Review Article **OPEN ACCESS**

Natural products and body weight control

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Abstract
The purpose of the review was to summarise the effect of some commonly available natural products used for body weight management. We collected data from PubMed and scientific journals. There are numerous publications on this topic, however we have summarized the most commonly available and potent natural products from recent 53 publications. The natural products analyzed in this paper include catechins, capsaicin, conjugated linoleic acid, fucoxanthin, soy isoflavone, glabridin, astaxanthin and cyaniding-3-glucoside. These natural products are effective and safe for body weight management. Further studies need to be conducted to investigate the mechanism of action, metabolism, long term safety and side effects of these natural products, as well as interactions between these natural products with dietary components.

Keywords: Natural products, obesity, catechins, capsaicin, conjugated linoleic acid, fucoxanthin, soy isoflavone, glabridin, astaxanthin, cyaniding-3-glucoside.

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Introduction
Obesity is a worldwide epidemic with prevalence increasing year on year. WHO estimated that by 2015, there will be more than 1.5 billion people overweight, incurring health costs beyond $117 billion per year in the US alone. The opportunities for scientifically substantiated food products used for body weight management are impressive. Diet and lifestyle changes remain the cornerstone of therapy for obesity, but the resultant weight loss is often small and long-term success is extremely uncommon and disappointing. Drug therapy has been considered for individuals with a body mass index (BMI) greater than 30 kg/m^2, or 25 to 30 kg/m^2 if person suffers from other co-morbidities. Antiobesity agents can be used for some patients to help achieve and maintain meaningful weight loss, but these pharmaceuticals are of limited effectiveness in the face this worldwide problem. At present, only two drugs, orlistat and sibutramine, are approved for long-term use in the treatment of obesity, and each of these typically promotes 5% to 10% loss of total body weight [1]. Although very effective in promoting clinically meaningful weight loss, reduction in waist circumference and improvements in several metabolic risk factors, rimonabant, a cannabinoid-1 receptor antagonist, was withdrawn from the market due to concerns about its safety, including risk of suicide and seizures [2, 3].

Natural ingredients are effective and practical remedies for treatment of obesity, and relatively safe. The most popular supplements are catechins, capsaicin, soy isoflavone, fucoxanthin, glabridin, conjugated linoleic acid, astaxanthin, cyaniding-3-glucoside etc.

Catechins
Catechins are a group of polyphenolic compounds found in tea [4]. In general, green tea contains about 30% w/w catechins in the dry tea leaves. The major catechins, which are found in abundant proportion, are (−)-epigallocatechin gallate (EGCG) (Fig. 1A), (−)-epigallocatechin (Fig. 1B), (−)-epicatechin (Fig. 1C) and (−)-epicatechin gallate (Fig. 1D), with EGCG amounting to over 60% of the total catechins [5]. Other compounds obtainable in green tea are the flavonols (quercetin, kaempferol and rutin), caffeine, phenolic acids, theanine, and flavour compounds. Black tea contains less tea catechins (3–10% w/w), while theaflavins and thearubigins account for about 2–6% w/w and 10–20% w/w of the dry weight of the tea leaves, respectively [4].

