Herbal Approach for the Management of Obesity – A Review

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ABSTRACT

Obesity is primarily considered to be a disorder of energy balance, and it has recently been suggested that some forms of obesity are associated with chronic low-grade inflammation. There are anti-obesity drugs, affecting the fundamental processes of the weight regulation; however they have shown serious side effects, which outweigh their beneficial effects. Alternatively, dietary phytochemicals and natural health products offer great potential as an efficient weight loss strategy by modulating lipid metabolism and/or increasing BMR and thermogenesis. Specifically, Polyphenols such as Chlorogenic acid, Ferulic acid, Gallic acid, Cinnamaldehyde, Curcumin, Naringin, Quercetin, Capsaicin and Caffeine have been reported to increase lipolysis and induce fatty acid β-oxidation through modulation of genes. In this review article, we discuss selected phytochemicals and medicinal plants in relation to their integrated functionalities and specific mechanisms for weight loss.

Key words: Obesity, low-grade inflammation, anti-obesity drugs, phytochemicals, medicinal plants.

INTRODUCTION

Obesity is a most common metabolic disorder in the societies, which results from excess fat accumulation in the body. It is not the single disorder but, a heterogeneous group of conditions with multiple causes. Obesity is accredited to genetic and family link, health of an individual, certain medications, emotional factors, age, smoking, pregnancy, lack of sleep etc. Hormone treatment often prescribed for hypothyroidism, Cushing’s syndrome, Polycystic Ovarian disease may lead to overweight. Corticosteroids, antidepressants, and seizure medicines also results in weight gain, boredom, anger, anxiety and too much of stress which contribute to obesity. Nicotine level helps to burn calories; therefore quitting smoking often leads to reduction in calorie burning, thereby causing obesity. Aging process results in muscle relaxation, more particularly for those indulged in sedentary life style that ultimately leads to weight gain due to inhibition of calorie burning. Adequate sleep is an essential for maintaining a good health. Sleep maintains a balance between hormones like ghrelin, leptin that are responsible for hunger. Insufficient sleep disturbs the balance and thereby increases appetite, consequently leading to excess fat.

Excessive day sleepiness (EDS) and tiredness are common symptoms of obesity and are linked to an individual’s health issues.

**Measurement of Obesity:**

There are many methods that can be used to evaluate body fat in different populations. While anthropometric measurements of weight-for-height have been traditionally used to evaluate obesity, more recently, BMI has become a standard parameter. BMI is defined as weight in kilograms divided by height in square meters. The normal range is 19–24.9 kg/m², while overweight defined as 25–29.9 kg/m², and obesity as ≥30 kg/m². Unfortunately, BMI does not provide any insight into regional body fat distribution. Thus, simple anthropometric measurements, such as waist circumference, can also be used to determine the valid index of visceral fat accumulation, in addition to being able to serve as an indicator of health risks associated with visceral obesity. A waist circumference of greater than 102 cm in men and 88 cm in women is a risk factor for cardiovascular disease. A particularly important anthropometric parameter that has been increasingly applied in recent years is sagittal abdominal diameter. Using a simple caliper that was originally developed by Kahn and this anthropometric indicator can measure visceral fat tissue alone. With tetra polar bioelectric impedance analysis, body density can be measured by exposing the body to an alternate current of 50 kHz at strength of 800 μA which provides the information on the relationship between the body mass and volume. Radio isotopic techniques use deuterium or tritium as markers to measure the total body liquid and total body potassium. Ultrasonography measures fat tissue and is currently considered to be a favoured technique by which one can measure both subcutaneous and visceral fat tissues. Measurements are carried out by using a 7.5- and 3.5-MHz transducer for the subcutaneous and visceral fat tissue, respectively. The most accurate method of measuring central obesity is through the use of magnetic resonance imaging or computer-assisted tomographic scanning. Unfortunately, these approaches are too expensive for routine use.

