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### **Citation**

Yuliana, N. D., Jahangir, M., Korthout, H. A., Choi, Y. H., Kim, H. K., & Verpoorte, R. (2011). Comprehensive review on herbal medicine for energy intake suppression. *Obesity Reviews*, 12(7), 499-514. doi:10.1111/j.1467-789X.2010.00790.x

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**Note:** To cite this publication please use the final published version (if applicable).

## Obesity Management

# Comprehensive review on herbal medicine for energy intake suppression

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Received 4 March 2010; revised 4 May 2010, 3 June 2010; accepted 8 June 2010

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### Summary

The obesity drug development is present not a bright and successful story. So far, drugs reported to be effective, either from synthetic or natural sources, mostly stimulated controversy because of serious adverse effects, which ended with stopping clinical trials or even withdrawal from the market. However, obesity and its comorbidities have become rapidly a major problem in both developed and developing countries. This has encouraged pharmaceutical companies and academia to keep on struggling on developing novel effective but safe obesity drugs, and on characterizing novel obesity drug targets. From existing scientific work on obesity drug discovery and commercial slimming preparations, compounds originating from nature, especially from plants, seem to be the first choice. Traditional belief that herbal medicine is safer than synthetic ones is one of the classical arguments, although scientifically this is not always true (e.g. ban on *Ephedra*). But in general, it has been widely acknowledged that a plant compound, with its unique scaffolds and rich diversity is an unlimited source of novel lead compounds. This paper aims to summarize all works focused on screening plant materials by targeting important pathways related to energy intake regulation, either by *in vivo* or *in vitro* experiments.

**Keywords:** Drugs, energy intake, obesity, plants.

**obesity reviews** (2011) **12**, 499–514

### Introduction

Historically there is little success in anti-obesity drug development because of the low efficiency and undesired side effects (1). Some disappointing cases were also reviewed for agents that were originally tried for more than 70 years such as thyroid extract, dinitrophenol, amphetamine, some noradrenaline reuptake inhibitors, serotonergic agents and fenfluramine/phentermine (2). Currently only one drug is approved in the USA, Canada and Europe for long-term use in obesity, i.e. orlistat, a pancreatic and gastrointestinal (GI) lipases inhibitor. The use of Accomplia (rimonabant), appetite suppressant acting as cannabinoid (CB1) receptor antagonist previously approved in European Union since June 2006, was suspended by the European Medicines

Agency in October 2008. The decision was taken after an extensive review on its safety, which mentioned that the risk of psychiatric side effects, including depression, sleep disorders, anxiety and aggression, was doubled in patients taking Accomplia, compared with patients taking placebo. Apparently the CB1 receptor is a difficult target for treating obesity. Surprisingly, in January 2010 European Medicines Agency also recommended to suspend the use of another appetite suppressant, sibutramine, a monoamine reuptake inhibitor. The data from Sibutramine Cardiovascular Outcome Trial showed that there is an increased risk of serious, non-fatal cardiovascular events (e.g. stroke, heart attack) in patient taking sibutramine compared with placebo, prolonging the list of the dissatisfying stories of obesity drug development.

Nature is the most productive source of leads for novel drugs against various pharmacological targets. Of a number of reviews describing the use of dietary supplements for weight loss management, agents from natural sources are predominant, although the efficacy is stated as not convincing (3–9). Few of them specifically deal with the potential of herbal medicine (3,7,9). The mechanisms of action of medicinal plants on obesity can be divided as direct and indirect action (3). Medicinal plants with direct action combat obesity by stimulating the rate of metabolism and suppressing the appetite. Iodine, synephrine, xanthine and caffeine are active principals found in several medicinal plants that stimulate metabolism. Plants may suppress appetite by their high dietary fibre content, but the effect will only be achieved at high dose use. Indirect mechanisms that might be useful to treat obesity are diuretics and central nervous system (CNS) suppressants, although the first type only affects the weight by lowering the body water content (3).

As obesity results from the imbalance between energy intake and energy expenditure several strategies can be applied for obesity drug development; reduction of energy intake by appetite suppression; inhibition of nutrient absorption; increase of energy expenditure; and modulation of fat (10). Food restriction is the first line treatment of obesity (11). A small increase of calories as 20–30 kcal d<sup>-1</sup>, which is not compensated by a proper increase in energy expenditure, within several years may raise the body weight significantly. This will lead to obesity. The phrase ‘If human beings are the most intelligent life force on this planet, why is it that they cannot adjust their (eating) behaviour by the very small amounts which would be required for weight stability rather than weight escalation?’ (12) underlines that appetite control is crucial for long-term regulation of body weight.

In this paper, plants reported for energy intake suppressant activity are reviewed and grouped based on the two mechanisms involved; appetite regulation and inhibition of nutrient absorption. The efficacy and safety are also discussed.

## Energy intake reduction

### Appetite regulation

Approximately 40 orexigenic and anorexigenic hormones, neuropeptides, enzymes, other cell signalling molecules and their receptors are involved in a complex human appetite and satiety regulation (1). These abundant signalling molecules are positively or negatively correlated with each other by mechanisms, which are still not fully understood.

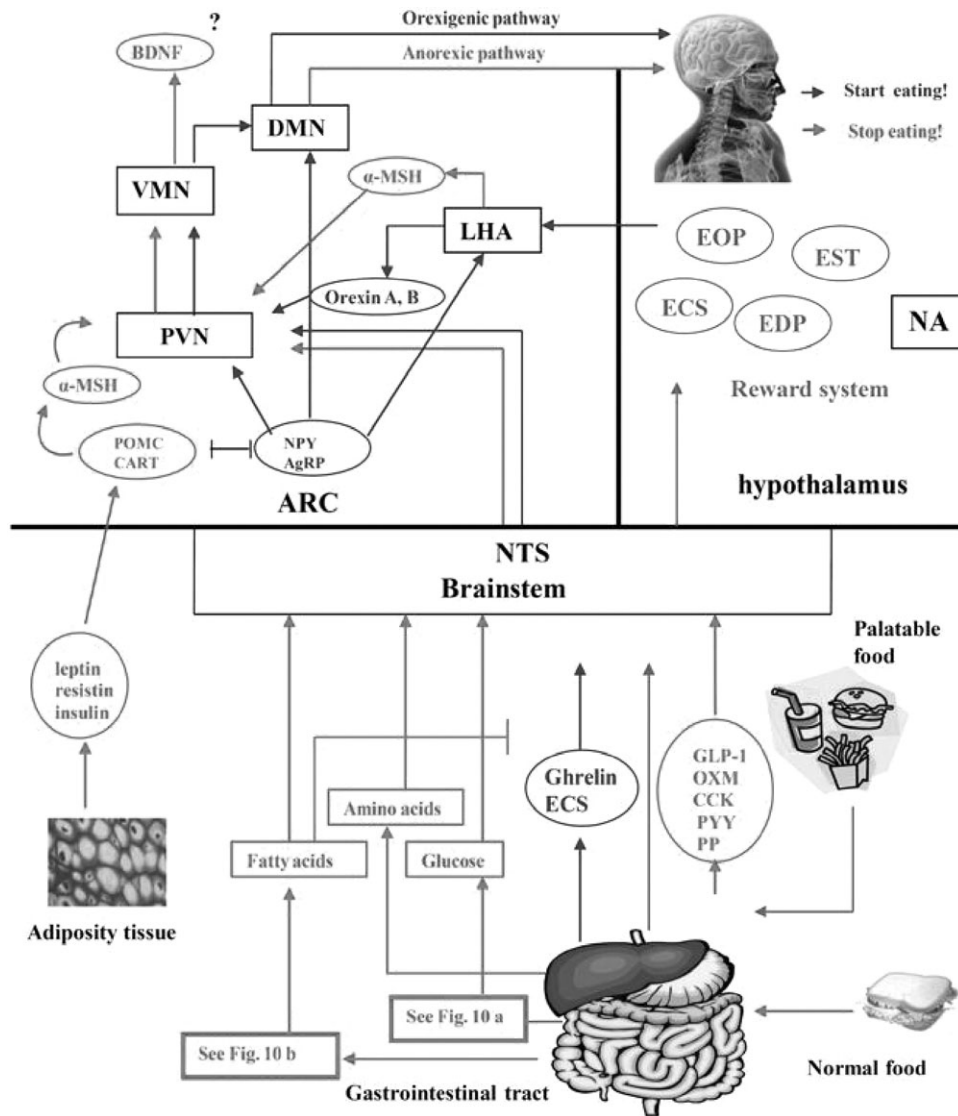
The hunger and satiety signalling molecules are produced centrally in the brain and peripherally in, e.g. the digestive tract, adipose tissue and liver (13,14). The most important part of the brain responsible for appetite regulation is the hypothalamus arcuate nucleus (ARC). An illustration of