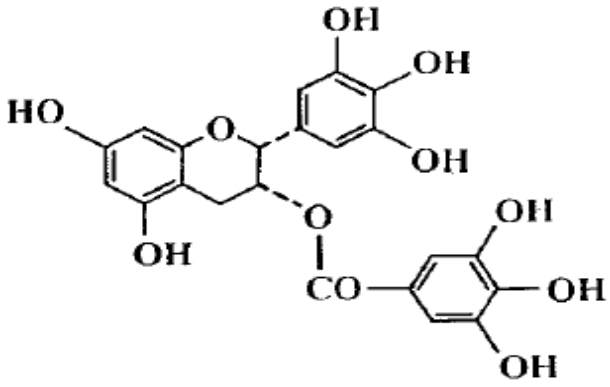

Fig. 1A (–)–epigallocatechin gallate

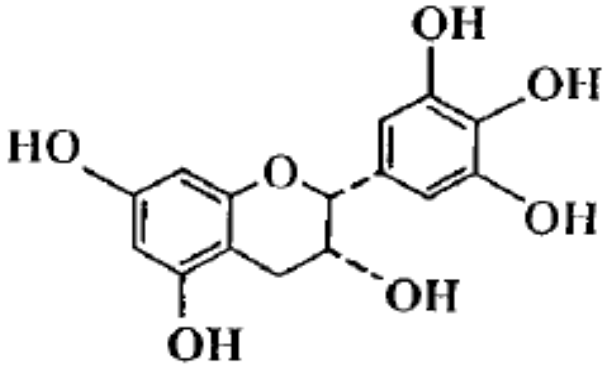

Fig. 1B (–)-epigallocatechin

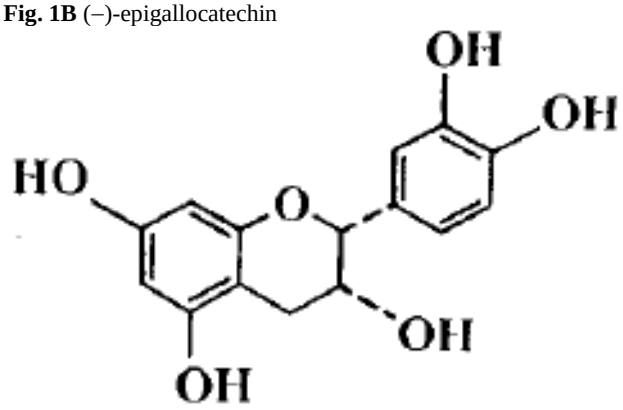

Fig.1C (–)-epicatechin

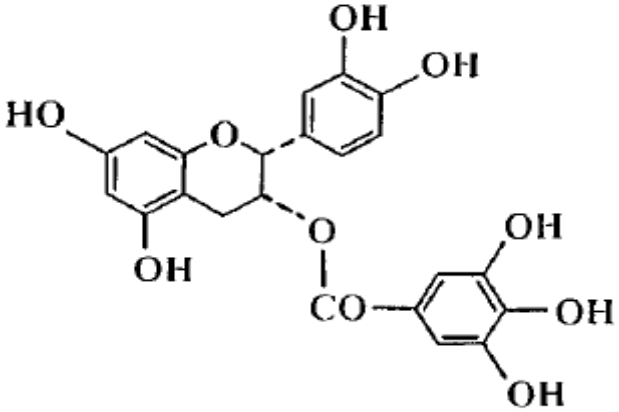

Fig. 1D (–)-epicatechin gallate

It is known that green tea possesses various biological functions. Ingestion of high dose catechins results in loss of body and adipose tissue weights, and regulation of lipid metabolism [6].

Green tea and its extracts have been shown to increase energy expenditure and fat oxidation in the short term in both animals and humans. In a randomized, controlled trial, 60 Thai obese subjects (BMI > 25kg/m^2) were randomized into green tea and control groups. Body weight reduction, resting energy expenditure and respiratory quotient were significantly different between the two groups ($p<0.05$) at 8 weeks, with no significant differences on satiety score, food intake and physical activity. Urine vanillylmandelic acid was significantly higher in green tea group than in control at 12 weeks ($p<0.05$) [7]. Green tea extract along with a low-energy diet resulted in modest weight loss, improved HDL-cholesterol and blood pressure, but had no effect on other parameters [8]. Eva *et al*. suggested that weight maintenance after 7.5% body-weight loss was not affected by green tea, and that habitual caffeine consumption affected weight maintenance in the green tea treatment [9]. EGCG apparently promoted fat oxidation, but its fat-reducing effect could be explained by its effect in reducing diet digestibility [10].

Green tea extract exhibits marked inhibition of digestive lipases *in vitro*, which is likely to reduce fat digestion in humans [11]. Catechins prevent obesity through the suppression of adipocyte differentiation [12]. EGCG can act directly to inhibit differentiation of preadipocytes and to induce apoptosis of mature adipocytes [13] as indicated by formation of DNA fragments which was induced by EGCG in dose-dependent manners [14].

Capsaicin

Capsaicin is the active ingredient of hot pepper, it not only adds spice to foods, but can cause the body to heat up, promoting calorie expenditure. It is a potent afferent nerve stimulant.

