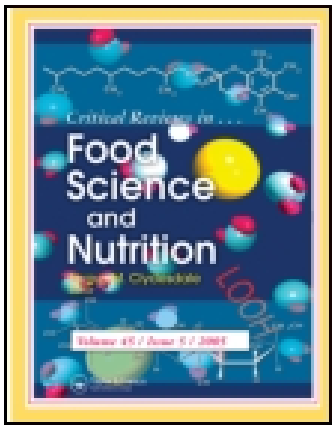

Critical Reviews in Food Science and Nutrition
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/bfsn20

Plant-Derived Food Ingredients for Stimulation of Energy Expenditure

Nancy Dewi Yuliana [a b] , Henrie Korthout [c] , Christofora Hanny Wijaya [b] , Hye Kyong Kim [a] & Robert Verpoorte [a]

[a] Department of Pharmacognosy, Section of Metabolomics , Leiden University , Einsteinweg 55, 2333 CC, Leiden , The Netherlands

[b] Department of Food Science and Technology , Bogor Agricultural University , IPB Dramaga Campus, Bogor , 16680 , Indonesia

[c] Fytagoras BV Plant Science, Sylviusweg 72 , 2333 BE, Leiden , The Netherlands

Accepted author version posted online: 24 Sep 2012.Published online: 04 Nov 2013.

To cite this article: Nancy Dewi Yuliana , Henrie Korthout , Christofora Hanny Wijaya , Hye Kyong Kim & Robert Verpoorte (2014) Plant-Derived Food Ingredients for Stimulation of Energy Expenditure, Critical Reviews in Food Science and Nutrition, 54:3, 373-388, DOI: 10.1080/10408398.2011.586739

To link to this article: http://dx.doi.org/10.1080/10408398.2011.586739

Critical Reviews in Food Science and Nutrition, 54:373–388 (2014)

ISSN: 1040-8398 / 1549-7852 online
DOI: 10.1080/10408398.2011.586739

Taylor & Francis
Taylor & Francis Group

Plant-Derived Food Ingredients for Stimulation of Energy Expenditure

NANCY DEWI YULIANA,[1,2] HENRIE KORTHOUT,[3] CHRISTOFORA HANNY WIJAYA,[2] HYE KYONG KIM,[1] and ROBERT VERPOORTE[1]

[1]Department of Pharmacognosy, Section of Metabolomics, Leiden University, Einsteinweg 55, 2333 CC, Leiden, The Netherlands
[2]Department of Food Science and Technology, Bogor Agricultural University, IPB Dramaga Campus, Bogor 16680, Indonesia
[3]Fytagoras BV Plant Science, Sylviusweg 72, 2333 BE, Leiden, The Netherlands

The development of obesity is related to the regulation of energy intake, energy expenditure, and energy storage in the body. Increasing energy expenditure by inducing lipolysis followed by fat oxidation is one of the alternatives which could help to reverse this increasingly widespread condition. Currently, there is no approved drug targeting on stimulation of energy expenditure available. The use of herbal medicines has become a preferred alternative, supported by the classical consensus on the innocuity of herbal medicine vs synthetic drugs, something that often lacks a scientific basis (ban on Ephedra*, for example). The inclusion of functional food in the daily diet has also been promoted although its efficacy requires further investigation. This review summarizes the results of recent work focused on the investigation of edible plant materials targeted at various important pathways related to stimulation of energy expenditure. The aim is to evaluate a number of plants that may be of interest for further studies because of their potential to provide novel lead compounds or functional foods which may be used to combat obesity, but require further studies to evaluate their antiobesity activity in humans.*

Keywords Obesity, plants, functional food, energy expenditure

INTRODUCTION

Obesity has become a serious global health concern both in developed and developing countries. Obesity is not only a cosmetic problem. It is associated to several diseases, especially cardiovascular disorders, type 2 diabetes, degenerative joint diseases, and cancer, therefore diminishing life expectancy and lowering the quality of life of affected individuals (Haslam and James, 2005; Chaput et al., 2007; Hofbauer et al., 2007; Bessesen, 2008). Obesity can be diagnosed, among other ways, by measuring the body-mass index (BMI), which according to WHO standards, is above 25.0 kg/m^2 in overweight individuals and equal or above 30.0 kg/m^2 in the case of obesity.

Obesity results from the imbalance between energy intake and energy expenditure, therefore mechanisms such as the reduction of energy intake by appetite suppression, inhibition of nutrient absorption, increase of energy expenditure, and reduction of fat mass involved in these processes can be targeted for antiobesity drug development (Chiesi et al., 2001). Although it is still not clear whether suppressing energy intake or increasing energy expenditure is the most effective method to combat obesity, it has been reported that particularly the latter plays an important role in propensity to obesity in humans (Dulloo and Samec, 2000). Energy expenditure relates to the basal metabolism, physical activity, and adaptive thermogenesis (Spiegelman and Flier, 2001). Adaptive thermogenesis refers to energy release in the form of heat as a response to environmental changes such as exposure to cold or diet modification (Spiegelman and Flier, 2001). The latter will be the main focus of this review.

A number of papers have reported the use of medicinal plants to combat obesity by stimulating the rate of metabolism, revealing the importance of plants as a valuable source for weight management. Synephrine, xanthine, and caffeine are examples of active principles found in several medicinal plants that stimulate metabolism. In this review, several papers reporting botanicals with energy expenditure stimulation activity are discussed with special attention to edible plants that are consumed on a regular basis. The possible mechanisms involved, the efficacy and safety are also discussed.

Address correspondence to Dr. Hye Kyong Kim, Dept. of Pharmacognosy Section of Metabolomics, Leiden University, Einsteinweg 55 2300 RA, Leiden, The Netherlands. E-mail: h.k.kim@chem.leidenuniv.nl

PATHWAYS FOR ENERGY EXPENDITURE REGULATION

Energy expenditure is centrally and peripherally regulated through neural pathways which activate thermogenesis and peripheral pathways in which energy is released by oxidation of stored fats (Spiegelman and Flier, 2001). In neural pathways, some markers for thermogenesis are closely interrelated to food intake regulation such as the melanocortin receptor (MCR) and melanine-concentrating hormone (Walters and Namchuk), and leptin (Spiegelman and Flier, 2001). Peripherally, when energy intake is greater than energy expenditure, most of the excess calories are stored as triglycerides (TG) in white adipose tissue (WAT) (Arner, 2005).

Lipolysis takes place as a response to energy demand where TG in WAT is hydrolyzed yielding free fatty acids and glycerol. Stimulation of TG hydrolysis leading to mobilization of stored fat can be a choice to combat obesity but this step should be followed by oxidation of the newly released fatty acids (Langin, 2006). TG mobilization is a highly regulated process involving several facilitators at a molecular level, as summarized in Fig. 1. Catecholamines, insulin, and natriuretic peptide, are the three main mediators in the human lipolytic pathway (Arner, 2005). Catecholamines (adrenaline, noradrenaline) mediate human WAT lipolysis via lipolytic ß-adrenoceptors and antilipolytic α2-adrenoceptors (Langin, 2006). Insulin is lipolytic inhibitor acting via insulin receptors. Natriuretic peptide, a lipolytic agent specific for primate fat cells, activates guanylate cyclase via non-GPCR dependent pathways (Sengenes et al., 2000). To a lesser extent, other possible pathways involved are TNF-α induced lipolysis which is important at basal level, as well as signaling pathways of nicotinic acid, prostaglandin, and adenosine receptors (Arner, 2005).

The subsequent downstream lipolytic pathways are regulated by two important enzymes; hormone sensitive lipase (HSL) which is predominant under stimulated conditions (Fernandez et al., 2008) and adipose triglyceride lipase (ATGL) active in basal lipolysis (Zimmermann et al., 2004). Other WAT enzymes such as triacylglycerol hydrolase are also found to play a role (Soni et al., 2004). HSL activity is regulated via phosphorylation and translocation mechanisms (Yeaman, 2004), while ATGL expression is upregulated by fasting and glucocorticoids (Zimmermann et al., 2004).

Several nonenzyme proteins are indirectly involved in lipolysis regulation by interaction with HSL, for example, lipotransin which is able to fit the enzyme's active site to the lipid droplet surface, thus improving the activity (Syu and Saltiel, 1999), and perilipin that blocks the enzyme access by covering the

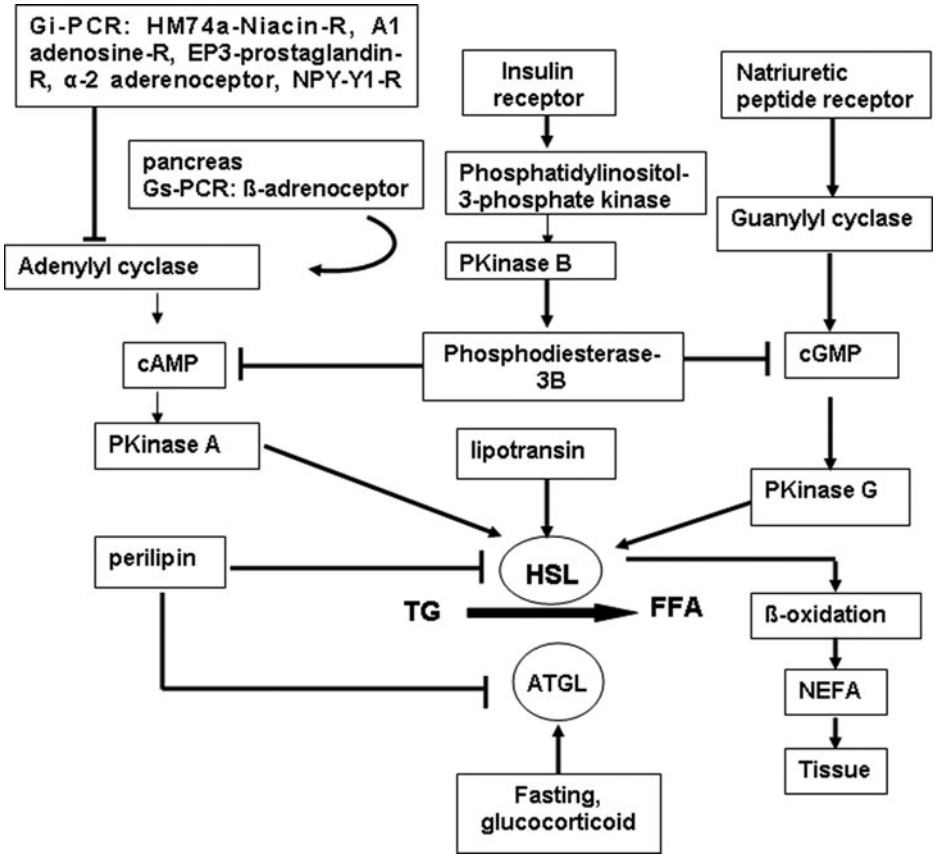

Figure 1 Diagrams of receptors and enzymes/co-enzymes network in lipolysis leading to thermogenesis regulation. Hormone sensitive lipase (HSL) and adipose triglyceride lipase (ATGL) are key regulators for triglyceride hydrolysis to free fatty acids which will further undergo ß-oxidation, resulting in nonesterified fatty acids (NEFA) as a source of energy for requiring tissue. $\dashv$ = inhibit.

adiposity lipid droplets (Sztalryd et al., 2003). Subsequent to lipolysis, free fatty acids and glycerol are transferred from adipocytes into the blood stream and distributed into energy demanding body tissues, a process which is mediated by a passive diffusion mechanism and several facilitating proteins (Langin, 2006).

