

**OBESITY: ITS COMPLICATIONS AND AVAILABLE MEDICATIONS****OBEZİTE: KOMPLİKASYONLARI VE TEDAVİSİNDE KULLANILAN İLAÇLAR**

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Abstract

Obesity is one of the common metabolic diseases which is tremendously on the rise. According to the World Health Organization (WHO), the number of patients has increased three times since 1975. A person with Body Mass Index (BMI) equal to or higher than 30.0 is considered obese. Previously considered only as a cosmetic concern, obesity has now been shown to be an aggravating element for various diseases and disorders including diabetes and cardiovascular diseases (CVD). The most common drugs subscribed by physicians include orlistat, rimonabant, liraglutide and sibutramine which have been proven to be effective to reduce body fat in patients. However, in the long run, patients have complained about symptoms which are mild like nausea, insomnia and dizziness to severe complications such as increase in risk of heart attack or stroke. The following review provides insights about synthetic drugs, their classification and their side-effects on human health. Furthermore, a gist of natural products i.e. phytochemicals that can be used as an alternative to these synthetic drugs has also been discussed in the review.

Keywords: *Body mass index, obesity, orlistat, sibutramine, phytochemicals, rimonabant*

Öz

Obezite olağanüstü düzeyde bir artış gösteren yaygın görülen metabolik hastalıklardan biridir. Dünya Sağlık Örgütü'ne (WHO) göre, hasta sayısı 1975'ten bu yana üç kat artmıştır. Beden kitle indeksi (BKİ) 30'a eşit veya 30'dan daha yüksek olan bir kişi obez olarak kabul edilmektedir. Daha önce sadece kozmetik bir sorun olarak kabul edilen obezitenin günümüzde diyabet ve kardiyovasküler hastalıklar (KVH) gibi çeşitli hastalıklar ve bozukluklar için ağırlaştırıcı bir unsur olduğu gösterilmiştir. Doktorlar tarafından en çok reçetelenen ilaçlar olan orlistat, rimonabant, liraglutid ve sibutraminin hastalarda vücut yağ oranını azaltmada etkili oldukları kanıtlanmıştır. Bununla birlikte, uzun vadede hastalar bulantı, uykusuzluk ve baş dönmesi gibi hafif semptomlardan ve kalp krizi veya inme gibi ciddi komplikasyonlardan şikayet etmektedir. Mevcut derleme sentetik ilaçlar, bu ilaçların sınıflandırılması ve insan sağlığı üzerindeki yan etkileri hakkında bilgi vermektedir. Ek olarak, bu sentetik ilaçlara alternatif olarak kullanılabilir doğal ürünler olan fitokimyasalların bir özeti de mevcut derlemede tartışılmıştır.

Anahtar Kelimeler: *Beden kitle indeksi, obezite, orlistat, sibutramin, fitokimyasallar, rimonabant*

Introduction

Obesity is tremendously affecting global health in the 21st century, with numbers as high as 400 million clinically obese subjects and 1.5 billion overweight adults. It has been considered as the most common health condition which affects the low-, middle- and high-income countries with the epidemiological concern.¹ Obesity, in simple terms, can be called as a phenomenon in which the bodyweight is higher than the stipulated amount for a specific height of an individual. There is an elevated chance of diseases such as hyperlipidemia, hypertension, diabetes mellitus, colorectal cancer, atherosclerotic cerebrovascular disease, coronary heart disease along with high mortality rate associated with obesity.² The causes of the disease are a multitude, and they are not well known. Obesity is in part a contribution of consumption of high calorie diet than the energy utilization.^{1,2} Other factors capable of causing obesity are food addiction, depression, side effects of pharmaceuticals or personality traits.

Obesity in children is another problem which is growing around the globe at a faster rate.³ Estimation is being made that worldwide, 10% of school-going children (5-17 years) are obese.⁴ Insulin resistance, dysglycemia, fatty liver disease, hypertension, and dyslipidemia are the effects of obesity during childhood; it can greatly also affect organ systems. The increasing commonness of overweight and the major cause for noncommunicable chronic disease (NCDs) is obesity, which accounts for 44% of diabetes, 23% of ischaemic heart disease and 7-41% certain cancer burden.⁵ Nowadays, food consumed by humans has a very high energy value. Intake of fatty foods gives 9kcal/g as compared to 4kcal/g carbohydrates. Thus, food with higher fat content will result in higher energy content. When consuming a high-fat diet, the thermogenic effect induced by the diet is lower than compared to a diet with high carbohydrate and protein, meaning lower expenditure of energy. Because of the lower capability for inducing sufficiency than carbs and proteins, dietary fat usually indicates an increase in energy intake. Increased prevalence of obesity is due to high-fat diets and can trigger the development of hyperglycemia. Normally when consuming dietary fats an individual also consumes a large number of refined carbohydrates which result in the development of visceral adiposity and weight gain, the manifestation of ailments that are linked with obesity, e.g. diabetes and CVD are promoted by high intake of sucrose. The lipids found in the diet contribute to the increased amount of calories.

