

Exploring herbal natural bioactives to treat obesity

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ABSTRACT

Worldwide, obesity has gained attention as a major health pandemic that can lead to mortality. It is caused by genetics, medicines, stress, sleep and physical inactivity. Over the past three decades, the incidences of obesity has grown. Conventional methods to manage obesity are medication, surgery, and lifestyle changes. However, there is an increasing interest in alternative methods, especially herbal, due to the adverse effects of conventional therapies. To control obesity, the development of novel, and non-toxic techniques are required. Herbs are primary sources of bioactive components used to treat several diseases, including obesity. Various active constituents in plants showed anti-obesity activity through inhibition of adipocyte differentiation, lipogenesis, suppression of appetite and enhancing lipolytic activity. One potential effective way to treat obesity is use of nanoparticles. These minute particles have the potential to directly transport anti-obesity medications to adipose tissue. Plant extracts are also used to synthesize nanoparticles, which is called "Green Synthesis". This review explores the herbs (*Allium cepa*, *Moringa oleifera*, *Tamarindus indica*) used to treat obesity and discusses phytoconstituents (apigenin, lycopene, myricetin, and green synthesized nano-formulations) to manage obesity.

Key words: Alkaloids, Flavonoids, Herbs, Mechanisms, Nanoparticles, Obesity, Phytochemicals, Saponins, Terpenoids.

1. INTRODUCTION

Obesity has emerged as a major worldwide health issue in recent times (28). Over 1/3rd of global populace suffers from obesity, that raises the risk of cardiovascular disease, dyslipidemia, diabetes, malignancies and metabolic syndrome (56). It can be described as higher body fat percentage than normal or as an accumulation of excess fat in the body. It is characterized as a body mass index (BMI) of $\geq 30\text{kg/m}^2$, whereas, a BMI of 25kg/m^2 to

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29.9 kg/m² is termed as overweight (pre-obesity) (63). Numerous factors contribute to obesity (sedentary lifestyle, heredity and a disparity between the amount of calories consumed and spent (32). Its global prevalence rate is 39 %, making it one of the noncommunicable diseases that is rising at a fast pace (42). Many drugs (liraglutide, naltrexone or bupropion, phentermine or topiramate, and orlistat) are available for long-term obesity management (65). But these drugs have side effects. So, researchers have concentrated the safer and more efficient alternatives such as herbal plants (27). Plant-based natural products, whether as pure phytochemicals or as crude extracts anti-obesogenic activities and are non-toxic than conventional drugs. These plant-based products treat obesity by focusing on the several metabolic pathways and/or regulatory processes associated with obesity (1).

2. HERBAL PLANTS TO TREAT OBESITY

Worldwide, the use of plants as complementary medicine for many ailments is growing in popularity because a vast array of plant species provide therapeutic properties (50). To manage obesity, a variety of synthetic drugs are available, but had serious side effects. So, the main emphasis is given to herbs due to their fewer side effects. Many herbs (*Allium cepa* L., *Annona muricata* L., *Moringa oleifera* Lam., *Moringa peregrine* (Forssk.), *Tamarindus indica* L. (Table. 1) can help to reduce weight and increase metabolism, these burning fat by speeding up the metabolism. Some anti-obesity plants, along with their mechanisms of action and other therapeutic uses are given in Table 1. Certain herbs make you feel satiety for long period that helps in reducing the calorie intake, while others have thermogenic effects to increases your metabolism. These herbal formulations must be used carefully to maximize weight loss while minimizing harmful side effects. When combined with a diet and exercise routine, herbs use can reduce weight. Natural therapies used in ancient medical systems have been effectively applied in clinical practice to develop less hazardous anti-obesity drugs in future (13,53).

Table 1. Promising herbal plants used to treat obesity using High Fat Diet induced obesity model

S. No.	Plants, Family	Mechanism of Action	Uses/ Therapeutic Activity	Ref
AQUEOUS EXTRACTS				
LEAF EXTRACTS				
1.	<i>Achyranthes aspera</i> L., (Amaranthaceae)	Inhibits pancreatic lipase, activates thermogenesis, decreases adipocytes, reduces serum leptin, and modulates adipocytokines. Also, improves lipid profile as well as oxidative stress.	Used in rheumatism, skin diseases, scabies, and liver complaints. Other therapeutic activities include hypoglycemic, spermicidal, anti-inflammatory, anti-arthritis, antipyretic, analgesic, laxative, purgative, and hepatoprotective.	8
2.	<i>Annona muricata</i> L., (Annonaceae)	Downregulate the FTO and STAT-3 genes.	Antiparasitic, anti-arthritis, anticancer, antidiabetic, anti-convulsant, hepatoprotective, and antimalarial.	21

