Genetic and Biochemical Basis of Obesity and Its Herbal Remedies: A Review

**ABSTRACT**

Obesity and overweight has become a global health problem. Obesity is increasing due to excessive calorie intake and sedentary lifestyle. Apart from that genes and environment play a role in the development of this menace. Variation in body weight can partly be explained by genetic differences. Due to their genetic profile, individuals react differently on changes in energy intake and expenditure. Recent data suggest that mutations and polymorphism identified in various genes contribute to a higher predisposition to obesity. A body mass index of ≥30 is classified as obese. This global health problem has become an alarming issue affecting developed and developing countries. Obesity pose potential risk for the development of several diseases like cardiovascular diseases, NIDDM, arthritis, varicose veins and several inflammatory diseases of the body. Various treatment methods are available for obesity. Modern methods of treatment, such as synthetic drugs and surgery, still have to be improved to show safety and efficacy. The main concerns associated with such treatments are the rising costs and adverse drug reactions. Pharmacological interventions appear to be effective for up to 9 months; after which regain occurs. For obese children, family therapy and lifestyle modification appear to be effective in prevention and treatment, respectively. The effectiveness of interventions to prevent and treat obesity in adults is not clear. But behavioral therapy and multicomponent strategies may be useful. Usage of herbs for the management of obesity in recent times is attracting attention. Literature, survey revealed that several herbal and polyherbal formulations has successfully being used in the management of obesity and associated health problems. A literature survey was conducted using both print and electronic medium to assess the information and compiled. This review attempts to provide information on genetic and biochemical basis of obesity along with the herbal remedies to reduce weight with safer and efficient treatments for management of obesity.
INTRODUCTION

Obesity can be stated as body weight more than 20% above a desirable standard due to an excessive accumulation of adipose tissue. Even moderate obesity is dangerous to health and can pose potential risk for the development of several diseases like CV diseases, pulmonary diseases, NIDDM, arthritis certain cancers like breast, uterus & colon, varicose veins & gall bladder diseases. Obesity is a chronic, multifactorial, neurochemical disease. It is a global health problem in the present era. Obesity leads to development of various diseases like blindness, cardiovascular diseases, diabetes, renal failure, amputation and compromised quality of life. A better understanding of molecular mechanism of pathogenesis and role of environmental, biochemical and genetic factors will provide hope for planning the treatment strategies of weight reduction.

The commonly used clinical methods of fat assessment and classification are body mass index (BMI) that is weight in kg/height in m² and waist to hip ratio (WHR) respectively. BMI is highly correlated with body fat. BMI of ≥30 are said to be obese.

Table No. 1: Garrow classification (Garrow, J.S. & Webster, J., Quetelet’s index (W/H2) as a measure of fatness. Int. J. Obes., 1985; 9(2): 147–153)

<table>
<thead>
<tr>
<th>BMI</th>
<th>Category</th>
</tr>
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<tbody>
<tr>
<td>20-25</td>
<td>Healthy</td>
</tr>
<tr>
<td>25-30</td>
<td>Overweight</td>
</tr>
<tr>
<td>≥30</td>
<td>Obese</td>
</tr>
</tbody>
</table>

Table No. 2: BMI values according to the WHO data

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
</tr>
<tr>
<td>Normal weight</td>
<td>18.5–24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>25–29.9</td>
</tr>
<tr>
<td>Class I obesity</td>
<td>30–34.9</td>
</tr>
<tr>
<td>Class II obesity</td>
<td>35–39.9</td>
</tr>
<tr>
<td>Class III obesity</td>
<td>≥40</td>
</tr>
</tbody>
</table>
A BMI cut off of >23 has been suggested by WHO as an indicative of overweight for Asia-Pacific inhabitants due to their greater fat deposits. The level of BMI is an integral part of the energy balance equation. Hence, obesity can be defined as that it is a multifactorial disorder of energy balance in which chronic calorie intake has been greater than energy output resulting in an excessively large BMI.

**Risk factors:**

Genetic factor is an important risk factor for the development of obesity, such as children in families where one or both parents are overweight or obese. Certain groups of people are at more risk of developing obesity than others, due to various reasons. Risk of obesity is also associated with social class. The risk of obesity may vary between different ethnic groups. Asians are at greater risk of developing obesity when compared to Caucasians and Carribeans. South Asians are more susceptible to development of abdominal obesity and prevalence of insulin resistance is more in this group.