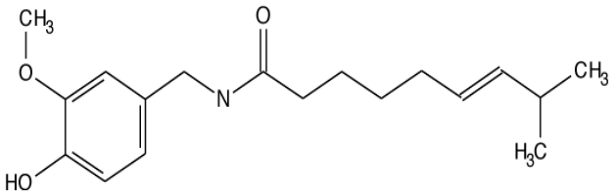

Fig. 2 Capsaicin

Epidemiological data revealed that the consumption of foods containing capsaicin was associated with a lower prevalence of obesity. In experimental studies, when oral capsaicin was provided to rodents as 0.014% of the diet; a dose equivalent to that ingested by rural Thai people, there was a significant 24% and 29% reduction in the weight of visceral (peri-renal) fat, but no effect on total caloric intake [15]. Systemic treatment with capsaicin or its analogue is an accepted experimental method to induce functional ablation of the capsaicin-sensitive afferent nerves at different body sites [16]. Such functional impairment retarded body weight gain and reduced total body fat in rats. The capsaicin (vanilloid) receptor agonist (resiniferatoxin) reduced body fat and body weight and

improved glucose tolerance in obese rats [17, 18]. Although the effect on subcutaneous fat was not assessed, these two studies suggest the possibility that oral capsaicin treatment might regulate adipose tissue distribution. Since capsaicin absorbed from the gut lumen is almost completely metabolized before reaching the general circulation, a direct effect of oral capsaicin on adipose tissue at remote sites is unlikely. In support of this is also the fact that repeated administration of oral capsaicin functionally desensitized the intestinal mucosal but not the corneal afferent nerves. Taking this information into account, if oral capsaicin could regulate adipose tissue distribution, the process might involve the intestinal mucosal afferent nerves [19, 20]. Capsaicin-sensitive intestinal mucosal afferent mechanism plays a role in regulating body fat distribution.

In an intervention study, 34 subjects were randomized to take either placebo or supplements containing the non-burning pepper analog dihydrocapsiate (DCT) for 28 days. Two dosage levels of DCT were tested. At the beginning and end of the study, body weight and body fat were assessed, and energy expenditure (heat production) in each subject after he or she consumed one serving of the test meal was determined. Results showed that energy expenditure was significantly increased in the group consuming the higher amount of DCT. In fact, it was almost double that of the placebo group. This suggests eating this pepper-derived substance that doesn't burn can have the same potential benefit as hot peppers at least in part by increasing food-induced heat production. They were also able to show that DCT significantly increased fat oxidation, pushing the body to use more fat as fuel [21].

Cell culture studies showed that capsaicin has a direct effect on adipocytes [22]. Oral capsaicin significantly increases transient receptor potential vanilloid type-1 (TRPV1) channel expression as well as TRPV1 messenger ribonucleic acid (mRNA) in visceral adipose tissue [23].

Fucoxanthin

Fucoxanthin, a member of the carotinoid family, is extracted from edible seaweed and undaria pinnatifida, etc.

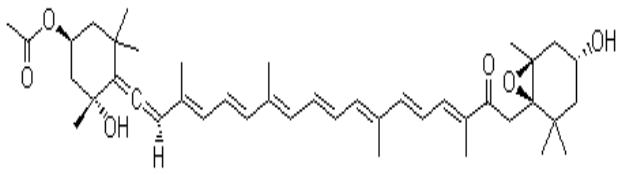

Fig. 3 Fucoxanthin

Animal studies showed that fucoxanthin has anti-obesity activity. It may do this through mitochondrial uncoupling protein 1 (UCP1) expression in white adipose tissues (WAT). UCP1 is usually expressed only in brown adipose tissue (BAT) and it is a key molecule for metabolic thermogenesis to avoid an excess of fat accumulation. However, there is little BAT in adult humans. Therefore, UCP1 expression in tissues other than BAT is expected to reduce abdominal fat. In the fucoxanthin-fed mice, WAT weight significantly decreased and UCP1 was expressed in the WAT, while there was no difference in WAT weight and little expression of UCP1 in the glycolipids-fed mice. This result indicates that fucoxanthin upregulates the expression of UCP1 in WAT, which may contribute to reducing WAT weight [24]. Combination of fucoxanthin and fish oil was shown to be more effective for attenuating the weight gain of WAT than feeding with fucoxanthin alone [25]. The anti-obesity effect of fucoxanthin was increased by mixing fucoxanthin with medium-chain triacylglycerols. This may due to the increase in the absorption rate of fucoxanthin by medium-chain triacylglycerols [26]. The anti-obesity effect of fucoxanthin could be mediated by altering lipid-regulating enzymes and UCPs in the visceral fat tissues and plasma adipokine levels. In epididymal adipose tissue of fucoxanthin-fed mice, adipocyte sizes and mRNA expression of lipogenic and fatty acid beta-oxidation enzymes were significantly down-regulated in a dose-dependent manner. Plasma leptin levels were significantly lower in the fucoxanthin groups than in the control group, while the adiponectin level was elevated [27]. Fucoxanthin regulates mRNA expression of inflammatory adipocytokines involved in insulin resistance, iNOS, and COX-2 in WAT and has specific effects on diabetic/obese KK-A(y) mice, but not on lean C57BL/6J mice [28]. Randomized controlled trails are needed to confirm if fucoxanthin has an anti-obesity activity in humans.