Obesity and BMI

Obesity is a medical condition which is caused by excess fat storage in the body resulting in harmful effects on the individual's health. BMI or Body Mass Index is broadly used to determine obesity, which includes the parameters of weight-height that specify the quantity of body fat and is used for classification amongst overweight and obese adults.⁶ Obesity increases the chance of getting affected by various diseases, e.g. type 2 diabetes (T2D), bone and joint disease, CVD, osteoarthritis and depression. CVD and T2D are widely associated with a higher BMI, and when compared to white populations, due to higher waist circumference thus for a given body weight the total and central adiposity are higher, south Asians have higher risk.^{7,8,9} Circumferences of waist and hip as well as waist-

hip ratio are other indicators used to measure the regional distribution of fat.

Body Mass Index (BMI)

When the weight of an individual in kilograms is divided by the square of their height in meters, is known as Body Mass Index (BMI). Higher BMI indicates high-fat levels. By measuring an individual's height and weight, BMI can be determined in this BMI Index Chart.

- BMI is less than 18.5, underweight range.
- BMI between 18.5 –<25, normal range.
- BMI between 25 –<30, overweight range.
- BMI is 30 or higher, obese range.

Obesity is normally subdivided into categories:

- Class 1: BMI of 30 to less than 35
- Class 2: BMI of 35 to less than 40
- Class 3: BMI of 40 or more. Class 3 obesity is usually categorized as extreme or severe obesity.

The measure of waist circumference has become more important and deciding the measure of overweight or obesity. It is irrational that the fat in the vicinity of the organs is metabolically active and is also associated with deregulation in metabolism and that the individuals are prone to CVD and related conditions.¹⁰

According to the internationally used guidelines of metabolic syndrome the classification of adults per —a collection of dysmetabolic conditions that makes individuals liable to CVD of which abdominal adiposity is one component—a waist circumference (WC) resulting in increased cardiovascular risk is defined as ≥ 94 cm in European men, and ≥ 80 cm in European women, with different criterion for individuals belonging to other ethnic group (e.g., ≥ 90 and ≥ 80 cm in males and females, respectively amongst most Asian people).¹⁰ Bodyweight classification in children differs from adults; his/her body composition varies greatly during the developmental stage. Due to the difference in sexual development and maturation, there is a further difference between boys and girls. Currently, Child Growth Standards provided by WHO is widely used.

It is necessary to set up a firm attitude and good knowledge about overweight and obesity as these are considered to be related with several chronic disorders such as joint pain, heart disease, and diabetes.⁵ Obesity is also one of preventable disease cause of death. The levels of awareness are insufficient when it comes to risks associated with obesity. Media does not see obesity as a threat even after being suggested by the available evidence,¹¹ In the US during the years 2001-2002, a study among children and adolescents showed that there was a 31.5% risk for overweight, whereas 16.5% were already obese. Another study in England showed a sign of obesity and overweightness among girls aged 7-11 years were 23.6% and for boys of the same age group it was 17%.³

Effects of Obesity

Various diseases and conditions are associated with excessive body weight, resulting in a reduction in life expectancy (Figure 1). Increase in blood flow, hypertension, and cardiac output has been related with obesity-induced disorders. Increased sympathetic tone, hyperinsulinemia (increased insulin levels in the blood),

structural changes in the kidney, activation of the renin-angiotensin system (RAS), and elaboration of adipokines (hormones produced in fat itself) such as leptin are some of the few changes in the pathophysiological condition induce by obesity.



Figure 1. Effects of obesity on human health

The major disorders resulting from obesity have been listed below.

1. **High blood pressure** – more blood is needed to be circulated to the fat tissue because additional fat tissue will require oxygen and nutrients for living. The heart pumps more blood through the remaining blood vessels in order to achieve this task. The pressure on the artery walls also increases due to more circulating blood. Thus, an increase in blood pressure occurs. The ability of the body to transport blood through the vessels is affected due to extra weight gain. Elevated ubiquity of hypertension and an array of associated cardio-renal and metabolic disorders are the consequence observed in an obese or overweight individual. A linear relationship between BMI and systolic and diastolic blood pressure (BP) can be observed in studies of world population.^{12,13} According to the Framingham Heart Study, there is an observation that in 78% of men and 65% of women that surplus weight gain is the primary cause of hypertension.