Life cycle also brings changes in the body weight pattern. During the late thirties, the risk of obesity increases. For women, the risk of obesity increases at several stages of their life, for example when entering marriage, during pregnancy, during menopause and at retirement. Smoking cessation is also an important risk factor for weight gain in both the sex.

Avoiding overweight and obesity and achieving weight loss in obese or overweight persons, is beneficial to health. The obese people have an increased tendency to a number of health conditions such as coronary artery diseases, hypercholesterolemia, hypertension, diabetes, cholelithiasis, degenerative joint disease, social and psychological problem and obstructive sleep apnea. Due to the health hazards associated with obesity, health care professionals are under pressure to intervene the progression of this menace and increase the quality of life of the individual and the society at large. This review aims at focusing various facts of the condition and highlight the herbal remedies for the management of obesity.

**Pathophysiology:**

Obesity and overweight occurs due to imbalance between calories consumed and calories utilized. There are two major reasons of obesity & overweight (1) an increase in intake of energy rich foods that are high in fat, salt, sugars but low in vitamins, minerals & other micronutrients and (2) a decrease in physical activity due to the sedentary life style, changing
mode of transport and increasing urbanization. In other words, overweight can be defined as the consequence of a long term disruption of the energy balance where daily energy intake exceeds daily energy expenditure. The surplus of energy is mainly stored as fat. It is generally accepted that environmental, lifestyle and genetic factors play a role in the development of human obesity. All components of energy balance (energy intake, energy expenditure and energy storage) may be affected by genetic factors. Changes in dietary and physical activity patterns mostly results from sedentary lifestyle, inadequate sleep, endocrine disruptions because of certain foods that interfere with lipid metabolism, certain drugs that make patients put on weight, medical and psychiatric illness and infectious agents.

**Genetic factor:**

Genes play an important role in the etiopathogenesis of obesity. Mutations identified in various genes contribute to a higher predisposition to excessive accumulation of adipose tissue. Interaction between genetic and environmental factor is a major contributing factor for common obesity, apart from lifestyle and is a current challenge in many developed and developing countries. Presumably, obesity is due to interaction of genetic factors with an abundance of high calorie food and decline in physical activity. Genome scan in different ethnic populations have shown major obesity loci on chromosomes 2, 5, 10, 11& 20. It is believed that a good number of genes in humans are responsible for regulating the body weight and adiposity. The involvement of genetic mechanisms was also confirmed by many experimental studies regarding etiology and pathogenesis of obesity, conducted on animals models (the gene knock out mouse). Monogenic obesity belongs to a group of relatively rare but significant disease. Monogenic obesity is inherited in line with the Mendel’s laws. Individual cases of monogenic obesity have been explained and observed with rare mutations occurring in various genes e.g. in the genes of Leptin (LEP), leptin receptor (LEPR), pro-opiomelanocortin (POMC) and melanocortin 4 receptor (Mc4r). Food intake and body weight are controlled by centres located in various regions of the central nervous system (CNS). Melanocortin receptor (McR) plays an important role in conditioning of hypothalamus in mediating the food intake and body weight regulation along with other mechanisms. Malfunctioning of these mechanisms may result in serious food intake disorders, which may lead to obesity. Neural melanocortin 3 & 4 receptors affect various aspects of maintaining the energy homeostasis in the body and neuroendocrine disorders, driven by melanocortin receptors mutations, have an obesogenic effect.
Till date, a number of mutations of various genes have been described, which ultimately leads to monogenic obesity e.g. mutations in the genes of leptin (LEP), leptin receptor (LEPR), melanocortin 4 receptor (Mc4r), propiomelanocortin (POMC), prohormone convertase-1 (PCSK1), neurotrophine 2 receptor (NTRK2) and brain derived neurotrophic factor (BDNF). 22

The mutations in the genes participating in hypothalamic regulation of appetite i.e. LEP, LEPR & Mc4r are of highest importance. Because of incorrect leptin functioning due to lack of that gene expression & defect of its receptor, hyperphagia & subsequently. Obesity occurs in the initial months of life. A defect in the melanocortin 4 receptor is the most common form of monogenic obesity. It has been observed that a correct body weight has largely a polygenic basis, which implies that obesity may be a result of a number of genetic mutations. 23

