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Review

Possible anti-obesity therapeutics from nature – A review

Jong Won Yun *

Department of Biotechnology, Daegu University, Kyungsan, Kyungbuk 712-714, Republic of Korea

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ABSTRACT

Obesity is associated with many diseases, particularly diabetes, hypertension, osteoarthritis, and heart disease. The obesity incidence has increased at an alarming rate in recent years, becoming a worldwide health problem, with incalculable social costs. Two different obesity-treatment drugs are currently on the market: orlistat, which reduces intestinal fat absorption via inhibiting pancreatic lipase; and sibutramine, an anorectic or appetite suppressant. Both drugs have hazardous side-effects, including increased blood pressure, dry mouth, constipation, headache, and insomnia. For this reason, a wide variety of natural materials have been explored for their obesity treatment potential. These are mainly complex products having several components with different chemical and pharmacological features. This review aimed to survey the literature covering natural products with anti-obesity activity and to review the scientific data, including experimental methodologies, active components, and mechanisms of action against obesity.

Contents

1. Introduction

On a global scale, obesity has reached epidemic proportions and is a major contributor to the global burden of chronic disease and disability. Currently, more than one billion adults worldwide are overweight and at least 300 million of them are clinically obese (WHO, 2009).

Two different types of obesity-treatment drugs are currently available on the market (Chaput et al., 2007). One of these is orlistat (Xenical), which reduces intestinal fat absorption through inhibition of pancreatic lipase (Ballinger and Peikin, 2002; Drew et al., 2007; Hutton and Fergusson, 2004; Thurairajah et al., 2005). The other is sibutramine (Reductil), which is an anorectic,

Abbreviations: ACC, acetyl-CoA carboxylase; AMPK, adenosine 5′-monophosphate-activated protein kinase; BAT, brown adipocyte tissue; C/EBP, CCAAT enhancer binding protein; CNS, central nervous system; CPT, carnitine palmitoyltransferase-1; DHA, docosahexaenoic acid; ECG, (−)-epicathin-3-gallate; EGG, (−)-epigallocatechin; EGCG, (−)-epigallocatechin-3-gallate; EPA, eicosapentaenoic acid; ERK, extracellular signal-regulated kinases; FA, fatty acid; GLUT, glucose transporter; GPDH, glycerol-3-phosphate dehydrogenase; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; HFD, high fat diet; 5-HT, 5-hydroxytryptamine; IC_{50}, the half maximal inhibitory concentration (with triolein as a lipase substrate); MAPK, mitogen-activated protein kinase; MCH, melanin-concentrating hormone; PPAR, peroxisome-proliferator activated receptor; PUFA, polyunsaturated fatty acids; RQ, respiratory quotient; TG, triglyceride; TNF, tumor necrosis factor; UCP, uncoupling protein; WAT, white adipocyte tissue.

* Tel./fax: +82 53 850 6559.
E-mail address: jwyun@daegu.ac.kr

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or appetite suppressant (Lean, 2001; Poston and Foreyt, 2004; Tziomalos et al., 2009). Both drugs have side-effects, including increased blood pressure, dry mouth, constipation, headache, and insomnia (de Simone and D'Addeo, 2008; Karamadoukis et al., 2009; Slovacek et al., 2008; Thurairajah et al., 2005). A number of anti-obesity drugs are currently undergoing clinical development, including centrally-acting drugs (e.g. radafaxine and oleoyl-estrone), drugs targeting peripheral episodic satiety signals (e.g. rimonabant and APD356), drugs blocking fat absorption (e.g. cetilistat and AOD9604), and human growth hormone fragments (Halford, 2006; Melnikova and Wages, 2006).

At present, because of dissatisfaction with high costs and potentially hazardous side-effects, the potential of natural products for treating obesity is under exploration, and this may be an excellent alternative strategy for developing future effective, safe anti-obesity drugs (Mayer et al., 2009; Nakayama et al., 2007; Park et al., 2005). A variety of natural products, including crude extracts and isolated compounds from plants, can induce body weight reduction and prevent diet-induced obesity. Therefore, they have been widely used in treating obesity (Han et al., 2005a; Moro and Basile, 2000; Rayalam et al., 2008).

A wealth of information indicates numerous bioactive components from nature are potentially useful in obesity treatments. A good example of such is the polyphenols. These show strong anti-obesity activity and include apigenin, genistein, and the catechins (Rayalam et al., 2008; Thielecke and Boschmann, 2009; Wolfram et al., 2006).

To date, despite the appearance of several excellent reviews of anti-obesity agents in the literature, no reviews have focused on summarizing real, natural-product data on anti-obesity activity, active compound types, and mechanisms of action. In 2000, Moro and Basile reviewed the use of certain well-known medicinal plants that had claimed to be useful in treating obesity (Moro and Basile, 2000). Five years later, Han et al., 2005a reviewed the anti-obesity effects of natural products from more diverse sources. More recently, the review of anti-obesity phytochemicals by Rayalam et al. (2008) focused on adipocyte life cycle regulation. However, these reviews do not provide updates from the literature regarding various natural products that have anti-obesity effects.

Therefore, in this review, we surveyed natural products with anti-obesity potential and reviewed the scientific data, including experimental methodologies, active components, and mechanisms of action against obesity. A growing body of evidence indicates that natural products having anti-obesity effects can be arranged into five categories based on their distinct mechanisms; they produce (1) decreased lipid absorption, (2) decreased energy intake, (3) increased energy expenditure, (4) decreased pre-adipocyte differentiation and proliferation, or (5) decreased lipogenesis and increased lipolysis. Therefore, in this review, we addressed naturally-occurring compounds possessing anti-obesity activity addressed by categorizing them per these mechanisms.

2. Natural materials for treatment of obesity

2.1. Lipase inhibitory effect

Among treatments for obesity, one of the most promising strategies in the effort to reduce energy intake through gastrointestinal mechanisms, without altering the central mechanisms, is the development of nutrient digestion and absorption inhibitors (Birari and Bhutani, 2007). Dietary fat is not directly absorbed by the intestine unless the fat has been subjected to the action of pancreatic lipase. Therefore, pancreatic lipase is one of the most widely studied mechanisms for determining natural products' potential efficacy as anti-obesity agents (Birari and Bhutani, 2007).

Pancreatic lipase is a key enzyme in dietary triacylglycerol absorption, hydrolyzing triacylglycerols to monoacylglycerols and fatty acids. Only a few substances interact directly with the lipases themselves. One example is tetrahydrolipstatin (orlistat), a derivative of the naturally-occurring lipase inhibitor produced from *Streptomyces toxytricini* (Ballinger and Peikin, 2002). Orlistat's lipase inhibition mechanism acts through a covalent bond to the lipase's active site serine (Hadváry et al., 1988, 1991; Tsujita et al., 2006). Although this pancreatic lipase inhibitor is clinically approved for obesity treatment, orlistat has certain unpleasant gastrointestinal side-effects (Karamadoukis et al., 2009; Thurairajah et al., 2005). These side-effects result from orlistat's mode of action and include oily spotting, liquid stools, fecal urgency or incontinence, flatulence, and abdominal cramping (Chaput et al., 2007). Therefore, researchers are screening novel inhibitors, derived from plants or other natural sources, that lack some of these unpleasant side-effects (Birari and Bhutani, 2007).

Natural products provide a vast pool of pancreatic lipase inhibitors with potential for being developed into clinical products. Birari and Bhutani, 2007 reviewed various extracts and secondary metabolites, derived from plants and microorganisms, that have pancreatic lipase inhibitory activity. Drug development programs should focus on these extracts and metabolites.

A wide variety of plants possess pancreatic lipase inhibitory effects, including *Panax japonicus* (Han et al., 2005b), *Platycodi radix* (Han et al., 2000), *Salacia reticulata* (Kishino et al., 2006), *Nelumbo nucifera* (Ono et al., 2006), and so on (see Table 1 for details). These pancreatic lipase inhibitory phytochemicals include mainly saponins, polyphenols, flavonoids, and caffeine (Kim and Kang, 2005; Han et al., 2006; Moreno et al., 2006; Shimoda et al., 2006).

Several carbohydrates also possess pancreatic lipase inhibitory effects (Takao et al., 2006). For example, when researchers fed experimental animals a high-fat diet containing 7–15% chitin/chitosan, fat excretion in the feces increased, resulting in reduced body weights (Han et al., 2005a). However, the effects these carbohydrates have on body weight reduction in animals and humans are controversial (Bondiolotti et al., 2007; Gades and Stern, 2003, 2005; Gallaher et al., 2002; Han et al., 1999a; Hayashi and Ito, 2002; Ho et al., 2001; Kaats et al., 2006; Sumiyoshi and Kimura, 2006). We recently found a distinct body weight reduction in *ob/ob* mice fed on chitosan oligosaccharides; proteome analysis of mouse plasma before and after these treatments suggested chitosan oligosaccharide's molecular actions (Kumar et al., 2009). The expression of many genes is altered significantly during the anti-obesity effect, in response to the chitosan oligosaccharide in the diet (Kumar et al., 2009).

