Chapter 6

Antiobesity Effects of Natural Products from an Epigenetic Perspective

Esther C.Y. Woon and Joel D.W. Toh
Department of Pharmacy, National University of Singapore, Singapore, Singapore

Chapter Outline

INTRODUCTION

Obesity is one of the world's most serious public health problems. It is the fifth leading cause of premature death worldwide, with more than 2.8 million adults dying each year as a result of being overweight or obese [1]. Obese individuals are also at major risk for several serious comorbidities, such as type 2 diabetes, cardiovascular diseases, and certain cancers, predisposing them to disabilities, a poor quality of life, and imposing a crushing burden on healthcare [2–4]. It is estimated that, by 2030, about 58% of the world population will be obese (body mass index >30) [5]. Despite the gravity of the problem and the urgent need for therapeutic intervention, there is currently no safe and effective treatment for the disease.

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At present, only five medications are approved by FDA for the treatment of obesity, namely phentermine, diethylpropion, phendimetrazine, orlistat, and lorcaserin [6–11]. They achieve weight loss via one of three main mechanisms: (i) reduction in calorie intake by either curbing appetite or suppressing the craving for food, such as phentermine, diethylpropion, phendimetrazine, and Qsymia™ (combination of phentermine and topiramate), (ii) preventing the absorption of dietary fat through the inhibition of pancreatic lipase, such as orlistat, or (iii) suppression of hunger by stimulating the serotonin receptor, such as lorcaserin. However, many of these drugs showed relative lack of efficacy, with most patients achieving only 5–10% weight loss over a 1-year period of medication. This is further complicated by severe cardiovascular and/or neurological side effects, which have largely limited their use to short-term therapy, as highlighted by the dramatic approval and withdrawal of sibutramine, rimonabant, and fenfluramine. Currently, only orlistat is approved for long-term use [12–14]. In this regard, alternative forms of obesity treatment are of intense medical interest. The use of natural product and food supplements that have both weight loss and nutritional benefits is particularly appealing.

Natural products isolated from plants and microorganisms, and bioactive constituents from food have traditionally been, and continue to be, used for the treatment of a variety of human diseases. Many were found to exhibit remarkable pharmacological activities which are promising for the treatment of obesity. This is the subject of several excellent reviews [15–21]. Their beneficial or preventive effects against obesity, and their proposed mechanisms of action are briefly described in Table 1–11. Majority of the natural products were studied for their weight loss efficacy based on five broad mechanisms of action, namely, (1) decreased lipid absorption, (2) decreased energy intake, (3) increased energy expenditure, (4) decreased preadipocyte differentiation and proliferation, or (5) decreased lipogenesis and increased lipolysis [19]. This stems from an understanding of the pathophysiology of obesity from an energy balance point of view; hence weight loss can only occur if energy consumption is less than energy expenditure, thereby creating a negative energy balance.

On the surface, it seems that the rise in obesity is due to a sedentary lifestyle, coupled with an easy and ready access to food, particularly fat-saturated, calorie-dense food. It is estimated that most of us consume, on average, 200 more calorie than we require daily. When our primitive biology, which evolved from a world where food is scarce, feed so richly, the result is obesity [144]. However, the relationship is a puzzling one. Not all people are affected by the environmental changes equally, and there is great variability in response to the obesogenic environment between individuals and populations. Indeed, obesity is a complex disease with multifactorial etiology, involving

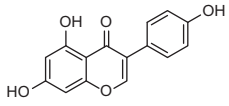
a complex interplay of dietary, lifestyle, environmental, and genetic factors. It is estimated that approximately 40–70% of the variation of adiposity within a population is due to genetic factors [145,146]. This could also explain, at least in part, the failure of exercise and dietary regime to bring about long-term weight loss in some individuals. In fact, obesity is increasingly being considered an epigenetic disease. Among the different mechanisms that could lead to obesity, the epigenetic regulation of the gene expression has emerged as an important contributor [147–151]. Obese individuals often present a different epigenetic pattern on DNA and histones in comparison to healthy normal-weight individual. Importantly, several natural products and bioactive food components have been reported to influence epigenetic mechanisms, such as DNA methylation and histone modifications, thereby modifying the expression of key genes that were potentially involved in the pathogenesis of obesity.

To date, there is no review examining the antiobesity effects of natural products from an epigenetic perspective. In this chapter, we focus on a selected group of natural products and bioactive compounds that have been investigated for their antiobesity effects. We described their bioactivity, clinical data, and mechanism of actions against obesity. We further highlighted their activities against nucleic acid- and histone-modifying enzymes, providing insights into possible epigenetic mechanism underlying their antiobesity effects.

NATURAL PRODUCTS WITH ANTIOBESITY EFFECTS

TABLE 1 Isoflavonoid

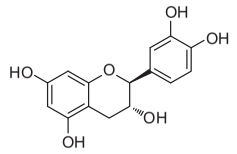
Antiobesity Compound	Natural Sources	Mechanism of Action	Epigenetic Effect	References
Genistein	*Glycine max* (soybean)	AMPK activation, inhibit adipocyte differentiation and promotes apoptosis	Inhibit DMNTs Inhibit HDAC6	[22–31]



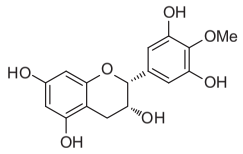
Genistein

TABLE 2 Flavanols

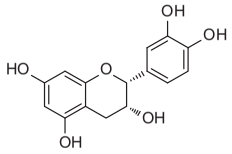
Antiobesity Compound	Natural Sources	Mechanism of Action	Epigenetic Effect	References
(−)-Catechin	*Centaurea maculosa* (spotted knapweed)	Increase expression of adiponectin	Inhibits DMNT1	[32–42]
(−)-Epicatechin	Most fruits and vegetables	AMPK activation, downregulation of PPARγ	Inhibits DMNT1	[32–42]
ECG	*Camellia sinensis* (tea)	Inhibition of lipase	Inhibits DMNT1	[32–42]
EGCG	*Camellia sinensis* (tea)	Increase energy expenditure, promoting fat oxidation, appetite modification and decrease glucose and fat absorption, inhibit adipocyte differentiation, AMPK activation, pancreatic lipase inhibition	Inhibits DMNT1 Inhibits HAT Increases HDAC3 recruitment	[32–42]
(−)-4′-*O*-Methylepigallocatechin	*Salacia reticulate* (marking nut tree), *Maytenus rigida* Mart	Pancreatic lipase inhibition	Decreases DNA methylation	[43,44]
(2*S*)-3′,4′,7-Trihydroxyflavan-(4α→8)-catechin	*Cassia mimisoides* (Nomame Herba)	Pancreatic lipase inhibition	Decreases DNA methylation	[45]



