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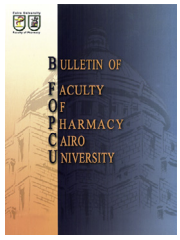

REVIEW ARTICLE

Natural anti-obesity agents

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Abstract Obesity is a complex disease caused by the interaction of a myriad of genetic, dietary, lifestyle, and environmental factors, which favors a chronic positive energy balance, and leads to increased body fat mass. The incidence of obesity is rising at an alarming rate and is becoming a major public health concern with incalculable social costs. Indeed, obesity facilitates the development of metabolic disorders such as diabetes, hypertension, and cardiovascular diseases in addition to chronic diseases such as stroke, osteoarthritis, sleep apnea, some cancers, and inflammation-based pathologies. Recent researches demonstrated the potential of natural products to counteract obesity. Multiple-natural product combinations may result in a synergistic activity that increases their bioavailability and action on multiple molecular targets, offering advantages over chemical treatments. In this review, we discuss the anti-obesity potential of natural products and analyze their mechanisms.

Contents

Abbreviations: WHO, World Health Organization; BMI, body mass index; WHR, Waist to Hip Ratio; WC, Waist Circumference; FTO, fat mass and obesity associated; MC4R, melano-cortin-4 receptor; POMC, proopiomelanocortin; DRD4, dopamine receptor D4; PPARy2, peroxisome proliferator-activated receptor y2; HDL, high-density lipoprotein; LDL, low-density lipoproteins; TG, triglyceride; WLS, Weight Loss Surgery; ABA, abscisic acid; CVD, cardiovascular diseases; BAT, brown adipose tissue; UCP1, Uncoupling protein; PUFA, polyunsaturated fatty acids; HCA, hydroxycitric acid.

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1. Introduction

In 1997, the World Health Organization (WHO) described obesity as an epidemic hazard worldwide, based on the data analysis of body mass index (BMI).[1] Since then, obesity incidence increased at an alarming rate and is becoming a major public health concern.[2] Indeed, obesity facilitates the development of metabolic disorders (e.g. diabetes, hypertension), and cardiovascular diseases in addition to chronic diseases (e.g. stroke, osteoarthritis, sleep apnea, cancers, and inflammation-based pathologies).[3,4] According to studies in different countries, an obese person incurs health care expenditures at least 25% higher than a healthy person.[5] Adding production losses to health care costs, obesity accounts for a considerable percentage loss of gross domestic product in most countries ($>1\%$ in US, $>3.6\%$ in China).[6]

Obesity could be iatrogenic, i.e. secondary to drug treatments (antipsychotic, antidepressant, antiepileptic, steroids, and insulin), or due to certain diseases (Cushing syndrome, hypothyroidism, and hypothalamic defects).[7] Obesity as a primary disorder follows a positive energy balance. The identification of the primary causes of this imbalance remains challenging and comprises the majority of cases usually diagnosed after causes for secondary obesity are ruled out.[8] This chronic disease results from complex interactions of genetic, behavioral, and environmental factors correlating with economic and social status and lifestyles.[9] In fact, obesity is more frequent in populations living in environments characterized by a long-term energy positive imbalance due to sedentary lifestyle, low resting metabolic rate, or both.[10] Causes of obesity involve genes, metabolism, diet, physical activity, and the socio-cultural environment that characterizes 21st century living style.[11] The identification of potential molecular targets susceptible to be manipulated from external factors, particularly food and drug agents may assist people in gaining control over appetite allowing obesity prevention. Nutritional genomics could determine which specific nutrients bring phenotypic changes that influence the obesity risk and could establish which interactions are the most important.[12]

Global strategies are focused on dietary and lifestyle modifications, i.e. restrict calorie intake and increase physical activity to slow obesity development.[13] Researches demonstrated the potential of natural products to counteract obesity.[14] Multiple natural product combinations may result in a

synergistic activity that increases their bioavailability and action on multiple molecular targets, offering advantages over chemical treatments.[15,16] The anti-obesity effects of these compounds are mediated by regulation of various pathways, including lipid absorption, energy intake and expenditure, increasing lipolysis, and decreasing lipogenesis, differentiation and proliferation of preadipocytes.[15]

2. Definition

The word obesity comes from the Latin obesitas, which means stout, fat, or plump. Medically, obesity is a condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health, leading to reduced life expectancy and/or increased health problems.[17]

3. How to assess obesity?

Body weight is not a good indicator as it does not distinguish between fat and muscle mass. Various measures, including body mass index (BMI) and Waist to Hip Ratio (WHR) have been developed to identify those at risk of serious health problems.

3.1. Body mass index (BMI)[18]

Body mass index is a measurement which correlates weight and height: BMI = Mass (kg)/[Height (m)]^2. Table 1 lists the BMI values according to the WHO data which have been published in 2000.

3.2. Waist Circumference (WC) and Waist to Hip Ratio (WHR)[19]

WHR is used as a measurement of obesity, which in turn is a possible indicator of other more serious health conditions, WHO states that abdominal obesity is defined as a waist–hip ratio above 0.90 for males and above 0.85 for females. Women with waist–hip ratios of more than 0.8, and men with more than 1.0, are at increased health risk because of their fat distribution. WHR has been shown to be a better predictor of cardiovascular disease than Waist Circumference and body-mass index.[19]

WHR is more recent evidence, which deals with the central distribution of body fat as an indicator of health risks. Waist distribution of fat has been assessed by calculating the waist/hip ratio.

WHR = Waist Circumference/Hip circumference

4. Causes of obesity

At individual level, the combination of excessive food energy intake and lack of physical activity is thought to explain most of obesity causes.[20] In limited cases, obesity is due to genetic factors, medical reasons, or psychiatric illness.[21] On the other hand, increasing rates of obesity at a societal level are felt to be due to easily accessible and palatable diet, increased reliance on cars, and mechanized manufacturing.[22] A 2006 review identified ten other possible contributors to the recent increase of obesity including insufficient sleep, endocrine disruptors, decreased variability in ambient temperature, decreased rates of smoking, as smoking suppresses appetite, increased use of medications that can cause weight gain (e.g., atypical antipsychotics), proportional increases in ethnic and age groups that tend to be heavier, pregnancy at a later age (which may cause susceptibility to obesity in children), epigenetic risk factors passed on generationally, natural selection for higher BMI, and assortative mating leading to increased concentration of obesity risk factors.[23]

Table 1 BMI values according to the WHO data.

