Journal of Biochemistry & Cell Biology

Sharma and Kanwar, J Biochem Cell Biol 2018, 1:1

Research Article Open Access

Phytomolecules for Obesity and Body Weight Management

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Received date: November 30, 2017; **Accepted date:** December 20, 2017; **Published date:** January 05, 2018

Abstract

Obesity is one of the most prevailing health issues worldwide. It has been commonly found to be associated with metabolic disorders such as diabetes, hypertension, cardiovascular diseases and some form(s) of cancers. Excessive energy intake, physical inactivity and genetic susceptibility are main causal factors for obesity. In the modern era, various medicines have been developed for overweight and obese people, but nearly all these have serious side effects. Currently, plant-based natural products as anti-obesity therapeutics are largely unexplored. Many plant-derived molecules have been found to possess anti-obesity effects with advantages over chemical treatments. So there is a basic need to develop effective drugs for obesity management/treatment with minimal side effects. Plants may prove promising options for the same. Natural plant products are widely used in healthcare or as dietary supplements. The important phytomolecules include flavonoids, terpenoids, saponin, phenols and alkaloids. The majority of plant extracts are not single compounds but rather a mixture of different molecules, therefore their mechanism of action usually targets several organ and cellular systems. The phytomolecules would act through their inhibitory activities for pancreatic lipases, adipocyte differentiation or by increasing thermogenesis and anorexia. In this review, we discuss the anti-obesity potential of phytomolecules and also analyze their mechanisms for treating obesity.

Keywords: Phytomolecules; Obesity; Anti-obesity; Flavonoids; Terpenoids; Alkaloids; Phytosterol

Introduction

Obesity is one of the foremost health problems reflected by accumulation of excess amount of body fat. Obesity or adiposity is the 'New World Syndrome' and its incidence is rising at a high rate in both developed and developing country. There are over 600 million clinically obese and 1.9 billion overweight adults worldwide up to year 2014 according to a report of World Health Organization. Since 1980, incidence of obesity has nearly doubled which is predominantly because of changes in human lifestyle, intake of high energy diet and obesity becoming a challenging risk factor to the children [1,2]. It is a serious and chronic disease with associated increased risk of insulin resistance, type 2 diabetes, cardiovascular disease, cancer, gallstones, fatty liver disease, osteoarthritis, oxidative stress and inflammation-based pathologies in human population [3,4]. The number of obese patients is increasing globally over the last couple of decades [5,6]. The mechanisms underlying the development of obesity manifest in the dysfunction of lipid and carbohydrate metabolism [7]. Factors which also play contributory role in obesity include age, gender, environmental and genetic factors. Obesity can be measured by body mass index (BMI), waist circumference, weight distribution and associated co-morbidities [8]. A BMI of 30 or more indicates the person as obese or a person with waist circumference 40 (for man) and 35 (for woman) inches is considered as obese.

Pharmacological approaches to control obesity have become a prime priority. Due to unclear etiology, the cure of obesity is difficult and challenging. Current trends for obesity management involve multiple pharmacological strategies including blocking nutrient absorption, modulating fat metabolism, regulating adipose signals and modulating the satiety centers [9]. Although a few medications are available to control obesity yet most of them have been withdrawn due to their hazardous side effects. To seek safer remedies now many natural products are being recommended for curing obesity in most Asian countries. Currently approved medicines for treatment of obesity can be divided into two major classes; (i) Orlistat, which reduces fat absorption through inhibition of pancreatic lipase and (ii) Subutramine which is an anorectic or appetite suppressant [10]. Plant products such as saponins, flavonoids, phenols and alkaloids possess anti-obesity properties. Presence of multiple-phytochemical combinations in plant drugs may result in synergistic effect by their action on multiple molecular targets, thus offering advantages over treatments which often use a single constituent [11].

Definition of obesity

Medically obesity is a condition characterized by the excessive accumulation and storage of fat in the body leading to reduced life expectancy and/ or increased health problems [12]. Obesity affects not just appearance of a person but disease processes as well.

