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Anti-Obesity Potential of Natural Products

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Abstract

Obesity is a complex chronic disease that shows increasing incidence around the world. Although behavioral and lifestyle interventions remain the cornerstones of weight loss, it's a big challenge to maintain the lifestyle. The lack of effective anti-obesity drugs exacerbates this global health problem. As a result, the utilization of natural products could be a viable alternative to the development of novel anti-obesity drugs. It's also thought that combining many natural compounds can have synergistic effects, enhancing anti-obesity effect by regulating several targets. Many multidimensional approaches that combine pharmacological, chemical and biological factors in determining the potential anti-obesity impact of natural products are done *in vivo* and *in vitro* throughout the year. A wide range of plants from many families have shown potent anti-obesity effects. The presence of a large number of phytochemicals, unsaturated fatty acids and fibers, in these natural materials is primarily responsible for their biological advantages. The current review focused on the recent advances in the anti-obesity potential of natural products, their mechanisms of action as anti-obesity agents, preclinical and clinical trials will be discussed.

Keywords: Anti-obesity agents; Natural products; Obesity; Phytochemicals.

Introduction

Obesity has risen at an alarming rate in recent decades. It affects more than a third of the world's population today. In 2016, nearly 2 billion adults worldwide were classified as overweight, while the obese were approximately 650 million **[1].** Obesity is a disease that is characterized by accumulation of excess body fat due to imbalance between energy intake and energy expenditure **[2].** Obesity results from an increase in calorie consumption and/or a decrease in calorie expenditure as a result of environmental, genetic and behavioral factors **[3].** Obesity is a complicated multifactorial disease, it results in numerous complications such as, atherosclerosis, cardiovascular abnormalities, hyperlipidemia, cancer, stroke, diabetes mellitus and hypertension **[4, 5].** In addition, obesity affects the female reproduction as a result of disturbance in the hormonal metabolism **[6].** Obesity treatment options include dietary control, physical activity, lifestyle modification, medication, and surgical interventions **[7].** Although, most synthetic anti-obesity medications have proven to be effective in weight loss, high cost, drug abuse, misuse as well as, undesired side effects have been reported, which may be due to the lack of clarity on the mechanisms of action and safety profiles of the various chemicals included in anti-obesity medications **[8, 9].** On the other hand, there are various complications regarding the surgical intervention such as malnutrition, anemia, thrombosis and infection. These complications are also common in patients who are severely obese and have undergone surgery **[9, 10].** Therefore, it is an urgent need to discover new approaches for the management of obesity. Plant-based medications serve a critical role in sustaining health by treating diseases and their complications **[11].** The synergistic effect of polyherbal preparations will increase the potency of anti-obesity effect by acting on multiple targets. Furthermore, these herbs have numerous health benefits in addition to their anti-obesity properties **[12].** Therefore, using certain plants and their compounds could be a useful strategy for managing obesity and related disorders. Because of increased consumer health awareness, natural plant products are predicted to be prospective ingredients in the development of nature-sourced anti-obesity products in the weight loss segment. In the current review, the recent advances in the anti-obesity potential of natural products, their mechanisms of action as anti-obesity agents, preclinical and clinical trials will be discussed.

Obesity

Obesity is a medical term for a condition in which the body accumulates and stores too much fat, resulting in more health problems. Obesity has an impact not

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only on a person's appearance but also their health **[13].**

The degree of obesity

The Body Mass Index (BMI) is the most widely used method for measuring and identifying the obesity. Body mass index is measured by dividing the weight in kilograms by the square of the height in centimeters. Based on BMI, the obesity can be classified into overweight, obese, and sever obese **[14].** Overweight is characterized by BMI range (25-29.9), obese (BMI of 30-39.9) and sever obese with BMI greater than 40 **[15, 9].**

Etiology of obesity

There are many factors that cause obesity. However, the most prominent factors are physical inactivity and overeating. A person's weight is affected by the balance between energy expenditure and calories intake. A person gains weight if she or he burns less calories than she or he eats, so the excess energy will be stored as fat **[16, 17].** A diet rich in carbohydrates increase blood glucose levels, which stimulate pancreas to secrete insulin which in turn stimulates the growth of fat tissue causing weight gain **[2].** In addition, it was reported that people who eat two or three large meals daily, have higher blood sugar and higher cholesterol levels than people who eat small meals four or five times daily. This is because the small frequent meals produce more stable insulin levels than large, less frequent ones **[18].** Genetics also play a vital role in obesity, if one or both parents are obese, a person is more likely to be obese. In addition, leptin deficiency is a genetic cause of obesity. The hormone leptin is generated by fat cells and the placenta. When body fat storage is too high, leptin signals to the brain to eat less **[16].** Some diseases may result in obesity such as Cushing's syndrome, polycystic ovarian syndrome, insulin resistance, and hypothyroidism **[19].** Moreover, some medications can cause weight gain such as most corticosteroids, oral contraceptives, some antidiabetic drugs such as sulfonylureas and insulin, certain anticonvulsants and antidepressants drugs **[16].** Eating habits are also affected by psychological factors. Many people overeat in response to their emotions as in the cases of anger, stress, sadness or boredom **[18]. The etiology of obesity was summarized in figure 1.**

Synthetic Anti-Obesity Drugs

The Food and Drug Administration (FDA) approved two medications as weight loss drugs which are orlistat (Orlistat, Chitocal and Xenical) and sibutramine (Meridia) **[20].** These drugs affect the body weight by reducing the intestinal absorption of the lipid through inhibiting pancreatic lipase, reducing the appetite, or increasing energy consumption **[21, 22].** On the other side, undesired side effects have been reported for many weight loss drugs. For example, in 2010 Xenical as weight loss drug, was reported to cause severe liver injury. Also, Meridia was found to cause strokes and increase the risk of heart attacks, so it was withdrawn from the market **[12].**

Natural products and obesity

Natural products are now preferred over synthetic drugs due to their effectiveness in treating overweight and many other chronic conditions and to face the side effects of the synthetic drugs. Traditional herbal treatments with a long history of use, as well as other natural ingredients, may reduce appetite and aid weight loss. When compared to synthetic materials, it was widely assumed that natural materials would be less expensive and have less or no toxic side effects **[9, 23].** A previous study collected the data from year 2000 to 2018, which related to natural agents with anti-obesity effect **[16].** It showed that the research effort on anti-obesity agents that could be effective in the management of obesity was dramatically increasing day by day. The data of various parts of the plants that have been reported as anti-obesity agents are collected. It has been discovered that the leaves, followed by the fruits, have the greatest medicinal potential against obesity. Moreover, different phytochemical constituents in the medicinal plants play a vital role in weight loss. It showed that the flavonoids have shown the highest report followed by polyphenolic compounds **[16].**

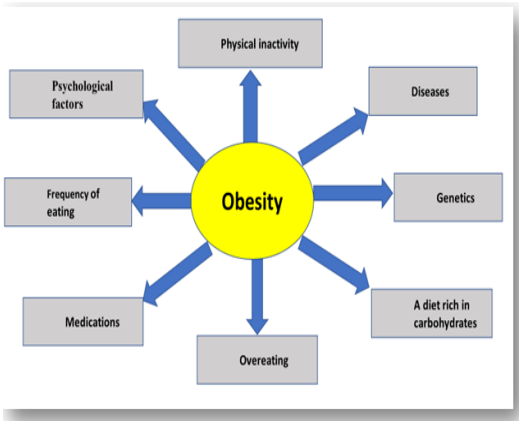


Figure 1. Etiology of obesity

Anti-obesity mechanisms of natural products

Appetite suppression

As the nagging feeling of hunger is often one of the key concerns with excessive energy intake, appetite suppression may be an effective method for anti-obesity agents **[12].** Appetite regulation is linked to hormones; leptin hormone activates the receptors in

central nervous system that inhibit the appetite and increase energy expenditure. Also, insulin sends a signal to the brain, regulating energy homeostasis and suppressing the appetite. Leptin and insulin signals work together to suppress the appetite **[24].** As a result, any natural substances that modify the brain signals linked to appetite regulation should be investigated further for their potential in the treatment of obesity.

