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EDITORIAL

A systematic review of the efficacy and safety of herbal medicines used in the treatment of obesity

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Abstract

This review focuses on the efficacy and safety of effective herbal medicines in the management of obesity in humans and animals. PubMed, Scopus, Google Scholar, Web of Science, and IranMedex databases were searched up to December 30, 2008. The search terms were "obesity" and ("herbal medicine" or "plant", "plant medicinal" or "medicine traditional") without narrowing or limiting search elements. All of the human and animal studies on the effects of herbs with the key outcome of change in anthropometric measures such as body weight and waist-hip circumference, body fat, amount of food intake, and appetite were included. *In vitro* studies, reviews, and letters to editors were excluded. Of the publications identified in the initial database, 915 results were identified and reviewed, and a total of 77 studies were included (19 human and 58 animal studies). Studies with *Cissus quadrangularis* (CQ), *Sambucus nigra*, *Asparagus officinalis*, *Garcinia atroviridis*, ephedra and caffeine, Slimax (extract of several plants including *Zingiber officinale* and Bofutsushosan) showed a significant decrease in body weight. In 41 animal studies, significant weight loss or inhibition of weight gain was found. No significant adverse effects or mortality were observed except in studies with supplements containing ephedra, caffeine and Bofutsushosan. In conclusion, compounds containing ephedra, CQ, ginseng, bitter melon, and zingiber were found to be effective in the management of obesity. Attention to these natural compounds would open a new approach for novel therapeutic and more effective agents.

Key words: Animal; Herbal medicine; Human; Obesity

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INTRODUCTION

The prevalence of obesity is increasing worldwide[1] resulting in an association with major health problems such as type 2 diabetes, ischemic heart disease, stroke, and cancer. It is necessary to treat obese individuals by both lifestyle interventions and/or pharmacological therapy. Pharmacologic treatment and surgical interventions used in some circumstances are not always appropriate[2]. Unfortunately, drug treatment of obesity despite short-term benefits, is often associated with rebound weight gain after the cessation of drug use, side effects from the medication, and the potential for drug abuse[3]. Pharmacologic options include sibutramine, orlistat, phentermine, diethylpropion, and fluoxetine or bupropion. Phentermine and diethylpropion have potential for abuse and are only approved for short-term use. Approved medications for long term use in the treatment of obesity are sibutramine and orlistat, however, these agents should be used with caution in patients with a history of cardiovascular disorders[4]. The general public uses many other methods for weight

loss including herbs, vitamins, nutritional supplements, and meal replacement preparations. Rigorous scientific studies have not been carried out on these products, and in many cases safety and efficacy take a back seat to marketing.

Complementary and alternative therapies have long been used in the Eastern world but recently these therapies are being used increasingly worldwide[5]. When conventional medicine fails to treat chronic diseases and conditions such as obesity efficaciously and without adverse events, many people seek unconventional therapies including herbal medicine[6]. Although the number of randomized trials on complementary therapies has doubled every 5 years and the Cochrane library included 100 systematic reviews of unconventional interventions[7], none of these studies specifically mentioned herbal therapy in obesity.

This review aimed to evaluate the current science on the efficacy and safety of herbal medicines in the management of obesity.

DATA SOURCES AND STUDY SELECTIONS

PubMed, Scopus, Google Scholar, Web of Science, and IranMedex databases were searched up to December 30, 2008 for all human and animal studies investigating the effects (both harmful and beneficial) of treating obesity with herbal medicines. The search terms were "obesity" and ("herbal medicine" or "plant", "plant medicinal" or "medicine traditional") without narrowing or limiting search elements. Only publications with available abstracts were reviewed. The main outcome measures sought at the end of treatments as anti-obesity effects, were body weight, body fat including fat mass/fat weight or fat percentage/visceral adipose tissue weight, triceps skin fold thickness, waist or hip circumference, and appetite or amount of food intake.

Herbal medicines are defined in this review as raw or refined products derived from plants or parts of plants (e.g. leaves, stems, buds, flowers, roots, or tubers) used for the treatment of diseases. The synonyms of herbal medicines are herbal remedies, herbal medications, herbal products, herbal preparations, medicinal herbs, and phytopharmaceuticals, *etc.*

All of the abstracts from human and animal studies with the main outcome of change in anthropometric measures such as body weight and waist-hip circumference, body fat (weight or mass of visceral adipose tissue, fat mass or percent), amount of food intake, and appetite in participants were included. Even studies on other relevant diseases such as diabetes were also reviewed and included if the appropriate outcomes were shown. *In vitro* studies, review articles, and letters to the editor were excluded. Unpublished data such as theses were also excluded. Two reviewers independently examined the title, abstract and references of each article meeting the inclusion criteria and eliminated duplications and those showing exclusion criteria.

FINDINGS

Of the publications identified from the initial database search, 915 results were identified and reviewed for inclusion or exclusion. A total of 77 studies were included (19 human and 58 animal studies). Human studies included 17 randomized clinical trials (RCTs) and two before-after clinical trials[8-26]. RCTs reported random allocation of humans to herbal medicines *vs* (placebo/another plant/combination of plants) with or without specific dietary and exercise programs outlined in Tables 1 and 2 as weight loss programs. Human subjects were healthy overweight, obese or with impaired glucose tolerance test volunteers. Animal studies included healthy, genetically or experimentally obese or diabetic mice, rats and other rodents. The route of administration of herbs in almost all studies was oral intake with the exception of some animal studies as indicated in Table 2.