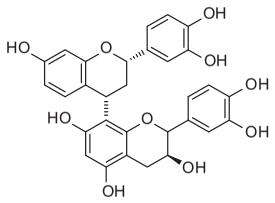
(–)-Catechin



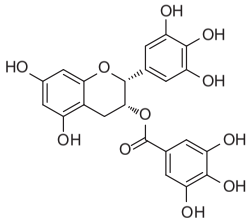
(–)-4′-*O*-methylepigallocatechin



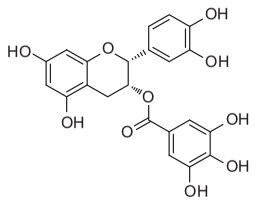
(–)-Epicatechin



(2*S*)-3′,4′,7-Trihydroxyflavan-(4α→8)-catechin



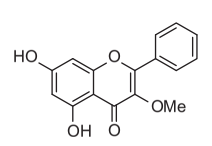
EGCG



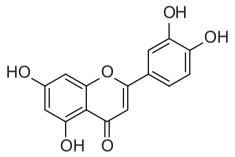
ECG

TABLE 3 Flavones

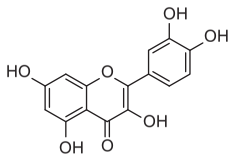
Antiobesity Compound	Natural Sources	Mechanism of Action	Epigenetic Effect	References
Astragalin	*Nelumbo nucifera* (lotus)	Impair digestion, inhibit absorption of lipid, accelerating lipid metabolism and upregulating energy usage		[46–49]
Apigenin-7-*O*-glucoside	*Salix matsudana* (Chinese Willow) and *Spirodela polyrhiza* (Schleid)	Lipolysis and inhibit palmitic acid uptake	Inhibits HDAC1, HDAC3	[50–54]
Chrysoeriol-7-*O*-glucoside	*Salix matsudana* (Chinese willow) and *Olea europaea* (olive)	Lipolysis and inhibit palmitic acid uptake		[55,56]
Isoquercitrin	*Conriandrum sativum* (coriander) and *Lactuca sativa* (lettuce)	Prevents the differentiation of 3T3-L1 preadipocytes by the increment of Wnt/β-catenin signaling	Inhibits DNMTs Inhibits HDACs	[57,58]
Luteolin	*Arachis hypohaea* (peanuts) and *Eminium spiculatum* (Blume)	Pancreatic lipase inhibition	Inhibits DNMTs Inhibits HDACs	[59]
3-Methyl ethergalangin	*Alpinia officinarum* (Siamese ginger)	Pancreatic lipase inhibition, decrease fat absorption		[60]
Quercetin	Ubiquitous in all plants	Prevent adipocyte cells grown, decrease cell viability, promotes apoptosis	Inhibits DNMT1 Inhibits HDAC1 Induces histone hyperacetylation	[61–64]
trans-Tiliroside	*Helichrysum italicum* (curry plant) and *Helianthemum glomeratum* (clustered forstweed)	AMPK and PPARα activation		[65–67]
Myricetin	Most food and vegetables	PPARα activation, inhibit lipid droplet accumulation in adipocyte	Inhibits DNMTs	[68,69]



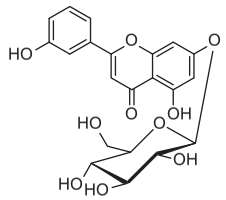
3-Methylethergalangin



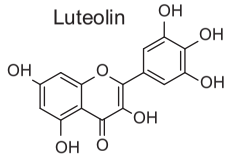
Luteolin



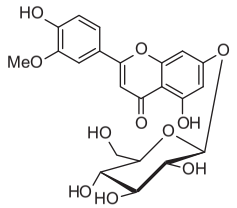
Quercetin



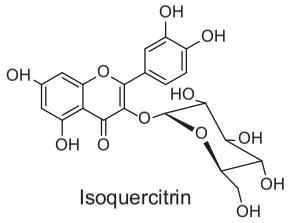
Apigenin-7-*O*-glucoside



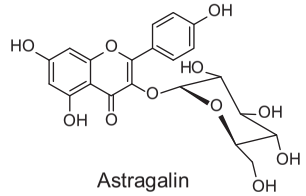
Myricetin



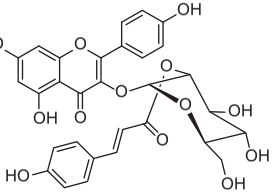
Chrysoeriol-7-*O*-glucoside



Isoquercitrin



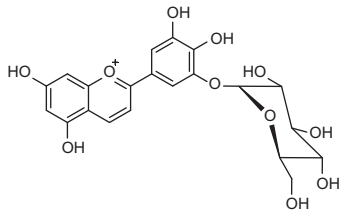
Astragalin



trans-Tiliroside

TABLE 4 Anthocyanidins

Antiobesity Compound	Natural Sources	Mechanism of Action	References
Cyanidins 3-*O*-β-D-glucoside	*Zea mays* (purple corn)	AMPK activation	[70,71]



Cyanidins3-*O*-β-D-glucoside

EPIGENETICS AND OBESITY

Epigenetics has been defined as the study of heritable changes in gene expression without any change in the underlying DNA sequence [152]. Epigenetic regulation of gene expression is highly dynamic, changing in response to factors, such as diet, lifestyle, and emotional state. This provides a mechanism whereby an individual is able to respond or adapt quickly to changes in the environment [153,154]. At the chemical level, epigenetic control is achieved primarily through posttranslational modifications on DNA, histone proteins, and microRNAs. These "epigenetic marks" corroborate with a complex network of other proteins, such as chromatin-modifying proteins and DNA-binding proteins, to bring about changes in the chromatin conformation, to achieve either a euchromatic state (where packaging of DNA around nucleosomes is in an open, transcriptionally active state), or a heterochromatic state (where DNA is in a compact, transcriptionally silent state) [155–157]. For the purpose of this review, we will focus on the two most well-studied epigenetic mechanisms, DNA methylation and histone modifications.