Many metabolites from microorganisms, including lipstatin from *Streptomyces toxytricini* (Weibel et al., 1987), panclicins from *Streptomyces* sp. NR0619 (Mutoh et al., 1994; Yoshinari et al., 1994), valilactone and ebelactones from *Streptomyces albolongus* (Kitahara et al., 1987; Umezawa et al., 1980), esterastin from *Streptomyces lavendulae* (Umezawa et al., 1978), caulerpenyne from *Caulerpa taxifolia* (Tomoda et al., 2002), vibralactone from *Boreostereum virans* (Liu et al., 2006), and percyquinin from *Basidiomycete stereum complicatum* (Bitou et al., 1999) also possess pancreatic lipase inhibitory activity. Moreover, certain fruiting bodies or mycelia of macrofungi reportedly possess lipase inhibitory activity (Ahn et al., 2007b; Slanc et al., 2004).

Some of the most widely-studied materials among the many natural sources of pancreatic lipase inhibitors are the different types of tea (e.g. green, oolong, and black tea). A significantly different type of polyphenols (e.g. L-epicatechin, ECG, EGG, and EGCG), isolated from tea leaves, showed strong inhibitory activity against pancreatic lipase (Han et al., 1999b; Lin and Lin-Shiau, 2006; Nakai et al., 2005; Thielecke and Boschmann, 2009). These polyphenols require galloyl moieties within their chemical

Table 1
Anti-obesity biomaterial compounds showing inhibition of pancreatic lipase.

Source	Active component	Experimental methods[a] (treated dose, subjects, duration of treatment)	Major activity[b]	References[c]
Juniperus communis (bark) and *Illicium religiosum* (wood)	Crude ethanol/water extract	Inhibitory activity of pancreatic lipase	IC_{50} = 20.4 and 21.9 μg/mL, respectively	Kim and Kang (2005)
Panax japonicus (rhizomes)	Chikusetsusaponins	3%, ICR mice with HFD, 9 weeks	22%* decrease in body weight gain	Han et al. (2005b)
Platycodi radix	Platycodin saponins	70 mg/kg, SD rats with HFD, 4 weeks	13% decrease in body weight gain	Zhao et al. (2005), Zhao and Kim (2004), Han et al. (2002) Xu et al. (2005)
Platycodi radix	Crude aqueous/ethanolic extract (saponin)	5%, ICR mice with HFD, 8 weeks	12%* decrease in body weight gain	Han et al. (2000)
Acanthopanax senticosus (stem bark)	10.6% ellagic acid	800 mg/kg, ICR mice with HFD, 5 weeks	54%* decrease in body weight gain	Lei et al. (2007); Han et al. (2000)
Thea sinensis (oolong tea)	Crude aqueous extract (caffeine)	5%, ICR mice with HFD, 10 weeks	10%* decrease in body weight gain	Han et al. (1999b)
Cassia mimosoides	Proanthocyanidin	Inhibitory activity of pancreatic lipase; 2.5%, SD rats with HFD, 8 weeks	IC_{50} = 0.11 mg/ml; 60%* decrease in body weight gain	Yamamoto et al. (2000)
Kochia scoparia (fruits)	Crude aqueous extract (saponins)	3%, ICR mice with HFD, 9 weeks	19%* decrease in body weight gain	Han et al. (2006)
Afromomum meleguetta, *Spilanthes acmella*	Crude ethanolic extract	2 mg/ml, inhibitory activity of pancreatic lipase	90%, 40% lipase inhibition, respectively	Ekanem et al. (2007)
Salacia reticulate (mixed with cyclodextrin)	Crude aqueous extract	0.5%, SD rats with HFD, 8 weeks	27% decrease in body weight gain	Kishino et al. (2006)
Thea sinensis (leaf)	Saponin	0.5%, ICR mice with HFD, 11 weeks	17%* decrease in body weight gain	Han et al. (1999b, 2001)
Nelumbo nucifera (leaf)	Crude ethanolic extract	5%, ICR mice with HFD, 5 weeks	28%* decrease in body weight gain	Ono et al. (2006)
Trigonella foenum graecum L. (seed)	Crude ethanolic extract	0.3%, ddY obese mice, 22 days	14%* decrease in body weight gain	Handa et al. (2005)
Salix matsudana (leaf)	Poly phenol (PP)	5% PP, Wistar King rats with HFD, 9 weeks	20%* decrease in body weight gain	Han et al. (2003a,b)
	Flavonoid glucoside	5%, rats of ICR strain with HFD, 9 weeks	19%* decrease in body weight gain	Han et al. (2003b)
Vitis vinifera	Crude ethanolic extract	1 mg/ml, 3T3-L1 adipocyte, 8 days	Inhibitory effect on lipase activity = 80%	Moreno et al. (2003)
Eriochloa villosa	Crude methanolic extract	0.2 mg/ml, inhibitory activity of pancreatic lipase	Inhibitory effect on lipase activity = 83%	Sharma et al. (2005)
Orixa japonica	Crude methanolic extract	0.2 mg/ml, inhibitory activity of pancreatic lipase	Inhibitory effect on lipase activity = 81%	Sharma et al. (2005)
Salvia officinalis L. (leaf)	Methanolic extract (carnosic acid)	Inhibitory activity of pancreatic lipase	IC_{50} = 36 μg/ml	Ninomiya et al. (2004)
Setaria italic	Crude methanolic extract	0.2 mg/ml, inhibitory activity of pancreatic lipase	Inhibitory effect on lipase activity = 80%	Sharma et al. (2005)
Scabiosa tschiliensis Grun.	Triterpenoid saponins	Inhibitory activity of pancreatic lipase	Maximum activity: almost 100% with prosapogenin 1B (1 mg/ml)	Zheng et al. (2004)
Acanthopanax sessiliflorous	Lupane-type saponins	0.5%, ICR mice with HFD, 4 weeks	40%* decrease in body weight gain	Yoshizumi et al. (2006)
Aesculus turbinate (seed)	Escin	Inhibitory activity of pancreatic lipase	IC_{50} = 14 μg/ml with escin IIb	Kimura et al. (2006)
Cyclocarya paliurus (Batal) Iljinskaja	Crude aqueous extract	Inhibitory activity of pancreatic lipase	IC_{50} = 9.1 μg/ml	Kurihara et al. (2003)
Cassia nomame	Flavan dimers	Inhibitory activity of pancreatic lipase	IC_{50} = 5.5 μM with (2S)-3′,4′,7-trihydroxyflavan-(4α → 8)-catechin	Hatano et al. (1997)
Gardenia jasminoides (fructus)	Crocin, crocetin	Inhibitory activity of pancreatic lipase; 50 mg/kg/d, Triton WR-1339-induced hyperlipidermic mice, 5 weeks	IC_{50} = 2.1 mg/ml with crocetin; 25%* decrease in body weight gain with crocin	Lee et al. (2005), Sheng et al. (2006)
Dioscorea nipponica	Crude methanolic extract	5%, SD rats with HFD, 8 weeks	IC_{50} = 5–10 μg/ml, 37% decrease in body weight gain	Kwon et al. (2003)
Coffea canephora	Caffeine, chlorogenic acid, neochlorogenic acid, feruloyquinic acids	0.5%, ddy mice with standard diet, 14 days	157% decrease in body weight gain	Shimoda et al. (2006)
Peptide	ε-Polylysine	0.4%, C57BL/6 mice with HFD, 60 days	29%* decrease in body weight gain	Tsujita et al. (2006)
Glycyrrhiza uralensis	Licochalcone A	Inhibitory activity of pancreatic lipase	IC_{50} = 35 μg/ml, K_i = 11.2 μg/ml	Won et al. (2007)
Chitosan	Not specified	3 g/day, human overweight adults, 8 weeks	22% decrease in body weight gain	Kaats et al. (2006)
	MW 125–145 kD	2%, Wistar rats, 4 weeks	9% decrease in body weight gain	Bondiolotti et al. (2007)
	MW 46 kDa	300 mg/kg, C57BL/6 J mice with HFD, 10 weeks	14%* decrease in body weight gain	Sumiyoshi and Kimura (2006)

(*continued on next page*)

Table 1 (*continued*)

Source	Active component	Experimental methods[a] (treated dose, subjects, duration of treatment)	Major activity[b]	References[c]
Chitosan–chitin	Chitosan (80%), chitin (20%)	15%, ICR mice with HFD, 9 weeks	143%* decrease in body weight gain	Han et al. (1999a), Gades and Stern (2003, 2005), Gallaher et al. (2002)
Manno-oligosaccharides		1%, ICR mice with HFD, 12 weeks	40% decrease in hepatic triglyceride, no body weight change	Takao et al. (2006)
Levan		10%, SD rats with HFD, 4 weeks	160% decrease in body weight gain	Kang et al. (2006)
Fungus, *Laetiporus sulphureus*	Mycelia extract	2 mg/ml fungal extract, lipase activity	Inhibitory effect on lipase activity = 83%	Slanc et al. (2004)
Fungus, *Tylopilus felleus*	Mycelia extract	2 mg/ml fungal extract, lipase activity	Inhibitory effect on lipase activity = 96%	Slanc et al. (2004)
Fungus, *Hygrocybe conica*	Mycelia extract	2 mg/ml fungal extract, lipase activity	Inhibitory effect on lipase activity = 97%	Slanc et al. (2004)
Basidiomycete, *Boreostereum vibrans*	Vibralactone	Inhibitory activity of pancreatic lipase	IC_{50} = 0.4 μg/ml	Liu et al. (2006)
Streptomyces toxytricini	Lipistatin	Inhibitory activity of pancreatic lipase	IC_{50} = 0.14 μM	Weibel et al. (1987), Hochuli et al. (1987)
Streptomyces sp. NR0619	Panclicins	Inhibitory activity of pancreatic lipase	IC_{50} = 0.89 μM with panclicin D	Mutoh et al. (1994), Yoshinari et al. (1994)
Actinomycetes sp. MG147-CF2	Valilactone	Inhibitory activity of pancreatic lipase	IC_{50} = 0.00014 μg/ml	Kitahara et al. (1987)
	Esterastin	Inhibitory activity of pancreatic lipase	IC_{50} = 0.2 μg/ml	Umezawa et al. (1978)
	Ebelactone B	Inhibitory activity of pancreatic lipase	IC_{50} = 0.001 μg/ml	Umezawa et al. (1980)
	Ebelactone A	Inhibitory activity of pancreatic lipase	IC_{50} = 0.003 μg/ml	Umezawa et al. (1980)
Citrus unshiu	Hesperidin	Inhibitory activity of pancreatic lipase	IC_{50} = 32 μg/ml	Kawaguchi et al. (1997)
Marine algae (*Caulerpa taxifolia*)	Caulerpenyne	Inhibitory activity of pancreatic lipase	IC_{50} = 2 mM	Tomoda et al. (2002)