HUMAN STUDIES

Change in human body weight

All studies showed loss of body weight except one[21] which seemed to have problems with the study design, and one other study[10] which showed a significant decrease only in body fat. Studies with *Cissus quadrangularis* (CQ)[26] or combined with *Irvingia gabonensis* (IG)[15], a combination of *Sambucus nigra* and *Asparagus officinalis*[16], calcium hydroxycitrate in *Garcinia atroviridis*[18], supplements containing ephedra and caffeine[9,13,20], and Slimax as an extract of several plants including *Zingiber officinale*[8] and Bofutsushosan[14] showed significant decreases in body weight.

Body fat

A significant decrease in body fat was shown with CQ[26], supplements containing ephedra and caffeine[9,13], a natural compound containing capsicum and some lipotropic nutrients[10], Bofutsushosan[14], and calcium hydroxycitrate in *Garcinia atroviridis*[18]. These phytopharmaceuticals showed a significant decrease in triceps skin fold thickness indicating significant loss of fat.

Waist and hip circumference

Efficient decreases in both waist and hip circumferences in trials with a supplement containing ephedra and caffeine[9] and Slimax (extract of several plants including *Zingiber officinale*[8] were shown whereas *Caralluma fimbriata*[19] and CQ with or without IG[15] significantly decreased waist size.

Food intake

Decreases in appetite or amount of food or energy intake with a supplement containing ephedra and caffeine[20] and *Caralluma fimbriata*[19] were shown (not significant) but hydroxycitric acid (HCA-SX) with or without *Gymnema sylvestre*[23] decreased the amount of food intake efficiently. A natural compound containing capsicum and other lipotropic nutrients[10] did not significantly change energy intake.

Table 1 Human studies considering the anti-obesity effects of herbal medicines

Authors	Target	Herbs (scientific name)	Study	Dose/duration	Groups	Main outcome	Other relevant effects & complications
Ignjatovic *et al*[8] 2000	Healthy volunteers	Slimax: extract of several plants: Hordeum vulgare, Polygonatum multiflorum, Dimocarpus longan, Ligusticum sinense, Lilium brownie, and *Zingiber officinale*	RCT	6 wk	C: Placebo I: Compound	Sig. decrease in body wt. & waist & hip Cir. & BMI	Modification of lipid metabolism with sig. effect on the accumulation & the release of lipid from adipose tissue
Boozer *et al*[9] 2001	Over wt. (n = 35)	An herbal supplement: (*Ma Huang* & Guarana)	RCT (double-blind)	72 mg (ephedra) 240 mg (caffeine)/8 wk	C: Placebo (n = 24) I: Compound (n = 24)	Sig. decrease in body wt. & total body fat & sig. greater reduction in hip & waist Cir.	Greater reduction in serum TG, potentially treatment-related dropouts (23%) in the active group and none in the placebo group. Dry mouth, insomnia & headache were reported
Hoeger *et al*[10] 1998	Healthy	A natural dietary compound of chromium picolinate, inulin, capsicum, L-phenylalanine, and other lipotropic nutrients	RCT (double-blind)	4 wk	C: wt. loss program (n = 67) I: wt. loss program + compound (n = 56)	Sig. decrease in body fat percent, fat mass & FFM, but no sig. difference in body wt. BMI and energy intake	
Ziauddin *et al*[11] 2004	Hhyperlip-idemic (n = 30)	Terminalia arjuna Roxb	Before-after CT			Sig. improvement in obesity. Reduction in body wt. in some cases	Sig. decrease in serum total lipid levels. Sig. relief of palpitation, dyspnea, chest & joint pain. Reduction in BP in some cases
Abidov *et al*[12] 2006	Obese non-diabetic women (n = 32)	A compound of Aralia mandshurica (A) and Engelhardtia chrysolepis (E) extracts named ARALOX	RCT	450 mg (A) & 450 mg (E)/d	C: Diet + placebo I: Diet + compound	Decrease in total body wt. & fat wt.	Reduction in perilipin content in adipocytes and plasma TG. Stimulate activity of hormone sensitive lipase
Greenway *et al*[13] 2004	Human (obese & over wt.) healthy	Herbal supplement containing caffeine and ephedra	RCT (double-blind)	210 mg (e) & 72 mg (c)/12 wk	C: Placebo I: Compound	Sig. decrease in body wt. & the percentage of fat	No differences in lipid levels, or BP were shown. No serious adverse effect
Hioki *et al*[14] 2004	Obese women with IGT (n = 80)	Bofu-tsusho-san containing (Ephedrae Herba, Glycyrrhizae Radix, Forsythiae Fructus, Schizonepetae Spica &…)	RCT (double-blind)	Equivalent of (24 mg/ephedrine & 280 mg caffeine/24 wk)	C: wt. loss program I: wt. loss program + compound	Compared to baseline the I group lost significantly more body wt. & abdominal visceral fat & the placebo group lost sig. body wt. & had no sig. change in abdominal visceral fat	No decrease in RMR. Sig. improvement in insulin resistance compared to week 0. Loose bowel movements resulted in three withdrawals
Oben *et al*[15] 2008	Human (obese & over wt.)	A combination of *Cissus quadrangularis* (CQ) & *Irvingia gabonensis* (IG)	RCT (double-blind)	300 mg (CQ) & 500 mg (IG) per day/10 wk	C: Placebo I: CQ CQ + IG	Sig. decrease in body wt. & body fat percent & waist size in both I groups but the combination group (CQ + IG) resulted in larger reductions	Sig. decrease in Chol & LDL of plasma and fasting blood glucose levels
Chrubasik *et al*[16] 2008	Healthy (n = 80)	A combination of *Sambucus nigra* (S) and *Asparagus officinalis* (A)	Before-after CT	(S): 1 mg anthocyanin, 370 mg flavonol, 150 mg hydroxycinnamate (A): 19 mg saponin per day	-	Sig. decrease in mean of the wt.	Sig. improvement of BP, physical and emotional well-being and quality of life