DNA METHYLATION

DNA is found to be modified by methylation, normally on a cytosine base, especially the CpG islands of the promoter region of the gene. DNA methylation is catalyzed by a family of enzymes called DNA methyltransferases (DNMTs), which transfer a methyl group from *S*-adenosyl-L-methionine

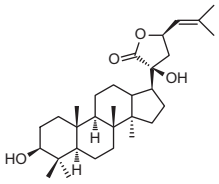
TABLE 5 Dammaranes

Antiobesity Compound	Natural Sources	Mechanism of Action	References
(20*S*,23*R*)-3β,20β-Dihydroxydamma-24-diene-21-oic acid 21,23-lactone	*Gynostemma pentaphyllum* (Jiaogulan)	Pancreatic lipase inhibition	[72–75]
(20*S*,24*S*)-20,24-Epoxydammarane-3β, 12β,25-triol	*Gynostemma pentaphyllum* (Jiaogulan)	Pancreatic lipase inhibition	[72–75]
2α,3β,12β-Trihydroxydammar-20(22)-*E*,24-diene-3-*O*-[β-D-glucopyranosyl-(1 → 2)-β-D-glucopyranoside]	*Gynostemma pentaphyllum* (Jiaogulan)	AMPK activation	[72–75]
2α,3β,12β-Trihydroxydammar-20, 24-diene-3-*O*-[β-D-glucopyranosyl-(1 → 2)-β-D-glucopyranoside]	*Gynostemma pentaphyllum* (Jiaogulan)	AMPK activation	[72–75]
Ginsenoside Rg3	*Panax ginseng* (Asian ginseng)	Pancreatic lipase inhibition, HMG-CoA reductase inhibition, inhibits PPARγ transcription activity, inhibits adipocyte differentiation and inhibit triglyceride accumulation	[76–80]
Ginsenoside Rh2	*Panax ginseng* (Asian ginseng)	Pancreatic lipase inhibition, HMG-CoA reductase inhibition, inhibits PPARg transcription activity, inhibits adipocyte differentiation and inhibit triglyceride accumulation	[76–80]
Ginsenoside Rk1	*Panax ginseng* (Asian ginseng)	Inhibit triglyceride accumulation	[76–80]
Ginsenoside Rb1	*Panax quinquefolium* (American ginseng)	Pancreatic lipase inhibition, appetite suppression	[81–88]
Ginsenoside Rb2	*Panax quinquefolium* (American ginseng)	Pancreatic lipase inhibition	[81–88]

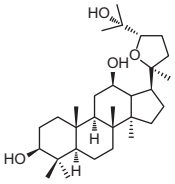
Continued

TABLE 5 Dammaranes—Cont'd

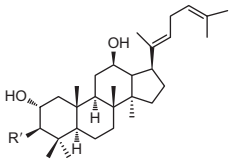
Antiobesity Compound	Natural Sources	Mechanism of Action	References
Ginsenoside Rc	*Panax quinquefolium* (American ginseng)	Pancreatic lipase inhibition	[81–88]
Ginsenoside Rd	*Panax quinquefolium* (American ginseng)	Pancreatic lipase inhibition	[81–88]



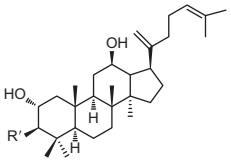
(20*S*, 23*R*)-3β,20β-Dihydroxydamma-24-diene-21-oic acid 21,23-lactone



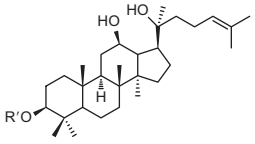
(20*S*,24*S*)-20,24-Epoxydammarane-3β,12β,25-triol



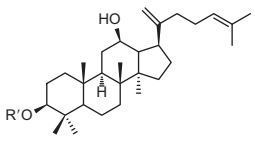
2a,3β,12β-Trihydroxydammar-20(22)-E,24-diene-3-*O*-[β-D-glucopyranosyl-(1→2)-b-D-glucopyranoside]



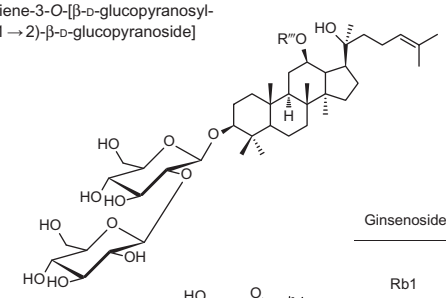
2α,3β,12β-Trihydroxydammar-20,24-diene-3-*O*-[β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside]

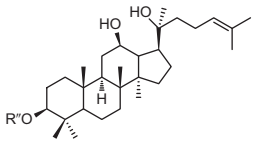


Ginsenoside Rg3



Ginsenoside Rk1

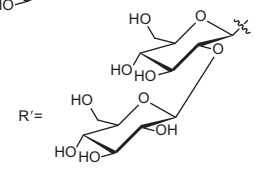




Ginsenoside Rh2

Ginsenoside	R‴
Rb1	
Rb2	
Rc	
Rd	

R′=



R″=

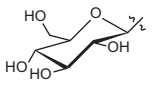
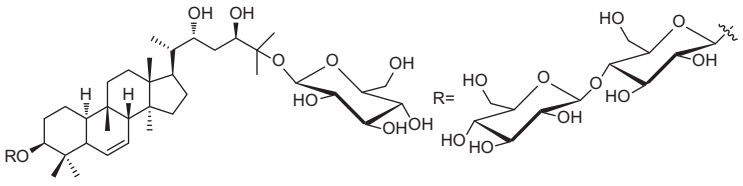
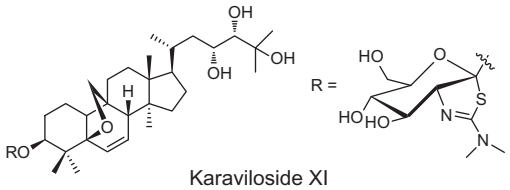


TABLE 6 Cucurbitanes

Antiobesity Compound	Natural Sources	Mechanism of Action	References
Momordicoside S	*Momordica charantia* (bitter melon)	AMPK activation	[89,90]
Karaviloside XI	*Momordica charantia* (bitter melon)	AMPK activation	[89,91]



Momordicoside S



Karaviloside XI

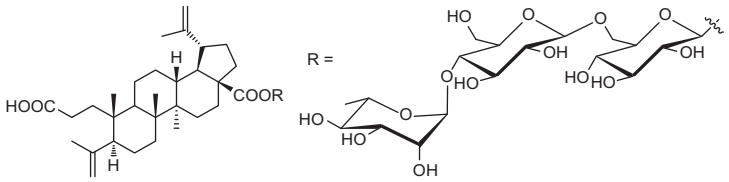
(SAM, a methyl group donor) onto the 5-position of cytosine [158–160]. In human, three major isoforms of DNMT are involved in establishing and maintaining the DNA methylation patterns; DNMT3A and DNMT3B are primarily responsible for *de novo* methylation of specific DNA sites, while DNMT1 maintains the established DNA methylation patterns. In general, activation of DNMTs is often associated with hypermethylation at gene promoter, and this resulted in a silencing of the associated gene [161–163].