Classification	BMI*
Under weight	< 18.5
Normal weight	18.5–24.9
Over weight	25–29.9
Class I obesity	30–34.9
Class II obesity	35–39.9
Class III obesity	40 ⩾

* BMI of ⩾40–44.9 or 49.9, is morbid obesity. BMI of ⩾45 or 50, is super obese.

4.1. Diet

Obesity rates in the US (1971–2000) increased from 14.5% to 30.9%.[24] During the same period, there was an increase in the average amount of food consumed (average increase for women 335 and 168 cal./day). Most of this extra food energy was due to the increase in carbohydrates rather than fat consumption.[24]

4.2. Sedentary lifestyle

There is a large shift toward less physically demanding work worldwide. Currently, at least 60% of the world's population gets insufficient exercise, due to increased use of mechanized transportation and a greater prevalence of labor-saving technology at home.[25] The WHO indicates people worldwide are taking up less active recreational pursuits. In both children and adults, there is an association between television viewing time and the risk of obesity.[26]

4.3. Genetics

Like many other medical conditions, obesity is the result of interplay between genetic and environmental factors. Polymorphisms in various genes controlling appetite and metabolism predispose to obesity when sufficient food energy is present. People with two copies of the FTO gene (fat mass and obesity associated gene) have been found on average to weigh 3–4 kg more and have a 1.67 fold greater risk of obesity compared to those without the risk allele.[27] Some cases of obesity are related to single-gene mutations, e.g. melano-cortin-4 receptor (MC4R) gene[28], dopamine receptor D4 (DRD4)[29], peroxisome proliferator-activated receptor y2 (PPARy2)[30] or the leptin genes.[31]

4.4. Medical and psychiatric illness

Certain physical and mental illnesses and medications used to treat them can increase the risk of obesity. Medical illnesses that increase obesity risk include several rare genetic

syndromes (Cohen syndrome), as well as some congenital or acquired conditions: hypothyroidism, growth hormone deficiency,[32] and eating disorders (binge eating disorder and night eating syndrome).[33] The risk of overweight and obesity is higher in patients with psychiatric disorders than in persons without psychiatric disorders.[34]

4.5. Social determinants

Genetic influences are important to understand obesity. They cannot explain the current dramatic increase in obesity. Though, excess energy consumption than energy expenditure leads to obesity on individual basis. The cause of the shifts in these two factors on societal scale is much debated.[35] In developing countries women of a high social class were less likely to be obese. No significant differences were seen among men of different social classes. In the developing world, population of high social classes had greater rates of obesity.[36] Smoking has a significant effect on an individual's weight. Those who quit smoking will gain an average of 4.4 kg (men) and 5.0 kg (women) over ten years. However, changing rates of smoking have little effect on the overall rates of obesity.[37]

4.6. Infectious agents

The study of infectious agent's effect on metabolism is still in its early stages. The gut flora in obese and lean individuals can affect the metabolic potential. This apparent alteration is believed to confer a greater capacity to gain energy contributing to obesity. An association between viruses and obesity has been found in humans and several different animal species.[38]

4.7. Pathophysiology

Leptin and ghrelin are internal mediators that affect feeding and appetite. Ghrelin is produced by the stomach modulating short-term appetitive control (i.e., to eat when the stomach is empty and to stop when the stomach is stretched). Leptin is produced by white adipose tissue to signal fat storage reserves in the body and mediates long-term appetitive controls (i.e., to eat more when fat storages are low and less when fat storages are high). It plays a critical role in the regulation of body weight and energy balance by inhibiting food intake and stimulating energy expenditure.[39] Although, administration of leptin may be effective in a small subset of obese individuals who are leptin deficient. Most obese individuals are thought to be leptin resistant and have been found to have high levels of leptin.[40] This resistance is thought to explain in part why administration of leptin has not been shown to be effective in suppressing appetite in most obese people.[41] Although leptin and ghrelin are produced peripherally, they control appetite through their actions on the central nervous system. Thus, a deficiency in leptin signaling either via leptin deficiency or leptin resistance leads to overfeeding and may account for some genetic and acquired forms of obesity.[41,42]

5. Pathologies associated with obesity and its effects on health

In addition to, mechanical effects on the body (i.e., exacerbating osteoarthritis and back pain due to extra weight) because of the extra weight placed on the skeleton, obesity is associated with a higher incidence of several pathologies.

5.1. Diabetes mellitus

Accumulated data demonstrate the association between obesity and noninsulin-dependent diabetes mellitus, which is the most common primary form of diabetes and impaired glucose tolerance. In obese individuals, adipose tissue releases high amounts of non-esterified fatty acids, glycerol, pro-inflammatory cytokines, and hormones. They are linked with the development of insulin resistance, which generate compensatory hyperinsulinemia with overstimulation of pancreatic cells and reduction of insulin receptors.[43]

5.2. Hypertension

Epidemiological studies have demonstrated that 65–75% of the risk of hypertension is accounted for by obesity.[44] Endocrinological studies of the adipose tissue revealed links between obesity and hypertension, likely consequent to the fact that the adipose tissue secretes bioactive molecules and immunomodulators.[45]

5.3. Dislipidemia

Obesity is the most common cause of dislipidemia. Lipid oversupply in a state of obesity, hyperinsulinemia, and/or insulin resistance results in increased non-esterified fatty acid availability and, in turn, higher TG stores in non-adipose tissues, e.g. the muscle, liver, and pancreas.[46,47] Fatty acid-induced disorders are referred to as lipotoxicity. Thus, elevated TG level is often accompanied by a slight increase in total cholesterol and a marked drop in high-density lipoprotein (HDL) cholesterol. Moreover, low-density lipoproteins (LDL) rich in TG, partially metabolized by hepatic lipase, are converted into small LDL, with higher atherogenic potential.[48]

5.4. Cardiac alterations

Obesity increases the risk of heart failure, sudden cardiac death, angina or chest pain, and abnormal heart rhythm.[49] Increased electrical alterations in obesity lead to frequent ventricular dysrhythmias even in the absence of heart dysfunction. The annual sudden cardiac death rate was nearly 40 times higher in obese people than in non obese population.[50]

