



Review article

Obesity management therapies

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Abstract

Obesity is prominently referred as a lifestyle disease that exhibits itself as one of the major health threat of this day. 65% of the world's population lives in developed countries where overweight and obesity kills more people than malnourished and underweight. These extra kilos add stress to every part of the body and create many risks to health. This review is about various therapies that are available to deal with the problem of obesity from physical therapies to pharmacotherapies and from bariatric surgeries to herbal therapies. A weight-loss drug formulation is the one that is compatible with the profile of individual obese patients in terms of efficacy, safety and durability. Such drugs can be very effective in inducing weight loss. The history of successful dietary supplements in terms of efficacy is many and so the numbers of success stories matched the number of tragic records in terms of safety. A perusal of these supplements reveal that most of the supplements are phytoconstituents like *Commiphora mukul*, *Garcinia cambogia*, *Capsicum annum*, *Camellia sinesis*, *Gymnema slyvestre*, *Glycyrrhiza glabra* and *Nelumbonucifera* are used. They act in reducing the fat cells through varying mechanisms such as increasing lipid oxidation, inhibiting glucose absorption from intestine or inhibiting adipogenesis. The author thus concludes that the current trend is to use a combination of herbal with modern formulations for wondrous effects to address obesity.

Keywords: Obesity, herbal formulations, green tea, fat reduction.

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1. Introduction

Obesity is a state of being grossly fat or overweight. As per WHO, obesity is defined as abnormal or excessive fat accumulation that may impair health. Most of the world's population lives in developed countries where obesity kills more people than malnourishment with the most common causes like overeating and physical inactivity. Ultimately, body weight is directly proportional to resultant impact of genetic, metabolic, environment, behavior and culture issues. The main cause of obesity is due to energy imbalance between calories consumed and calories exhausted [1]. Exercise and dieting

remains the first option along with drugs to aid in reducing fats and appetite, besides increasing thermogenesis for anti-obesity treatment. For the overly obese patients, bariatric surgeries are performed to lessen the stomach volume and lessen the nutrient absorption to induce faster satisfaction with less hunger feeling.

According to WHO, in 2014 more than 1.9 billion adults— 18 years and older— were reported overweight— of these over 600 million were obese. This was attributed to major changes in dietary and physical activity patterns due to increasing urbanization [2].

Obesity can be due to two reasons:

- Due to excessive intake of food, salt, sugars, carbohydrates and less intake of vitamins, minerals and other nutrients;
- Due to stagnant life style, lack of exercise, more increase in consumption of junk food, psychological factors, increase in workload, stress level, etc [3].

Obesity is a major risk factor for a long list of chronic diseases and hence requires careful attention and assessment. The assessment of obesity can be done in two ways: first, by measuring the Body Mass Index (BMI) and second, by waist circumference. 1. WHO defines The Body Mass Index the weight in kilograms divided by the square of the height in meters (kg/m^2) [4].

Table1: The international classification of adult underweight, overweight and obesity according to BMI

Classification	BMI(kg/m^2)	
	Principal cut-off points	Additional cut-off points
Underweight	<18.50	<18.50
Severe thinness	<16.00	<16.00
Moderate thinness	16.00 - 16.99	16.00 - 16.99
Mild thinness	17.00 - 18.49	17.00 - 18.49
Normal range	18.50 - 24.99	18.50 - 22.99
		23.00 - 24.99
Overweight	≥ 25.00	≥ 25.00
Pre-obese	25.00 - 29.99	25.00 - 27.49
		27.50 - 29.99
Obese	≥ 30.00	30.00 - 32.49
		32.50 - 34.99
Obese class I	30.00 - 34.99	35.00 - 37.49
		37.50 - 39.99
Obese class II	35.00 - 39.99	37.50 - 39.99
		37.50 - 39.99
Obese class III	≥ 40.00	≥ 40.00

Source: Table adapted from WHO 1995, WHO 2000 and WHO 2004 publications

2. Waist circumference is considered as a good estimate of body fat, especially internal fat deposits. Waist circumference thresholds that

indicate increased risk of disease are described below:

