice (n = 10) - High fat diet (n = 10)	8 weeks	Quantitative PCR (qPCR) and	↑ Bifidobacterium, E. rectale/C. coccoides in prebiotic

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Table 3 (*continued*)

Study (year)	Quality score (SYRCLE)	Target species	Sample size (n)	Intervention group	Control group	Duration	Methods of microbiota analysis	Results (Intervention vs control after supplementation)
			40 in 4 equal groups	- Oligofructose, 0.3 g/d + high fat diet (n = 10)			pyrosequencing of the 16S rRNA genes and phylogenetic microarrays	group ↓ Firmicutes, Roseburia in prebiotic group ↔ Bacteroidetes, Lactobacillus, Bacteroides-Prevotella, total bacteria in prebiotic group ↑Actinobacteria, Proteobacteria in prebiotic group
Van den Abbeele et al. (2011)	6/10	8-week-old male humanized Fisher 344 albino rats	24 in 3 equal groups	- Long-chain arabinoxylans, 10% (n = 8) - Inulin, 10% (n = 8)	- Control diet (n = 8)	3 weeks	High-resolution phylogenetic micro-array (HITChip) and Fluorescence in situ hybridisation (FISH combined with flow cytometry) and denaturing gradient gel electrophoresis (DGGE)	↓ Weight gain in arabinoxylans and inulin groups ↑ SCFA in arabinoxylans and inulin groups ↑ Akkermansia muciniphila, Atopobium cluster and Lactobacillus-Enterococcus goup, butyrate producers in arabinoxylans and inulin groups ↑ Clostridium coccoides in arabinoxylans group ↓ Enterobacteria and Clostridium leptum group in arabinoxylans group
Parnell et al. (2012)	7/10	8-week-old male lean and obese JCR:LA-cp rats	48 in 6 equal groups	- OF: obese rats,10% inulin and oligofructose (n = 8) - OHF: obese rats,20% inulin and oligofructose (n = 8)	- LC: lean rats (n = 8) - LF: lean rats, 10% inulin and oligofructose (n = 8) - LHF: lean rats, 20% inulin and oligofructose (n = 8) - OC: obese rats (n = 8)	10 weeks	Quantitative PCR (qPCR)	↔Body weight, fat mass ↑ Bifidobacterium dose-dependently in prebiotic lean and obese rats ↑ Lactobacillus in OHF group vs OC and OF groups ↓C. coccoides in OF vs OHF group ↑ Clostridium leptum in OHF group vs OC and OF groups ↑ Entherobacteriaceae in OHF group vs OC and OF groups ↑ Bacteroidetes dose-dependently in prebiotic lean and obese rats ↓ Firmicutes in prebiotic lean and obese rats ↑ Bacteroides in prebiotic lean and obese rats
Pyra et al. (2012)	6/10	8-week-old male Sprague-Dawley rats	40 in 4 equal groups	- Oligofructose, 10%+high fat/sucrose diet (n = 10) - Metformin, 300 mg/kg + high fat/sucrose diet (n = 10) - Metformin, 300 mg/kg + Oligofructose, 10%+high fat/sucrose diet (n = 10)	- High fat/sucrose diet (n = 10)	7 weeks	Quantitative PCR (qPCR)	↓ Food and energy intake, body weight, body fat in 3 intervention groups ↑ total bacteria, Bifidobacterium in oligofructose group ↓ C. leptum in oligofructose

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Table 3 (*continued*)