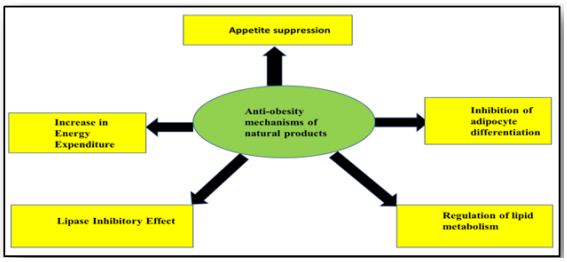


Figure 2. Anti-obesity mechanisms of natural products

Increase in Energy Expenditure

The accumulation of excess body fat is due to the imbalance between energy intake and energy expenditure **[2].** So, in order to lose weight, a person should increase the energy expenditure to create a negative energy balance. The energy expenditure can be increased by physical activity as well as by adaptive thermogenesis. Brown adipose tissue is responsible for converting energy from food into heat. Thermogenin protein is a critical component of the thermogenic action in brown adipose tissue. As a result, a substance capable of increasing energy expenditure by upregulating the gene expression of thermogenin, which could be a possible method for attaining an anti-obesity impact **[25].**

Lipase Inhibitory Effect

The pancreatic lipase enzyme is a crucial enzyme in the human digestive system for breaking down dietary fat. Interfering with fat absorption along the gastrointestinal tract is one of the potential ways for treating obesity. The discovery and development of inhibitors for food digestion and absorption has piqued researchers' interest for a long time. The basic idea is that all dietary fat that enters the human gut should be broken down enzymatically by pancreatic lipase. As a result, one of the most important indications for determining the anti-obesity potential of natural compounds is pancreatic lipase activity **[26].**

Regulation of lipid metabolism

Increased lipolysis enhances triglyceride hydrolysis, which reduces fat storage and manages obesity. Many studies have explored the critical points to improve lipolysis. For example, the stimulation of adenosine monophosphate-activated protein kinase (AMPK), which increased fatty acid oxidation and glucose transport in skeletal muscle. Another example, was the stimulation of the β-adrenergic receptor in white adipocytes induced lipolysis and non-shivering thermogenesis in brown fat. As a result, transcription factors that can mimic lipolysis are becoming increasingly relevant in the development of anti-obesity products **[9].**

Inhibition of adipocyte differentiation

Adipocytes are essential for maintaining lipid homeostasis and a healthy energy balance. They have a very significant capacity for both storing triglycerides and releasing free fatty acids as a result of fluctuating energy needs. Because adipocyte hypertrophy and hyperplasia are linked to adipocyte tissue growth, natural products targeting adipogenesis suppression have been developed for anti-obesity therapy. Blocking many transcription factors has also been suggested as a way to prevent adipocyte differentiation **[24].** Figure 2 summarize the anti-obesity mechanisms of natural products

Pre-clinical studies on natural products for the management of obesity

Natural products have been employed in traditional medicine throughout the world since the dawn of time **[16].** Many natural products have been discovered and investigated, which have gained substantial interest for their potential in the creation of innovative anti-obesity agents as these products have the ability to control many biological targets with fewer adverse effects **[16, 27, 28].** Various bioactive phytochemicals, including unsaturated fatty acids, saponins flavonoids and steroids contribute to the biological effects of these natural agents **[12, 28].** Table 1 represents the pre-clinical studies on the natural products with anti-obesity potential along with their mechanisms of action. While, table 2 represents the chemical structures of the mentioned anti-obesity compounds.

Recent clinical trials on natural products for the management of obesity

Only a few clinical trials have been conducted to date, which are insufficient to determine the therapeutic effects of natural products in obese patients. These natural compounds have exhibited potent anti-obesity effects in both *in-vitro* and *in-vivo* pre-clinical research. However, due to the presence of a complicated biological media within the human body, such findings may dramatically differ from those of clinical trials **[9].** In order to ensure the success of the clinical application of natural products for the treatment of obesity in the future, more clinical trials and ethnopharmacological studies are required to establish the parameters for effectiveness, quality, toxicity, and safety of natural products for the management of obesity. Recent clinical trials of natural products for the management of obesity were listed in table (3).

Table 1. Pre-clinical studies on the natural products with anti-obesity potential

Plant	Family	Organ	Active constituents	Dose	Result	Mechanism of action	Ref.
Moringa oleifera (MO) *Murrya koenigii* (MK) *Curcuma longa* (CL)	Moringaceae Rutaceae Zingiberaceae	leaves leaves rhizome	A novel herbal formulation of aqueous ethanol extracts of leaves of (MO) and (MK) and rhizome of (CL) with ratio of 6: 3 :1, respectively, standardized to (95%) total curcuminoids	250 & 500 mg/kg of the formulation, for 13 weeks	Significant decrease in body fat mass and body weight	Regulation of lipid metabolism by increasing lipolysis	[13]
Vitis vinifera Grapevine	Vitaceae	Leaves	Unsaturated fatty acids, fatty alcohols, phytol, lupeol and phytosterol.	200 mg /kg /day of petroleum ether extract for 12 weeks	Significant decrease in the body weight	Regulation of lipid metabolism	[29]
Terminalia chebula	Combretaceae	Fruit	Phytosterol (stigmasterol & brassicasterol), trans-cinnamic acid and chebulic acid.	50g/kg of fruits ethanolic extract for 9 weeks	Reduction in body weight, serum cholesterol and triglyceride	Inhibition of lipogenesis and increasing lipolysis	[30]
Curcuma longa	Zingiberaceae	Roots	Curcumin	500 g/kg of ethanol extract /day for 12 weeks	Reduction of serum cholesterol, and triglyceride, and decreasing the body weight gain	Increased lipolysis and beta-oxidation, decreased lipogenesis and decreased adipocyte differentiation	[31]
Solanum nigrum	Solanaceae	The whole plant	Polyphenol (gallic acid, epigallocatechin gallate, epicatechin, rutin, catechin and quercetin)	0.5, 1 and 2% of water extract with high fat diet for 10 weeks	Decreasing in body fat and body weight	Increasing the lipolysis and decreasing the lipogenesis	[32]
Alpinia officinarum	Zingiberaceae	Rhizome	Phenolics and flavonoids	3% & 5% ethanolic extract for 6 weeks	Decreased serum triglyceride, total cholesterol, and body weight.	Lipase inhibitory effect	[33]
Alpinia galangal	Zingiberaceae	Rhizome	Galangin	50 mg/kg galangin for 6 weeks	Decreased serum triglycerides LDL, total cholesterol and body weight.	Lipase inhibitory effect	[34]
Camellia sinensis (Green tea)	Theaceae	Flower buds	Saponins, caffeine	125 to 500 mg/kg for 14 days	significantly decreased in food intake, visceral fat weight, liver triglyceride and body weight gain	Increasing the energy expenditure	[35]
Camellia sinensis	Theaceae	-	(−)-Epigallocatechin-3-gallate (EGCG)	1% EGCG in high-fat diet for 4 weeks	Significant decrease in lipid accumulation in adipose tissues, decrease in triglyceride and body weight gain	Lipase Inhibitory effect. Increasing the energy expenditure	[36]
Camellia oleifera	Theaceae	Fruit hull	Triterpenoids and polyphenols	100 to 300 mg/kg ethanol extract for 30 days	Decreased the accumulation of intracellular lipid, epididymal fat, total cholesterol triglycerides and decreased body weight	Increasing the energy expenditure, and inhibiting the lipogenesis	[37]