5.5. The metabolic syndrome

Obesity is the major component of the metabolic syndrome (multiple metabolic disorders). This syndrome is characterized by the co-occurrence of multiple metabolic disorders, namely overall and abdominal obesity, insulin resistance, hypertension, hyperglycemia, impaired glucose tolerance, and the combination of low HDL cholesterol and elevated TG level.[51]

5.6. Lung diseases

Obesity is associated with an increased risk of chronic respiratory disorders (e.g. asthma, hypoventilation syndrome, and

sleep apnea). Accordingly, weight loss often leads to symptomatic improvement.[52]

5.7. Cancer

The link between diet, obesity, and cancer is not completely understood, but the rising world-wide trend in obesity and cancer might be at least in part causal. The putative cause of these obesity-related cancers has been primarily ascribed to excess estrogen production by the adipose tissue, inflammation due to adipocytokines secreted by adipocytes, infiltrating macrophages or associated stromal cells that might also play an important role.[53,54]

5.8. Neurological disorders

Psychological damage caused by overweight and obesity ranges from lowered self-esteem to frank clinical depression. Indeed, rates of anxiety and depression are three to four times higher among obese individuals.[55] Obesity significantly increases the risk of Alzheimer's disease. A strong correlation exists between BMI and high levels of amyloid, i.e. the protein that accumulates in the Alzheimer's brain, destroying nerve cells and producing cognitive and behavioral problems.[56]

5.9. Treatment of obesity

Diet, exercise, pharmacotherapy, behavioral therapy, and lifestyle modification each can produce a modest weight loss in the severely obese. Pharmacotherapy, in addition to diet and exercise, has been demonstrated to facilitate a weight loss of 2–10% per year.[57] Long-term maintenance of significant weight loss, continues to be the most challenging problem in the medically based treatment for obesity.

6. Prevention of obesity

As a result of the recent exponential increase in obesity, the American Heart Association has released several guidelines for identification and early intervention for both adult and adolescent weight gain.[58] Losing weight can reverse the harmful health effects attributed to excess weight, and may improve or prevent obesity-related diabetes mellitus, dyslipidemia, hypertension, and diastolic cardiac dysfunction.[59]

6.1. Dietary intervention

Arrays of diets have been proposed for weight loss in obese patients. Commercial weight loss programs have become increasingly popular for targeted weight loss. However, long-term success is variable, and directly related to patient compliance with these programs. The proposed weight loss programs involved an in person center-based program, a telephone-based weight loss counseling program, and a control group of "usual care". The usual care group received individualized weight loss counseling sessions and monthly contacts; however they did not receive free prepackaged meals. The patients participating in the center and telephone-based groups were provided with prepackaged food items and a planned menu. They were encouraged also to make behavioral changes regarding physical activity.[60]

6.2. Diet control

The daily requirements of persons with moderate physical activity vary with age and sex, (3200–2550 kcal for males in temperate climate and 2300–1800 kcal for females). 800–1000 kcal/day ranges are frequently used in weight reduction programs. Fasting or semi-starvation is sometimes proposed as a mean of weight reduction in obesity.[61] Maintaining a well-balanced diet (rich in fibers and low in fats and containing multiple vitamins) will provide the body with nutrients required to function properly.[61] Nutrition education is important for weight management (e.g., low-fat food may still cause weight gain, since both protein and carbohydrates can be metabolically converted to fat). Low calorie diets (<1200 kcal/day) and very low calorie diets (<800 kcal/day) may be associated with diverse effects such as increased uric acid level, increased risk of gall stone formation, loss of lean body mass, electrolyte disturbances and mild liver dysfunction.[62]

The number of calories needed to maintain a certain body weight can be estimated by multiplying a person's REE times an appropriate Activity Factor (AF) where REE is the Resting Energy Expenditure and the AF is the Activity Factor (AF) for different levels of activity.[63]

6.3. Physical activity

Weight gain and obesity are responses to long term positive energy balance where:

$$\text{Energy Balance} = \text{Energy Intake} - \text{Energy Expenditure}$$

Energy balance involves equilibrium between calorie intake and energy utilization (physical activity, basal metabolism, and adaptive thermogenesis).[64] The development of overweight and obesity is a consequence of the easy and cheap availability of high-calorie foods, which is combined with sedentary lifestyle (Fig. 1). A variety of exercises such as walking, cycling, swimming, and aerobics are effective and easy to implement.

Regular physical activity is an essential component to lose weight. To lose weight, one must achieve a negative energy balance (i.e., decreased energy intake and increased energy expenditure). Overweight patients who participate in at least 30 min of moderate physical activity most days of the week, or who have moderate to high cardio-respiratory fitness have decreased all-cause mortality than those who are sedentary and un-fit.[65,66] Exercise as a treatment for obesity is most effective when combined with diet and weight-loss programs. Exercise alone without dietary changes will have a limited effect on weight because one has to exercise a lot to lose one pound. However, regular exercise is important to maintain a healthy weight for the long term. Another advantage of regular exercise as part of a weight-loss program is a greater loss of body fat versus lean muscle in comparison to diet alone.[59]

6.4. Pharmacotherapy

Medications can facilitate weight loss in obese persons. Similar to Weight Loss Surgery, there are certain BMI criteria

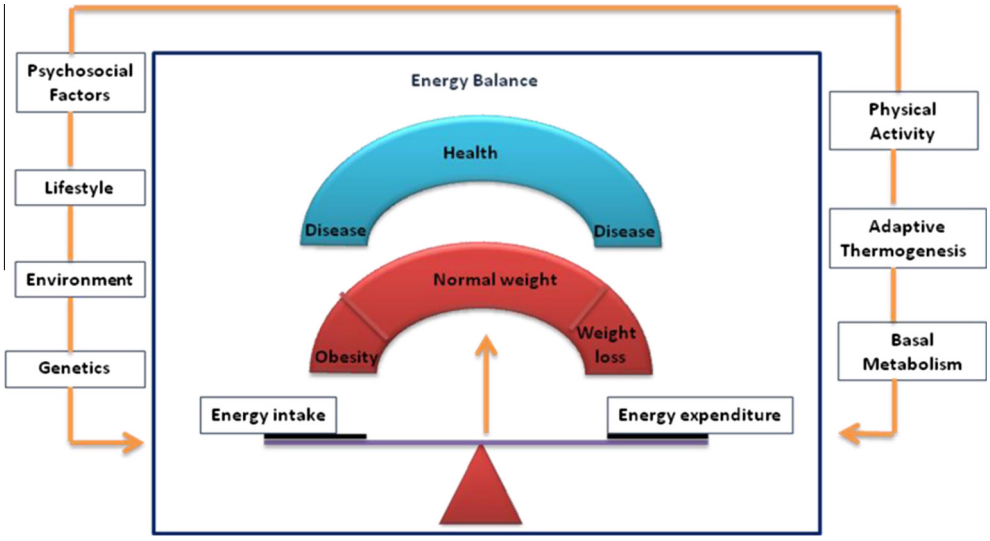

Figure 1 Fundamental principles of energy balance.

