Review Article

Efficacy of natural products as antiobesity agents: An insight into their therapeutic targets

Puneet Mankoo[1], Goyal Pradeep[2], Bhatia Gursimran[3], Gupta Monika[4]

[1]Department of Pharmaceutical Chemistry, Chandigarh College of Pharmacy, Mohali, Punjab, India, [2]Department of Pharmacy, Chandigarh University, Mohali, Punjab, India, [3]Department of Pharmacy, Government Polytechnic College for Girls, Jalandhar, Punjab, India, [4]Department of Pharmacy, Amar Shaheed Baba Ajeet Singh Jujhar Singh Memorial College of Pharmacy, Ropar, Punjab, India

Correspondence:
Puneet Mankoo, Department of Pharmaceutical Chemistry, Chandigarh College of Pharmacy, Landran, Sector 112, Mohali - 140 307, Punjab, India.
E-mail: puneet.ccp@cgc.edu.in

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ABSTRACT

Obesity has become a serious health problem. This complex condition has reached widespread proportions in large parts of the world, and it constitutes a threat for several chronic disorders, such as hypertension, heart disorders, and Type-2 diabetes. Curative approach comprises synthetic drugs and surgery, which may involve high costs and serious side effects. Plant-based medicinal agents offer an alternate approach. This paper thus attempt to enhance the knowledge of the anti-obesity effects of natural products, provide effective therapeutic strategies, and attract the reader's interest in developing novel and safe antiobesity drugs.

Keywords: Antiobesity agents, lignans, polyphenols, stilbene

Introduction

Obesity is a challenging, inveterate medical condition with a damaging impact on human health. Obesity occurrence and its additional disorders are on the rise in developed and developing countries extend beyond age and sex.[1,2] Over the past 30 years, there has been an aggressive growth in the prevalence of obesity worldwide with doubling rates for adult and childhood obesity (6–11 years) and tripling rates of adolescent obesity (12–19 years).[3] At present, various therapeutic options are available to treat obesity such as diet alteration, exercise, surgery, behavioral changes, and pharmacotherapy. Among these, pharmacotherapy is the most common, although numerous drugs used to reduce weight have associated side effects.[4] Therefore, alternative approaches that are safe and well tolerated, and can lower the risks associated with obesity are urgently required.[5] Other sources of weight loss drugs, such as natural products, have also been investigated.[6] Researches demonstrated the potential of natural products to counteract obesity.[7] Several natural product mixtures may result in a mutually reinforcing activity that increases their bioavailability and action on several molecular targets, providing advantages over chemical treatments.[8,9] The antiobesity effects of these compounds are mediated by regulation of various pathways, including lipid absorption, energy intake and expenditure, increasing lipolysis, and decreasing lipogenesis, differentiation, and proliferation of pre-adipocytes.[10]

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The potential of phytochemicals

Nature represents an enormous reservoir of biologically active compounds to treat various ailments from times immemorial.[11] The naturopathic treatment for obesity has been explored extensively since ancient times and gaining momentum in the present scenario.[12] The

ability of natural products for the treatment of obesity is yet mostly unexplored and can be a great substitute for the safe and effective development of antiobesity drugs.[13] A range of phytochemicals such as polyphenols, alkaloids, tannins, flavonoids, saponins, terpenoids, glycosides, proteins, and steroids present in plants and their products are crucial ingredients in the therapy of several diseases.[14] Various studies suggest that antiobesity effects could be attained by consuming reduced levels of phytochemicals [Table 1] but in definite combinations.[15-21]

Polyphenols

It is a class of phytochemicals [Figure 1] that are likely antiobesity agents, as several studies have suggested, they can modulate the adipocyte lifecycle.[23] Polyphenols holding at least two phenol subunits are the flavonoids and those compounds holding three or more phenol subunits are known as the tannins. Polyphenols including their functional derivatives, esters, and glycosides have one or more phenol groups with one hydroxyl substituted aromatic ring.[24] The three main types of polyphenols are phenolic acids, flavonoids, and stilbenoids.