According to the clinical studies, the effective measure of preventing hypertension is maintaining the BMI < 25kg/m² and in most of the hypertensive subjects the weight loss also reduces the blood pressure.^{13,14} Not all obese people are hypertensive, even though there is striking data to support the role of excessive weight in the increase of blood pressure. The excess weight gain by an individual will shift the blood pressure frequency distribution towards higher level thus increasing the chance that the person's BP will register in the hypertensive range. Even the subject classified as normotensive obese people has blood pressure higher than that they would have at a lower weight and in most of the normotensive and hypertensive obese subjects the loss of weight results in a reduction in blood pressure.¹²

2. **Diabetes**-a chronic disorder capable of changing the metabolism of carbohydrate, protein, and fat is known as Diabetes mellitus (DM). Diabetes is caused by lower or no insulin secretion or due to irregularities in insulin uptake in

the peripheral tissue or due to either the higher or lower insulin production by the β -Langerhans islet cells in the pancreas. Type 1 and type 2 diabetes which are the subcategories of Diabetes mellitus (DM). T2D is mainly caused by obesity. It can be described as the combined result of insulin resistance and low insulin production by pancreatic β -cells.¹⁵ Compared to normal weight, the chance of developing type 2 diabetes for an obese person is by the factor of seven and for an overweight individual the chance of developing T2D by a multiple of three. Earlier it was found in adult but, now it is also found in children.

Excess weight is one of the strong element for the onset of diabetes in all stages of life.¹⁶ An obese person can develop resistance to insulin, the hormone that regulates the blood glucose level. Insulin resistance can lead to an elevation in blood glucose

Even in a healthy individual, obesity can raise the chance of diabetes. Low glucose exchange into the muscle cells, higher fat breakdown and increased amount of fatty acids in the plasma are the results of insulin resistance, thus leading to increase hepatic glucose production. For T2D to develop, malfunctioning of pancreatic cells and must occur simultaneously. Even if an individual is overweight or obese, will only develop diabetes when the degree of insulin resistance is matched by enough lack of insulin secretion, Insulin is not enough to combat with the level of glycemia in such people. It is due to dysfunction of the β -cells the prediabetes progresses to diabetes. The postprandial blood glucose levels increase, once the normal glucose tolerance progress to abnormal glucose tolerance. Thereafter, the failure in the suppression of hepatic gluconeogenesis develops fasting hyperglycemia.

3. **Heart diseases** – Atherosclerosis is observed 10 times more in obese people as compared to that of non-obese people. Atherosclerosis is initiated by hypercholesterolemia making it the risk factor amongst other CVDs. A cascade of highly specific molecular and cellular responses to vascular endothelium initiates chronic inflammatory diseases. The coronary artery disease develops when there is deposition of fat in the arteries transporting blood to the heart. Reduce blood flow and narrowed arteries can result in chest pain or even a heart attack. Due to the given obesity rates, recently the researchers are studying the effect of obesity in early life and following adulthood disease. There is a twofold or greater chance of adult hypertension, coronary heart disease, and stroke because of obesity in childhood or adolescence.¹⁶ The potential health effects of childhood obesity can be offset by weight loss prior to or while entering into adulthood and were confirmed by comparing individuals who were obese in their childhood but in non-obese their adulthood with individuals who were never obese.¹⁷

4. **Joint problems** – As the extra weight is gained, stress is placed on the joints and can affect the hips and knees. It is not advisable to patients who have undergone joint replacement surgery as there is an elevated chance of damage to the joint.

In the USA, an estimated 27 million afflicted adults have been reported to have musculoskeletal conditions with the most prevalent one being Osteoarthritis (OA).¹⁸ Numerous studies have linked obesity to the presence, development, and severity of osteoarthritis. The complication in recovery from joint replacement surgery may be expected along with obesity being a risk factor for OA.¹

5. **Sleep apnea** – For a brief period obese people are not able to breathe, thus interrupting sleep and causing sleepiness during the day. The person also starts snoring heavily. The

added weight to the chest of the obese person may squeeze the lungs, restricting breathing. With multiple organs and systems are adversely affected by obstructive sleep apnea, particularly related to CVDs. Romero-Corral *et al.* found that attenuation of the cardio-metabolic abnormalities and reduction in Obstructive sleep apnea (OSA) severity is favored by weight loss.²⁰

6. **Cancer**- There is an increased threat in women for being overweight, as it may cause a variety of cancers including colon, breast, gallbladder, and uterus. For obese men, there is a increased risk of colon cancer. According to Kolb *et al.*, the risk of developing several different types of cancer is increased with obesity which can be associated with a much worse clinical outcome.²¹ Obesity-associated inflammation promotes the progression of cancer in a tissue-specific manner along with the involvement of the interplay between different signaling events. Allott and Hursting suggest the need for clinical trials to rely on the role of weight loss in cancer prevalence and mortality in humans.²²

7. **Psychological effects**- In a society where overly thin people are physically attractive are ideology; obese or overweight people always have a disadvantage. They may be considered as weak-willed or lazy. They may be subjected to discrimination.