How to diagnose obesity

Obesity can be diagnosed by BMI, weight distribution, waist circumference and waist to hip ratio. BMI describe body weight relative to height i.e. BMI=Mass (kg)/[Height (m^2)]. A BMI of 30 or more indicates a person as obese or a person with waist circumference 40 (for man) and 35 (for woman) inches is also considered as obese [13]. The current recommended upper limit for waist circumference is 102 cm for a man and 88 cm for women. Waist to hip ratio more than 1 in men or more than 0.85 in women is considered obese.

Citation: Sharma T, Kanwar SS (2018) Phytomolecules for Obesity and Body Weight Management. J Biochem Cell Biol 1: 101.

Etiology of obesity

Obesity is the result of an imbalance between energy intake and expenditure [14]. As in most human pathological conditions, genetic and environmental conditions play vital role(s) in its pathogenesis. Environmental factors like availability and variety of food, amount of pollution in the air, water, homes and communities, vegetation and infrastructure all influence our lifestyle and behavior – such as what a person eats and how energetic he or she is. Source of these factors unknowingly affect our metabolism. Around 60% of the world's population is getting insufficient exercise. This is mostly due to labor-saving technologies at home and mechanized transportation. Like environmental factors, genetic factors also contribute to obesity. Energy stored as fat is an essential factor for survival and adaptation during human evolution. This effect is considered polygenic and may also depend on sex and age of the subjects [15-17].

Effects of obesity on the human health

Obesity is a chronic condition and a major risk factor for cardiovascular disease (CVD) and type 2 diabetes. Overweight or obese people have a greater probability than normal-weight people for developing metabolic syndrome, a condition characterized by high blood pressure, insulin resistance and dyslipidemias (high levels of total cholesterol, triglycerides and LDL and low levels of HDL) [18]. Obesity during pregnancy may cause congenital malformations, such as neural tube effects, hypertension and gestational diabetes. In addition to these conditions, obesity also increases the risk of polycystic ovary disease, ischemic stroke, sleep apnea, gallbladder disease, gastro esophageal reflux, osteoarthritis, colon cancer, postmenopausal breast cancer and psychological disorders, such as depression [19]. Approximately 300,000 people die every year in the United States because of obesity-associated diseases. Overweight subjects account for about 37% of the global burden of disease [20].

Treatment and prevention of obesity

Any intervention aimed at treating obesity should also focus on how to restore balance of energy intake and energy expenditure. In a simplified form, these interventions could be divided into three classes: i) change in lifestyle; ii) pharmacological interventions and iii) surgical treatment. The first treatment option to lose weight is an energy-reduced diet and regular physical movement. Increased physical movement can be used to balance energy expenditure by increasing the quantity of energy a body uses. Walking, cycling, swimming and aerobics are variety of exercises which are really effective and easy to implement. Unfortunately, for obesity treatment there is no 'magic pill'. Orlistat is the hydrogenated derivative of lipstatin, which inhibits gastrointestinal lipase. This medicine acts in the lumen of the gut where it blocks the movement of gastrointestinal lipase [21,22]. Orlistat is also associated with high incidence of side effect(s) which includes steatorrhea, flatulence and fecal incontinence. Sibutramine is a serotonin and noradrenaline inhibitor but it may cause an increase in blood pressure. It acts mainly as an appetite suppressant [23,24]. Bariatric or Weight Loss Surgery (WLS) was formerly classified as restrictive, malabsorptive or a combination of both. Sleeve gastrectomy, Roux-en-Y gastric bypass and laparoscopic adjustable gastric banding are generally used surgical procedures [25]. Some disadvantages of these procedures are long-term complications such as anemia and malnutrition in the subjects [26,27].

