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Review Article

The Golden Role of Natural Products in Obesity

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ABSTRACT:
Objective: Obesity is considered a serious syndrome that can have a negative impact on the whole systems in the body which leads to many health problems, such as osteoarthritis, heart disease, diabetes, and certain cancers. Up to date reports revealed that there are more than 700 million obese people throughout the world. However, surgery and synthetic drugs may be a choice for the treatment of obesity; they showed unsatisfying results with serious adverse effects. So the best option for the management of obesity is a lifestyle modification together with using natural alternatives that showed the minimal side effects. Natural Products are rich of bioactive compounds that have been used as traditional medicine. Some active natural products were tested by clinical trials and they showed a powerful impact in the treatment of obesity.
Aim: This review is focused on the recent advances in the natural products as anti-obesity potential. A major focus is to highlight the mechanisms of action of natural products as anti-obesity agents, as well as the structure-activity studies, preclinical and clinical trials were also discussed.
Results: The current review revealed that natural products include diversity of phytoconstituents that play an important role in the treatment of obesity.

Keywords: Anti-obesity, bioactive compounds, natural products, Obesity.

1. INTRODUCTION

Obesity is a medical condition in which excess body fat accumulates as a result of imbalance between energy intake and energy expenditure [1]. It is a major public health problem that leads to many diseases, including type 2 diabetes mellitus, hypertension, dyslipidemia, coronary heart disease, some cancers, osteoarthritis, kidney disease, and sleep disorders [2]. Body mass index is used to identify excess weight and obesity based on epidemiologic research. Particularly in females, there is a relation between body mass indexand lifestyle. Body mass index can be calculatedby dividing the weight (kg.) by the height square (cm), Values between 18.5 to 24.9 is normal, while low weight if it lower than, 18.5 and values of 25 and above are considered as obese [3]. Obesity is the major public health problem with about 1.9 billion adults (18 years and older) worldwide are overweight and about 600 million of them are clinically obese [4]. Annually, 30 million people die worldwide due to obesity and overweight [3]. Besides weight loss diet, exercise, and behavioral changes, using anti-obesity drugs have been reputed as a weight loss strategy in overweight and obese individuals. For the treatment of obesity, synthetic pharmaceutical drugs are used imposing high price and many complications. For this reason, patients and researchers are looking for alternative treatment methods such as the use of medicinal plants and their products for the treatment of obesity [5]. So the best option for the management of obesity is a lifestyle modification together with using natural alternatives that showed the minimal side effects. Natural Products are rich of bioactive compounds that have been used as traditional medicine. Some active natural products were tested by clinical trials and they showed a powerful impact in the treatment of obesity [6]. The main objective of this review is to focus on the recent advances in the natural products as anti-obesity potential. A major focus is to highlight the mechanisms of action of natural products as anti-obesity agents, preclinical and clinical trials were also discussed.

2.OBESITY

2.1. Definition

As it is a significant contributor to the global burden of chronic diseases such as; different types of cancer, type 2 diabetes mellitus and cardiovascular disease, obesity is currently one of the major public health issues. Obesity is a medical disorder, it is found as a result of imbalance between energy consumption and energy spending that leads to accumulation of excess body fat [1].

2.2. Classification

There are various methods for measuring the obesity, but the most widely-used method is Body Mass Index (BMI). Body mass index can be determined by dividing the weight (kg.) by the square of the height (cm). BMI is not a percentage of body fat. BMI is only part of a diagnosis of obesity [3].

2.2.1. Overweight

Having a BMI in the overweight range (25.0-29.9) is a health concern. Excess weight is hard on your body. It can lead to other health problems including obesity. People who have a BMI in the overweight range and have other health problems (such as type 2 diabetes or heart disease) need to see their healthcare provider for treatment options [7].

2.2.2. Obesity

Obesity is a disease where a person's weight is in an unhealthy range (BMI of 30.0-39.9). It is a disease that can lead to other health problems [7].

2.2.3. Severe Obesity

The person with BMI greater than 40 is considered as severe obesity case. Severe obesity has the greatest risk of other health problems. People with severe obesity need to see their healthcare provider for treatment options [7]. Increased weight circumference can also be a marker for increased risk even in persons of normal weight.

2.3. Causes

The weight of an individual is determined by the balance between intake of calories and energy consumption. The person gains weight if he eats more calories than he burns.A person will lose weight if he eats less calories than he metabolizes. Hence, physical inactivity and overeating are the most common causes of obesity [8, 9].