Soy Isoflavone

Soy isoflavones are secondary metabolites formed during soybean growth, they have a similar structure with estrogen; they have a non-steroidal structure but possess a phenolic ring that enables them to bind the estrogen receptor (ER) and act as estrogen agonists, therefore soy isoflavones are also called phytoestrogen.

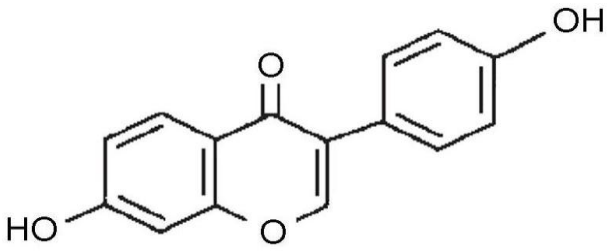

Fig. 4 Soy isoflavone

Studies in humans and rodents support the hypothesis that soy isoflavones (phytoestrogens) may be beneficial for the prevention of obesity and diabetes by affecting glucose and lipid metabolism [29, 30]. In fact, estradiol itself is a well known modulator of glucose homeostasis, which also affects obesity development. For instance, postmenopausal women develop visceral obesity and insulin resistance and are at an increased risk of diabetes, but estrogen

replacement therapy normalizes these abnormalities [31].

Postmenopausal Japanese women treated for 24 weeks with 100 mg/day of soy isoflavones exhibited a reduction in fat mass and body mass index [32]. A 6-month clinical trial was conducted to compare the effects of isoflavones with that of conjugated estrogens on blood glucose, insulin, and lipid profiles in postmenopausal Taiwanese women. The study revealed that during fasting, both glucose and insulin levels were significantly reduced by soy isoflavones (100 mg/day) and conjugated estrogens (0.625 mg/day) [33]. In contrast to the above mentioned trials, a number of studies reported an absence of beneficial effects of soy isoflavones on classical metabolic parameters such as bodyweight, serum lipid profiles, fat mass, blood glucose and insulin profiles [34,35]. These discrepancies make it difficult to draw firm conclusions regarding the beneficial effect of soy isoflavones on these parameters. When comparing these different clinical trials, the underlying causes of conflicting results are probably related to the variability of experimental designs and exposition protocols (route of administration, composition, dose, and duration), the capacity of individuals to produce equol and the genetic susceptibility. Clearly more standardized studies are needed to further evaluate these putative beneficial effects of soy isoflavones on body weight management.

Conjugated Linoleic Acid

Conjugated linoleic acid (CLA) is mainly derived from ruminant animals and dairy products, however commercially available CLA is synthesized. CLA has different isomers, the main ones are c9,t11 and t10,c12.

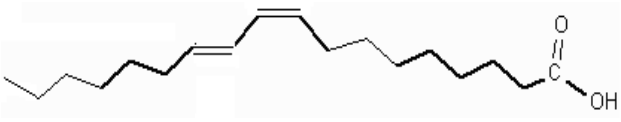

Fig. 5A c9,t11-conjugated linoleic acid

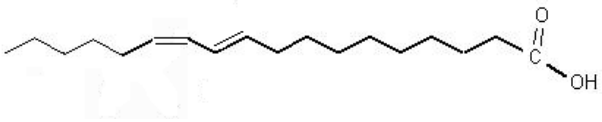

Fig. 5B t10,c12-conjugated linoleic acid

The anti-obesity effects of CLA have been supported in studies on animals when given at high enough doses [36-38]. In particular, dietary CLA decreases body fat and increases lean body mass in animals depending on the isomer, dose, and duration of treatment. Most of these studies used synthetically prepared CLA, a mixture of different isomers. Commercially prepared CLA supplements usually contain two major isomers, c9,t11 and t10,c12 in equal amounts. The t10,c12 isomer may be the active form affecting energy metabolism, weight gain and body fat deposition in animals, as indicated by the results of two studies in which mice were supplemented with CLA mixtures varying in the ratio of t10,c12 and c9,t11 isomers. Studies that have not shown a significant reduction in weight gain in animal model generally are those having applied either low levels (≤0.5% in the diet) of CLA or CLA mixtures that contained low concentrations of the t10,c12 isomer [39].