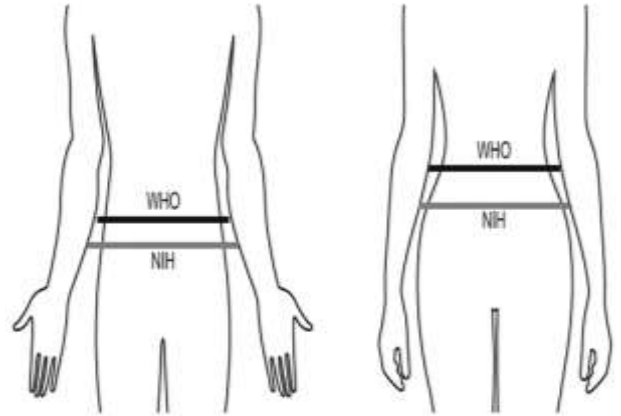


Figure 1: Waist circumference measurement sites for men and women based on WHO and NIH protocols

For women:

- Risk is increased at ≥ 80 cm
- Risk is high at ≥ 88 cm

For men:

- Risk is increased at ≥ 94 cm
- Risk is high at ≥ 102 cm for men
- Obesity has a far-ranging negative effect on health. Being obese can increase your risk of many severe health conditions and they are not limited to the following: High blood pressure, Diabetes, Joint problems including osteoarthritis, Sleep apnoea, respiratory problems, Cancer, Metabolic syndromes and Psycho-social effects [9].

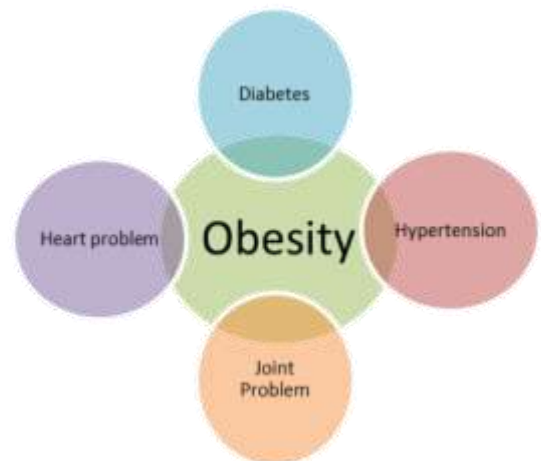


Figure 2: Represents metabolic syndrome seen in obese patients

- Obesity decreases the life expectancy by 3 to 10 years depending on the severity of its impact on health conditions.

The various options that are currently available towards reducing obesity and are in practice are:

1) **Exercise:** It is the natural and the hardest way. Physically strengthening your body by pushing it to limits keeps your body fit and healthy but the modern day stress and increased work load has lessened the time for people to work out.

2) **Reducing calorie intake:** It does not mean to reduce the amount of fat, protein or carbohydrate in the diet but by reducing the total calorie intake. The amount of calorie depends on the proportion of the food that you have taken along with recommended dietary compositions. There are many types of diets which are available in the market e.g., low-calorie diet, low carbohydrate diet, meal replacement diet, low glycemic index diet, low fat diet, very low fat diet and carbohydrate restricted diet [5].

3) **Pharmacotherapy:** Drugs commonly used to suppress obesity are Fluoxetine, Amphetamine, Phentermine, Sibutramine, Orlistat, Pramlintide etc. Each drug act in its own and different ways — some are serotonergic drugs, noradrenergic drugs, appetite suppressants and some act on gastrointestinal system [6].

4) **Bariatric surgery:** There are 3 surgical treatments available at present which result in the weight loss of at least 20-40kg and a BMI reduction of 10-15 kg/m². The three types are a) Laproscopic adjustable gastric banding (LAGB), b) laproscopic gastric sleeve (LGS), c) Roux-en Y gastric bypass (RYGB)[7].

5) **Natural phytogetic substances:** Herbal anti-obesity products are being popular due to the belief of being safe, effective and easy to use. Some of the natural substances that are available are *Commiphora mukul*, *Garcinia cambogia*, *Capsicum annum*, *Camellia sinesis*, *Gymnema slyvestre*, *Glycyrrhiza glabra*, *Nelumbonuciferasp.*, etc. Some act by increasing the energy expenditure, some act on lipid metabolism and some by inhibiting the appetite [8].