Udani *et al*[17] 2007	Healthy (*n* = 25)	Proprietary fractionated white bean extract	RCT (double-blind)	2000 mg/14 wk	C: Placebo + wt. loss program I: Extract + wt. loss program	In both groups, decrease in body wt. & waist size from baseline was sig. but no sig value between groups	There were no adverse effect
Roongpisu-thipong *et al*[18] 2007	Obese women	Calcium hydroxycitrate in *Garcinia atroviridis*	RCT	2 mo	C: Diet I: Diet + extract	Sig. decrease in body wt. & greater reduction in BMI. Sig. decrease in the triceps skin fold thickness	
Kuriyan *et al*[19] 2007	Over wt. (*n* = 50)	Caralluma fimbriata	RCT	1 g/60 d	C: wt. loss program I: wt. loss program + extract	Sig. decrease in waist Cir. & hunger levels. Greater decrease in body wt., BMI, hip Cir., body fat & energy intake but not sig.	
Hackman *et al*[20] 2007	Obese & over wt. women (*n* = 41)	Multinutrient supplement containing ephedra (e) and caffeine (c)	RCT (double-blind)	40 mg (e) and 100 mg (c)/9 mo	C: Control supplement I: Multinutrient supplement	Sig. decrease in body wt. decrease in appetite	Sig. decline in serum chol, TG, glucose, fasting insulin & leptin levels & minor adverse effects like dry mouth, insomnia, nervousness and palpitation were reported
Garrison *et al*[21] 2006	Over wt. women	Proprietary extracts of Magnolia officinalis and phellodendron amurense	RCT	750 mg/6 wk	C: Placebo I: Extract	No sig. wt. gain for the I group but sig. wt. gain in C. groups	The I groups tended to have lower levels of cortisol in the evening
Coffey *et al*[22] 2004	Human (over wt. & obese) (*n* = 102)	Product containing ephedrine, caffeine & other ingredients.	RCT (double-blind)	12 wk	C: Placebo I: Compound	Additional wt. loss (1/5 kg) & greater reduction in BMI & waist Cir. No difference in body fat & fat mass percent was shown	No difference in pulse, diastolic & systolic BP & adverse events
Preuss *et al*[23] 2004	Obese (*n* = 60)	Hydroxycitric acid (HCA -SX) and a combination of HCA-SX and niacin-bound chromium (NBC) and Gymnema sylvestre extract (GSE)	RCT (double-blind)	HCA-SX: 4667 mg GSE: 400 mg NBC: 4 mg/8 wk	C: Placebo I1 = HCA-SX I2 = GSE + NBC + HCA-SX All groups had wt. loss program	5%-6% decrease in body wt. & BMI & sig. decrease in food intake in both I groups	Sig. decrease in serum lipids & leptin & increase in HDL & excretion of urinary fat metabolites in both I groups. There were mild adverse effects but not significant between groups
Udani *et al*[24] 2004	Obese (*n* = 24)	A proprietary fractionated white bean (Phaseolus vulgaris)	RCT (double-blind)	3000 mg/8 wk	C: Placebo I: Extract	Decrease of body wt. with 129% difference	Reduction of TG three times greater than C. group. No adverse effect was shown
Bhatt *et al*[25] 1995	Healthy (*n* = 58)	Guggulu (Medohar)	RCT	1/5, 3 g/30 d	C: wt. loss program I: wt. loss program + extract	Higher mean wt. reduction in I group. In I group, all patients > 90 kg lost wt. but 3 in C group did not lose wt.	
Oben *et al*[26] 2007	Over wt. & obese	*Cissus quadrangularis*	RCT (double-blind)	300, 1028 mg	C: Placebo I: Two extract formulation: CQR-300, CORE	Sig. decrease in body wt & body fat	Sig. decrease in serum lipids and glucose. Sig. increase in HDL-C plasma 5-HT and creatinine levels

Cir: Circumference; BP: Blood pressure; BMI: Body mass index; sig.: Significant; C: Control; I: Intervention; RCT: Randomized control trial; CT: Clinical trial; TG: Triglyceride; HDL: High density lipoprotein; LDL: Low density lipoprotein; Chol: Cholesterol; IGT: Impaired glucose tolerance.

Other effects

Anti-hyperlipidemic, antihyperglycemic, and other relevant anti-obesity effects of medicinal plants in human studies are summarized in Table 1.

Adverse effects

No significant adverse effects compared to controls were mentioned and no mortality was reported, except in studies with supplements containing ephedra and