3.	<i>Capsicum annuum</i> L., (Piperaceae)	It decreases fat accumulation in adipocytes; PGC-1 α ; CPT-1 and concentration of adiponectin. It also downregulates lipogenic genes such as SREBP1 and chREBP.	Antimutagenic, antioxidant	54
4.	<i>Thymus vulgaris</i> L., (Lamiaceae)	It shows its action by regulating the serum markers associated with obesity, and bile acids associated with fat absorption. Further research is required in understanding the mechanism.	Antibacterial, antifungal, antiviral, antioxidant, anticancer, and antihypertensive.	45
ROOT EXTRACTS				
5..	<i>Drynaria fortunei</i> (Kunz) J.Sm., (Polypodiaceae)	It suppresses the adipogenic transcription factors and decreases adipocyte size.	Used in bone diseases such osteoporosis, bone fracture.	29
SEED KERNEL EXTRACTS				
6.	<i>Mangifera indica</i> L., (Anacardiaceae)	Inhibits pancreatic lipase, which results in decreased intestinal fat absorption, and also enhances oxidative stress by acting as potent antioxidant.	Anti-carcinogenic, anti-inflammatory, anti-allergic, anti-microbial, antioxidant, and antidiabetic.	41
ETHANOL EXTRACTS				
LEAF EXTRACTS				
7.	<i>Allium cepa</i> L., (Amaryllidaceae)	Manage obesity by reducing body weight, lipid deposits, liver weight, fat mass, and improve lipid profiles such as lowering serum LDL, triglycerides, total cholesterol, VLDL, and increasing HDL. However, further research is required on its mechanism of action for weight reduction.	Antidiabetic, antibacterial, anti-inflammatory, hypolipidemic, anti-microbial, antihypertensive, analgesic, anti-oxidant, anti-arthritis, and anti-thrombotic.	52
8.	<i>Brassica juncea</i> (L.) Czern., (Brassicaceae)	It enhances the level of fatty acid oxidation protein (CPT-1), and thermogenesis-associated protein (PGC-1 α). It also suppresses adipogenic proteins (PPAR- γ , C/EBP- α , and aP2) and stimulates phosphorylation of lipid synthesis proteins (ACC).	Antifungal, anticancer, antibacterial, antioxidant, anti-inflammatory	47
9.	<i>Moringa oleifera</i> Lam., (Moringaceae)	Increase leptin levels (a hormone that regulates body weight), and also increase adiponectin levels, which are inversely proportional to	Anti-inflammatory, anticancer, anti-ulcer, and immunostimulant.	24

		adiposity. Apart from this, it decreases serum LDL-C, triacylglycerol, and total cholesterol and increases the level of HDL-C, which is also elevated in obesity.		
10.	<i>Moringa peregrine</i> (Forssk.) (Moringaceae)	Decrease in the absorption of fats in the intestine may be via inhibiting pancreatic lipase enzyme. It modifies the activity of leptin by suppressing leptin expression (PPAR γ), and other transcription factors. Still, the mechanism is not clearly known; further investigations are required.	Hypoglycemic, anti-oxidant, anti-inflammatory.	4
11.	<i>Nelumbo nucifera</i> Gaertn., (Nelumbonaceae)	Decrease adipocyte differentiation through upregulation of PPAR- α , LPL, CPT-1, and CYP7A1, and downregulating PPAR- γ , and C/EBP- α . Also downregulate the mRNA expression of inflammatory genes (Caspase-1, TNF- α , TLR4, IL-1 β , IL-18, SREBP-1c), and lipid synthesis genes. So, it inhibits fat deposition, and lipogenesis in 3T3-L1 adipocytes and improves oxidative stress.	Anti-oxidant, anti-cancer, and anti-cardiovascular.	70
12.	<i>Tamarindus indica</i> L., (Fabaceae)	Show its action by controlling the gene expression of transcription factors (LXR α , PPAR γ , SREBP-1c). It significantly upregulates HSL (Hormone Sensitive Lipase) and some other enzymes (MAGL, ATGL), but somewhat in a smaller amount.	Anti-oxidant, hypolipidemic, anti-hypertensive, and hypoglycemic.	40
STEM EXTRACTS				
13.	<i>Acacia nilotica</i> L., (Fabaceae)	Decrease cytokine production, inhibit leptin resistance, and boost adiponectin.	Free radical scavenger, anti-inflammatory, antispasmodic, anti-hypertensive, and anti-platelet.	36