Study (year)	Quality score (SYRCLE)	Target species	Sample size (n)	Intervention group	Control group	Duration	Methods of microbiota analysis	Results (Intervention vs control after supplementation)
								group ↓ Bifidobacterium in metformin group ↑ Enterobacteriacae in metformin group
Cox et al. (2013)	6/10	18-week-old adult C57B6/L6 J mice	30 in 3 equal groups	- Hydroxypropyl methylcellulose (HPMC), 10% + High fat diet (n = 10)	- Low fat diet (n = 10) - High fat diet (n = 10)	4 weeks	pyrosequencing of the 16S rRNA genes and quantitative PCR (qPCR)	↓Microbial diversity in HPMC group ↑Erysipelotrichaceae, peptostreptococcaceae in HPMC group ↓ Lachnospiraceae, Ruminococcaceae in HPMC group ↓Johnsonella, Lactobacillus in HPMC group ↑Erysipelotrichaceae incertae sedis, Peptostreptococcus inc. sed. in HPMC group
Respondek et al. (2013)	7/10	4-week-old axenic C57BL/6 J mice inoculated with a sample of faecal human microbiota	48 in 3 equal groups	- Short-chain fructo-oligosaccharides, 10% + high fat diet (n = 16)	- High fat diet (n = 16) - Control diet (n = 16)	7 weeks	Fluorescence in situ hybridisation (FISH)	↓ fat mass ↑ Bifidobacteria, Clostridium coccoides in prebiotic group ↓ Clostridium leptum in prebiotic group ↓ Bacteroides-Prevotella/C. cocooides ratio in prebiotic group
Bomhof et al. (2014)	7/10	Male diet-induced obese Sprague Dawley rats	40 in 4 equal groups	- Oligofructose, 10% + high fat/sucrose diet (n = 10) - Bifidobacterium animalis subsp. lactis BB-12 (10^{10} cfu/d) + high fat/sucrose diet (n = 10) - Oligofructose, 10% + Bifidobacterium animalis subsp. lactis BB-12 (10^{10} cfu/d) + high fat/sucrose diet (n = 10)	- High fat/sucrose diet (n = 10)	8 weeks	Quantitative PCR (qPCR)	↓energy intake, weight gain, fat mass in oligofructose group ↑ Bacteroides, Bifidobacterium, Lactobacillus, B. animalis in oligofructose group ↓ C. coccoides, C. leptum, Clostridium Cluster XI and I, Enterobacteriacae in oligofructose group ↑ B. animalis in probiotic group ↓ Firmicutes to Bacteroidetes ratio in probiotic and prebiotic groups
Everard et al. (2014)	6/10	10-week-old C57BL/6 J mice	40 in 4 equal groups	- Oligofructose, 0.3 g/d + high fat diet (n = 10) - Oligofructose, 0.3 g/d + control diet (n = 10)	- High fat diet (n = 10) - Control diet (n = 10)	8 weeks	Sequencing	↑ SCFAs in oligofructose group ↓ Firmicutes to Bacteroidetes ratio in oligofructose group ↓Tenericutes, Cyanobacteria, Verrucomicrobia in oligofructose group ↑ Akkermansia, Bifidobacterium, Sutterella in oligofructose group ↑ Scardovia,

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Study (year)	Quality score (SYRCLE)	Target species	Sample size (n)	Intervention group	Control group	Duration	Methods of microbiota analysis	Results (Intervention vs control after supplementation)
								Propionibacterium in oligofructose group ↓ Bilophila, Butyrivibrio, LE30, Oribacterium in oligofructose group ↑ Allobacullum, Prevotella in oligofructose group ↓ Paenibacillus, Ethanoligenes
Saha et al. (2014)	6/10	Male and female wistar rats which consumed high fat/high sucrose diet to perturb metabolism	8 to 10 animals in each three groups	- Inulin/oligofructose, 21% (n = 8-10)	- Control diet (n = 8-10) - High protein diet, 40% (n = 8-10)	4 weeks	Quantitative PCR (qPCR)	↑ Bifidobacteria, Bacteroides/Prevotella, Bacteroidetes in fiber group ↓ Firmicutes, Clostridium leptum, C coccoides, Clostridium cluster I, XI, Roseburia, Firmicutes/ Bacteroidetes in fiber group ↑ Methanobrevibacter, Roseburia in high protein group ↓ Bifidobacteria, Lactobacillus in high protein group
Cluny et al. (2015)	7/10	Male diet-induced obese (DIO) and diet-resistance (DR) Wistar rats	46 in 4 groups	- Oligofructose, 10%+high fat/sucrose diet in DIO rats (n = 12) - Oligofructose, 10%+high fat/sucrose diet in DR rats (n = 12)	- High fat/sucrose diet in DIO rats (n = 11) - High fat/sucrose diet in DR rats (n = 11)	6 weeks	Quantitative PCR (qPCR)	↓Energy intake, body weight, fat mass in oligofructose group ↑ Bifidobacterium, Lactobacillus, Roseburia in oligofructose group ↓ C. leptum in oligofructose group ↑ C. cluster I and XI in DIO group ↑ Firmicutes to Bacteroidetes ratio in DIO group
Perez-Chabela et al. (2015	5/10	Two-week-old male Wistar rats	24 in 3 equal groups	- cactus pear (*Opuntia ficus*) peel flour (n = 8) - apple marc (*Malus domestica*) flour (n = 8)	- inulin (n = 8)	90 days	Cultivation	↓ Body weight gain in both treatment groups ↑ Acetic, propionic and butyric acids in apple marc group ↑ Lactic acid bacteria in apple marc group ↓ Enterobacterias and Bacteroides in apple marc group ↑ Lactic acid bacteria, Enterobacterias and Bacteroides in cactus pear peel group
Bomhof et al. (2016)	7/10	18-week-old male high fat/sucrose diet-induced obese Sprague Dawley rats	60 in 6 equal groups	- Oligofructose, 10% wt/wt (n = 10) - Ampicillin+ Oligofructose, 10% wt/wt (n = 10)	- High energy control (n = 10) - Ampicillin (n = 10) - Ampicillin/ Neomycin (n = 10)	6 weeks	Quantitative PCR (qPCR) and 16 s rRNA illumine	↓ Weight gain, body weight, body fat percentage, retroperitoneal fat mass and energy intake in

