OBESITY AND ITS PERSPECTIVES

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Summary

Obesity and related risks even life threatening are continuously increasing through out world in all age groups. Many marketed formulations claim to possess antiobesity actions, but still many herbs which have claims to this need to be investigated and there claims be authenticated. In recent era there is a great thrust on screening of herbal extracts and formulations for antiobesity action. In this article efforts have been taken to list as well as discuss various models and parameters used for antiobesity activity. The motto is to discuss the models, to bring them under one title, which would surely prove to be some help to the researchers.

Keywords: Obesity, BMI, anorectic assay, metabolic assay, thermo genesis, RMR

Introduction

Obesity is a condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health, leading to reduced life expectancy. The problem of obesity is prevalent in all age groups especially in childhood, adolescence and in youth in both male and female. The problem is global and increasingly extends into the developing world including India. Table 1 is showing the probable causes and the associated health risks[1].

Who can be called obese?

The prevalence of overweight and obesity is commonly assessed by using body mass index (BMI), which compares weight and height, defined as the weight in kilograms divided by the square of the height in metres (kg/m2). A BMI over 25 kg/m2 is defined as overweight, and a BMI of over 30 kg/m2 as obese[1]. These markers provide common benchmarks for assessment, but the risks of disease in all populations can increase progressively from lower BMI levels.

Table 1: Causes and Health Risks of Obesity

Sr.No.	Parameters
Causes of Obesity	
1	Medicines (steroids and some antidepressants)
2	Consumption of more calorie food
3	Psychological disturbances
4	Genetic factors
5	Diseases and conditions Hypothyroidism, Cushing's syndrome, Depression, and certain neurological problems
Health Risks of Obesity	
1	Polycystic ovary syndrome (PCOS), Infertility, Irregular menstruation
2	Various types of cancer
3	Diabetes-II
4	Kidney Disorders, Gout, gallstones (An accumulation of bile that hardens in the gallbladder forms gallstones)
5	Fatty liver inflammation (scarring, permanent liver damage)
6	Insulin resistance and diabetes
7	Pseudotumor cerebri (pressure builds in the brain which causes headaches, symptoms may include vomiting, an unsteady way of walking, and vision problems)
8	High cholesterol. Heart attack and stroke, High blood pressure.

9	Sleep apnea. where a person temporarily stops breathing during sleep Asthma (breathing problems)
10	Blount's disease (bone deformity)
11	Arthritis (Wear and tear on the joints due to extra weight) and Slipped capital femoral epiphyses (SCFE).
12	Depression, psychological problems, lack of confidence, stress

Treatments [2, 3]:

Several weight loss drugs have been marketed to date which work by either suppressing the appetite (e.g. Sibutramine- Reductil) or reducing absorption of fats (e.g. Orlistat-Xenical). These drugs should always be prescribed by a medical professional. These agents can cause weight loss of up to 10% of body weight. However, following cessation of treatment much of this weight will be regained. In addition many of these drugs can have nasty side effects (such as diarrhoea) and are still being investigated in clinical trials. Some older drugs such as fenfluramine have been withdrawn form the market due to bad side effects on the heart.

Combined drug treatment using fenfluramine and phentermine ("fen/phen") is no longer available due to the withdrawal of fenfluramine from the market. Little information is available about the safety or effectiveness of other drug combinations for weight loss, including fluoxetine/phentermine, phendimetrazine/phentermine, Xenical/sibutramine, herbal combinations, or others. Until more information on their safety or effectiveness is available, using combinations of medications for weight loss is not recommended except as part of a research study.

In order for medications to really work, they need to be combined with lifestyle modifications such as a low fat diet and regular exercise. Medications for weight loss should only be taken for short periods (up to 3 months) and always be used with caution as they have the potential for abuse. At present they are only indicated if you are morbidly obese, have significant co-morbidities or if you have failed other lifestyle treatments.

Surgical treatments tend to be considered if you are morbidly obese (defined as a BMI greater than 40). You must however consider the operative risks associated with each of the procedures. In most cases however, the benefits to your mental and physical health and appearance will outweigh the risks of surgery. If you are markedly obese with co-morbidities, surgery is considered the only available treatment that can reliably produce significant and sustained weight loss. Surgical procedures may help you lose up to 30-40kg of excess weight; however this is only achieved if you adhere to the required lifestyle changes. A variety of surgical procedures have been used which can be broadly classified into restrictive (gastroplasty and laparoscopic gastric banding) and mal-absorptive procedures (gastric bypass).