14.	<i>Euphorbia humifusa</i> Wild., (Euphorbiaceae)	It down-regulates the adipogenic transcription factors (PPAR- γ , SREBP-1c, C/EBP- α) as well as improves the lipid profile.	Used in inflammation, diabetes, asthma, kidney disease, heart disease, cancer, bacterial infections, and mental anxiety.	44
FRUIT EXTRACTS				
15.	<i>Cydonia oblonga</i> Mill., (Rosaceae)	Activates AMPK which results in reduce expression of adipogenesis-associated genes (ACL, ACC1, Ap2, FAS); transcription factors (PPAR- γ , C/EBP α , SREBP-1c), and increase the expression of lipolysis-associated genes (CPT1, HSL).	Anti-allergy, anticancer, anti-inflammatory, antidiabetic, antihypertensive, and anti-depressant.	43

3. ROLE OF PHYTOCHEMICALS IN OBESITY

The Phytochemicals (chemical compounds found in plants), are responsible for biological activities (60). More than thousand phytochemicals have been identified and are present in whole grains, fruits, vegetables, nuts and herbs (62). Phytochemicals are basically secondary metabolites. Many naturally occurring secondary metabolites or phytochemicals (alkaloids, flavonoids, glycosides, tannins, terpenoids, polyphenols, carboxylic acid etc.) are found in various plants and possess anti-obesity properties through diverse mechanisms of action (10).

3.1 Flavonoids

Flavonoids are biologically active substances with variety of biological functions and are abundant in plants kingdom. These are potent inhibitors of obesity and associated metabolic problems. In its structure, it has a pyrone ring joined to a benzene ring, where a phenyl ring is substituted at position 2 or 3. Flavonoids are categorized as flavonols, isoflavones, flavones, anthocyanidins, flavanols, flavanones and chalcones. Their mechanism of action is by alteration of proteins, genes and transcriptional factors involved in promoting fatty acid B-oxidation, lowering lipogenesis, raising lipolysis, burning energy and break down and metabolize carbohydrates. Furthermore, oxidative stress is suppressed, and inflammatory reactions are mitigated (5,55). Several active constituents (apigenin, genistein, quercetin, myricetin, kaempferol, daidzein, and naringenin) contribute to anti-obesity effects and their mechanisms are described (Table 2).

3.2 Alkaloids

These are indigenous bioactive compounds, whose structures include one or more nitrogen atoms. Their pharmacological properties are: impact human health, including anti-oxidant, anti-tumor, anti-hypertensive, anti-microbial, anti-inflammatory and anti-

diabetic (59). They show their anti-obesity activity by regulating lipid metabolism and they basically target AMPK (Activated Protein Kinase). The availability of lipids like fatty acids is reduced because it inhibits anabolic metabolism and increases lipid catabolic metabolism (14). Their active constituents (piperine, nuciferine, trigonelline, and capsaicin) with anti-obesity effects and are mechanisms described (Table 2).

3.3 Terpenoids

Terpenoids ("isoprenoids") are the biggest groups of natural compounds and are composed of isoprene units containing five carbons. Based on the number of isoprene units present, they are categorized as monoterpenoids, hemiterpenoids, sesquiterpenes, diterpenes, triterpenes, tetraterpenes, and polyterpenes. Several active constituents (betulinic acid, ursolic acid, and oleanolic acid) demonstrate anti-obesity effects their mechanisms detailed in Table No. 2. To treat metabolic disorders like diabetes and obesity, AMPK (Activated Protein Kinase) is a perfect therapeutic target. The terpenoids found in dietary or herbal plants activates AMPK, which acts as a "fuel sensor" to regulate energy homeostasis. Eating daily these terpenoids may manage obesity and other metabolic disorders associated with obesity (64). PPAR (Peroxisome Proliferator Activated Receptors) plays a significant role in the metabolism of lipids, which is a biomarker of obesity. They are involved in the formation of adipose tissue and adipogenesis, especially PPAR- α and PPAR- γ . Through these receptors, terpenoids affects the obesity and associated metabolic disorders (49, 75). Besides, terpenoids have antiviral, antimalarial, anti-cancer, anti-inflammatory and antibacterial properties. They also have hypoglycemic properties, enhance transdermal absorption and prevent and cure cardiovascular illnesses. Furthermore, terpenoids have many uses [immunoregulation, neuroprotection, insect resistance, antioxidation, and antiaging (74)].