HISTONE MODIFICATIONS

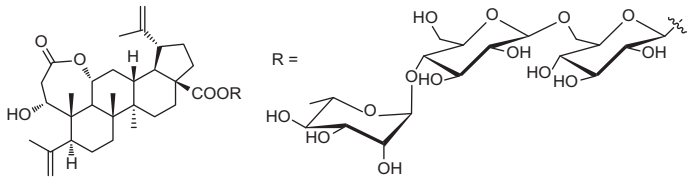
Histone proteins, on the other hand, are subjected to a wide range of posttranslational modifications. This usually occurs at the N-terminal tails, such as acetylation, methylation, phosphorylation, ubiquitination, biotinylation, ADP ribosylation and the addition of small ubiquitin-like modifier (or SUMO) proteins (sumoylation), and several others [164,165]. A host of enzymes are involved in the regulation of these histone modifications. For instance, histone

TABLE 7 Lupanes

Antiobesity Compound	Natural Sources	Mechanism of Action	References
Sessiloside	*Acanthopanax sessiliflorus* (wu jia) and *A. senticosus* (Rupr. Maxim) Harms	Pancreatic lipase inhibition	[92–94]
Chiisanoside	*Acanthopanax sessiliflorus* (wu jia) and *A. chiisanensis*	Pancreatic lipase inhibition	[92–94]



Sessiloside



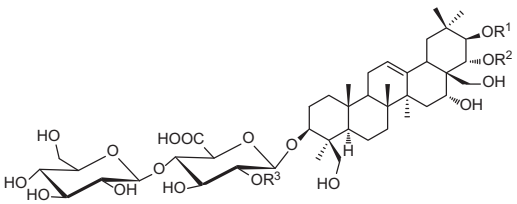
Chiisanoside

TABLE 8 Oleananes

Antiobesity Compound	Natural Sources	Mechanism of Action	References
Escin Ia	*Aesculus turbinate* (Japanese horse chestnut) and *Aesculus* hippocastanum (European horse chestnut)	Pancreatic lipase inhibition	[95–98]
Escin IIa	*Aesculus turbinate* (Japanese horse chestnut) and *Aesculus* hippocastanum (European horse chestnut)	Pancreatic lipase inhibition	[95–98]
Escin Ib	*Aesculus turbinate* (Japanese horse chestnut) and *Aesculus* hippocastanum (European horse chestnut)	Pancreatic lipase inhibition	[95–98]

TABLE 8 Oleananes—Cont'd

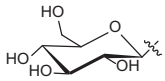
Antiobesity Compound	Natural Sources	Mechanism of Action	References
Escin IIb	*Aesculus turbinate* (Japanese horse chestnut) and *Aesculus* hippocastanum (European horse chestnut)	Pancreatic lipase inhibition	[95–98]
Silphioside F	*Acanthopanax senticosus* (Siberian ginseng)	Pancreatic lipase inhibition	[99]
Copteroside B	*Acanthopanax senticosus* (Siberian ginseng)	Pancreatic lipase inhibition	[99]
Glycyrrhetinic acid	*Glycyrrhiza glabra* (liquorice)	Reduce the expression of PPARγ, inhibit adipocyte differentiation, and inhibit triglyceride accumulation	[100–102]



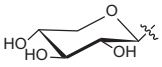
Tigloyl =

Angeloyl =

D-Glucopyranosyl =

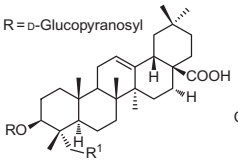


D-Xylopyranosyl =

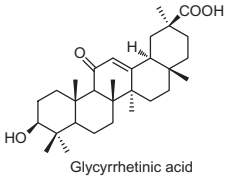


Compounds	R^1	R^2	R^3
Escin I a	Tigloyl	Acetyl	D-Glucopyranosyl
Escin II a	Tigloyl	Acetyl	D-Xylopyranosyl
Escin I b	Angeloyl	Acetyl	D-Glucopyranosyl
Escin II b	Angeloyl	Acetyl	D-Xylopyranosyl

R = D-Glucopyranosyl



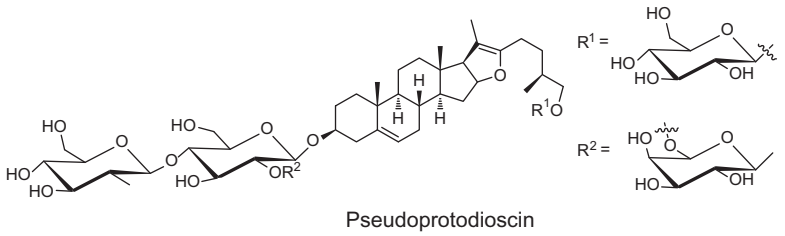
Compounds	R^1
Silphioside F	H
Copteroside B	OH



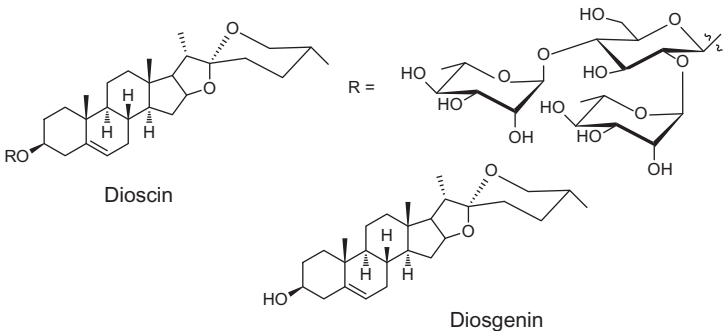
Glycyrrhetinic acid

TABLE 9 Steroids

Antiobesity Compound	Natural Sources	Mechanism of Action	References
Pseudoprotodioscin	*Dioscorea nipponica* Makino (wild yam)	Pancreatic lipase inhibition, reduced expression of C/EBPα and PPARγ	[103–108]
Dioscin	*Dioscorea nipponica* Makino (wild yam)	Pancreatic lipase inhibition	[103–108]
Diosgenin	*Dioscorea nipponica* Makino (wild yam)	Pancreatic lipase inhibition	[103–108]
P57AS3	*Hoodia gordonii* (hoodia, ghaap) and *Hoodia pilifera* (ghaap, guaap, ngaap)	Appetite and thirst suppressant	[109–115]