Table 2 Animal studies on the anti-obesity effects of herbal medicines

Authors	Target	Herbs (scientific name)	Dose/duration	Groups	Main outcome	Other relevant effects & complications
Wang *et al*[27] 2000	Rat (obese)	Haidonghua powder: Laminaria japonica Aresch & Benincasa hispida (Thunb.) Cogn. *etc*	(2.5 g/kg)	-	Sig. decrease in Lee's index & size of fat cells	Did not influence the function of thyroid gland & metabolism of water & salt
Jeon *et al*[28] 2003	Mouse	Rhus vemiciflua Stokes	8 wk	C: HFD I: HFD + extract	Sig. suppression of body wt. gain and lower wt. of subcutaneous adipose tissue	Lowered plasma TG
Alarcon-Aguilar *et al*[29] 2007	Mouse	Hibiscus sabdariffa	120 mg/kg 60 d	C: Healthy & obese (by MSG) + placebo I: Same groups + extract	Sig. decrease in body wt. gain in obese mice & increased liquid intake in both groups	No sig. change in TG & Chol levels. Increase in ALT levels was shown but was not sig.
Urías-Silvas *et al*[30] 2008	Mouse	Fructans extracted from Agave tequilana (TEQ) and Dasylirion spp (DAS)	10% supplement	C: STD I: STD + Raftilose/ DAS/TEQ	Sig. decrease in body wt. gain & food intake. The (TEQ) group had the lowest value	Lower serum glucose & Chol level but Sig. decrease in TG levels was shown in Raftilose group. Higher concentration of GLP-1 & it's precursor & proglucagon mRNA in I groups
Park *et al*[31] 2007	Rat	Platycodon grandiflorum	150 mg/kg 7 wk	C: NLD/HFD I: Same groups + extract	Sig. decrease in body wt & subcutaneous adipose tissue wt. & adipocytes size in I group	Sig. decrease in plasma TG & Chol concentrations, up-regulation of FABP mRNA expression induced by HFD
Jongwon *et al*[32] 2005	Rat (obese by HFD)	Allium victorialis var. platyphyllum leaves	100 mg/kg 2 wk	-	Considerable reduction of retroperitoneal, epididymal and total abdominal fat pad wt.	Sig. decrease in hyperlipidemia and increased lipid content in feces
Kobayashi *et al*[33] 2001	Rat	Evodiamine an alkaloid of a fruit: Evodia rutaecarpa	0/02%, 0/03% of the diet 12 wk	C: Control I: Extract	Sig. decrease in perirenal fat wt. & decrease of epididymal fat mass	Sig. decrease of lipid in liver & serum FFAs. Sig. increase of lipolytic activity in perirenal fat tissue & specific GDP binding in brown adipose tissue mitochondria as the biological index of heat production
Jin *et al*[34] 1994	Rat	Jiang-zhi jian-fei yao: the refined Rhubarb	Injected intragastrically		No sig. increase in body wt. but reduction of food intake. Decreased size of abdominal adipose cells	Prolongation of stomach evacuation time and acceleration of intestinal movements
Kim *et al*[35] 2008	Rat	Juniperus chinensis	1% supplement /79 d	C: NLD/HFD I: HFD + extract	Sig. decrease in body wt gain & visceral fat pad wt.	Sig. decrease in blood lipid, leptin & insulin levels. Sig. reversal of the down-regulation of genes implicated in adipogenesis & increased gene expressions & phosphorylations related to FABO
Shih *et al*[36] 2008	Mouse (obese by HFD)	Momordica charantia (bitter melon)	4 wk	C: Control I: Rosiglitazone/ extract	Sig. decrease in epididymal white adipose tissue wt. & visceral fat wt.	Sig. improvement in blood glucose, leptin, and FFA. Influenced PPARα/ PPARγ expression
Pang *et al*[37] 2008	Rat (obese by HFD)	Ilex paraguariensis			Sig. decrease in body wt. of visceral fat-pad wt.	Sig. decrease in blood and hepatic lipid, glucose, insulin and leptin levels. Reversed the down-regulation of genes implicated adipogenesis, thermogenesis & enhanced expression of uncoupling proteins in adipose tissue
Bruno *et al*[38] 2008	Mouse	Green tea	0%, 1%, 2% (wt.:wt.)/6 wk	C: Obese/lean I: Same groups + extract	Sig. decrease in body wt. of both I groups	In obese I group, sig. decrease in hepatic steatosis was observed dose dependently. Liver enzymes decreased. 30%-41% and 22%-33% lower serum ALT and AST activities were shown, respectively