Just reducing caloric intake is not necessarily a good idea for weight loss. Instead, doctors recommend that you concentrate on eating healthy foods that are nutrient rich and limit your intake of "empty calories": foods that may taste good but that do not contain recommended nutrients (soda pop, for example). You should also limit the intake of trans and saturated fats, cholesterol, sodium, and foods with a high glycemic index. Consult your doctor or nutritionist to develop a diet that is right for you.

Anti obesity Drugs Development

The high incidence of obesity, its multifactorial nature, the complexity and lack of knowledge of the bodyweight control system, and the scarcity of adequate therapeutics have fuelled anti-obesity drug development during a considerable number of years. As a consequence of anti-obesity research, our knowledge of the bodyweight control system increased but, despite this, the pharmacological approaches to the treatment of obesity have not resulted yet in effective drugs. The multiple different approaches developed to obtain workable drugs rely in only four main lines of action: [1]

1 control of energy intake, mainly through modification of appetite ,
2 control of energy expenditure, essentially through the increase of thermogenesis;
3 control of the availability of substrates to cells and tissues through hormonal and other metabolic factors controlling the fate of the available energy substrates;
4 Control of fat reserves through modulation of lipogenesis and lipolysis in white adipose tissue.

Future trends in anti-obesity drug research follow closely the approaches outlined; however, the increasing mass of information on the molecular basis of bodyweight control and obesity will in the end prevail in our search for effective and harmless anti-obesity drugs.

Mechanisms of action of antiobesity drugs[1]:

Anti-obesity drugs operate through one or more of the following mechanisms:

- Suppression of the appetite. Catecholamines and their derivatives (such as amphetamine-based drugs) are the main tools used for this. Drugs blocking the cannabinoid receptors may be a future strategy for appetite suppression
- Increase of the body's metabolism .Interference with the body's ability to absorb specific nutrients in food. For example, Orlistat (also known as Xenical and Allī) blocks fat breakdown and thereby prevents fat absorption. The OTC fiber supplements glucomannan and guar gum have been used for the purpose of inhibiting digestion and lowering caloric absorption
- Inhibits the reuptake of norepinephrine, serotonin, and dopamine in the CNS, with the inhibition of norepinephrine and serotonin being three times greater than that of dopamine.
- Anorexics are primarily intended to suppress the appetite, but most of the drugs in this class also act as stimulants (dexedrine, e.g.), and patients have abused drugs "off label" to suppress appetite (e.g. digoxin).
- Suppress appetite by stimulating the release of norepinephrine and dopamine in nerve terminals in the hypothalamic feeding center. Other effects such as decreased gastric secretion and increased energy, may also contribute to decreased appetite and weight loss

ANTIOBESITY ACTIVTY (ANIMAL MODELS)[4]:

Food induced obesity:

Obesity is induced by a diet containing corn oil and condensed milk. Rats of 6 months and 450 gm are selected. Feed the one group ordinary normal diet and to another group give naormal diet plus corn oil and condensed milk (15 % protein, 44 % carbohydrate, 16 % lipid, 2.5 % fiber, 1.2 % vitamin and 19 % water). Change the diet after 3-4 days.

After 3 months sacrifice the rats to determine adipose tissue cell size, number, carcass composition and levels of plasma lipids, hormone and glucose.

Hypothalamic obesity:

Surgical lesions develops hyperphagia and thus obesity in rodents. Select the healthy female rats of 190 mg weight. Keep them on high fat diet for 5-9 days. Then fasted over them for one night, anesthetized intraperitoneally with 35 mg/kg Phenobarbital sodium and 1 mg atropine methyl nitrate. Then give the cut at hypothalamus with bilateral knife or lesions with stainless steel electrode. The cuts are made 1 mm lateral to midline and extended from 8.5 to 5.5 mm anterior to the ear bars and from the base of brain dorsally 3 mm. Lesions are made by passing 2 mA current for 20 seconds.