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Table 3 (*continued*)

Study (year)	Quality score (SYRCLE)	Target species	Sample size (n)	Intervention group	Control group	Duration	Methods of microbiota analysis	Results (Intervention vs control after supplementation)
				- Ampicillin/ Neomycin + Oligofructose, 10% wt/wt (n = 10)			sequencing (MiSeq platform)	oligofructose group ↑ Actinobacteria, Bifidibacterium and Lactobacillus in oligofructose group ↓ Firmicutes, Clostridiales and Enterobacteriaceae in oligofructose group ↓ Firmicutes to Bacteroidetes ratio in oligofructose group ↓ Microbial diversity in oligofructose group
Phytochemicals								
Zhang et al. (2012)	7/10	Eight-week old male high-fat diet-fed Wistar rats	40 in 4 equal groups	- Berberine (100 mg/kg) + high-fat diet (n = 10) - Berberine (100 mg/kg) + normal chow diet (n = 10)	- Control, normal chow diet (n = 10) - High-fat diet-fed controls (n = 10)	18 weeks	Pyrosequencing of the V3 region of 16S rRNA genes	↓ Body weight ↓ Adiposity index ↓ Microbiota diversity ↓ Total bacteria ↑ SCFA-producing bacteria (Blautia and Allobaculum) ↓ Actinobacteria and Verrucomicrobia ↑ Bacteroides, Butyricimonas, Phascolarctobacterium, Prevotella, Porphyromonadaceae, Ruminococcaceae
Singh et al. (2015)	7/10	6-8-week-old male swiss albino mice	8 to 10 animals in each 11 groups	- Lycopene, 5 mg/kg + high fat diet (n = 9) - Lycopene, 10 mg/kg + high fat diet (n = 10) - Isomalto-oligosaccharides, 0.5 g/kg + high fat diet (n = 10) - Isomalto-oligosaccharides, 1 g/kg + high fat diet (n = 10) - Lycopene, 5 mg/kg + Isomalto-oligosaccharides, 0.5 g/kg + high fat diet (n = 8) - Lycopene, 10 mg/kg + Isomalto-oligosaccharides, 1 g/kg + high fat diet (n = 8) - Lycopene, 10 mg/kg + Normal pellet diet (n = 8) - Isomalto-oligosaccharides, 1 g/kg + Normal pellet diet (n = 8) - Lycopene, 10 mg/kg + Isomalto-oligosaccharides, 1 g/kg + Normal pellet diet (n = 8)	- Normal pellet diet (n = 10) - High fat diet (n = 10)	12 weeks	Quantitative PCR (qPCR)	↓ Weight gain and adiposity in lycopene, isomalto-oligosaccharides and their combination groups ↑ SCFAs in lycopene [10] and combination groups ↑ Lactobacillus, Bifidobacterium in lycopene and isomalto-oligosaccharides groups ↓ Enterobacteriaceae in isomalto-oligosaccharides group ↔ Bacteroidetes, Firmicutes, Roseburia and Akkermansia muciniphila