**Central obesity:**

The location of the body fat is a major determinant of the degree of morbidity and mortality due to obesity. Mainly two components of body fat are associated with obesity-related adverse health outcomes. These are the amount of visceral fat located in the abdomen and the amount of subcutaneous fat on the trunk. These fats are associated with various metabolic abnormalities and are the main determinants of adverse health outcomes. Central obesity can be defined on the basis of waist-to-hip ratio (WHR) where waist is defined as the smallest circumference between the rib cage and the iliac crest and hip measurement includes the largest circumference between the waist and the thighs. For women, the ratio should be less than 0.85 (waist less than 88cm or 35inch) and for men, it is less than 1.0 (i.e. waist less than 102cm or 40inch). These ratios are the measures of abdominal and/or visceral fat and imply the degree of risk associated with obesity related disorders. 24, 25

Obesity is characterized by an increase in subcutaneous adipose tissue. Its metabolic consequences such as insulin resistance are primarily attributable to increased fat deposition at sites such as omentum, liver and skeletal muscles. Recently a virus has also been found to be associated with obesity. Human adenovirus Ad-36 causes adiposity in animal models and enhances differentiation and lipid accumulation in human and 3T3-L1 pre-adipocytes which may in part, explain the adipogenic effect of Ad-36. 26 Obesity results because of imbalance between energy output and expenditure. There is a set point for weight regulation. In a few cases, obesity may result from trauma of or tumors in the food regulating centers in the
hypothalamus. No specific cause can be identified for most cases of obesity. Several factors contribute for obesity as, genetic factors, several peptides, neurotransmitters and receptors in hypothalamus, eating habits, social customs. Several biomolecules in the hypothalamus and neighboring area regulate appetite and body weight. Studies have shown that some obese people burn fewer calories during digestion and absorption of a meal, a food-induced thermogenesis effect. Obese people who lose weight required about 15% fewer calories to maintain normal body weight than nonobese people. People who gain weight easily when fed deliberately demonstrate less NEAT (nonexercise activity thermogenesis) than people who resist weight gains with excess calories. 5, 6

Neuropeptide which increases appetite is neuropeptide Y. Leptin suppresses appetite and produces satiety in experimental animals; it is not deficient in most obese people. The surplus calories in the diet are converted to triglycerides and stored in adipose cells. Adipocytes increase in size and finally start to divide. Proliferation of adipocytes occurs in extreme obesity. The enzyme lipoprotein lipase regulates triglyceride storage. This enzyme is very active in abdominal fat but less active in hip fat. Accumulation of fat in the abdomen is associated with higher blood cholesterol level and other cardiovascular risk factors because adipose cells in this area appear to be more metabolically active. Several inflammatory mediators contribute for the obesity in susceptible individuals. Many adipocytokines involved in inflammation like IL-1 (IL=>Interleukin), IL-6, IL-8, IL-10, IL-18, TNF-α (tumor necrosis factor), TGF-β (tumor growth factor) have been found to increase in the metabolic syndrome. TNF-α and IL-6 released from adipocytes increase appetite. Glucagon and somatostatin from pancreas decrease appetite but having hyperglycemic effects. Some peptides like cholecystokinin and peptide YY (PYY) released from intestine and colon are also responsible for appetite and body weight regulation. Polypeptide Ghrelin released from stomach is having orexogenic effect. 27, 28

Glucostatic hypothesis states that reduced blood glucose level increase appetite, frequent fasts lead to decrease basal metabolic rate and increase in adiposity. Thermostatic hypothesis holds that decrease in body temperature below normal stimulates appetite and above setpoint inhibits.
Treatments:

Treatment of obesity is difficult because most people who are successful at losing weight gain it back within 2 years. Still, a modest weight loss is associated with health benefits. Treatments for obesity include behavior modification programs, very low calorie diets, drugs and surgery (bariatric). Behavior modification programme aim to alter eating behaviors and increase exercise activity. The nutrition programme includes plenty of vegetables but low in fats especially saturated fats. An exercise programme of 30 minutes’ walks a day, five to 7 times a week. Regular exercise increases weight loss and weight loss maintenance. Very low calorie diet includes 400 to 800 kcal/day, at least for 12 weeks under close medical supervision. Two drugs are available for treatment of obesity; (i) Sibutramine an appetite suppressant and (ii) Orlistat act by inhibiting lipases released into lumen of the G.I. tract with less lipase, less dietary triglycerides are absorbed. Sibutramine acts by inhibiting reuptake of serotonin and epinephrine in brain areas that regulates eating behavior. For extreme obesity, who has not responded to other treatments, a surgical procedure may be considered. The two operations most commonly performed are: gastric bypass and gastroplasty; both significantly reduce the stomach size so that it can hold just a small quantity of food.