**Metabolism during Obesity:**

The two major sources of energy in a human body are carbohydrates and fatty acids. The body produces energy in the form of ATP by oxidation of carbohydrates, fats and proteins through tricarboxylic acid (TCA) cycle; and by oxidation of fatty acid through β-oxidation. Under normal conditions, more ATPs are produced through β-oxidation of fatty acids in the mitochondria than through oxidation of carbohydrates. The first requirement in β-oxidation of fatty acid is the presence of fatty acyl-CoA and its transport into the mitochondria which is facilitated by CPT-1 (Carnitine Palmitoyl transferase -1). Acetyl-CoA carboxylase (ACC) plays a central role both in fatty acid β-oxidation and fatty acid biosynthesis. ACC catalyses the carboxylation of acetyl-CoA to malonyl-CoA, which can be used by fatty acid synthase for fatty acid biosynthesis. As malonyl-CoA is the substrate for fatty acid biosynthesis, malonyl-CoA is a direct inhibitor of mitochondrial fatty acid uptake as well as inhibition of CPT-1. Therefore, the enzymes CPT-1 and fatty acid synthase (FAS) directly regulate catabolism and anabolism of fatty acids. Adenosine monophosphate-activated protein kinase (AMPK) regulates fatty acid metabolism by inhibition of ACC activity and stimulation of CPT-1 production. Thus AMPK stimulate fatty acid β-oxidation and down regulate fatty acid biosynthesis. SIRT1 and SIRT3 belong to the sirtulin family of the silent information regulator 2 enzymes which have been found to regulate hepatic lipid metabolism by the activation of the AMPK pathway thus facilitating fatty acid oxidation. Obesity can lead to impaired cellular metabolism due to dependence on glucose oxidation (for ATP production) and decrease in fatty acid oxidation, thus leading to more fat deposition in skeletal muscles, hepatocytes and other cells.

**Adipokines:**

Fat cells called adipocytes actively secrete a variety of products that create a link between...
obesity and other components of metabolic syndrome. These biologically important substances are called adipocytokines (Leptin, Resistin, Adiponectin, Free fatty acid (FFA), Tumor necrosis factor α (TNF-α), Interleukin - 6 (IL-6), Plasminogen activator and inhibitor (PAI), Angiotensinogen, Vistafin and Glucocorticoids) 15. Peroxisome proliferator activated receptor-γ (PPAR-γ) and CCAAT/enhancing binding proteins (C/EBPα, C/EBPβ & C/EBPδ) are key transcription factors in adipogenesis. C/EBPβ & C/EBPδ are induced during the early adipogenesis. Activation of these transcription components is then followed by activation of PPAR- γ and C/EBPα, the central transcriptional regulators in adipogenesis. Once PPAR- γ and C/EBPα are activated, they cooperatively enhance each other, which then induce further expression of adipogenic genes required for maintaining adipogenic characteristics and terminal differentiation. In particular, PPAR- γ is a central regulator of adipogenesis and represents a good target for antiobesity therapy 16, 17. PPAR- γ coactivator -1α (PGC-1α) is recognised as key regulators of mitochondrial biogenesis and function through interactions with nuclear receptors 18. Severe calorie restriction 19 and exercise 20 increases PGC-1α expression in skeletal muscle of obese subjects. PR domain containing 16 (PRDM 16) is a zinc finger protein that directs the white adipocyte lineage towards brown fat in vivo, by activating a robust pattern of brown fat gene program and simultaneously suppressing the white fat gene program 21. Leptin can alter insulin action and has recently been recognized as an important mediator of obesity-related hypertension 22. Angiotensinogen, the precursor of angiotenin II, a key mediator of vascular injury, can be produced and secreted by adipose tissue 23. In contrast, excessive visceral adipose tissue has been shown to be associated with decreased adiponectin levels 24 and an important hormone that exerts antidiabetic 25, 26 and antiatherogenic functions 27, 28. Adiponectin activates AMP-activated protein kinase, which promotes skeletal muscle glucose uptake and suppresses hepatic glucose production 26. Importantly, adiponectin also inhibits NF-κB activation, thus, attenuating inflammation 29. Unlike adiponectin, plasma levels of visfatin increase in parallel with visceral fat in both mice and humans 30 so the role of visfatin in insulin resistance needs additional investigation. Taken together, these observations suggest that the adipocyte is an integral coordinator of the relationship among obesity, diabetes, and CAD. Infiltration of adipose tissue by macrophages and lymphocytes has been associated with insulin resistance. It is believed that these inflammatory cells alter adipogenesis via secretion of pro-inflammatory cytokines which may result in impaired hyperplasia of adipose tissue in response to high caloric intake 31. Proinflammatory cytokines like TNF-α and IL-6 are secreted by macrophage infiltrated adipose tissue 32. IL-6 promotes insulin resistance by inducing lipolysis and inhibition of adiponectin secretion. IL-6 has also been suggested to have role in the early stages of atherosclerosis 33. TNF-α binds to TNF-α receptor and activates the C-JUN terminal kinase (JNK) and /or Nuclear factor-κB (NF-κB). Increased JNK activity in obesity leads to fortified insulin resistance as Insulin receptor substrate-1 (IRS-1) activity is decreased 34. TNF-α affects the expression of several adipokines with central role in mediating the health risks associated with obesity like decrease in adiponectin levels, increase in leptin, more FFA are released, circulating PAI levels are elevated and more MCP-1 (Monocyte chemoattractant protein-1) are secreted 35. The increased PAI-1 concentration in the vessel wall as well as in the plasma could participate in increased cardiovascular risk and unfavourable plaque formation in type 2 diabetes 36. MCP-1 is elevated in type 2 diabetic patients, 37 it is suggested to be involved in regulation of insulin sensitivity in 3T3-L1 adipocytes in vitro 38. These observations suggest that the adipocyte is an integral coordinator of the relationship among obesity, diabetes, and CAD.
General approach in management of obesity:
Weight management is a commonly recommended approach which is based on lifestyle modifications including dieting, increased physical activity and exercise. However, physical exercise and dieting is often a difficult routine to maintain for lifetime and the results can be disappointing in long term. At present, the combination therapy of reducing calorie intake, increased energy expenditure and pharmacotherapy is becoming more popular. To this end, several drugs such as Fenfluramine, R-Fenfluramine, Temin, Sibutramine, Orlistat, Qsymia, and Belviq are approved by FDA towards weight management aid. However, four of these drugs were removed later on, due to their adverse health effects 39. In addition, all current weight management drugs in the market have high cost as well as potential side effects thus causing dissatisfaction to the consumers. Finally, Gastric surgery has been the most effective approach in severely obese to show long term effects. Despite the progress in weight management strategy in recent years, obesity still poses a serious challenge to the scientific community 39, 40. Therefore, there is a considerable demand to explore natural therapies in developing an alternative, safer and effective therapy. For this reason, a variety of natural phytochemicals have been explored for their ability to increase fatty acid β-oxidation, fat absorption and suppress appetite control. This review article focuses on those phytochemicals and the medicinal plants that potentially increase fatty acid β-oxidation in relation to weight loss.