Plants are promising source for anti-obesity therapy

Plants are in use since time immemorial as traditional and natural pharmaceutical aids. Scientists are moving towards natural product-based therapeutic formulations to get safer anti-obesity drugs. In current pharmaceutical aids, the phytomedicines are prominent alternatives to the synthetic drugs. Phytomolecules are the plant-derived secondary metabolites eliciting pharmacological or toxicological effects in man and animals which have little important role(s) in plant growth and development [28]. Medically important secondary metabolites include flavonoids, terpenoids, alkaloids and phenylpropanoids. Terpenoids are particularly numerous, there being around 45 000 in plants alone; they are used widely as drugs (e.g. taxol, forskolin, ingenol and angelate). However, these compounds must be extracted directly from plants in good quantities. Unfortunately these compounds are very often present in low abundance and quite difficult or impossible to synthesize chemically [29]. The screening and evaluation of therapeutic potential of natural products for treating obesity is currently being pursued vigorously. This may be an exceptional substitute approach for emerging future effective, safe anti-obesity drugs [30]. A variety of plant products, including crude extracts and isolated pure natural compounds can counteract diet-induced obesity and thus induce body-weight reduction [31]. For that reason, they have been commonly used in treating obesity (Figure 1).

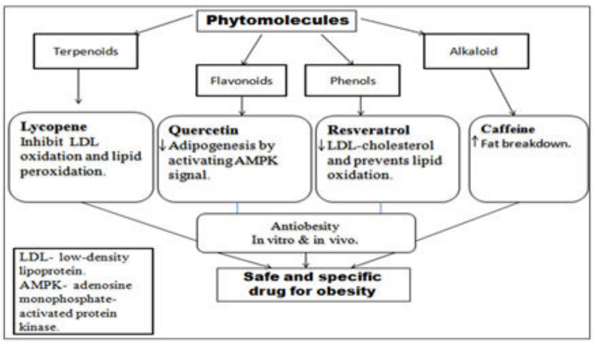

Figure 1: Molecular actions of phytomolecules need to be considered for discovery of safe and specific anti-obesity drugs.

Mechanisms of action of Phytomolecules on Adiposity

A phytomolecule can exert its anti-obesetic function through several approaches. The possible mechanisms of action of certain phytomolecules include:

Preventing adipocyte differentiation

The adipocyte life cycle includes alteration of cell shape and growth arrest, clonal expansion and a complex sequence of changes in gene expression leading to storage of lipid and finally cell death. Phytomolecules inhibit the formation of fat cells in adipose tissues and adipogenesis. The first characteristic of the adipogenesis process is a change in cell shape paralleled by alteration in the type and expression levels of cytoskeletal components and extracellular matrix components [32]. These events further promote the expression of adipogenic transcription factors, including CCAAT-enhancer-binding proteins (C/EBPα) and peroxisome proliferator-activated receptors (PPARγ). C/EBP and PPAR are the central transcriptional regulators of

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adipogenesis and are required for the synthesis of many adipocyte associated functional proteins. C/EBP up-regulation mediates the downstream up-regulation of PPAR and C/EBP expression [33]. A number of studies have demonstrated that natural compounds like epigallocatechin gallate (EGCG), quercetin, p-synephrine, genistein, esculetin, berberine, resveratrol, guggulsterone and capsaicin inhibited adipogenesis [34-37]. EGCG, *p*-synephrine and quercetin induce apoptosis in preadipocyte whereas genistein and ECGC induce apoptosis in maturing adipocyte (Figure 2).

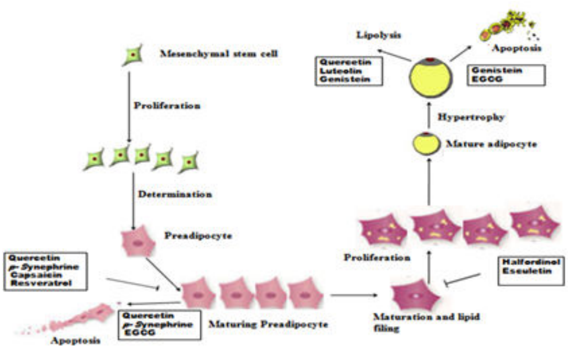


Figure 2: Phytomolecules that affect specific stages of the adipocyte life-cycle.
(⊣ Indicates inhibition; → Indicates faclitation).