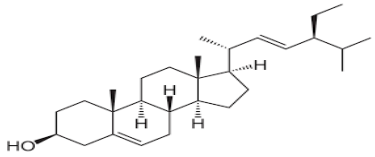
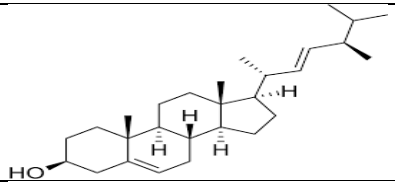
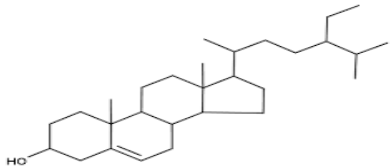
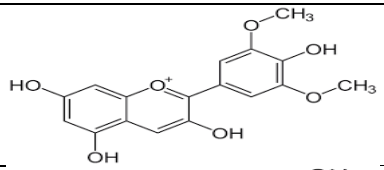
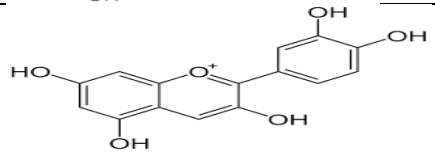
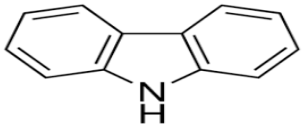
Capsicum annuum	Solanaceae	Seeds	Capsicoside, capsaicin	10 and 100 mg/kg of capsicoside for 7 weeks	Decreased body weight	Inhibition of adipocyte differentiation	[38]
Zanthoxylum piperitum	Rutaceae	Fruits	Alkaloids, flavonoids, terpenoids and aliphatic acid	0.25 to 0.75 ug/mL ethanol extract for 6 weeks	Reduced serum triglyceride, epididymal adipocyte size and body weight gain	Suppression of the lipogenesis.	[39]
Murraya koenigii	Rutaceae	Leaves	Alkaloids carbazole	30 mg/kg/day methanol, ethyl acetate and dichloro-methane extracts for 4 weeks	- Dichloro-methane extract significantly reduced serum triglyceride And total cholesterol. -Reduced body weight gain.	Lipase inhibitory effect.	[40]
Theobroma cacao (Cocoa bean)	Malvaceae	Bean	Polyphenol extract	40 and 200 mg/ kg /day for 5 weeks	Reduction in body weight gain	Suppression of lipogenesis	[41]
Citrus sunki	Rutaceae	Fruit peels	Auraptene synephrine,	150 mg/kg/ day ethanol extract for 70 days	Decreased fats accumulation in the liver tissue, decreased serum triglycerides, total cholesterol, and the body weight	Stimulation of lipolysis, and inhibition of lipogenesis	[42]
Aegle marmelos	Rutaceae	Leaves	Esculetin (E), umbelliferon (U)	300 mg/kg/day of E&U for 4 weeks	Esculetin and umbelliferon decreased the serum glucose, triglyceride and total cholesterol, decreased body weight gain.	Stimulating lipolysis and inhibiting lipogenesis.	[43]
Morus alba (mulberry)	Moraceae	Fruits and leaves	Deoxynojirimycin resveratrol, rutin and anthocyanin,	67 and 167 mg/kg/day fruit extract, 133 and 333 mg/kg/ day leaves extract for 9 weeks	Combined extract of fruit and leaves at high and low doses lowered body weight gain, and reduced the accumulation of fats	Inhibition of adipocyte differentiation and regulation of lipid metabolism	[44]
Vaccinium caesariense (Blueberry)	Ericaceae	Pulp	Purified polyphenol extract	200 mg/ kg body weight/ day for 12 weeks	Significant reduction in body weight gain and reduction in the levels of leptin, LDL and triglycerides	Stimulating the lipolysis	[45]
Rosmarinus officinalis	Lamiaceae	Leaves	Carnosol and carnosic acid,	500 mg/kg/day extract for 16 weeks	Increased the excretion of fecal fat, reduction in total cholesterol and final body weight.	Inhibition of adipocyte differentiation and inhibition of lipase activity.	[46]
Daucus carota Fermented black carrot (FBC)	Apiaceae	Roots	Malvidin and cyanidin	2% (FBC) for 12 weeks	Significant reduction in LDL, triglyceride and body weight gain	Regulation of lipid metabolism, and increasing the expenditure of energy	[47]
Clerodendrum phlomidis	Lamiaceae	Roots	β-sitosterol	100 to 400 mg/kg/day methanolic extract for 13 weeks	Reduction in serum LDL and total cholesterol, and reduced body	Inhibition of adipocyte differentiation, inhibition of lipase	[48]