Therapies for anti- obesity:

1) **Physical therapies:**

The first and initial step is to have healthy diet along with physical activity such as walking, running, climbing, weight-lifting, etc. to improve and maintain one's body structure and increase physical health [10]. A healthy diet means required amount of calorie intake with consultation of a registered dietician. The dietician checks patient's BMI, their eating preferences and lifestyle to suggest accordingly the meals along with of the required physical exercises. It takes at least 6 months for 5% to 10 % drop in their initial weight [11]. The diet changes are advised according to patient's metabolic rate and preferences [12]. The patients should monitor their food as well as their calorie intake according to the portion and inhibition of certain food suggested by the dietician and should track their weight regularly [13]. Sleep plays a vital role in weight loss. Sleep is an important modulator of neuroendocrine function and glucose metabolism, and thus sleep loss has been shown to result in metabolic and endocrine alterations including decreased glucose tolerance, decreased insulin sensitivity, increased evening concentrations of cortisol, increased levels of ghrelin and decreased levels of leptin, and increased hunger and appetite [14].

2) **Pharmacotherapies:**

According to the US Food and Drug Administration (FDA) guidance, pharmacotherapy is approved for the patients with BMI ≥ 30 kg/m² or BMI ≥ 27 kg/m²[15]. There are two major categories of medications — one is appetite suppressing medication and the other is gastrointestinal fat blocker.

Appetite suppressing medication have targeted on the three monoamine receptor systems in the hypothalamus: noradrenergic, dopaminergic and serotonergic [16]. There have been five centrally acting adrenergic agents in the market for the treatment of obesity which are— Phentermine, Benzphetamine, Phendimetrazine, Diethylpropion, and Mazindol [17]. The most important side effects were insomnia, drymouth, constipation and increased blood rate. Orlistat approved by US Food and Drug Administration (FDA) reduces gastrointestinal lipase reducing fat absorption. The most common adverse effect of Orlistat is steatorrhea. Despite its approved status, Orlistat had a number of safety issues, including hepatotoxicity, nephrotoxicity, pancreatitis and kidney stones[18]. As a weightloss drug

formulation must be compatible with the profile of an individual obese patient to be truly meaningful in terms of efficacy, safety and durability, as of April 2014 only three drugs were approved by the USFDA as adjunctive therapy for chronic weight management: Orlistat (Alli, GlaxoSmithKline; Xenical, Roche) approved in 1999; Lorcaserin (Belviq, Arena Pharmaceuticals) approved in 2012; and Phentermine/ Topiramate extended-release formulation (Qsymia, Vivus) approved in 2012 [19]. On approval of Lorcaserin and Phentermine/Topiramate, the FDA introduced a new step with clinical relevance. According to the package insert the patient should lose at least 5% of baseline of the body weight by week 12 [20].

Drugs can be very effective in inducing weight loss. The history of dietary supplements is full of success stories in terms of efficacy, but this success is matched by tragedy with regard to safety. These unsafe drugs have had their regulatory approval withdrawn, although their unregulated use may still continue to some extent.

3) **Bariatric Surgeries:**

Bariatric surgery is defined as a surgical procedure with patients who have morbid obesity. Patients with BMI ≥ 40 kg/m² or BMI ≥ 35 kg/m² are associated with high comorbid conditions like diabetes, arterial hypertension, hypercholesterolemia, sleep apnea syndrome, arthritis and decreased life expectancy. Dieting, exercise and pharmacotherapies remain unsuccessful during these co-morbid conditions [21]. The three most common bariatric surgical procedures performed are Laproscopic adjustable gastric banding (LAGB), b) laproscopic gastric sleeve (LGS) and c) Roux-en Y gastric bypass (RYGB) [7]. Laparoscopic gastric banding and laparoscopic Roux-en-Y gastric bypass are the two procedures that differ significantly in a number of ways: the gastric band is an exclusively restrictive procedure whereas the gastric bypass has both restrictive and malabsorptive features. Furthermore, the laparoscopic implantation of a gastric band is technically much less challenging and does not require any intra-corporeal anastomosis. Conversely, the laparoscopic gastric bypass is a high-end laparoscopic procedure as it entails 2 intra-corporeal anastomoses (an enteroenterostomy and a gastro-jejunoanastomosis) and requires the mastering of intra-corporeal suturing skills. This is usually performed by surgeons with advanced laparoscopic