parts of the brain, neurons and peripherally secreted hormones that are important for appetite regulation, and their interaction is presented in Fig. 1. The ARC and brainstem neurons receive and translate information from peripheral hormones about acute nutritional status and adiposity level, while neural and endocrine signalling from GI tract regulate appetite on the short term (15). The ARC contains the orexigenic neurons neuropeptide Y (NPY) and agouti-related protein (AgRP) (16); and anorexigenic neuron pro-opiomelanocortin (POMC) – cocaine-amphetamine-regulated transcript (CART) (17). Leptin and insulin regulate both types of ARC neurons by inhibiting NPY and stimulating POMC (18), beside this, NPY/AgRP – POMC/CART inhibitory cross-talk also exists (16,19). The other orexigenics, orexin A and B, are expressed in the lateral hypothalamic area (LHA). Both are inhibited by POMC/CART and stimulated by NPY (13).

The peripheral signals enter the ARC via the brainstem area, the nucleus tractus solitarius (14,20). These peripheral signals encode information about acute nutritional state and adiposity. Leptin transduces the size of adipose tissue to the brain. However, targeting on this pathway is not a choice as the obese mostly suffer from leptin resistance. Short-term appetite regulation by signals from GI tract reflects the postprandial satiety and hunger felt before a meal, and might be a more reasonable target for obesity treatment (15). The GI tract is considered as the largest endocrine organ in the body, which secretes more than 20 distinct hormonal regulatory peptides, mostly sensitive to nutritional status of the gut, thus mediating a short-term appetite regulation (15). Cholecystokinin (CCK), glucagon-like peptide-1 and peptide YY (3–36) (PYY(3–36)) seem to be the only ideal models of anorexigenic signals produced in the GI tract, as other hormones do not show any responses in knock-out animals or antagonist activity (14). Ghrelin, the only orexigenic GI peptide, opposes leptin action in NPY/AgRP (21), while the CCK anorexigenic effect is probably enhanced by leptin/insulin (22).

The signals from both pathway are affecting the second level of the hunger-satiety neuronal signalling area; paraventricular nucleus (PVN), perifornical area and LHA (13,23) to give an orexigenic or anorexic response, depending on which pathway is activated (13,24).

Prolonging consumption of palatable food (fat- and sugar-rich diet) may alter the regulation of abovementioned appetite regulating peptide expression, as has been reviewed elsewhere (24). With palatable food, registration of the attractive taste of the food activates the reward system and interferes with hypothalamic appetite regulation. Satiety signals are increased, but hunger signals are either increased (e.g. ghrelin and NPY), or decreased (e.g. orexins and AgRP). Beside, palatable food might also induce resistance to some satiety signals such as leptin, insulin and CCK, leading to over-eating. Three neurotrans-



**Figure 1** Central and peripheral appetite regulation. Area of appetite regulation in the brain: NTS (nucleus tractus solitarius), ARC (arcuate nucleus), NA (nucleus accumbens), PVN (paraventricular nucleus), LHA (lateral hypothalamic area), VMN (ventromedial nucleus), DMN (dorsomedial nucleus). Orexigenic neuropeptides: NPY (neuropeptide Y), AgRP (agouti-related protein), orexin A and B. Anorexigenic neuropeptides: POMC (pro-opiomelanocortin), CART (cocaine- and amphetamine-regulated transcript),  $\alpha$ -MSH ( $\alpha$ -melanocyte-stimulating hormone), BDNF (brain-derived neurotrophic factor, detail pathway to be determined). Peptides involved in reward systems: ECS (endocannabinoids), EOP (endogenous opioids), EST (endogenous serotonin), EDP (endogenous dopamine). Peripheral orexigenics from gastrointestinal tract: ghrelin, ECS (endocannabinoids). Peripheral anorexigenics: GLP-1 (glucagon-like peptide-1), OXM (oxyntomodulin), PYY (peptide YY), PP (pancreatic polypeptide). Hormones signalling an adiposity size: leptin, resistin, insulin. Red arrow: anorexigenic pathway; Blue arrow: orexigenic pathway; Green arrow: reward system.  $-$ , inhibit;  $\vdash$ , inhibitory crosstalk.

mitter systems important for food rewarding response are located between the nucleus accumbens and lateral hypothalamus: the opioid, dopamine and serotonin system (24). The cannabinoid system was changed to also influence the feeding behaviour via this reward circuitry (25). Synergism between the cannabinoid and the opioid system has been reported as well (26)

The existence of fuel sensing in CNS has been reviewed (27). Some specific neurons in ventromedial, ARC and nucleus tractus solitarius have been found to be sensitive to

a very narrow fluctuation of glucose level in CNS. A specific neuron subset gives positive feedback while the other gives negative feedback to an increase of glucose level, resulting in food intake reduction (28). Glucose, lipids and fatty acids sensing exist not only in the hypothalamus, but also particularly in the melanocortin system (29). Reduction in hypothalamic AMP-activated kinase activity is also found to decrease food intake (30).

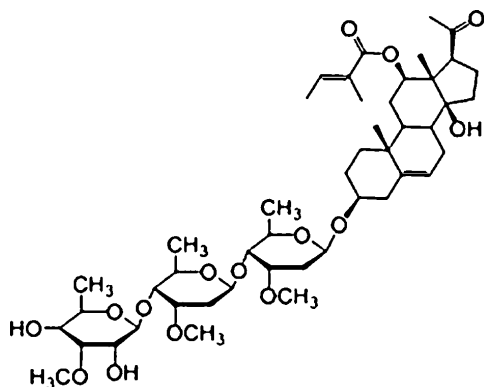
The mammalian target of rapamycin (mTOR) protein, a serine-threonine kinase, which regulates cell-cycle progres-

sion and growth, was found to be expressed in 90% of ARC NPY/AgRP neurons and in 45% of ARC POMC/CART. Centrally administered L-leucine increase mTOR expression followed by food intake and body-weight reduction. Leptin also modulates hypothalamic mTOR signalling, and leptin's effect on food intake is mTOR-dependent (31).

Botanicals with appetite suppressant activity are summarized below:

#### *Hoodia* sp.

The genus *Hoodia* (Apocynaceae) is a member of the stapeliads, a group of stem succulents widely distributed in South Africa and Namibia. *Hoodia* plants are used by the San people of South Africa as an appetite suppressant, thirst quencher, a cure for abdominal cramps, haemorrhoids, tuberculosis, indigestion, hypertension and as anti-diabetes medicine (32). The finding of several *Hoodia* sp. compounds having anti-obesity activities has resulted in more than 20 patents, including on the active compound responsible for the appetite suppressant activity, 3 $\beta$ -[ $\beta$ -d-thevetopyranosyl-(1  $\rightarrow$  4)- $\beta$ -d-cymaropyranosyl-(1  $\rightarrow$  4)- $\beta$ -d-cymaropyranosyloxy]-12 $\beta$ -tigloyloxy-14 $\beta$ -hydroxypregn-5-en-20-one (P57 or P57A53, Fig. 2), which is a minor compound in *Hoodia* extract. Appetite suppressant properties were found in *H. gordonii* and *H. pilifera* (33), but P57 was also identified in *H. currorii*, *H. ruschii* and *H. parviflora* (34). Intracerebroventricular injection of P57 in rats resulted in reduced food intake by 50%–60%, but no effect was found when P57 was intraperitoneally injected, suggesting that this compound acts on the CNS. As there was an increase of hypothalamic Adenosine 5' triphosphate (ATP) content following P57 treatment, the authors presumed that the P57 mechanism of food intake inhibitor is probably via an intervention of ATP sensitive-nutrient and energy sensing activity in the hypothalamus (35). However, reports regarding the safety of long-term administration of *Hoodia* extract are still missing.



