Review Article

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ANTI-OBESE THERAPEUTICS FROM MEDICINAL PLANTS-A REVIEW

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Abstract: Obesity is a global health problem. It is also known to be a risk factor for the development of metabolic disorders such as type 2 diabetes, systemic hypertension, cardiovascular disease, dyslipidemia, and atherosclerosis. Two different obesity-treatment drugs are currently on the market: Orlistat, which reduces intestinal fat absorption via inhibiting pancreatic lipase; and Sibutramine, an anorectic or appetite suppressant. Both drugs have hazardous side-effects, including increased blood pressure, dry mouth, constipation, headache, and insomnia. For this reason, a wide variety of natural materials have been explored for their obesity treatment potential. These are mainly complex products having several components with different chemical and pharmacological features. This presented review focused on literature covering natural products with anti-obesity activity, including experimental methodologies, active components, and mechanisms of action against obesity.

Keywords: Obesity, Orlistat, Sibutramine, Pancreatic Lipase

INTRODUCTION

Obesity is serious disorder in which one can take in more calories than required by body on a daily basis, those surplus calories will be converted into fat. This type of imbalance continues for an extended period of time, it will lead to overweight or obesity. Obesity is an increasingly serious global problem, not only for the harm it causes in its own right, but also due to the associated health threats, especially type 2 diabetes, systemic hypertension, cardiovascular disease, certain cancers, asthma, and sleep apnea[1,2,3]. Multiple factors have contributed to the obesity epidemic. Social, sensory, cultural, medical, perceptual, conditioning, and developmental influences have combined to disrupt well established feeding controls. Recent research suggests that the rise in obesity is primarily due to altered, sedentary lifestyles, energy-dense diets and low-levels of physical activity. Currently, more than one billion adults worldwide are overweight and at least 300 million of them are clinically obese[4]. The most common causes of obesity are.

Heredity:

Heredity influences the distribution of fat tissue. Generally, heavy newborns grow into heavy adolescents, more so when either parent is overweight. Moreover, weight regulation in the human body depends upon various genetically determined factors such as hormones. Any abnormality in these factors could result in substantial weight gain. Almost 60% of obese people are said to have inherited this condition. There are several genetic conditions that also contribute or lead to weight gain.

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Endocrinological causes:

Some people in rare cases genetically predisposed to obesity due to hormonal imbalance or glandular problems. Cushing syndrome, hypothyroidism, hypogonadism in men and polycystic ovarian syndrome in women, hypothalamic lesions like tumors, infections or severe trauma are some of the genetic causes that are known to lead to obesity.

Medication:

Certain steroidal drugs are now known to accelerate weight gain such as corticosteroids, sulfonylureas for diabetes, steroidal contraceptives and anticonvulsants such as valproate used in epileptic therapy. Antipsychotics, antidepressants, mood stabilizers like lithium are also known to possess the same properties.

Psychological causes:

The relationship between obesity and one's emotional fluctuations is now widely recognized. Several patients reduce depressive symptoms by eating hence they gain weight. Over time this becomes a repetitive process and eventually leads to obesity.

Dietary factors:

The world today is more affluent than it ever was; this means that more people have access to a multitude of dietary options. People nowadays are also less active than their predecessors, however the calorific content of their diet hasn't decreased; instead it has increased. Diets around the world have drastically changed; we have transitioned from a high-protein, high-fat diet to a high-carbohydrate, high-fat diet. Moreover, the consumption of empty-calorie

foods like alcohol, aerated drinks, candies etc. has also risen sharply. All of this, coupled with a sedentary lifestyle, makes the ideal combination for susceptibility to obesity and diabetes.