Enhancing lipid metabolism

Hormone-sensitive lipase (HSL) catalyses the process of lipolysis and it is stimulated by protein kinase A (PKA) activation, which phosphorylates HSL by G protein-coupled receptors and cyclic AMP-activated extracellular signal-regulated kinase (ERK) [38]. Pre-adipocytes do not have lipolytic activity until they are differentiated to mature adipocytes. In rat adipocytes quercetin, genistein, diadzein, zearalenone, coumestrol, fisetin and luteolin cause an increase in lipolysis [39]. Umbelliferone and esculetin isolated from *Aegle marmelos* deplete lipid content (Figure 2) in the maturing pre-adipocytes [40].

Inhibiting pancreatic lipase activity

Pancreatic lipase enzyme secreted by pancreas is a key enzyme that breaks down dietary fat in the human digestive system [41]. Many plant extracts such as those obtained from *Nelumbo nucifera*, *Cassia nomame*, *Salacia reticulate*, *Platycodi grandiflorum* and *Gardenia jasminoids* possess antilipolytic function(s) towards pancreatic lipase [42-45]. The active constituent of *Gardenia jasminoids* is crocin which inhibits pancreatic lipase *in vitro*. This molecule reduces serum triglyceride *in vivo* in high fat-diet fed mice [46].

Decreasing appetite

Plant extracts like those derived from *Citrus aurantium*, *Phaseolus vulgaris* and *Hoodia gordoni* have appetite-suppressant properties [47-49]. An oxypregnane steroidal glycoside known as P57 isolated from *Hoodia gordoni* raises the adenosine triphosphate (ATP) content in hypothalamic neurons that control food intake after intra-cerebroventricular injection in rats [50].

Phytomolecules with anti-obesity potential

Secondary metabolites present in stem, bark, leaf, flower and roots perform important pharmacological function in human system. Various compounds with anti-obesity potential, obtained from plants have been listed in Table 1. The chemical constituents that have been found in plants and appeared to possess anti-obesity properties are as follows;

Flavonoids

Flavonoids are group of plant metabolites containing 15 Carbon (C) atoms. Flavonoids are gaining interest because of their potential role in the prevention of diseases such as cancer and gastrointestinal, cardiovascular and neurodegenerative diseases [51]. Quercetin shows anti-lipase activity prevents adipogenesis and induces cell death in mouse pre-adipocytes [52,53]. Kaempferol extracted from *Bauhinia forficate* leaves reduced hyperglycemia [54]. Isorhamnetin found in medicinal plants such as *Ginkgo biloba, Hippophae rhamnoides*, *Oenanthe javanica* and *Opuntia ficus-indica* has anti-obesity activities [55].

Alkaloids

Alkaloids are a class of naturally occurring secondary metabolites with more than 2000 known compounds, mostly containing basic nitrogen atoms. Alkaloids include synephrine from *Citrus aurantium*, piperine from *Piper nigrum*, piperlongumine from *Piper longum* and liensinine, isoliensinine, neferine and nuciferine from *Nelumbo nucifera* have potential effect on obesity [56]. Caffeine and chlorogenic acid are the principal constituents of green coffee bean extract. Green coffee causes reduction in body mass and body fat due to a decrease in the absorption of glucose. Decrease in glucose absorption would eventually cause an increase in the utilization of fat reserves, due to the reduced availability of glucose as an energy source [57,58].