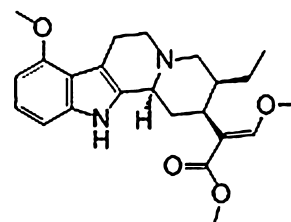
**Figure 2** Appetite suppressant from *Hoodia* sp.: 3 $\beta$ -[ $\beta$ -d-thevetopyranosyl-(1  $\rightarrow$  4)- $\beta$ -d-cymaropyranosyl-(1  $\rightarrow$  4)- $\beta$ -d-cymaropyranosyloxy]-12 $\beta$ -tigloyloxy-14 $\beta$ -hydroxypregn-5-en-20-one (P57 or P57A53).

#### *Benincasa hispida*

*Benincasa hispida* (Cucurbitaceae) is widely consumed as vegetable or as ingredient to make fresh drinks and candy in tropical countries, especially in India and Pakistan. At the dose of 0.2, 0.6 and 1 g kg<sup>-1</sup> body weight, intraperitoneal injection of the fruit methanol extract in male Swiss albino mice, caused decrease in 27%, 38% and 54% of food intake, respectively, but no significant difference in gastric emptying was found between control mice and extract-treated mice (36). The authors suggested that this extract suppresses food intake by targeting central appetite regulation, this is supported by a previous report that *B. hispida* extract showed antidepressant activity in rats and mice (37) probably by a mechanism similar to a serotonin reuptake inhibitor. However, side effects and body-weight loss following administration of this extract were not reported, thus the safety and efficacy of this botanical are questionable.

#### *Mitragyna speciosa*

*Mitragyna speciosa* (Rubiaceae) is an alkaloids-rich plant from Thailand, which leaves have been traditionally used for wound healing, to cure coughing and diarrhoea (38). The main alkaloid is mitragynine (Fig. 3). Total alkaloids extract of young leaves was intraperitoneally injected in male Wistar rats. Acute intraperitoneal administration of 45 and 50 mg extract per kilogram reduced food intake similar to the positive control (40 mg kg<sup>-1</sup> imipramine). The chronic intraperitoneal administration of the extract at 40 mg kg<sup>-1</sup> dose for 60 d also resulted in lower food intake and smaller weight gain compared with saline-treated rats (38). Although there is no further report to confirm whether mitragynine is the responsible active compound, the author proposed the central targeting mechanism of these activities, supported by previous work on pure mitragynine, which showed an interaction with central opioid (39), adrenergic (40) and serotonergic (41) systems in mice. Adverse effects of the long treatment period were not reported in this study. However, this plant might be abused as a result of its euphoric ('coca like') effect and is illegal in Thailand and Australia. Some symptoms like nausea, vomiting, diarrhoea, anorexia, weight loss, hyperpigmentation and psychosis were reported among *Mitragyna* users (42).



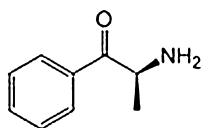
**Figure 3** Mitragynine, the main alkaloid in *Mitragyna speciosa* with anorectic effect.

### Caralluma fimbriata

*Caralluma fimbriata* or *C. ascendens* (Asclepiadaceae), an edible succulent cactus, is indigenously used as a famine food, appetite suppressant and thirst quencher among the tribal population in Western India. It is also consumed as vegetable in the Kolli Hills of South India, or preserved as pickles and chutney in the arid regions of Andhra Pradesh (43). Two capsules, each contains 500 g powder of 40% alcohol extract, were given to 62 volunteers (body mass index greater than 25 kg m<sup>-2</sup>) daily for 60 d. The result showed that the treated group has greater weight loss, i.e. 2.5%, compared with 1.3% of placebo ( $P < 0.05$ ). The experimental group showed a significant reduction in energy and macronutrient intake at the end of the study period. Mild symptoms of the GI tract, such as abdominal distention, flatulence, constipation and gastritis, were reported in 24% of the experimental group subjects and 20% of the placebo subjects (44). The responsible compounds for appetite suppressant activity might be ascribed to pregnane glycosides similar to P57, the active compound from *Hoodia* species, which is also a pregnane glycoside (44). Eleven pregnane glycosides from *Carraluma fimbriata* have been isolated (45). More investigations are needed to identify whether one of them is responsible for the activity and to elucidate the mechanism of action. The fact that the experimental group had a lower intake of sugar and sweets for example, indicates that the reward circuit interruption is involved in the activity (39). A standardized extract of *C. fimbriata* is commercially available (Slimaluma) and has been patented.

### Catha edulis

*Catha edulis* (khat) is widely found in East Africa and south-western Arabia where traditionally most of people have a habit to chew the fresh leaves because of its stimulating effect, besides it is also used to cure melancholia, depression, and to suppress hunger and fatigue (46). After chewing khat, the sensation of hunger of six male subjects was decreased while fullness was increased compared with control but no significant changes in ghrelin and PYY level were observed. The alkaloid cathinone (Fig. 4), the main active ingredient with a structure related to amphetamine, was positively correlated with fullness and negatively with hunger (47). It was also reported that chewing the khat leaves for 2 h significantly delayed the gastric emptying of a radio-labelled semi-solid meal in humans. That cathinone is the active compound is supported by the unpublished *in*



**Figure 4** Cathinone, alkaloid from *Catha edulis* with anorectic effect.

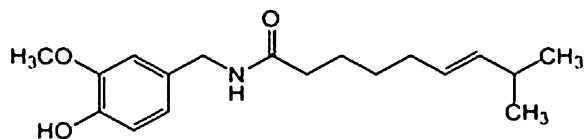
*vitro* experiment that cathinone causes relaxation of the rat stomach (48). There is no further report that explains the possible central or peripheral anorectic mechanism of khat. Some papers reported the adverse effect of chewing khat in human, such as insomnia, hyperthermia, mydriasis and endocrinological disturbances (49). Cathinone may cause cardiovascular complications, increased blood pressure and heart rate via noradrenaline (norepinephrine) release from peripheral neurons similar to the effects of amphetamine (46,50).

### Capsicum annuum

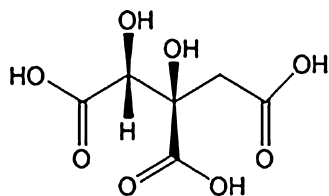
Capsaicin (Fig. 5), the main pungent compound of hot red pepper, is commonly used as food ingredient. A study on its effect on food intake was conducted by including red pepper into a standardized breakfast meal (% energy: protein 18, fat 39, carbohydrate 43) and appetizer (% energy: protein 15, fat 29, carbohydrate 56). It was found that red pepper fortification in breakfast meals decreased protein intake, fat intake, and desire to eat in the subsequent meal while satiety and fullness was not significantly changed (51). The authors assumed that this effect correlated with sympathetic nervous system activation in the presence of capsaicin (51). A similar study was performed with 30 subjects who were used to eat spicy foods, to assess whether the decrease on energy intake was due to a sensory or GI satiety effect of capsaicin, because in the first study capsaicin was given orally as red pepper. In this study, capsaicin was given in a capsule form, which was swallowed with 200 mL tomato juice, or capsaicin was incorporated in 200 mL tomato juice (52). The result showed that the reduction in energy intake was related to a change in food choices as the carbohydrate-rich foods and less-fat-rich food consumption were preferred by the subjects, while weight of food intake was unchanged, but the satiety sensation was increased (52). Capsaicin-containing lunch was also found not to affect satiety, energy expenditure and plasma PYY concentration, but increased plasma glucagon-like peptide-1 while plasma ghrelin tended to decrease (53).