[a] The mg/kg indicates a dose (mg) based on the experimental animal's body weight (kg), and% refers to proportion of the diet.
[b] The author recalculated values with an asterisk (*) from the original data (shown as figures) in each reference.
[c] Data from the first reference cited.

structures and/or polymerization of their flavan-3-ols for enhanced pancreatic lipase inhibition (Nakai et al., 2005).

In their search for a pancreatic lipase inhibitor Bitou et al. (1999) screened 54 marine algae. Interestingly, almost all algaes showed lipase inhibitory activity, in either methanol or ethyl acetate extracts (see Table 1 of Bitou et al., 1999).

Reportedly, the IC_{50} value of orlistat, a clinically-approved lipase inhibitor, is 0.75 μg/mL. Because crude extracts include, not only active substances, but also non-active components, the inhibitory potencies of crude extracts from plants and other natural sources are significantly weaker than that of orlistat (Kim and Kang, 2005).

Numerous natural compounds and decoctions prepared from plants resemble orlistat, in that they inhibit gastrointestinal lipase reactions. However, their inhibitory mechanisms differ from orlistat's; some are reversible reaction inhibitors, whereas others, like orlistat, are irreversible inhibitors (Tsujita et al., 2006; Birari and Bhutani, 2007). Irreversible inhibitors interact with lipase and inactivate it through formation of a stable covalent intermediate (Bitou et al., 1999).

2.2. Suppressive effect on food intake

Body weight regulation through appetite control is a multifactorial event resulting from neurological and hormonal interrelationships. A line of evidence indicates that serotonin, histamine, dopamine, and their associated receptor activities are closely associated with satiety regulation. These receptors may enable researchers to better target their searches for drugs that treat obesity through energy intake reduction (Chantre and Lairon, 2002).

Agents that act via peripheral satiety peptide systems, alter the various hypothalamic neuropeptides' CNS levels, or alter the key CNS appetite monoamine neurotransmitters' levels may be suitable candidates for drugs that will suppress appetite (Halford and Blundell, 2000; Wynne et al., 2005).

Any changes a potential appetite suppressant induces should be considered in terms of: (1) the psychological experience and behavioral expression of appetite, (2) metabolism and peripheral physiology, and (3) the CNS neural pathways' functioning (Halford and Blundell, 2000). In general, natural appetite suppressants are dietary supplements that aid in appetite control. Appetite suppressant mechanisms of action typically affect hunger control centers in the brain, resulting in a sense of fullness. However, in animals and humans, ghrelin secretion in the stomach may increase with decreased food intake, stimulating increased intake. Therefore, ghrelin antagonism may decrease or blunt the increased appetite that potentially occurs with decreased feeding, and, thus, may be a potential adjunctive treatment for obesity (Bays, 2004). MCH receptor antagonism may also prove an important target for obesity treatment through appetite regulation.

Sibutramine is the first new drug for treating obesity via appetite suppression to be approved by the FDA within the past 30 years (Tziomalos et al., 2009). Its main mechanism causes an increase in the feeling of satiety by controlling noradrenalin, serotonin, 5-hydroxytryptamine, and dopamine (Lean, 2001; Poston and Foreyt, 2004). However, sibutramine has some known adverse effects, including dry mouth, constipation, and insomnia (Chaput et al., 2007).

One clear example of a natural appetite suppressant is *Hoodia gordonii*, a leafless, spiny, succulent plant growing in some South African countaries (van Heerden, 2008). Despite its popularity, there is insufficient clinical information on *H. gordonii* to prove its efficacy. However, the consensus now is that *H. gordonii* regulates appetite and can significantly reduce calory intake and boost weight loss (Lee and Balick, 2007; MacLean and Luo, 2004; van Heerden et al., 2007; van Heerden, 2008). There are currently more

than 20 international patents on compounds originating in *H. gordonii*, and many hoodia-containing commercial preparations are available on the market (van Heerden, 2008). However, there has been no confirmation that these preparations actually contain hoodia. A common and noteworthy problem with the commercialization of botanicals is that commercially-available products often lack botanical or active ingredients.

Natural (−)-hydroxycitric acid (HCA), prepared from *Garcinia cambosia*, is another potential natural appetite suppressant. Currently, it is commercial available under the names HCA-SX and Super CitriMax™ (Ohia et al., 2002; Life Extension Vitamin Supplies and Life Extension Institute, Inc., Place Scottsdale, AZ, USA). This phytochemical acts by increasing the release/availability of 5-hydroxytryptamine and/or serotonin; the latter is a neurotransmitter implicated in the regulation of eating behavior and appetite control (Ohia et al., 2002). Another similar natural appetite suppressant available on the market is CQR-300, an extract of *Cissus quadrangularis* (Oben et al., 2007; WellCrops International, LLC, San Francisco, CA, USA).

Reportedly, other plant extracts and herbal supplements, including Korean red ginseng (Kim et al., 2005), *Camellia sinensis* (Kao et al., 2000; Moon et al., 2007; Dulloo et al., 1999; Nagao et al., 2005; Wolfram et al., 2006), *Caralluma fimbriata* (Kuriyan et al., 2007), ephedra (Fleming, 2007), *Citrus aurantium* (Klontz et al., 2006), *Phaseolus vulgaris* (Baintner et al., 2003; Celleno et al., 2007), *Robinia pseudoaccacia* (Baintner et al., 2003), and sunflower oil (Ferrer-Lorente et al., 2007; Remesar et al., 2000; Romero et al., 2007; Salas et al., 2007), possess appetite-suppressive properties. Although research has identified several active constituents in these substances possessing appetite-suppressive capabilities (e.g. glycosides, saponin, and flavonoids), the ways in which they work to suppress appetite are unclear; they are thought to amplify signaling in the basal hypothalamus's energy-sensing function.

The endogenous mechanisms of appetite regulation by these materials depend on the plant type. For example, *H. gordonii* extract increased ATP content in the hypothalamic neurons regulating food intake in the rat brain (MacLean and Luo, 2004) (Table 2). As is well known, central metabolism of glucose suppresses food intake, mediated by the hypothalamic AMPK/malonyl-CoA signaling system (Lane and Cha, 2009). Central administration of glucose increases hypothalamic malonyl-CoA, decreases orexigenic neuropeptide expression, and suppresses food intake. Centrally-administered fructose provokes feeding, via the AMPK/malonyl-CoA signaling pathway. Thus, decoctions prepared from natural sources containing excessively high fructose levels may suppress the hypothalamic malonyl-CoA signaling pathway, thereby exerting an orexigenic effect (Cha et al., 2008; Lane and Cha, 2009).

Many other natural appetite suppressants mediate the reduced expression of hypothalamic neuropeptide Y (NPY) or serum leptin levels (Kim et al., 2005; Weigle, 2003). For instance, Kim et al. (2005) proved that, in HFD-induced obesity in rats, a crude saponin of Korean ginseng effectively regulated serum leptin and NPY expression in the rat hypothalamus.

Some investigators have found that supplementation with certain dietary fats (e.g. conjugated linoleic acid, lauric acid, and salatrim) had suppressive effects on energy intake. However, their effects on body weight reduction were not significant (Feltrin et al., 2008; Kamphuis et al., 2003; Sørensen et al., 2008). Fat's gastrointestinal effects depend on fatty acid acyl lengths. Fatty acids with over 12 carbon atoms slow gastric emptying, modulate gastrointestinal hormone secretion, and suppress energy intake (Feltrin et al., 2008).

2.3. Stimulatory effects on energy expenditure

Abundant evidence indicates many rodent models of obesity show reduced energy expenditures, which contribute to the development of obesity, whereas the role of reduced energy expenditure in the promotion of human obesity is much less clear. Excessive adiposity results from an imbalance in energy homeostasis, in which the consequences of excessive food intake are not balanced by increased energy expenditure (Flatt, 2007; Redinger, 2009). Energy expenditure has many components. It can be separated into

Table 2
Anti-obesity biomaterials showing appetite-repression activity.