Herbal remedies for obesity management:

Herbal products have the ability to affect body systems. The effects are dependent on the phytochemical present in the various parts of the plant. Scientists first started extracting and isolating chemicals from plants in the 18th century and since that time we have been accustomed to looking at herbs and their effects in terms of active constituent they contain. Several studies have shown that natural food ingredients and medicinal plant preparation are able to enhance satiety, boost metabolism and expedite weight loss. Usage of plants and plant products has potential to keep the increasing prevalence of metabolic derangement in control. Consistent and safe herbal product for weight reduction is a need of development and developing countries.

The potential of natural products for treating obesity is under exploration. This may be an excellent alternative for developing future effective, safe anti-obesity drugs. A variety of natural products including crude extracts and isolated natural compounds can reduce body weight and prevent diet-induced obesity. Therefore, they have been widely used in treating obesity. Dietary phytochemicals may be employed as anti-obesity agents because they may
suppress the growth of adipose tissue, inhibit differentiation of preadipocytes, stimulate lipolysis and induce apoptosis of existing adipocytes, thereby reducing adipose tissue mass. Below are the phytochemicals having antiobesity effect by various mechanisms.

Polyphenols e.g; Simple phenolic acids, Stilbenes, Curcumins, Lignans, flavonoids (quercetin) etc. Phenolic acid like ferulic acid has hypolipidemic effect and it lowers the risk of high fat diet-induced obesity and reduces serum cholesterol.\textsuperscript{34} Stilbenes like resveratrol decreases LDL-cholesterol prevent lipid oxidation, decrease adipogenesis by downregulation of adipocyte transcription factors, altering the expression of adipocyte specific genes.\textsuperscript{35,36} Curcumins prevent lipid accumulation, regulate, energy metabolism and decrease intracellular lipid level. Besides curcumins regulate transcription factor which is an important factor in adipogenesis and lipogenesis. Flavonoids like quercetin suppress adipogenesis by decreasing expression of associated factors.\textsuperscript{37-39}

Alkaloids e.g.; Capsaicin, Ephedrine, Caffeine, Nicotine.

Capsaicin reduces food intake and increases energy expenditure and lipid oxidation. Attenuates obesity-induced inflammation, obesity associated metabolic disorder etc.\textsuperscript{40,41}

Ephedrine increases norepinephrine causing appetite suppression, increase basal metabolic rate & increases energy expenditure.\textsuperscript{42}

Caffeine stimulates fat break down, increases the thermogenic effect & anorectic effect in addition to its diuretic effect.\textsuperscript{43}

Nicotine decreases food intake and fat oxidation and energy expenditure.\textsuperscript{44,45}

Terpenoids e.g. Carotenoids, lycopene Carotenoids are having protective effect. They may prevent inflammation associated diseases such as obesity and atherosclerosis.\textsuperscript{46}

Lycopene inhibits LDL oxidation & lipid peroxidation.\textsuperscript{47}

Phytosterols e.g.:- Dioxgenin, Sitosterol, Protodioscin

High intake of these phytosterols protects against atherosclerosis and decrease LDL. They also inhibit cholesterol absorption in the intestinal lumen. Protodioscin reduces blood levels of TG (triglyceride), Cholesterol, LDL and increase HDL level. Diosgenin inhibits TG accumulation and lipogenic gene expression.\textsuperscript{48-50}
A good number of herbal supplements are currently available in the market for obesity management. These supplements act by different mechanisms. Similarly, various phytomolecules act by different mechanisms and target different biomolecules for the management of obesity. The basic principle involved in the mechanism of action of antiobesity supplement is regulation of energy balance in the body which includes balance between energy intake and energy expenditure. For convenience of explanation different studies follows different approached for classifying the mechanism of action on the basis of the effect of drug on various physiological systems or on the nervous system. Yun et al\textsuperscript{51} has classified the antiobesity action on the following basis, such as decreased lipid absorption, decreased energy intake, increased energy expenditure, decreased pre-adipocyte differentiation and proliferation and/or, decreased lipogenesis and increased lipolysis.

