Natural inhibitors of Pancreatic Lipase as new players in obesity treatment

Authors: de la Garza AL, Milagro FI, Boque N, Campion J, Martinez JA

Ana Laura de la Garza, Fermín I. Milagro, Noemi Boque, Javier Campión, J.Alfredo Martinez

Affiliation

Department of Nutrition and Food Science, Physiology and Toxicology, University of Navarra, Pamplona, Spain

Correspondence

Prof. J. Alfredo Martinez, Department of Nutrition and Food Science, Physiology and Toxicology, University of Navarra. c/Irunlarrea 1, 31008, Pamplona, Spain
jalfmtz@unav.es Phone: +34 948425600 Fax: +34 948425649
Abstract

Obesity is a multifactorial disease characterized by an excessive weight for height due to an enlarged fat deposition as adipose tissue, which is attributed to a higher calorie intake than the energy expenditure. The key strategy to combat obesity is to prevent chronic positive impairments in the energy equation. However, it is often difficult to maintain energy balance, because many available foods are high energy-yielding, which is usually accompanied by low levels of physical activity.

The pharmaceutical industry has invested many efforts in producing antiobesity drugs; but only a lipid digestion inhibitor obtained from an actinobacterium is currently approved and authorized in Europe for obesity treatment. This compound inhibits the activity of pancreatic lipase, which is one of the enzymes involved in fat digestion.

In a similar way, hundreds of extracts are currently being isolated from plants, fungi, algae or bacteria and screened for their potential inhibition of pancreatic lipase activity. Among them, extracts isolated from common foodstuffs such as tea, soybean, ginseng, yerba mate, peanut, apple or grapevine have been reported. Some of them are polyphenols and saponins with an inhibitory effect on pancreatic lipase activity, which could be applied in the management of the obesity epidemic.

Keywords: Orlistat, high fat diet, polyphenols, saponins, obesity, fat digestion
Introduction

Obesity is becoming one of the greatest threats to global health in this century, with more than 1.5 billion overweight adults and at least 400 million of clinically obese subjects [1]. Due to these increasing obesity rates, the World Health Organization (WHO) has prompted to consider it as the epidemic of XXI century and to promote strategies to prevent and control its progress [2].

The development of obesity is characterized by a chronic imbalance between energy intake and energy expenditure [3-5] and it is often ascribed to changing lifestyles and inadequate dietary habits [3]. Also, decreased energy expenditure is often associated with an inherited low basal metabolic rate, low energy cost of physical activity and low capacity for fat oxidation [6]. To reduce body weight and adiposity, a change in lifestyle habits is still the crucial cornerstone [7]. Physical activity might be helpful in the prevention of obesity by elevating average daily metabolic rate and increased energy expenditure [3]. Unfortunately, this clinical approach is not-long term lasting and weight regain is often seen. Drugs that prevent weight regain appear necessary in obesity treatment [7]. Thus, the development of natural products for the treatment of obesity is a challenging task, which can be launched faster and cheaper than conventional single-entity pharmaceuticals [8]. Many medicinal plants may provide safe, natural, and cost-effective alternatives to synthetic drugs [9,10]. Currently, one of the most important strategies in the treatment of obesity includes development of inhibitors of nutrient digestion and absorption. For example, acarbose is an anti-diabetic drug that inhibits glycoside hydrolases, preventing thus the digestion of complex carbohydrates and decreasing postprandial hyperglycemia [11,12]. Similar compounds with alpha-amylase inhibiting activity that can be used for diabetes control are being isolated from different plants. The list includes valoneaic acid dilactone [13], obtained
from banaba (*Lagerstroemia speciosa*), the ethanol extract obtained from chestnut astringent skin [14] or the purified pancreatic alpha-amylase inhibitor isolated from white beans (*Phaseolus vulgaris*), which is able to reduce glycemia in both non-diabetic and diabetic rats [15].

In this context, since dietary lipids represent the major source of unwanted calories, the inhibition of fat digestion is an interesting approach for reducing fat absorption [16]. Orlistat is the only authorised anti-obesity drug in Europe and has been shown to act through inhibition of pancreatic lipase (PL), which is a key enzyme for the digestion of dietary triglycerides [17]. Orlistat is the saturated derivative of lipstatin, an inhibitor of PL isolated from the bacterium *Streptomyces toxytricini* [18]. This molecule exerts a modest weight lowering effect when accompanying a suitable dietary advice. Thus, in a recent meta-analysis [19], the mean BMI change with Orlistat (120 mg three times daily) was a reduction of 0.83 kg m$^{-2}$ (95% CI: 0.47–1.19) compared with placebo. Accompanying this anti-obesity action, Orlistat is also able to modestly reduce blood pressure, improve oral glucose tolerance and prevent the onset of type 2 diabetes [20,21].