Flavonoids

It comprises flavonols, flavones, flavanones, flavanols, isoflavones, and anthocyanidins. Both flavonols and flavones commonly present in plant as glycosides.

Flavonols: Quercetin and kaempferol

Quercetin

Quercetin is the most abundant of flavonoids and is found in vegetables, fruits, tea, and wine.[25] Quercetin stimulates lipolysis [Table 2] of primary rat adipocytes in a dose- and time-dependent form by stimulating cyclic adenosine monophosphate levels and hormone-sensitive lipase (HSL) activity.[26-28]

Kaempferol

Kaempferol is a flavonoid found in several natural sources including apples, onions, broccoli, tomatoes, grapes, and berries.[29] Kaempferol reduces the conversion from pre-adipocytes to mature adipocytes, suggesting an antiadipogenic [Table 2] effect in 3T3-L1 cells. Kaempferol also selectively downregulates the CEBPA mRNA levels.[30]

Flavones: Apigenin and luteolin

Apigenin

Apigenin is abundant in our daily fruits and vegetables such as parsley, onions, oranges, chamomile, and wheat.[33] Apigenin reduces or had no effect on the expression of lipolytic genes such as adipose triglyceride lipase, hormone sensitive lipase, and monoacylglyceride lipase, thus reducing glycerol discharge from adipocytes.[36]

Luteolin

Luteolin is an abundant flavonoid in many fruits, medicinal herbs, and vegetables. Plants rich in luteolin have been utilized in Chinese traditional medicine for the treatment of various diseases, such as hypertension, inflammatory disorders, osteoarthritis, and cancer.[37]

Flavanones: Naringenin and hesperetin

Naringenin

Naringenin is significant flavanone that is rich in citrus fruits such as grape, oranges, and tomatoes.[38] The antiobesity effect of naringenin

Table 1: Selected antiobesity Polyphenols and their natural sources

S. No.	Category	Phytoconstituents	Natural sources	References
1.	Flavonols	Quercetin Kaempferol Myricetin	Onions, scallions, kale, broccoli, apples, berries, teas	25,29,31,32
2.	Flavones	Apigenin Luteolin	Parsley, thyme, celery, hot peppers	33,34,35,37
3.	Flavanones	Naringenin Hesperetin	Citrus fruit and juices, e.g., oranges, grapefruits, lemons	38,41
4.	Isoflavones	Diadzein Genestein	Soybeans, soy foods, legumes	44
5.	Flavanols	Catechin Epigallocatechin-3-Gallate	Teas, cocoa-based products, grapes, berries, apples	47,49
6.	Anthocyanidins	Cyanidin Pelargonidin Delphinidin Malvidin	Red, blue, and purple berries, red and purple grapes; red wine	55,57,58
7.	Stibenes	Resveratrol	Red grapes, blue berries	61,63,66
8.	Phenolic acids	Ferulic acid Coumaric acid Cafeic acid Gallic acid	Cereals, legumes, oilseeds, fruits, vegetables,herbs.	65,67, 69,71,73
9.	Lignans	Secoisolariciresinol Matairesinol	Seeds (flax, pumpkin, sunflower, poppy, sesame), whole grains (rye, oats, barley), bran (wheat, oat, rye), beans, fruit (particularly berries) and vegetables	77