Drugs

In an obese person, weight loss can be facilitated by using

medication. In order to prescribe pharmacotherapies, certain BMI criteria are necessary, similar to that in weight loss surgery. The patient must have a BMI greater than 30 kg/m² or BMI of at least 27 kg/m² with obesity-related co-morbidities. Long-term medications are generally prescribed to such patients discontinuance of which may again lead to weight gain. In addition, the cost of the drugs, inability to acquire insurance coverage, and unwanted side effects, a person's assent with these daily medications raises alarm. The sympathetic nervous system being the primary site where obesity affects, the first class of medication imitates it to control the body weight. Thus, the individual appears to be under stress or nervous resulting in high blood pressure making it the major side effect of these drugs. Decreased appetite and feeling satiated are also caused by these medications. Hunger and satiety are operated by neurotransmitters in the brain, and hence appetite suppression is another way to tackle obesity. These class of antiobesity drugs increase the level of neurotransmitters at the synapse junction, (e.g., serotonin, norepinephrine, and dopamine).^{23,24} Figure 2 represents the mechanisms of anti-obesity drugs.

Description of Drugs and Mechanism of Action, Side Effects and Current Scenario

Four drugs that are commonly used for antiobesity treatment are described below (Table 1.).

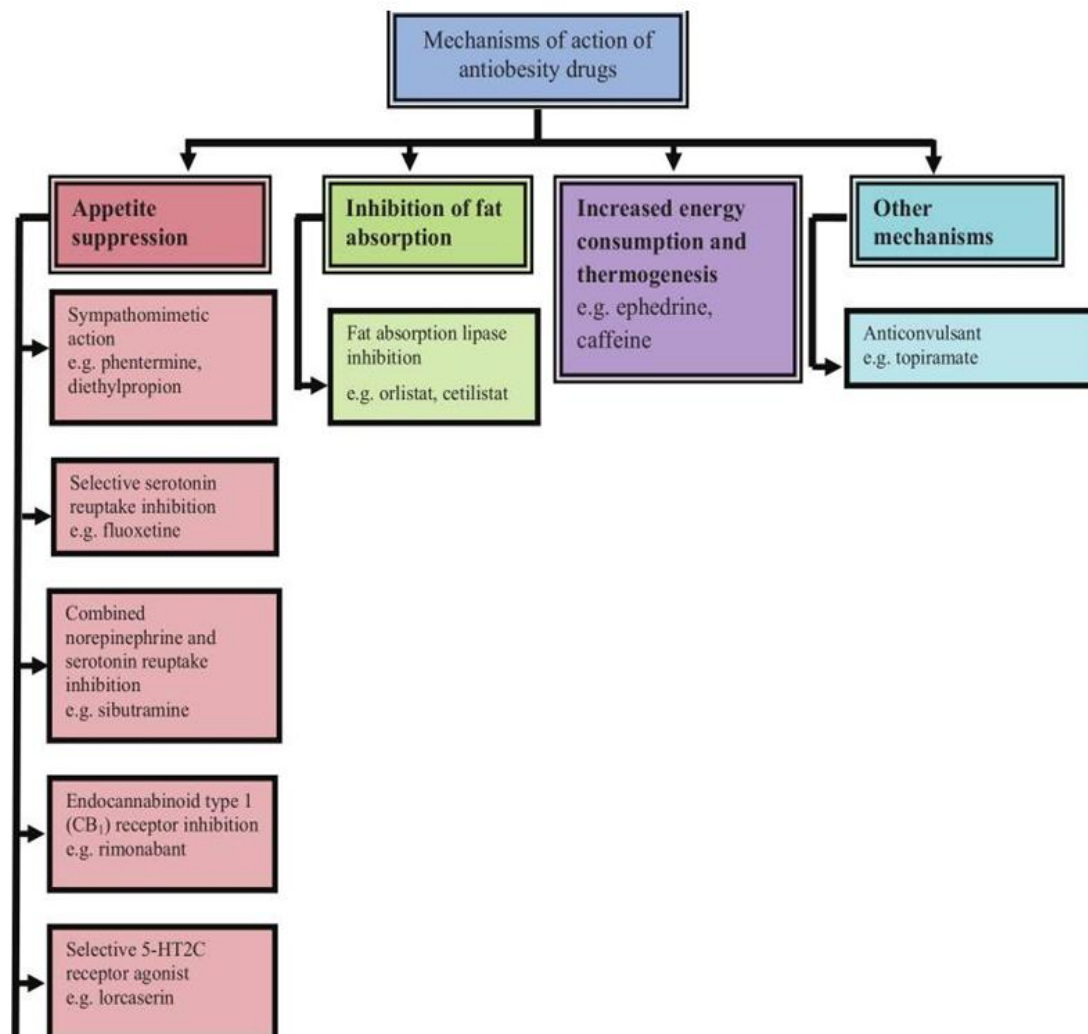


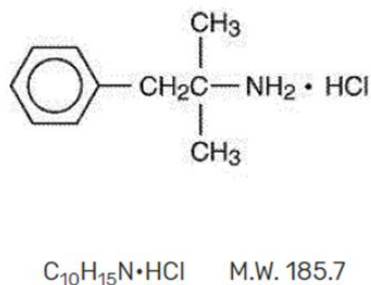
Figure 2. Mechanism of action of anti-obesity drugs. 5-HT: 5-hydroxytryptophan²⁵

Table 1. Some common anti-obesity drugs.²⁶

Drug	Common name	Mechanism of action	Effect in weight		Side effects
			Weight (in kgs)	Time	
Phentermine	Fastin	Appetite-suppressant	3.6	6 months	Headache, insomnia, irritability, palpitation, and nervousness
Sibutramine	Meridia	Reduces food intake through combined norepinephrine and serotonin reuptake inhibition.	4.45	1 year	Headaches, insomnia, dry mouth and constipation.
Rimonabant	Accomplia	Selective CB1 receptor blocker reduces food intake	5.1kg	1 year	Long term treatment increases the risk of heart attack and stroke.