Adenosine 5′- monophosphate-activated protein kinase (AMPK) is a phosphorylating enzyme important for fatty acid and glucose metabolism. The activation of AMPK leads to the stimulation of hepatic fatty acid oxidation and ketogenesis, inhibition of cholesterol synthesis, lipogenesis, and TG synthesis, inhibition of adipocyte lipolysis and lipogenesis, stimulation of skeletal muscle fatty acid oxidation and muscle glucose uptake, and modulation of insulin secretion by pancreatic ß-cells. In the liver, AMPK activation causes a decrease in fatty acid, TG, and sterol synthesis but an increase in fatty acid oxidation and ketogenesis by phosphorylation of acetyl-CoA carboxylase and 3-hydroxy-3-methylglutaryl-CoA reductase. The same effects are also obtained when the ratio of insulin-to-glucagon decreases but whether it is an AMPK independent pathway is unclear yet (Winder and Hardie, 1999). In adipose tissue, AMPK activation targets HSL which leads to inhibition of lipogenesis by phosphorylation of acetyl-CoA carboxylase (Hardie et al., 1998). The physiological function of AMPK depends on the level of activation. Antilipolytic action is generated when AMPK is activated doubly, while apoptosis is observed at a higher magnitude of activation.

The use of β3-adrenoceptor agonists to accelerate thermogenesis has also been proposed (Arch et al., 1984). Selective β3-adrenoceptor agonists stimulate lipolysis in brown adipose tissue (BAT), leading to an increase of thermogenesis. The potential of these agents as antiobesity compounds has been reviewed (Lowell and Flier, 1997; Arch, 2008). Treatment with CL 316,2439, a β3-adrenoceptor agonist, delayed the onset of high-fat diet induced obesity in rats. Metabolic rate and mitochondrial uncoupling protein (UCP) in both BAT and WAT were found to be increased while food intake was unaffected (Ghorbani et al., 1997). In rodents, β3-adrenoceptors are found to be highly expressed in WAT and BAT, while in humans only in BAT (Granneman and Lahners, 1994). In the past, it was well accepted that BAT is prominent in rodents and infant humans but is rapidly lost during postnatal development (Lean, 1989). Therefore, the interest in the development of antiobesity drugs targeting on BAT stimulation has dropped. However, recent findings unexpectedly revealed the presence of this tissue in adult humans as recently reviewed (Nedergaard et al., 2007). Recent studies reported that the BAT in adult humans is metabolically active (Cypess et al., 2009; Saito et al., 2009), suggesting its possible role in the regulation of thermogenesis and body fat content. Based on the observation of 2-[^{18}F]fluoro-2-deoxyglucose (FDG) uptake into BAT, it was found that the amount of BAT is higher in the same subjects in winter than in summer, and similarly when the same subjects were exposed to cold and warm conditions. BAT was also found to inversely correlate with BMI, total and visceral fat of the subjects.

Despite whether BAT is a feasible target for antiobesity in humans needs further investigation, several studies on plant extracts having thermogenesis stimulator activity via this pathway have in fact been published.

FOOD INGREDIENTS WITH ENERGY EXPENDITURE STIMULATING ACTIVITY

1. Vitis vinifera

The health promoting properties of *Vitis vinifera* (grape) are believed to be due to its phenolics content. Resveratrol, a phytoalexin found in red wine and grapes (Fig. 2a), was found to increase basal energy expenditure and adaptive thermogenesis in HF-fed mice treated with resveratrol at the daily dose of 2 or 4 g/kg diet. An increase in mitochodria size and activity was observed in the treated mice. The body weight gain and fat content of the treated group were also lower then the control group while the food intake was unchanged. There were no changes in hepatic toxicity parameters and water intake, indicating that resveratrol treatment was well tolerated by the mice at the given dose (Lagouge et al., 2006).

Resveratrol down-regulates the expression of *ppar*γ, *c/ebp*α, *srebp1*, *fas*, *lpl*, and *hsl* mRNA in 3T3-L1 adipocytes. While *sirt3*, *ucp1*, and *mfn2* mRNA expression was upregulated (Rayalam et al., 2008). In another study, C57BL/6NIA mice were fed with high calorie diet supplemented with resveratrol.

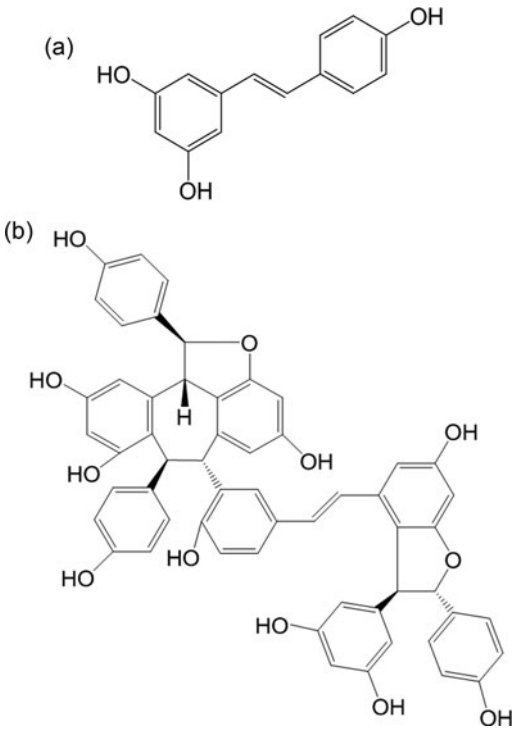

Figure 2 Antiobesity compounds isolated from *Vitis vinifera*. (a) Resveratrol (b) Vitisin A.

Resveratrol markedly altered 144 out of 153 pathways in high fat diet mice toward those of standard diet. Some of them are important markers to prolong lifespan when downregulated or upregulated, such as upregulated insulin sensitivity, downregulated insulin signaling, downregulated IGF-1 and mTOR signaling, downregulated glycolysis, upregulated AMPK and PPARγ coactivator 1α(PGC-1α) activity, upregulated Stat3 signaling, and upregulated mitochondrial number (Baur et al., 2006). The resveratrol doses used in this study were 5.2 and 22.4 mg/day. Resveratrol content of Italian red wine and grape juice ranged between 2–6 and 0.2–0.3 μg/L, respectively (Wang et al., 2002), and the recommended safe dose for humans is 5–10 mg/day (van der Spuy and Pretorius, 2009). From this data, it is clear that the reported dose is not equal to reasonable amount of wine daily intake.

There are some reports on antiobesity related activities of other grape and grape seeds derived compounds, such as procyanidin and vitisin (Fig. 2b). The reported activities concern the inhibition of adipogenesis by in-vitro methods (Ardevol et al., 2000; Pinent et al., 2005a, 2005b; Kim et al., 2008b).

Only few studies reported the relevance and potential of grape seeds or its related compounds for obesity treatment in humans. In a randomized, placebo-controlled, double-blind, cross-over study, and subjects who received 300 mg grape-seeds extract supplement (containing > 90% procyanidines) showed no difference in 24 h energy intake with the placebo in the total study population. Only subjects whose energy requirement was lower than the median of 7.5 MJ/day have 4% less 24 h energy intake compared to placebo (Vogels et al., 2004). It was reported that daily consumption of 480 ml of concord grape juice for 12 weeks did not lead to significant weight gain in overweight subjects, but consumption of polyphenol-free grape-flavored drink did (Hollis et al., 2009). In another study which involved overweight and obese subjects who regularly consumed 20–30 g alcohol/day, consumption of an iso-caloric diet (1500 kcal/day) with 10% of energy either from white wine or grape juice showed a significant body weight reduction. There was no placebo group in this study (Flechtner-Mors et al., 2004).

From the available data, it is too early to recommend grape seeds extract or compounds derived from it as a new therapy to reverse obesity in humans. The animal studies may reveal an activity on SIRT1, the well-known mammalian sirtuin, or other human energy expenditure related pathways, but whether a reasonable dose allows the absorption of an effective level of the active compounds needs to be investigated further.

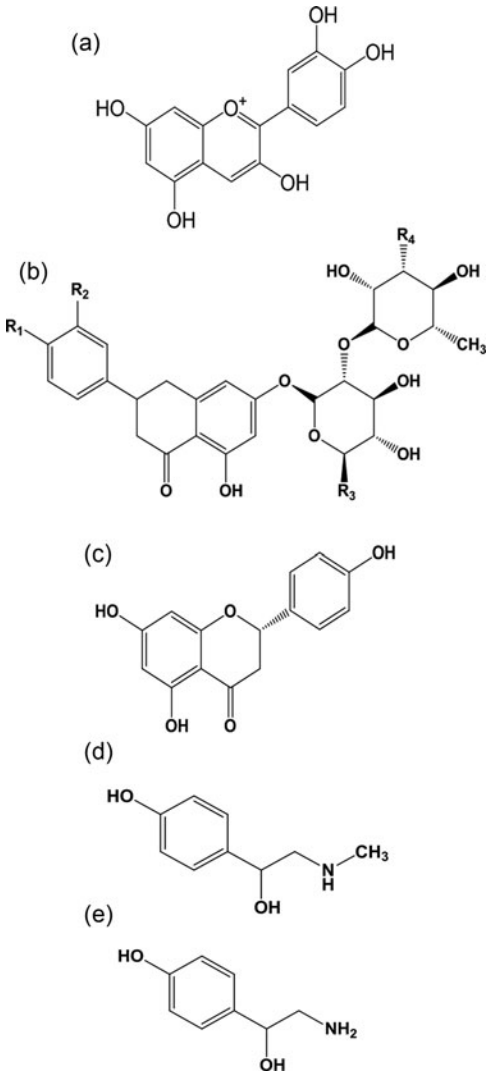

Figure 3 Polyphenolics which induce lipolysis (a–c) and sympathomimetic amines which act as ß-3 adrenoreceptor agonist ligands (d–e) from *Citrus sp*. (a) Cyanidin, (b) Naringin (R1 = OH, R2 = H, R3 = –OCH_3, R4 = OH), Narirutin (R1 = OH, R2 = H, R3 = OH, R4 = OH), Hesperidin (R1 = OCH_3, R2 = OH, R3 = OH, R4 = CH_3, (c) Naringenin, (d) Synephrine, (e) Octopamine.

2. Citrus sp

Obese subjects consuming *Citrus paradise* (grapefruit) juice or grapefruit capsules or half of fresh grapefruit before each meal three times a day lost body weight more than placebo (Fujioka et al., 2006). The mechanism is not known yet. Sinetrol is a citrus-based polyphenolic dietary supplement. It is a mixture of *Citrus sinensis* (sweet orange), *Citrus aurantium* (bitter orange, Seville orange), *Citrus paradise*, and *Paullinia cupanna* (guarana). Overweight and obese subjects consuming 350 mg of Sinetrol extract daily for 12 weeks had more pronounced body weight and body fat loss than placebo. The mechanism was proposed to be through induction of lipolysis since the extract exhibited strong phosphodiesterase inhibition (97%), stronger than caffeine (56%), at 0.01% concentration. The activity was assumed to be due to the synergistic effect between polyphenolics present in the extract such as cyanidin, naringin, naringenin, narirutin, and hesperidin (present at 5–10% in Sinetrol, Fig. 3a–3c) (Dallas et al., 2008).

Herbal preparations containing *Citrus aurantium* fruit/rind extract are commercially available as weight loss promoting agents. These preparations are usually sold as "ephedra free" preparations. This is as a response to the FDA ban

of *Ephedra* containing products in 2004 because of the side effects. The active principles, the sympathomimetic amines synephrine (phenylephrine) and octopamine (Fig. 3d–3e) are structurally similar to epinephrine and norepinephrine (Penzak, 2001). Synephrine and octopamine are selective ß-3 adrenoreceptor agonists (Airriess et al., 1997; Carpéné et al., 1999). The activation of ß-3 adrenoreceptor by its agonist stimulates cAMP generation and increases lipolysis rate (Murphy et al., 1993). Dried fruits, extracts, and commercial *C. aurantium* products contain significant amounts of synephrine, but octopamine content might be too low to consider to be involved in activity (Fugh-Berman and Myers, 2004). Subjects consuming capsules containing 26 mg of synephrine increased energy expenditure by 29%. No effect on pulse rate and blood pressure was observed (Gougeon et al., 2005). Several reports point to possible toxicity problems. Oral administration of 2.5–20 mg/kg *Citrus aurantium* alcoholic extract, which contains 4–6% active principal synephrine, significantly reduced food intake and body weight gain in rats. However, 10–50% mortality and myocardium toxicity was observed in the experiments. This finding is a serious contra-indication for the use of bitter orange, and specifically synephrine as a potent substitute of *Ephedra* containing products (Calapai et al., 1999). Tachycardia symptoms were reported on a woman treated with 50 mcg thyroxine daily for hypothyroidy, after taking *Citrus aurantium* at the daily dose of 500 mg of extract (equal to 30 mg synephrine daily) (Firenzuoli et al., 2005). A systematic review revealed seven randomized controlled clinical trials of products containing *Citrus aurantium* articles in the period of 1966–2004 (of which only one satisfied the authors' criteria) found no evidence that herbs containing *Citrus aurantium* are effective for weight loss (Bent et al., 2004). Similarly, another review mentioned that the available information is insufficient to support the efficacy or safety claims of *Citrus aurantium* (Fugh-Berman and Myers, 2004).