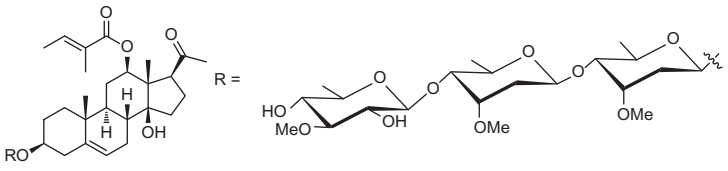


Pseudoprotodioscin



Dioscin

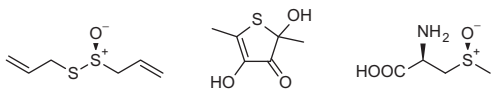
Diosgenin



P57AS3

TABLE 10 Organosulfur Compounds

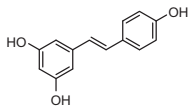
Antiobesity Compound	Natural Sources	Mechanism of Action	Epigenetic Effect	References
Allicin	*Allium sativum* (garlic)	Reduced expression of C/EBPα, PPARγ, and adiponectin, inhibit adipocyte differentiation	Inhibits HDACs	[116,117]
Thiacremonone	*Allium sativum* (garlic)	Inhibit adipocyte differentiation, oxidation of fatty acid through AMPK activation, decreased expression levels of acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS)	Decreases DNA methylation	[118]
S-Methyl cysteine sulfoxide (SMCS)	*Allium cepa* (onion)	Decrease serum triglyceride level and prevent accumulation of oil drop in cells	Inhibits HDACs	[119–122]

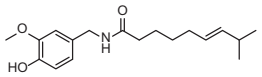


deacetylases (HDACs), histone acetyl transferases (HATs), histone methyl transferases (HMTs), histone demethylases (HDMs), and sirtuins have been described in humans [166]. Each of these enzymes is responsible for a specific epigenetic mark, and on a specific histone location. In general, histone acetylation and phosphorylation activate gene expression, whereas histone deacetylation, sumoylation, and biotinylation silence gene expression [167,168]. Methylation and ubiquitination of histones are more complex; they can act as silencers or activators depending on the affected histone residue [169–172]. There also seems to be some sort of combinatorial code, frequently known as the "Histone Code," where different combinations of histone modifications work together to modify the overall conformation of the chromatin, and hence either activates or silences the gene [173–177].

TABLE 11 Miscellaneous

Antiobesity Compound	Natural Sources	Mechanism of Action	Epigenetic Effect	References
Resveratrol	*Vitis vinifera* (common grape vine), *Arachis hypogaea* (peanut)	AMPK activation, decrease expression of PPARγ inhibiting adipocyte differentiation, adipocyte apoptosis	Activates SIRT1 Activates HDACs Decreases DNA methylation	[123–135]
Curcumin	*Curcuma longa* (turmeric)	Fatty acid oxidation, adipocyte apoptosis, AMPK activation, decrease expression of PPARγ and C/EBPα	Inhibits HDAC1, HDAC3 Inhibits p300 HAT	[136–140]
Capsaicin	*Capsicum annuum* (red pepper)	Thermogenesis, apoptosis, inhibition of adipogenesis, decrease PPARγ expression	Inhibits DNMTs Inhibits HDACs	[141–143]

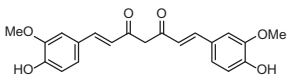


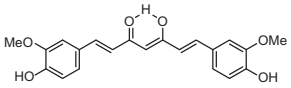


Resveratrol

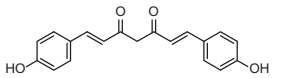
Capsaicin

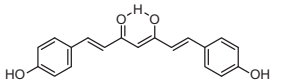
Curcumin



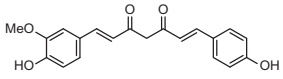


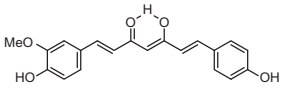
Bidemethoxycurcumin





Demethoxycurcumin





OBESIGENIC GENE

Obese individuals often present a different epigenetic pattern on DNA and histones in comparison to healthy normal-weight individual. The recognition of an important epigenetic influence on obesity has led to a search for human genes that are susceptible to epigenetic regulations, particularly those with a role in obesity development and related processes, such as adipogenesis, inflammation, and insulin signaling [178,179].

Several key genes that were potentially involved in the pathogenesis of obesity were since discovered, including insulin-like growth factor-binding protein 2 (IGF2), peroxisome proliferative activated receptor gamma (PPARγ), atrial natriuretic peptide (ANP); as well as those that played important roles in adipogenesis such as fibroblast growth factor-2, cyclin-dependent kinase inhibitor 1A, and leptin. In addition, genes participating in energy homeostasis, such as lipoprotein lipase and insulin signaling-related genes were also found to be under epigenetic control [180,181]. In particular, aberrant promoter hypermethylation was observed with IGF2, PPARγ, and ANP while other obesogenic genes, such as PPARα and phosphoenolpyruvate carboxykinase 1 appeared to be hypomethylated [182–185].

NATURAL PRODUCTS AFFECTING EPIGENETIC MECHANISMS

Importantly, there is compelling evidence that many natural products and bioactive compounds can reverse some of the epigenetic changes as DNA methylation and histone modifications, thereby modifying the expression of genes that are associated with the development of many human diseases, including obesity. Many have been identified as natural inhibitors of epigenetic enzymes, such as DNMTs and histone-modifying enzymes, while others act indirectly by altering the availability of substrates necessary for these enzymes. This suggests that their antiobesity effects likely involved a complex series of genetic and epigenetic events, affecting multiple pathways, in addition to more well-studied, classical mechanisms outlined in Table 1–11. Natural products and bioactive compounds of particular interest to this chapter are flavonoids, catechols, polyphenols, resveratrol, curcumin, organosulfur compounds, and dietary methyl donors.

Flavonoids

Flavonoids are polyphenolic secondary metabolites commonly found in higher plants, and food products derived from plants, such as wine, tea, and coffee [186].