Lee *et al*[39] 2008	Mouse	A combination of Morus alba, Melissa officinalis and Artemisia capillaries	12 wk	-	Sig. decrease in body wt. gain & adipose mass	Decreased serum levels of TG, Chol & inhibited hepatic lipid accumulation, and increased hepatic mRNA levels of enzymes responsible for FABO
Choi *et al*[40] 2008	Mouse (obese by HFD)	Cucurbita moschata	500 mg/kg 8 wk	_	Sig. suppression of body wt. & fat storage increase but amount of food intake was not affected	
Huang *et al* 2008[41]	Rat	Momordira charantia L. (Bitter melon)	5%	C: HFD I1: HFD + plant I2: HFD + thiazolidinedione	Sig. decrease in the number of large adipocytes in both I groups. Sig. decrease in adipose tissue mass in I_1 group compared to I_2 group	Sig. decrease in enzymes of adipose tissue implicating reduction of insulin resistance in I group as compared to C group
Lemaure *et al*[42] 2007	Rat (obese)	Cyperus rotundus L. tubers	45, 220 mg/kg 60 d	_	Sig. decrease in wt. gain without affecting food consumption	
Lei *et al*[43] 2007	Mouse	Pomegranate leaf	400/800 mg per kilogram 5 wk	C: HFD/NLD I: Same groups + extract	Sig. decrease in body wt. & energy intake and adipose pad wt. percents in I. group. Sig. decrease in appetite of obese mice on NLD was shown	Sig. decrease in serum TG, Chol, glucose levels & Chol/ HDL ratio, inhibition of intestinal fat absorption
Aoki *et al*[44] 2007	Mouse (obese by HFD)	Licorice flavonoids oil (LFO)	0/5%, 1%, 2% 8 wk	C: Placebo I: Extract	Sig. decrease of abdominal white adipose tissue & body wt. gain with 1% & 2% LFO groups, decrease of adipocyte size	Improvement of fatty degeneration of hepatocytes and changes in genes implicating regulation of lipid metabolism with 2% concentration
Oluyemi *et al*[45] 2007	Rat	Garcinia cambogia seed (bitter cola)	200, 400 mg/kg 5 wk	C: Placebo I: Extract	Sig. decrease in body wt.	Sig. decrease in TG pool of adipose tissue & liver but sig. increase of HDL & decreased LDL
Han *et al*[46] 2006	Mouse (obese by HFD)	Kochia scoparia	1%, 3%/3 d	-	Prevented the increases in body & parametrial adipose tissue wt.	Sig. increase the fecal content & fecal TG levels in day 3
Goyal *et al*[47] 2006	Mouse (obese gold thioglucose)	*Zingiber officinale*	250 mg/kg 8 wk	C: Placebo I: Extract	Sig. decrease in body wt.	Sig. decrease in serum Chol, TG, glucose, and insulin
Kishino *et al*[48] 2006	Rat and mouse	Salacia reticulata	0/5% 8 wk in mice 0/2% 35 d in rats	C: HFD I: HFD + plant	Sig. decrease in the body wt. and visceral fat mass increase	Sig. decrease in plasma TG, 4 h after ingestion; Sig. decrease in energy efficiency, plasma leptin and adiponectine levels
Jayaprakasam *et al*[49] 2006	Mouse	Cornelian cherry (cornus mas) (Purified anthocyanins (A) & ursolic acid (u)	1 g/kg (A), 500 mg/kg (u) 8 wk	C: HFD I: HFD + A/A + u	24% decrease in wt. gain in (A) group	Elevated insulin levels; Sig. decrease of liver TG in A + u group
Moreno *et al*[50] 2006	Rat	Arachis hypogaea nutshell	1% (wt:wt) /12 wk	C: HFD I: HFD + extract	Sig. decrease in body wt. gain and liver size	Increased fecal lipid excretion. Reduced TG content of liver and serum glucose and insulin
Galisteo *et al*[51] 2005	Rat (obese)	Plantago Ovata	3/5% 25 wk	C: STD I: STD + extract	Sig. decrease in body wt. gain	Sig. improvement of lipid profile, FFA & insulin & TNF-α & hypoadinectinemia
Zhao *et al*[52] 2005	Mouse (obese by hyperalimentation)	Phillyrin (Fructose forsythia)			Sig. decrease in wet wt. of fat & fat index & diameter of fat cells & lee index	Decrease in jejunum microvillus area, and serum levels of TG & Chol
Chen *et al*[53] 2005	Rat	Bitter melon (Momordica charantia)	0/75% or 7/5 g per kilogram 7 wk	C: LFD/HFD I: LFD/HFD + extract	Lower energy efficiency and visceral fat mass after 4 wk in I group	Reduced plasma glucose and hepatic TG but higher serum FFA after 4 wk; Higher plasma catecholamine after 7 wk in I group; Sig. decrease in hepatic TG & steatosis and sig. increase of serum epinephrine & FFA in HFD group of I

Han *et al*[54] 2005	Rat	Coleus forskohlii	50 g/kg	C: Sham operated/ ovariectomized + control diet I: Same groups + extract	Reduced body wt.& food intake & fat accumulation	
Han et al[55] 2005	Mouse	Chikusetsu saponins isolated from Panax japonicus rhizomes	1%, 3%/9 wk	C: HFD I: HFD + extract	Prevented body wt. gain & increase of parametrial adipose tissue wt.	Sig. increase of the fecal content & TG level in day 3; reduction of plasma TG 2 h after oral lipid intake & inhibition of pancreatic lipase activity
Han *et al*[56] 2005	Mouse	*Zingiber officinale* Roscoe	1%, 3%/8 wk	C: HFD I: HFD + plant	Sig. decrease in body wt. gain at 2-8 wk with 3% & in final parametrial adipose tissue wt. with 1% concentration	
Cha *et al*[57] 2004	Mouse	Acanthopanax senticosus	0/5 g per kilogram 12 wk	C: NLD/HFD I: NLD/HFD + extract	HFD group of I had lower wt. gain but no difference in food consumption was shown	In HFD group of I, lower serum LDL and restoration of liver TG at the same level as fed by LFD was shown; No alteration in carnitine status
Kim *et al*[58] 2005	Rat	Crude saponin of Korean red ginseng	200 mg/kg 3 wk, ip	C: NLD/HFD I: NLD/HFD + extract	Reduced body wt., food intake & fat content in HFD group of I similar to those fed with NLD	Reduction of hypothalamic NPY expression and serum leptin level in HFD group of I
Yun *et al*[59] 2004	Mouse	Wild Ginseng	250, 500 mg/kg	C: HFD I: HFD + extract	Sig. inhibition of body wt. gain dose dependently. Decrease of white & brown adipocytes diameters	Sig. inhibition of FBG, TG, and FFAs dose-dependently; insulin resistance improved
Junbao *et al*[60] 2004	Rat (obese)	Semen cassiae	6%	-	Sig. decrease in body wt. & lee index	Reduction of fasting serum TG, insulin & malondialdehyde
Kim *et al*[61] 2004	Rat	Adlay seed (CoixLachrymajobi var. mayuen)	50 mg/100 g of body wt.	C1: NLD C2: HFD + saline (sham group) I: HFD + plant	Sig. decrease in body wt. & food intake & epididymal and peritoneal fat & white adipose tissue size as compared to sham group	Increase of brown adipocytes as compared to NLD group but not significant
Kwon *et al*[62] 2003	Rodent	Dioscorea nipponica Makino	5%/8 wk	C: HFD I: HFD + plant	Sig. decrease in body wt. & adipose gain	Suppression of time dependent increase of serum TG level after lipid intake
Lu *et al*[63] 1999	Rat (obese by hyperalimentation)	Inspissation tea (Guangdong kudingcha)		C: Control I1: Extract I2: Fenfluramine	Stronger modulation on lymphocytes hypertrophy and quantity was shown in I1 group	Only fenfluramine showed sig. difference in small intestine villus model
Yoshikawa *et al*[64] 2002	Rat (obese)	Salacia reticulata	125 mg/kg 27 d		Suppression of body wt. and periuterine fat storage increase in female rats but no effect on male rats	
Xie *et al*[65] 2002	Mouse	Ginseng berry	150 mg/kg 12 d, ip	C: Diabetic/lean diabetic + placebo I: Same groups + extract	Sig. decrease in body wt. as compared to day 0 in diabetic group of I. wt. loss in lean mice was shown	Sig. increase in glucose tolerance in diabetic mice but no sig. decrease of FBG in lean mice.
Yamamoto *et al*[66] 2000	Rat	CT-Ⅱ, an extract from Nomame Herba	8 wk, 12 wk, 6 mo	C: Lean/obese + HFD I: Same groups + HFD + plant	Sig. inhibition of body wt. gain dose dependently without affecting food intake in lean rats after 12 wk. Sig. decrease in body wt. gain in obese mice after 24 wk	Sig. inhibition of TG elevation
Han *et al*[67] 1999	Mouse	Oolong tea	10 wk	C: HFD I: HFD + extract	No sig. difference in food intake but prevented obesity & liver induced by a HFD	Enhancement of noradrenalin induced lipolysis & inhibition of pancreatic lipase activity