By using a high-performance liquid chromatography (HPLC) method, it was found that the content of synephrine is 0.10–0.35% in the dried fruit, 3.00–3.08% in dried extract, and 0.25–0.99% in commercial slimming preparation (Pellati et al., 2004). The synephrine recommended effective safe dose found in previous reports has been reviewed, which varies between 100–300 mg/day, which more or less equal to 34–100 g of dried fruit/day (Haaz et al., 2006). This should be taken into consideration although the culinary use of *C. aurantium* is not so common since the fruit is too sour to be consumed as a table fruit, but the fresh or dried ripe fruit is eaten in Iran and Mexico while immature fruits are sometimes pickled and used as a condiment (Fugh-Berman and Myers, 2004). The peel of *C. aurantium* is often used as ingredients in marmalade and beer, and the flower is used in some teas (Louw, 2008).

3. Salvia miltiorrhiza

Salvia miltiorrhiza (red Sage) is a famous Traditional Chinese Medicine, especially for treatment of coronary heart diseases. The leaves are commonly used as a meat seasoning while its medicinal benefit is attributed most to the root. Cryptotanshinone (Fig. 4a), a diterpene quinone derivative, has been isolated from the dried roots of *S. miltiorrhiza* (Ji et al., 2000). This compound was found to be a potent AMPK activator in the presence of AMP by in-vitro and in-vivo experiments. From in-vitro experiments using mouse C2C12 skeletal myoblasts cell lines, cryptotanshinone was found to indirectly activate AMPK by reducing intracellular ATP. This AMPK activation effect was also associated with the phosphorylation of AMPKα Thr172, an important intermediate for AMPK activation, and the phosphorylation of ACC Ser^{79}, the intracellular substrate for AMPK. At a 20 μM concentration, cryptotanshinone was more potent than positive controls 5-amino-imidazole-4-carboxamide riboside AICAR (500 μM) and Metformin (2 mM).

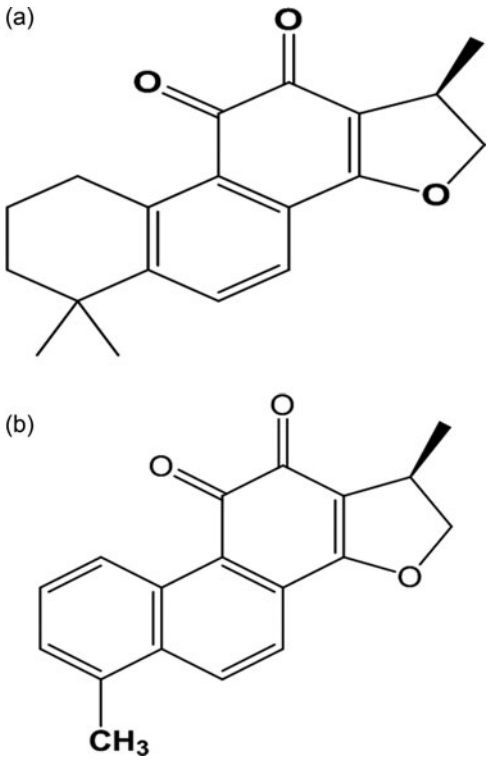

Figure 4 Antiobesity compounds from *Salvia miltiorrhiza*: (a) Cryptotanshinone, a weak AMPK activator and DGAT inhibitor (b) 15, 16-dihydrotanshinone, a weak DGAT inhibitor.

In parallel with AMPK activation, cryptotanshinone was also found to be as potent as insulin to facilitate glucose uptake by stimulating translocation of *glut4* to the plasma membrane and *glut1* mRNA expression. Cryptotanshinone exerted intense suppression of *acc1* and *acc2* mRNA expression and a simultant increase in the *cpt-i* mRNA expression, as well as *pgc-1*α and *ucp2* mRNA expression. The authors also conducted an in-vivo experiment using *ob*/*ob* (C57BL/6J-Lep^{ob}) mice. Oral administration of cryptotanshinone for a month resulted in a significant decrease of the body weight at 200, 400, and 600 mg/kg/day dosage and less fat in adipose tissue. At the maximal dosage (600 mg/kg/day), food intake was also reduced. Serum TGs and cholesterol levels were reduced, while AMPK activity of

the skeletal muscles was higher in the treated group, whereas AMPKα level was only slightly increased. Reduction in blood sugar level was also observed in treated *ob*/*ob*, *db*/*db*, and Zucker Diabetic Fatty (ZDF) mice (Kim et al., 2007).

Diacylglycerol acyltransferase (DGAT) is a microsomal enzyme important in the metabolism of glycerolipids. The inhibition of this enzyme was reported to associate with an increase of energy expenditure in mice (Smith et al., 2000). In-vitro, cryptotanshinone and 15,16-dihydrotanshinone (Fig. 4b) isolated from S. *miltiorrhiza* were reported as a weak DGAT inhibitor with IC50 values of 10.5 and 11.1 μg/mL (Ko et al., 2002). Apart from these in-vitro and animal data, there are no reports on the thermogenic efficacy of this herbal in humans.

4. Camellia sinensis

Theaflavins (Fig. 5a–5c) are considered as one of the major active phenolic principal in tea (*Camellia sinensis*). A mixture of the major theaflavins in black tea, that is, theaflavin, theaflavin-3-gallate, and theaflavin-3,3-digallate suppressed intracellular lipid accumulation in HepG2 cells in-vitro at 50 μM dose. It increased the phosphorylation level of AMPK Thr^{172} and ACC serine79, and as a result, hepatic fatty acids decreased. Treatment with theaflavins also induced fat oxidation. It was concluded that AMPK activation was involved in the activity of theaflavins (Lin et al., 2007). Incorporation of oolong tea powder into high fat diet at the dose of 5% has reduced body weight and final parametrial adipose tissue, and the accumulation of liver TG as compared to the high-fat diet-fed rats. From the in-vitro data, the authors concluded that this is due to pancreatic lipase inhibitory activity of several compounds present in the tea extract, besides the enhancement of noradrenaline-induced lipolysis in adipose tissue by the caffeine present in the tea extract (Han et al., 1999). In another study, 20 g/kg diet of green tea extract added into a high-fat diet did not affect the body weight gain and food intake of experimental rats but prevented the increase in body fat gain induced by high-fat diet which was correlated with the restoration of energy expenditure to a similar level as in the control group. The administration of the β-adrenoceptor antagonist propanolol and the green tea extract into high-fat diet rats inhibited the changes in body weight gain, as well as energy expenditure although not significant (Choo, 2003).

The role of tea catechins as compounds that significantly contribute to anti-obesity activity of tea has been reviewed (Rains et al., 2011). Epigallocatechin-3-gallate (EGCG) is the most abundant catechin in green tea extract (Khan and Mukhtar, 2007). Several studies reported the role of EGCG (Fig. 5d) and caffeine (Fig. 5e) present in tea in increasing energy expenditure in humans. Normal subjects that consumed capsulated green tea extract, which equals to 50 mg caffeine and 90 mg EGCG/day, showed significantly higher 24 h energy expenditure but lower 24 h respiratory quotient (RQ) than placebo or 50 mg caffeine group (Dulloo et al., 1999). Interestingly, carbohydrate oxidation was significantly lower but fat oxidation was significantly higher in the green tea extract group than the caffeine or placebo

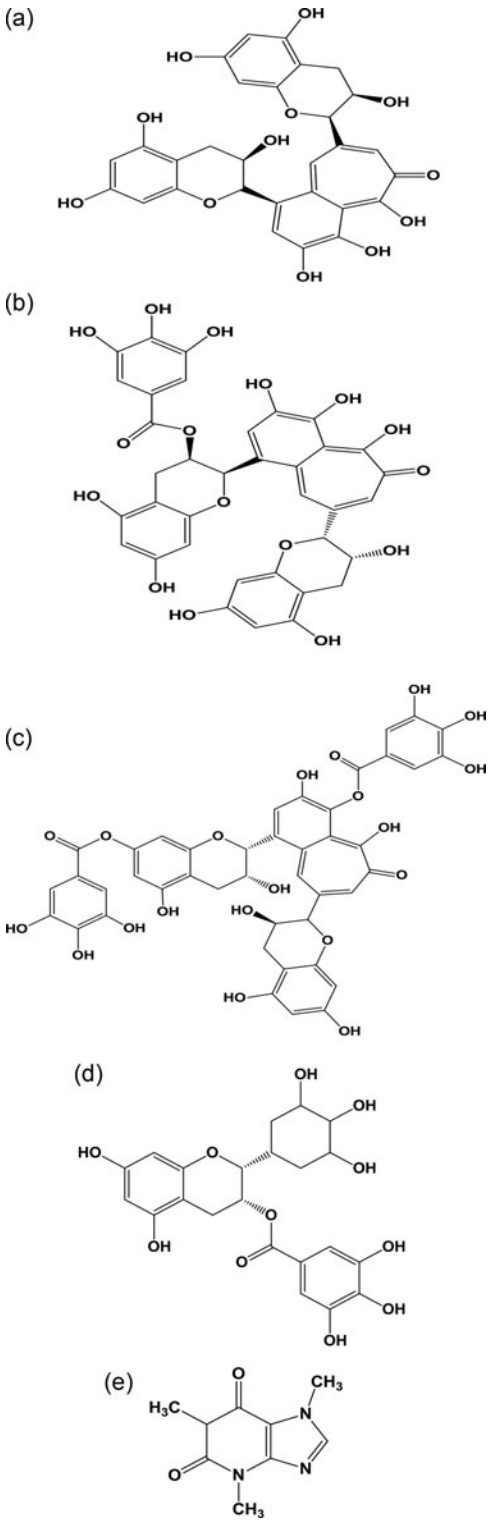

Figure 5 Compounds from black tea (*Camellia sinensis*) with antiobesity activity as a thermogenic agent: (a) Theaflavin, (b) Theaflavin-3-gallate, (c) Theaflavin-3,3-digallate, (d) EGCG, (e). Caffeine.

group. A similar study was conducted where an oolong tea beverage which was brewed according to normal daily consumption was used. Healthy subjects receiving a full-strength tea (equal to total consumption of caffeine and EGCG 244 mg and 270 mg, respectively) showed siginificantly higher 24 h energy

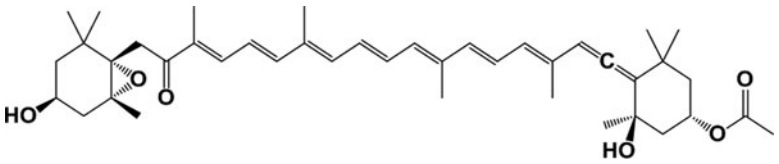

Figure 6 Fucoxanthine from *Undaria pinnatifida*, improves fat metabolism possibly via WAT UCP1 activation.

expenditure and fat oxidation than the placebo treated group (only water), but not different with the caffeinated water treated (135 mg caffeine/day) group (Rumpler et al., 2001). From the results of these studies it is not clear whether EGCG alone has an activity. In a more recent report describing a randomized double blind, placebo-controlled, cross-over pilot study, the 24 h energy expenditure of overweight/obese subjects receiving 300 mg EGCG was not significantly different from the placebo although fat oxidation was increased (Boschmann and Thielecke, 2007). A synergy between caffeine and EGCG was previously proposed (Dulloo et al., 2000).