### Garcinia cambogia

The dried fruit rind of *G. cambogia* has been used in many Southeast Asian countries as food preservative, flavouring



**Figure 5** Capsaicin, the main pungent compound from *Capsicum annuum*.

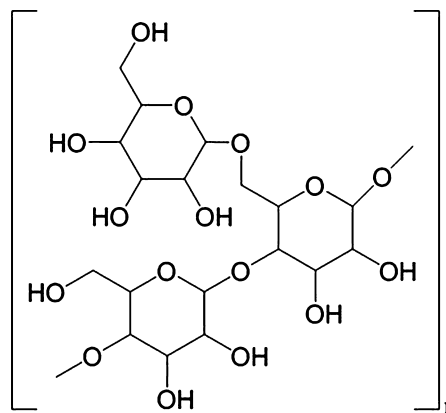


**Figure 6** HCA ((-)-hydroxycitric acid), appetite suppressant from *Garcinia cambogia*.

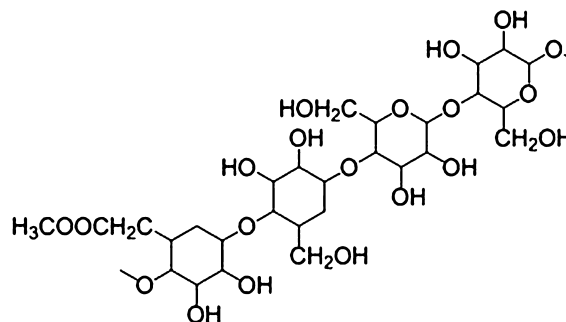
and carminative. Recently it was introduced to the market worldwide as dietary supplement for weight loss (54). The primary acid principle in the fruit rind is (-)-hydroxycitric acid (HCA, Fig. 6), which was found to be up to 30% of fruit rind weight (55). Experimental animals fed by HCA-containing *G. cambogia* extract showed suppressed appetite and body fat accumulation. There are several suggestions for the mechanism. HCA has been reported as a competitive inhibitor of ATP citrate lyase. By inhibiting this enzyme, HCA is suggested to divert carbohydrates and fatty acids into hepatic glycogen, which will be followed by satiety signalling to the brain, resulting in suppression of appetite (55). It was also previously reported that HCA increases serotonin release in rat brain cortex *in vitro* (56). This finding is further supported by the more recent report that HCA inhibited the time-dependent uptake of serotonin similar to the well-known serotonin receptor re-uptake inhibitors fluoxetine and clomipramine. The theory that an increase of serotonin brain level takes part in appetite suppression may provide information on the mechanism of appetite suppression induced by HCA (57). No adverse effects were observed in their study, and in their unpublished results it was shown that HCA supplementation over 8 weeks increases serum serotonin levels significantly in human volunteers, showing good bioavailability of HCA. HCA is not detected in the brain suggesting that the use of HCA will not give a side effect on the CNS (58). High dose of HCA-containing *G. cambogia* (102 mmol HCA per kilogram diet and higher) caused potent testicular atrophy and toxicity in rats (54). Administration of *G. cambodia* extract at recommended dose levels for human use does not show any significant adverse effect on serum testosterone and blood parameters (59). The studied extract dose was 1667.3 mg d<sup>-1</sup> equivalent to 1000 mg HCA per day. Commercial HCA preparations are reported to have in average 25 mg HCA per kilogram per day or less (60).

#### Cyamopsis tetragonolobus

Guar gum refers to a water-soluble galactomannan (Fig. 7), extracted from guar bean (*Cy. tetragonolobus*). Currently, Pakistan and India supply 60% of the world production of guar gum (61). Several studies demonstrated the ability of guar gum to reduce the appetite in humans (62,63). It was



**Figure 7** Polysaccharide from *Cyamopsis tetragonolobus* with galactomannan as a major compound, which may have anti-obesity effect by delaying gastric emptying and delaying abdominal fat absorption.

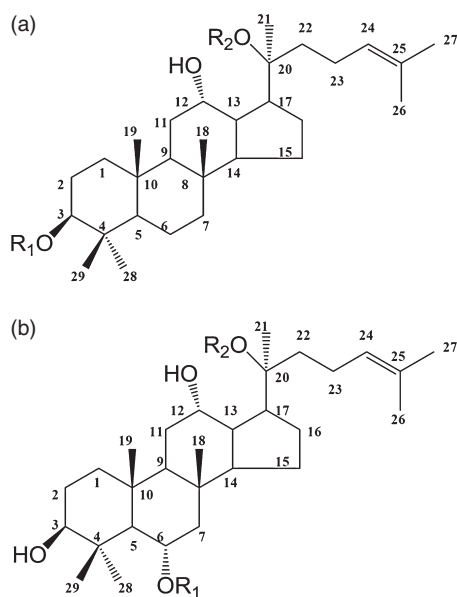


**Figure 8** Polysaccharide from *Amorphophallus konjac* with glucomannan as a major compound, which may have anti-obesity effect by delaying gastric emptying and delaying abdominal fat absorption.

suggested that the mechanism by delaying the gastric emptying time is most likely, although in another study, the addition of guar gum to a semi-solid meal did not affect GI transit time in non-obese human subjects (64). On the contrary, a meta-analysis of randomized trials regarding the efficacy of guar gum to reduce body weight in humans, both published and unpublished, concluded that guar gum is ineffective for reducing body weight and even not recommended as an obesity therapeutic option because of adverse effects (abdominal pain, flatulence, diarrhoea and cramps) (65).

#### Amorphophallus konjac

Similarly to guar bean, *A. konjac* root extracts contains glucomannan (Fig. 8) as a major compound. This plant is especially found in East Asia and promoted as anti-obesity agent as a result of its ability to produce satiety sensation and to reduce intestinal fat absorption (66) as cited by Vasques *et al.* (67). However, short administration of *A.*



**Figure 9** Two type of saponin from red Korean ginseng. (a) Protopanaxadiol type; ginsenoside Rg3 (R1 = Glc-(1-2)-Glc-, R2 = H), ginsenoside Rb1 (R1 = Glc-(1-2)-Glc-, R2 = Glc-(1-6)-Glc-), ginsenoside Rd (R1 = Glc-(1-2)-Glc-, R2 = Glc), ginsenoside Rc (R1 = Glc-(1-2)-Glc-, R2 = Ara(*f*)-(1-6)-Glc-), ginsenoside Rb2 (R1 = Glc-(1-2)-Glc-, R2 = Ara(*p*)-(1-6)-Glc-), ginsenoside Rh2 (R1 = Glc, R2 = H). (b) Protopanaxatriol type; ginsenoside Rg1 (R1 = Glc, R2 = Glc), ginsenoside Re (R1 = Rha-(1-2)-Glc-, R2 = Glc), ginsenoside Rg2 (R1 = Rha-(1-2)-Glc-, R2 = H). Ara, arabinose; Glc, glucose; Rha, rhamnose.

*konjac* extract to hyperlipidaemic type 2 diabetic patients does not result in significant weight loss and food intake (68). A daily administration of *A. konjac* (1.5 g) extract in combination with *G. cambogia* (2.4 g) extract for 12 weeks significantly reduced cholesterol level in obese human subjects but the body weight was not affected (67). Some adverse effects such as flatulence, abdominal pain, esophageal and lower GI obstruction were observed.

### Panax ginseng

Reduction in body weight, food intake and adiposity was observed after administration of crude saponin extract of red Korean ginseng to high-fat diet-induced obesity rats and normal rats. This anorexic effect is proposed via the activation of the central appetite regulation pathway, as the reduction in serum leptin level and hypothalamic NPY expression were observed in both groups (69). In a more recent study, protopanaxadiol and protopanaxatriol type saponins from red Korean ginseng were suggested to be the active compounds (Fig. 9). More specifically, daily intraperitoneal injection of protopanaxadiol (50 mg kg<sup>-1</sup>) in the high-fat diet rats was found to reduce the NPY level of the LHA and PVN, and increased the CCK level of the PVN compared with the control group, while protopanaxatriol reduced the CCK level of the ventromedial hypothalamic

nucleus, suggesting that protopanaxadiol was more effective than protopanaxatriol in reducing appetite. As the NPY level was only reduced in the LHA and PVN and not in the ARC, it is assumed that protopanaxadiol may not inhibit NPY synthesis in the ARC but inhibit the release of NPY or its transport to the PVN instead (70).

### Inhibition of nutrient absorption

Inhibiting fat absorption is the most common target to reduce energy intake as fats contribute more than carbohydrates or proteins to unwanted calories deposition (7). As many as 58 compounds having pancreatic lipase inhibitor activity have been isolated from plant and microbial sources and have been reviewed recently (7). Only a few more recent studies will be mentioned in this review.