The mechanism behind obesity:

Adipose tissue was primarily considered an organ used to store energy in the form of triacylglycerols, with secondary functions of insulation and shock absorption. However, within the last several years, adipose tissue is recognized as a functional endocrine organ with the ability to secrete a number of cell-signaling peptides called adipokines. These adipokines act both locally and distally in tissues, and have effects on a large number of bodily functions. These include lipid metabolism, inflammation, atherosclerosis, insulin resistance, reproduction, vascular homeostasis, food intake, thermoregulation, angiogenesis and immune function[5]. Unlike other secretory organs, adipose tissue is located throughout the body, with the contributions of metabolic secretions depending upon the location and size of the adipose tissue[6]. Furthermore, because fat cells have the ability to "network" with other tissues and organs such as skeletal muscle and the brain *via* hormone circulation and sympathetic nervous system activation, adipose tissue is highly integrated into overall metabolism and physiological processes of the body[7].

Adipocyte size and microenvironment may affect the cadre of adipokines secreted by adipocytes. Intra-abdominal adipose tissue appears to produce many of the adipokines in amounts greater than that of fat deposits elsewhere in the body, causing android obesity to be both a symptom of and a diagnostic indicator for MS[8]. Metabolic syndrome in turn is a risk factor for the development of cardiovascular disease, diabetes mellitus, peripheral vascular disease and stroke. Multiple studies have also found circulating adipokines to be contributing factors for increased risk of many types of cancer, including cancers of the breast, colon, kidney and esophagus[9]. The influence of adipokines on insulin sensitivity, glucose metabolism, inflammation and atherosclerosis may provide the molecular link between increased adiposity and development of obesity- related cancers[10]. Production and excretion of several adipokines and other adipose tissue-related hormones, including visfatin, omentin, resistin, insulin, leptin, interleukin- 6 and adiponectin, are significantly altered in obesity[11]. Several of these are pro-inflammatory cytokines that are released from adipose tissue even in the absence of acute injury or inflammation, supporting the characterization of obesity as a disorder of chronic mild inflammation. Significant evidence indicates that these adipokines are associated with the etiology of atherogenesis[12,13]. This review will focus on the role of adipokines in the process of carcinogenesis.

Treatment methods available for Obesity:

Two different types of obesity-treatment drugs are currently available on the market[14]. One of these is orlistat (Xenical), which reduces intestinal fat absorption through inhibition of pancreatic lipase[15,16,17,18]. The other is sibutramine (Reductil), which is an anorectic, or appetite suppressant[19,20]. Both drugs have side-effects, including increased blood pressure, dry mouth, constipation, headache, and insomnia[21,22,23,24]. A number of anti-obesity drugs are currently undergoing clinical development, including centrally-acting drugs (e.g. radafaxine and oleoyl-estrone), drugs targeting peripheral episodic satiety signals (e.g. rimonabant and APD356), drugs blocking fat absorption (e.g. cetilistat and AOD9604), and human growth hormone fragments[25,26]. At present, because of dissatisfaction with high costs and potentially hazardous side-effects, the potential of natural products for treating obesity is under exploration, and this may be an excellent alternative strategy for developing future effective, safe antiobesity drugs[27,28,29]. A variety of natural products, including crude extracts and isolated compounds from plants, can induce body weight reduction and prevent diet-induced obesity. Therefore, they have been widely used in treating obesity[30,31].

Nature as best alternative for Obesity:

Herbs, spices and medicinal plants have been cherished by many ancient cultures for their use in curing common ailments and promoting good health[33]. Dietary spices are a heterogeneous collection of a wide variety of volatile and non-volatile chemicals obtained from dried aromatic parts of plants-generally the seeds, berries, roots, pods, and sometimes leave. Populations that use spices and/or herbs in their diets have been shown to have lower incidences of chronic disease[33]. Naturally occurring phytochemicals present an exciting opportunity for the discovery of newer anti-obesity agents. As per literature indicates numerous bioactive components from nature are potentially useful in obesity treatments.

According to previous studies (Table.1) a variety of natural products, including crude extracts and isolated compounds from plants, can induce body weight reduction and prevent diet-induced obesity. Therefore, they have been widely used in treating obesity[34,35,36]. For thousands of years, tea has been the most widely consumed beverage in Asian countries. Today, the health benefits of tea have gained more recognition from consumers and scientists. Tea has been investigated for its ability to prevent several chronic diseases, including cancer, neurodegenerative diseases and obesity[37]. Polyphenols show strong anti-obesity activity and include apigenin, genistein, and the catechins[38].