They serve as plant pigments in nature and are responsible for the beauty and splendor of flowers and fruits. Most of them exhibit potent antioxidant, radical scavenging, and metal-chelating properties, which are thought to be

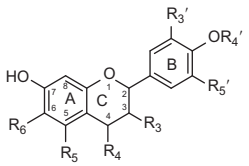


FIGURE 1 General structure of flavonoids.

responsible for their numerous health benefits, including anti-inflammatory, anticancer, and antiobesity effects [187,188].

Flavonoids constitute a diverse sets of natural product based on a common structural motif (Fig. 1). Members of the flavonoid family generally contain two aromatic rings (A and B), each with at least one hydroxyl group on the aromatic ring. They are both connected to a third ring (C), which is formed through a three-carbon bridge and an oxygen atom [186].

Flavonoids are further classified into five main classes, based on how the B ring is connected to the C ring, the types of groups present on the C ring, and their oxidation state.

1. *Isoflavonoids* (genistein and other phytoestrogens)
2. *Flavanols* (catechin, gallocatechin, epigallocatechin-3-gallate (EGCG))
3. *Flavones* (luteolin, quercetin, myricetin, fisetin)
4. *Neoflavonoids* (nevetin, coutareagenin)
5. *Anthocyanidins* (cyanidin, petunidin).

Isoflavonoids

Genistein (5,7-dihydroxy-3-(4-hydroxyphenyl)chromen-4-one) is one of the most extensively studied isoflavonoids. It constitutes a significant portion of Asian diet, including Japanese and Chinese cuisine, in the form of soy (*Glycine max*) and soy food products. The obesity prevention benefits of this phytoestrogen are well reported, and several mechanisms of action have been proposed [22–31].

In one study, mice fed with 500–1500 ppm of dietary genistein for 12 days resulted in a decrease in adipose deposition, which was believed to be caused by a decrease in the level of lipoprotein lipase. Genistein was further reported to suppress adipogenesis, possibly through AMPK (5′ adenosine monophosphate-activated protein kinase, an enzyme important for cellular energy homeostasis) activation, where genistein, at 50–200 μM, was able to inhibit adipocyte differentiation, and to promote apoptosis of mature adipocytes in a dose-dependent manner [22,23]. Other mechanisms that could also have contributed to genistein's antiobesity effects include the suppression of fatty acid synthase expression, and the prevention of Janus-activated kinase 2 phosphorylation, which indirectly prevents adipocyte differentiation [24].

In relation to epigenetics, recent studies have provided direct evidence which elegantly demonstrate the association between maternal exposure to genistein and the lifelong epigenetic changes in mouse offspring [25]. Experiments on Agouti mouse model showed that supplementing a pregnant mother's diet with genistein is able to induce hypermethylation of the Agouti gene in her offspring (via the inhibition of DMNT), thereby decreasing the expression of this gene, and protecting her offspring from obesity [26]. In addition, a diet rich in genistein is also able to protect the mice against obesity by reversing the effect of gene hypomethylation, such as those induced by DNA-hypomethylating compound bisphenol A. Finally, genistein was recently reported to inhibit the activities of HDACs, and this was linked to the suppression of a number of key genes that are involved in body weight regulation, such as adiponectin [27,30].

Taken together, the antiobesity effect of genistein likely involves a combination of several mechanisms; these are, at least in part, mediated through its modulating effects on the levels of DNA methylation and histone acetylation, resulting in the activation or silencing of associated genes. It should be noted that the antiobesity effects of genistein have yet to be confirmed in human. However, it is tempting to speculate that genistein may provide a promising natural therapeutic agent for obesity, since Asians, whose diets are typically rich in soy product, have a lower rate of obesity compared to the Westerners. Nevertheless, caution should be exercised about consuming large amounts of the soy products or soy supplements, as it is currently unclear whether soy phytoestrogens is linked to an increase in breast cancer risk [31].

Flavanols

Flavanols are found in large abundance in many types of human diets such as fruits, vegetables and, in particular, green tea, which is brewed from the unfermented, dried leaves of *Camellia sinensis* [189]. It is traditionally consumed by Chinese, Koreans, and Japanese, and is an especially rich source of catechins, such as (−)-catechin, epicatechin, (−)-EGCG. These compounds account for up to 35% of the dry weight of green tea, of which EGCG is the most abundant, representing 50–80% of the total constituents [189]. It is also believed to be the putative compound responsible for the observed antiobesity effects of green tea. In addition to catechins, green tea contains a host of other polyphenolic compounds, among which, quercetin and gallic acid are also of particular interest in this chapter.

Epidemiological evidence and several randomized controlled trials have shown that habitual consumption of green tea decreases the levels of body fat and waist circumference [190–193]. The mechanisms by which green tea flavonoids influence body weight and body composition remain an active area of research. Much of the work in humans focused on the effects of catechins on appetite modification, energy expenditure, and fatty acid oxidation.

Other potential mechanisms include downregulation of enzymes involved in hepatic lipid metabolism, and decreased glucose and fat absorption [194–198].

EGCG is reported to exhibit pancreatic lipase inhibitory effect *in vitro* [32]. It is also believed to prevent obesity by blocking the adipocyte differentiation of 3T3-L1 cells through the activation of AMPK, and inducing the apoptosis of mature adipocytes. Moreover, there was also an increase in UCP2-mediated fatty acid oxidation in the liver of mice that were fed EGCG [33–36]. To date, there is no clear clinical data on the antiobesity effect of EGCG on human, albeit several studies indicating that EGCG supplementation could increase fat oxidation in human [37].

As with EGCG, epicatechin and catechin also caused an increase in AMPK activity in the skeletal muscle and liver. Mice treated with 189 mg/L of epicatechin demonstrated higher level of fatty acid oxidation [38]. Moreover, catechin is reported to upregulate the expression and secretion of adiponectin protein in adipocytes [39,40]. Interestingly, there is evidence to suggest that epigenetic mechanisms may be driving these processes. Notably, recent studies indicated that green tea catechins (EGCG, epicatechin, and catechin) could decrease the activity of DNMT1, and DNMT1-mediated DNA methylation in a concentration-dependent manner, with EGCG being the most potent inhibitor among the catechins studied [41]. In addition, EGCG is also a natural inhibitor of HAT. Hence, it is likely that green tea catechins prevent obesity through influencing the epigenetic regulation of adipocyte differentiation and apoptosis [42].