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Table 3 (*continued*)

Study (year)	Quality score (SYRCLE)	Target species	Sample size (n)	Intervention group	Control group	Duration	Methods of microbiota analysis	Results (Intervention vs control after supplementation)
Cheng et al. (2016)	6/10	Germ-free male C57BL/6 J mice	24 in 3 equal groups	- epigallocatechin 3-O-methyl gallate in oolong tea, 0.1% w/w + high fat diet (n = 8)	- High fat diet (n = 8) - Low fat diet (n = 8)	8 weeks	High-throughput sequencing	↓ Body mass ↑ Bacteroidetes, Proteobacteria, Actinobacteria ↓ Firmicutes ↑ Prevotellaceae, Bacteroidaceae ↓ Lachnospiraceae ↑Bacteroides, Sutterella, Megasphaera, Faecalibacterium, Mitsuokella, Coprococcus, Roseburia ↓ Prevotella, Lachnospira, Haemophilus, Oscillospira, Turicibacter, Odoribacter, Bilophila
Porras et al. (2017)	6/10	Seven-weeks-old male C57BL/6 J mice	40 in 4 equal groups	- aglycone quercetin, 0.05% wt/wt + high fat diet (60%:fat) (n = 10)	- High fat diet (n = 10) - Control diet (10%:fat) (n = 10) - Control diet + quercetin, 0.05% wt/wt (n = 10)	16 weeks	16S ribosomal RNA Illumina next-generation sequencing and Quantitative Real-Time PCR	↓ Body weight gain and fat accumulation ↑ SCFA ↑ total bacteria ↓ Proteobacteria ↔ Firmicutes ↑ Bacteroidetes ↓ Firmicutes/Bacteroidetes ↓ Deltaproteobacteria ↑ Bacteroidia, Erysipelotrichi, Betaproteobacteria ↓ Desulfovibrio ↓ Helicobacter ↑ Parabacteroides, Alkaliphilus, Flavobacterium, Allobaculum, Sutturella, Akkermansia

sequencing depth, bioinformatics tools, clustering methodology and operational taxonomic units (OTU)-picking approaches were present. Moreover, the lack of uniformity in the methodology of the studies including, faecal collection and storage may alter the results of microbial composition.[11] These differences among studies were the key obstacle to conducting a meta-analysis. Another challenge was differences in prebiotics types and intervention durations. Furthermore, the presence of chronic disorders which is common in obesity could be a confounder for gut microbiota composition.

Despite the aforementioned challenges in the interpretation of the results of the included studies, we showed that inter-individual differences in the gut microbiota composition might result in the inconsistent changes in gut microbial taxa after herbal product interventions. Previous microbiome studies tried to find a relationship between Firmicutes/Bacteroides ratio and obesity. However, there is no simple taxonomic signature of obesity in gut microbiota,[90] supporting the importance of inter-individual variations of gut microbiota in interventions. Therefore, the baseline gut microbiota composition should be considered in these studies, highlighting the beneficial role of personalized medicine approach to weight management.[91]

Some of the herbal supplements contained a high concentration of polyphenols. Regarding the low bioavailability and limited absorption of polyphenols, they reach to the colon in adequate concentration and contact with the intestinal microbiota. Biotransformation of polyphenols into their metabolites by gut microbiota increases their bioavailability.[92] In addition to activating cellular processes such as autophagy regulation and stress resistance in the body, polyphenols exert an antimicrobial effect too.[93–95] Therefore, the growth of detrimental species such as *Clostridia* and *Entrobacteria* is inhibited while the growth of Lactic acid bacteria is enriched.[45,96] *Akkermansia muciniphila*, a mucin-degrading bacterium which has been associated with intestinal integrity and lean phenotype, enriched after polyphenols intakes.[53] Polyphenols provide a favorable environment for growth of *Akkermansia* via acting on goblet cells and increasing mucus secretion.[96] Moreover, polyphenols could scavenge free oxygen radicals in favor of the growth of *Akkermansia*, as an obligate anaerobe. *Akkermansia* regulates the expression of genes related to lipid metabolism and increases the intestinal expression of FIAF which reduces fat storage.[96]