Table 2 Some common anti-obesity drugs.

Drug	Mechanism of action	Effect on weight	Side effects
Phentermine (Fastin) Diethylpropion	Appetite suppressant reduces food intake. Sympathomimitic amine causes release of norepinephrine by the cells.	3.6 kg at 6 months	Headache, insomnia, irritability, palpitation and nervousness
Fluoxetine (Prozac)	Reduces food intake through selective inhibition of serotonin re-uptake.	4.74 kg at 6 months and 3.15 kg at 1 year	Agitation and nervousness
Sibutramine (Meridia)	Reduces food intake through combined norepinephrine and serotonin re-uptake inhibition.	4.45 kg at 1 year	Headache, insomnia, dry mouth and constipation. Long term treatment increases the risk of heart attack and stroke.
Orlistat (Xenical)	Lipase inhibitor reduces fat absorption.	2.59 kg at 6 months and 2.89 kg at 1 year	Diarrhea, flatulence, bloating, abdominal pain, and dyspepsia
Rimonabant (Acomplia)	Selective CB1 receptor blocker reduces food intake.	51 kg at 1 year	Nausea, dizziness, arthralgia, and diarrhea

necessary to prescribe pharmacotherapies. The patient must have a BMI greater than 30 kg/m^2 or BMI of at least 27 kg/m^2 with obesity-related co-morbidities. Medications are often required long-term as many persons regain weight when they are discontinued. In addition, person's compliance to these daily medications is of concern, especially in light of cost, potential lack of insurance coverage, and possible side effects. The first class of medication used for weight control causes symptoms that mimic the sympathetic nervous system. They cause the body to feel "under stress" or "nervous". As a result, the major side effect of this class of medication is high blood pressure. These medications also decrease appetite and create a sensation of fullness. Another class of anti-obesity medications suppresses appetite by increasing the level of neurotransmitters at the synapse junction, where hunger and fullness (satiety) are regulated by brain neurotransmitters (e.g., serotonin, norepinephrine, and dopamine). Several common medications for weight loss are listed in Table 2.[67–70]

6.5. Diuretics

Diuretics cause loss of fluids that may result in gradual weight reduction. Diuretics cause temporary weight loss with no loss in body fat. Their use should be avoided due to the serious side effect of electrolytes imbalance.[71,72]

6.6. Surgical treatment for obesity

Bariatric or Weight Loss Surgery (WLS) was previously categorized as malabsorptive, restrictive, or a combination of both. However with a greater understanding of the extensive neural-hormonal effects of WLS on satiety, hunger and metabolism, the above mentioned broad categories are no longer appropriate. In fact, today Bariatric or WLS is perhaps better referred to as Metabolic Surgery. The most common metabolic surgical procedures include Roux-en-Y gastric bypass, adjustable gastric band, sleeve gastrectomy, and biliopancreatic

Table 3 Classes of dietary phytochemicals.

Phytochemical	Examples	Effects
Polyphenols	Simple phenolic acids (e.g. ferulic, caffeic)	Ferulic acid has hypolipidemic effect and lowers the risk of high fat diet-induced obesity and reduces serum cholesterol[76]
	Stilbenes (resveratrol)	Resveratrol decreases LDL-cholesterol and prevents lipid oxidation[77]
		Decreases adipogenesis by downregulating adipocyte transcription factors, altering the expression of adipocyte specific genes[78]
		In mature adipocytes, it increases lipolysis, induces apoptosis, and reduces lipogenesis, proliferation and lipid accumulation[79]
		Dietary supplements of resveratrol, vitamin D, quercetin, and genistein reduce weight gain and body fat leading to potential novel therapies for obesity[77,80,81]
	Curcumins	Prevent lipid accumulation[82]
		Regulate energy metabolism and decrease level of intracellular lipids[83]
		In adipose tissues, curcumins suppress angiogenesis necessary for tissue growth[84]
		Curcumins regulate transcription factors that play key roles in adipo- and lipogenesis[83,85]
	Lignans (e.g. secoisolariciresinol, matairesinol)	They are converted to mammalian lignans enterodiol and enterolactone that may reduce the risk of chronic diseases including obesity[86]
	Flavonoids (e.g. quercetin)	Attenuate *in vitro* adipogenesis by activating AMPK signal pathway in preadipocytes and decreasing expression of adipogenesis related factors[87]
Alkaloids	Capsaicin	Attenuates obesity-induced inflammation, obesity related metabolic disorders, and liver diseases[88]
		Reduces food intake and increases energy expenditure and lipid oxidation[89]
	Ephedrine	Increases norepinepherine causing appetite suppression[90]
		Produces thermogenic effect (increase basal metabolic rate) and energy expenditure[91]
	Caffeine	Stimulates fat breakdown, potentiates the anorectic and thermogenic effects in addition to its diuretic effect[91,92]
	Nicotine	Decreases food intake and increases fat oxidation and energy expenditure[93,94]
Terpenoids	Abscisic acid (ABA)	Effective in treatment of diabetes and obesity-related inflammation[95]
	Carotenoids	Carotenoids may prevent inflammation associated diseases such as obesity and atherosclerosis[96]
	Lycopene	Lycopene rich diets lower the risk of CVD (inhibition of LDL oxidation and lipid peroxidation)[97]
Organosulfur	Ajoene	Decreases cholesterol synthesis, lowers blood pressure, and stimulates non-specific immunity[98]
		Decreases fat cell number suggesting some therapeutic possibility for obesity[99]
Phytosterols	Diosgenin, Campesterol, Brassicasterol, Sitosterol	High intakes of these sterols can protect against atherosclerosis and decrease LDL-cholesterol[100]
		Phytosterols compete with cholesterol for micelle formation in the intestinal lumen and inhibit cholesterol absorption[101]
	Protodioscin	Significantly reduces blood levels of TG, cholesterol, LDL and increases high-density lipoproteins[102]
	Diosgenin	Inhibits accumulation of TG and expression of lipogenic genes[103]

diversion.[73] The National Institute of Health consensus has suggested the following guidelines for surgery in obese patients:

a- Patients with BMI more than 40.
b- Patients with BMI more than 35 who have serious medical problems such as sleep apnea, that would be improved with weight loss.