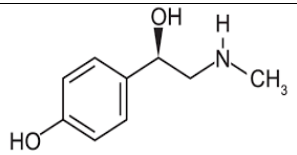
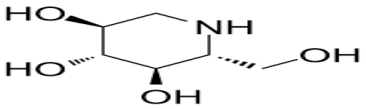
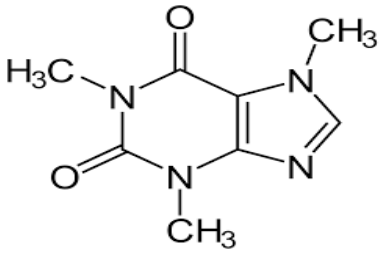
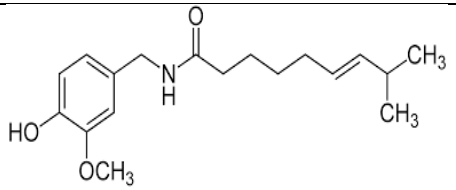
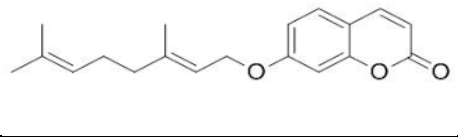
					weight gain and food consumption	activity and inhibition of lipogenesis.	
Allium sativum	Amaryllidaceae	Bulb	Diallyl disulfide	10 and 20 mg/kg/ day of diallyl disulfide for 12 weeks	Reduction of serum total cholesterol and triglycerides levels. Decreased body weight and body weight gain	Inhibition of adipocyte differentiation, suppression of lipogenesis and regulation of lipid metabolism	[49]
Eucommia ulmoides	Eucommiaceae	Leaves	Asperuloside (As)	0.03 to 0.3% of (AS) for 3 months	Decreased serum total cholesterol and triacylglycerol levels. Decreased body weight gain and body weight	Increasing energy expenditure. Inhibition of adipocyte differentiation, suppression of lipogenesis and regulation of lipid metabolism	[50]
Glycine max (soybean)	Fabaceae	seed coat	Anthocyanins	6 and 24 mg/kg of the extract for 40 days	Significant reduction in daily food intake and body weight	Appetite suppression	[51]
Tripterygium wilfordii	Celastraceae	Roots	Celastrol	100 ug/kg celastrol for 16 weeks	Significantly decreased the body weight	Suppression of the appetite and increasing energy expenditure	[52]
Walnut	Juglandaceae	Nut	Polyphneolic extract	200 µg/ g body weight for 8 weeks	Significantly reduction in the body weight	Lipase inhibitory effect.	[53]
Sigesbeckia orientalis	Asteraceae	-	Kirenol	10 to 60 uM kirenol)	Significantly reduction in the accumulation of lipid	Inhibition of adipocyte differentiation, suppression of lipogenesis and regulation of lipid metabolism	[54]
Mangifera indica	Anacardiaceae	Pulp	Pyrogallol polyphenols	2.5, 5, 10, 20 mg/ L for 6 days	Significant reduction in Lipid accumulation	Increasing the lipolysis, and suppression of lipogenesis	[55]
Acorus calamus	Acoraceae	rhizome	β-asarone	0.03 to 0.25 mM β-asarone and 25 to 125 ug/mL calamus oil	Calamus oil showed the highest inhibitory effect of intracellular lipid accumulation. Asarone exhibited the highest inhibitory effect against adipocyte differentiation.	Inhibition of adipocyte differentiation, suppression of lipogenesis and regulation of lipid metabolism	[56]
Coffea arabica (Green Coffee bean)	Rubiaceae	Beans or seeds	Chlorogenic acids Polyphenols, caffeine	0.5- 1.0% of the extract for 2-15 weeks	Significant decrease in the accumulation of fat in the liver, as well as reduction in body weight	Increase Energy expenditure	[57]
Ginko biloba	Ginkgoopsida	Leaves	Biflavones: ginkgetin bilobetin, isoginkgetin,	1, 10, 100 µM of each compound for 40 min	Lipase inhibitory effect with the IC_{50} 2.90 -12.78 μM	Lipase inhibitory effect	[58]
Salicornia herbacea	Amaranthaceae	Entire plant	Isorhamnetin 3-O-β-D-glucopyranoside	1 to 20 uM of the isolated compound	Reduction of the lipid accumulation.	Inhibition of adipocyte differentiation, suppression of lipogenesis	[59]

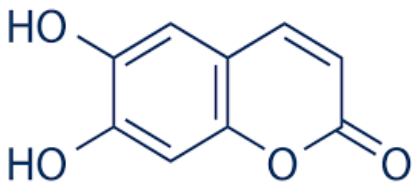
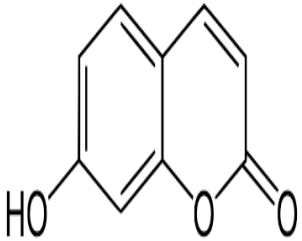
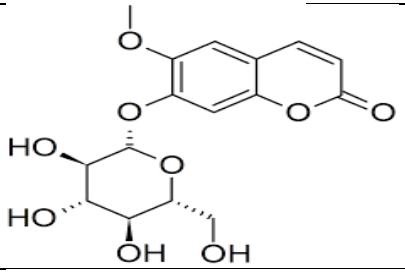
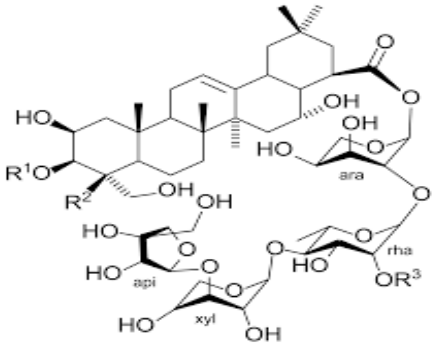
Vitis rotundifloia	Vitaceae	fruit	Anthocyanin	100 µL of the extract for 30 min	The methanol extract showed Lipase inhibitory effect with the IC_{50} =16.90	Lipase inhibitory effect	[60]
Cinnamomum zeylanicum	Lauraceae	Bark	Eugenol, cinnamic acid, and cinnamaldehyde.	2 g/day of the extract for 12 weeks.	Significant decrease in body weight and fat mass	Suppression of lipogenesis and inhibition of adipocyte	[61]
Cirsium setidens	Asteraceae	Leaves	Pectolinarin	25 to 200 mg/kg/day ethanol extract for 8 weeks	Significant reduction in body weight gain, and in the levels of total cholesterol and triglycerides	Inhibition of adipocyte differentiation, suppression of lipogenesis and regulation of lipid metabolism	[62]
Cuscuta pedicellata	Convolvulaceae	aerial parts	quercetin aromadendrin kaempferol naringenin	10 mg/kg isolated compounds and 400 mg/kg ethanol extract, for 4 weeks	Significant decrease in serum lipid profile and body weight	Increase Energy expenditure	[63]
Chrysanthemum indicum	Asteraceae	Fruit	Cynarine quercitrin	2 to 50 mg/kg ethanol extract	significant decrease in serum triglyceride and total cholesterol levels, decreased body weight gain	Increase Energy expenditure, suppression of lipogenesis and regulation of lipid metabolism.	[64]
Carissa carandas	Apocynaceae	Bark	Baicalein, chrysin and oroxylin A	250µg/mL dose 50µg/mL	suppress pancreatic lipase decrease fat accumulation	Lipase inhibitory effect Inhibition of adipogenesis	[65]
Atractylodes lancea	Asteraceae	Rhizome	Polyacetylenic compounds	250 and 500 mg/kg ethanol extract for 4 weeks	Significant reduction in the body weight gain.	Regulation of lipid metabolism. Inhibition of pancreatic lipase	[66]
Crocus sativus	Iridaceae	Flower	Crocin	25 to 100 mg/kg for 10 days	Significant decrease in the level of serum LDL, total cholesterol and triglyceride.	Lipase inhibitory effect	[67]
Artemisia iwayomogi	Asteraceae	Aerial parts	Chlorogenic acids Scopolin,	0.1 to 0.5% ethanol extract for 10 weeks	Significant reduction in serum lipid profile and in weight gain	Stimulation of fatty acid oxidation, inhibition of lipogenesis and inhibition of adipocyte differentiation.	[68]
Panax ginseng,	Araliaceae	Berries Roots	Saponins (protopanaxatriol protopanaxadiol,)	50mg/kg for 3 weeks. 200 mg/kg 3 weeks	Decreased fat content, food intake, and body weight	Lipase inhibitory effect and appetite suppression.	[69] [70]
Allium cepa	Amaryllidaceae	onion peel	Quercetin	0.72 and 0.36 % onion peel extract for 8 weeks	Reduced body weight, decreased intracellular triglyceride content and decreased fat accumulation.	Inhibition of adipocyte differentiation, suppression of lipogenesis and regulation of lipid metabolism.	[71]
Salvia officinalis	Lamiaceae	Leaves	Carnosol and carnosic acid	500 and 1000 mg/kg for 14 days	Decreased the body weight gain, and the elevated triglycerides levels.	Lipase inhibitory effect	[72]