Pusztai *et al*[68] 1998	Rat	Kidney bean (Phaseolus vulgaris)	130, 150, 280 g/kg 10-70 d	C: Lean/obese + LFD/HFD I: Same groups + extract	The growth was retarded dose-dependently lower body fat	Sig. decrease of body protein in lean I group. Sig. decrease in plasma insulin levels in obese I group. Sig. pancreatic growth after long term feeding in all I groups
Nagasawa *et al*[69] 1991	Mouse (obese)	Tree peony root (Paenia suffruticosa)	0/5% 30 wk	C: Control I: Extract	Sig. decrease in food intake and Lee index	Improvement in glucose tolerance. No sig. difference in serum FFA levels
Wang *et al*[70] 2008	Mouse	Parasitic loranthus from Loranthacea or Viscaceae	20 d	-	Sig. decrease in body wt. & food intake	High inhibitory ability on FAS-Loran thacea was nearly 400 fold stronger than that from the viscaceae
Hu *et al*[71] 2008	Mouse (female)	Escins extracted from Aesculus turbinata Blume (Hippocastanaceae)	2%/11 wk	I: HFD C: HFD + extract	Suppressed the increase in body & parametrial adipose tissue wt.	Suppressed the increase of liver TG content; increased TG in feces after fat ingestion
Ohkoshi *et al*[72] 2007	Mouse	Nelumbo nucifera Gaertn leaves (Nymphaceae)	50%	C: STD/HFD I: Same groups + extract	Sig. suppression of body wt. gain	Exhibition of lipolytic activity especially in visceral adipose tissue; β adrenergic receptor pathway was partly involved
Kang *et al*[73] 2004	Rat	PM-F2-OB composed of *Lycii Fructus*, *Rehmanniae Radix*, *Coicis Semen*, *Carthami Flos*, *Hoelen*, *Angelicae Radix*, *Nelumbinis Semen*, *Radix Dioscorea* and *Aurantii Fructus*	6 wk	C: STD/HFD I: Same groups + plant	No sig. difference in wt. change if STD was used but in HFD group of I resulted in sig. decrease in body wt. gain but showed no sig. difference in amount of food intake	Sig. decrease in serum Chol/LDL and total lipids; reduction of kidney fat wt./FFA/PL & TG to levels equal or below the normal diet
Mary *et al*[74] 2003	Rabbit	Caps HT2 A herbal formulation	5 mg/kg (iv) 30 d 100/200/300/400/mg per kilogram orally	-	Sig. decrease in body wt.	Sig. increase in HDL after oral administration and decrease in atherogenic index in oral administration; Sig. increase of the release of LPL enzyme and sig. hypolipidemic effect in Ⅳ groups
Wu *et al*[75] 2005	Rat (diabetic by STZ)	Astragalus polysaccharide (APS) a component of Astragalus membranaceus roots	400 mg/kg (APS) 5 wk	-	Sig. decrease in body wt.	Sig. decrease in plasma glucose; improved insulin sensitivity
Xie *et al*[76] 2005	Mouse (Genetically obese)	Total, Ginsenosides in Chinese ginseng (TG CG), from leaves and the stem of Panax ginseng	100, 200 mg/kg (ip) 12 wk & 150, 300 mg/kg (oral)/12 wk	C: Placebo I: Extract	Sig. decrease in body wt.	Sig. decrease in FBG in 200 mg/kg dose after injection Sig. decrease in FBG in 300 mg/kg dose
Palit *et al*[77] 1999	Mouse	Galega officinalis	10% (w/w) of the diet 28 d	C: Diabetic/NL I: Same groups + plant	Sig. decrease in body wt. in both I groups, sig. wt. loss in normal mice independent of a reduction in food intake but in diabetic mice wt. loss was with reduced food intake	Striking loss of body fat in both groups; Sig. decrease in serum glucose in both groups but Sig. decrease in serum insulin in diabetic mice
Oi *et al*[78] 1999	Rat	Garlic	8 g/kg of diet 28 d	C: HFD I: HFD + extract	Sig. decrease in body wt. & perirenal adipose tissue wt. & epididymal fat pad	Sig. decrease in plasma TG levels; sig. decrease in mitochondrial protein and (UCP) in brown adipose tissue, and in urinary noradrenaline and adrenaline excretion
Yoshida *et al*[79] 1995	Mouse (obese and lean)	Bofu-tsusho-san	1/4%, 4/7% of wt. of food 8 wk	-	Sig. decrease in body wt. & retroperitoneal white adipose tissue wt. and no change in food intake	Sig. increase in GDP binding dose dependently
He *et al*[80] 2008	Rat (obese by STZ & HFD	Yi-Qi-Yang-Yin-Ye	2, 4, 8 g/kg 4 wk	-	Body wt. decreased	Decrease in TG/Chol/LDL/FFA/FBG/insulin; improvement of glucose tolerance