6.7. Natural products for treatment of obesity

The potential of natural products for treating obesity is under exploration. This may be an excellent alternative strategy for developing future effective, safe anti-obesity drugs.[74] A variety of natural products, including crude extracts and isolated pure natural compounds can induce body weight reduction and prevent diet-induced obesity. Therefore, they have been widely used in treating obesity.[75]

6.7.1. Dietary phytochemicals

Dietary phytochemicals might be employed as anti-obesity agents because they may suppress the growth of the adipose tissue, inhibit differentiation of preadipocytes, stimulate lipolysis, and induce apoptosis of existing adipocytes, thereby reducing adipose tissue mass (Table 3 and Fig. 2).

6.7.2. Natural products

6.7.2.1. Natural products with lipase inhibitory effect. Dietary fat is absorbed by the intestine when it has been subjected to the action of pancreatic lipases. Pancreatic lipase is a key enzyme in dietary triacylglycerol absorption, hydrolyzing triacylglycerols to monoacylglycerols and fatty acids. Few

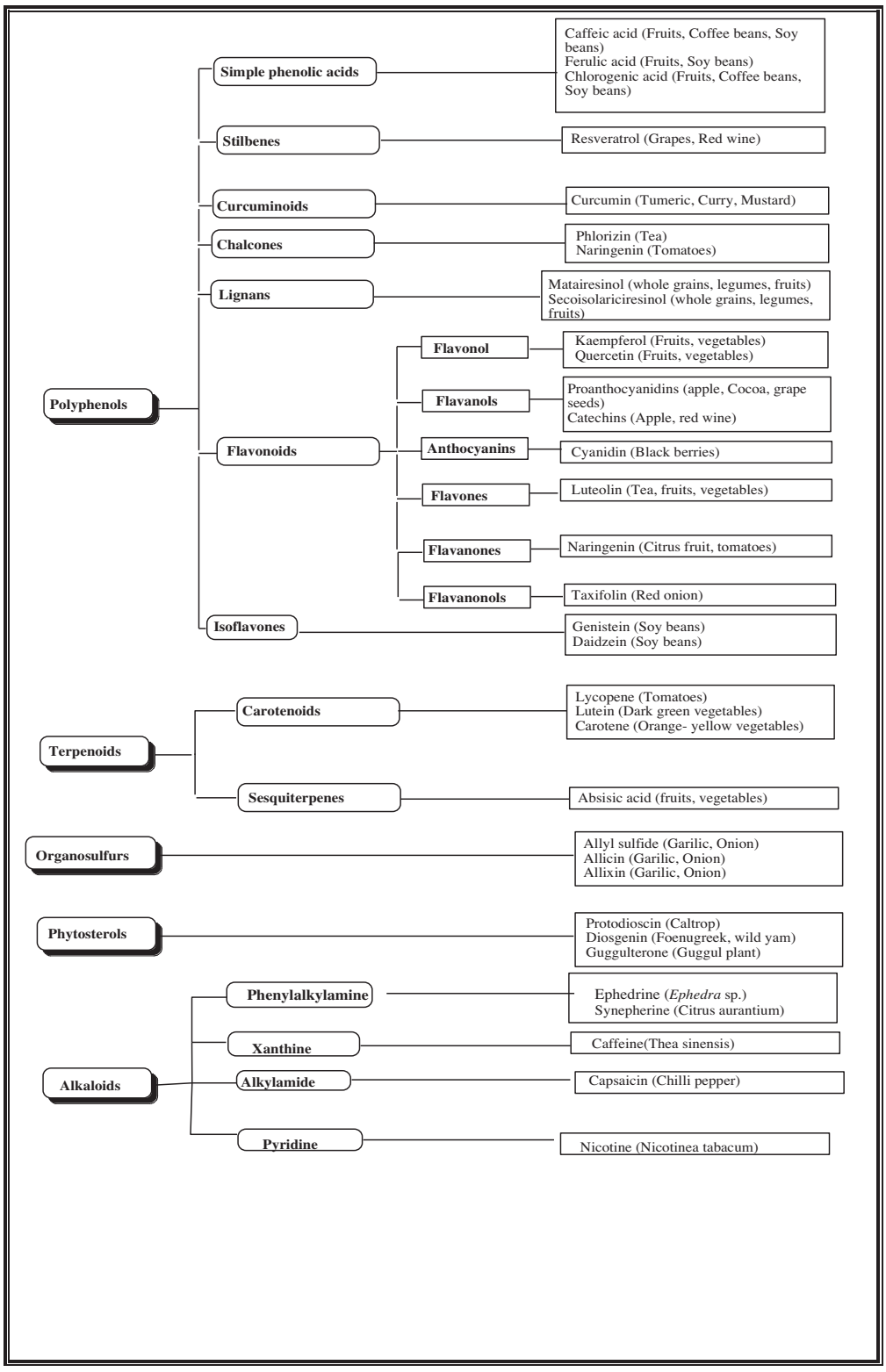

Figure 2 Classification of common dietary phytochemicals.

substances interact directly with the lipases as orlistat. It is a derivative of the naturally-occurring lipase inhibitor from *Streptomyces toxytricini*.[104] Orlistat inhibits by forming a covalent bond to the lipase's serine active site.[105] Although it is clinically approved for obesity treatment, it has certain unpleasant gastrointestinal side-effects.[106]