Goldthioglucose induced obesity:

Swiss albino mice of either sex are used to produce obesity by injection of (IM / IP) goldthioglucose which is supposed to destruct hypothalamic and extrahypothalamic areas of brain. Swiss albino mice of either sex and 6 weeks are injected intraperitoneally with single dose of 30-40 mg/kg of gold-thioglucose.

Monosodium glutamate induced obesity:

Continuous doses of monosodium-L-glutamate from the birth of mice produces obesity. After the immediate birth of Male mice, inject subcutaneously the 2 g/kg of monosodium-L-glutamate for 5 consecutive days. Observe the weight gain weekly.

Genetically (e.g. diabetic), spontaneously (e.g chromosomal changes) and transgenic obese rats or mice are also preferred for antiobesity studies.

- **Anorectic assay:**

Select the obese female rats. Divide the 5-10 animals in different Groups, standard, control, test etc. Offer the food in special dishes to reduce spilage. Measure the individual food intake and body weight daily from the day 2 between 8 pm to 9 am. Collect the spilled food in collecting paper air dry if necessary and weigh accurately. Mazindol (3 mg/kg, i.p.) can be used as standard antiobesity drug. Carry out the study upto 7 days. Compare the average value of food intake and body weight of test with control group.

- **Metabolic assay:**

1. GDP binding in brown adipose tissue

Brown adipose tissue is major cite of non-shivering thermo genesis in mammals. In contrast to white adipocytes (fat cells), which contain a single lipid droplet, brown adipocytes contain numerous smaller droplets and a much higher number of mitochondria, which contain iron and make it brown. The recent study could lead to a new method of weight loss, since brown fat takes calories from normal fat and burns it. The binding of GDP to Brown adipose tissue membrane protein i.e. thermogenin is indication of metabolic activity and energy utilization. Drugs activating Brown adipose tissue thermo genesis via beta-3 adrenoreceptars cause uncoupling of oxidative phosphorylation from electron transport.

Fed orally the doses of test and standard drugs to selected obese male rats of 13 weeks for 21 days. Measure the food intake daily and body weight every other day. On 21st day sacrifice the rats by decapitation and dissect the brown adipose tissue. Then measure the GDP binding according to the method of Nicholls (1976) and protein content of mitochondrial solution by Peterson (1977).

2. Uncoupling protein and GLUT4 in brown adipose tissue

Uncoupling protein found in the mitochondria of brown adipose tissue (BAT). It is used to generate heat by non-shivering thermo genesis. Non-shivering thermo genesis is the primary means of heat generation in hibernating mammals and in human infants. GLUT4, the protein, the insulin-regulated glucose transporter found in adipose tissues and skeletal and cardiac muscles. This protein is expressed only in muscle and fat cells. The

measurement of Uncoupling protein and GLUT4 in brown adipose tissue is an indication of metabolic activity.

Fed the doses of test and standard drugs subcutaneously to selected obese male rats at the age of 10 weeks for 14 weeks. At the end of treatment sacrifice the rats by decapitation and dissect the brown and white adipose tissue. Measure the Uncoupling protein and GLUT4 by Northen blot analysis and protein content by western blot analysis or radioimmunoassay.

3. Resting metabolic rate

Resting metabolic rate (RMR), is the amount of energy expended while at rest in a neutrally temperate environment, in the post-absorptive state (meaning that the digestive system is inactive, which requires about twelve hours of fasting in humans). The release of energy in this state is sufficient only for the functioning of the vital organs, the heart, lungs and kidneys and the rest of the nervous system, liver, lungs, sex organs, muscles and skin. BMR decreases with age and with the loss of lean body mass. Resting metabolic rate (RMR) is the energy required to perform vital body function.

Fed the doses of test and standard drugs by intramuscular injection to selected Female mice at the age of 12 weeks for 2 weeks. Measure the food intake daily and body weight every other day. Estimate the RMR by using closed –circuit metabolic system. (Molnar 1986).

4. beta-3 adrenoreceptors

Beta3-adrenoceptors are involved in metabolism, gut relaxation, and vascular vasodilation. This receptors increases thermogenesis in brown adipose tissue, lipolysis in white adipose tissue and suppression and serum leptin levels. Chinese hamster ovary cells expressing Beta-3- adrenoreceptars are used in $_{C}$AMP response-luciferase receptor gene assay where luciferase activity can be measured using the Luc Lite assay kit.