Jeong *et al*[81] 2008	Rat (fatty)	Gyeongshang angjeehwan: Liriope platyphylla F.T./Wang & T. Tang (Liliaceae), Platycodongrandiflorum A. DC. (Campanulaceae). Schisandrachinensis K. Koch (Magnoliaceae). Ephedra sinica Stapf (Ephedraceae)	8 wk	C: Placebo I: Compound	Sig. decrease in food intake & body wt. gain & abdominal fat	Sig. decrease in plasma leptin levels; decrease in circulating TG and inhibition of lipid accumulation in liver; increase of mRNA of genes responsible for FABO
Park *et al*[82] 2005	Rat (obese by diet)	Platycodon grandiflorum	150 mg/kg 7 wk	C: Convert to NLD/HFD I: Same groups + extract	Sig. decrease in wt. of body & adipose tissues in rats converted to NLD as compared to those remained on HFD	Sig. decrease in fat cell number & size in both I groups as compared to their state before intervention; decrease of FABP expression in HFD group of I
Akagiri *et al*[83] 2008	Mouse (obese by HFD)	Bofutsushosan (BOF)	1%/4 wk	C: Placebo I: Compound	The wt. of WAT and increase in size of adipocytes inhibited	Expression of UCP1 mRNA in WAT was found but not sig.
Kim *et al*[84] 2005	Mouse (diabetic)	Pine extract (bark and needle)	21 d	C: Control I: Extract	Sig. decrease in body wt.	Effectively suppressed the increase of postprandial blood glucose level by delaying absorption of diet
Attele *et al*[85] 2002	Mouse (obese diabetic)	Panax ginseng berry	150 mg/kg (ip) 12 d	C: Control I: Extract	Sig. loss of wt. with a sig. reduction in food intake & a very sig. increase in energy expenditure & body temperature	Sig. improvement in glucose tolerance & sig. reduction in serum insulin levels & plasma chol levels

MSG: Monosodium glutamate; FABO: Fatty acid β oxidation; STD: Standard diet; LFD: Low fat diet; NLD: Normal diet; HFD: High fat diet; FABP: Fatty acid binding protein; FFM: Fat free mass; sig.: Significant; AST: Aspartate transaminase; ALT: Alanine transaminase; C: Control; I: Intervention; FAS: Fatty acid synthetase; UCP: Uncoupling protein; GDP: Guanosine 5' diphosphate; FAS: Fatty acid synthetase; TG: Triglyceride; HDL: High density lipoprotein; LDL: Low density lipoprotein; FBG: Fasting blood glucose; ip: Intraperitoneal; iv: Intravenous. Caps HT2 is a herbal formulation containing methanolic extract of selected parts of plants: commiphora mukul; Allium Sativum; Plumbago indica/some carpus anacardium/Hemidesmus indicus/Terminalia arjuna/Tinospora cordifolia/Withania somnifera ocimum sanctum.

caffeine[9,20] which caused minor adverse effects such as dry mouth, insomnia, nervousness, palpitation and headache. Bofutsushosan[14] caused loose bowel movements.

ANIMAL STUDIES

Change in body weight and body fat

The majority of animal studies (41 out of 58) showed significant weight loss or inhibition of weight gain when supplemented with high fat diets containing extracts of plants, with or without an efficient decrease in fat mass[27-85] (Table 2).

Food intake

Clinical trials with *Agave tequilana* (TEQ) and Dasylirion spp (DAS)[30], Pomegranate leaf[43], Korean red ginseng[58], Tree peony[69], Gyeongshang angjeehwan containing a variety of plants including platycodongrandiflorum, Magnoliaceae and Ephedra[81], Parasitic loranthus[70], and Panax ginseng berry[85] showed significant reductions in food intake or appetite. In studies with *Cucurbita moschata*[40], *Cyperus rotundus*[42], Nomame Herba[66], *Acanthopanax senticosus*[57] PM-F2-OB (a traditional herbal medicine used for the treatment of obesity in Korea composed of Lycii Fructus), and several other plants[73], bofu-tsusho-san[79], *Galega officinalis*[77], and Oolong tea[67], no change in the amount of food intake or appetite was observed.

DISCUSSION

In many studies[8-10,12-16,20-23,27,39,73,74,79-81,83], a combination of plants or compounds containing minerals and or chemical extracts of plants were investigated and the scientific names are summarized in Tables 1 and 2. Most of these studies showed anti-obesity effects such as decreasing body weight in humans or body weight gain in animals with or without changes in body fat.

Currently available anti-obesity medications attack the body fat dilemma in three different ways. They can stimulate metabolism, suppress appetite, affect serotonin, or they can impede digestion of fat. In this review, we can categorize the target effects of herbal medicines in the same way.