Table.1: Medicinal plants with active bioactive compounds

Medicinal Plant	Family	Region	Active part	Reference
Achyrathus aspera	Amaranthaceae	Asia, Africa, Australia and America	Alcoholic extract of this plant at 100mg/kg dose	39
Allium sativum	Alliaceae	Central Asia	Garlic protein (16% of diet) and garlic oil (100mg/kg/day)	40,41
Acorus calamus	Araceae	India	Tannins from this plant at 10mg/kg Alcoholic extracts of roots	42,43
Cissus quadrangularis	Vitaceae	India	Proprietary extract of this plant (CQR-300) at a dose of 300 mg	44
Coleus forskohlii	Lamiaceae	India, Nepal, Sri Lanka, and Thailand	This plant extract (10% forskolin) at a dose of 500 mg	45,46
Commiphora mukul	Burseraceae	Rajputana, Khandesh, Berar, Mysore, Sind and Baluchistan	Guggul an extract from the resin of this tree at a dose of 2160 mg. 50 mg guggulipid	47,48
Garcinia cambogia	Guttifera	Western Ghats in India	Crude ethanol extracts of *G. cambogia* (bitter kola) seeds showed dose-dependent	49,50
Gymnemasylvestre	Asclepiadaceae	Deccan Peninsula and western India	*G. sylvestre* leaf extract at 25-100 mg/kg	51
Hemidesmus indicus	Asclepiadaceae	India	Oral treatment of 2-hydroxy 4-methoxy benzoic acid (HMBA)at 200microgkg-1 Cell culture extract of *H. indicus* (2, 4 and 16 mg/kg, p.o)	52,53
Hibiscus sabdariffa	Malvaceae	WestIndies Cultivated in Uttar Pradesh, Andhra Pradesh, West Bengal, Bihar, Punjab, Assam and Tamilnadu.	Aqueous extract of dried calyces of *H. sabdariffa* at 0.8 ml/kg	54,55
Lagerstroemia speciosa	Lythraceae	Southeast Asia	This plant extract alpha-and beta- penta-O-galloyl-D-glucopyranose (PGG)	56,57
Momordica charantia	Cucurbitaceae	India	5 % lyophilized Bitter melon (*M. charantia*; BM) powder. Oral administration of fruit extract at (150 mg/kg & 300 mg/kg)	58,59
Myristica fragrans	Myristicaceae	Moluccas	ethanol extract of this plant , Seed extract	60,61
Panax ginseng	Aralioideae	Cultivated in Korea, Japan, China, Russia and Germany.	Protopanaxadiol (PD) and Protopanaxatriol (PT) of saponin fractions. Crude saponin (CS) from RG (200 mg/kg, i.p.)	62,63
Panax japonicus	Aralioideae	Japan	Chikusetsu saponins are the active principle	64,65
Piper nigrum	Piperaceae	India, Ceylon	Piperine supplementation at 40 mg piperine/kg	66
Plumbago zeylanica	Plumbaginaceae	India	Ethanolic extract (50% v/v) of root	67
Solanum melongena	Solanaceae	Asia,Africa, Africa and Asia	Flavonoids extracted from the fruits of *S. melongena* at a dose of 1mg/100g BW/day	68
Tamarindus indica	Fabaceae	cultivated and naturalized in the tropics throughout the world	aqueous pulp extract of the plant at 2700-4500mg/kg dose	69
Zingiber officinale	Zingiberaceae	Asia	Aqueous extract of *Z. officinale* at 0.4 ml/kg Ethanolic extract of ginger (200mg/kg)	70,71

Therefore, in this review, we surveyed natural products with anti-obesity potential and reviewed the scientific data, including experimental methodologies, active components, and mechanisms of action against obesity.