Phenols

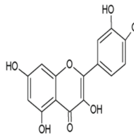
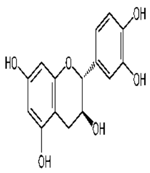
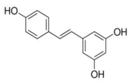
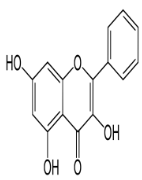
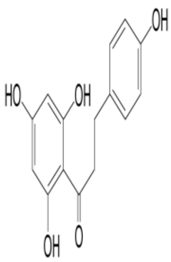
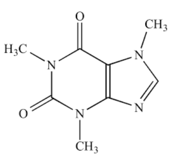
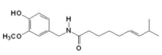
Phenols are an abundant class of naturally occurring phytochemicals such as *p*-coumaric, caffeic acid, ferulic acid, cinnamic acid, ellagic and *p*-hydroxybenzoic acid which have shown to modulate physiological and molecular pathways that are involved in energy metabolism, adiposity and obesity [59]. Simple phenolic acids are non-flavonoid phenolic compounds conjugated with other natural chemicals such as flavonoids, alcohols, hydroxyfatty acids, sterols, and glucosides. Ferulic acid has hypolipidemic, hypocholesterolemic, hypoglycemic effect and thus it could be effective in lowering the risk of high fat diet-induced obesity [60,61]. Chlorogenic and coumaric acid cause significant inhibition of cell growth as well as enhance apoptosis. Gallic acid although does not affect the adipocyte cell cycle yet it did increase the number of apoptotic cells [62].

Phytosterols

Phytosterols predominantly occurring in nature are structurally similar to mammalian cell-derived cholesterol [63]. Phytosterols exist in both esterified and free alcohol forms. The prominent sources of phytosterols are unrefined vegetable oils, seeds, cereals, nuts and legumes [64]. Phytosterols appear to reduce obesity are diosgenin, campesterol, brassicasterol, sitosterol, stigmasterol and guggulsterone. High intakes of these compounds decrease LDL-cholesterol levels. In the intestinal lumen, phytosterols compete with cholesterol for micelle formation and thus effectively inhibit the cholesterol absorption [65]. Their influence on intestinal genes and transcription factors make phytosterols the key regulators in metabolism and cholesterol transport in the expression of liver genes [66].

Terpenoids

Terpenoids (isoprenoids) are chemically-modified terpenes usually found in plants, and comprise more than 40,000 compounds of both primary and secondary metabolism. Gymnemic acid (from *Gymnema sylvestre*), oleanolic acid (from *Panax ginseng*) and corosolic acid (from *Lagerstroemia speciosa L*) have potential therapeutic on obesity [67-69]. PPARγ activation attenuates obesity and type-2 diabetes. Geranyl geraniol, farnesol and geraniol terpenoids are ligands with potential to activate PPAR, dietary lipid sensors that control energy homeostasis as well as lipid and carbohydrate disorders [70,71].

Phytomolecule	**Example**	**Structure**	**Plant source**	**Antiobesity effect**	**Reference**
Flavonoids	Quercetin		*Coriandrum sativum*, *Brassica oleracea*, *Allium cepa*	Activates AMPK signal pathway in preadipocytes as a result decrease *in vitro* adipogenesis.	[72,73]
	Catechins		*Camellia sinensis*, *Coffea* and *Vitis vinifera*	Decreases the carbohydrate absorption because catechin inhibits α-glucosidase activity and small-intestine micelle formation.	[74-76]
	Resveratrol		*Arachis hypogaea*, *Vitis vinifera* and *Cyanococcus*	Inhibits adipogenesis by reducing the transcriptional activity of PPARγ and it enhances lipolysis.	[77,78]
	Galangin		*Alpinia galangal*, *Helichrysm aureonitens*	Decreases accumulation of hepatic triglycerides, serum lipids, liver weight and lipid peroxidation.	[79]
	Phloretin-3′,5′-di-C-glucoside		*Cyclopia falcata*, and *Cyclopia subternata*	Inhibit adipogenesis, intracellular triglyceride and down regulate peroxisome proliferator-activated receptor-2 (PPAR-2) expression and in *in vitro* condition.	[80]
Alkaloids	Caffiene		*Camellia sinensis* and, *Coffea arabica*	Exert lipolytic and thermogenic actions.	[81,82]
	Capsaicin		*Capsicum annuum*	Enhanced lipid oxidation and increased energy expenditure.	[83]