Source	Active component	Experimental methods[a] (treated dose, subjects, duration of treatment)	Major activity[b]	References[c]
Panax ginseng (root)	Crude saponins	200 mg/kg, SD rats with HFD, 3 weeks	37% decrease in body weight gain	Kim et al. (2005)
Garcina cambogia	(−)-Hydroxycitric acid (HCA)	154 nmol HCA/kg, Zucker obese rats, 92 days	8% decrease in body weight gain	Saito et al. (2005), Heymsfield et al. (1998), Ohia et al. (2002)
Camellia sinensis (leaf)	(−)-Epigallo-cathechin gallate (EGCG)	① 82 mg/kg SD rats (7 days), ② 81 mg/kg lean Zucker rats (8 days), ③ 92 mg/kg obese Zucker rats (4 days)	① 53% decrease in body weight gain, ② 32% decrease in body weight gain, ③ 11% decrease in body weight gain	Kao et al. (2000), Moon et al. (2007), Dulloo et al. (1999), Nagao et al. (2005); Wolfram et al. (2006)
Caralluma fimbriata (cactus)	Crude ethanolic extract (pregnane glycosides)	1 g/day, overweight adult Indian men and women, 60 days	2.5% decrease in body weight gain	Kuriyan et al. (2007)
Coix lachrymajobi var. mayeun (seed)	Crude aqueous extract	500 mg/kg, SD rats with HFD, 4 weeks	36%* decrease in body weight gain	Kim et al. (2004b)
Hoodia gordonii and *H. pilifera*	Steroidal glycoside (P57AS3)	Intracerebroventricular injection, 24 h	40–60% reduction in food intake	MacLean and Luo (2004), van Heerden (2008), van Heerden et al. (2007), Lee and Balick (2007)
Not specified	Oleoyl-estrone	4.4 μmol/g/day, Zucker lean rats with HFD, 12 days	30% decrease in body weight gain	Remesar et al. (2000), Salas et al. (2007), Ferrer-Lorente et al. (2007), Romero et al. (2007)
Phaseolus vulgaris and *Robinia pseudoaccacia*	Lectins	100 mg/kg, Harlan–Wistar rats, 16 h	8.25-fold* decrease in food intake	Baintner et al., 2003
Pinus koraiensis (pine nut)	Pine nut fatty acids	3 g, obese women, 4 h	60% increase in cholecystokinin -8 (satiety hormone) secretion	Pasman et al. (2008), Hughes et al. (2008)

[a] The mg/kg indicates a dose (mg) based on the experimental animal's body weight (kg), and% refers to proportion of the diet.
[b] The author recalculated values with an asterisk (*) from the original data (shown as figures) in each reference.
[c] Data from the first reference cited.

Table 3
Anti-obesity biomaterials promoting energy expenditure.

Source	Active component	Experimental methods[a] (treated dose, subjects, duration of treatment)	Major activity[b]	Mechanism of action	References[c]
Pinellia ternata	Crude aqueous extract	400 mg/kg, obese Zucker rats, 6 weeks	Slight decrease in body weight gain (data not shown)	Increased UCP1 expression in BAT and PPARα in WAT	Kim et al. (2006d)
Nelumbo nucifera (leaf)	Crude ethanolic extract (flavonoid)	1%, A/J mice with HFD, 12 weeks	15%* decrease in body weight gain	Activation of β-adrenergic receptor	Ohkoshi et al. (2007)
Camellia sinensis	EGCG	300 mg/d, obese men, 2 days	8% decrease in RQ	Decrease in RQ	Boschmann and Thielecke (2007), Chantre and Lairon (2002), Thielecke and Boschmann (2009)
Panax ginseng (berry)	Crude ethanolic extract	150 mg/kg, ob/ob mice, 12 days	13% decrease in body weight gain	Increased energy expenditure and body temperature	Attele et al. (2002)
Glycine max (soybean)	β-conglycinin, glycinin (globulins)	23.7% β-conglycinin, and 21.9% glycinin, KK-A^y obese mice, 4 weeks	10% decrease in body weight gain	Acceleration of β-oxidation, suppression of fatty acid synthesis	Moriyama et al. (2004), Ishihara et al. (2003)
Undaria pinnatifida (sea weed)	Fucoxanthin	2%, KKAy mice with soybean oil diet, 4 weeks	17% decrease in body weight gain	UCP1 expression in WAT	Maeda et al. (2005, 2007a,b)
Not specified	Medium-chain tryglycerides (MCT)	Diet containing 64.7% MCT, 24 obese men, 28 days	1.3% decrease in body weight gain	Increased energy expenditure	St-Onge et al. (2003a,b), St-Onge and Jones (2002), Papamandjaris et al. (1998), Bourque et al. (2003), Geliebter et al. (1983)
Fish oil	EPA and DHA	C57BL/6 J mice with 60% fish oil diet containing 7% EPA and 24% DHA, 5 months	58% decrease in body weight gain	Upregulation of UCP2 in liver	Tsuboyama-Kasaoka et al. (1999)

[a] The mg/kg indicates a dose (mg) based on the experimental animal's body weight (kg), and % refers to proportion of the diet.
[b] The author recalculated values with an asterisk (*) from the original data (shown as figures) in each reference.
[c] Data from the first reference cited.

a number of different categories. The simplest scheme divides energy expenditure into three categories: (1) physical activity, (2) obligatory energy expenditure, and (3) adaptive thermogenesis.

To regulate body weight and energy expenditure, mammalian BAT establishes non-shivering thermogenesis through dissipation of excess energy as heat (Cannon and Nedergaard, 2004). BAT plays an important role in obesity control by controlling energy balance. The key player in this process is UCP1, which discharges the proton gradient generated in oxidative phosphorylation, thereby dissipating energy as heat. Thus, searching for substances that upregulate UCP1 gene expression may be a worthy strategy for achieving obesity control through increased energy expenditure (Kumar et al., 1999). One analogue of UCP1, UCP3, is also a potentially potent anti-obesity agent, because it mediates the thermogenesis regulated by the thyroid hormone, β_3-adrenergic agonists, and/or leptin in some organs (Gong et al., 1997). An example is the ethanolic extract of *Solanum tuberosum*, which activated the expression of UCP3 in BAT and the liver and significantly reduced fat weight in HFD-fed rats (Yoon et al., 2008).

BAT can be recruited under certain conditions. For example, earlier studies have described remodeling mature WAT into mitochondria-rich cells with a high capacity for fatty acid oxidation (Cinti, 2002; Mercader et al., 2006). Several naturally occurring agents, including $n-3$ polyunsaturated fatty acids and fucoxanthin, which is of marine origin, stimulate thermogenesis in BAT and promote WAT deposits *in vivo* acquisition of BAT features in rodents (Cabrero et al., 2001; Orci et al., 2004; Flachs et al., 2005; Maeda et al., 2007a). Thus, finding natural compounds that can recruit BAT within WAT may be a useful obesity treatment strategy.

Numerous naturally-occurring compounds have been proposed as treatments for weight loss via enhanced energy expenditure, including caffeine (Dulloo, 1993; Racotta et al., 1994) and capsaicin (Kawada et al., 1986; Rayalam et al., 2008). However, researchers attribute most of such putative effects on energy expenditure to green tea and its extract, where the catechins, such as EGC and EGCG, have received tremendous attention (Wolfram et al., 2006; Moon et al., 2007). Several lines of evidence suggest EGCG also stimulates thermogenesis through inhibition of the catechol *O*-methyltransferase involved in degradation of norepinephrine (Borchardt and Huber, 1975; Boschmann and Thielecke, 2007; Chantre and Lairon, 2002; Rayalam et al., 2008; Thielecke and Boschmann, 2009). Extracts of *Pinellia ternate* (Kim et al., 2006d) and *Panax ginseng* (berry) (Attele et al., 2002) also show activity for increasing energy expenditure (Table 3).

The ethanolic extract of *Ilex paraguariensis* ameoliorated HFD-induced obesity through enhanced β-oxidation of fatty acids, increasing AMPK activation in visceral adipose tissue and subsequently reducing ACC activity (Pang et al., 2008). Activated AMPK phosphorylates (inactivates) ACC and lowers levels of intracellular malonyl-CoA, which is the fatty acid synthesis substrate. At the same time, malonyl-CoA inhibits CPT-1, the rate-limiting enzyme in mitochondrial fatty acid oxidation. Accordingly, these processes lead to the promotion of fatty acid oxidation (Pang et al., 2008).

2.4. Inhibitory effect on adipocyte differentiation

Adipocytes play a central role in the maintenance of lipid homeostasis and energy balance, by storing triglycerides and releasing free fatty acids in response to changing energy demands. Because adipocyte tissue growth can be due to both hyperplasia and hypertrophy of adipocytes, several studies screening for anti-obesity materials have focused on the processes of adipocyte proliferation and differentiation (Kim et al., 2006a). In this search, 3T3-L1 pre-adipocytes cells are currently used as an *in vitro* model for the study of obesity, because such cells accumulate triglycerides upon differentiating in culture (Cowherd et al., 1999; Green and Kehinde, 1975). This is due to the expression of adipocyte-specific genes, such as PPARγ and C/EBPα (Wu et al., 1999; Lefterova and Lazar, 2009). For this reason, natural products that specifically target adipogenesis inhibition had been considered

Table 4
Anti-obesity biomaterials inhibiting adipocyte differentiation.