Table 2. List of some phytochemicals used to treat obesity

Phyto-chemicals	Active constituents	Mechanism of action	Ref.
Flavonoids	Apigenin	Apigenin inhibits the porcine pancreatic lipase enzyme. Its binding may affect the typical spatial shape of the pancreatic lipase active pocket. Docking tests revealed that apigenin shows its antiobesity activity by binding to 6 hub target proteins (ESR1, PPARA, MAPK14, MMP9, NR3C1, and IGF1).	46
	Genistein	It shows its action by promoting lipolysis, stimulating fatty acid oxidation, reducing adipose tissue formation, enhancing differentiation of fat cells, and provoking adipocyte apoptosis. It also upregulates genes such as PPAR γ , Cebp α , and Cebp β .	17, 71
	Kaempferol	It has the ability to stimulate thermogenesis and impede adipogenesis through the control of C/EBP α , PPAR γ , and SREBP-1c expression. These three are recognized as the primary regulators of adipocyte development.	76
	Myricetin, Quercetin	It inhibits the human pancreatic lipase enzyme by binding to its allosteric site.	58

	Daidzein	It inhibits lipid formation and adipogenesis by controlling C/EBP, SREBP-1c, FAS, and ACC.	16
	Naringenin	It suppresses the accumulation of fats by stimulating AMPK.	12
Alkaloids	Nuciferine	Activates brown adipose tissue and increases thermogenesis.	73
	Piperine	Impedes the absorption of intestinal fatty acids by downregulating genes linked to the uptake of fatty acids. It improves gut barrier function and aids in the reduction of obesity-related chronic inflammation.	69
	Trigonelline	By increasing the expression of genes specific to beige (Tmem26, Tbx1, Cited1, Cd137) along with brown-fat signature proteins and genes, it causes 3T3-L1 white adipocytes to brown. It also enhances white adipocyte lipid metabolism by promoting fatty acid oxidation and lipolysis while reducing lipogenesis and adipogenesis.	15
	Capsaicin	It shows its action by changing the gut microbiome, inhibiting low-grade chronic inflammation, modifying the gut-brain axis to modulate hormones that control appetite and fullness, and controlling obesity by regulating energy metabolism.	22
	Terpenoids	Betulinic acid	It reduces the deposition of fats, decreases the enzymes associated with lipogenesis (desaturases), and alters important transcription factors (hlh-11 and nhr-49) as well as microRNAs (miR-786, miR-60, let-7, and lin-4) related to lipid metabolism.
	Ursolic acid	It shows its action by altering the metabolism of amino acids and the gut microbiome. By changing the JNK signaling pathway and insulin, it also demonstrates its anti-obesity properties.	66, 67
	Oleanolic acid	It induces lipolysis via PKA pathway, stimulates heme oxygenase-1 expression, and decreases the oxidative stress inside the cells.	33
Saponins	Diosgenin	It inhibits lipogenesis by reducing the expression of two genes (FASN, and SREBP-1c).	38
	Ginsenoside	It combats obesity by browning the white adipose tissue.	57

3.4 Saponins

Plants have high concentration of bioorganic chemicals called 'saponins'. They are naturally occurring glycosides having soap-like property as they produce foam when shaken in an aqueous solution. They are classified as steroid glycosides and triterpene glycosides. In terms of structure, saponins are made up of a lipophilic triterpene molecule coupled with one or more water-loving glycoside sugar residues. Chemically, they have a minimum of one C-O sugar bond, or glycosidic linkage, at position C-3, connecting an aglycone to a sugar chain (20). They have various therapeutic properties: anti-inflammatory, antiviral, anticancer, antifungal, immunomodulatory, and antioxidant (11). The anti-obesity effects of several active constituents, including ginsenoside and diosgenin, and their mechanisms are given in Table 2. The dietary saponins, also known as

bio-detergents reduces lipid synthesis, preventing intestinal lipid absorption, suppressing adipogenesis encouraging the elimination of triglycerides and bile acids in faeces. Dietary saponins suppresses appetite, prevent formation of fatty liver, protect epithelial vasculature, regulates body weight, and act as antagonists to suppress appetite and *in-vitro* lipid synthesis (34).