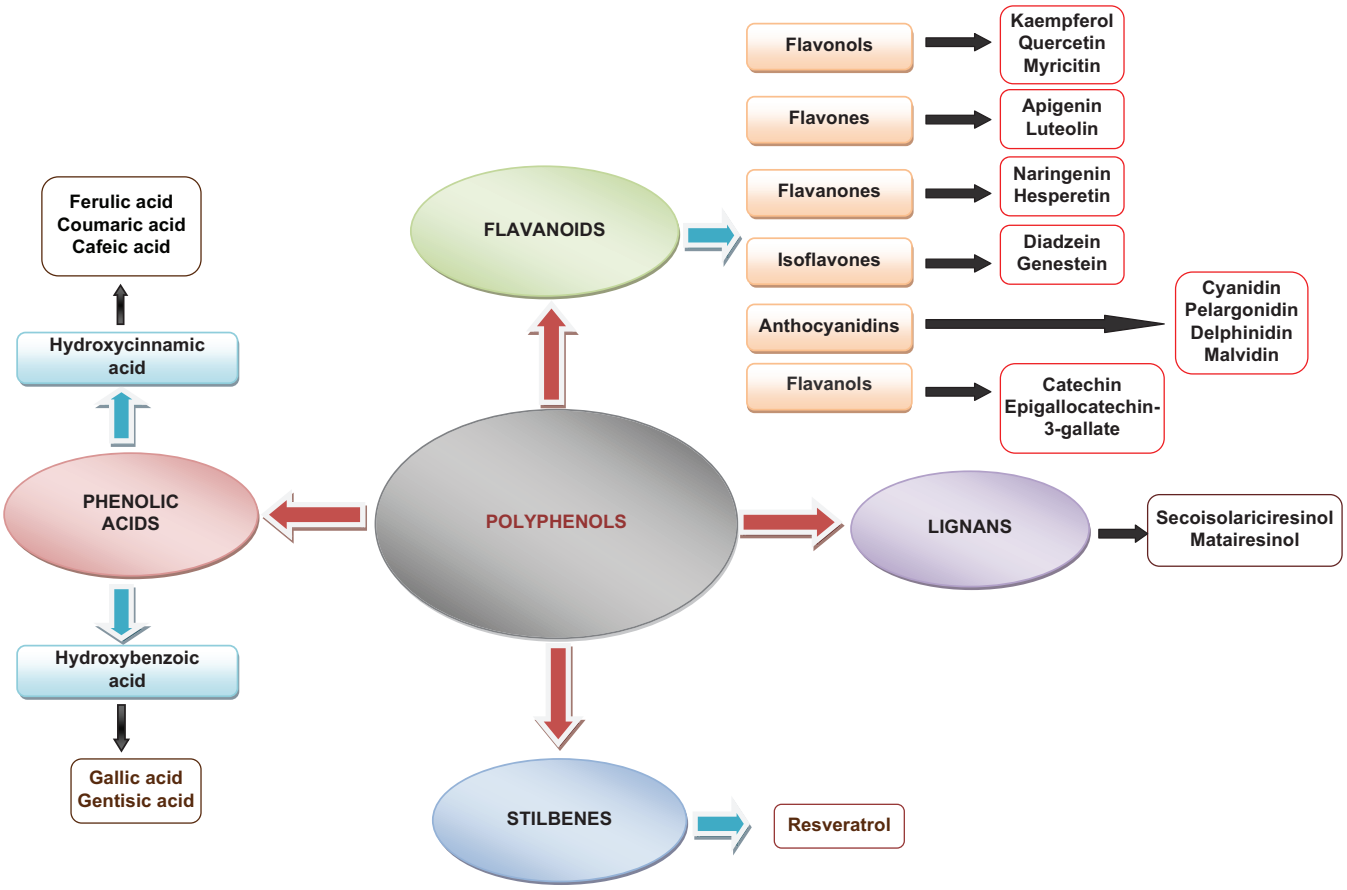

Figure 1: Classification of polyphenols

was due to the reduction in adipose tissue mass and suppression of pre-adipocyte proliferation.[39] Moreover, naringenin increased fatty acid oxidation [Table 2] in hepatocytes by enhancing peroxisomal β-oxidation in mice.[40]

Hesperetin

Hesperetin, the aglycone of the flavanone glycoside, occurs naturally in citrus fruits.[41] Hesperetin shows pharmacological effects linked to antiobesity by suppressant effect on appetite by increasing the release of cholecystokinin (CCK), which is one of appetite-regulating hormones.[42]