Source	Active component	Experimental methods[a] (treated dose, subjects, duration of treatment)	Major activity[b]	References[c]
Garcina cambogia	(−)-Hydroxycitric acid (HCA)	4 μg/ml, 3T3-L1 adipocyte, 8 days	35% decrease in lipid accumulation	Kim et al. (2004a)
Pinus densiflora	Crude aqueous extract	10 g/kg, SD rats with HFD, 6 weeks	12% decrease in body weight gain	Jeon and Kim (2006)
Cortidis rhizome	Berberine	5 mg/kg, db/db mice, 26 days	13% decrease in body weight	Lee et al. (2006b), Huang et al. (2006a), Hu and Davies (2009)
Not specified (product of Sigma)	Esculetin	200–800 μM, 3T3-L1 adipocyte, 48 h	① 200 μM, pre-adipocyte apoptosis ② 800 μM, inhibition of adipogenesis	Yang et al., 2006a
Glycine max (product of GIBCO)	Genistein	100 μM, 3T3-L1 adipocyte, 48 h	Inhibition of preadipiocyte differentiation by 60%	Harmon and Harp (2001), Harmon et al. (2002), Zhang et al. (2009), Kim et al. (2006b), Naaz et al. (2003), Kandulska et al. (1999), Szkudelska et al. (2000)
Not specified (product of GIBCO)	Naringenin	100 μM, 3T3-L1 adipocyte, 48 h	Inhibition of preadipiocyte differentiation by ~40%	Harmon and Harp (2001)
Not specified (product of Sigma)	Quercetin	250 μM, 3T3-L1 adipocyte, 48 h	Inhibition of preadipiocyte differentiation by 71.5%, IC_{50} = 40.4 μM	Hsu and Yen (2006)
Chili pepper (*Capsicum*)	Capsaicin	3T3-L1 adipocyte, 72 h	① Inhibition of population: IC_{50} = 45 μM ② Apoptosis percentage: 26.7% at 250 μM	Hsu and Yen (2007)
Deep sea water	Minerals (mainly Ca and Mg)	Hardness 1000, 3T3-L1 adipocyte, 72 h	27% decrease in lipid accumulation	Hwang et al. (2009b)
Chitosan oligosaccharides	MW 1–3 kDa	3T3-L1 adipocyte, 72 h	90% decrease in lipid accumulation	Cho et al. (2008), Rahman et al. (2008a,b), Kim et al. (2006c)
Kochujang (fermented red pepper paste)	Not identified	1 mg/ml, 3T3-L1 adipocyte, 24 h	70–75% decrease in adipogenic transcription factors	Ahn et al. (2006)
Fish oil	Docosahexaenoic acid	200 μM, 3T3-L1 adipocyte, 4 h	90% increase in lipolysis	Kim et al. (1999, 2006), Parrish et al. (1990), Flachs et al. (2005)
Perilla oil (product of Ajinomoto Co., Japan)	Rich in α-linolenic acid	12% dietary fat, SD rats, 12 weeks	94% decrease in TG accumulation	Okuno et al. (1997)
Palm oil	γ-tocotrienol	24 μM, 3T3-L1 adipocyte, 21 days	48% decrease in TG accumulation	Uto-Kondo et al. (2009)
Sterol (product of Sigma)	β-sitosterol	16 μM, 3T3-L1 adipocyte, 72 h	65% decrease in preadipiocyte differentiation	Awad et al. (2000)
Scutellaria baicalensia (product of Sigma)	Baicalein	100 μM, 3T3-L1 adipocyte, 48 h	1.86-fold decrease in lipid accumulation	Cha et al. (2006)
Lagerstroemia speciosa L. (banana leaf)	Hot water extract (tannic acid)	0.1–0.25 extract (20 mg/l tannic acid), 3T3-L1 adipocyte, 48 h	No differentiation	Liu et al. (2001, 2005), Bai et al. (2008), Klein et al. (2007)
Undaria pinnatifida (brown algae)	Fucoxanthin	15 μM, 3T3-L1 adipocyte, 120 h	Inhibition of preadipiocyte differentiation by 70%	Maeda et al. (2006)
Conjugated linoleic acids (CLA)	*trans*-10, *cis*-12 CLA	100 μM, 3T3-L1 adipocyte, 3 days	36% decrease in TG accumulation	Evans et al. (2000), Joseph et al. (2009)
Camellia sinensis (green tea)	(−)-Epigallocatechin gallate	20 μM, 3T3-L1 adipocyte, 48 h	Inhibition of preadipiocyte differentiation by 7-fold*	Ku et al. (2009), Lee et al. (2008b), Sakurai et al. (2009)
Lithospermum erythrorhizon	Shikonin	20 μM, 3T3-L1 adipocyte, 48 h	Inhibition of preadipiocyte differentiation: IC_{50} = 1.1 μM	Lee et al. (2009a)
Panax ginseng	Ginsenosides	40 μM, 3T3-L1 adipocyte, 6 days	40%* decrease in TG accumulation with gensenoside Rg3	Hwang et al. (2009c), Park et al. (2008b), Kim et al. (2009a,c)
Brown algae	Fucoidan	100 μM, 3T3-L1 adipocyte, 24 h	Inhibition of preadipiocyte differentiation by 33%	Kim et al. (2009b)
Zizyphus jujuba (fruit)	Extract of choroform fraction	50 μM, 3T3-L1 adipocyte, 24 h	Inhibition of GPDH activity by 80%*	Kubota et al. (2009)
Silybum marianum	Silibinin	30 μM,, 2 days	60%* decrease in TG accumulation	Ka et al. (2009)
Combined natural compounds	Genestein (G), quercetin (Q), resveratrol (R)	50 μM G, 100 μM Q, 100 μM R, 3T3-L1 adipocyte, 3 days	92% decrease in lipid accumulation	Park et al. (2008a)
Garlic	Ajoene	100 μM, 3T3-L1 adipocyte, 24 h	Inhibition of preadipiocyte differentiation by 86%	Ambati et al. (2009)
Humulus lupulus	Xanthohumol	75 μM, 3T3-L1 adipocyte, 24 h	Inhibition of preadipiocyte differentiation by 51%	Yang et al. (2007) Mendes et al. (2008)
Lagerstroemia speciosa (leaf)	Ellagitannins	0.04–0.5 mg/ml, 3T3-L1 adipocyte, 24 h	Inhibition of preadipiocyte differentiation by max. 100%	Bai et al. (2008)
Ascophyllum nodosum	Aqueous methanolic extract	75 μg extract, 3T3-L1 adipocyte, 8 days	Inhibition of GPDH activity by 20%	Uto-Kondo et al. (2009)
Seabuckthorn	Isorhamnetin	50 μM, 3T3-L1 adipocyte, 3 days	2.75-fold* decrease in TG accumulation	Lee et al. (2009b)
Not specified	Retinoic acid	10 μM, cultured porcine pre-adipocytes, 24 h	Inhibition of GPDH activity by 80%	Suryawan and Hu, 1997
Red yeast rice fermented by *Monoscus ruber*	Not identified	2 mg/ml, 3T3-L1 adipocyte, 8 days	86% decrease in TG accumulation	Jeon et al. (2004)
Wasabia japonica (leaf)	Not identified	667 μg/ml, 3T3-L1 adipocyte, 6 days	Inhibition of GPDH activity by 36%	Ogawa et al. (2009)

(*continued on next page*)

Table 4 (*continued*)

Source	Active component	Experimental methods[a] (treated dose, subjects, duration of treatment)	Major activity[b]	References[c]
Coriolus versicolor (mushroom fruit body)	(−)-Ternatin	1.3 μM, 3T3-L1 adipocyte, 9 days	87% decrease in TG accumulation	Ito et al. (2009)
Cordyceps militaris	Mycelial extract	0.2%, 3T3-L1 adipocyte, 12 days	93.7% decrease in lipid accumulation	Shimada et al. (2008)
Ipomoea batatas (root)	Sporamin	0.5 mg/ml, 3T3-L1 adipocyte, 5 days	Inhibition of preadipiocyte differentiation by 84%	Xiong et al. (2009)
Rosmarinus officinalis	Carnosic acid	0–10 μM, 3T3-L1 adipocyte, 2 days	Inhibition of preadipiocyte differentiation: IC_{50} = 0.86 μM	Takahashi et al. (2009)
Curcuma longa	Curcumin	50 μM, 3T3-L1 adipocyte, 8 days	2.4-fold* decrease in TG accumulation	Lee et al. (2009c), Ejaz et al. (2009), Miller et al. (2008), Wang et al. (2009)
Linum usitatissimum (flax seed)	(−)-Secoisolariciresinol	0.15 μM, 3T3-L1 adipocyte, 14 days	Almost 100%* decrease in TG accumulation	Tominaga et al. (2009)
Hibiscus sabdariffa	Flower extract	100 μg/ml, 3T3-L1 adipocyte, 4 days	50% decrease in TG accumulation	Kim et al. (2003)
Solanum tuberosum	Ethanolic extract	0–200 μg/ml, 3T3-L1 adipocyte, 24 h	Inhibition of preadipiocyte differentiation: IC_{50} = 46.2 μg/ml	Yoon et al. (2008)
Soy isoflavone	Genistein	200 μM, 3T3-L1 adipocyte	90%* inhibition of adipocyte differentiation, 43%* decrease in cell adipocyte viability	Hwang et al. (2005)
Undaria pinnatifida	Neoxanthin	20 μM, 3T3-L1 adipocyte	64% reduction in lipid accumulation, 40% reduction in GPDH activity	Okada et al. (2008)
Commiphora mukul	Cis-guggulsterone	200 μM, 3T3-L1 adipocyte, 24 h	90%* decrease in adipocyte differentiation	Yang et al. (2008a)
Rehmannia glutinosa	Crude ethanolic extract	1 mg/ml, 3T3-L1 adipocyte, 48 h	2-fold* decrease in adipocyte differentiation	Jiang et al. (2008)
Eriobotrta japonica	Corosolic acid	45 μM, 3T3-L1 adipocyte	4.17-fold* decrease in adipocyte differentiation	Zong and Zhao (2007)
Irvingia gabonesis (seed)	Extract	250 μM, 3T3-L1 adipocyte, 72 h	81% decrease in TG accumulation	Oben et al. (2008)