2.3.1. A diet high in simple carbohydrates

Blood glucose levels are elevated by carbohydrates , that activate pancreas to release insulin , and insulin stimulates the development of fat tissue and may induce weight gain. Some researchers suggest that simple carbohydrates lead to weight gain because they are absorbed into the bloodstream more easily than complex onesresulting in more insulin being released **[1].**

2.3.2. Genetics

When one ore both parents are obese, person is more likely to develop obesity.Hormones involved in fat control are also affected by genetics.For instance, leptin deficiency is one genetic cause of obesity. When body fat reserves are too high, leptin controls weight by signaling the brain to eat less. If, for some cause, the body cannot produce enough leptin or leptin cannot signal the brain to eat less, this control is lost, and obesity occurs. The role of leptin replacement as a treatment for obesity is under exploration [8].

2.3.3. Effect of drugs

Medications associated with weight gain include certain antidepressants, anticonvulsants (medications used in controlling seizures such as carbamazepine and valproate , some diabetes medications (medications used in lowering blood sugar such as insulin, sulfonylureas, and thiazolidinediones), certain hormones such as oral contraceptives, and most corticosteroids such as prednisone. Some high blood pressure medications and antihistamines cause weight gain. The reason for the weight gain with the medications differs for each medication [8].

2.3.4. Physical inactivity

Active people burn more calories than sedentary people. There is a strong correlation between physical inactivity and weight gain in both sexes [10].

2.3.5. Overeating

Overeating leads to weight gain, especially if the diet is high in fat. Foods high in fat or sugar (for example, fast food, fried food, and sweets) have high energy density (foods that have a lot of calories in a small amount of food). Epidemiologic studies have shown that diets high in fat contribute to weight gain [11].

2.3.6. Frequency of eating

The relationship between frequency of eating (how often you eat) and weight is somewhat controversial. There are many reports of overweight people eating less often than people with normal weight. Scientists have observed that people who eat small meals four or five times daily, have lower cholesterol levels and lower and/or more stable blood sugar levels than people who eat two or three large meals daily. One possible explanation is that small frequent meals produce stable insulin levels, whereas large meals cause large spikes of insulin after meals [12].

2.3.7. Psychological factors

For some people, emotions influence eating habits. Many people eat excessively in response to emotions such as boredom, sadness, stress, or anger. While most overweight people have no more psychological disturbances than normal weight people, about 30% of the people who seek treatment for serious weight problems have difficulties with binge eating [12].

2.3.8. Diseases

Some diseases such as hypothyroidism, insulin resistance, polycystic ovary syndrome, and Cushing's syndrome are also contributors to obesity. Some diseases, such as Prader-Willi syndrome, can lead to obesity [9].

2.4. Health problems

People who have obesity, compared to those with a normal or healthy weight, are at increased risk for many serious diseases and health conditions, including: some types of cancer, cardiovascular disease, low quality of life, gallbladder disease, osteoarthritis, coronary heart disease, type 2 diabetes and dyslipidemia [2].

2.5. Treatment

2.5.1. Lifestyle Modification

The change in lifestyle includes introduction of behavioral and dietary changes that can be sustained indefinitely to promote health [13].

2.2.1. Dietary interventions

Dietary interventions for obesity are designed to create a negative energy balance (i.e., calories ingested < calories expended) by reducing daily energy intake below energy requirements. Uniformly, however, greater energy deficits result in greater weight losses [14].

2.2.2. Physical activity

The physical activity causes improving cardiovascular fitness, sparing fat-free mass during weight loss and increasing in calorie expenditure. Physical activity, however, produces minimal weight loss in the absence of caloric restriction. The greatest benefit of physical activity is in facilitating the maintenance of weight loss. Case studies have shown that people who exercise regularly are more successful in maintaining weight losses than are those who do not exercise [15].

2.2.3. Medications

As BMI or disease risk increase, more intensive options are available for the treatment of obesity. Pharmacotherapy is recommended for individuals with a BMI ≥30 kg/m^2. Two medications—sibutramine (Meridia) and orlistat (Xenical)—are approved by the Food and Drug Administration for the induction and maintenance of weight loss[16].There are several barriers, however, to the long-term use of weight loss medications, including findings that most patients must pay out-of-pocket for anti-obesity agents[17].

2.2.4. Surgical Interventions

Bariatric surgery is appropriate only for those individuals with a BMI ≥40 kg/m^2 or BMI ≥35 kg/m^2 in the presence of comorbidities [18]. The two most common surgical procedures for obesity are vertical banded gastroplasty (VBG) and gastric bypass (GB). Both entail isolating a small (15- to 30-ml) pouch of stomach with a line of staples, thereby drastically limiting food intake. In VBG, the pouch empties into the remaining stomach, where the digestive process continues as normal. GB, however, not only restricts food intake, but also reduces absorption by bypassing the remaining stomach and 45–150 cm of small intestine. Bariatric surgery produces significant improvements in hypertension, asthma, sleep apnea, and diabetes. Improvements in mood have also been reported, but they appear to wane with time [19].