Lipase inhibitory effect:

Among treatments for obesity, one of the most promising strategies in the effort to reduce energy intake through gastrointestinal mechanisms, without altering the central mechanisms, is the development of nutrient digestion and absorption inhibitor. Dietary fat is not directly absorbed by the intestine unless the fat has been subjected to the action of pancreatic lipase. Therefore, pancreatic lipase is one of the most widely studied mechanisms for determining natural products' potential efficacy as anti-obesity agents[72].

Pancreatic lipase is a key enzyme in dietary triacylglycerol absorption, hydrolyzing triacylglycerols to monoacylglycerols and fatty acids. Only a few substances interact directly with the lipases themselves. One example is tetrahydrolipstatin (orlistat), a derivative of the naturally-occurring lipase inhibitor produced from Streptomyces toxytricini[73]. Orlistat's lipase inhibition mechanism acts through a covalent bond to the lipase's active site serine[74,75]. Although this pancreatic lipase inhibitor is clinically approved for obesity treatment, orlistat has certain unpleasant gastrointestinal side-effects[76,77]. These side-effects result from orlistat's mode of action and include

oily spotting, liquid stools, fecal urgency or incontinence, flatulence, and abdominal cramping[78]. Therefore, researchers are screening novel inhibitors, derived from plants or other natural sources that lack some of this unpleasant side-effects[79].

Natural products provide a vast pool of pancreatic lipase inhibitors with potential for being developed into clinical products. Birari and Bhutani, 2007 reviewed various extracts and secondary metabolites, derived from plants and microorganisms, that have pancreatic lipase inhibitory activity. Drug development programs should focus on these extracts and metabolites.

Suppressive effect on food intake:

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 researchers to better target their searches for drugs that treat obesity through energy intake reduction[80]. Agents that act via peripheral satiety peptide systems, alter the various hypothalamic neuropeptides' CNS levels, or alter the key CNS appetite monoamine neurotransmitters' levels may be suitable candidates for drugs that will suppress appetite[81]. Any changes a potential appetite suppressant induces should be considered in terms of: (1) the psychological experience and behavioral expression of appetite, (2) metabolism and peripheral physiology, and (3) the CNS neural pathways' functioning[81]. In general, natural appetite suppressants are dietary supplements that aid in appetite control. Appetite suppressant mechanisms of action typically affect hunger control centers in the brain, resulting in a sense of fullness. However, in animals and humans, ghrelin secretion in the stomach may increase with decreased food intake, stimulating increased intake. Therefore, ghrelin antagonism may decrease or blunt the increased appetite that potentially occurs with decreased feeding, and, thus, may be a potential adjunctive treatment for obesity[82]. MCH receptor antagonism may also prove an important target for obesity treatment through appetite regulation.

Stimulatory effects on energy expenditure:

Abundant evidence indicates many rodent models of obesity show reduced energy expenditures, which contribute to the development of obesity, whereas the role of reduced energy expenditure in the promotion of human obesity is much less clear. Excessive adiposity results from an imbalance in energy homeostasis, in which the consequences of excessive food intake are not balanced by increased energy expenditure[83]. Energy expenditure has many components. It can be separated into a number of different categories. The simplest scheme divides energy expenditure into three categories: (1) physical activity, (2) obligatory energy expenditure, and (3) adaptive thermogenesis. To regulate body weight and energy expenditure, mammalian BAT establishes non-shivering thermogenesis through dissipation of excess energy as heat[84]. BAT plays an important role in obesity control by controlling energy balance.

Inhibitory effect on adipocyte differentiation:

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 changing energy demands. Because adipocyte tissue growth can be due to both hyperplasia and hypertrophy of adipocytes, several studies screening for antiobesity materials have focused on the processes of adipocyte proliferation and differentiation[85].

In this search, 3T3-L1 pre-adipocytes cells are currently used as an in vitro model for the study of obesity, because such cells accumulate triglycerides upon differentiating in culture (86). This is due to the expression of adipocytespecific genes, such as PPARc and C/EBPa (87, 88). For this reason, natural products that specifically target adipogenesis inhibition had been considered promising with regard to their potential in treatment of obesity.