[a] The mg/kg indicates a dose (mg) based on the experimental animal's body weight (kg), and% refers to proportion of the diet.
[b] The author recalculated values with an asterisk (*) from the original data (shown as figures) in each reference.
[c] Data from the first reference cited.

promising with regard to their potential in treatment of obesity. However, current research suggests that inhibiting adipogenesis or adipose tissue expansion is unhealthy, leading to type 2 diabetes and other metabolic diseases, such as atherosclerosis (Lefterova and Lazar, 2009).

Fatty acids, particularly polyunsaturated fatty acids (PUFA), act as signal transducing molecules in adipocyte differentiation. In adipocyte tissue, saturated and monounsaturated fatty acids are more readily acylated into triglycerides than PUFA are (Awad et al., 2000; Evans et al., 2000; Okuno et al., 1997). Thus, PUFA play a central role in suppressing fatty acid synthesis and regulating adipocyte differentiation through suppression of late-phase adipocyte differentiation (Madsen et al., 2005; Okuno et al., 1997). Recent reports have demonstrated another interesting mechanism, in extract of macrofungus *Cordyceps militaris* mycelia, which suppressed 3T3-L1 adipocyte differentiation through activation of the aryl hydrocarbon receptor (Shimada et al., 2008). Table 4 lists the wide variety of natural products found to inhibit pre-adipocyte proliferation and/or the apoptotic effect.

In addition to showing inhibitory activity against adipocyte differentiation, several naturally-occurring compounds have displayed apoptotic effects on maturing pre-adipocytes. For example, some phytochemicals, such as esculetin, resveratrol, quercetin, genistein, EGCG, capsaicin, and conjugated linoleic acids induced apoptosis of maturing 3T3-L1 pre-adipocytes through suppression of ERK1/2 phosphorylation, activation of the mitochondrial pathway, AMPK activation, or anti-oxidant activity (Hargrave et al., 2002; Hwang et al., 2005; Hsu and Yen, 2006; Yang et al., 2006a, 2008b). Thus, inducing apoptosis in mature adipocytes may be important for treating obesity with naturally-occurring compounds.

The cell cycle is closely associated with adipocyte growth and proliferation and is thus an important factor to consider in targeting anti-obesity natural products. Recent evidence has indicated that certain phenolic compounds lead to cell cycle arrest at the G_1 phase during 3T3-L1 adipocyte differentiation (see review by Hsu and Yen (2008)). Recent reports have shown that phenolic compounds also efficiently induce apoptosis in 3T3-L1 adipocytes through AMPK activation (Hwang et al., 2005; Lin et al., 2005). A combined treatment, of ajoene and conjugated linoleic acid, enhanced apoptosis in mature 3T3-L1 adipocytes through a synergistic increase of expression in several proapototic factors (Rayalam et al., 2008). Sirtuin 1 is another target molecule for anti-obesity treatment. Decreased adipogenesis due to resveratrol correlated with increased expression of Sirtuin1, which promotes fat mobilization by repressing PPARγ (Picard et al., 2004; Rayalam et al., 2008).

2.5. Regulatory effect on lipid metabolism

The pharmacological targeting of lipolysis can be envisaged in two different ways. The first strategy entails stimulating triglyceride hydrolysis in order to diminish fat stores, thereby combating obesity. This option requires the associated oxidation of the newly released fatty acids and led to the development of the β_3-adrenergic agonists (Langin, 2006). However, considering that excessive lipolysis contributes to high circulating fatty acid levels and development of dyslipidemia (as seen in metabolic syndrome), a blockade of such a fatty acid release may be of therapeutic interest (Langin, 2006). Some examples of the natural compounds involved in β-adrenergic receptor activation are the various flavonoids in the leaves of *Nelumbo nucifera* (NN). Through this pathway, NN extract dietary supplementation resulted in significant suppression of body weight gain in A/J mice fed a HFD (Ohkoshi et al., 2007).

Table 5
Anti-obesity biomaterials promoting lipid metabolism.

Source	Active component	Experimental methods[a] (treated dose, subjects, duration of treatment)	Major activity[b]	Mechanism of action	References[c]
Salacia oblonga (root)	Mangiferin	900 mg/kg, ZDF rats, 28 days	40% decrease in liver/body weight ratio	Hepatic PPARα activator	Rong et al. (2008), Huang et al. (2006b)
Ilex paraguariensis	Crude water extract	0.24%, SD rats with HFD, 60 days	11% decrease in body weight gain	Down regulation of adipose tissue genes	Pang et al. (2008)
Mixture of *Morus alba*, *Melissa officinalis*, *Artemisia capillaris* (leaf)	Crude aqueous extract	0.2%, C57BL/6 J mice with HFD, 12 weeks	7% decrease in body weight gain	Hepatic PPARα activator	Lee et al. (2008a)
Cortidis rhizoma	Berberine	5 mg/kg, db/db mice, 26 days	13% decrease in body weight	AMPK activation	Lee et al. (2006b), Huang et al. (2006a)
Nelumbo nucifera (leaf)	Crude ethanolic extract (flavonoid)	1%, A/J mice with HFD, 12 weeks	15%* decrease in body weight gain	Activation of β-adrenergic receptor	Ohkoshi et al. (2007)
Curcuma longa L.	Curcumin	3%, ob/ob mice with HFD, 4 weeks	7%* decrease in body weight gain	Reversal of inflammatory and metabolic derangements	Weisberg et al. (2008, Manjunatha and Srinivasan (2007)
	Curcuminoids	0.2%, SD rats with HFD, 2 weeks	11% decrease in body weight gain	Alterations in fatty acid metabolism	Asai and Miyazawa (2001)
Eucommia ulmoides (leaf)	Crude aqueous extract	1%, db/db mice, 6 weeks	No data	Down regulation of lipogenic enzymes	Park et al. (2006a)
Arachis hypogaea (shell)	Crude ethanolic extract	1%, Wistar rats with HFD, 12 weeks	12% decrease in body weight gain	Inhibition of fat absorption, activation of lipid metabolism	Moreno et al. (2006)
Coix lachrymajobi var. mayeun (seed)	Crude aqueous extract	500 mg/kg, SD rats with HFD, 4 weeks	36%* decrease in body weight gain	Modulation of leptin and TNF-α	Kim et al. (2004b)
Salacia reticulate (root)	Aqueous extract (polyphenolic compounds)	125 mg/kg, Zucker fatty rats, 27 days	7%* decrease in body weight gain	Inhibition of lipid-metabolizing enzymes and stimulation of lipolysis	Yoshikawa et al. (2002)
Glycyrrhiza glabra L. (root)	Licorice flavonoid oil (LFO)	2% LFO, KK-A^y obese mice, 4 weeks	30% decrease in body weight gain	PPARγ agonistic activity	Nakagawa et al. (2004)
Diospyros kaki (leaf)	Crude methanolic extract	5%, SD rats with HFD, 6 weeks	11% decrease in body weight gain	Modulation of leptin and lipogenic enzymes	Lee et al. (2006a)
Morus alba L. (leaf)	Crude aqueous extract	0.5%, db/db mice, 12 weeks	7% decrease in body weight gain	PPARs agonistic activity	Park et al. (2005)
Panax ginseng	Crude aqueous extract	0.5%, db/db mice, 12 weeks	8% decrease in body weight gain	PPARs agonistic activity	Park et al. (2005)
Lagerstroemia speciosa L. (leaf)	Crude aqueous extract	0.5%, db/db mice, 12 weeks	3% decrease in body weight gain	PPARs agonistic activity	Park et al. (2005)
Zea mays L.	Purple corn color (PCC) (anthocyanins)	PCC 1.1%, C57BL/6J mice with HFD, 12 weeks	21%* decrease in body weight gain	AMPK activation	Tsuda et al. (2003, 2004), Kong et al. (2003)
Glycyrrhiza uralensis	Crude ethanolic extract (flavonoids)	0.2%, C57BL/6 J mice with HFD, 4 weeks	22% decrease in body weight gain	PPARγ agonistic activity	Mae et al. (2003)
Evodia rutaecarpa (fruit)	Crude ethanolic extract (evodiamine)	0.02%, SD rats with HFD, 21 days	23% decrease in body weight gain	Vanilloid receptor agonistic activity	Kobayashi et al. (2001)
Aralia mandshurica (AM) and *Engelhardtia chrysolepis* (EC)	Aralox	150 mg/d AM and 150/d mg EC, 32 women, 15 weeks	4% decrease in body weight gain	Stimulation of hormone-sensitive lipase	Abidov et al. (2006)
Commiphora mukul	E- and Z-guggulsterone	4.5 g/d, 40 patients, 16 weeks	Reduction in cholesterol and triglyceride levels by 22, and 27%, respectively	Antagonist of the bile acid receptor farnesoid X receptor	Urizar and Moore (2003), Verma and Bordia (1988)
Rhynchosia volubilis (black soybean)	Tripeptide (Ile-Gln-Asn)	10 mg/ml, 3T3-L1 adipocyte, 8 days	IC_{50} = 0.014 mg protein/ml	AMPK activation	Kim et al. (2007)
Not specified	Ginsenoside Rg3	40 μM, 3T3-L1 adipocyte	40%* decrease in TG accumulation	PPARγ agonistic activity	Hwang et al. (2009c)
Soybean	Genistein+ L-carnitine (soy isoflavone)	0.2% genistein + 0.5% L-carnitine, C57BL/6 J mice with HFD, 12 weeks	254% decrease in body weight gain	PPARs agonistic activity	Yang et al. (2006b)
Coffea canephora	Caffeine, chlorogenic acid, neochlorogenic acid, feruloyquinic acids	0.5%, ddy mice with standard diet, 14 days	157% decrease in body weight gain	Inhibition of fat absorption, activation of fat metabolism	Shimoda et al. (2006)
Soybean	β-conglycinin, glycinin (globulins)	23.7% β-conglycinin, and 21.9% glycinin, KK-A^y obese mice, 4 weeks	10% decrease in body weight gain	Acceleration of β-oxidation, suppression of fatty acid synthesis	Moriyama et al. (2004)
Fish oil	Eicosapentaenoic acid (n-3 polyunsaturated fatty acid)	1 g/kg, Wistar rats with cafeteria diet, 5 weeks	9%* decrease in body weight gain	Down regulation of PPARγ, apoptosis in WAT	Pérez-Matute et al. (2007)
Phytochemicals	Resveratrol (R), Quercetin (Q)	R25 + Q25 μM (R100 + Q100 μM), 3T3-L1 adipocyte, 6 days	69% decrease in lipid accumulation (R25 + Q25 μM), 74% decrease in adipocyte viability (R100 + Q100 μM)	Down regulation of PPARγ and C/EBPα, apoptosis	Yang et al. (2008b), Ahn et al. (2007a)