During our literature review, it was observed that the natural products can control obesity by the following mechanisms.

Natural products with lipase inhibitory activity: Pancreatic lipase plays an important role in the absorption of triglycerides by hydrolysing triacylglycerol to monoacylglycerol and fatty acids. Orlistat is such a drug which interacts with lipases. It is derived from a inhibitor from \textit{Streptomyces toxytricini}. A wide variety of plant products like carbohydrates, saponins, polyphenols, flavonoids and caffeine possess lipase inhibitory activity. Different types of tea (e.g. green tea, black tea) have also lipase inhibitory activity.\textsuperscript{52}

Natural compounds with appetite suppressant activity: These group of substance act on central nervous system, which results in a feeling of fullness hence no urge for food. Some examples are Ephedra species (ephedrine), Camellia sinensis, Panax ginseng root \textit{etc}.\textsuperscript{53}

Similarly, there are varieties of natural compounds available which control the obesity by different mechanisms. For example; chilli pepper (capsicum), fish oil, green tea, garlic, curcumin etc has been found to decrease obesity by decreasing lipogenesis. Some other compounds like liquorice flavonoid, curcuma longa, soybean, crude aqueous extract of papax ginseng has been found to have increased lipolytic activity. They act as natural lipid metabolism regulator. They act by increasing lipid metabolism.\textsuperscript{54,55}
CONCLUSION

The rising prevalence of obesity is a worldwide problem affecting both developed and developing countries. Obesity is a multifactorial disorder involving environment and the genome. Even if there is sufficient evidence for a genetic component to obesity, the specific genetic factors are yet to be ascertained. Obesity comorbidities include coronary heart disease, hypertension and stroke, certain types of cancer, non-insulin-dependent diabetes, Mellitus, gall bladder disease, dyslipidaemia, osteoarthritis and gout, and pulmonary diseases, including sleep apnoea.

In addition, the obese suffer from social bias, prejudice and discrimination, on the part not only of the general public but also of health professionals, and this may make them reluctant to seek medical assistance.

The pathogenesis of central obesity is complex. Identification of an effect of a polymorphism will be the first, simple step on a more challenging path toward elucidation of the biological pathways involved, and crucially, the gene–gene and gene–environment interactions.

There are several allopathic remedies available for weight management but some of them are not successful or some having toxic adverse effects. Herbal products for effective control of obesity and associated diseases is a need of the present world. In our literature survey, herbal products are found to control obesity to a greater extent by several mechanisms. There are several plants described in various journals and also in Ayurveda for weight management. But so far, a very few systematic scientific screening has been attempted for an effective, safe antiobesity herbal drug. A better understanding in the existing evidence based science on herbs will further guide a qualitative research in obesity management that will attract the end users by the effective benefits. True randomized, double blind, placebo-controlled clinical trials using herbal products will demonstrate their potential benefits.

This short review focuses on compilation of literatures aimed at finding out the biochemical and pathological basis of obesity and the scientifically documented some of the herbal remedies available for controlling obesity by various mechanisms. This may be helpful for the researchers doing extensive screening works in the field of obesity and body weight management.
REFERENCES

7. NHS CRD report number 5, Ethnicity and health: reviews of literature and guidance for purchasers in the areas of CVD, mental health and hemoglobinopathy, University of York, 1996; 46-47.

Citation: Biman Kumar Panigrahi. Ijppr.Human, 2019; Vol. 17 (1): 156-168.
29. Tortora GJ, Derrickson BH, Metabolism and nutrition In Principles of anatomy and physiology, 12th edn, John willey and sons inc, 2009; 1012.
31. Keith SW, Redden DT, Katzmanzyk PT, Putative contributors to the secular increase in obesity; exploring the roads less travelled. Int. J. obesity, 2006; 30(11): 1585-1594.

Citation: Biman Kumar Panigrahi. Ijppr.Human, 2019; Vol. 17 (1): 156-168.
55. Park MY, Leeks, Sung MK, Effects of dietary mulberry, Korean red ginseng and banaba on glucose homeostasis in relation to PPAR-â(omega), PPAR-Î³(gamma) and LPL m RNA expressions. Life Sci, 2005; 77: 3344-3354.