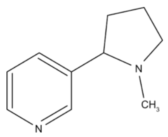
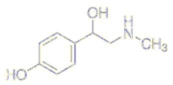
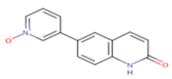
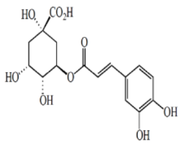
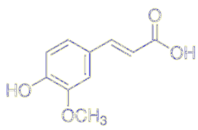
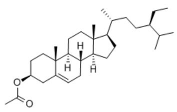
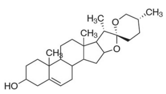
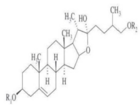
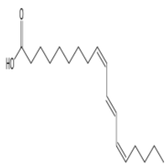
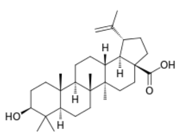
	Nicotine		*Nicotiana tabacum* and *Capsicum annum*	Nicotine increases metabolic rate and decrease food intake.	[84]
	p-synephrine		*Citrus aurantium* and *Citrus unshiu*	The active constituent *p*-synephrine increases metabolic rate, energy expenditure and increase in weight loss.	[85,86]
	Halfordinol		*Aegle marmelos*	Anti-adipogenic activity and responsible for the decrease in adipocyte accumulation.	[87]
Phenols	Chlorogenic acid		*Glycine max* and *Coffea canephora*	Reduce body fat due to a reduction in the absorption of glucose.	[88]
	Ferulic acid		*Hordeum vulgare* and *Asparagus officinalis*	Hypolipidemic effect, dysregulated lipid profiles and inhibition of adipocyte differentiation.	[89,90]
Phytosterol	Sitosterol		*Arachis hypogaea*, *Citrullus Colocynth* and *Bauhinia variegata*	Decreases cholesterol absorption by lowering the level of low density lipoprotein-cholesterol and inhibits pancreatic lipase.	[91-93]
	Diosgenin		*Trigonella foenum-graecum* and *Dioscorea villosa*	Inhibits accumulation of triglyceride and expression of lipogenic genes.	[94,95]
	Protodioscin		*Trapa natans* and *Tribulus terrestris*	Significantly reduces blood levels of triglyceride, cholesterol, low density lipoprotein (LDL) and increases high-density lipoproteins (HDL).	[96]
Terpenoid	Punicic acid		Punica *granatum*, *Momordica balsamina* and *Trichosanthes bracteata*	Punicic acid binds and activates PPAR-α and γ, thus upregulating PPAR α and its responsive genes (Stearoyl-CoA desaturase-1, SCD1;Carnitinepalmitoyltransferase 1, Cpt-1; and acyl-coenzyme A dehydrogenase) as well as PPAR γ-responsive genes expression (CD36 and Fatty Acid Binding Protein 4, FABP4) in intra-abdominal white adipose tissue while suppressing expression of the inflammatory cytokine TNF-α and NF-κB activation.	[97,98]
	Betulinic acid		*Orthosiphon aristatus* and *Syzygium aromaticum*	Active constituent suppresses hypothalamic protein tyrosine phosphatase 1B and enhances the antiobesity effect of leptin.	[99,100]

Table 1: Classes of phytochemical and their antiobesity effect(s)

Conclusion

Complete understanding of plant-derived metabolites involved in fat metabolism in our body will open the avenues to develop the phytomolecules-based therapeutic approaches to combat obesity in human. Hardly any of the existing drugs including statins (Orlistat) has been established to firmly cure obesity. Phytomolecules are potential alternative treatment strategies for the development of effective and safe anti-obesity drugs. Phytomolecules being of biological origin have little side effects in comparison to statins. Emerging studies have described the promising role of phytomolecules in treating obesity with little side effects in human. Hence concerted efforts are required to explore plants as important natural resources for their therapeutic potential, not only to manage and treat obesity but other diseases, too.

Acknowledgements

The financial support from Department of Environment, Science and Technology (DEST), Government of Himachal Pradesh, Shimla to one of the authors (SSK) as well as to the Bioinformatics Centre, Department of Biotechnology, Himachal Pradesh University, Shimla (India) are thankfully acknowledged. Further the authors have no conflict of interest either among themselves or with the parent institution at their place of work.

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