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Table 5 (*continued*)

Source	Active component	Experimental methods[a] (treated dose, subjects, duration of treatment)	Major activity[b]	Mechanism of action	References[c]
Glycine max (Soy) isoflavone	Genistein	200 μM, 3T3-L1 adipocyte	90%* inhibition of adipocyte differentiation, 43%* decrease in cell adipocyte viability	AMPK activation,adipocyte apoptosis	Hwang et al. (2005)
Phytochemicals	Caffeine + arginine + soy isoflavones+L-carnitine (CASL)	CASL (250 mg, 6 g, 2 g, 1.5 g/kg) KK mice with HFD, 3 weeks	5.4% decrease in body weight gain	Inhibition of lipogenesis in liver	Murosaki et al. (2007)
Rubus idaeus (raspberry)	4-(4-Hydroxyphenyl) butan-2-one (RK)	2% RK, ICR mice with HFD, 10 weeks	17%* decrease in body weight gain	Increased lipolysis	Morimoto et al. (2005)
Deep sea water	Minerals (mainly Ca and Mg)	Deep sea water of hardness 1000, ob/ob mice, 84 days	7% decrease in body weight gain	GLUT and AMPK activation	Hwang et al. (2009a)
Chitosan	Not specified	3 g/day, human overweight adults, 8 weeks	22% decrease in body weight gain	Decrease in fat absorption	Kaats et al. (2006)
Chitosan oligosaccharides	MW 125–145 kD	2%, Wistar rats, 4 weeks	9% decrease in body weight gain	Decrease in fat absorption	Bondiolotti et al. (2007)
	MW 3–5 kD	200 mg/kg, *ob*/*ob* mice, 28 days	12% decrease in body weight gain	Down regulation of obesity-related genes	Kumar et al. (2009)
Palatinose		55.7% palatinose, 23.9% branched dextrin, SD rats with standard chow, 8 weeks	237% decrease in body weight gain	PPARs agonistic activity	Matsuo et al. (2007)
Levan		10%, SD rats with HFD, 4 weeks	160% decrease in body weight gain	PPARα agonistic activity	Kang et al. (2006)
Not specified	Oleoylethanolamide	5 mg/kg, Wistar rats with HFD, 2 weeks	3.6%* decrease in body weight change	PPARα agonistic activity	Guzmán et al. (2004), Fu et al. (2005)
Not specified	PEGylated conjugated linoleic acid (PCLA)	200 μM PCLA, 3T3-L1 adipocyte, 72 h	80% increase in body lipolysis	PPARγ agonistic activity	Moon et al. (2006)
Not specified	Conjugated linoleic acid (CLA)	1.5% CLA, C57Bl/6 mice with HFD, 6 weeks	52%* decrease in body weight gain	Inhibition of FA uptake into adipose	Liu et al. (2007), Lin et al. (2001), Li et al. (2008a), Lei et al. (2004), Wang and Jones (2004)
Solanum tuberosum	Crude ethanolic extract	200 mg/kg, SD rats, 4 weeks	5%* decrease in body weight gain	Down regulation of P38 MAPK and Upregulation of UCP3	Yoon et al. (2008)
Momordica charantia	Crude ethanolic extract	0.2 mg/ml, 3T3-L1 pre-adipocytes	61% increase in glucose uptake with 0.5 nM insulin and 75% increase in adiponectin secertion	Enhanced glucose uptake and adiponectin secretion	Roffey et al. (2007)
Toona sinensis (leaf)	Crude ethanolic extract	0.1 mg/ml, 3T3-L1 pre-adipocytes, 6 h	156% increase in glycerol release	Lipolytic activity	Hsu et al. (2003)
Cinnamoni cassiae	Cinnamon	0.6 mg/ml, 3T3-L1 pre-adipocytes, 5 days	3.1-fold in crease in PPARγ levels	PPARγ agonistic activity	Sheng et al. (2008)

[a] The mg/kg indicates a dose (mg) based on the experimental animal's body weight (kg), and% refers to proportion of the diet.
[b] The author recalculated values with an asterisk (*) from the original data (shown as figures) in each reference.
[c] Data from the first reference cited.

PPARγ is a transcription factor predominantly expressed in adipose tissue, and it activates adipocyte differentiation both *in vivo* and *in vitro* (Cornelius et al., 1994). When PPARγ is overexpressed, 3T3-L1 pre-adipocyte induction begins. This suggests that PPARγ suppression blocks adipogenesis and lipogenesis (Lefterova and Lazar, 2009). Thus, PPARγ agonism leads to the amelioration of lipid abnormalities in dyslipidemic patients. Findings from a number of rodent studies have demonstrated that PPARγ agonists can improve insulin resistance, as well as dyslipidemia. Concomitantly, rodent disease models have demonstrated that PPARγ agonists prevented increased adiposity and body weight without any reduction in food intake (Kersten, 2002). Similarly, PPARα activation mediated the expression of genes that regulate lipid oxidation. Aqueous extract of *Salacia oblonga* root (active main component, magniferin) has demonstrated PPARα activator properties, which then improved postprandial hyperlipidermic and hepatic steatosis in a genetic-obesity animal model (Huang et al., 2006b). Additionally, a mixture of three herbal extracts improved lipid metabolism by increasing hepatic mRNA levels of PPARα, the target enzyme responsible for fatty acid β-oxidation (Lee et al., 2008a).

AMPK is an enzyme found in numerous tissues throughout the body. It has been characterized as a metabolic master switch that regulates the activities of a number of target proteins controlling metabolism. The role of AMPK in the exercising skeletal muscle has been studied extensively. In broad terms, AMPK activation in skeletal muscle appears to increase glucose transport (Hayashi et al., 2000) and fatty acid oxidation (Winder and Hardie, 1999; Ruderman et al., 1999). One of the most well-characterized AMPK activation targets in skeletal muscle is ACC. Activated AMPK phosphorylates ACC, inhibiting its action (Saha and Ruderman, 2003). ACC in turn catalyzes synthesis of malonyl-CoA, a potent inhibitor of CPT-1, which controls the fatty acids' entry into the mitochondria. There, the fatty acids can be oxidized or converted to ketone bodies (in the liver) for use as fuel in other organs (Flier, 2004). Thus, the net result of this chain of events is that an increase in muscle AMPK leads to an increase in CPT-1 and in fatty acid oxidation. Table 5 summarizes the many natural AMPK activators that have been found.

Tomoda et al. (2002) contributed to the discovery of novel microbial metabolites showing inhibitory activity against lipid

metabolism, particularly those affecting fatty acid and cholesterol metabolic pathways. They discovered numerous compounds, including cerulenin, thiotetromycin, chlorogentisylquinone, and the beauverolides, pyripyropenes, terpendoles, and ferroverdins (Tomoda et al., 2002). These compounds function as fatty acid synthase inhibitors (cerulenin), acyl-CoA synthetase inhibitors (triacsin C), and HMG-CoA synthase inhibitors (hymeglusin).