4. NANO BASED HERBAL PREPARATIONS

Nanotechnology is study of creating, analyzing, and applying materials at the nanoscale size range of 0.1-100 nm (18). These nanomaterials are composed of carbon, organic matter, metal oxides, and other substances (9). These have many advantages [cost-effectiveness, environmental friendliness, a large surface area, chemical reactivity, absorption capacity, sensitivity, stability, mechanical strength, biological activity, and mechanical strength (37)]. Their nanostructures, including nanospheres, nanorods, nanowires, nanocomposites, nano-capsules, nanotubes, nanofilms, nanocrystals, nanorings, and nanostars are being studied (19). The medical and health sciences nanotechnology have found several applications (31). Table 3 lists some recent herbal extract-based nano-formulations. Many synthetic medications are available to treat obesity, but have serious negative effects. To address this issue, researchers are focusing more to create natural substances to treat obesity (35). Several phytochemicals (polyphenols, flavonoids, terpenoids, tannins, and glycosides), showed promising effects to treat obesity; however, their low specificity of target, low aqueous solubility and stability limit their practical application. Utilizing nanoparticles encapsulated with phytochemicals can help overcome these limitations because they improve the bioavailability, specificity to target and solubility of compounds and prevents their premature degradation (30).

Table 3. Nano-based herbal preparations to manage obesity

#	Plant	Family	Extract	Nanoparticles	Ref
1.	<i>Salacia chinensis</i> L.	Celastraceae	Aqueous	Gold nanoparticles	26
2.	<i>Dendropanax morbifera</i> H.Lév.	Araliaceae	Aqueous	ZnO nanoparticles	77
3.	<i>Bauhinia rufescens</i> Lam.	Fabaceae	Methanol	Titanium oxide nanoparticles	6
4.	<i>Gynostemma pentaphyllum</i> (Thunb.) Makino	Cucurbitaceae	Aqueous	Gold nanoparticles	2
5.	<i>Cyperus rotundus</i> L.	Cyperaceae	Aqueous, methanol	ZnO nanoparticles	3
6.	<i>Persea Americana</i> Mill.	Lauraceae	Methanol	Silver nanoparticles	51
7.	<i>Garcinia cambogia</i> (L.) N.Robson	Clusiaceae	Ethanol	Zinc oxide nanoparticles	23

CONCLUSIONS

With a long history of herbal therapy and a wide range of plant-based substances, it presents a viable path for further treatments. Certain herbs, (*Euphorbia humifusa* Wild., *Acacia nilotica* L., *Allium cepa* L.) have weight-reduction property. Additionally, herbs

rich in specific phytochemicals, like kaempferol, increase thermogenesis and inhibit adipogenesis by controlling gene expression associated with obesity (PPAR γ , SREBP-1c, and C/EBP α). Developing focussed and efficient herbal treatments depends on our ability to comprehend how different metabolic pathways related to weight management are affected by these plants. An exciting new prospect in this discipline is presented by nanotechnology. Nano-formulations are formulated using herbal extracts so that the bioavailability, stability, and targeted administration of these extracts within the body can all be enhanced by encasing them in nanoparticles. This minimizes adverse effects, while increasing the therapeutic efficiency of herbal treatments. Future studies in this field have great potential to help treat obesity through the use of herbal medicine. In conclusion, a synergistic strategy is probably a part of obesity management in future. Conventional medicines and herbal remedies and novel approaches like nano-formulation may offer a greater array of tools to medical practitioners.

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AUTHOR'S CONTRIBUTION

In the present review, Pooja Rawat analysed the herbs, phytochemicals, and nanoparticles used for the treatment of obesity and was the primary contributor in making the manuscript. The systematic evaluation was carried out by Saumya Das, Bhavani Pentela and Avijit Mazumder. The final manuscript was read and approved by all authors.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

DECLARATION

We declare that all authors of this Ms. have made substantial contributions. We did not exclude any author who substantially contributed to this Ms. We have followed our ethical norms established by our respective institutions.

ETHICAL STATEMENT

This is to inform you that in this study, we have not been involved in any animal and human studies.

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