or specifically laparoscopic-bariatric surgery training [22,23]. Bariatric surgery reduces the size of the stomach, increases the feeling of fullness and reduces the amount of food intake. Bariatric surgery has demonstrated efficacy in inducing sustained weight loss and improvements in blood pressure, glycemic control and lipid profiles. Improvements and innovations in surgical techniques have reduced invasiveness, surgical risk and recovery times [24]. Notably, bariatric surgery has been increasingly prominent in diabetes management with a dramatic effect on glycemic control independent of weight loss. Nonetheless, bariatric surgery still has serious risks of surgical and metabolic complications and it remains very expensive making it less than ideal for the majority of the obese population [25].

4) **Herbal Medicines / Phyto-genic Substances:**

Herbal medicines or phyto-genic substances are the natural compounds that have been used to develop drugs for many decades. They have a vast range of advantages with minimum side effects that makes a good source for drug development. Natural compounds are crude extracts of either fresh or dried material. The extraction process is carried out differently for each ingredient to purify a single compound [26]. High-performance liquid chromatography, nuclear magnetic resonance and mass spectroscopy had made the analysis of the drugs much easier [27]. These herbal medicines are good sources for developing new drugs. They have multidimensional actions [28]. The disadvantage in isolating the single compound is the smaller quantities. Preclinical trials require few grams to kilograms [29]. There are various compounds with anti-obesity properties available in the market such as:

a) *Commiphora mukul* (Guggul/Guggulu) :

This is an oleo gum resin from the family of Burseraceae known as guggulipid. This acts as a lipid lowering agent and is standardised from the ethyl acetate extract of guggul gum which also contains other steroids, esters and higher alcohols known as guggulipid [30]. Guggul inhibits liver cholesterol biosynthesis which increases the body fat burning activity and augments the thermogenesis which in turn treats the obesity by reducing weight [31]. Crude gum guggul has been found to contain 2% guggulsterones. Its ethyl acetate extract contains 4% to 4.5%

guggulsterones. The neutral subfraction contains 4.2% to 4.7% guggulsterones. The ketonic subfraction of the neutral subfraction contains 35% to 40% guggulsterones from which the 10% E and Z guggulsterones are derived.

The concentrations of guggulsterones in gum guggul may be determined by thin layer chromatography (TLC) and high performance liquid chromatography/mass spectrometry (HPLC/MS) and by a colorimetric method [32]. Crude Guggulu was found to reduce the body weight of hydrogenated groundnut oil treated rabbits. In a preliminary clinical trial study on 22 patients of hypercholesterolaemia associated with obesity, crude Guggulu was administered orally 6-12mg in three divided doses for 15 days to one month. A fall in total serum cholesterol and serum lipid was found in all the cases treated with Guggulu. The body weight of 10 patients of obesity was also found to be reduced significantly [30].

b) *Garcinia cambogia* (Vrikshamla):

A small pumpkin shaped fruit which is yellow to pale green in color from the family Clusiaceae. Fruit rind contains tartaric acid 10.6%, reducing sugars (glucose) 15%, phosphoric acid (calcium triphosphate) 1.52% and (-)-hydroxycitric acid [33]. The principal active substance of *Garcinia cambogia* is the (-)-hydroxycitric acid which works against obesity by suppressing appetite and inhibiting lipid synthesis. This substance inhibits the activity of citrate lyase as one of the key enzymes of the citrate transport mechanism. The biologic role of the citrate transport system is to supply acetyl-CoA to the synthesis systems of cytoplasm, which are the most important source of carbon atoms in the lipids molecules and the unique source of carbon in the cholesterol molecules. In conclusion, since hydroxy citric acid reduces the activity of the citrate lyase cycle, the concentration of Acetyl-CoA in the cytosol of the cells also becomes lower and this causes the reduction of the substratum's availability to work for the mechanisms of the lipid synthesis. Studies suggest that this natural extract may also slow down the conversion of excess calories to body fat [34]. *Garcinia cambogia* is thus a very effective herbal medicine for controlling obesity and cholesterol level. HCA or hydroxycitric acid is a natural substance extracted from the peels of the fruits of *Garcinia cambogia*. In animal studies, HCA successfully inhibits lipogenesis and