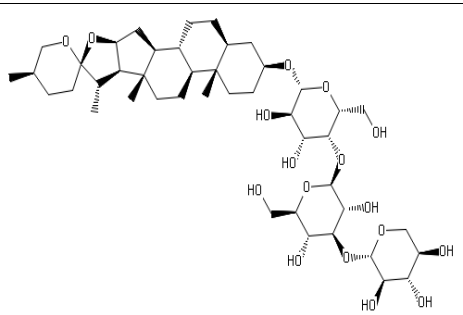
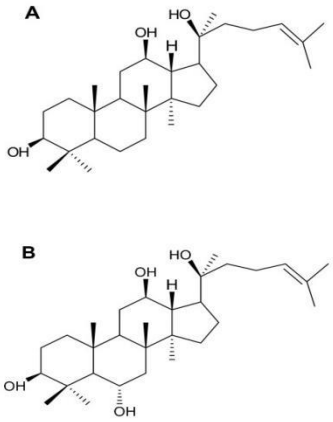
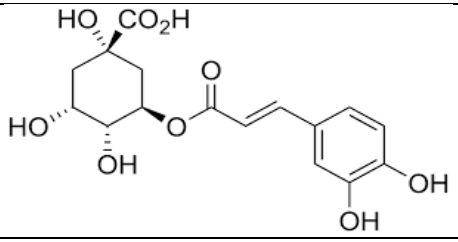
Salicornia europaea	Amaranthaceae	Aerial parts	Trans-ferulic acid	250, 500 mg/kg/day dried powder for 12 weeks	Reduction in lipid profile, final body weight, and in abdominal fat mass.	Inhibition of adipocyte differentiation.	[73]
Salix matsudana (Chinese willow)	Salicaceae	Leaves	Chrysoeriol-7-O-D-glucoside, apigenin-7-O-D-glucoside and luteolin-7-O-D-glucoside	50 to 200 µg/ml for 9 weeks	Reduction in body weight gain and in fat accumulation	Lipase inhibitory effect	[74]
Achyranthes bidentata	Amaranthaceae	Roots	Rutin, O-coumaric acid	0.5 g/ kg/day aqueous extract for 6 weeks	Decreased body weight gain, body weight, triglyceride level, and fat accumulation	Inhibition of adipocyte differentiation, suppression of lipogenesis and regulation of lipid metabolism.	[75]
Achyranthes aspera	Amaranthaceae	Seeds	Saponins	900 mg/kg ethanol extract for 2 weeks	Decreased serum lipid profile, body weight and the body weight gain.	Regulation of lipid metabolism.	[76]
Platycodi radix	Campanulaceae	Root	Platycodin	5% aqueous extract for 8 weeks	Reduction of parametrial adipose tissue weights, and body weight.	Lipase inhibitory effect	[77]
Coffea Arabica (Green Coffee bean) *Zingiber officinale (Ginger)* *Cinnamomum zeylanicum (Cinnamon)*	Rubiaceae Zingiberaceae Lauraceae	Beans Rhizome Bark	chlorogenic acids volatile oils including zingerone shogaol, gingerol, and zingiberene Eugenol, cinnamic acid, and cinnamaldehyde,	The isolated powder (200mg/kg for each), and the combined 200mg/kg in the ratio 50, 30, and 20 % green coffee, cinnamon and ginger, respectively, for 6 weeks.	The combined administration exhibited more potent effects in reduction of the serum lipid profiles, and in body weight	Appetite suppression and increasing energy expenditure	[78]
Chenopodium quinoa	Amaranthaceae	Seeds	20-hydroxyecdysone (20E)	6mg/kg/ day of methanol extract for 3 weeks	Decrease in the weight of subcutaneous and epididymal adipose tissue	Lipase inhibitory effect and regulation of lipid metabolism.	[79]
Garcinia cambogia	Hypericaceae	Fruit	hydroxycitric acid	10 ml/kg for 14 days	Reduce body weight	Appetite suppression, and decreasing the lipogenesis	[80]

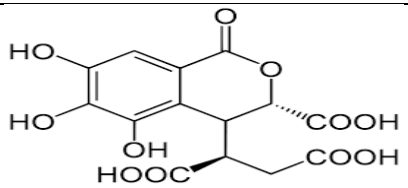
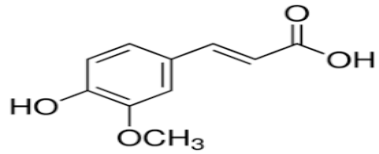
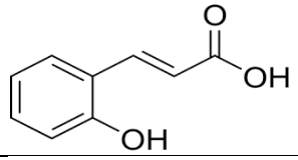
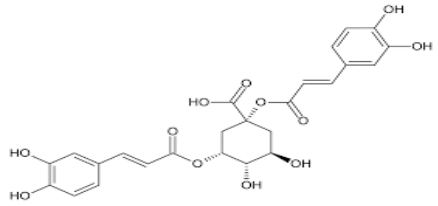
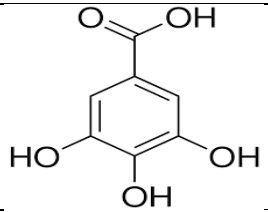
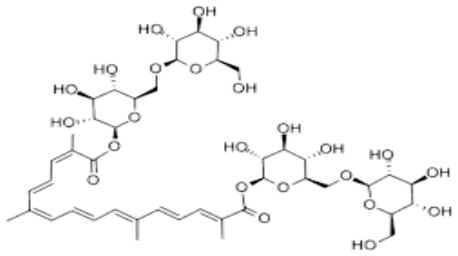
Table 2. The plant derived anti-obesity compounds.

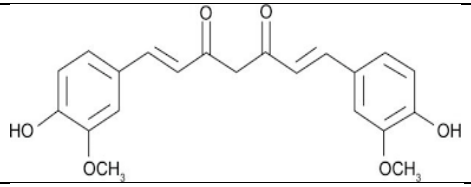
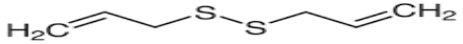
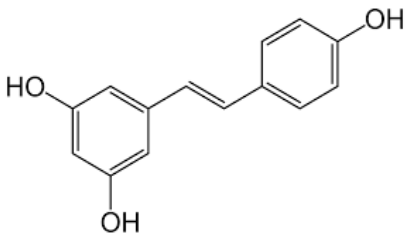
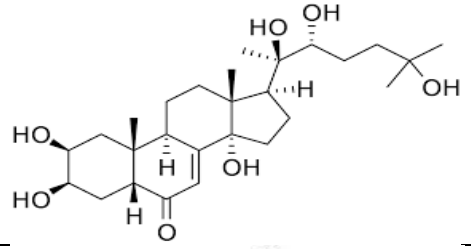
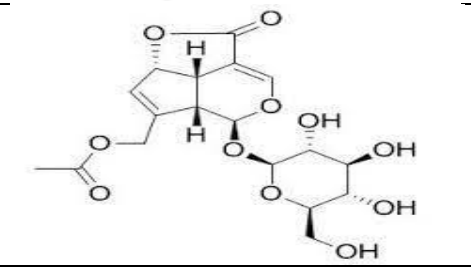
Classes	Compounds	Chemical structures	Source	Ref.
Phytosterol	Stigmasterol		*Terminalia chebula*	[30]
	Brassicasterol		*Terminalia chebula*	[30]
	β-sitosterol		*Clerodendrum phlomidis*	[48]
Anthocyanins	Malvidin		*Daucus carota*	[47]
	Cyanidin		*Daucus carota*	[47]
	Carbazole		*Murraya koenigii*	[40]