Fecalibacterium prausnitzii, a butyrate-producing bacterium, which is related to gut barrier function, has been documented to increase after supplementation in some studies.[21,34,69,77,82] Although herbal products had limited effects on reducing body weight, their intake exerted beneficial effects on gut microbiota. Prebiotics which are resistant to digestion reached the colon and fermented by gut microbes. Therefore, butyrate-producing bacteria were increased after the intervention and contributed to the source of energy for colonocytes and improved gut barrier function, immunomodulatory and anti-inflammatory activities.[97] Prebiotics exerted bifidogenic effects and enriched the *Bifidobacterium* species. Several functions have been attributed to bifidobacteria including fermentation of non-digestible carbohydrates, stimulation of the immune system, and production of vitamin B, antioxidants, and conjugated linoleic acids.[97] During life and in obesity, the abundance of bifidobacteria decrease and modification with prebiotics could compensate this reduction.[97] On the other hand, since depletion of butyrate-producing bacteria and enrichment of *Proteobacteria* are common after dietary restrictions and bariatric surgeries, modulation of gut microbiota with herbal products could be effective.[11]

Short chain fatty acids, including acetic, propionic and butyric acids as microbiota-derived metabolites have remarkable effects on host physiology and their changes after herbal and prebiotics interventions were inconsistent. Most bacteria, such as *Akkermansia muciniphila*, *Bacteroides* spp., *Bifidobacterium* spp., *Prevotella* spp., *Ruminococcus* spp., *Blautia hydrogenotrophica*, *Clostridium* spp., and *Streptococcus* spp., are among the main producers of acetic acid which suppress appetite through a central hypothalamic mechanism.[98,99] *Bacteroides*spp., *Dialister* spp., *Veillonella* spp., *Megasphaera elsdenii*, *Coprococcus* catus, *Salmonella*spp., *Roseburia inulinivorans*, and *Ruminococcus obeum* are propionic acid-producing bacteria. Propionate could inhibit fatty acid production and suppress low-grade inflammation.[98,99] Moreover, acetate and propionate might suppress adipogenicity through the FFA2 receptor. *Firmicutes* phylum members including *Anaerostipes* spp., *Coprococcus* catus, *Eubacterium* rectale, *Eubacterium* hallii, *Faecalibacterium prausnitzii*, *Roseburia* spp. are among the intestinal bacteria which produce butyric acid. Butyric acid as the main energy source for colonocytes regulates gene expression and affects energy homeostasis.[99,100] Moreover, fermentation end products are reported to affect the epigenetic regulation of inflammatory reactions via free fatty acid receptors.[98,101]

This review provides a comprehensive summary about the effects of a variety of natural plants (herbs, fruits and vegetables) and their extractions and bioactive ingredients (oligosaccharides, fibers and phytochemicals) on gut microbiota composition as a target of obesity management. However, some limitations of this study should be acknowledged. Lack of comparison of the intestinal microbiota of obese subjects after intervention with the gut microbial composition of lean individuals makes it difficult to assess how much improvement in obese microbiota is achieved. Considering the normal weight control group in these trials could be useful for better understanding of the effects of herbal products on gut microbiota. Furthermore, different types of interventions and study designs, diverse methodologies of faecal samples collection and gut microbiota assessment, various durations of interventions and differences in the population characteristics caused the heterogeneity of included studies. Therefore, meta-analysis of the results was not feasible and this is a limitation in generalizations of the results. More focused future systematic review by narrowing the selection criteria of articles is warranted.

5. Conclusion

Various herbal interventions have different effects on the gut microbiota composition. However, this impact is not always correlated with the amount of weight loss. Moreover, the baseline composition of the gut microbiota has effects on alteration of gut microbiota after interventions. This systematic review shows that consumption of herbal products might have beneficial effects on gut microbiome in addition to body fat reduction and its use could be recommended to obese persons who take low-calorie diets. However, for better conclusions and generalizations, more well designed human clinical trials with similar techniques for microbiota assessment are needed.

Conflict of interests

There is no conflict of interest to declare.

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