It is not clear yet if inhibition of protein-digestive enzymes is advantageous for obesity treatment as high-protein diets are able to prolong satiety (71). Inhibition of enzymes activity related to carbohydrate metabolism, such as  $\alpha$ -amylase, maltase and saccharase, is specifically useful for the treatment of non-insulin-dependent diabetes. But they can be also considered in obesity treatment because usually carbohydrates are the major constituent of human diet. These enzyme inhibitors, which are commercially known as 'starch blockers', delay carbohydrate digestion, reduce postprandial hyperglycaemia, therefore reduce the uptake of glucose into adipose tissue and its further conversion into triacylglycerol. The potential of polyphenols from berries as digestive enzymes inhibitors has been recently reviewed (72). Phenolics have a wide spectrum of digestive enzymes inhibition activity especially against  $\alpha$ -glucosidases and lipases whereas for proteinases, there is no confirmation whether the activity is only due to non-specific protein binding of tannin-like compounds. Figure 10 summarizes the dietary carbohydrate and fat digestion pathways, and where particular enzymes could be blocked by plant-derived inhibitors.

Plants that have been reported to have inhibitory activity against human carbohydrase or lipase are the following:

#### *Lagerstroemia speciosa*

The pentacyclic triterpene corosolic acid (Fig. 11), which was isolated from the EtOAc extract of *Lagerstroemia* leaves showed uncompetitive  $\alpha$ -glucosidase inhibitor activity *in vitro* with IC<sub>50</sub> 3.53  $\mu$ g mL<sup>-1</sup> (73). Additionally, alone and in the mixture with *Morus alba* leaves and *P. ginseng* roots, incorporation of this plant extract into experimental diet at 0.5% of dose induced the expression of rat liver peroxisome proliferator-activated receptor  $\alpha$  (*ppar* $\alpha$ ) mRNA and rat adipose tissue peroxisome proliferator-activated  $\gamma$  (*ppar* $\gamma$ ) mRNA (74). Type 2 diabetic patients receiving 32 and 48 mg of *Lagerstroemia* extract (equal to 0.32 and 0.48 mg of corosolic acid) for 2 weeks showed a

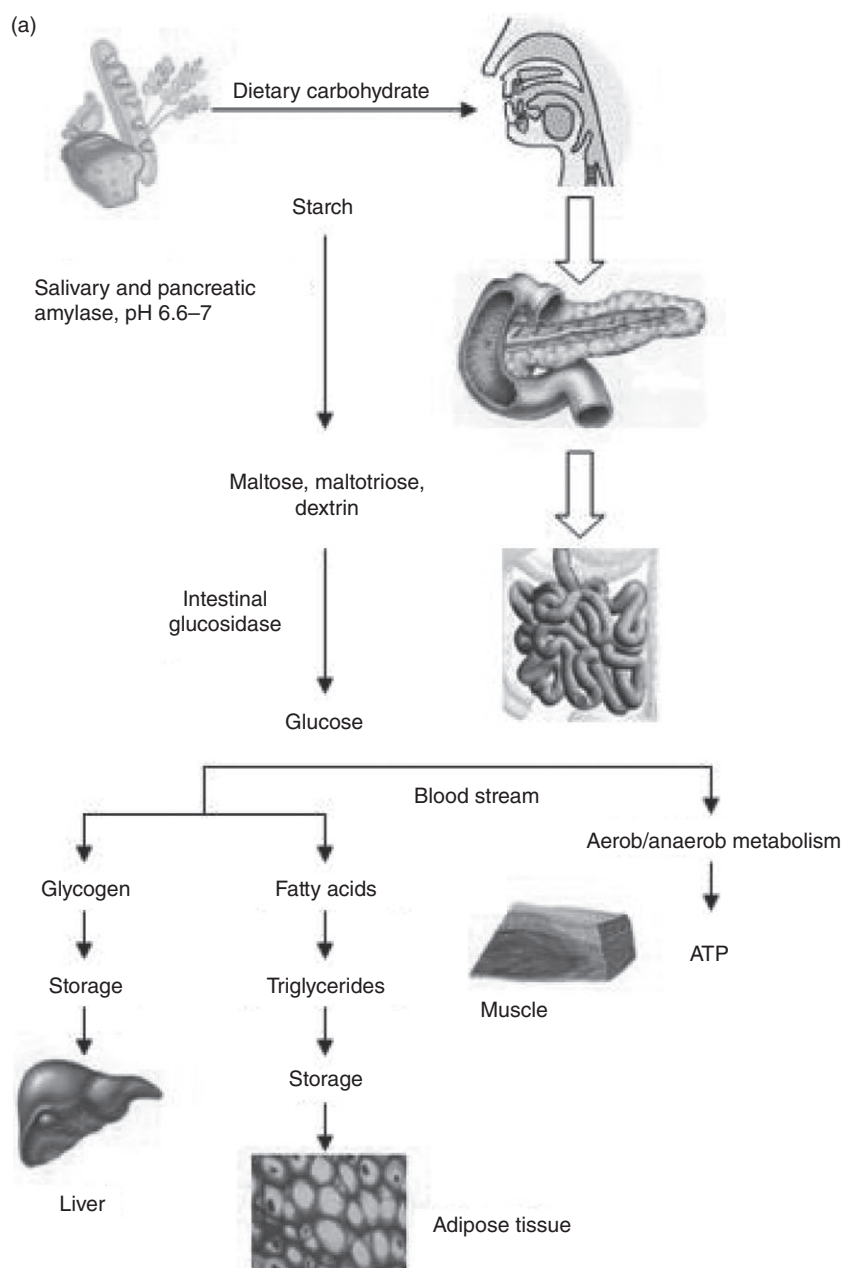


significant reduction in blood glucose level ( $P < 0.001$ ) as compared with placebo group (75). The change in body weight was not reported in this study.

#### *Hibiscus sabdariffa*

*Hibiscus* acid and its 6-methyl ester, a lactone form of (+)-allo-hydroxycitric acid (Fig. 12), have been isolated

from the methanol extract of commercial *Hi. sabdariffa* (roselle) tea, which was made from dried flowers. Both major compounds showed a weak inhibitory activity to porcine pancreatic  $\alpha$ -amylase *in vitro* ( $IC_{50}$  3.22 mM and 1.10 M, respectively). The activity was remained within a 3.5–7 pH range (76). There is no further report on the *in vivo* efficacy of these two compounds.



**Figure 10** (a) The fate of dietary carbohydrate. Excessive carbohydrate intake leads to an increase of adiposity; therefore, the blockage of carbohydrate metabolism by amylase or glucosidase inhibitors might benefit obesity treatment. (b) The dietary fat metabolism via multisteps digestion involves different enzymes at different locations. Blockage of one of the pathways may cause decrease of triglycerides reformation leading to reduction in adipocytes differentiation or hepatic triglycerides, which might be crucial for obesity treatment. DG, diglycerides; FA, fatty acids; MG, monoglycerides; TG, triglycerides.

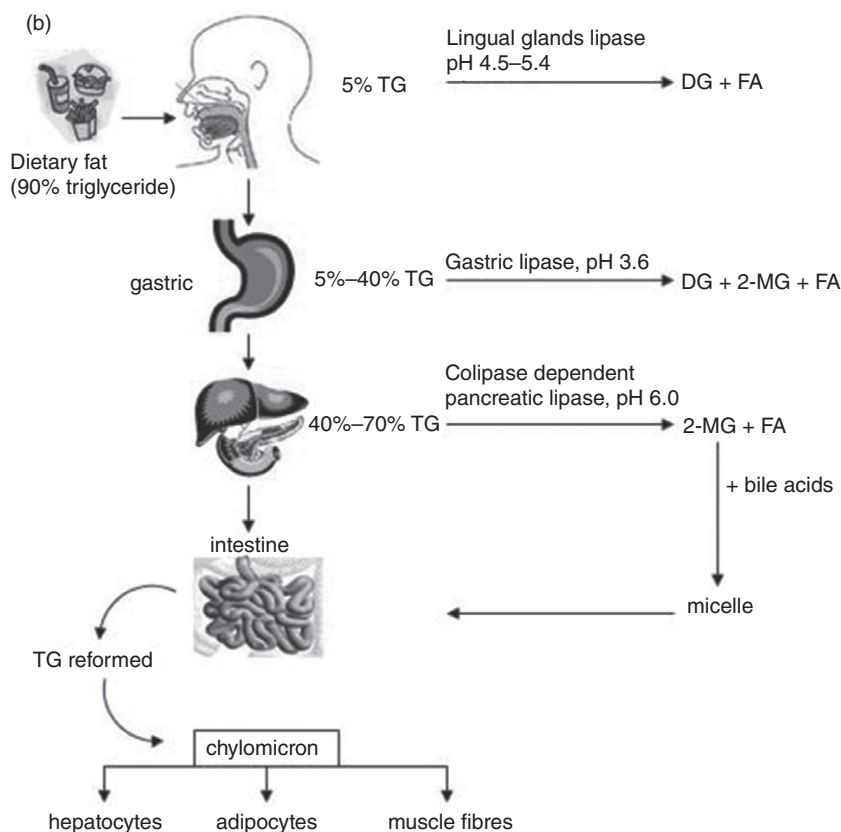


Figure 10 Continued.