In a randomized controlled trial (RCT), 60 overweight or obese subjects (body mass index 25–35 kg/m^2) were divided into five groups receiving placebo (9 g olive oil), 1.7, 3.4, 5.1 or 6.8 g CLA (ratio of t10,c12 and c9,t11 was 1:1) per day for 12 weeks, respectively. No differences among treatment groups were found regarding adverse events. Repeated-measures analysis showed that a significantly higher reduction in body fat mass (BFM) was found in the CLA groups compared with the placebo group (P=0.03). The reduction of body fat within the groups was significant for the 3.4 and 6.8 g CLA groups (P =0.05 and P=0.02, respectively). No significant differences among the groups were observed in regards to lean body mass, body mass index, blood safety variables or blood lipids. The data suggests that CLA may reduce BFM in humans and that no additional effect on BFM is achieved with doses higher than 3.4g CLA/d [40]. However, two other long-term (1 and 2 years) RCT showed no significant difference in body weight and BFM between supplementation of 3.4 g/d of CLA (mixture of 40% t10,c12 and 40% c9,t11 in triacylglycerol form) and placebo groups in healthy obese and overweight subjects [41, 42].

Potential anti-obesity mechanisms of CLA include decreased pre-adipocyte proliferation and differentiation into mature adipocytes, decreased fatty acid and triglyceride synthesis, and increased energy expenditure and energy loss in the excreta [43]. CLA induces ectopic expression of uncoupling protein 1 (UCP1) in white adipose tissue (WAT), which may contribute to increased energy expenditure and weight loss [44].

CLA does have a beneficial effect on body weight control, however this depends on the dosage and levels of CLA isomers. Studies in humans and animals have demonstrated that t10,c12-CLA is the anti-adipogenic isomer of CLA.

Glabridin

Glabridin is the major flavonoid of licorice (*Glycyrrhiza glabra*). Human and animal studies have shown that glabridin from licorice flavonoids has a beneficial effect on body weight control.

KK-A^y mice aged 6 weeks were assigned to 5 groups (n=6), and fed a high-fat diet containing 0 (control), 0.5%, 1% or 2% of licorice flavonoids (containing 1.2% of glabridin), or 0.5% CLA for 4 weeks. Compared with the control group, body weight gain and weights of abdominal adipose tissues were suppressed ($p<0.05$) in 2% licorice flavonoids group, and blood glucose levels after 2 and 4 weeks were decreased in all three licorice flavonoids groups. CLA suppressed body weight gain ($p<0.05$), however it increased blood glucose level ($p<0.05$) after 2

weeks compared with the control group. Licorice flavonoids also stimulated human adipocyte differentiation *in vitro*. These results indicate that licorice flavonoids have abdominal fat-lowering and hypoglycemic effects, possibly mediated via activation of peroxisome proliferator-activated receptor-γ (PPAR-γ) [45]. Gene expression of beta-oxidation enzyme was up-regulated and fatty acid synthesis enzyme was down-regulated in the 2% licorice flavonoids group in C57BL/6J mice liver. These findings suggest that licorice flavonoids prevent and ameliorate diet-induced obesity via the regulation of lipid metabolism-related gene expression in the liver [46].

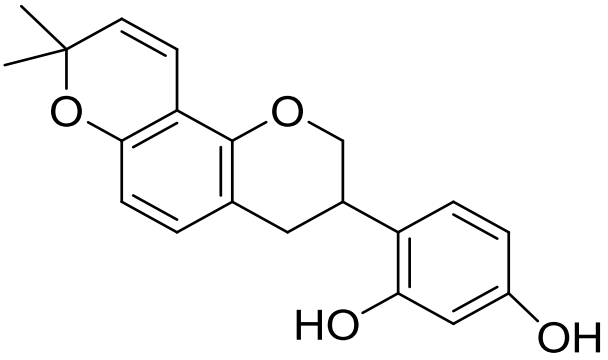

Fig. 6 Glabridin

In a placebo-controlled, double-blind trail, 103 overweight subjects aged 24-64 years (BMI 24-30) were divided into licorice flavonoids (n=51) and placebo (n=52) groups. Licorice flavonoids group ingested 300 mg/day of licorice flavonoids for 12 weeks. Body weight and BMI showed significant differences ($P<0.05$) between the licorice flavonoids group and the placebo group at each time-point. To confirm the safety of licorice flavonoids for practical use, the authors have also conducted a placebo-controlled, double-blind safety study in 40 overweight subjects who they were divided into licorice flavonoids (1800mg/day) and placebo groups for 4-weeks. Licorice flavonoids group exhibited a significant weight-reducing effect, and no clinically significant adverse events were observed during the 4-week study period [47].