In addition to showing inhibitory activity against adipocyte differentiation, several naturally-occurring compounds have displayed apoptotic effects on maturing pre-adipocytes. For example, some phytochemicals, such as esculetin, resveratrol, quercetin, genistein, EGCG, capsaicin, and conjugated linoleic acids induced apoptosis of maturing 3T3-L1 pre-adipocytes through suppression of ERK1/2 phosphorylation, activation of the mitochondrial pathway, AMPK activation, or anti-oxidant activity (89).

Thus, inducing apoptosis in mature adipocytes may be important for treating obesity with naturally-occurring compounds. The cell cycle is closely associated with adipocyte growth and proliferation and is thus an important factor to consider in targeting anti-obesity natural products.

Regulatory effect on lipid metabolism:

The pharmacological targeting of lipolysis can be envisaged in two different ways. The first strategy entails stimulating triglyceride hydrolysis in order to diminish fat stores, thereby combating obesity. This option requires the associated oxidation of the newly released fatty acids and led to the development of the b3-adrenergic agonists (90). However, considering that excessive lipolysis contributes to high circulating fatty acid levels and development of dyslipidemia (as seen in

metabolic syndrome), a blockade of such a fatty acid release may be of therapeutic interest (90). Some examples of the natural compounds involved in b-adrenergic receptor activation are the various flavonoids in the leaves of Nelumbo nucifera (NN). Through this pathway, NN extract dietary supplementation resulted in significant suppression of body weight gain in A/J mice fed a HFD (91). PPARc is a transcription factor predominantly expressed in adipose tissue, and it activates adipocyte differentiation both in vivo and in vitro. When PPARc is overexpressed, 3T3-L1 pre-adipocyte induction begins. This suggests that PPARc suppression blocks adipogenesis and lipogenesis (92). Thus, PPARc agonism leads to the amelioration of lipid abnormalities in dyslipidemic patients. Findings from a number of rodent studies have demonstrated that PPARc agonists can improve insulin resistance, as well as dyslipidemia.

Combined effect for obesity treatment:

As mentioned above, many natural products show anti-obesity activities of varying mechanisms. Perhaps the recommended approach to researching more efficient obesity treatments and achieving the synergistic effects of natural products should be to seek treatments using multiple products or products having multiple activities. Some natural biomaterials possessing multi-functional antiobesity activities have been discovered. Green tea and Garcina cambogia are good examples. Researchers originally found green tea possessed higher anti-oxidant activity than anti-obesity activity, owing to its high concetration of catechins, including epicatechin, ECG, and EGCG. Subsequent research proved the antiobesity activity of catechins resulted from the combined actions of appetite reduction, greater lipolytic activity and energy expenditure, and less lipogenic activity and adipocyte differentiation (93). *G. cambogia* is widely known for its anti-obesity activity (94). Its commercially-available extract is derived from the dried fruit of the *G. cambogia* tree, which grows in the forests of South India and Southeast Asia. Its main active ingredient is (_)-hydroxycitric acid. *G. cambogia* prevents the metabolism of carbohydrates into fats by inhibiting lipogenesis, burning excess fats, and suppressing appetite.

CONCLUSIONS

Anti-obesity pharmacological treatment should be administered only when considered safe and effective for obese subject. Over the past 30 years, few obesity-treatment drugs have been developed or approved. Only two drugs are currently available, and some drugs have been withdrawn from the market due to serious side-effects. Sibutramine and orlistat may cause weight loss of up to 10% when used in combination with dietary, behavioral, and exercise therapy. The need exists for anti-obesity drugs having greater effectiveness, which are better tolerated. In the future, the active exploration of many natural sources may provide hope for new developments based on a growing understanding of the complex and highly redundant physiological mechanisms involved in body fat content regulation. Ideally, such exploration and research will lead to a safer and more effective pharmacological treatment for obesity. It is also worth noting that the United States' FDA is particularly sensitive to anti-obesity claims. Furthermore, any anti-obesity medicine entering the market becomes immediately subject to abuse and overdose.

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