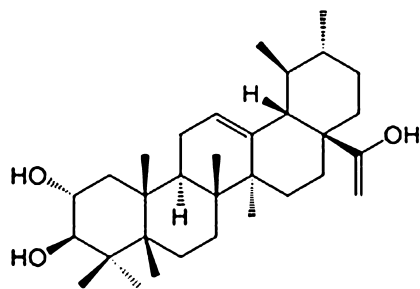


Figure 11 Corosolic acid, a pentacyclic triterpene from *Lagerstroemia speciosa* with  $\alpha$ -glucosidase inhibitor activity.

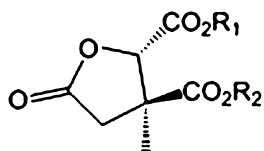


Figure 12  $\alpha$ -Amylase inhibitors from *Hibiscus sabdariffa*: Hibiscus acid (R1 = R2 = H), 6-methyl ester hibiscus acid (R1 = H R2 = -CH3).

**Nelumbo nucifera**

The anti-obesity effect of ethanol extract of *N. nucifera* leaves was examined *in vivo* and *in vitro*. The extract

showed *in vitro* inhibitory activity on  $\alpha$ -amylase and lipase with  $IC_{50}$  0.82 mg mL<sup>-1</sup> and 0.46 mg mL<sup>-1</sup>, respectively. Phenolic compounds were assumed to be the active compounds although there is no further report to support this. Also lipolytic activity in 3T3-L1 adipocytes was observed. *In vivo*, the inhibitory effect of the extract on the rats pancreatic lipase resulted in a significant decrease of the plasma triacylglycerol level 1 h after oral administration to rats fed with the extract, compared with the untreated controls. The food intake was not affected by the treatment. The body weight, parametrial adipose tissue weight and liver triacylglycerol level were reduced significantly in exercised and extract-treated rats, but not in rats treated with exercise only, or in rats treated with extract only. Additionally, also the rats skeletal muscle uncoupling protein 3 was up-regulated only in the combined treatment (77). These results emphasized the importance of drugs therapy in combination with exercise as the more effective obesity treatment.

**Phaseolus vulgaris**

Phaseolamin is an  $\alpha$ -amylase inhibitor isolated from kidney beans (*Ph. vulgaris*). It was further discovered that slightly overweight human subjects taking tablets with 445 mg (56% w/w) *Ph. vulgaris* extract before consuming the main

carbohydrate-rich meal for 30 d had significantly greater decrement on body weight compared with placebo (78). After 9 months of study, the lipoprotein profile of overweight and obese subjects receiving dietary supplement was improved. Low-density lipoprotein and the ratio of low- to high-density lipoprotein decreased and fat excretion in feces increased. Unfortunately, significant levels of anti-nutritional factors such as lectins and trypsin inhibitors are also present in commercial preparations containing *Ph. vulgaris* extract (79). It was found that processing the extracts to reduce anti-nutritional compounds also reduced amylase inhibitor activity to some extent (80). The toxicity of Blockal, a commercial starch blocker containing a standardized *Ph. vulgaris* extract was tested. No toxicity symptoms were found after oral administration of 2500 mg kg<sup>-1</sup> body weight of the extract to rats (81). On the other hand, some studies failed to show the effectiveness of starch blockers in delaying glucose or insulin response to a meal in humans. No marked differences were observed in blood insulin and glucose level between the test meal containing commercial starch blockers and placebo. A breath hydrogen test was used to measure undigested dietary carbohydrates as this method is sensitive to small amount of carbohydrates (82). There was no significant different of breath hydrogen level between the two groups. This implicates that all carbohydrates consumed with the test meal were completely digested. Furthermore, *in vitro* experiments showed that maltase and glucoamylase were capable to hydrolyse starch in the presence and absence of these starch blockers (83).

#### Triticum aestivum

The obese women consumed weight reduction regiment (1000 kcal d<sup>-1</sup>), which contain an expanded-whole wheat protein product for 12 weeks had a significant greater weight loss (5.5 kg) than the isocaloric standard low-calorie diet control group (2.8 kg,  $P = 0.05$ ) (84). The suggested mechanism is via  $\alpha$ -amylase inhibition, which was confirmed by the more recent report where  $\alpha$ -amylase inhibitor preparation isolated from wheat protein was infused into human duodenum. The concentration needed to inhibit 90% of amylase activity *in vivo* was 4.5 mg mL<sup>-1</sup> extract, while *in vitro* 4 mg mL<sup>-1</sup> was needed to inhibit 75% of amylase activity. In spite of the decrease in amylase activity, the level of plasma glucose and several hormones (e.g. insulin, c-peptide, glucagon, gastric inhibitory polypeptide, neurotensin, PYY) concentrations were not affected. This was due to the fact that the amylase inhibitor from wheat and white bean only affect postprandial glucose and insulin, while in this study no carbohydrates were infused to the intestine before intervention with inhibitors. Pancreas secretion of lipase, trypsin, chymotrypsin and bile acids was also unaffected. This is important as the amylase inhibitors of

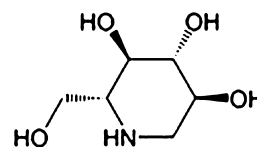


Figure 13 1-Deoxynojirimycin, glycosidase inhibitor from *Morus alba*.

wheat have homology with the trypsin inhibitor, and prolonged pancreatic protease inhibition might stimulate pancreas carcinogenesis. The  $K_i$  value of the inhibitor of wheat was 57.3 nM, while the  $T_{50}$  (temperature giving 50% inactivation after 30 min incubation) was 88.1°C (85). Because of this high activity and thermal stability, this purified wheat inhibitor has potential for obesity treatment.

#### Morus alba

In several countries, such as India, Pakistan and Thailand, *M. alba* leaves has been traditionally used to cure diabetes. Glycosidases inhibitor activity of the leaf extract has been reported by several authors. *In vitro* disaccharidase inhibitor activity of ethanol extract of *M. alba* leaf in human and rat intestine was examined (86). A strong correlation between the level of 1-deoxynojirimycin (Fig. 13) content and  $\alpha$ -glucosidase inhibitory activity of *M. alba* leaves was found (87). The extract, which contained 0.24% 1-deoxynojirimycin showed similar strong inhibition of sucrase, maltase and isomaltase, in both human and rat small intestine *in vitro*. Only for rat small intestine  $K_i$  values were mentioned: 21, 25 and 45  $\mu$ M for sucrase, maltase and isomaltase, respectively. *In vivo*, when administered together with sucrose, the extract suppressed the rat blood glucose level but the suppression level depends on the ratio of extract to sucrose. Some reports support the wider use of *M. alba* as a potent source of anti-obesity drugs (87–89). The potential of *M. alba* hot water extract to be consumed as an anti-diabetic herbal tea was reported. The brewing time of 3–5 min for tea preparation was found to be the most optimum compared with the longer ones (7, 10 and 30 min) as the maltase and sucrase inhibitor activity of *M. alba* leaf tea, *in vitro*, was the highest (90).

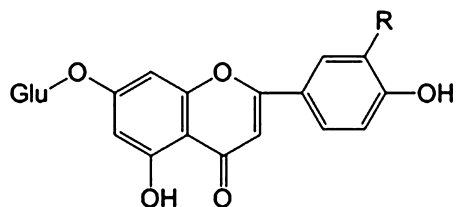
#### Panax ginseng and Panax quinquefolius

Besides *P. ginseng* roots, apparently ginseng berries are considered to be at least equivalently potent. Saponin extract from both root and berry were found to suppress mice body-weight gain and plasma triacylglycerol level when orally administered. The proposed mechanism is via inhibition of pancreatic lipase leading to inhibition of intestinal dietary fat absorption (91). The efficacy of this botanical was tested in C57BL/KsJ db/db mice and their lean littermates. Intraperitoneal injection of *P. ginseng* berry

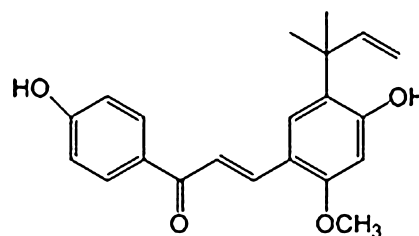
extract (150 mg kg<sup>-1</sup> body weight), reduced fasting blood glucose levels significantly in db/db mice but not in lean mice, while significant decrease in body weight in both groups was observed (92). Furthermore, it was found that ginsenoside Re (Fig. 9b), the major steroidal saponin in ginseng, is correlated with the ginseng hypoglycaemic effect but not correlated with body weight, food intake and energy expenditure. The other possible responsible compounds for the last activities were not identified. Daily administration of 6 g ginseng extract improved plasma glucose and insulin profiles in humans but the body weight was not affected (93).