2.2.5. A new approach for the treatment

Actually, medications for the treatment of obesity are of two types; orlistat, which inhibits the absorption of fat via pancreatic lipase inhibition, and subutramine which is an appetite suppressant. Both medications induce complications such as; constipation, insomnia, headache dry mouth and increased blood pressure .In 1997, the US FDA approved subutramine for the treatment of obesity. But in 2010due to increased cardiovascular events and strokes, the drug was withdrawn from the market. Some medications can be abused such as diethylpropion and phentermine and hence are approved for short term use. So the conventional therapy of obesity mainly involves synthetic moieties and surgical procedures, which has many harmful side effects and chances of recurrence with severity. At the present, using anti-obesity drugs from natural products is in need because of the high cost and complications of synthetic drugs [4, 8].

2.2.6. Natural Products against obesity

This review focus on natural phyto extracts with their mechanism of action and their preclinical experimental model for further scientific research. Table 1 showed some important developments in the field of natural drug developments. The various phytoconstituents from these plants have shown more than one type of anti-obesity mechanisms including; increasing expression of PPAR-α and PPAR- β, inhibition of ghrelin, reducing accumulation of white adipose tissue, regulating gene expression, inducing anorexia, pancreatic lipase inhibition and regulating plasma lipid profile . Furthermore, the major mechanism is reducing the lipid levels of plasma followed by suppression the activity of pancreatic lipase enzyme. While, no detailed researches highlight the molecular mechanism for anti- obesity activity. So, researchers have been motivated by the increasing threat of obesity to global health to put more effort into discovering an effective mechanism of action at molecular level.

Table 1: Medicinal plant for anti obesity activity

No.	Botanical name	Family	Plant part	Mode of action	Chemical constituents	Reference
1	*Platycodon grandiflorum*	*Campanulaceae*	Root	Increase lipid metabolism	Platycodins	[20]
2	*Garcinia cambogia*	*Hypericaceae*	Fruit	-Increase Hepatic acyl-CoA oxidase activity and lower the lipid levels	Curcumin,	[21,22]
				-The release and availability of 5-hydroxytryptamine which is responsible for controlling apatite	hydroxycitric acid	
3	*Prunussalicina*	*Rosaceae*	Plums	Suppress adipocyte differentiation ,reduce lipid accumulation ,modulation and regulations of molecular expressions like adenosine monophosphate-activated protein kinase.etc.	Polyphenols, flavonoids	[23]
4	*Glycine hispida*	*Fabaceae*	Whole soyben	Anti-oxidant and pancreatic lipase inhibition, controls serum lipid profile	Flavonoids and phenolic compounds	[24]
5	*Limonia acidissima*	*Rutaceae*	Bark	Anti-adipogenic effect and pancreatic lipase inhibition ,inhibition of PPARγ and C/EBPα, major adipogenic transcription factors, in 3T3L-1 preadipocytes	Flavonoids -oroxylin A, chrysin and baicalein	[25]
6	*Salix matsudana* (Chinese willow)	*salicaceae*	Leaves	Reduce plasma triglycerol levels and hepatic total cholesterol content ,also enhance nor-epinephrine induced lipolysis in fat cells	Apigenin-7-O-D-glucoside	[26]
7	*Camellia sinensis*	*Theaceae*	Leaves	Inhibiting the pancreatic lipase activity.	Flavonoids (theaflavin and thearubigins) Epigallocatechin 3-O-gallate (EGCG)	[27]
8	*Carallumafimbriata Wall*	*Asclepiadaceae*	Aerial parts	Reduce body weight gain by increasing water intake and decreasing hypothalamic levels of NPY and ORX peptides	Pregnaneglycosides,tannins and flavonoids	[28]
9	*Acanthopanaxs enticosus*	*Araliaceae*	Whole plant	Reduce serum LDL-cholesterol and liver Triglycerides	Carnitine	[29]
			Fruits	-Pancreatic lipase inhibition	Triterpenoid saponins	[30]
10	*Acanthopanaxs essiliflorus*	*Araliaceae*	Leaves	Pancreatic lipase inhibition	Saponins - lupane-type triterpene triglycosides	[31]
11	*Paulliniacupana*	*Sapindaceae*		Prevents triglycerol accumulation , up-regulation of the anti-adipogenic genes and down-regulation of pro-adipogenic genes	Phenolic compounds, flavonoids, Caffeine	[32]
12	*Salvia officinalis*	*Lamiaceae*	Leaves	Reduce the elevated triglycerides levels, reduced the weight gain of body	Carnosic acid and carnosol	[33]
13	*Gardenia jasminoides*	*Rubiaceae*	Fruit	Inhibition of pancreatic lipase	Crocetin and crocin	[34]
			Flower	Decreases the absorption of fat and cholesterol from the diet by inhibiting the pancreatic lipase activity		[35]
14	*Panax ginseng*	*Araliaceae*	Roots,	Regulates body weight by reducing food intake and regulating pancreatic lipase	Ginseng crude saponins	[36]
			Berries, whole plant	Controls the obesity by inhibiting energy gain , regulating hypothalamic neuropeptides and serum biochemical	(protopanaxadiol, protopanaxatriol)	[37]
15	*Crocus sativus*	*Iridaceae*	Flower	Decreases the absorption of fat and cholesterol from the diet by inhibiting the pancreatic lipase activity	Crocin	[35]
16	*Glycyrrhizauralensis*	*Fabaceae*	Root	Reduce the production of oleic acid by inhibiting pancreatic lipase	Licochalcone A	[38]