Flavones

Quercetin and the structurally similar luteolin are ubiquitous dietary flavones found in a large variety of fruits, vegetables, and herbs, such as carrots, green tea, olive oil, green peppers, and celery. They display many of the properties of the flavonoid group, including antioxidant, prooxidant, and anti-inflammatory functions. Their antiobesity effects are well established; this is believed to be mediated through increasing the expression of AMPK, which subsequently reduces the differentiation and proliferation of human 3T3-L1 preadipocytes, and induces their apoptosis [59,62–64,199].

The action of quercetin as epigenetic modifiers is reported mainly in cancer-related models, where the potential of quercetin to interfere with multiple aberrant signal transduction pathways in cancer cells has been demonstrated *in vitro* [200–205]. There is also a positive correlation between the inhibition of HDAC1 and DNMT1 by quercetin through its antiproliferative, proapoptotic, anti-invasive, and antiangiogenic properties. Although there have not been any studies exploring the relationship between quercetin inhibitory effects on epigenetic enzymes and obesity prevention, it is conceivable that its antiobesity effects could be mediated, either directly or indirectly, via an increased expression of methylation-controlled genes, and through altering the level of acetylation in histones.

FLAVONOID-RELATED COMPOUNDS

Currently available data suggest that flavonoid-related compounds, such as catechols, including 3,4-dihydrobenzoic acid, epinephrine, gallic acid, and catechol, and coffee polyphenols, such as caffeic acid, and chlorogenic acid are inhibitors of JmjC histone lysine demethylases [206]. The latter is a large family of iron- and 2-oxoglutarate-dependent oxygenases, which is responsible for the removal of methylation epigenetic mark on histone lysine residues. They play a central role in modifying the chromatin structures and, hence, are important in gene regulation. Many of the catechols and polyphenols are believed to inhibit the JmjC enzymes by either binding to iron (an important cofactor for the JmjC enzymes) in the active site, or by sequestering iron in solution [206].

Importantly, the JmjC histone demethylase JMJD1A, also known as JHDM2A and KDM3A, is recently found to be associated with obesity, where a loss of JMJD1A function in mice results in obesity and hyperlipidemia, suggesting an important link between histone methylation status, metabolism, and obesity [207].

These findings indicate that the antiobesity effects of flavonoid and flavonoid-related compounds are probably more complicated than initially believed, since these compounds appear to also function on the level of DNA methylation and histone modifications, through the inhibition of epigenetic enzymes, such as DMNTs, HDACs, sirtuins, HATs, and HDMs [208,209].

RESVERATROL

Resveratrol (3,4′,5-trihydroxystilbene) is a plant antioxidant found in a wide variety of plant species, where it acts as a natural mechanism to fight against bacterial infection. This polyphenol is particularly rich in nuts, grapes, and processed grapes products such as red wine; with fresh grape skin representing one of the best sources of resveratrol, amounting to 5–10 mg per 100 g. Many beneficial effects were attributed to resveratrol, such as anti-inflammatory, anticancer, and cardiovascular protective effects [210,211].

The antiobesity effects of resveratrol are particularly well studied. In a mice study, resveratrol was able to protect mice that were fed a high-calorie diet from obesity, as well as improving their health, and extending their lifespan by mimicking the effects of calorie restriction. In the study, 58% of the mice fed a high-calorie diet died at the end of the 114-day trial compared to 42% for the high-calorie resveratrol group, and 42% for the control group which was fed a standard diet. Similar observation is obtained in a separate study on 11 obese human males, where resveratrol is able to mimic a calorie-restricted diet, and confer obesity protection to the subjects [123].

Several plausible mechanisms of actions were proposed. Resveratrol could activate AMPK which plays a key role in fatty acid oxidation and inhibition of 3T3-L1 preadipocyte differentiation. Resveratrol could also reduce food

intake and satiety by downregulating neuropeptide Y and Agouti-related proteins, both of which are associated with increased food intake [124–126].

Notably, resveratrol is one of the most potent activator of SIRT1. Sirturins typically exhibit their activity through deacetylation of nonhistone proteins, but are also important in the maintenance of histone acetylation patterns [127]. There is increasing evidence suggesting that resveratrol could alter the metabolic functions of white adipose tissue, and suppress the proliferation of preadipocytes via SIRT1-mediated epigenetic regulation of several genes that are important for adipocyte differentiation and adipogenesis, such as PPARγ and C/EBPα [128–133]. In a cell-based study, resveratrol was reported to prevent the preadipocytes from growing and differentiating into mature adipocytes. Hence, 200 μM of resveratrol was reported to decrease 3T3-L1 cells viability by 75.3% and 100 μM of resveratrol increase apoptosis by 76%. In maturing preadipocytes, 50 μM of resveratrol is able to decrease lipid accumulation by 94.3% [128].

Finally, it is interesting to note that resveratrol stimulates the formation of adiponectin (a cardioprotective protein), and reduces the production of certain cytokines (interleukins 6 and 8) that may be linked to the development of obesity-related disorders, such as diabetes and cardiovascular diseases. This may help explains the "French paradox"—the observation that French people have a relatively low death rate from coronary heart disease despite having a diet that is relatively rich in saturated fat. While the health benefits of resveratrol seem promising in preventing or treating obesity, there is currently insufficient knowledge with respect to the long-term effect of resveratrol treatment. As with genistein (another phytoestrogen) resveratrol may stimulate the growth of human breast cancer cells, hence caution should be exercised when consuming large quantity of resveratrol [135].

CURCUMIN

Curcumin is a polyphenol which can be isolated from *Curcuma longa* (turmeric). The rhizome tumeric is commonly cultivated in countries such as India, China, and Southeast Asia, where it is used in traditional Chinese medicine, as a spice, and as coloring agent in cooking, as exemplified by the characteristic yellow color in curry. Tumeric contains curcumin as the main active constituent (77%), in addition to demethoxycurcumin, bidemethoxycurcumin, and cyclocurcumin. All four components together are termed curcuminoids [212–215].

Other than possessing anticancer, anti-inflammatory, and antioxidation activities, the potential for curcumin in preventing obesity is well documented [216–225]. Studies showed that curcumin, at a dose of 0.05 g/100 g, produces a hypolipidemic effect on hamsters fed on a high-fat diet. There was also a significant decrease in hepatic cholesterol and triglyceride levels, and an increase in fatty acid beta-oxidation compared with the control [136].