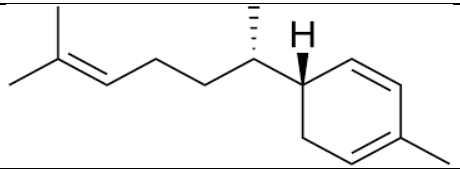
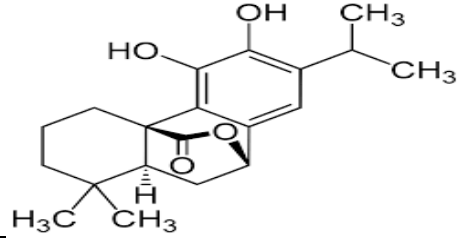
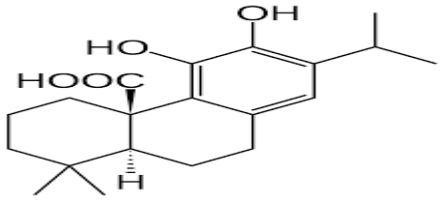
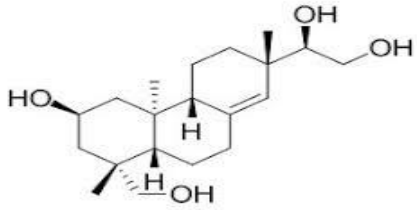
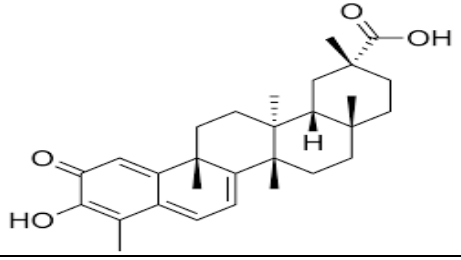
Alkaloids	Synephrine		*Citrus sunki*	[42]
	Deoxynojirimycin		*Morus alba*	[44]
	Caffeine		*Camellia sinensis* *Coffea arabica*	[35] [57]
	Capsaicin		*Capsicum annuum*	[38]
Coumarins	Auraptene		*Citrus sunki*	[42]

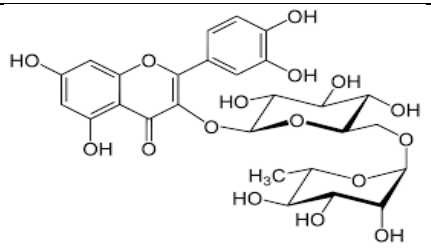
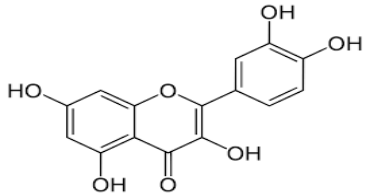
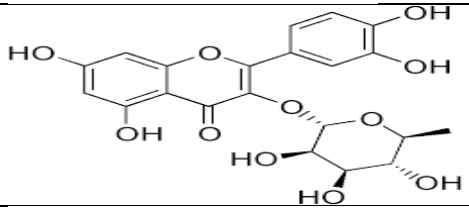
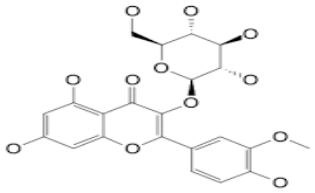
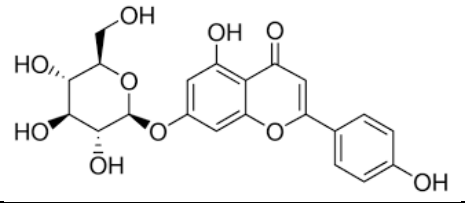
	Esculetin		*Aegle marmelos*	[43]
	Umbelliferon		*Aegle marmelos*	[43]
	Scopolin		*Artemisia iwayomogi*	[68]
Saponins	Platycodin		*Platycodi radix*	[77]

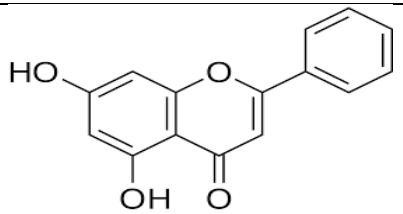
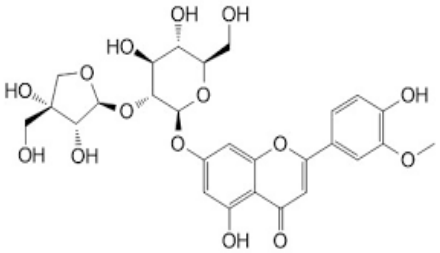
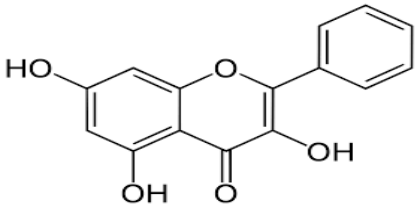
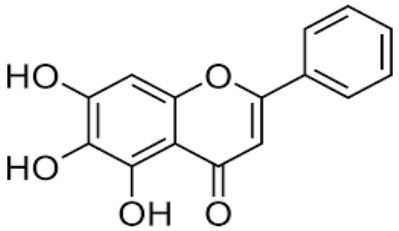
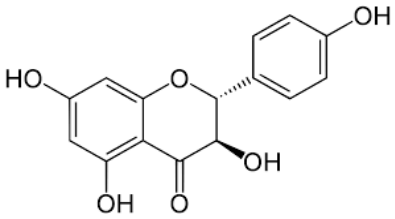
	Capsicoside		*Capsicum annuum*	[38]
	A. Protopanaxadiol B. Protopanaxatriol		*Panax ginseng*	[69, 70]
	Chlorogenic acids		*Coffea arabica* *Artemisia iwayomogi*	[57] [68]