Astaxanthin

Astaxanthin is a natural antioxidant carotenoid that occurs in a wide variety of living organisms. It has many highly potent pharmacological effects, including antioxidant, anti-tumor and anti-cancer, anti-diabetic, and anti-inflammatory activities.

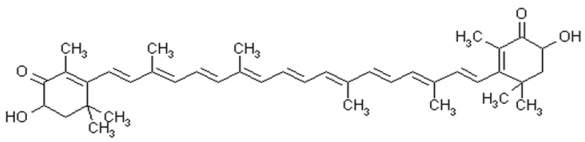

Fig. 7 Astaxanthin

Recent animal studies have also shown that astaxanthin may have a beneficial effect on body weight control. Fifty 4 week old female ddY mice were divided into five groups (n=10), normal diet (control group), high-fat diet group (placebo) and the other three groups were high-fat diet supplemented with 1.2, 6, 30 mg/kg body weight of astaxanthin, respectively. Astaxanthin at levels of 6 mg/kg or 30 mg/kg body weight significantly reduced the body weight gain induced by the high-fat diet. In addition, astaxanthin reduced liver weight, liver triacyglycerol, plasma triacyglycerol and total cholesterol [48]. Another study with similar design from the same research group found that astaxanthin treatment stimulated an enhancement of fatty acid utilization in mice [49]. Further studies are warranted to elucidate the mechanisms of astaxanthin on body weight management.

Cynidin-3-Glucoside

Cynidin-3-Glucoside, one of the anthocyanins, is a pigment widespread in the plant kingdom.

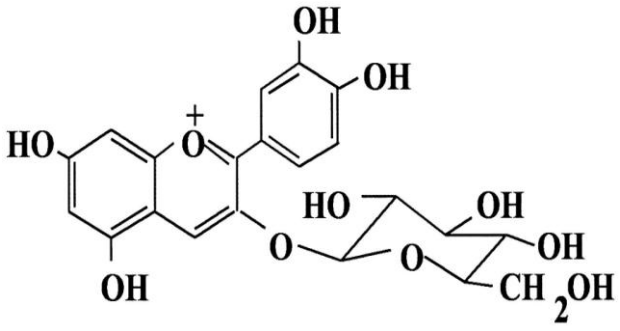

Fig. 8 Cyaniding-3-glucoside

In mice, cyanidin 3-glucoside-rich purple corn color (PCC) significantly suppressed the high fat diet-induced increase in body weight gain, and white and brown adipose tissue weights. PCC suppressed the mRNA levels of enzymes involved in fatty acid and triacylglycerol synthesis and lowered the sterol regulatory element binding protein-1 mRNA level in white adipose tissue [50]. In isolated rat adipocytes, anthocyanins enhanced adiponectin and leptin secretion, and up-regulated the adipocyte specific gene expression without activation of PPARgamma. The gene expression of adiponectin was also up-regulated in white adipose tissue in mice fed an anthocyanin supplemented diet [51]. Anthocyanins also up-regulated the hormone sensitive lipase, and enhanced the lipolytic activity [52].

In human adipocytes, treatment with anthocyanins significantly up-regulated adiponectin and down-regulated plasminogen activator inhibitor-1 and interleukin-6, and also significantly induced uncoupling protein2, acylCoA oxidase1 and perilipin, which are related to lipid metabolism [53].

Conclusions

The potential for natural products as sources of nutraceuticals or drugs to manage body weight is now being realized which including catechins, capsaicin, conjugated linoleic acid, fucoxanthin, soy isoflavone, glabridin, astaxanthin and cyaniding-3-glucoside etc.

Theses natural products are effective and safe on body weight management in both human and animal studies. Further studies need to be conducted to investigate the mechanism of action, metabolism, long term safety and side effect of these natural products, as well as interactions between these natural products with dietary components.

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