The effect of habitual caffeine intake to the effect of green tea—caffeine mixture on overweight/obese subjects was studied (Westerterp-Plantenga et al., 2005). It was found that after receiving a green tea-caffeine mixture (270 mg EGCG and 150 mg caffeine) per day, subjects that normally consume relatively much caffeine (>300 caffeine mg/day) had a greater weight loss, thermogenesis and fat oxidation level than the low caffeine consumer subjects (<300 caffeine mg/day).

The studies of green tea antiobesity effect in humans have been reviewed (Wolfram et al., 2006; Rains et al., 2011). Most of them showed significant decrease in body weight and body fat as compared to baseline or placebo and the underlying mechanism of these effects are on thermogenesis and fat oxidation. However, the authors suggested additional studies with a fixed nutrient, energy intake, and physical activity to confirm these results.

5. Cyperus rotundus

Cyperus rotundus (coco-grass, purple nut sedge) was used in ancient eastern Mediterranean as food, perfume, and medicine. The root and shoot are edible and commonly used as a famine food in India and Africa (Paroda and Mal, 1989). In Ayurvedic classical text, this plant was mentioned as having antiobesity activity (Mangal and Sharma, 2009).

The ability of *C. rotundus* to prevent body weight gain in obese Zucker rats was tested. Incorporation of hexane extract of *C. rotundus* tuber into chow diet at either 0.075% or 0.375% dose resulted in significantly decreased body weight gain, and in the end of the study their body weight was lower than control. Food intake and retroperitoneal fat were not significantly changed. No visible toxicity signs were observed. In-vitro, lipolytic activity of the extract was measured in differentiated 3T3-F442 A adipocytes expressing ß-Adrenergic receptors. Significant increase of fatty acid release was only observed at 250 μg/mL dose (Lemaure et al., 2007).

However, there is no further report on the thermogenic activity or other obesity-related activities of this plant in humans. Moreover, the above mentioned study used a hexane fraction. This extract contains a mixture of nonpolar compounds such as unsaturated fatty acids which may bind unspecifically to several receptors (Loh and Law, 1980; Ingkaninan et al., 1999).

6. Undaria pinnatifida

Fucoxanthine (Fig. 6) and a glycolipids rich fraction (*Undaria* lipids) from *Undaria pinnatifida*, a popular edible seaweed in Japan and Korea, was incorporated in experimental diet at 0.5% and 2% dose and given to normal Wistar rats fed with normal diet and obese KK-A^y mice fed with high fat diet. In rats with normal diet, no significant difference was found in body weight, food intake, as well as weight of liver and other organs. But the weight of WAT was significantly lower in rats treated with 2% *Undaria* lipids. In case of obese mice fed with high-fat diet, 2% extract treatment caused significant decrease in WAT and body weight but not of food intake. When glycolipids and fucoxanthine were given separately, it was shown that fucoxanthine was the responsible active fraction. The weight of BAT was found to be increased in 2% extract treated mice, but there was no significant difference in the BAT uncoupling protein 1 (UCP1) expression in control and treated groups. Therefore, the decrease in abdominal fat pad weight was not because of an increase of energy expenditure in BAT mitochondria by UCP1. In fact, UCP1 was present in WAT of 2% *Undaria* lipids and 2% fucoxanthine treated groups. The decrease of WAT weight on rats and mice fed by *Undaria* lipids and fucoxanthine diet is thus probably via WAT UCP1 induced fat metabolism (Maeda et al., 2005).

In a sixteen-week, double-blind, randomized, placebo-controlled study, Xanthigen^{TM}, a commercial standardized botanical food supplement containing 300 mg pomegranate seed oil and 2.4 mg fucoxanthin, was found to promote weight loss, reduce body and liver fat content, and improve liver function in obese nondiabetic women (Abidov et al., 2010). In the end of a 16-week trial, resting energy expenditure (REE) of the treated group was significantly higher than the placebo. In this study, the effect of fucoxanthine alone on REE was also observed. Subjects who consumed 4.0 and 8.0 mg/day fucoxanthin showed a significant increase in REE compared to placebo. In another study which used a double-blind crossover study design, the waist circumference and blood pressure of the subjects consuming a capsulated seaweed at the dose of 4g/day followed by

6 g/day had decreased (Teas et al., 2009). There are no reports conforming the antiobesity effect of *U. pinnatifida in* humans.

Daily oral administration of 500 and 1000 mg/kg fucoxanthine extract (>93% purity) for 30 days did not result in any mortality or abnormality in liver, kidney, spleen, and gonadal tissue of experimental mice. However, total cholesterol plasma of the treated mice was significantly higher than control (Beppu et al., 2009). This finding illustrates the need of more detailed studies on the safety of this popular edible seaweed in human objects.

7. Glycine max

Glycine max or soya bean is a staple food mainly in Asian countries. It has been suggested that the consumption of soy-based food is correlated to the relatively low occurrence of cancer in Japan and China. It is believed that this benefit can be attributed to soya bean isoflavones content (Messina et al., 1994).

Two main soya protein components; ß-conglycinin (7S-globulin) and glycirin (11S-globulin) were fed to high-fat diet induced obese male normal (ICR) and genetically obese (KK-A^y) mice. The proteins were incorporated to an energy restricted diet at 20% dose with casein as control. At the end of the experiment, the body weight of soya protein treated animals was lower than control, with ß-conglycinin having the most pronounced effect. Differences in food intake were not significant for all groups. In the ICR ß-conglycinin group, blood levels of TGs, glucose, and insulin, are significantly lower than those of casein (Moriyama et al., 2004). In another study, 40.6% soya protein isolate was incorporated into calories restricted diet fed to KK-A^y mice. There was no significant difference in body composition of soya and casein control groups. Plasma triglycerides and glucose level were significantly lower in soy group. Adiponectin mRNA expression and its plasma level were increased in soya group, indicating higher fat oxidation activity (Nagasawa et al., 2002).

Apart from their weak estrogenic activity on the nuclear estrogen receptor, the two main soya isoflavones, daidzein and genistein can also exhibit biological effects by nonestrogen receptor mediated mechanisms, such as activation or inactivation of several enzymes as shown in an in-vivo study (Ae Park et al., 2006). Both daidzein and genistein (Fig. 7a–7b) exerted antihyperglycemic activity in *db*/*db* mice, which is thought to be mediated via the activation of glucokinase and inhibition of glucose-6-phosphatase, phosphoenolpyruvate carboxykinase, fatty acid synthase, β-oxidation, and carnitine palmitoyltransferase in the liver.

Several human studies regarding the weight reducing effect of soya bean have been reported. It was reported that soya consumers have a lower BMI as compared to non soya consumers. In this study, actual soya consumption was measured by the soya foods frequency questionnaire (Schryver et al., 2007). Obese subjects who consumed a high-soya-protein low-fat diet for 6

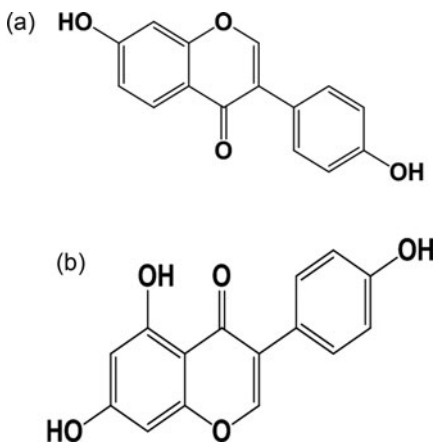

Figure 7 Isoflavones from *Glycine max* exhibitan antiobesity effect via estrogen and nonestrogen receptor mediated mechanism: (a) Daidzein, (b) Genistein.

months, with or without physical exercise, lost more weight than subjects with a standard diet. They also showed higher BMI and fat mass reduction but there was no reduction of the muscle mass, which is commonly observed in subjects treated with low calorie diets (Deibert et al., 2004). In a 12 week randomized controlled clinical trial, obese subjects treated with soya-based meal replacement formula had a greater weight loss than standard diet group. Five subjects withdrew from the study due to indigestion related adverse effects (Allison et al., 2003). A larger and longer randomized clinical trial was performed involving obese subjects who were previously diagnosed and being treated for type II diabetes mellitus (Li et al., 2004). The study period was 12 months. Subjects treated with soya-based meal showed significantly greater weight loss than the standard group. Fasting plasma glucose was significantly reduced in the treated group but only after 6 months treatment. They also showed a greater reduction of sulfonylureas or metformin medication dosages.

Studies on the efficacy of soya proteins to reduce body weight and to increase energy expenditure in obese humans have been reviewed (Velasquez and Bhathena, 2007). The authors stressed the necessity to conduct long-term prospective randomized human trials involving larger number of obese subjects to confirm a long-term benefit and safety of soya protein in obese humans.

8. Glycyrrhiza glabra

Licorice extract has been widely used in tobacco, pharmaceutical and food industries. In food industry, it is used as flavouring, sweetening, and foaming agents (Maskan, 1999), while its therapeutic uses include laxative, antitussive, and expectorant (Isbrucker and Burdock, 2006).

A licorice hydrophobic flavonoid mixture, prepared by medium chain triglycerides extraction of ethanol licorice root extract, was incorporated in a mice high-fat diet in 0.5, 1.0, or 2% dose. Concentration of glabridin (Fig. 8a), a typical licorice flavonoid in this mixture, was 1.2% w/w. Leptin and insulin levels, as well as abdominal adipose tissue mass and size and

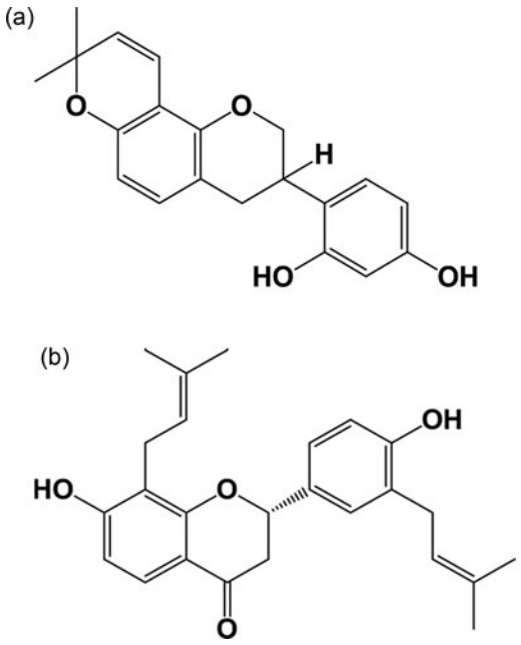

Figure 8 Typical flavonoids from *G. glabra*: (a) Glabridin, showsi antiobesity effect in mice probably via suppression of fatty acid synthesis and acceleration of fatty acid metabolism. (b) Glabrol, a DGAT inhibitor in-vitro.

body weight gain in treated mice were significantly suppressed as compared to control. According to DNA microarray analysis, apparently the flavonoids mixture down-regulates the ATP citrate lyase and Acetyl-coenzyme A synthetase-2 genes involved in acetyl-CoA synthesis, but upregulates enoyl-coenzyme A hydratase and 3-hydroxy-acyl coenzyme A dehydrogenase, resulting in suppression of fatty acid synthesis and acceleration of fatty acid metabolism (Aoki et al., 2007a). Another flavonoid isolated form the ethanolic extract of licorice, glabrol (Fig. 8b), was reported to inhibit DGAT activity with an IC_{50} value of 8.0 μM (Choi et al., 2010).

Reports on weight reducing effect of licorice in humans are very few. In a placebo-controlled, double blind study, moderately overweight subjects who received licorice flavonoid oil (LFO) at the dose of 300, 600, and 900 mg/day showed a decrease in total body fat content, while significant weight reduction was only found in the 900 mg/day dose (Tominaga et al., 2009). The same authors conducted a placebo-controlled, double blind safety study with healthy subjects given a dose of LFO up to 1200 mg/day for four weeks. They found no significant changes in physiology, hematology, or urine of the participants (Aoki et al., 2007b).