therefore lowers cholesterol and fats, increases glycogen production in the liver, suppresses appetite and increases the body's thermogenesis process there by promoting weight reduction. Furthermore, by changing metabolic activity HCA decreases the conversion rate of carbohydrates to fats. Some studies also indicate that HCA suppresses the activity of the enzyme ATP citrate lyase, which is responsible for the conversion of carbohydrates to fats, present in the liver [35, 36].

c) *Capsicum annuum* (Chilli Peppers):

Capsaicin is the main compound in *Capsicum annuum*, which is known as red chilli peppers. It is used widely as pungent spice due to its alkaloid compound. Capsaicin has been found to increase thermogenesis [37]. The specialized capsaicin receptors are located on the taste buds within the papillae of the tongue. The receptor responsible for detecting capsaicin is called transient receptor potential vanilloid-1 (TRPV1). Capsaicin chemical structure allows it to bind to TRPV1. In the presence of capsaicin, a lipid portion of the receptor called P1P2 separates and allows calcium ions to enter the receptor cell. A pain message is then carried to the brain by substance P, a neurotransmitter. The bond between capsaicin and TRPV1 is temporary so feeling of pain subsides when the bond is broken. TRPV1 is broadly distributed in tissues of the brain, bladder, kidneys, intestines, keratinocytes of epidermis, glial cells, liver, mast cells and macrophages. Capsaicin accelerates the secretion of catecholamine from the adrenal medulla in response to activation of the sympathetic nervous system. Catecholamine interact with adrenergic receptors in the liver or adipose tissue and increase energy expenditure by stimulating lipolysis and thermogenesis and decrease accumulation of body fat in high fat diet [38]. Thermogenesis and lipid metabolism-related proteins are altered upon capsaicin treatment in white adipose tissue. Capsaicin induces apoptosis and inhibits adipogenesis in preadipocytes and adipocytes. Epidemiologic data shows that consumption of foods containing capsaicin is associated with a lower prevalence of obesity. Clinical evidence supports a role of capsaicin as an anti-obesity agent. Both oral and gastrointestinal exposure to capsaicin increase satiety and reduce energy and fat intake; the stronger reduction with oral exposure suggests a sensory effect of capsaicin. Bioactive components

containing capsaicin may support weight maintenance after a hypocaloric diet [39].

d) *Camellia sinensis* (Green Tea):

The tea plant, *Camellia sinensis*, is a member of the Theaceae family. The black, oolong and green tea are produced from its leaves. Green tea is produced from steaming fresh leaves at high temperatures thereby inactivating the oxidizing enzymes and leaving the polyphenol content intact [40]. The major constituents of green tea accounting for up to 35% of the dry weight are the polyphenols, which include flavonols, flavones and flavan-3-ols. Of these, 60–80% is the flavanols commonly known as catechins. Epigallocatechin-3-gallate (EGCG) is the most abundant catechin of green tea representing 50-80% of the total catechin content. It is also considered to be the most bioactive component of green tea. Other minor catechins include epicatechin-3-gallate (ECG), epigallocatechin (EGC), epicatechin and catechin [41]. It induces thermogenesis and stimulates fat oxidation, thus enhancing the metabolic rate by 4% without increasing the heart rate. Studies have also shown green tea extracts are capable of reducing fat digestion by inhibiting the activity of lipid synthesis which leads to increase lipid oxidation and glucose utilisation and decreasing glucose storage which leads to decreased body fat [42]. The Green Tea acts by inducing thermogenesis and substrate oxidation both of which are mediated by sympathetic nervous system activity. Other potential mechanisms include modifications in appetite control; down-regulation of enzymes involved in hepatic lipid metabolism and decreased nutrient absorption. Green tea polyphenols have also been shown to markedly inhibit digestive lipases *in vitro*, resulting in decreased lipolysis of triglycerides, which may translate to reduced fat digestion in humans [43, 44].