17	*Cassia siamea*	*Magnoliaceae*	Bark	Anti-adipogenic effect and pancreatic lipase inhibition	Flavonoids -oroxylin A, chrysin and baicalein	[25]
18	*Nelumbonucifera gaertn*	*Nymphaeceae*	Leaves	Accelerates lipid metabolism ,inhibition of alpha amylase and lipase, lower the serum total cholesterol, triglycerides, low density lipoproteins levels	Phenolic compounds	[39-41]
19	*Aesculus turbinate*	*Sapindaceae*	Seeds	Inhibition of pancreatic lipase	Saponins	[42]
20	*Cudraniatricuspidata*	*Moraceae*	Whole soyben	Anti-oxidant and pancreatic lipase inhibition	Polyphenolic compounds	[24]
21	*Citrus depressa*	*Rutaceae*	Fruits	Reduce white adipose tissue , reduced the plasma triglyceride , decreasing leptin levels	Flavonoids	[43]
22	*Carissa carandas*	*Apocynaceae*	Bark	Anti-adipogenic effect and pancreatic lipase inhibition	Flavonoids chrysin and baicalein	[25]
23	*Coffeaarabica* (Green Coffee bean)	*Rubiaceae*	Beans or seeds	Increase Energy expenditure	Polyphenols,chlorogenic acids	[44,45]
24	*Citrus unshiu*	*Rutaceae*	*Dried peels*	Significant reduction of serum triacylglycerol, total cholesterol through pancreatic lipase inhibition	Flavonoids and phenolic compounds	[46]
25	*Loniceracaerulea*	*Caprifoliaceae*	Whole soyben	Anti-oxidant and pancreatic lipase inhibition, controls serum lipid profile	Flavonoids and phenolic compounds	[24]
26	*Swertiachirayita*	*Gentianaceae*	Bark	Anti-adipogenic effect and pancreatic lipase inhibition	Flavonoids -oroxylin A, and chrysin	[25]
27	*Diospyros kaki*	*Ebenaceae*	Unripe fruit	Significant reduction of serum triacylglycerol, total cholesterol levels, and visceral fat through pancreatic lipase inhibition	Flavonoids and phenolic compounds	[46]
28	*Capsicum annuum*	*Solanaceae*	Flowers	Anti-oxidant and pancreatic lipase inhibition	Flavonoids and phenolic compounds	[47]
29	*Oroxylumindicum*	*Bignoniaceae*	Bark	Anti-adipogenic effect and pancreatic lipase inhibition	Flavonoids	[25]
30	*Acacia mearnsii*	*Mimosaceae*	Bark	Suppression of body weight , maintain plasma glucose & insulin	Polyphenols – catechins	[48]
31	*Capparis decidua*	*Capparaceae*	Bark	Anti-adipogenic effect and pancreatic lipase inhibition	Flavonoids	[25]
32	*Cuscuta pedicellata*	Convolvulaceae		The reduction of insulin resistance and glucose tolerance, improving the cellular energy homeostasis and possession of antioxidant activity	Naringenin , kaempferol ,aromadendrin , quercetin	[1, 49,50]
33	*Zingiber officinale (Ginger)*	Zingiberaceae	rhizomes	Increasing thermogenesis and energy expenditure, increasing the lipolysis, inhibition of the intestinal absorption of dietary fat, and controlling the appetite	volatile oils including zingiberene,gingerol, shogaol, and zingerone.	[51-55]
34	*Cinnamomum zeylanicum*	Lauraceae	Bark	-Significantly reduced fat mass at the dosages of 2 g/d, when administered for 12 weeks. Inhibition of adipocyte by polyphenolic compounds; also they inhibited lipolysis, lipogenesis and intestinal lipid absorption that they tend to lowering weight.	Polyphenolic compounds cinnamaldehyde, cinnamate, cinnamic acid and eugenol	[51, 56-60]

3. CONCLUSION

This review points to the role of natural product in the management of obesity. It revealed that natural products include diversity of phytoconstituents that play an important role in the treatment of obesity. Furthermore, more researches are required to confirm the effect of natural product as anti-obesity agents and to enter the drug discovery field.

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