9. Capsicum annuum

Many papers discussed the thermogenic effect of capsaicin, a pungent compound of *Capsicum annuum* (red pepper) (Fig. 9a). It was mentioned that consumption of capsaicin-containing food, when the concentration reaches a physiological level, may increase catecholamine secretion in human body

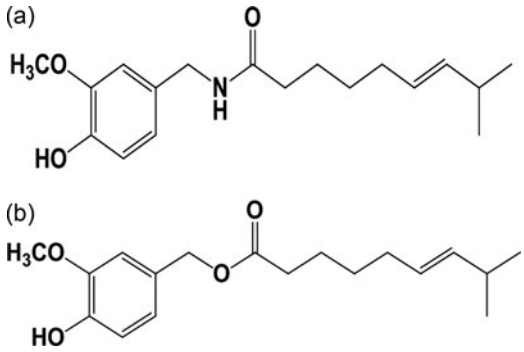

Figure 9 (a) Capsaicin, pungent capsinoid from red chilli. (b) Capsiate, unpungent capsinoid from CH-19 Sweet red chilli, both exert an anti-obesity activity by increasing fat oxidation in humans.

(Watanabe et al., 1987). Rats intraperitoneally injected with capsaicin (6.0 mg/kg) showed metabolite alterations similar to those in the metabolism of epinephrine intervention, suggesting an activation of the β-adrenergic receptor as mode of action (Kawada et al., 1986).

Ingestion of 0.4 g/kg body weight of frozen-uncooked CH-19 Sweet red chili (nonpungent type of red chili) daily during 2 weeks, did not affect the food intake of healthy Japanese subjects. The body weight decreased significantly compared to the control after 3 days treatment, as well as the body fat accumulation especially in the visceral area, suggesting the activation of β-adrenoreceptor as mechanism since the receptor is found to be higher in that part of the body. Capsiate (Fig. 9b), the main capsinoid in CH-19 Sweet which structure is similar to capsaicin was thought to be the active compound (Kawabata et al., 2006), since the daily administration of 10 mg/kg body weight capsiate via a stomach tube in mice was found to increase the expression of *ucp1* mRNA in BAT, *ucp2* mRNA in WAT, and *ucp3* in muscles (Masuda et al., 2003).

A study regarding the safety and efficacy of capsinoids in humans has been recently published (Snitker et al., 2009). Oral administration of 6 mg/day capsinoids oil extracted from CH-19 Sweet was found to be safe and associated with an increase in fat oxidation. Of the 13 genes of which expression was measured, *TRPV1* (transient receptor potential cation channel, subfamily V, member1; vanilloid receptor 1 (VR1) or capsaicin receptor), Val585Ile, and *UCP2* –866 G/A were found to correlate with abdominal adiposity change.

10. Rubus idaeus

Raspberry ketone (4-(4-hydroxyphenyl) butan-2-one (RK, Fig. 10) is a major compound in the red raspberry (*Rubus idaeus*) fruit. A study on its antiobesity activity was performed. Rats fed with high-fat-diet plus RK (particularly at 2% dose of the diet) had a significant lower final body weight, as well as liver and visceral adipose tissues. Raspberry ketone alone did not stimulate lipolysis or bind to β-adrenergic receptors but it acted synergistically with norepinephrine to induce lipolysis at the

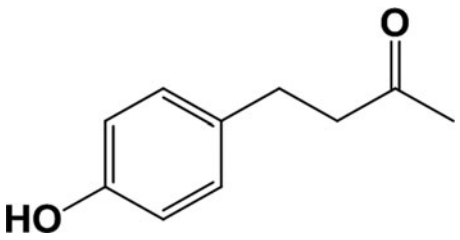

Figure 10 Raspberry ketone (4-(4-hydroxyphenyl) butan-2-one) from *Rubus idaeus*, acts synergistically with norepinephrine to induce lipolysis in mice.

concentration of 10^{-3} M. At the same concentration, it did not enhance the HSL activity but the amount of HSL protein in the fat layer was increased. Thus, the proposed mechanism is by increasing the translocation of HSL from cytosol to the lipid droplets (Morimoto et al., 2005). There are no further reports on the efficacy of this plant either in animals or humans.

11. Evodia rutaecarpa

The seed of *Evodia rutaecarpa* (Evodia fruit) is believed to be used as alternative to true pepper (*Piper nigrum*) in ancient Chinese cuisine (Simoons, 1991). It is also mentioned in Traditional Chinese Medicine for treatment of inflammation related disorders (Moon et al., 1999).

Evodiamine (Fig. 11) is a major alkaloid in *E. rutaecarpa*. *Evodia* fruit ethanol extract was incorporated into a high fat diet at a concentration of 1.35% (corresponding to 0.02% evodiamine). After 21 days of treatment, the evodiamine treated rats had a lower final body weight, smaller perirenal, and epididymal fat than those of the control group. The evodiamine group also had better lipids and sugar plasma profile, as well as lipids liver profile. Based on the two liver damage indexes, GPT and GOT, no liver toxicity was observed. Subcutaneous administration of evodiamine at 1–3 mg/kg body weight dose resulted in a hypothermic effect in the food fasted mice, but in the food satiated mice the higher dose of 10 mg/kg body weight was needed to induce the effect. This hypothermic effect was inhibited by pretreatment with capsazepine, a vanilloid receptor antagonist. Specific mitochondrial guanosine diphosphate (GDP) binding in BAT mitochondria was also found to be higher in the treated group (Kobayashi et al., 2001).

In a double-blind, randomized and placebo-controlled clinical trial, obese women who received 3 g *Evodia* extract (containing 6.75 mg evodiamine and 0.66 mg rutaecarpine) did not show

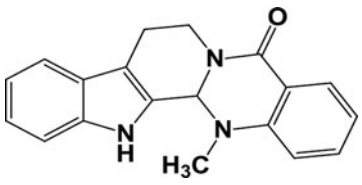

Figure 11 Evodiamine, major alkaloid in *Evodia rutaecarpa*, displays a hypothermic effect especially in food fasted mice.

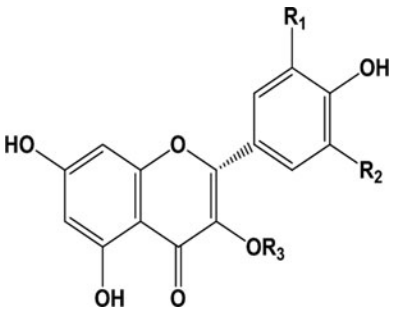

Figure 12 Flavonoids from *Nelumbo nucifera*, exhibit thermogenic and lipolytic activity in mice probably via activation of UCP3 and β-adrenoceptor: Quercetin 3-*O*-α-arabinopyranosyl-(1→2)-β-galactopyranoside (R1 = H, R2 = OH, R3 = α-arabinopyranosyl–(1→2)-β-galactopyranoside), hyperoside (R1 = OH, R2 = H, R3 = galactose), isoquercitrin (R1 = OH, R2 = H, R3 = glucose), (+)-catechin (R1 = H, R2 = OH, R3 = H), astragalin (R1 = H, R2 = H, R3 = glucose).

significant reduction of body weight or increment of resting metabolic rate as compared to placebo group. Several adverse effects such as headache, insomnia, dizziness, and constipation were reported for the Evodia group although not siginificant (Kim et al., 2008a). Despite the lack of any further efficacy study in humans, this fruit is used as an ingredient of commercial slimming preparations.

12. Nelumbo nucifera

Almost all part of *Nelumbo nucifera* (lotus/water lily) are edible. In Indonesia, the flour made from its seed and rhizome has been promoted as a substitute to rice or wheat flour. It is also traditionally used to cure gastrointestinal related illness.

The food intake of rats fed by a high-fat diet containing 1% (w/w) *Nelumbo* ethanol extract was not affected, but had a significantly lower final body weight compared to the control group. Several flavonoids have been isolated from this plant, those are quercetin 3-*O*-α-arabinopyranosyl-(1→2)-β-galactopyranoside, hyperoside, (+)–catechin, isoquercitrin, and astragalin (Fig. 12). They showed lipolytic activity at 100 μM concentration. This lipolytic activity was abolished by the addition of 10 μM propanolol, a β-adrenoceptor antagonist, suggesting activation of the β-adrenoceptor as the mode of action (Ohkoshi et al., 2007). Additionally, as mentioned above, this plant extract also showed the upregulation of UCP3 in rat muscles, suggesting its potential as a thermogenic agent (Ono et al., 2006). However, there is no report on the efficacy of thermogenic activity of this plant in humans.

13. Solanum tuberosum

The ethanol extract of a new potato variety containing purple pigments, *Solanum tuberosum* L. cv. Bora Valley, was tested for the proliferation and differentiation of 3T3-L1 preadipocytes as well as the leptin and insulin levels. By in-vitro experiment, it

was found that the extract significantly inhibited the proliferation and differentiation of 3T3-L1 preadipocytes at 10 μg/mL concentration, while in-vivo it reduced the leptin and insulin levels at 500 mg/kg diet in high fat diet fed rats. Oral administration of the extract at the dose of 200 mg/kg diet for 4 weeks did not reduce rats' body weight although hyperlipidemic parameters improved and the size of abdominal fat was significantly reduced. The expression of p38 MAPK in 3T3-L1 adipocytes was downregulated but the expression of ERK was unchanged, whereas the *ucp-3* mRNA expression in the fats and liver tissues of high fat diet fed rats was upregulated. Thus, the authors suggest that the antiobesity effect of the extract is exerted via inhibition of lipid metabolism and induction of thermogenesis through the p38 MAPK and UCP-3 pathways, respectively. Anthocyanins are thought to be the active compounds but this needs to be confirmed by further studies (Yoon et al., 2008).

The potential of anthocyanins (cyanidin or cyanidin 3-glucoside) to prevent high fat-diet induced obesity in rats has been reported (Tsuda et al., 2004), suggesting that other anthocyanin-rich plants could be interesting to study. There is no report on antiobesity activity of purple potatoes in humans, neither white potatoes. Instead, a positive correlation between white potato consumption and BMI in American adults has been reported (Lin and Morrison, 2002).

Table 1 Summary of botanicals active as thermogenic agents, responsible active compounds, and their potential for further clinical use

Plant's name	Active compounds	Potential for clinical trial	Reported active dose/day of use in humans, references	Remarks
Vitis vinifera Linn.	Resveratrol, vitisin	–	–	300 mg grape seed extract/day did not give significant difference in 24 h thermogenesis compared to placebo (Vogels et al., 2004)
Citrus sp.	cyanidin, naringin, naringenin, narirutin, hesperidin, synephrine, octopamine	+	350 mg extract of *Citrus sp* mixture for 12 weeks (Dallas et al., 2008), *C*. *aurantium* extract contains 26 mg synephrine and 4 mg octopamine (Gougeon et al., 2005)	Need more data on efficacy and safety in humans
Salvia miltiorrhiza Bunge	Cryptotanshinone, 15, 16-dyhydrotanshinone	–	–	Weak AMPK activator and DGAT inhibitor in-vitro, no report on efficacy in humans
Camellia sinensis (L.) O. Kuntze	EGCG, caffeine, theaflavines	+	270 mg–1200 mg green tea extract (Rains et al., 2011), or green tea extract equal to 50 mg caffeine and 90 mg EGCG (Dulloo et al., 1999),	Need more data on efficacy and safety in humans
Cyperus rotundus L.	–	–	–	Possible false positive.**No report on efficacy in humans
Undaria pinnatifida (Harvey) Suringar	Fucoxanthine	+	Extract containing 4 mg fucoxanthine for 16 weeks (Abidov et al., 2010)	Mice fed with 500 mg fucoxanthine/day for 30 days showed an increase of total cholesterol plasma (Beppu et al., 2009)
Glycine max (L.) Merr.	β-conglycinin, glycinin, daidzein, genistein	+	One to five portion of high soy protein diet, 3 to 12 months (Allison et al., 2003; Li et al., 2004)	Need more data on efficacy and safety in humans
Glycyrrhiza glabra L.	Glabridin, glabrol	–	–	Effective dose in human is not reasonable, 900 mg licorice flavonoids oil/day (Tominaga et al., 2009)
Capsicum annuum L.	Capsaicin, capsiate	+	6 mg capsinoids oil (Snitker et al., 2009)	–
Rubus idaeus L.	Raspberry keton	–	–	No report on efficacy in humans
Evodia rutaecarpa (Juss.) Benth	Evodiamine	–	–	No significant effects in subjects receiving 3 g Evodia extract/day for 8 weeks (Kim et al., 2008a)
Nelumbo nucifera Gaertn.	Quercetin glycoside, hyperoside, (+)–catechin, isoquercitrin, astragalin	–	–	No report on efficacy in humans
Solanum tuberosum L. cv. Bora Valley	Anthocyanin	–	–	No report on efficacy in humans
Coffea sp.	Caffeine	+	4–8 mg caffeine/kg body weight (Acheson et al., 1980; Astrup et al., 1990)	Need more data on efficacy and safety in humans