Orlistat	Xenical	Lipase inhibitor reduces fat absorption.	2.59	6 months	Nausea, dizziness, arthralgia, and diarrhea
			2.89	1 year	Diarrhea, flatulence, bloating and abdominal pain

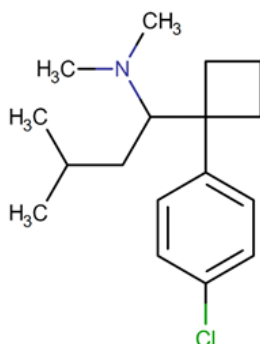
Phentermine

Loamin and many other brand names the drug phentermine is sold in the market as a medication to treat obesity. High blood pressure, increased heartbeat, dizziness, trouble sleeping, and restlessness are the common side effects of the drug. The drug is not supposed to be used during pregnancy or breastfeeding. Phentermine is a TAAR1 agonist, where the efflux is facilitated by activation of TAAR1 in monoamine neurons. Neurons release norepinephrine when the drug is present and to some extent, serotonin and dopamine are released in the synapses. The reduction of hunger perception is the primary mode of action for treating obesity. It is a cognitive process which involves many nuclei present in the hypothalamus. Phentermine outside the brain is known to release adrenaline and noradrenaline resulting in the breakdown of fats stored in the fat cells. The drug is still available in the market in most countries but classified as a controlled substance. Also, it is classified as Scheduled IV drug under the Convention on Psychotropic Substances. Structure of the drug is shown below in Figure 3.

**Figure 3.** Phentermine²⁷

Sibutramine

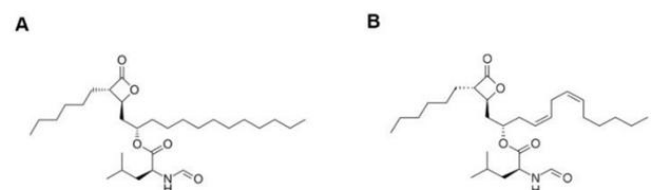
Originally developed in 1988 by Boots in Nottingham, U. K. Previously sold as Meridia, sibutramine is an appetite suppressant. Structure of the drug is shown below in Figure 4.

**Figure 4.** Sibutramine²⁷

At present, it is not sold in many countries. It was prescribed to the patient as an addition in the treatment of obesity along with proper exercise and diet. By altering the neurotransmitters within the brain, the drug assist with weight loss. The reuptake of neurotransmitters norepinephrine, serotonin and dopamine is blocked by the drug sibutramine, thus, disturbing the balance of neurotransmitters within the nerves and also disturbing the function and interaction. Most common side effects are the inability to sleep, headache, constipation, abdominal pain, dry mouth, chest pain, and anxiety. The drug is also not recommended for pregnant women and nursing mother.