Herbal approach in management of obesity:

Phytochemicals:
Phytochemicals are non-nutritive components present in plant-based diet that exert protective or disease-preventing effects. They have been associated with protection from and/or treatment of chronic diseases such as heart disease, cancer, hypertension, diabetes and other medical conditions 41. Phytochemicals are classified as primary and secondary constituents. Primary constituents include the common sugars, amino acids, proteins, purines & pyrimidine of nucleic acids, chlorophyll etc. Secondary constituents are the remaining plant chemicals such as Alkaloids, Terpenes, Flavonoids, Ligands, Plant Steroids, Saponins, Phenolics, and Glucosides 42.

Phenolic acid:
Chlorogenic acid: Chlorogenic acid significantly lowered body weight, visceral fat mass, and plasma leptin and insulin levels compared to high fat control group in which adiponectin level was elevated in plasma 43 and in visceral adipose tissue (VAT) 44. Chlorogenic acid increased the protein expressions of PPAR-γ and PPAR-α 44 in liver. Chlorogenic treatment attenuated inflammation in the liver and white adipose tissue (WAT) accompanied by a decrease in mRNA levels of macrophage marker genes that included F4/80, Cd68, Cd11b, Cd11c and TNF-α 45.

Ferulic acid: Ferulic acid was shown to improve lipid and glucose homeostasis by modulating the expression of lipogenesis genes (SREBP1C, FAS, ACC), stimulating β-oxidation genes (CPT1α, PPAR-α) and gluconeogenesis enzymes, PEPCK (Phosphoenolpyruvate carboxy kinase) and G6pase (Glucose 6 phosphatase) 46. Additionally, Ferulic acid regulated hepatic GLUT2 gene expression via modulation of transcription factors have been observed in high fat and fructose induced type 2 diabetic adult male rats 47. Furthermore Ferulic acid has contributed to the modulation of inflammatory processes via suppression of NO production by down regulating the expression of NF-kB mediated iNOS gene 48.

Gallic acid: Gallic acid improved glucose tolerance and lipid metabolism in obesity mice, thereby showing evidence of anti-hyperglycaemic activity 49, 50, and 51. Gallic acid stimulated PPARγ expression and inhibited TNF–α and IL-6 expression in treated animals 49, 50. Gallic acid consumption reduced oxidative stress and GSSG (Oxidised glutathione) content and enhanced the levels of reduced glutathione (GSH), GSH peroxidase, GSH reductase and GSH-S-transferase in the hepatic tissue of rats 51.
**Flavonoids:**

**Cinnamaldehyde:** Cinnamaldehyde treatment decreased body weight, fat mass, food intake and serum lipid and improved insulin sensitivity\(^{52, 53, 55}\). Cinnamaldehyde treatment significantly decreased the mRNA expression of TNF-\(\alpha\)\(^ {53}\) that stimulates the AMPK activation, PPAR\(\alpha\)\(^ {54}\), PPAR\(\gamma\), PRDM 16 and PGC-1\(\alpha\)\(^ {55}\) in adipose tissue. Additionally, cinnamaldehyde inhibited the hypertrophy of adipose tissue and induced browning of white adipose tissue\(^ {55}\).