Anti obesity Herbal Drugs:

India has got a rich heritage of Ayurveda. Due to vast diversity in climatic conditions, India provides a wide range of flora & fauna. In other system of medicines also like unani, siddha and folklore medicines, the plants and plant products are used as therapeutic agents for the treatment of various disorders. Recently the interest in plant as a source of as anti obesity agents is stimulated due to the lack of progress in development of effective, safe and economical anti obesity agents and probably because of high incidence of side effects and toxicity with allopathic medicine.

Collaborative studies conducted by various biomedical and pharmaceutical research institutes in India have revealed the potential of some regional plants as anti obesity drug during the screening of these plants. Experimental approach has been followed which was designed to postulate the possible mechanism(s) of anti obesity agents. Through this approach various plant extracts have been found to be active which may be potential targets for modern anti obesity drugs research.

Most traditional uses of plants involve consumption of an aqueous extract. But very less effort have been taken for the development of effective herbal anti obesity formulation.

Table 2: Anti obesity plants [5-55]

Sr. No.	Common name	Name of plant	Part use	Chemical constituents	Mode of action
1.	Guggul	*Commiphora wightii/commiphora mukul Burseraceae*	Gum resin	guggulsterones E and Z, guggulsterol-I, II, III, cholesterol, sesamin and camphorene.	Enhance thyroid function and thus increases fat burning.
2.	Garlic	*Allium sativum*	bulb	alliin, ajoene, diallylsulfide, dithiin, S-allylcysteine, saponins, flavonoids,	flavonoids isolated from Allium sativum L.shows its effect on body fat and blood lipid profile of high fat animals.
3.	Onion, garden onion,	*Allium cepa, Alliaceae*	bulb	Quercetin,. protein, sugars, cellulose, minerals, a fixed oil, an essential oil	-

4.	ginseng	*Panax ginseng Araliaceae.*	Root,berries	Ginsenoside, panaxdiol	Saponins inhibit pancreatic lipase and delay the intestinal absorption of dietary fat.
5.	Bitter melon,bitter gourd,	*Momordica chanrantia Cucurbitaceae*	Seed, fruit	Steroidal saponins-charantin, insulin-like peptides, and alkaloids. Proteins- alpha- and beta-momorcharin	Improved insulin resistance
6.	Green tea	*Camellia sinensis*	Leaf,	Volatile oils, vitamins, minerals, and caffeine, polyphenols- catechin, epigallocatechin gallate (EGCG).	catechins, and epigallocatechin gallate (EGCG) reduces adipocyte differentiation and proliferation, lipogenesis, fat mass, body weight, etc., as well as to increase beta-oxidation and thermogenesis**.**
7.	Aloe vera,	*Aloe barbadensis Liliaceae.*	Dried juice	mannans, polymannans, anthraquinone C-glycosides, anthrones and anthraquinones and various lectins	Not known
8.	Bahera, Myrobalan	*Terminalia belerica Combretaceae*	fruit	Belleric acid, glycoside saponins bellericoside and bellericanin, sterols such as β-Sitosterol Polyphenols - Phyllembin, ellagic acid, gallic acid, ethyl gallate, chebulagic acid	Not known
9.	Kokum Brindonia indica	*Garcinia indica Clusiaceae*	Seeds, fruit	Hydroxycitric acid (HCA) is a derivative of citric acid, oleic, Palmitic, Linoleic, Stearic acid vitamin E, Garnicol.	Hydroxycitric acid, inhibits the extramitochondrial enzyme adenosine triphosphate–citrate (pro-3S)-lyase. As a citrate cleavage enzyme that may play an essential role in de novo lipogenesis inhibition