Orlistat

Orlistat is a drug marketed under the brand name of Xenical by Roche as a prescription drug to treat obesity. A derivative of lipstatin, which is natural pancreatic lipase inhibitor isolated from *Streptomyces toxytricini*.²⁷ Serine residues are the target site for orlistat, which presents in the active site of gastric and pancreatic lipase. It lowers the absorption of monoglycerides and free fatty acids by partially inhibiting the hydrolysis of triglycerides.²⁸ Thus the triglycerides which are not digested are now excreted undigested. The drug has gastrointestinal related side effects, urgent bowel movements, and fecal incontinence. These side effects can be avoided by consuming a low-fat diet. The drug is available in the market as anti-obesity drug. In European countries, the drug was sold without any prescription after it was approved by the European Medicine Agency. Structure of the drugs is shown below in Figure 5.

**Figure 5.** Chemical structures of orlistat (A) and lipstatin (B)²⁹

Liraglutide

Liraglutide is a medication usually prescribed to patients for treatment of obesity and diabetes. Liraglutide is an acylated glucagon-like peptide-1 (GLP-1) agonist, derived from human GLP-1-(7-37), a less common form of endogenous GLP-1. It is advisory for the patients to follow a strict diet plan and exercise regularly along with the intake of drug. It is prescribed to individuals with BMI greater than 30 kg/m² or greater than 27 kg/m² together with high blood pressure, T2D, or dyslipidemia. The drug has been known to induce temporary appetite suppression which might return after prolonged use (after 56 weeks) of

liraglutide. Liraglutide is currently sold in European markets and the United States under the brand names Victoza and Saxenda, after its approval in 2009 in the former and 2010 in the latter.^{3,11}

Drugs Under Clinical Trial

Tesofensine

Tesofensine (serotonin-noradrenaline-dopamine reuptake inhibitor) is a novel treatment for obesity, manufactured by NeuroSearch, a Pharmaceutical company based in Denmark. It was predominantly used for treatment of Parkinson's disease (PD), Alzheimer's disease and other neurological disorders. During clinical trials, although the drug seemed inefficient in PD, overweight individuals exhibited significant weight loss and thus, the company shifted its focus to obesity.

Efficacy of Tesofensine- The drug has been exhibiting efficiency in Phase II trials. A randomized trial was carried out amongst 203 patients wherein participants were prescribed with tesofensine 0.25mg (n=52), 0.5mg (n=50) or 1.0mg (n=49), or placebo (n=52) once daily for 24 weeks. Patients with placebo showed a mean 2.0% of weight loss while patients with 0.25mg, 0.5mg and 1.0mg tesofensine showed a mean weight loss of 4.5%, 9.2% and 10.6% respectively ($p < 0.001$).³⁰

Currently, tesofensine is in Phase III trials of anti-obesity medications. The approval for the protocol of this work was granted in 2010 by the US Food and Drug Administration.³¹

Beloranib

Beloranib is a first-in-class injectable small molecule therapy and a potent MetAP2 inhibitor. It acts by breaking

down stored fats for energy and reducing hunger. MetAP2 is a key enzyme that controls the major cellular processes during metabolism. Beloranib inhibits MetAP2 by directing it to stress mediator which reduces the lipid synthesis. This increases fat metabolism throughout the body and utilizing it as an energy source. The drug focuses on reducing the Prader-Willi syndrome (PWS) which is the most common known genetic cause of life-threatening obesity.³²

Phase II trials of Beloranib showed promising results. However, after several deaths in the Phase 3 study, the evaluation of beloranib in PWS has been halted and the drug is no longer in development.³²

Treatment of Obesity by Natural Products

Researchers are exploring the possibility of treating obesity with the help of natural products. For the development of safe and effective anti-obesity drugs, the use of natural products is an excellent strategy. Crude extract and pure isolated compounds are capable of reducing body weight and avoid diet-induced obesity. Thus, these are known for their use in the treatment of obesity.³³

Dietary Phytochemicals

Dietary phytochemicals might be employed as anti-obesity agents because they may suppress the growth of the adipose tissue, inhibit differentiation of pre-adipocytes, raise levels of lipolysis, and bring about apoptosis of existing adipocytes, resulting in the reduction of adipose tissue mass. Figure 6 gives examples of various natural dietary phytochemicals.