**Curcumin:** Curcumin inhibited adipocyte differentiation and promoted antioxidant activities by reducing the expression of TNF-\(\alpha\), MCP-1 and PAI-1 and induces the expression of adiponectin, the principal anti-inflammatory agent secreted by adipocytes\(^ {56}\). Thus Curcumin regulated lipid metabolism which plays a central role in the development of obesity and its complications\(^ {57}\).

**Naringin:** Naringin normalised systolic blood pressure and improved vascular dysfunction and ventricular diastolic dysfunction in high carbohydrate and high fat fed rats. These beneficial effects of naringin may be mediated by reduced inflammatory cell infiltration, reduced oxidative stress, lowered plasma lipid concentration and improved mitochondrial dysfunction in rats\(^ {58}\). Naringin decreased aortic fatty streak area\(^ {59}\) and reduced plaque progression\(^ {60}\) in high fat diet induced animal model.

**Quercetin:** Quercetin exerts antiadipogenic activity by modulation of ERK and JNK pathways which plays a pivotal role in apoptosis of mature adipocytes\(^ {61}\). It decreased the adipose tissue inflammation by enhancing the expression of AMPK and SIRT1\(^ {62}\) and decreasing the expression the JNK, NF-\(\kappa\)B\(^ {63}\).

### Table 1: Mechanism of Antiobesity Compounds

<table>
<thead>
<tr>
<th>Phytochemicals</th>
<th>Antiobesity compounds</th>
<th>Mechanism of action</th>
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<tbody>
<tr>
<td>Phenolic acid</td>
<td>Chlorogenic acid</td>
<td>↑ PPAR-(\gamma), PPAR-(\alpha), Adiponectin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ β-oxidation, gluconeogenesis enzymes</td>
</tr>
<tr>
<td></td>
<td>Ferulic acid</td>
<td>↑ PPAR-(\gamma), GSH, GPO, GSH-reductase, GSH-S-transferase</td>
</tr>
<tr>
<td></td>
<td>Gallic acid</td>
<td>↑ PPAR-(\gamma), TNF (\alpha), IL-6, GSGG</td>
</tr>
<tr>
<td></td>
<td>Naringin</td>
<td>Improve mitochondrial and vascular dysfunction</td>
</tr>
<tr>
<td></td>
<td>Quercetin</td>
<td>↑ AMPK, SIRT1</td>
</tr>
<tr>
<td></td>
<td>Alkaloids</td>
<td>↑ PPAR-(\gamma), PPAR-(\alpha), UCP-2</td>
</tr>
<tr>
<td></td>
<td>Capsaicin</td>
<td>↑ TNF (\alpha), IL-6</td>
</tr>
<tr>
<td></td>
<td>Caffeine</td>
<td>↑ Catecholamine, FFA</td>
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<td></td>
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<td>↓ Systolic BP, IR</td>
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</table>
Alkaloids:
Capsaicin: Capsaicin increased the expression of adiponectin, PPARα, PPARγ and (Uncoupling Protein 2) UCP 2 and decreases the expression of TNF-α and IL-6. UCP 2 does not mediate adaptive thermogenesis, but they may be significantly thermogenic under specific pharmacological conditions. There is strong evidence that the mild regulated UCP 2 attenuates mitochondrial reactive oxygen species production, protects against cellular damage and diminishes insulin secretion. Thus Capsaicin decreased lipid accumulation and inflammation in adipose tissue and increased insulin sensitivity in animal model.

Caffeine: The treatment with caffeine in the rats fed with high-carbohydrate, high-fat diet decreased body fat and systolic blood pressure, improved glucose tolerance and insulin sensitivity and attenuated cardiovascular and hepatic abnormalities. Moreover, Caffeine has increased the serum concentrations of catecholamine and free fatty acids in HFD rats. This treatment showed that the intake of caffeine reduced the body fat by lipolysis via catecholamine.