14. Coffea sp.

Coffee is one of the most widely consumed beverages in the world. The stimulant effect of coffee is attributed to its main alkaloid, caffeine (Fig. 5e). Several studies reported the thermogenic effect of caffeine in humans. One of these found that caffeine increased energy expenditure in a dose-dependent manner in healthy subjects with moderate caffeine habitual intake as compared with a placebo group (Astrup et al., 1990). Caffeine was orally administered at the dose of 100, 200, and 400 mg/day. In another study, either caffeine (8 mg/kg body weight) or caffeinated coffee (4 mg/kg body weight caffeine) was found to increase the metabolic rate in normal and obese subjects. The authors also studied the effect of the caffeinated coffee after a meal, finding that the thermic effect of the food after caffeinated coffee was greater than after decaffeinated one. They also determined that fat oxidation was also increased in the caffeinated coffee group (Acheson et al., 1980). Another report found that the consumption of 100 mg caffeine/day increased metabolic rate and 24 h energy expenditure of lean and postobese subjects (Dulloo et al., 1989). A prospective study reported that there is a correlation between an increased coffee and tea consumption and lower weight gain (Lopez-Garcia et al., 2006). However, more trials on the ability of coffee or caffeine to cause weight loss in humans are required. Moreover, it is important to consider the possibility of other compounds that are present in coffee, apart from caffeine, which could contribute to its thermogenic effect.

A summary of botanicals, responsible active compounds and the potential of each plant for clinical trial of herbs reported in this review is presented in Table 1.

CONCLUSIONS

Obesity results from the imbalance between energy intake and energy expenditure. Therefore, obesity treatment can be focused on increasing energy expenditure (inducing lipolysis followed by fat oxidation) and/or suppressing energy intake. We have summarized the existing literatures on botanicals, the compounds reportedly responsible for their activity and the mechanisms involved in antiobesity activity in this review. Most of them are consumed as daily food (e.g., grapes, tea, coffee, licorice, chilli, and soya). It is clear that the investigation of the role of food consumed on a daily basis on weight management is a key research area.

Considering the reports of most of the studies, it is important to note that in most cases extracts has been tested, and only in a few cases pure compounds. In a view of this, unfortunately a number of problems in the experimental design of the studies are quite evident, such as:

– The extracts studied have neither a reference to the specific plant material used (species, cultivar, variety) nor a chemical profile. Considering the large differences in the metabolome of different varieties of a plant, it means that very little can be said about the validity of the results, and this could even be the reason for the often contradictory results which have sometimes been reported.
– Most studies concern a reductionist approach in which activity on a target receptor or cell culture is measured and thus do not deal with the problem of bioavailability in oral human use.
– The results in animal experiments are difficult to translate to an effect on humans (Reagan-Shaw et al., 2008)
– Compounds or extracts are sometimes said to be very active, but considering the dosage or concentrations used in the experiments they have very little physiological meaning (Gertsch, 2009).

Considering these problems, it is understandable that all research so far has not lead to many new leads for evidence-based antiobesity preparations from food plants. The question, thus, is how to increase the chances for success in the search for food which could have an effect on obesity. Besides the above mentioned experimental problems in measuring activity one should also consider the following facts:

– Food is processed before consumption.
– There may be more than one active compound in the complex mixture of thousands of compounds present in a plant.
– There are many possible targets for an antiobesity activity in the human body.
– Synergism may occur.
– Certain active compounds may be formed in the GI-tract or in the body (e.g., liver) from inactive pro-drugs.

In other words, it is a multifactorial problem: multitargets—multicompounds. A possible solution to such a problem is a systems biology approach. In such an approach, a metabolomics analysis (NMR, LC-MS, GC-MS, or MS) is performed on different varieties of the same species, different extracts or fractions of the extract (converting chemical variability into an advantage instead of a disadvantage as mentioned above). These results then must be correlated through multivariate analysis with measurements of the activity of these samples. In this context, what is understood by detecting "activity" is actually measuring the widest range of parameters that relate to the desired activity, in this case, loss of weight. These parameters can be the levels of certain metabolites in, that is, plasma or urine, levels of signal compounds, levels of enzyme activity and gene expression patterns. Such an approach is presently being developed for the study of the activity of various traditional medicines (Verpoorte et al., 2005; Wang et al., 2005; Cardoso-Taketa et al., 2008; Kim et al., 2010).

In using such an approach in combination with in-vivo experiments, and preferably clinical trials, one may find correlations between activity and the occurrence of certain compounds, which does not necessarily mean that the compound(s) is/are active *per se*, but could be pro-drugs or compounds that work in synergy. The design of the in-vivo experiments should be

based on the fact that the desired effects are long-term events and thus probably involve changes in the homeostasis, that is, of gene (transcriptomics), protein (proteomics), and metabolite (metabolomics) expression patterns.

After confirming an activity in clinical trials and the identification of compound(s) involved in this activity, a more reductionist approach can be used to find and explain the mechanism of action.

ACKNOWLEDGMENT

The Phytochemical Society of Europe is gratefully acknowledged for financial support to Nancy Dewi Yuliana. The project was supported by Nobesinkas.

CONFLICT OF INTEREST

No conflict of interest was declared.

REFERENCES

Abidov, M., Ramazanov, Z., Seifulla, R. and Grachev, S. (2010). The effects of Xanthigen™ in the weight management of obese premenopausal women with non-alcoholic fatty liver disease and normal liver fat. *Diabetes Obes. Metab.* **12**:72–81.

Acheson, K. J., Zahorska-Markiewicz, B., Pittet, P., Anantharaman, K. and Jequier, E. (1980). Caffeine and coffee: Their influence on metabolic rate and substrate utilization in normal weight and obese individuals. *Am. J. Clin. Nutr.* **33**:989–997.

Ae Park, S., Choi, M.-S., Cho, S.-Y., Seo, J.-S., Jung, U. J., Kim, M.-J., Sung, M.-K., Park, Y. B. and Lee, M.-K. (2006). Genistein and daidzein modulate hepatic glucose and lipid regulating enzyme activities in C57BL/KsJ-db/db mice. *Life Sci.* **79**:1207–1213.

Airriess, C. N., Rudling, J. E., Midgley, J. M. and Evans, P. D. (1997). Selective inhibition of adenylyl cyclase by octopamine via a human cloned α_{2A}-adrenoceptor. *Br. J. Pharmacol.* **122**:191–198.

Allison, D. B., Gadbury, G., Schwartz, L. G., Murugesan, R., Kraker, J. L., Heshka, S., Fontaine, K. R. and Heymsfield, S. B. (2003). A novel soy-based meal replacement formula for weight loss among obese individuals: A randomized controlled clinical trial. *Eur. J. Clin. Nutr.* **57**:514–522.

Aoki, F., Honda, S., Kishida, H., Kitano, M., Arai, N., Tanaka, H., Yokota, S., Nakagawa, K., Asakura, T., Nakai, Y. and Mae, T. (2007a). Suppression by licorice flavonoids of abdominal fat accumulation and body weight gain in high-fat diet induced obese C57BL/6J mice. *Biosci. Biotechnol. Biochem.* **71**:206–214.

Aoki, F., Nakagawa, K., Kitano, M., Ikematsu, H., Nakamura, K., Yokota, S., Tominaga, Y., Arai, N. and Mae, T. (2007b). Clinical safety of licorice flavonoid oil (LFO) and pharmacokinetics of glabridin in healthy humans. *J. Am. Coll. Nutr.* **26**:209–218.

Arch, J. (2008). The discovery of drugs for obesity, the metabolic effects of leptin and variable receptor pharmacology: Perspectives from beta-3 adrenoceptor agonists. *Naunyn. Schmiedebergs Arch. Pharmacol.* **378**:225–240.

Arch, J. R. S., Ainsworth, A. T., Cawthorne, M. A., Piercy, V., Sennitt, M. V., Thody, V. E., Wilson, C. and Wilson, S. (1984). Atypical beta-adrenoceptor on brown adipocytes as target for anti-obesity drugs. *Nature* **309**:163–165.

Ardevol, A., Blade, C., Salvado, M. and Arola, L. (2000). Changes in lipolysis and hormone-sensitive lipase expression caused by procyanidins in 3T3-L1 adipocytes. *Int. J. Obes.* **24**:319–324.

Arner, P. (2005). Human fat cell lipolysis: Biochemistry, regulation and clinical role. *Best Pract Res Cl En.* **19**:471–482.

Astrup, A., Toubro, S., Cannon, S., Hein, P., Breum, L. and Madsen, J. (1990). Caffeine: A double-blind, placebo-controlled study of its thermogenic, metabolic, and cardiovascular effects in healthy volunteers. *Am. J. Clin. Nutr.* **51**:759–767.

Baur, J. A., Pearson, K. J., Price, N. L., Jamieson, H. A., Lerin, C., Kalra, A., Prabhu, V. V., Allard, J. S., Lopez-Lluch, G., Lewis, K., Pistell, P. J., Poosala, S., Becker, K. G., Boss, O., Gwinn, D., Wang, M., Ramaswamy, S., Fishbein, K. W., Spencer, R. G., Lakatta, E. G., Le Couteur, D., Shaw, R. J., Navas, P., Puigserver, P., Ingram, D. K., de Cabo, R. and Sinclair, D. A. (2006). Resveratrol improves health and survival of mice on a high-calorie diet. *Nature* **444**:337–342.

Bent, S., Padula, A. and Neuhaus, J. (2004). Safety and efficacy of *Citrus aurantium* for weight loss. *Am. J. Cardiol.* **94**:1359–1361.

Beppu, F., Niwano, Y., Tsukui, T., Hosokawa, M. and Miyashita, K. (2009). Single and repeated oral dose toxicity study of fucoxanthin (FX), a marine carotenoid, in mice. *J. Toxicol. Sci.* **34**:501–510.

Bessesen, D. H. (2008). Update on obesity. *J. Clin. Endocrinol. Metab.* **93**:2027–2034.

Boschmann, M. and Thielecke, F. (2007). The effects of epigallocatechin-3-gallate on thermogenesis and fat oxidation in obese men: A pilot study. *J. Am. Coll. Nutr.* **26**:389S–395S.

Calapai, G., Firenzuoli, F., Saitta, A., Squadrito, F., Arlotta, M. R., Costantino, G. and Inferrera, G. (1999). Antiobesity and cardiovascular toxic effects of *Citrus aurantium* extracts in the rat: A preliminary report. *Fitoterapia* **70**:586–592.

Cardoso-Taketa, A. T., Pereda-Miranda, R., Choi, Y. H., Verpoorte, R. and Villarreal, M. L. (2008). Metabolic profiling of the Mexican anxiolytic and sedative plant *Galphimia glauca* using Nuclear Magnetic Resonance spectroscopy and Multivariate Data Analysis. *Planta Med.* **74**: 1295–1301.

Carpéné, C., Galitzky, J., Fontana, E., Atgié, C., Lafontan, M. and Berlan, M. (1999). Selective activation of β3-adrenoceptors by octopamine: Comparative studies in mammalian fat cells. *Naunyn. Schmiedebergs Arch. Pharmacol.* **359**:310–321.

Chaput, J., St-Pierre, S. and Tremblay, A. (2007). Currently available drugs for the treatment of obesity: Sibutramine and Orlistat. *Mini Rev. Med. Chem.* **7**:3–10.

Chiesi, M., Huppertz, C. and Hofbauer, K. G. (2001). Pharmacotherapy of obesity: Targets and perspectives. *Trends Pharmacol. Sci.* **22**:247–254.