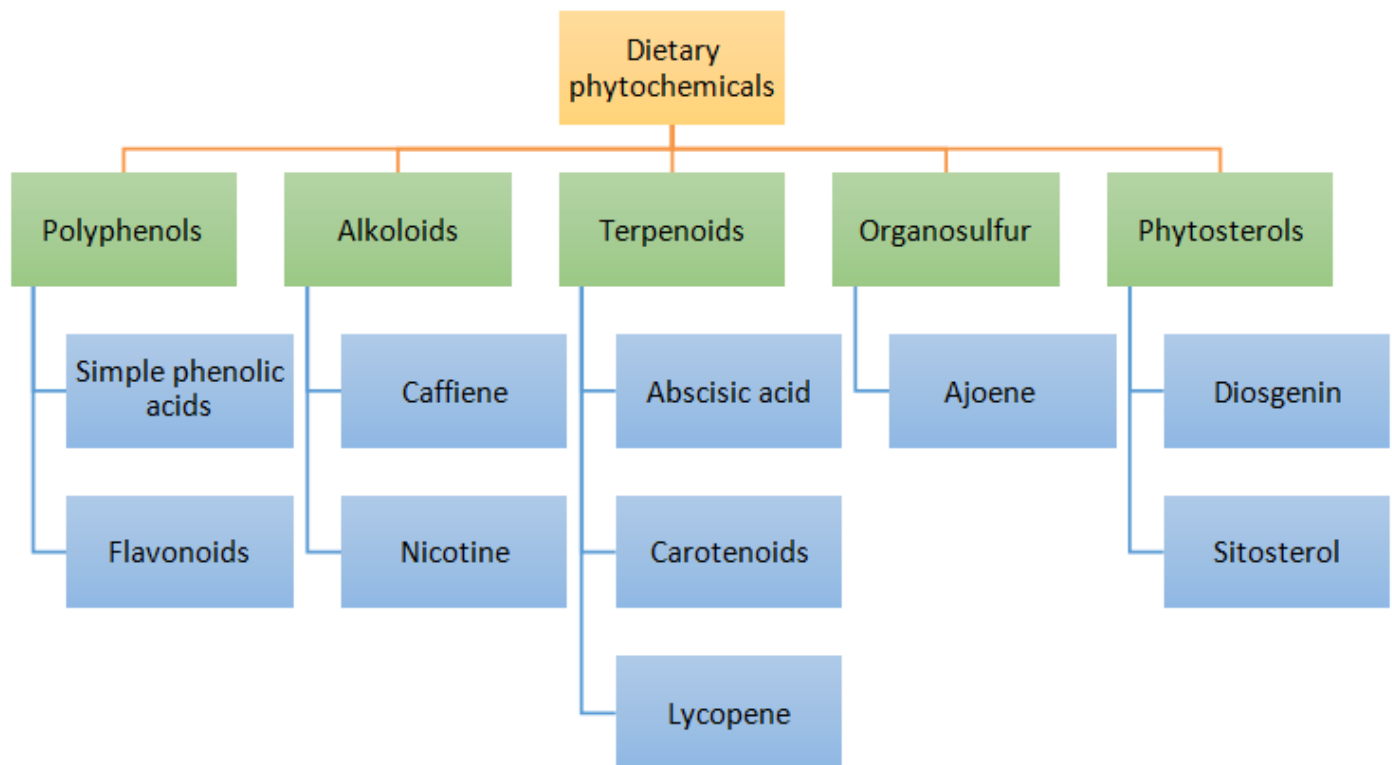


Figure 6. Classes of dietary phytochemicals used for treatment of obesity

Natural Products with Lipase Inhibitory Effect

The absorption of dietary fat takes place only when it is subjected to the pancreatic lipase enzyme. The enzyme hydrolyzes triglycerols to monoacylglycerols and fatty

acids, thus being the important enzyme in the process of fat absorption. Orlistat is one of the few substances capable of directly interacting with the lipase enzyme. Orlistat is a saturated derivative of the naturally-occurring lipase

inhibitor from *Streptomyces toxytricini*. By forming a covalent bond with the lipase's serine active site orlistat inhibits the enzyme. The drug shows some gastrointestinal related side-effects, even though it is clinically approved for the treatment of obesity.

There exists a vast variety of pancreatic lipase inhibitors while studying natural product (Table 2.). Lipase inhibitory effects can be observed in a variety of plant products such as polyphenols, flavonoids, and caffeine.³⁹ Many carbohydrates have exhibits inhibitory action against pancreatic lipase enzyme, for example, chitin/chitosan. Many metabolites from a microbial source such as lipstatin produced by *S. toxytricini* and panclicins by *Streptomyces* sp. also have an inhibitory action on pancreatic lipase.