Antioxidant plants:
Medicinal plant samples can be collected from the whole plant, or from parts of the plant, such as the stem, bark, leaf, flowers, and roots. These materials are then processed into different forms, such as powder or capsules. However, most of the medicinal plants which have shown antioxidant properties were prepared in the form of aqueous or alcoholic extracts. This may be because the decoction, distillation, and infusion procedures that can concentrate the constituents responsible for the therapeutic efficacy of the examined herb. Some components that inhibit the anti-obesity function of the bioactive compounds can be isolated by the extraction procedure. Extraction and partial purification, or the isolation of the active principle(s) could increase the bioavailability of the bioactive constituents in medicinal plant extracts and thereby consequently enhance the efficacy of the medicinal agent in weight loss process. In the screening study of all plants, despite the different parts chosen, they were extracted using ethanol. This is because alcohol has been proven to degrade cell walls and seeds more efficiently than water. The application of more alcohol in the solvent could reduce degradation of polyphenols by enzyme polyphenol oxidase. In addition, all of the identified constituents from plants are either aromatic or saturated organic compounds so the most appropriate method of extraction are often obtained through ethanol or methanol extraction. In support of the above illustration, a maximum amount of phytochemicals were noted in ethanolic extract of Glycyrrhiza glabra root, Alternanthera sessilis leaf and Punica granatum leaf. Antioxidants protect the human body from free radicals and reactive oxygen species. They retard the progress of many chronic diseases as well as lipid peroxidation. Plant phenolics and flavonoids are effective free radical scavengers and their antioxidant activities are well documented. Natural antioxidants tend to be safer and are known to exhibit a wide range of biological effects such as antilipase, antibacterial, antiviral, anti-inflammatory, antiallergic, antithrombotic and vasodilator activities. Similarly ethanolic extract of Benincasa hispida fruit and citrus paradisi fruit possess potent antioxidant activity. The extract of Benincasa hispida fruit and Carico papaya leaf contains β-sitosterol which possesses cardio protective effect and thus helps in the management of obesity, hyperlipidaemia and atherosclerosis. The compounds of Garcinia cambogia rind like tetra decanoic acid, hexa decanoic acid and octa decanoic acid showed better interaction with Retinol binding protein 4 (RBP4). Another research suggested that n-hexadecanoic acid, compound from Trigenella foenum graecum and β-sitosterol, compound from Carico papaya showed better interaction with fat mass and obesity-associated protein (FTO) increased serum RBP4 level and FTO gene variation are observed in obesity.
CONCLUSION

Obesity is a significant and increasing public health problem worldwide. Even though, there are several treatments, such as surgery and drugs, there seems to be no efficient treatment without potential side effects. Natural products identified from traditional medicinal plants have always paved the way for development of new types of therapeutics. Most studies describe phytochemicals in the plant species presenting the great evidence for effective obesity treatment, through both in vitro and in vivo studies. Experiments are yet to be conducted for providing innovative technologies aimed at research and development of phytotherapeutic medicines, with the possibility of high benefit-cost ratio, efficacy for obese patients, and improvement in the epidemiological profile of the disease among the population.

Abbreviation:

AMPK = 5’ Adenosine monophosphate activated protein kinase.
PPAR-γ = Peroxisome proliferator activating receptor- alpha.
PPAR-γ = Peroxisome proliferator activating receptor- gamma.
WAT = White adipose tissue.
VAT= Visceral adipose tissue.
F4/80 / EMR1 = EGF-like module-containing mucin like hormone receptor – like 1
Cd 68 = Cluster of differentiation 68.
Cd 11b = Integrin alpha M chain.
Cd 11c = Integrin alpha X chain.
TNF-α = Tumor necrosis factor – alpha.
SREBP 1c= Sterol regulatory element binding protein 1 c.
FAS = Fatty acid synthase.
ACC = Acetyl CoA synthase.
CPT1α = Carnitine palmitoyl transferase 1 alpha.
PEPCK = Phospho enol pyruvate carboxy kinase.
G6pase = Glucose 6 phosphatase.
NO = Nitric oxide.
NF-kB = Nuclear factor- kappa B.
iNOS = Inducible nitric oxide synthase.
IL-6 = Interleukin -6.

AKT / PKB = Protein kinase B.
GSSG = Oxidised glutathione.
GSH = Reduced glutathione.
PRDM = Pineal restrictive downstream module.
PGC-1α = Peroxisome proliferator activated receptor gamma coactivator – 1 alpha.
MCP-1 = Monocyte chemoattractant protein – 1.
PAI -1= Plasminogen activator inhibitor – 1.
Wnt /β catenin = Wingless typeMMTV integration site family member / β-catenin.
SIRT1= Silent mating type information regulation 2 homolog – 1.
UCP2 = Uncoupling protein 2.

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