e) *Gymnemasylvestre* (Gurmar):

Gymnemic acids, a group of triterpenoid saponins, are the main class of chemical constituents from the family of Asclepiadaceae. There are some possible mechanisms which the leaves extract of *G. sylvestre* or (Gymnemic acid) possess its hypoglycemic acid effects are: 1) it promotes regeneration of islet cells; 2) it increases secretion of insulin; 3) it causes inhibition of glucose absorption from intestine; and 4) it increases utilization of glucose as it increases the activities of enzymes responsible for utilization of glucose by

insulin-dependent pathways, an increase in phosphorylase activity, decrease in gluconeogenic enzymes and sorbitol dehydrogenase [45]. *Sylvestre* helps to promote weight loss possibly through its ability to reduce cravings for sweets and control blood sugar levels. It has been reported that the gurmarin peptide block the ability to taste sweet or bitter flavours and thus reduces sweet cravings [46,47]. In a study a standardized *G. sylvestre* extract in combination with niacin-bound chromium and hydroxycitric acid has been evaluated for anti-obesity activity by monitoring changes in body weight, body mass index (BMI), appetite, lipid profiles, serum leptin and excretion of urinary fat metabolites. This study showed that the combination of *Gymnemasylvestre* extract and hydroxycitric acid, niacin bound chromium can serve as an effective and safe weight loss formula that can facilitate a reduction in excess body weight and BMI while promoting healthy blood lipid levels [48].

f) *Glycyrrhizaglabra* (Licorice):

Licorice root of the *Glycyrrhiza* plant species from the family of Leguminosae [49]. Licorice and its aqueous extract containing Glycyrrhizin is the main component. Glabridin is a major isoflavonoids in [50]. Licorice flavonoid oil (LFO) which contains hydrophobic flavonoids from *Glycyrrhizaglabra*, suppresses abdominal fat accumulation by regulation of rate-limiting enzyme activities related to fatty acid synthesis and oxidation in the liver [51]. LFO decreases the size of hepatic lipid droplets, which mainly consists of triglycerides and abdominal adipose tissue weight in diet-induced mice [52]. The hepatic triglycerides content is significantly correlated with plasma triglycerides level and fat mass in humans. LFO suppresses fatty acid synthesis and induces fatty acid oxidation, which decreases the hepatic and plasma triglycerides level and the weight of abdominal fat [53].

g) *Nelumbonuciferasp.* (Indian Lotus):

Nelumbonucifera from the family of Nymphaeaceae, a perennial aquatic plant, has been used as a medicinal herb in China and India [54]. Anti-obesity activity is observed in the leaves. Combined gas/liquid chromatography–mass spectroscopy has shown that the leaves are rich in a number of alkaloids [55.] Ono et al. reported the effects of leaf extract on digestive enzymes, lipid metabolism and thermogenesis, together with the

anti-obesity effect using mice with obesity induced by a high-fat diet. The extract showed a concentration-dependent inhibition of the activities of α -amylase and lipase and up-regulated lipid metabolism and expression of uncoupling protein-3 mRNA in C2C12 (mouse myoblast cell line) myotubes. It also prevented increase in body weight, parametrical adipose tissue weight and liver triacylglycerol levels [56].

Conclusions

Obesity is becoming epidemic around the world, which is associated with increased morbidity and mortality. Natural products had been used for many decades but remained isolated. All the medicines available in the market are not specific as the pharmacotherapies are bound to have some side effects and bariatric surgery is less optional whereas the natural therapy are effective but requires long duration. There is need to create a novel drug delivery system with the use of natural herbs to create a safe and effective drug for addressing obesity.

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