The activity of oolong tea is a good example of another anti-obesity mechanism. Caffeine, one of the major bioactive components in oolong tea, possesses both a positive charge and a hydrophobic area like that of adrenaline. Caffeine's mechanism of lipolytic action might be due to its binding to the phospholipid phosphate groups and the subsequent interactions between the lipase and triglyceride portions of lipid droplets, eliciting lipolysis (Han et al., 1999b).

2.6. Combined effect for obesity treatment

As mentioned above, many natural products show anti-obesity activities of varying mechanisms. Perhaps the recommended approach to researching more efficient obesity treatments and achieving the synergistic effects of natural products should be to seek treatments using multiple products or products having multiple activities (Rayalam et al., 2008).

Some natural biomaterials possessing multi-functional anti-obesity activities have been discovered. Green tea and *Garcina cambogia* are good examples. Researchers originally found green tea possessed higher anti-oxidant activity than anti-obesity activity, owing to its high concetration of catechins, including epicatechin, ECG, and EGCG. Subsequent research proved the anti-obesity activity of catechins resulted from the combined actions of appetite reduction, greater lipolytic activity and energy expenditure, and less lipogenic activity and adipocyte differentiation (Boschmann and Thielecke, 2007; Chantre and Lairon, 2002; Dulloo et al., 1999; Hsu and Yen, 2006; Kao et al., 2000; Lin and Lin-Shiau, 2006; Moon et al., 2007; Nagao et al., 2005; Thielecke and Boschmann, 2009; Wolfram et al., 2006). *G. cambogia* is widely known for its anti-obesity activity (Heymsfield et al., 1998; Kim et al., 2004a). Its commercially-available extract is derived from the dried fruit of the *G. cambogia* tree, which grows in the forests of South India and Southeast Asia. Its main active ingredient is (−)-hydroxycitric acid (Kim et al., 2004a). *G. cambogia* prevents the metabolism of carbohydrates into fats by inhibiting lipogenesis, burning excess fats, and suppressing appetite (Kim et al., 2004a).

The aqueous extract of *Hibiscus sabdariffa* (containing mainly anthocyanins) has exhibited many potential anti-obesity mechanisms, including anti-hyperglycemic effects, plasma cholesterol level reduction, gastric and pancreatic lipase inhibition, thermogenesis stimulation, inhibition of lipid droplet accumulation in fat cells (without affecting adipose conversion), and fatty acid synthase inhibition (Alarcon-Aguilar et al., 2007). *G. cambogia* extract (active component, hydroxycitric acid) has also displayed multi-functional anti-obesity effects. Research has shown that it inhibits adipocyte differentiation, reduces fatty acid synthesis, lipogenesis, and apididymal fat accumulation through reducing ATP-citrate lyase activity, and suppresses appetite (Kim et al., 2004a; Saito et al., 2005). It has been on the market over 10 years with no adverse side-effects (Ohia et al., 2002; Saito et al., 2005).

Pomegranate extract (active components, ellagic acid and tannic acid) also has dual anti-obesity effects, in that it inhibits pancreatic lipase activity and suppresses energy intake. Its effect on energy intake was similar to sibutramine, but with a different mechanism (Lei et al., 2007). In obese rats, supplementation with aqueous extract of *Pinellia ternate* induced increased thermogenesis in BAT (i.e., increased UCP1 expression) and fatty acid oxidation (activated PPARα) in WAT (Kim et al., 2006d). Green tea extracts also exert anti-obesity activities in two ways: lipase inhibition and thermogenesis stimulation (Chantre and Lairon, 2002). Peanut (*Arachis hypogaea*) shell extract contribute to inhibiting fat absorption in the digestive tract, activating lipid metabolism in the liver, and reducing adipocyte lipolysis (Moreno et al., 2006). The *Nelumbo nucifera* leaf possesses multiple anti-obesity activities, including inhibition of lipid and carbohydrate absorption and acceleration of lipid metabolism and energy expenditure (Ono et al., 2006). Raspberry ketone exerts its anti-obesity effect via increasing

Table 6
Other anti-obesity biomaterials, whose mechanisms are unidentified.

Source	Active component	Experimental methods[a] (treated dose, subjects, duration of treatment)	Major activity[b]	References[c]
Hibiscus sabdariffa	Anthocyanin	120 mg/kg, ob/MSG mice, 60 days	10% decrease in body weight gain	Alarcon-Aguilar et al. (2007)
Panax ginseng (berry)	Crude ethanolic extract	150 mg/kg, ob/ob mice, 12 days	11% decrease in body weight gain	Dey et al. (2003)
Trigonella foenum graecum L. (seed)	Crude ethanolic extract	350 mg/kg, mice with HFD, 22 days	14%* decrease in body weight gain	Handa et al. (2005)
Acanthopanax senticosus (stem bark)	Crude aqueous extract	500 mg/kg, C57BL/6 J mice with HFD, 12 weeks	4%* decrease in body weight gain	Cha et al. (2004), Park et al. (2006b)
Ginseng	Crude ethanolic extract	500 mg/kg, ICR mice with HFD, 8 weeks	16% decrease in body weight gain	Yun et al. (2004)
Cissus quadrangularis	Standardized extract (phytosterols)	Two daily dose (514 mg each), obese persons, 8 weeks	23% decrease in body weight gain	Oben et al. (2006, 2007)
Panax quinquefolium L. (berry)	Crude aqueous extract (Ginsenosides)	0.6 ml/kg (juice), ob/ob mice, 10 days	250% decrease in body weight gain	Xie et al. (2007)
Eucommia ulmoides (leaf)	Crude aqueous extract	10 mg/ml, hMSC adipocyte, 7 days	1/12 decrease in TG accumulation	Lee et al. (2004)
Soy protein isolate (SPI)	Not specified	41.1%, yellow KK mice with energy restricted diet, 4 weeks	20% decrease in body weight gain	Aoyama et al. (2000)
Carotenoid pigment	Astaxanthin	30 mg/kg, ddy mice with HFD, 60 days	15%* decrease in body weight gain	Ikeuchi et al. (2007)
Fungi	Isaria sinclairii	10%, (fa/fa) Zucker mice, 17 weeks	17% decrease in body weight gain	Ahn et al. (2007b)

[a] The mg/kg indicates a dose (mg) based on the experimental animal's body weight (kg), and% refers to proportion of the diet.
[b] The author recalculated values with an asterisk (*) from the original data (shown as figures) in each reference.
[c] Data from the first reference cited.

norepinephrine-induced lipolysis in WAT and enhancing thermogenesis in BAT (Morimoto et al., 2005). One study found an Indian herb, *Salacia* met multiple obesity-reduction targets by both modulating PPARα-mediated lipogenic gene transcription and angiotension II type 1 receptor signaling and also inhibiting α-glucosidase and pancreatic lipase (Li et al., 2008b). Several polyunsaturated fatty acids also show combinations of anti-obesity actions, including upregulation of mitochondrial biogenesis, induction of β-oxidation, and suppression of adipocyte lipogenesis (Flachs et al., 2005). Taken together, combination therapies employing natural products that target different obesity genes and/or different stages of the adipocyte life cycle might prove beneficial in treating obesity.

Finally, Table 6 lists other natural anti-obesity products whose mechanisms of action are yet unidentified.

3. Conclusions

Anti-obesity pharmacological treatment should be administered only when considered safe and effective for obese subject. Over the past 30 years, few obesity-treatment drugs have been developed or approved. Only two drugs are currently available, and some drugs have been withdrawn from the market due to serious side-effects. Sibutramine and orlistat may cause weight loss of up to 10% when used in combination with dietary, behavioral, and exercise therapy. The need exists for anti-obesity drugs having greater effectiveness, which are better tolerated. In the future, the active exploration of many natural sources may provide hope for new developments based on a growing understanding of the complex and highly redundant physiological mechanisms involved in body fat content regulation. Ideally, such exploration and research will lead to a safer and more effective pharmacological treatment for obesity. It is also worth noting that the United States' FDA is particularly sensitive to anti-obesity claims. Furthermore, any anti-obesity medicine entering the market becomes immediately subject to abuse and overdose.

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Jong Won Yun received his MSc degree in 1987 from the Department of Chemical Engineering, Pusan National University, Pusan, Korea. He was employed for six years as research scientist in CJ Cheiljedang R&D Center. The focus of his laboratory was to development of functional sweeteners such as fructooligosaccharides and palatinose from natural resources. In 1992, he started his PhD study at the Department of Chemical Engineering, Pusan National University. The focus of his PhD studies was production of fructooligosaccharides and isomaltooligosaccharides by several transferases. In 1995, following his PhD study, he was employed as Assistant Professor at the Department of Biotechnology, Daegu University, where his work is focused on production of biomaterials with anti-diabetic and anti-obesity activity. Recently, he has studied clinical proteomics to discover anti-obesity biomarkers in response to anti-obesity drugs or medicinal compounds with anti-obesity activity. He is acting as an editor or editorial board member of several international journals including Journal of Chemical Technology and Biotechnology, Journal of Microbiology and Biotechnology, and Biotechnology and Bioprocess Engineering. He has published 130 international papers and 54 domestic papers in the fields of functional biomaterials and proteomics.