Arachis hypogaea[50] decreased body weight gain, liver triglyceride content and liver size in association with increased fecal lipid excretion, suggesting an inhibitory mechanism on lipid absorption. Phillyrin[52], *Allium victorialis*[32], Pomegranate leaf[43], *Kochia scoparia*[46], *Panax japonicus*[55], Oolong tea[67], and *Aesculus turbinata* Blume[71] also had the same effect.

A decrease in food intake as a result of a decrease in appetite and an influence on hormonal status was observed with TEQ and DAS[30], Pomegranate leaf[43], Korean red ginseng[58], Tree peony[69], Gyeongshang angjeehwan containing a variety of plants including platycodon grandiflorum and Magnoliaceae and

ephedra[81], and Parasitic loranthus[70], refined Rhubarb[34], *Caralluma fimbriata*[19] and Panax ginseng berry[85]. Possible stimulation of metabolism has been reported as a mechanism of action for compounds such as Slimax[8], supplements containing ephedra[9,13,14,20] and *Terminalia arjuna* Roxb[11] which showed modification of lipid metabolism and a reduction in serum lipid levels.

Ephedra known as *Ma Huang* is a well known natural product with amphetamine-like stimulation effects. Although it's efficacy in weight loss need more investigations, its adverse effects are well established in the literature. In this review, nine studies investigated the effects of ephedra as one of the major components in the combinations with caffeine[9,13,22] or with several other plants[14,20,79,81,83] 5 of which were human studies[9,13,14,20,22].

In one study[13], efficient decreases in body weight and fat were observed with the administration of 210 mg caffeine and 72 mg ephedra per day for 12 wk with an improvement in lipid metabolism and blood pressure without serious adverse effects. In this study, the weight loss at 12-wk was -3.5 ± 0.6 kg with the test compound which was significantly ($P < 0.02$) higher than that of the placebo. The percentage fat loss shown by DXA was -7.9% ± 2.9% and -1.9% ± 1.1%, respectively ($P < 0.05$). In another study[20], ephedra at a dose of 40 mg/d and caffeine at a dose of 100 mg/d for a longer time (9 mo) was found to be more efficient than the previous study in lowering body fat and weight, improving lipid metabolism and blood pressure and had no serious adverse effects. The treatment group lost significantly more body weight (-7.18 kg) and body fat (-5.33 kg) than the control group (-2.25 and -0.99 kg, respectively). The difference in data from these two studies possibly resulted from the different dosages and duration of interventions.

In a human study[9], a significantly greater weight loss was observed (-4.0 ± 3.4 kg or 3.5% of baseline) in the test group *vs* (-0.8 ± 2.4 kg or 0.09% of baseline) in the placebo group. Changes were significantly greater for body fat and percentage of body fat in the active group (-3.5 ± 3.3 kg and -2.1% ± 3.0%) in comparison to the placebo group (-0.7 ± 2.9 kg and -0.2% ± 2.3%). The tested product also produced several untoward side effects, leading to some actively treated subjects withdrawing from the study. Additional long-term studies are needed to elucidate the effects of chronic treatment. Thus further examinations in healthy individuals using scientific combinations and dose/duration adjustments are required.

Four studies[58,59,65,76] investigated different doses and types of ginseng which is a very popular Chinese herbal medicine. Ginseng significantly decreased weight gain and efficiently improved glucose tolerance[59,76].

It has been reported[58] that hormonal influences can reduce food intake and decrease serum leptin and neuropeptide Y in the brain hypothalamus although not significantly. Thus the anti-obesity effect of this plant requires further investigation.

CQ, a succulent vine native to West Africa and Southeast Asia, has been used in traditional African and Ayurvedic medicine for more than a century. Although some studies have examined other uses for CQ, its role in fighting against obesity and for symptoms of metabolic syndrome has recently attracted interest in other parts of the world, because of its milder adverse effects comparing to ephedra. In this review, two studies focused on this herb[15,26]. CQ in combination with IG[15] induced marked reductions in body weight and fat. In addition, a reduction in waist size of 1.0 cm in the placebo group *vs* 21.9 cm in the CQ-IG group was observed.

As we focused on herbal medicines, all dietary interventions such as the consumption of fruits and vegetables, whole grains, different types of fibers, functional food components including omega three fatty acids or phytochemicals such as flavonoids were omitted. Lifestyle modification is still the safest and efficacious method of inducing a persistent weight loss. In this review, some of the studies were carried out on subjects who simultaneously received diet and exercise programs (mentioned as weight loss programs in Tables). These results demonstrated that specific phytochemical supplements increase the effectiveness of weight loss programs and additional significant anti-obesity effects are observed.

Although few studies mentioned adverse effects, it should be noted that many serious adverse events which would have stopped a trial of a pharmaceutical agent would likely not have been identified by the authors' search methods. Moreover, important safety issues including significant adverse events or supplement-drug interactions relevant to many clinical populations may not be fully addressed by the trials available for review.

CONCLUSION

Compliance with conventional weight-management programs, which often include increasing energy expenditure *via* physical activity, is low. It is not surprising to see the marketing of many new dietary slimming aids aimed at satisfying the need for palatable (as well as safe, effective, and therapeutic) options. In accord with this approach there are numerous investigations on the effectiveness of medicinal plants as natural supplements to reduce body weight. In this paper a variety of herbal supplements had beneficial effects on obesity especially compounds containing ephedra, CQ, ginseng, bitter melon (*Momordica charantia*), and zingiber. Most of the introduced herbals (Tables 1 and 2) have also been shown to have antioxidant effects, and with regard to the role of oxidative stress in the pathophysiology of some diseases and conditions, their further positive effects may be very promising[86-95]. Attention to these natural compounds and further work on the isolation and characterization of their constituents is highly recommended.

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