Natural products provide a vast pool of pancreatic lipase inhibitors.[107] A wide variety of plant products such as saponins, polyphenols, flavonoids, and caffeine possess lipase inhibitory effects (Table 4).[108] Several carbohydrates also possess pancreatic lipase inhibitory effects,[109] for example chitin/chitosan.[110] Many metabolites from microorganisms, includ-

ing lipstatin from *S. toxytricini* and panclicins from *Streptomyces* sp. also possess pancreatic lipase inhibitory activity.[111] Different types of tea (e.g., green, oolong, and black tea) are among the most widely-studied materials for lipase inhibitors. Various polyphenols (e.g., L-epicatechin, epicatechin gallate (ECG), epigallocatechin (EGC) and epigallocatechin gallate (EGCG)) isolated from tea leaves showed strong inhibitory activity against pancreatic lipase (Fig. 3).[112] These polyphenols acquire galloyl moieties within their chemical structures and/or polymerization of their flavan-3-ols for enhanced pancreatic lipase inhibition.[113]

6.7.2.2. Natural appetite suppressants. Body weight regulation through appetite control is a multifactorial event resulting from neurological and hormonal interrelationships. A line of evidence indicates that serotonin, histamine, dopamine, and their associated receptor activities are closely associated with satiety regulation. These receptors may enable better targets for drugs treating obesity through energy intake reduction.[127] Agents that act *via* peripheral satiety peptide systems alter the various hypothalamic neuropeptide levels. Also, they alter the key CNS appetite monoamine neurotransmitter levels and may be suitable candidates for appetite suppressants.[128] Appetite suppressants control hunger centers in the brain, resulting in a sense of fullness. However, ghrelin secretion in the stomach may increase with decreased food intake, stimulating more food intake. Therefore, ghrelin antagonism may decrease the appetite that potentially occurs with decreased feeding, thus, may be a potential adjunctive treatment for obesity. An example of a natural appetite suppressant is *Hoodia gordonii*. It regulates appetite and significantly reduces calorie intake and boosts weight loss.[129] Natural (−)-hydroxycitric acid (HCA) from *Garcinia cambogia*, is a potential natural appetite suppressant. It is available under the names HCA-SX and Super CitriMax™.[130] *Hypericum perforatum* increases the serotonin quantity present within synaptosomes by inhibiting synaptosomal uptake of serotonin, which suppresses the appetite and reduces food intake. Thus increased serotonergic transmission might be the link between antidepressant and anti-obesity activities of *H. perforatum*.[131] Some natural appetite suppressants are listed in Table 5.

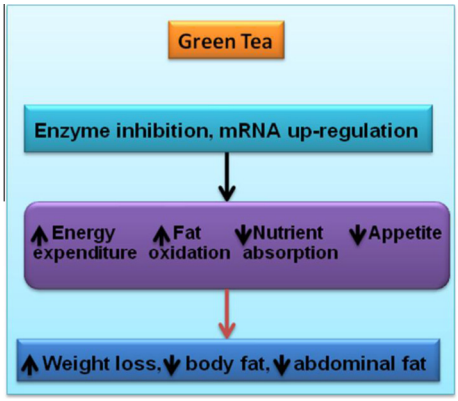

Figure 3 Proposed anti-obesity mechanisms of green tea.

6.7.2.3. Natural energy expenditure stimulants. Excessive adiposity results from energy imbalance, where the consequences of excessive food intake are not balanced by increasing energy expenditure. Energy expenditure has many components, and can be classified into physical activity, obligatory energy expenditure, and adaptive thermogenesis.[140] To regulate body weight and energy expenditure, mammalian brown adipose tissue (BAT) establishes non-shivering thermogenesis through dissipation of excess energy as heat. BAT plays an important role in obesity control by controlling energy balance through UCP1 (Uncoupling protein). UCP1 is responsible for oxidative phosphorylation. Thus, searching for substances that up-regulate UCP1 gene expression may be a worthy strategy for achieving obesity control through increased energy expenditure.[141] For example, the ethanolic extract of *Solanum tuberosum* activated the expression of UCP in BAT and the liver, and significantly reduced fat weight.[142] Many natural compounds have been proposed as treatments for obesity via enhanced energy expenditure including caffeine, capsaicin, and green tea and its extract.[143]

6.7.2.4. Natural adipocyte differentiation inhibitors (decreased lipogenesis). Adipocytes play a central role in the maintenance of lipid homeostasis and energy balance by storing triglycerides and releasing free fatty acids in response to change in

Table 4 Natural pancreatic lipase inhibitors.

Source	Used part and/or active constituents
Panax japonicus (rhizomes)	Chikusetsusaponins[114]
Thea sinensis (oolong tea)	Crude aqueous extract (caffeine)[115]
Cassia mimosoides	Proanthocyanidin[116]
Trigonella foenum graecum L. (seed)	Crude ethanolic extract[117]
Salix matsudana (leaf)	Polyphenol (PP)[118]
Vitis vinifera	Crude ethanolic extract[119]
Salvia officinalis L. (leaf)	Methanolic extract (carnosic acid)[120]
Cassia nomame	Flavan dimers[121]
Coffea canephora	Caffeine, chlorogenic acid, neochlorogenic, and feruloylquinic acids[122]
Citrus unshiu	Hesperidin[123]
Chitosan-chitin	Chitosan (80%), chitin (20%)[124]
Streptomyces toxytricini (fungus)	Lipistatin[111]
Actinomycetes sp.	Valilactone[125]
Caulerpa taxifolia (marine algae)	Caulerpenyne[126]

Table 5 Examples of natural appetite suppressants.

Source	Used part and/or active constituents
Panax ginseng (root)	Crude saponins[132]
Garcinia cambogia	(−)-Hydroxycitric acid (HCA)[133]
Camellia sinensis (leaf)	(−)-Epigallo-cathechin gallate (EGCG)[134]
Hoodia gordonii and *H. pilifera*	Steroidal glycoside (P57AS3)[135]
Phaseolus vulgaris and *Robinia pseudoacacia*	Lectins[136]
Pinus koraiensis (pine nut)	Pine nut fatty acids[137]
Ephedra species	Ephedrine[138]
Citrus aurantium	Synephrine[139]
Hypericum perforatum	Total extract[131]

Table 6 Natural adipocyte differentiation inhibitors.