Choi, J., Choi, J., Lee, S., Kim, K. and Kim, Y. (2010). Inhibitory activity of diacylglycerol acyltransferase by glabrol isolated from the roots of licorice. *Arch. Pharm. Res.* **33**:237–242.

Choo, J. J. (2003). Green tea reduces body fat accretion caused by high-fat diet in rats through β-adrenoceptor activation of thermogenesis in brown adipose tissue. *J. Nutr. Biochem.* **14**:671–676.

Cypess, A. M., Lehman, S., Williams, G., Tal, I., Rodman, D., Goldfine, A. B., Kuo, F. C., Palmer, E. L., Tseng, Y.-H., Doria, A., Kolodny, G. M. and Kahn, C. R. (2009). Identification and importance of brown adipose tissue in adult humans. *N. Engl. J. Med.* **360**:1509–1517.

Dallas, C., Gerbi, A., Tenca, G., Juchaux, F. and Bernard, F. (2008). Lipolytic effect of a polyphenolic citrus dry extract of red orange, grapefruit, orange (SINETROL) in human body fat adipocytes. Mechanism of action by inhibition of cAMP-phosphodiesterase (PDE). *Phytomedicine* **15**:783–792.

Deibert, P., Konig, D., Schmidt-Trucksaess, A., Zaenker, K. S., Frey, I., Landmann, U. and Berg, A. (2004). Weight loss without losing muscle mass in pre-obese and obese subjects induced by a high-soy-protein diet. *Int. J. Obes. Relat. Metab. Disord.* **28**:1349–1352.

Dulloo, A., Seydoux, J., Girardier, L., Chantre, P. and Vandermander, J. (2000). Green tea and thermogenesis: Interactions between catechin-polyphenols, caffeine and sympathetic activity. *Int. J. Obes.* **24**:252–258.

Dulloo, A. G., Duret, C., Rohrer, D., Girardier, L., Mensi, N., Fathi, M., Chantre, P. and Vandermander, J. (1999). Efficacy of a green tea extract rich in catechin polyphenols and caffeine in increasing 24-h energy expenditure and fat oxidation in humans. *Am. J. Clin. Nutr.* **70**:1040–1045.

Dulloo, A. G., Geissler, C. A., Horton, T., Collins, A. and Miller, D. S. (1989). Normal caffeine consumption: Influence on thermogenesis and daily energy expenditure in lean and postobese human volunteers. *Am. J. Clin. Nutr.* **49**:44–50.

Dulloo, A. G. and Samec, S. (2000). Uncoupling proteins: Do they have a role in body weight regulation? *News Physiol. Sci.* **15**:313–318.

Fernandez, C., Hansson, O., Nevsten, P., Holm, C. and Klint, C. (2008). Hormone-sensitive lipase is necessary for normal mobilization of lipids during submaximal exercise. *Am. J. Physiol. Endocrinol. Metab.* **295**:E179–186.

Firenzuoli, F., Gori, L. and Galapai, C. (2005). Adverse reaction to an adrenergic herbal extract (*Citrus aurantium*). *Phytomedicine* **12**:247–248.

Flechtner-Mors, M., Biesalski, H. K., Jenkinson, C. P., Adler, G. and Ditschuneit, H. H. (2004). Effects of moderate consumption of white wine on weight loss in overweight and obese subjects. *Int. J. Obes. Relat. Metab. Disord.* **28**:1420–1426.

Fugh-Berman, A. and Myers, A. (2004). Citrus aurantium, an ingredient of dietary supplements marketed for weight loss: Current status of clinical and basic research. *Exp. Biol. Med.* **229**:698–704.

Fujioka, K., Greenway, F., Sheard, J. and Ying, Y. (2006). The effects of grapefruit on weight and insulin resistance: Relationship to the metabolic syndrome. *J. Med. Food* **9**:49–54.

Gertsch, J. (2009). How scientific is the science in ethnopharmacology? Historical perspectives and epistemological problems. *J. Ethnopharmacol.* **122**:177–183.

Ghorbani, M., Claus, T. H. and Himms-Hagen, J. (1997). Hypertrophy of brown adipocytes in brown and white adipose tissues and reversal of diet-induced obesity in rats treated with a [beta]3-adrenoceptor agonist. *Biochem. Pharmacol.* **54**:121–131.

Gougeon, R., Harrigan, K., Tremblay, J.-F., Hedrei, P., Lamarche, M. and Morais, J. A. (2005). Increase in the thermic effect of food in women by adrenergic amines extracted from *Citrus aurantium*. *Obesity* **13**:1187–1194.

Granneman, J. and Lahners, K. (1994). Analysis of human and rodent beta 3-adrenergic receptor messenger ribonucleic acids. *Endocrinology* **135**:1025–1031.

Haaz, S., Fontaine, K. R., Cutter, G., Limdi, N., Perumean-Chaney, S. and Allison, D. B. (2006). *Citrus aurantium* and synephrine alkaloids in the treatment of overweight and obesity: An update. *Obes. Rev.* **7**:79–88.

Han, L., Takaku, T., Li, J., Kimura, Y. and Okuda, H. (1999). Anti-obesity action of Oolong tea. *Int. J. Obes.* **23**:98–105.

Hardie, D. G., Carling, D. and Carlson, M. (1998). The AMP-activated/SNF1 protein kinase subfamily: Metabolic sensors of the eukaryotic cell? *Annu. Rev. Biochem.* **67**:821–855.

Haslam, D. W. and James, W. P. T. (2005). Obesity. *Lancet* **366**:1197–1209.

Hofbauer, K. G., Nicholson, J. R. and Boss, O. (2007). The obesity epidemic: Current and future pharmacological treatments. *Annu. Rev. Pharmacol. Toxicol.* **47**:565–592.

Hollis, J., Houchins, J., Blumberg, J. and Mattes, R. (2009). Effects of concord grape juice on appetite, diet, body weight, lipid profile, and antioxidant status of adults. *J. Am. Coll. Nutr.* **28**:574–582.

Ingkaninan, K., von Frijtag Drabbe Kunzel, J. K., Ijzerman, A. P. and Verpoorte, R. (1999). Interference of linoleic acid fraction in some receptor binding assays. *J. Nat. Prod.* **62**:912–914.

Isbrucker, R. A. and Burdock, G. A. (2006). Risk and safety assessment on the consumption of Licorice root (*Glycyrrhiza* sp.), its extract and powder as a food ingredient, with emphasis on the pharmacology and toxicology of glycyrrhizin. *Regul. Toxicol. Pharmacol.* **46**:167–192.

Ji, X., Tan, B. and Zhu, Y. (2000). *Salvia miltiorrhiza* and ischemic diseases. *Acta Pharmacol. Sin.* **21**:1089–1094.

Kawabata, F., Inoue, N., Yazawa, S., Kawada, T., Inoue, K. and Fushiki, T. (2006). Effects of CH-19 sweet, a non-pungent cultivar of red pepper, in decreasing the body weight and suppressing body fat accumulation by sympathetic nerve activation in humans. *Biosci. Biotechnol. Biochem.* **70**:2824–2835.

Kawada, T., Watanabe, T., Takaishi, T., Tanaka, T. and Iwai, K. (1986). Capsaicin-induced beta-adrenergic action on energy metabolism in rats: Influence of capsaicin on oxygen consumption, the respiratory quotient, and substrate utilization. *Proc. Soc. Exp. Biol. Med.* **83**:250–256.

Khan, N. and Mukhtar, H. (2007). Tea polyphenols for health promotion. *Life Sci.* **81**:519–533.

Kim, E. J., Jung, S.-N., Son, K. H., Kim, S. R., Ha, T. Y., Park, M. G., Jo, I. G., Park, J. G., Choe, W., Kim, S.-S. and Ha, J. (2007). Antidiabetes and antiobesity effect of cryptotanshinone via activation of AMP-activated protein kinase. *Mol. Pharmacol.* **72**:62–72.

Kim, H.-J., Park, J.-M., Kim, J.-A. and Ko, B.-P. (2008a). Effect of herbal *Ephedra sinica* and *Evodia rutaecarpa* on body composition and resting metabolic rate: A randomized, double-blind clinical trial in Korean premenopausal women. *J. Acupunct. Meridian Stud.* **1**:128–138.

Kim, H. K., Wilson, E. G., Choi, Y. H. and Verpoorte, R. (2010). Metabolomics: A tool for anticancer lead-finding from natural products. *Planta Med.* **76**:1094–1102.

Kim, S.-H., Park, H.-S., Lee, M.-s., Cho, Y.-J., Kim, Y.-S., Hwang, J.-T., Sung, M. J., Kim, M. S. and Kwon, D. Y. (2008b). Vitisin A inhibits adipocyte differentiation through cell cycle arrest in 3T3-L1 cells. *Biochem. Biophys. Res. Commun.* **372**:108–113.

Ko, J., Ryu, S., Kim, Y., Chung, M., Kang, J., Rho, M.-C. and Lee, H. (2002). Inhibitory activity of diacylglycerol acyltransferase by tanshinones from the root of *Salvia miltiorrhiza*. *Arch. Pharm. Res.* **25**:446–448.

Kobayashi, Y., Nakano, Y., Kizaki, M., Hoshikuma, K., Yokoo, Y. and Kamiya, T. (2001). Capsaicin-like anti-obese activities of evodiamine from fruits of *Evodia rutaecarpa*, a vanilloid receptor agonist. *Planta Med.* **67**:628–633.

Lagouge, M., Argmann, C., Gerhart-Hines, Z., Meziane, H., Lerin, C., Daussin, F., Messadeq, N., Milne, J., Lambert, P., Elliott, P., Geny, B., Laakso, M., Puigserver, P. and Auwerx, J. (2006). Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1[alpha]. *Cell* **127**:1109–1122.

Langin, D. (2006). Adipose tissue lipolysis as a metabolic pathway to define pharmacological strategies against obesity and the metabolic syndrome. *Pharmacol. Res.* **53**:482–491.

Lean, M. E. J. (1989). Brown adipose tissue in humans. *Proc. Nutr. Soc.* **48**:243–257.

Lemaure, B., Touché, A., Zbinden, I., Moulin, J., Courtois, D., Macé, K. and Darimont, C. (2007). Administration of *Cyperus rotundus* tubers extract prevents weight gain in obese Zucker rats. *Phytother. Res.* **21**:724–730.

Li, Z., Hong, K., Saltsman, P., DeShields, S., Bellman, M., Thames, G., Liu, Y., Wang, H. J., Elashoff, R. and Heber, D. (2004). Long-term efficacy of soy-based meal replacements vs an individualized diet plan in obese type II DM patients: Relative effects on weight loss, metabolic parameters, and C-reactive protein. *Eur. J. Clin. Nutr.* **59**:411–418.

Lin, B. and Morrison, R. (2002). Higher fruit consumption linked with lower body mass index. *Food Review* **25**:28–32.

Lin, C.-L., Huang, H.-C. and Lin, J.-K. (2007). Theaflavins attenuate hepatic lipid accumulation through activating AMPK in human HepG2 cells. *J. Lipid Res.* **48**:2334–2343.

Loh, H. H. and Law, P. Y. (1980). The role of membrane lipids in receptor mechanisms. *Annu. Rev. Pharmacol. Toxicol.* **20**:201–234.

Lopez-Garcia, E., van Dam, R. M., Rajpathak, S., Willett, W. C., Manson, J. E. and Hu, F. B. (2006). Changes in caffeine intake and long-term weight change in men and women. *Am. J. Clin. Nutr.* **83**:674–680.

Louw, V. (2008). *Citrus aurantium*, beware of the bitter orange. *S. Afr. Med. J.* **98**:496.

Lowell, B. B. and Flier, J. S. (1997). Brown adipose tissue, beta-3 adrenergic receptors, and obesity. *Annu. Rev. Med.* **48**:307–316.

Maeda, H., Hosokawa, M., Sashima, T., Funayama, K. and Miyashita, K. (2005). Fucoxanthin from edible seaweed, *Undaria pinnatifida*, shows antiobesity effect through UCP1 expression in white adipose tissues. *Biochem. Biophys. Res. Commun.* **332**:392–397.