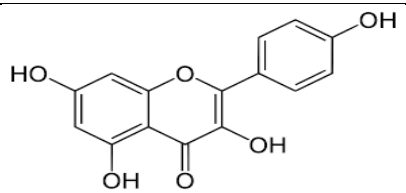
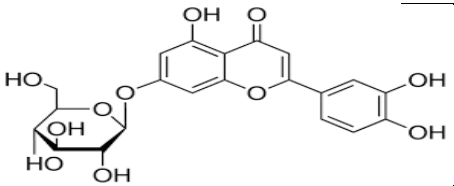
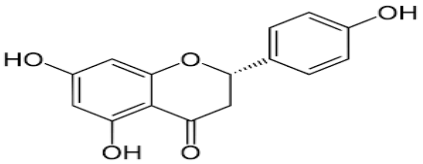
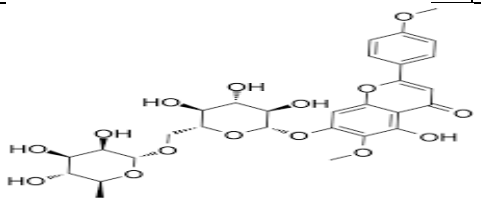
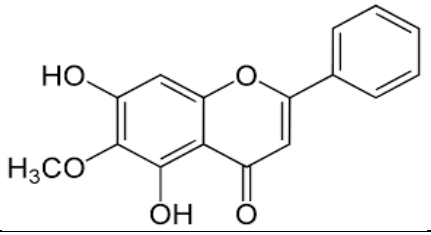
Phenolic acids	Chebulic acid		*Terminalia chebula*	[30]
	Trans-ferulic acid		*Salicornia europaea*	[73]
	O-coumaric acid		*Achyranthes bidentata*	[75]
	Cynarine		*Chrysanthemum indicum*	[64]
	Gallic acid		*Solanum nigrum*	[32]
Carotenoids	Crocin		*Crocus sativus*	[67]

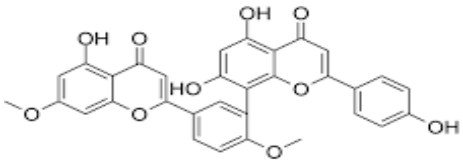
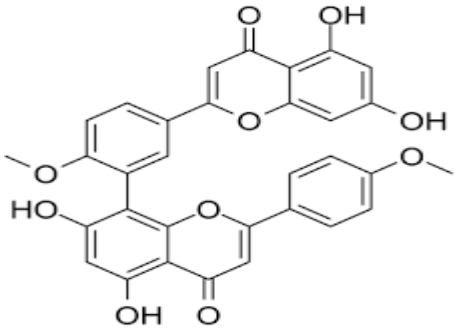
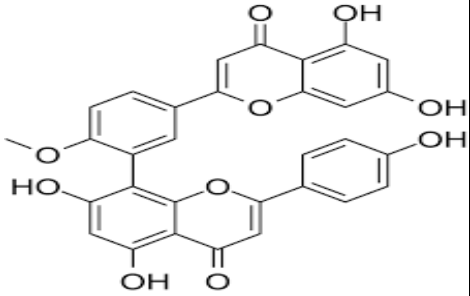
Curcuminoids	Curcumin		*Curcuma longa*	[31]
Organosulfur compounds	Diallyl disulfide		*Allium sativum*	[49]
Stilbenoids	Resveratrol		*Morus alba*	[44]
Steroid hormones	20-hydroxyecdysone		*Chenopodium quinoa*	[79]
Terpenoids Iridoid monoterpenoid	Asperuloside		*Eucommia ulmoides*	[50]

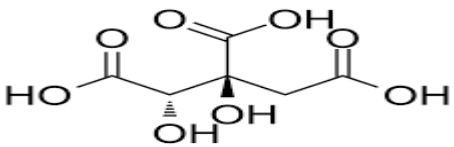
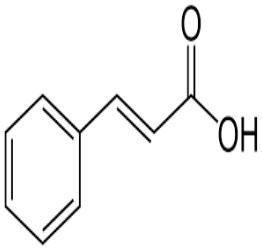
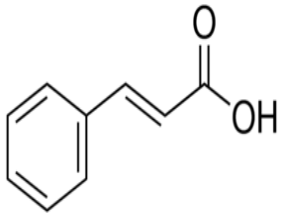
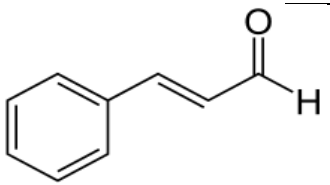
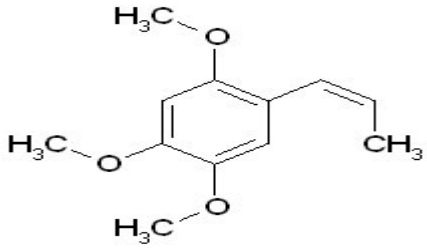
A monocyclic sesquiterpene	Zingiberene		*Zingiber officinale*	[78]
Diterpenoids	Carnosol		*Rosmarinus officinalis* *Salvia officinalis*	[46] [72]
	Carnosic acid		*Rosmarinus officinalis* *Salvia officinalis*	[46] [72]
	Kirenol		*Sigesbeckia orientalis*	[54]
Triterpenoids	Celastrol		*Tripterygium wilfordii*	[52]

Flavonoids	Rutin		*Solanum nigrum* *Morus alba* *Achyranthes bidentata*	[32] [44] [75]
	Quercetin		*Solanum nigrum* *Cuscuta pedicellate* *Allium cepa*	[32] [63] [71]
	Quercitrin		*Chrysanthemum indicum*	[64]
	Isorhamnetin 3-O-β-D-glucopyranoside		*Salicornia herbacea*	[59]
Flavonoids	Apigenin-7-O-D-glucoside		*Salix matsudana*	[74]

Flavonoids	Chrysin		*Carissa carandas*	[65]
	Chrysoeriol-7-O-D-glucoside		*Salix matsudana*	[74]
	Galangin		*Alpinia galangal*	[34]
	Baicalein		*Carissa carandas*	[65]
	Aromadendrin		*Cuscuta pedicellata*	[63]

	kaempferol		*Cuscuta pedicellata*	[63]
	Luteolin-7-O-D-glucoside		*Salix matsudana*	[74]
	Naringenin		*Cuscuta pedicellata*	[63]
	Pectolinarin		*Cirsium setidens*	[62]
	Oroxylin A		*Carissa carandas*	[65]

Flavonoids (Biflavonoids)	Ginkgetin		*Ginko biloba*	[58]
	Isoginkgetin		*Ginko biloba*	[58]
	Bilobetin		*Ginko biloba*	[58]

Organic acid	Hydroxycitric acid		*Garcinia cambogia*	[80]
Phenyl-propanoids	Cinnamic acid		*Cinnamomum zeylanicum*	[61]
	Trans-cinnamic acids		*Terminalia chebula*	[30]
	Cinnamaldehyde		*Cinnamomum zeylanicum*	[61]
	β-asarone		*Acorus calamus*	[56]