Source	Used part and/or active constituents
Garcinia cambogia	(−)-Hydroxycitric acid (HCA)[148]
Glycine max (product of GIBCO)	Genistein[149]
Chili pepper (Capsicum)	Capsaicin[150]
Fish oil	Docosahexaenoic acid[151]
Palm oil	γ-tocotrienol[152]
Sterol (product of Sigma)	β-sitosterol[145]
Camellia sinensis (green tea)	(−)-Epigallocatechin gallate[153]
Panax ginseng	Ginsenosides[154]
Silybum marianum	Silibinin[155]
Garlic	Ajoene[156]
Rosmarinus officinalis	Carnosic acid[157]
Curcuma longa	Curcumin[158]
Humulus lupulus	Xanthohumol[159]

energy demands.[144] Natural products that specifically target adipogenesis inhibition had been considered promising potentials in obesity treatment. Fatty acids, particularly polyunsaturated fatty acids (PUFA) act as signal transducing molecules in adipocyte differentiation.[145] Thus, PUFA play a central role in suppressing lipogenesis and regulating adipocyte differentiation through suppression of late-phase adipocyte differentiation.[146] Several natural products have apoptotic effects on maturing pre-adipocytes (eg. esculetin, resveratrol, quercetin, genistein, EGCG, capsaicin, and conjugated linoleic acids).[147] Examples of some natural products with adipocyte differentiation inhibitory effect are given in Table 6.

6.7.2.5. Natural lipid metabolism regulators (increased lipolysis). The pharmacological targeting of lipolysis can be achieved by stimulating triglyceride hydrolysis in order to diminish fat stores, thereby combating obesity. The flavonoids from *Nelumbo nucifera* leaves are examples of the natural products involved in β-adrenergic receptor activation.[160] Table 7 shows examples of natural products, which promote lipid metabolism.

6.7.2.6. Natural products with combined effect. As mentioned above, many natural products show anti-obesity activities with varying mechanisms. Perhaps the recommended approach to search for more efficient obesity treatments and achieving the synergistic effects of natural products should seek treatments using multiple products or products that have multiple activities.[143] Green tea is a good example of a natural drug which possesses multi-functional anti-obesity activities. Researches have proved the anti-obesity activity of catechins which is due to the combined actions of appetite reduction, greater lipolytic activity and energy expenditure, and less lipogenic activity and adipocyte differentiation.[112,113]

The aqueous extract of *Hibiscus sabdariffa* (mainly anthocyanins) has potential anti-obesity mechanisms including anti-hyperglycemic, lowering plasma cholesterol level, gastric and pancreatic lipase inhibition, thermogenesis stimulation, inhibition of lipid droplet accumulation in fat cells (no effects on adipose conversion), and fatty acid synthase inhibition.[167]

G. cambogia extract (HCA) has multi-functional anti-obesity effects. It inhibits adipocyte differentiation, reduces fatty acid synthesis (lipogenesis) and epididymal fat accumulation through reducing ATP-citrate lyase activity, and suppresses appetite.[148] Pomegranate extract (ellagic and tannic acids) also has dual anti-obesity effects. It inhibits pancreatic lipase activity and suppresses energy intake. Its effect on energy intake was similar to sibutramine but with a different mechanism.[168] *Arachis hypogaea* (Peanut) shell extract inhibits fat absorption, activates lipid metabolism in the liver, and reduces adipocyte lipolysis.[169] *Apium graveolens* juice significantly lowers TG concentrations and total cholesterol levels in animals fed with high-fat diet.[170] Ginger has a dual antiobesity effect. Gingerol and shogaol increase the metabolic rate and thus help to "burn off" excessive fat and also suppress the absorption of calorie-dense dietary fats from the intestines. The ginger extract inhibits the absorption of dietary fat by the intestine.[171]

6.7.2.7. Enzymatic treatment of obesity. Eating a whole fresh pineapple (*Ananas comosus*, *A. sativus*) per day can decrease the body weight by 100 pounds on a pineapple regimen. Its content of bromelain enzyme helps to digest both proteins and fats.[167]

6.7.2.8. Laxatives

6.7.2.8.1. Bulk producers. Many herbs and natural products are significant in the treatment of obesity through bulk-producing activity that produce a sense of fullness, thereby reducing appetite.[60] Fibers act through slowing the movement of food and acidic fluid from the stomach to the intestines. They may help people with duodenal ulcers by reducing the exposure of the small intestine to stomach acids. Dietary fibers lower cholesterol, reduce elevated blood levels of triglycerides, and protect against cancer and digestive disorders.[172]

National cancer Institute recommends incorporating 30 g of fibers into the daily diet. The bulk producers include natural polysaccharides or celluloses, in addition to semisynthetic polysaccharides (methylcellulose and carboxymethylcellulose) and synthetic resin polycarbophil.[172]

The bran layers of grains are the most important source of fibers. Bran contains more than 40% dietary fibers and is a convenient source of intestinal bulk. Mucilages in plant seeds have been shown to decrease glucose and insulin levels during post-meal and fasting periods in healthy and diabetic persons. When taken before meal they have also been shown to decrease weight and hunger in obese persons. It was also reported that mucilage contents of bran such as oat bran are effective cholesterol lowering agents. A diet with 5% oat bran

Table 7 Natural lipid metabolism regulators.

Source	Used part and/or active constituents
Morus albam, *Melissa officinalis*, *Artemisia capillaries* (leaf)	Crude aqueous extract[161]
Curcuma longa L.	Curcumin and curcuminoids[162]
Glycyrrhiza glabra L. (root)	Licorice flavonoid[163]
Panax ginseng	Crude aqueous extract[164]
Zea mays L.	Purple corn color (anthocyanins)[165]
Soybean	Genistein and L-carnitine (soy isoflavone)[166]
Coffea canephora	Caffeine, chlorogenic, neochlorogenic, and feruloyquinic acids[108]

showed reduction in total cholesterol and LDL levels of 19% and 29%, respectively.[173]