10.	Queen's flower	*Lagerstroemia Speciosa Lythraceae*	Barks fruits, flower	Triterpenoid- Corosolic acidCorrosolic acid Penta-O-galloyl-glucopyranose (PGG) Ellagitannin Lagerstroemin	Metabolic enhancer.
11.	Mango	*Mangifera indica L. Anacardiaceae*	Fruit, bark,	prebiotic dietary fiber, vitamin C, polyphenols and carotenoids. vitamins A, C and E and omega-3 and -6 polyunsaturated fatty acids.	inhibition of pancreatic lipase (PL) and lipoprotein lipase (LPL) as well as for the inhibition of lipolysis of 3T3-L1 adipocytes affect both fat absorption and the uptake of fattyacids.
12.	Cinnamon	*cinnamomum verum, nym C. zeylanicum Lauraceae*	bark	cinnamaldehyde, cinnamyl acetate, eugenol, and anethole	it reduce body wt by reducing cholesterol and lipid level
13.	Lotus	*Nelumbo nucifera Nelumbonaceae.*	leaves	it contain alkaloid nuciferin,romerinandnerenyuferin,seed containprotein17.2%,fat2.4%carbohydrate66.6%,calcium,phosphurus,iron,ascorbic acid,vitB.	inhibition of the activities of α-amylase and lipase, and up-regulated lipid metabolism
14.	Gymnema	*Gymnema Sylvester Asclepiadaceae*	leaves	triterpenoid saponins - gymnemic acids. 3-O-glucuronide of gymnemagenin gymnemic acids I-VII, gymnemosides A-F, gymnemasaponins	reduces wt by reducing the cholesterol and lipid level
15.	Liquorice	*Glycerrhiza glabra*		Glycyrrhizin, glycyrrhetinic acid flavonoids, isoflavonoids, chalcones, coumarins, triterpenoids, sterols, lignins, amino acids, amines, gums, volatile oils.	The flavonoid content controls the obesity by regulation of the rate-limiting enzymes in the fatty acid synthesis and oxidative pathways in the liver.

16.	Gokhru	*tribulus terestris Zygophylaceae*	fruit	Phytosterols and saponins Harman, harmin protodioscin, the terrestrosins A-E, desgalactotigonin, β-Sitosterol, stigmasterol. steroidal sapogenins	Not known
17.	Ginger	*Zingiber officinale Zingiberaceae*	rhizome	Sesquiterpenoids, with (-)-zingiberene gingerdiol, gingerol, kaempferol, shogaol, vanillic acid, vanillin, zingerone Geranial, neral, zinziberene	gingerol and shogao lincrease the metabolic rate and thus help to "burn off" excessive fat. They also help tosuppress the absorption of calorie-dense dietary fats from the intestines.
18.	Amla	*Emblica officinale Euphorbiaceae*	fruit	amino acids -alanine, aspartic acid, glutamic acid, lysine, and proline, protein, fat carbohydrates fibre, minerals, iron, niacin, and vitamin Ascorbic-Acid, Fiber, Pectin, Zinc	Ability to create a positive nitrogen balance and it also significantly reduces the levels of free fatty acids.
19.	Punarnava	*Boerhaavia diffusa Linn. Nyctaginaceae*		b-Sitosterol, a-2-sitosterol, palmitic acid, ester of b-sitosterol, tetracosanoic, hexacosonoic, stearic, arachidic acid, urosilic acid, Hentriacontane, b-Ecdysone, triacontanol etc	Not known
20.	Bramhi	*Bacopa Moneri Scrophulariaceae*	Whole herb	tetracyclic triterpenoid saponins, bacoside flavonoid, common phytosterols	Not known
21.	Plumbago	*Plumbago zeylanica Plumbaginnaceae*	Root, bark	Contains pungent, yellowish substance that is called as plumbagin	Not known

22.	Nutmeg	*Myristica fragran Myristicaceae*	fruit	myristicin	Not known
23.	China Rose	*Hibiscus rosa sinesis malvaceae*	flower	Taraxeryl acetate, beta-sitosterol, campesterol, stigmasterol	Not known
24.	Vairi, Ekanayakam	*Salacia raticulata Hippocrateaceae*	root	Mangiferin,epicatechin,epigallocatechin,epikokoondiol,salacenona,salaciquinonel	Decrease increased serum and liver triglyceride level
25.	Ragweed	*Kochia scoparia Chenopodiaceae*	fruit	Four new saponins called kochianosides I, II, III, and IV	Not known
26.	Doraji	*Platycodi radix Campanulaceae*		Triterpenoidal Saponin	Inhibit the intestinal absorption of dietary fat by inhibiting its hydrolysis.
27.	orange	*Citrus arantium Rutaceae*	fruit, flower	neohesperidin, synephrin, 5,8-epidioxyergosta-6,adenosine, asparagine, tyrosine, valine, isoleucine, alanine,beta-sitosterol and beta-daucosterol	significantly reduced food intake and body weight gain

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