Table 2. Natural pancreatic lipase inhibitors²⁶

Source	Used part and/or active constituents
<i>Panax japonicus</i> (rhizomes)	Chikusetsu saponins ³³
<i>Cassia mimosoides</i>	Proantho cyanidin ³⁴
<i>Trigonella foenum-graecum</i> L. (seed)	Crude ethanolic extract ³⁵
<i>Salix matsudana</i> (leaf)	Polyphenol (PP) ³⁶
<i>Vitis vinifera</i>	Crude ethanolic extract ³⁷
<i>Salvia officinalis</i> L. (leaf)	Methanolic extract (carnosic acid) ³⁸
<i>Cassia nomame</i>	Flavan dimers ⁵⁶
<i>Coffea canephora</i>	Caffeine, chlorogenic acid, neochlorogenic ³⁹
Chitosan-chitin	Chitosan (80%), chitin (20%) ⁴⁰
<i>Actinomycetes</i> sp.	Valilactone ⁴¹

Natural Appetite Suppressants

Neurological and hormonal interrelationships resulting in a multifactorial event helps in body weight regulation. Molecules closely associated with regulation of satiety are serotonin, histamine, dopamine, and their receptor. Through the reduction in energy intake, these receptors allow better targeting for anti-obesity drugs. Agents change different hypothalamic neuropeptide levels act by peripheral satiety peptide systems. Also, they change the levels of key CNS appetite monoamine-neurotransmitter and can be considered as candidates for appetite suppressants. By controlling the hunger centers in the brain appetite suppressants induce a feeling of fullness. However, ghrelin secretion in the stomach may increase with decreased food intake, stimulating more food intake. Therefore, the increase in appetite that normally occurs with a decrease in food intake can be reduced by ghrelin antagonism; thus, can be used as an adjunctive treatment for obesity.

An example of a natural substance capable of suppressing appetite is *Hoodia gordonii*. It promotes weight loss by regulating appetite and highly reducing calorie intake. Natural hydroxycitric acid (HCA) from *Garcinia cambogia*, is a potential natural appetite suppressant. HCA-SX and Super Citri Max are the brand names under which it is available. By increasing the serotonin level present within synaptosomes, *Hypericum perforatum* inhibiting synaptosomal uptake of serotonin, thus suppressing the appetite and reducing intake of food. The antidepressant and anti-obesity activities of *H. perforatum* are therefore linked with the serotonergic transmission.⁴²

Inhibition of Adipocyte Differentiation (Decreased Lipogenesis)

The lipid homeostasis and energy balance are maintained by storing triglycerides and releasing free fatty acids when energy is required and adipocytes have an important role in the process.⁴³ The signal-transducing molecules involved in differentiating adipocyte are polyunsaturated fatty

acids.⁴⁴ The list below gives various sources of natural adipocyte differentiation inhibitors and active constituents.

- Hydroxycitric acid (HCA) from *Garcinia cambogia*⁴⁵
- Epigallocatechin gallate from *Camellia sinensis* (green tea)⁴⁶
- Curcumin from *Curcuma longa* (turmeric)⁴⁷
- Ginsenosides from *Panax ginseng*⁴⁸
- Ajoene from garlic⁴⁹

Thus, by suppressing adipocyte differentiation in the late phase, polyunsaturated fatty acids play an important role in the suppression of lipogenesis and adipocyte differentiation regulation.^{50, 51} Several natural products have apoptotic effects on maturing pre-adipocytes (eg. esculetin, genistein, capsaicin, and conjugated linoleic acids).⁵²

Conclusion

Obesity is one of the rising disorders which are posing a threat to global health. It acts as a precursor to a varied range of health disorders ranging from high blood pressure to diabetes and other fatalities. Moreover, obesity can also affect the psychological health of an obese individual. Several documentations are available proving that obesity may arise due to genetic and metabolic factors. An individual's lifestyle such as eating habits, lethargy and lack of exercise are the contributing factors in obesity.

Obesity can be treated by several means such as doing exercise and maintain a proper healthy diet, taking anti-obesity drugs or by surgical method. It is also important to maintain the weight loss so that the individual is less likely to gain weight and be free of risks associated with obesity. The major drugs used for the treatment of obesity are Sibutramine, Orlistat, Rimonabant and Lorcaserin which are prescribed for long term use. However, with the concerns of side-effects arising from synthetic drugs, natural products have started to gain popularity for obesity treatment.

Conflict of Interest

The authors have no conflicts of interest to declare.

Compliance with Ethical Statement

This article does not contain any studies involving animals/human subject performed by any of the authors.

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Author Contributions

AA, AP: Design; AA, AP: Project development; AP, YJ: Data collection; AP: Analysis; AP, YJ: Literature search; AA, AP, YJ: Manuscript writing

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