Isoflavones: Daidzein and genistein

Daidzein

Daidzein shows antiobesity effects mediated through the inhibition of pancreatic lipase activity in the intestinal tract and lipoprotein lipase (LPL) activity.[43]

Genistein

Genistein (4, 5, 7-trihydroxyisoflavone), the most abundant isoflavone in soybean, is also present in several other plants which represent excellent sources of phytoestrogens such as lupine (*Lupinus* spp.), kudzu (*Pueraria lobata*), and *Psoralea* (*Psoralea corylifolia*).[44] Genistein decreases food intake, body weight, and fat pad weight and increases apoptosis of adipose tissue.[45] Genistein also activates transcriptional activity of PPAR, thereby induces the hypolipidemic and antiobesity effects.[46]

Flavanols: Catechin and epigallocatechin-3-gallate (EGCG)

Catechin

Green tea catechins influence body weight by thermogenesis and substrate oxidation, both of which are mediated by sympathetic nervous system activity [Table 2]. Other potential mechanisms include modifications in appetite control; downregulation of enzymes involved in hepatic lipid metabolism and decreased nutrient absorption.[48]

EGCG

EGCG, a component extracted from green tea, has been proved to have multiple effects on human pathological and physiological processes.[49] EGCG has antioxidant property which increases fat oxidation, lowering lipid peroxidation, and increases thermogenesis.[50]

Anthocyanidins: Cyanidin and pelargonidin

Cyanidin

Cyanidin improves obesity and triglyceride metabolism by activation of LPL in plasma and skeletal muscle, and inhibition of LPL in adipose tissue [Table 2] following the activation of protein kinase phosphorylation.[52]

Table 2: Mechanism of action of some phytochemicals

S. No.	Phytoconstituent	Mechanism of action	Receptor involved	References
1.	Quercetin	Induces lipolysis by increasing cAMP levels and hormone-sensitive lipase (HSL) activity.	Activate peroxisome proliferator activated receptor γ (PPARγ)	26,27
2.	Kaempferol	Modulates adipogenic differentiation	Down regulate the CEBPA mRNA levels	30
3.	Myricetin	Thermogenesis	Upregulation of Sirt3 expression.	31,32
4.	Luteolin	Inhibiting adipocyte differentiation and triglyceride	Inhibiting PPARc and C/EBPa	37
5.	Hesperetin	Suppressive effect on appetite	Stimulating the release of cholecystokinin (CCK)	42
6.	Diadzein	Inhibit the differentiation of preadipocytes, reduce the intracellular triglycerides concentration, and increase lipolysis by up-regulating	Hormone-sensitive lipase activity	43
7.	Genestein	Thermogenesis,decreases food intake, body weight and fat pad weight and increases apoptosis of adipose tissue.	Activate transcriptional activity of PPAR	45,46
8.	Catechin	Thermogenesis, Appetite suppressant effect and increases fat oxidation, stimulation of sympathetic nervous system activity.	Up regulation of mRNA level of fat β-oxidation genes, down regulation of expression of enzymes involved in fat synthesis, and increased expression of adipose tissue uncoupling proteins.	47,48
9.	Epigallocatechin-3-Gallate	It reduces plasma levels of triglycerides and cholesterol	Reduced gene expression of lipogenic enzymes, such as FASN, HMGR, and ACC	51
10.	Cyanidin	Lipolysis	Activation of lipoprotein lipase (LPL) and activation of protein kinase phosphorylation (pAMPK)	52
11.	Delphinidin	Inhibition of adipogenisis, inhibited lipid accumulation	Downregulationof PPARγ, C/EBPα, SREBP1, FAS and upregulation of SIRT1 and CPT-1	56
12.	Resveratrol	Inhibition of adipogenisis, Lipolysis	Down-regulation of C/EBPα and PPARγ	22,64
13.	Ferulic acid	Lipolysis	inhibition of serum amylase and lipase and suppression cytokines MCP-1 and TNF-α	68
14.	Gallic acid	SupressLipogenesis	Inhibitory effect on fat droplet formation and triglyceride accumulation	74
15.	Matairesinol	Lipolysis	Inhibited expression of the adipogenic genes PPARγ, C/EBPα and aP2	80