With regard to its mechanism of action, curcumin was reported to downregulate the expression of genes involved in energy metabolism and lipid accumulation, and decreasing the level of intracellular lipids. Moreover, curcumin suppresses angiogenesis, which is essential for tissue growth. This acts in close association with its effects on lipid metabolism, to bring about an overall lowering of body fat and body weight. Several key genes responsible for adipogenesis and lipogenesis, such as PPARγ and C/EBPα, were also observed to express at a much lower level [137]. In an *in vitro* study on 3T3-L1 adipocytes, curcumin, at 5–20 μM, prevented differentiation and caused apoptosis of the adipocytes. In the same report, supplementing high-fat diet mice with 500 mg/kg of curcumin for 12 weeks resulted in less weight gain, adiposity, and microvessel growth in adipose tissue. There was also a notable increase in oxidation of fatty acid [138,139,221].

It is likely that that the gene-regulatory effects of curcumin are achieved through the inhibition of several epigenetic enzymes, including HDACs, and HATs. Current evidence suggests that while its inhibitory potencies on these epigenetic enzymes are weaker than those reported for some other dietary epigenetic modifiers, such as EGCG and resveratrol, its activities on HAT correlate with a decrease in global histone H3 and H4 acetylation in the brain cells. Furthermore, curcumin-mediated promoter hypoacetylation also coincides with gene silencing. This suggests an additional epigenetic mechanism in the antiobesity property of curcumin [140].

ORGANOSULFUR COMPOUNDS

Allium vegetables including garlic, onion, scallion, chive, shallot, and leek contain proportionately high levels of organosulfur compounds, such as allicin and diallyl sulfides, while cruciferous vegetables, such as broccoli and brussel sprouts contain relatively large amount sulforaphane and isothiocyanate [226]. These organosulfur compounds are metabolized to allyl mercaptan, allyl methyl sulfide, methyl mercaptan, and ajoene in the body [227,228]. They account for the distinctive flavor and aroma, as well as the many purported medicinal benefits, including anticancer, antihypertensive, antimicrobial, and antiobesity [229–232].

In regard to obesity, they have been found to inhibit preadipocyte differentiation, and to decrease cholesterol synthesis in hepatocytes through the inhibition of HMG-CoA reductase. Although these beneficial effects have mostly been ascribed to their powerful antioxidant properties, a number of studies showed a promising link between these organosulfur compounds and histone deacetylation. Allyl mercaptan, in particular, inhibits the activity of HDACs, resulting in an increase in both global and local histone acetylation, and an activation of epigenetically silenced genes. *In vitro* cell culture studies performed using B16 and S91 melanoma cells further showed that sulforaphane could inhibit the growth and proliferation of cancer cells by downregulating

HDACs [233,234]. Another study demonstrated that diallyl sulfide increases histone H3 and H4 acetylation in colonocytes isolated from rats, along with alterations in the expression of associated genes [235].

At present, there is no study examining the HDAC inhibitory effects of organosulfur compounds on obesity.

METHYL DONOR METABOLISM

The functions of epigenetic enzymes involved in DNA and histone methylation, such as DNMTs and HMTs depend on the availability of methyl donor SAM and several enzyme cofactors, such as FAD, NAD, iron, and zinc. SAM is formed from methyl group precursors, such as methionine, choline, betaine, folate, and vitamin B12 (cobalamin) [236,237]. Thus, these nutrients are closely related with the methylation of epigenetic marks; perturbation in the intracellular levels of any one of these methyl donor precursors or enzyme cofactors will result in a loss of DNA and/or histone methylation patterns, and subsequently changes gene expression [238,239].

Experimental *in vivo* studies show that dietary restriction of methyl donors, in general, induces DNA hypomethylation, while supplementation produces DNA hypermethylation. Folic acid, for instance, has been linked to DNA methylation in a dose-dependent manner. In fact, in animal study using mature female sheep, a restriction of folate, vitamin B12, and methionine from the periconceptional diet resulted in obesity in adult offspring [240–243]. These data strongly suggest that epigenetic mechanisms may be boosted or impaired by methyl donors in the mother's diet, and could be involved in obesity susceptibility in the offspring [244–247].

Several dietary flavonoids, such as catechin, EGCG, and quercetin have been shown to interfere with the methyl donor metabolism, and affecting the available pool of SAM. This resulted in changes in both the DNA and histone methylation pattern. Furthermore, it is known that various dietary catechols undergo COMT-mediated O-methylation as part of the normal metabolism in humans [248]. This would not only reduce the cellular pools of SAM, but also result in the formation of demethylated SAM, which serves as a feedback inhibitor of various SAM-dependent methylation reactions.

CONCLUSION

Natural products and bioactive constituents from food possess a range of properties that are useful for the treatment of a variety of human diseases. The demand for safer and more effective therapeutic agents to combat the obesity epidemic has motivated efforts to look to natural products as alternative sources of therapy. In this chapter, we reported some obesigenic genes that are potentially involved in the pathogenesis of obesity, and discussed reports linking aberrant epigenetic mechanisms to their dysregulation.

We also examined how these epigenetic mechanisms can be controlled by natural products and dietary food components, and provided perspective on the potential of using these epigenetic-modifying natural products for the treatment of obesity.

Although many natural products and bioactive compounds possess remarkable pharmacological activities against obesity, and hold great promise for development into potential antiobesity drugs, current knowledge of their exact mechanism of actions remained to be fully elucidated. For instance, further studies are needed to help us understand their effect on the epigenetic regulation of obesigenic genes. It will be necessary to examine whether changes in epigenetic patterns, such as DNA methylation and histone modification, correspond with changes in the expression of key genes involved in obesity in humans, and how these could influence obesity-associated phenotypes. The antiobesity effects of many of the natural products described herein have yet to be confirmed in humans. Multiple mechanisms are probably involved, and these need to be clarified before nutritional therapy can be considered.

ABBREVIATIONS

ANP	Atrial Natriuretic Peptide
AMPK	AMP-activated Protein Kinase
C/EBP	CCAAT-enhancer-binding proteins
DNMT	DNA Methyltransferases
EGCG	Epigallocatechin-3-gallate
HAT	Histone Acetyl Transferase
HDAC	Histone Deacetylase
HDM	Histone Demethylase
HMT	Histone Methyl Transferase
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
IGF	Insulin-like Growth Factor-binding protein
JMJD1A	JmjC Histone Lysine Demethylase 1A
PPAR	Peroxisome Proliferative Activated Receptor
SAM	S-Adenosyl Methionine
SIRT1	Sirturins 1
SMCS	S-Methyl Cysteine Sulfoxide
SUMO	Small Ubiquitin-related Modifier
UCP	Mitochondrial Uncoupling Proteins

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