Pectin consists mainly of partially methoxylated galactouronic acids. It is found in a number of fruits and vegetables (e.g. apples, white inner layer of citrus rind, carrots, cabbage and okra). It slows down food digestion, helps the body to get rid of toxic metals, and reduces cholesterol levels by reducing the plasma LDL fraction.[173] Psyllium is a good source of soluble and insoluble fibers and can be indicated in the treatment of obesity because it absorbs water in the stomach creating a feeling of fullness and decreases appetite. It is also beneficial in diabetes and for lowering the cholesterol level.[93,174,175]

Other examples of bulk producers are *Laminaria* spp. (mucilage algin, polysaccharides laminarin), chitosans, *Fucus vesiculosis* (mucilage algin and fucin, cellulose), agar agar from *Gelidium* and *Petrocladi* spp. (polysaccharides agarose and agaropectin).[175]

6.7.2.8.2. Stimulant laxative (anthraquinones). Some herbal preparations used in obesity include anthraquinones containing plants such as senna (*Cassia* species), cascara (*Rhamnus* species), rhubarb (*Rheum palmatum*), and aloe (*Aloe vera*, *A. ferox*). The laxative effect of anthraquinones leads to rapid excretion of foods and water loss which can aid in weight reduction.[175]

6.7.2.9. Non calorie sweeteners. Sucrose substituents (e.g. saccharin, aspartame, sorbitol) may allow significant calorie reduction in certain patients.[176] Glycyrrhizin is a non caloric triterpene of liquorice root (50–100 times sweeter than sucrose). Stevioside (*Stevia rebaudiana*) is 300 times sweeter than sucrose.[176] There are a number of additional low calorie sweeteners waiting for approval for use in foods and beverages as neohesperidin dihydrochalcone derived from bioflavonoids of citrus fruits. Currently neohesperidin-DHC synthesized from Seville oranges has been found to have great potential in food applications. Naringin isolated from grapefruit (*Citrus paradisi*) is converted to naringin dihydrochalcone which is 1000 times sweeter than sucrose and is used to reduce body weight.[177]

6.7.2.10. Marine natural products. Iodine is the most important active component in *Fucus vesiculosus*, also it contains polyphenols, polysaccharides, sterols, and other minerals. Iodine is known to play an important role in the treatment of obesity. Iodine was believed to stimulate the thyroid gland, causing weight-loss.[178,179]

The brown seaweed *Undaria pinnatifida* contains fucoxanthin and fucoxanthinol. It was found that fucoxanthin significantly reduced plasma and hepatic triglyceride concentrations and the activities of adipocytic fatty acid synthesis, hepatic fatty acid and triglyceride synthesis, and cholesterol-regulating enzymes, and significantly increased the concentrations of plasma high-density lipoprotein-cholesterol, fecal triglyceride and cholesterol, as well as fatty acid oxidation enzyme activity, indicating that fucoxanthin ameliorated the plasma and hepatic lipid profile, fecal lipids and body fat mass, hepatic cholesterol metabolism, fatty acid synthesis, and lipid absorption.[180] In addition, fucoxanthin and fucoxanthinol inhibited both lymphatic triglyceride absorption and the increase of triglyceride concentration in systemic blood, likely due to their inhibitory effects on lipase activity in the gastrointestinal lumen.[181,182]

Astaxanthin, a xanthophyll carotenoid, isolated the marine algae *Haematococcus pluvialis*, *Chlorella zofingiensis*, and *Chlorococcum* sp. was found to inhibit the increases in body weight and weight of the adipose tissue, whereas reduce liver weight, liver triglyceride, plasma triglyceride, and total cholesterol.[183]

Krill oil is extracted from Antarctic krill, *Euphausia superba*, a zooplankton crustacean rich in phospholipids carrying long-chain omega-3 PUFAs, mainly EPA and DHA. Additionally, Krill oil also contains various potent antioxidants, including vitamins A and E and astaxanthin.[184] It has been reported that krill oil could reduce the level of glucose, total cholesterol, triglycerides, LDL and HDL, and could increase plasma eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), with no indication of adverse effects on safety parameters.[184,185]

7. Suggestions and recommendations

a- Be active, walk for 30 min a day especially before breakfast to burn off fat. Exercise is the best way to get rid of excess body fat and to maintain good muscle tone.
b- Check with the doctor, underactive thyroid can cause obesity to be a problem.
c- Rotate foods and eat a variety of foods, ask dietitian to regulate your food intake and drink 6–8 glasses of liquids every day.
d- Cut down on salt, it makes you thirsty and causes retention of water.
e- Make sure bowels are regular. Use extra fibers in the diet every day. Put less food in your plate. Chew slowly.
f- Do not chew gum, because it starts the gastric digestive juices flowing and will make you feel hungry sooner, in addition to overworking your digestive system.

g- Never consume animal fats; butter, cream, ice cream, whole milk, rich dressing, mayonnaise, and fried foods.
h- Do not eliminate sources of good fat, containing unsaturated fatty acids, such as avocados, olive oil, and nuts.
i- Avoid white flour products, salt, white rice, or processed foods. Avoid fast food restaurants. Do not consume sweets such as soda pastries, cakes, doughnuts, and candy. Eat complex carbohydrates that offer protein: lentils, plain baked potatoes, sesame seeds, beans, brown rice, and whole grains.
j- Eat fresh fruits and raw vegetables (good fiber sources). At least one meal a day should be only fruits and vegetables.
k- Make lunch the main meal of the day, no later than 3 PM to give the body time to burn some calories before bedtime.

8. Conclusion

Weight management is a life-long process and permanent weight reduction is difficult to achieve. The ultimate cause of obesity is an imbalance between calorie intake and energy expenditure resulting from complex interactions between many genetic and environmental factors. Obesity is a chronic disease that affects millions of people worldwide and contributes to substantial morbidity and mortality. A successful weight control program must balance calorie intake with energy expenditure. Diet and exercise have been the mainstays for weight control. Natural products can play a safe and effective role with obesity specially those containing fibers, polyphenols, sterols, and alkaloids. In addition, they are a good supplement for vitamins and minerals. In general, natural products with potential action in treatment of obesity act as a general body cleanser, regulate metabolism, dissolve fat in the body, help to eliminate craving of food, stimulate glandular secretions, reduce water retention, boot energy and help in constipation. However, their use should be in conjunction with regular exercise, as well as dietary and behavioral modifications. The use of multiple phytochemicals might result in synergistic and enhanced effects.

9. Conflict of interest

None declared.

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