Pelargonidin

One of the most widespread anthocyanidins in nature is the glycosides of pelargonidin.[53] Pelargonidin possesses pharmacological effects related to antiobesity by regulating lipid metabolism, suppresses food intake.[54]

Stilbenes

Natural stilbenes are a category of polyphenols which exhibit the presence of a 1, 2-diphenylethylene nucleus.[59] They exist in a restricted and heterogeneous group of plant families because the key enzyme taking part in stilbene biosynthesis, stilbene synthase, is not prevalently expressed.[60]

Resveratrol

Resveratrol is a stilbenoid polyphenol, holding two phenol rings attached to each other by an ethylene bridge.[61] It also decreases inflammation and oxidative stress, and prolongs the lifespan of various organisms.[62,63] Although the mechanisms of action which account for antiobesity effect are not entirely understood so far, various metabolic pathways such as apoptosis, lipogenesis, adipogenesis, lipolysis, fatty acid oxidation, and thermogenesis have been mentioned in the literature as being efficient targets for this polyphenol.[64]

Phenolic acids

Phenolic acids are polyphenols containing a phenolic ring and an organic carboxylic acid group (C6-C1 skeleton). Hydroxycinnamic acid and hydroxybenzoic acids are the naturally present phenolic acids, in which hydroxybenzoic acid derivatives are primarily present as glycosides.[65]

Ferulic acid

Ferulic acid falls into the family of phenolic acids.[67] Ferulic acid efficiently inhibited high-fat diet-induced visceral adiposity and body weight increases through mechanisms relating to the modulation of food regulatory peptide hormones (ghrelin, insulin, and leptin) suppression of serum amylase and lipase activity, and inhibition of adipocyte-derived pro-inflammatory cytokines, TNF-α and MCP-1.[68]

Coumaric acid

Coumaric acid is a hydroxy derivative of cinnamic acid and presents naturally in three isomers (Ortho, Meta, and Para); *p*-coumaric acid is the most commonly present isomer naturally. *p*-Coumaric acid, categorized as a nutraceutical and phytochemical, is present in various edible plants, such as carrots, cereals, and tomatoes.[69] Coumaric acid has an antiobesity effect through repression of lipodystrophy, fatty liver, and oxidative stress.[70]

Caffeic acid

Caffeic acid (3,4-dihydroxycinnamic acid), one of the most common phenolic acids, frequently occurs in fruits, grains, and dietary supplements for human consumption as simple esters with quinic acid or saccharides and is also found in traditional Chinese herbs.[71] Caffeic acid improves high-fat diet (HFD)-induced obesity through β-oxidation and lipolysis in liver tissue.[72]

Lignans

Lignans are polyphenols found in plants. Lignan precursors are found in a wide variety of plant-based foods, including seeds, whole grains, legumes, fruit, and vegetables.[75] Lignan metabolites function as antioxidants and free radical scavengers.[76]

Secoisolariciresinol

Secoisolariciresinol is one of the essential dietary lignans, found in high levels in flaxseed.[77] Secoisolariciresinol controls adipocyte differentiation through AMPKα pathway.[78]

Matairesinol

Matairesinol is a plant lignan. Matairesinol is present in numerous foods, some of which are pecan nut, caraway, cereals, and cereal products.[79] Matairesinol improves body weight, fat, and sugar metabolism by inhibiting expression of the adipogenic genes PPARγ, C/EBPα, and aP2.[80]

Conclusion and Future Prospects

This review focused on the extraordinary therapeutic potential of natural antiobesity agents. It is undoubtedly a fact that several plants from various families and diverse phytochemical constituents are accountable for the antiobesity activity. A better understanding of the fundamental mechanisms of obesity will lead to improved treatment. Therefore, consideration to these natural compounds would open a new avenue for novel, therapeutic, and more efficacious agents.

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