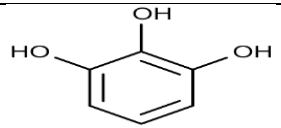
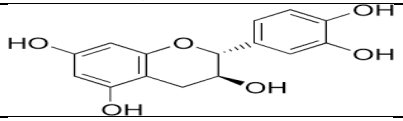
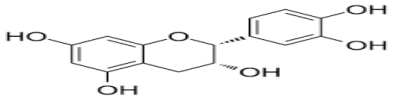
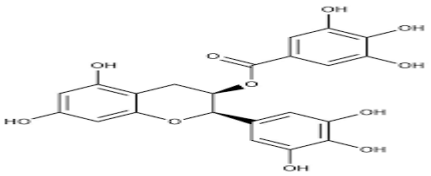
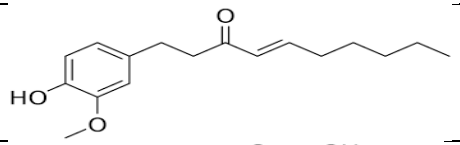
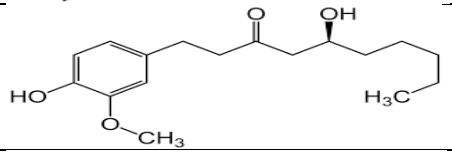
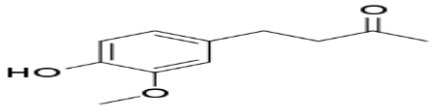
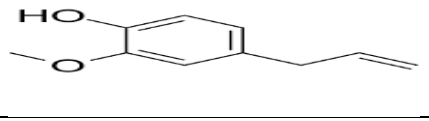
Phenolic Compounds	Pyrogallol		*Mangifera indica*	[55]
	Catechin		*Solanum nigrum*	[32]
	Epicatechin		*Solanum nigrum*	[32]
	Epigallocatechin gallate		*Solanum nigrum* *Camellia sinensis*	[32] [36]
	Shogaol		*Zingiber officinale*	[78]
	Gingerol		*Zingiber officinale*	[78]
	Zingerone		*Zingiber officinale*	[78]
	Eugenol		*Cinnamomum zeylanicum*	[61]

Table 3. Recent clinical trials of natural products for the management of obesity

Plant	Family	Active constituents	Dose and duration	Model	Result	Mechanism of action	Ref.
Coffea arabica	*Rubiaceae*	A standardized extract from green coffee beans (CGA-7), containing not less than 50% chlorogenic acids CGAs), contains seven isomers of (CGAs), the major constituent is 5-caffeoylquinic acid	500 mg of CGA-7/ day for 12 weeks	71 healthy overweight individuals	significant reduction in body weight and BMI as well as, significant decrease in body fat (%)	Regulation of lipid metabolism through stimulation of AMP-activated protein kinase (AMPK)	[81]
Euterpe edulis Mart.	Arecaceae	Pulp rich in anthocyanin	5 g of pulp powder /day orally for 6 weeks	35 obese individuals	Significant increase in HDL cholesterol significant decrease in body fat	Regulation of lipid metabolism	[82]
Zingiber officinale	Zingiberaceae	Ethanolic extract of ginger rich in 6-shogaol contents (5.89–8.83 mg/g)	200 mg /day for 12 weeks	80 obese females	significant reduction in body fat level and body mass index	Inhibition of adipocyte differentiation	[83]
Gnetum gnemon L.	Gnetaceae	Ethanolic extract of seed rich in resveratrol derivatives	150 and 300 mg/day for 14 days	42 healthy young males	Increase in the adiponectin level	Regulation of lipid metabolism	[84]
Lathyrus aphaca	Fabaceae	The hulls of yellow peas rich in fiber (82%)	15 g /day for12 weeks	50 obese individuals	significant reduction in body fat and weight	Appetites suppression	[85]
Vaccinium caesariense (Blueberry)	Ericaceae	Fruits rich in anthocyanins 12.83 mg/L	50 g / day for 12 weeks	54 obese and overweight individuals	significant decrease in LDLcholesterol, total cholesterol, and body weight	Regulation of lipid metabolism	[86]
Gynostemma Pentaphyllum	Cucurbitaceae	Ethanol extract of leaves rich in gynosaponins (damulin A and B)	450 mg /day for 12 weeks	80 overweight individuals	Significant decrease in body mass index, body fat (%), and total abdominal fat area	Regulation of lipid metabolism	[87]
Lippia citriodora (LC) and *Hibiscus sabdariffa* (HS)	Verbenaceae Malvaceae	Polyphenolic extract with 25% verbascoside and 10% anthocyanins	500 mg of HS (35%) and LC (65%) per day for 8 weeks	46 overweight and obese individuals	Significant decrease in abdominal circumference and body weight	Regulation of lipid metabolism	[88]
Aster spathulifolius	Asteraceae	Ethanol extract of leaves, rich in chlorogenic acid (CGA)	700 mg /day for 12 weeks	obese individuals (n=43)	Significant decrease in body fat mass compared to control group.	Regulation of lipid metabolism	[89]
Persea Americana (A*vocado)*	Lauraceae	Rich in monounsaturated fat and fiber contents	one Hass avocado / day for 12 weeks	51 overweight and obese individuals	Significant decrease in visceral adipose tissues total body fat, and body mass index	Regulation of lipid metabolism	[90]
Glycine max (Black soybean)	Fabaceae	Extract containing 12.58 mg of anthocyanins/ g of extract	2.5 g extract per day through two capsules each orally before	Overweight/ obese individuals (n=63)	Significant decline in waist circumference, hip circumference, triglyceride and LDL cholesterol	Modulation of adipogenesis and lipolysis	[91]

			three daily meals for 8 weeks				
Rhus coriaria (Sumac)	Anacardiaceae	Powdered fruits rich in polyphenols	1000 mg /day for 6 weeks	50 overweight individuals	significant reduction in body mass index and waist circumference	Lipase inhibitory effect	[92]
Paullinia cupana (guarana) *Citrus paradisi* (grapefruit) and *Citrus sinensis* (Red orange)	Sapindaceae Rutaceae Rutaceae	A citrus polyphenolic extract (Sinetrol-XPur), contains (1% to 3%) of natural caffeine, 20% of total flavanones (expressed as naringin) and 90% of total polyphenols (expressed as catechin)	Two capsules of 450 mg dry extract / day for 12 weeks	95 overweight individuals	Significant decrease in abdominal body fat and body weight	Appetite suppression and regulation of lipid metabolism	[93]
Camellia sinensis (Green tea)	Theaceae	Epigallocatechin gallate EGCG	856.8 mg / day for 12 weeks	77 overweight and obese individuals	Significant decrease in low-density lipoprotein cholesterol, total cholesterol level, and body weight	Appetite suppression	[94]

Conclusion

A wide range of natural-source materials, as well as their active components, have been examined as a source of natural anti-obesity agents. Plants, including herbs, vegetables, fruits and seeds, are the primary source of these natural materials. The presence of a large number of phytochemicals, unsaturated fatty acids and fibers, in these natural materials is primarily responsible for their biological advantages. The most prominent section of the functional supplement industry is the development of functional products based on what people consume in their daily life. It is more acceptable and safer for consumers to choose products manufactured from natural materials**.** However, more researches are needed to determine the anti-obesity mechanisms at the molecular level, as well as to pinpoint the phytoconstituents responsible for the anti-obesity effects. In addition, more ethnopharmacological researches are needed to determine the safety profile of each natural substance prior to clinical trials. In the future, natural products will be the main source for the production of safe, and effective anti-obesity drugs. Future research in the field of novel anti-obesity agents is expected to be particularly interesting, as there are still a number of plants that have yet to be identified and investigated around the world. As a result, scientific study should be pursued to discover more chances where natural products can be directly extrapolated to humans, as well as to create adequate evidence that natural products can be used as novel effective therapeutic techniques for the management of obesity.

Conflicts of Interest

The author declares no conflict of interest.

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