Apart from inhibition of carbohydrate-digestive enzymes, there is another mechanism described for hypoglycaemic activity of American ginseng roots (*P. quinquefolius*) namely by improving beta cell insulin production and protecting these cells from apoptosis (94). In

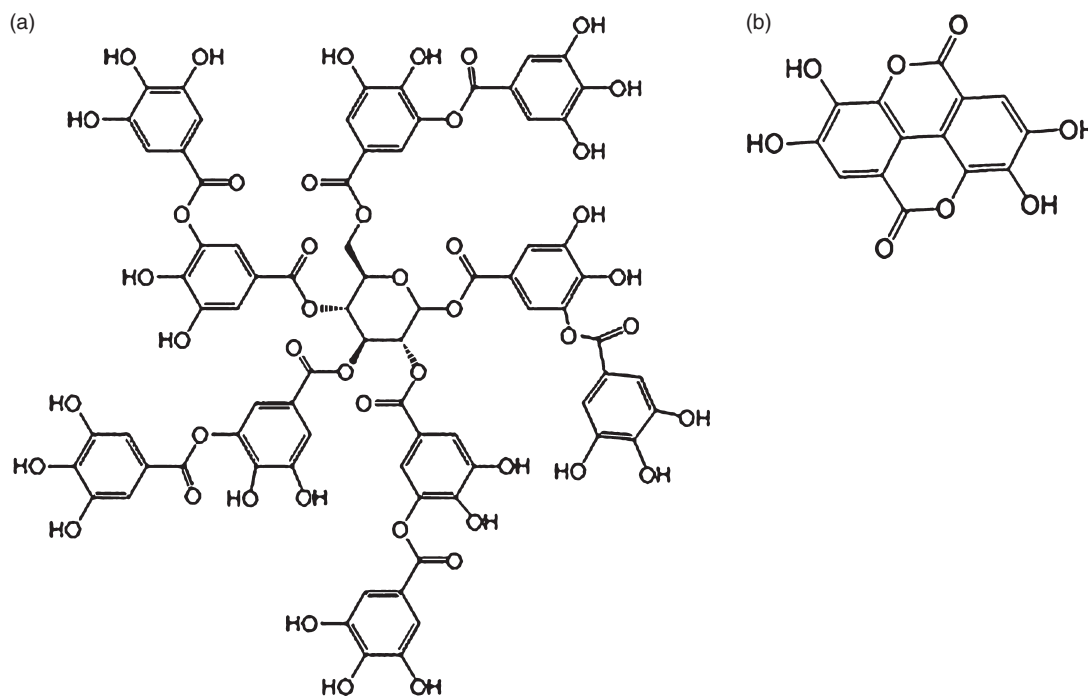
another study, crude saponin extract from stem and leaves of *P. quinquefolius*, containing nine major ginsenosides (Rg1, Re, Rg2, Rb1, Rc, Rb2, Rb3 and Rd, Fig. 9), was tested *in vitro* for pancreatic lipase inhibition. At 0.5 mg mL<sup>-1</sup> dose, the ginsenosides Rb1, Rb2, Rc and Rd showed strong inhibition almost similar to orlistat at a dose of 0.008 mg mL<sup>-1</sup>, with Rc being the most active. Oral administration of crude saponin in a lipid emulsion (1 g kg<sup>-1</sup> body weight) inhibited the increase of rat plasma triacylglycerol level compared with lipid emulsion only. When incorporated into rat high-fat diet at 1% and 3% dose, crude saponins suppressed parametrial adipose tissue weight compared with high-fat diet control but body weight and food intake were not different (95). American ginseng was found to be effective to improve blood glucose level in normal and type 2 diabetic patients but effect on body weight was not reported (96,97).



**Figure 14** Lipase and  $\alpha$ -amylase inhibitors from *Salix matsudana*: apigenin-7-*O*-**d**-glucoside (R = H), luteolin-7-*O*-**d**-glucoside (R = OH), chrysoeriol-7-*O*-**d**-glucoside (R = OCH<sub>3</sub>).



**Figure 15** Licochalcone A, a weak non-competitive lipase inhibitor from *Glycyrrhiza glabra*/*G. uralensis*.



**Figure 16** Lipase inhibitors from *Punica granatum*. (a) Tannic acid. (b) Ellagic acid.

**Table 1** Summary of botanicals used as energy intake regulation herbs, responsible active compounds and their mechanisms

Plant's name	Reduce body weight	Reduce food intake	Active compound(s)	Mechanism(s)				
				Central appetite suppressant	Delay gastric emptying	Amylase inhibitor	Lipase inhibitor	CB1 receptor
<i>Hoodia</i> sp.	+	+	3 $\beta$ -[ $\beta$ -d-thevetopyranosyl-(1 $\rightarrow$ 4)- $\beta$ -d-cymaropyranosyl-(1 $\rightarrow$ 4)- $\beta$ -d-cymaropyranosyloxy]-12 $\beta$ -tigloyloxy-14 $\beta$ -hydroxypregn-5-en-20-one	+	nm	nm	nm	nm
<i>Benincasa hispida</i> (Thunb.) Cogn	nm	+	nm	+	nm	nm	nm	nm
<i>Mitragyna speciosa</i> Korth.	+	+	Mitragynine	+	nm	nm	nm	nm
<i>Caralluma fimbriata</i> Wall.	+	+	nm	+	nm	nm	nm	nm
<i>Catha edulis</i> Forsk	nm	+	Cathinone	+	+	nm	nm	nm
<i>Capsicum annuum</i> L.	+	-	Capsaicin	+	nm	nm	nm	nm
<i>Garcinia cambogia</i> Desr.	+	+	(-)-hydroxycitric acid	+	nm	nm	nm	nm
<i>Cyamopsis tetragonolobus</i> L.	+	nm	Galactomannan	-	+	nm	nm	nm
<i>Amorphophallus konjac</i> K. Koch	-	-	Glucomannan	-	nm	nm	nm	nm
<i>Panax ginseng</i> C.A. Meyer	+	+	Ginsenosides Rg1, Re, Rg2, Rb1, Rc, Rb2, Rb3, Rd	+	nm	nm	+	nm
<i>Panax quinquefolius</i> L.	-	-	Ginsenosides Rg1, Re, Rg2, Rb1, Rc, Rb2, Rb3, Rd	nm	nm	nm	+	nm
<i>Lagerstroemia speciosa</i> (L.) Pers	+	nm	Corosolic acid	nm	nm	+	nm	nm
<i>Hibiscus sabdariffa</i> Linn.	+	-	(+)-allo-hydroxycitric acid	nm	nm	+	nm	nm
<i>Nelumbo nucifera</i> Gaertn.	+	-	nm	nm	nm	+	+	nm
<i>Phaseolus vulgaris</i> L.	+	nm	nm	nm	nm	+	nm	nm
<i>Triticum aestivum</i> L.	+	nm	nm	-	nm	+	nm	nm
<i>Morus alba</i> L.	+	nm	1-deoxyojirimycin	nm	nm	+	nm	nm
<i>Aframomum meleguetta</i> (Roscoe) K. Schum	nm	nm	nm	nm	nm	nm	+	nm
<i>Spilanthes acmella</i> (L.) Murray	nm	nm	nm	nm	nm	nm	+	nm
<i>Salix matsudana</i> Koidz.	+	nm	Apigenin-7-O-d-glucoside, luteolin-7-O-d-glucoside, chrysoeriol-7-O-d-glucoside	nm	nm	+	+	nm
<i>Glycyrrhiza uralensis</i> Fisch./ <i>G. glabra</i> L.	+	+	Licochalcone A	nm	nm	+	nm	nm
<i>Punica granatum</i> L.	+	nm	Tannic acid, ellagic acid	nm	nm	nm	+	nm

+, tested and active; -, tested but inactive; nm, not mentioned.