Mangal, A. and Sharma, M. (2009). Evaluation of certain medicinal plants for antiobesity properties. *IJTK* **8**:602–605.

Maskan, M. (1999). Rheological behaviour of liquorice (*Glycyrrhiza glabra*) extract. *J. Food Eng.* **39**:389–393.

Masuda, Y., Haramizu, S., Oki, K., Ohnuki, K., Watanabe, T., Yazawa, S., Kawada, T., Hashizume, S.-i. and Fushiki, T. (2003). Upregulation of uncoupling proteins by oral administration of capsiate, a nonpungent capsaicin analog. *J. Appl. Physiol.* **95**:2408–2415.

Messina, M. J., Persky, V., Setchell, K. D. R. and Barnes, S. (1994). Soy intake and cancer risk: A review of the in-vitro and in-vivo data. *Nutr. Cancer* **21**:113–131.

Moon, T. C., Murakami, M., Kudo, I., Son, K. H., Kim, H. P., Kang, S. S. and Chang, H. W. (1999). A new class of COX-2 inhibitor, rutaecarpine from Evodia rutaecarpa. *Inflamm. Res.* **48**:621–625.

Morimoto, C., Satoh, Y., Hara, M., Inoue, S., Tsujita, T. and Okuda, H. (2005). Anti-obese action of raspberry ketone. *Life Sci.* **77**:194–204.

Moriyama, T., Kishimoto, K., Nagai, K., Urade, R., Ogawa, T., Utsumi, S., Maruyama, N. and Maebuchi, M. (2004). Soybean beta-Conglycinin diet suppresses serum triglyceride levels in normal and genetically obese mice by induction of beta-oxidation, downregulation of fatty acid synthase, and inhibition of triglyceride absorption. *Biosci. Biotechnol. Biochem.* **68**: 352–359.

Murphy, G. J., Kirkham, D. M., Cawthorne, M. A. and Young, P. (1993). Correlation of beta-3-adrenoceptor-induced activation of cAMP-dependent protein kinase with activation of lipolysis in rat white adipocytes. *Biochem. Pharmacol.* **46**:575–581.

Nagasawa, A., Fukui, K., Funahashi, T., Maeda, N., Shimomura, I., Kihara, S., Waki, M., Takamatsu, K. and Matsuzawa, Y. (2002). Effects of soy protein diet on the expression of adipose genes and plasma adiponectin. *Horm. Metab. Res.* **34**:635–639.

Nedergaard, J., Bengtsson, T. and Cannon, B. (2007). Unexpected evidence for active brown adipose tissue in adult humans. *Am. J. Physiol. Endocrinol. Metab.* **293**:E444–E452.

Ohkoshi, E., Miyazaki, H., Shindo, K., Watanabe, H., Yoshida, A. and Yajima, H. (2007). Constituents from the leaves of *Nelumbo nucifera* stimulate lipolysis in the white adipose tissue of mice. *Planta Med.* **73**:1255–1259.

Ono, Y., Hattori, E., Fukaya, Y., Imai, S. and Ohizumi, Y. (2006). Anti-obesity effect of *Nelumbo nucifera* leaves extract in mice and rats. *J. Ethnopharmacol.* **106**:238–244.

Paroda, R. and Mal, B. (1989). New plant sources for food and industry in India. **In**: New Crops for Food and Industry, pp. 135–149. Wickens, G., Haq, N. and Day, P. Eds., Chapman and Hall, London.

Pellati, F., Benvenuti, S. and Melegari, M. (2004). High-performance liquid chromatography methods for the analysis of adrenergic amines and flavanones in *Citrus aurantium* L. var. *amara*. *Phytochem. Anal.* **15**: 220–225.

Penzak, S. (2001). Seville (sour) orange juice: Synephrine content and cardiovascular effects in normotensive adults. *J. Clin. Pharmacol.* **41**: 1059–1063.

Pinent, M., Blade, M. Cinta, Salvado, M. J., Arola, L. and Ardevol, A. (2005a). Intracellular mediators of procyanidin-induced lipolysis in 3T3-L1 adipocytes. *J. Agric. Food Chem.* **53**:262–266.

Pinent, M., Blade, M., Salvado, M., Arola, L., Hackl, H., Quackenbush, J., Trajanoski, Z. and Ardevol, A. (2005b). Grape-seed derived procyanidins interfere with adipogenesis of 3T3-L1 cells at the onset of differentiation. *Int. J. Obes.* **29**:934–941.

Rains, T. M., Agarwal, S. and Maki, K. C. (2011). Antiobesity effects of green tea catechins: A mechanistic review. *J. Nutr. Biochem.* **22**:1–7.

Rayalam, S., Yang, J.-Y., Ambati, S., Della-Fera, M. A. and Baile, C. A. (2008). Resveratrol induces apoptosis and inhibits adipogenesis in 3T3-L1 adipocytes. *Phytother. Res.* **22**:1367–1371.

Reagan-Shaw, S., Nihal, M. and Ahmad, N. (2008). Dose translation from animal to human studies revisited. *FASEB J.* **22**:659–661.

Rumpler, W., Seale, J., Clevidence, B., Judd, J., Wiley, E., Yamamoto, S., Komatsu, T., Sawaki, T., Ishikura, Y. and Hosoda, K. (2001). Oolong tea increases metabolic rate and fat oxidation in men. *J. Nutr.* **131**:2848–2852.

Saito, M., Okamatsu-Ogura, Y., Matsushita, M., Watanabe, K., Yoneshiro, T., Nio-Kobayashi, J., Iwanaga, T., Miyagawa, M., Kameya, T. and Nakada, K. (2009). High incidence of metabolically active brown adipose tissue in healthy adult humans. *Diabetes* **58**:1526–1531.

Schryver, T., Smith, C. and Wall, M. (2007). Self-identities and BMI of Minnesotan soy consumers and non-consumers. *Obesity* **15**:1101–1106.

Sengenes, C., Berlan, M., De Glisezinski, I., Lafontan, M. and Galitzky, J. (2000). Natriuretic peptides: A new lipolytic pathway in human adipocytes. *FASEB J.* **14**:1345–1351.

Simoons, F. (1991). Food in China: A Cultural and Historical Inquiry. CRC, Boca Raton.

Smith, S. J., Cases, S., Jensen, D. R., Chen, H. C., Sande, E., Tow, B., Sanan, D. A., Raber, J., Eckel, R. H. and Farese, R. V. (2000). Obesity resistance and multiple mechanisms of triglyceride synthesis in mice lacking Dgat. *Nat. Genet.* **25**:87–90.

Snitker, S., Fujishima, Y., Shen, H., Ott, S., Pi-Sunyer, X., Furuhata, Y., Sato, H. and Takahashi, M. (2009). Effects of novel capsinoid treatment on fatness and energy metabolism in humans: Possible pharmacogenetic implications. *Am. J. Clin. Nutr.* **89**:45–50.

Soni, K. G., Lehner, R., Metalnikov, P., O'Donnell, P., Semache, M., Gao, W., Ashman, K., Pshezhetsky, A. V. and Mitchell, G. A. (2004). Carboxylesterase 3 (EC 3.1.1.1) is a major adipocyte lipase. *J. Biol. Chem.* **279**:40683–40689.

Spiegelman, B. M. and Flier, J. S. (2001). Obesity and the regulation of energy balance. *Cell* **104**:531–543.

Syu, L.-J. and Saltiel, A. R. (1999). Lipotransin: A novel docking protein for hormone-sensitive lipase. *Mol. Cell* **4**:109–115.

Sztalryd, C., Xu, G., Dorward, H., Tansey, J. T., Contreras, J. A., Kimmel, A. R. and Londos, C. (2003). Perilipin A is essential for the translocation of hormone-sensitive lipase during lipolytic activation. *J. Cell Biol.* **161**:1093–1103.

Teas, J., Baldeon, M., Chiriboga, D., Davis, J., Sarriés, A. and Braverman, L. (2009). Could dietary seaweed reverse the metabolic syndrome? *Asia Pac. J. Clin. Nutr.* **18**:145–157.

Tominaga, Y., Nakagawa, K., Mae, T., Kitano, M., Yokota, S., Arai, T., Ikematsu, H. and Inoue, S. (2009). Licorice flavonoid oil reduces total body fat and visceral fat in overweight subjects: A randomized, double-blind, placebo-controlled study. *Obes. Res. Clin. Pract.* **3**:169–178.

Tsuda, T., Ueno, Y., Aoki, H., Koda, T., Horio, F., Takahashi, N., Kawada, T. and Osawa, T. (2004). Anthocyanin enhances adipocytokine secretion and adipocyte-specific gene expression in isolated rat adipocytes. *Biochem. Biophys. Res. Commun.* **316**:149–157.

van der Spuy, W. J. and Pretorius, E. (2009). Is the use of resveratrol in the treatment and prevention of obesity premature? *Nutr. Res. Rev.* **22**:111–117.

Velasquez, M. and Bhathena, S. (2007). Role of dietary soy protein in obesity. *Int. J. Med. Sci.* **4**:72.

Verpoorte, R., Choi, Y. H. and Kim, H. K. (2005). Ethnopharmacology and systems biology: A perfect holistic match. *J. Ethnopharmacol.* **100**: 53–56.

Vogels, N., Nijs, I. and Westerterp-Plantenga, M. (2004). The effect of grape-seed extract on 24 h energy intake in humans. *Eur. J. Clin. Nutr.* **58**:667–673.

Walters, W. P. and Namchuk, M. (2003). Designing screens: How to make your hits a hit. *Nat. Rev. Drug Discov.* **2**:259–266.

Wang, M., Lamers, R.-J. A. N., Korthout, H. A. A. J., van Nesselrooij, J. H. J., Witkamp, R. F., van der Heijden, R., Voshol, P. J., Havekes, L. M., Verpoorte, R. and van der Greef, J. (2005). Metabolomics in the context of systems biology: Bridging traditional Chinese medicine and molecular pharmacology. *Phytother. Res.* **19**:173–182.

Wang, Y., Catana, F., Yang, Y., Roderick, R. and van Breemen, R. B. (2002). An LC-MS method for analyzing total resveratrol in grape juice, cranberry juice, and in wine. *J. Agric. Food Chem.* **50**:431–435.

Watanabe, T., Kawada, T., Yamamoto, M. and Iwai, K. (1987). Capsaicin, a pungent principle of hot red pepper, evokes catecholamine secretion from the adrenal medulla of anesthetized rats. *Biochem. Biophys. Res. Commun.* **142**:259–264.

Westerterp-Plantenga, M. S., Lejeune, M. P. G. M. and Kovacs, E. M. R. (2005). Body weight loss and weight maintenance in relation to habitual caffeine intake and green tea supplementation. *Obesity* **13**:1195–1204.

Winder, W. W. and Hardie, D. G. (1999). AMP-activated protein kinase, a metabolic master switch: Possible roles in Type 2 diabetes. *Am. J. Physiol. Endocrinol. Metab.* **277**:E1–E10.

Wolfram, S., Wang, Y. and Thielecke, F. (2006). Anti-obesity effects of green tea: From bedside to bench. *Mol. Nutr. Food Res.* **50**:176–187.

Yeaman, S. (2004). Hormone-sensitive lipase-new roles for an old enzyme. *Biochem. J.* **379**:11–22.

Yoon, S. S., Rhee, Y. H., Lee, H. J., Lee, E. O., Lee, M. H., Ahn, K. S., Lim, H. T. and Kim, S. H. (2008). Uncoupled protein 3 and p38 signal pathways are involved in anti-obesity activity of *Solanum tuberosum* L. cv. Bora Valley. *J. Ethnopharmacol.* **118**:396–404.

Zimmermann, R., Strauss, J. G., Haemmerle, G., Schoiswohl, G., Birner-Gruenberger, R., Riederer, M., Lass, A., Neuberger, G., Eisenhaber, F., Hermetter, A. and Zechner, R. (2004). Fat mobilization in adipose tissue is promoted by adipose triglyceride lipase. *Science* **306**:1383–1386.