#### *Aframomum meleguetta* and *Spilanthes acmella*

Ethanol extracts of two native African plants, *Af. meleguetta* and *S. acmella*, were both tested for inhibitory activity against human pancreatic lipase *in vitro* in 0.75–2.0 mg mL<sup>-1</sup> concentration range. *Aframomum meleguetta* seed extract (90% at 2.0 mg mL<sup>-1</sup>) showed higher inhibition than *S. acmella* flower bud extract (40% at 2.0 mg mL<sup>-1</sup>) (98). However, no further work on the identification of the responsible compounds and *in vivo* experiment has been reported.

#### *Salix matsudana*

The polyphenol fraction of *Sa. matsudana* leaves was tested for lipase and  $\alpha$ -amylase inhibitory activity. *In vivo*, after

oral administration of the extract, there was a significant decrease in rat plasma triacylglycerol (lipid emulsion + 570 mg kg<sup>-1</sup> body-weight extract dose), parametrial adipose tissue and body weight, hepatic total cholesterol content and diameter of adipose tissue (high-fat diet + 5% extract dose) when compared with control (high-fat diet or lipid emulsion only). Feces fat content also increased while food intake was unaffected. *In vitro*, the polyphenolic extract acted synergistically with noradrenaline to induce lipolysis at a concentration of 1 mg mL<sup>-1</sup>. The extract was also found to inhibit  $\alpha$ -amylase activity at a concentration of 250–2500  $\mu$ g mL<sup>-1</sup> and the incorporation of palmitic acid into brush border membrane vesicles at concentrations of 500 and 1000  $\mu$ g mL<sup>-1</sup>. The responsible compounds

**Table 2** Summary of the potential of appetite suppressant botanicals for clinical practice

Plant's name	Potential for clinical trial	Reported active dose/duration of use in humans, references	Remarks
<i>Hoodia</i> sp.	+/-	-	No further data on efficacy and toxicity in humans
<i>Benincasa hispida</i> (Thunb.) Cogn	+/-	-	Lack data both <i>in vitro</i> and <i>in vivo</i> efficacy
<i>Mitragyna speciosa</i> Korth.	--	-	Addictive side effect
<i>Caralluma fimbriata</i> Wall.	++	0.5–1 g per 60 d, (44)	No further data on efficacy and toxicity in humans
<i>Catha edulis</i> Forsk	--	-	Side effects similar to amphetamine
<i>Capsicum annuum</i> L.	--	-	Sensory taste is a limiting factor
<i>Garcinia cambogia</i> Desr.	++	4667 mg d <sup>-1</sup> , (43)	
<i>Cyamopsis tetragonolobus</i> L.	--	-	Many contradictory reports on efficacy in humans
<i>Amorphophallus konjac</i> K. Koch	--	-	Many contradictory reports on efficacy in human
<i>Panax ginseng</i> C.A. Meyer	+/-	6 g per 12 weeks, (97)	Lack data on efficacy to reduce body weight in humans
<i>Panax quinquefolius</i> L.	+/-	3–9 g, duration time not mentioned, (98,99)	Lack data on efficacy to reduce body weight in humans
<i>Lagerstroemia speciosa</i> (L.) Pers	+/-	32–48 mg per 2 weeks, (75)	Lack data on efficacy to reduce body weight in humans
<i>Hibiscus sabdariffa</i> Linn.	--	-	Lack data on efficacy in humans
<i>Nelumbo nucifera</i> Gaertn.	--	-	Low <i>in vitro</i> activity
<i>Phaseolus vulgaris</i> L.	+/-	445 mg per 30 d, (78)	Many contradictory reports on efficacy in humans
<i>Triticum aestivum</i> L.	+/-	Not mentioned, (84)	Lack data on efficacy in humans
<i>Morus alba</i> L.	--	-	Lack data on efficacy in humans. Low <i>in vitro</i> activity
<i>Aframomum meleguetta</i> (Roscue) K. Schum	--	-	Lack data on <i>in vitro</i> and <i>in vivo</i> efficacy. Low <i>in vitro</i> activity
<i>Spilanthes acmella</i> (L.) Murray	--	-	Lack data on <i>in vitro</i> and <i>in vivo</i> efficacy. Low <i>in vitro</i> activity
<i>Salix matsudana</i> Koidz.	--	-	Lack data on <i>in vitro</i> and <i>in vivo</i> efficacy. Low <i>in vitro</i> activity
<i>Glycyrrhiza uralensis</i> Fisch./ <i>G. glabra</i> L.	--	-	Lack data on efficacy in humans. Low <i>in vitro</i> activity
<i>Punica granatum</i> L.	+/-	-	Lack of data on efficacy in humans

++, potential; +/-, can be potential but need more data; --, not potential.

were elucidated as apigenin-7-O-d-glucoside that inhibits  $\alpha$ -amylase, luteolin-7-O-d-glucoside and chrysoeriol-7-O-d-glucoside that inhibit palmitic acid incorporation into small intestine brush border membrane vesicles (Fig. 14). All compounds induced lipolysis synergistically with noradrenaline like the crude extract (99,100).

### Glycyrrhiza uralensis

Licochalcone A (Fig. 15) isolated from *Gl. uralensis* roots showed weak non-competitive lipase inhibitory activity *in vitro* with  $K_i$  value 32.8  $\mu$ M. Although weaker than orlistat, the inhibitory activity of this compound is reversible (101).

### Punica granatum

The body-weight gain of high-fat diet-induced obese mice given the *Pu. granatum* leaves extract by gavage at 800 mg kg<sup>-1</sup> dose for 5 weeks was suppressed compared with obese control mice, also final adipose pad weight, serum glucose, triglyceride, total cholesterol and high-density lipoprotein cholesterol were reduced. Food intake was lower in extract-treated obese mice, similar to sibutramine treated obese mice, but not in treated normal mice. Furthermore, after oral administration of lipid emulsion, extract-treated obese and normal mice had a lower level of serum triglycerides and total cumulative triglycerides

absorption but the normal mice had a lower triglycerides absorption. *In vitro*, the extract showed inhibition of pancreatic lipase activity almost to 100% inhibition at 0.1 mg mL<sup>-1</sup> concentration, this was confirmed *in vivo* by an increase of fecal fat secretion. Tannic acid and ellagic acid (Fig. 16) were thought to be responsible for the activity (102).

The summary of botanicals, responsible active compounds and its mechanisms involved in energy intake suppressant activity of herbs reported in this review is presented in Table 1. While in Table 2, their potential to reach clinical trial including the effective dose and duration of use is summarized.

### Conclusion

As described in this review, many plant-screening projects have been done, including important targets for energy intake regulation. One specific plant can be active in more than one pathway or mechanism, such as *P. ginseng*. Some active constituents are present or can be incorporated into food for daily consumption, such as capsaicin and curcumin. A few candidates went into clinical trials, such as P57 from *H. gordonii*, but none has reached the final stage for registration. The fact that most of the reported activities were based on animal studies but whether the results are

transferable to humans is questionable. However, despite of insufficient data for safety and efficacy, many are available as non-prescription herbal preparations. Examples are hydroxycitric acid from *G. Cambodia*, which reduces appetite or the amylase inhibitors from *Pb. vulgaris*. Mechanism and responsible compounds have been elucidated but whether they will go further into clinical trials remains unclear. The major question being asked is whether the effect is at a reasonable dose. Exploration of traditionally used plants could be very beneficial to uncover more potent candidates, such as the P57 experience. A good balance between data supported by scientific work and advertisement is needed to avoid dissatisfaction. The recently expanded metabolomics approach along with multivariate data analysis could be a valuable tool in obesity herbal discovery as it offers the potential of studying efficacy and safety in a holistic approach and thus would also reveal the presence of pro-drugs or synergy. It is also important for the quality control of herbal medicines.

### Conflict of Interest Statement

No conflict of interest was declared.

### Acknowledgements

Phytochemist Society of Europe and Nobesinkas are gratefully acknowledged for financial support to N. D. Yuliana.

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