Now, extracts from hundreds of species of medicinal plants, vegetables and fruits [22] as well as products from microorganisms [9], fungi [23] and marine algae [24] are being screened for potential lipase inhibitory activity. Ideally, these treatments will be viewed as adjuncts to behavioural and lifestyle changes aimed at maintenance of weight loss and improved health [8].

**Obesity and high fat diets**

Epidemiological studies have shown a direct relation between the incidence of overweight/obesity and dietary fat consumption [3,6,25].
Humans are frequently exposed to fat rich foods, which are usually associated to a high energy intake [6,26]. Thus, those foods with a high energy and dietary fat content are considered to promote body fat storage and weight gain in humans [8]. One explanation is that, in commercially available food items, the percentage of energy derived from fat is highly correlated with energy density. Given that fat contains 9 kcal/g compared with 4 kcal/g for carbohydrates and proteins, foods rich in fat are often high in energy density. Thus, when a similar volume of food is consumed, energy intake will be higher in high fat diets compared with low fat diets [3].

On the other hand, independently of an increased energy intake, specific dietary constituents may promote the development of obesity. This statement means that even consuming an equal amount of energy, the diet composition is important, especially the balance between nutrients [27,28].

Thus, macronutrient profile (high-protein, high-carbohydrate and high-lipid diets) can affect diet-induced thermogenesis, the oxidation pathway, energy intake, gene expression or the level of some hormones [29]. Following a high-fat diet, the diet-induced thermogenesis is lower than following high protein and carbohydrate diets, and also fat is more effectively absorbed from the gastrointestinal tract than are carbohydrates, which translates into lower energy expenditure when following a high fat diet [26]. So, high fat diets produce a metabolically more efficient state, at least in part because of the lower postprandial thermogenic effect of lipids in comparison with carbohydrates [30].

Furthermore, the consumption of a high fat diet has the capacity to modulate the gastrointestinal responses to ingested fat and, thereby, may lead to impairments in appetite regulation that favour the development of obesity. Dietary fat usually implies
an increase in energy consumption because it has a lower potential for inducing satiety than carbohydrate and protein [6,31].

Hence, high fat diets may play an important role in the increased prevalence of obesity and can be a triggering factor in the development of hyperglycemia and hyperinsulinemia [3,32]. Moreover, the intake of dietary fats is usually accompanied by a higher intake of refined sweet carbohydrates (fast food, desserts), where the high intake of sucrose promotes weight gain, visceral adiposity and the development of diseases that are related with obesity, such as diabetes and cardiovascular diseases [33]. Therefore, low fat diets often are prescribed in the prevention and treatment of overweight and obesity because a reduction in dietary lipids without restriction of total energy intake could cause weight loss [26].

Fat digestion

Recent studies indicate that fat digestion is a prerequisite for the effects of fat on gastric emptying, gastrointestinal hormone secretion, appetite, and energy intake [6]. An increasing number of gastrointestinal enzymes involved in nutrient digestion are being identified and characterized, representing a rich pool of potential therapeutic targets for obesity and other metabolic disorders [9]. Especially interesting are those enzymes that are related with dietary fat, which includes pre-duodenal lipases (lingual and gastric lipases), pancreatic lipase (PL), cholesterol-ester lipase, and bile-salt stimulated lipase [34].

Most dietary fat is ingested as triglycerides (90-95%) and their hydrolysis starts in the mouth, then through the stomach by an acid stable gastric lipase, continues in the duodenum, through the synergistic actions of gastric and colipase-dependent pancreatic lipases (PL), leading to the formation of monoglycerides and free fatty acids (FFA).
FFA are absorbed by the enterocyte to synthesize new triglyceride molecules, which are transported to the different organs via lipoproteins, especially chylomicrons, after a meal [34].

Pancreatic lipase (PL), encoded by the PNLIP gene in humans, plays a key role in the efficient digestion of triglycerides [35]. It is secreted into the duodenum through the duct system of the pancreas and is responsible for the hydrolysis of 50 – 70% of total dietary fats [9]. This enzyme has been widely used for the determination of the potential efficacy of natural products as antiobesity agents [36].

Orlistat is currently the only clinically approved drug for obesity management in Europe. This molecule acts by the inhibition of PL activity and the reduction of triglyceride absorption, and its long-term administration accompanying an energy restricted diet, results in weight loss [37]. Reduction on intestinal lipid digestion has been related to a decrease in the intra-abdominal fat content [7]. Thus, this compound is associated with a small, but statistically significant weight loss of about 3% more than diet alone in overweight and obese people [1]. In addition to losing weight, Orlistat within a prescribed diet has been shown to be safe and more effective than diet alone in modifying some of the risk of coronary artery disease and other obesity-related co-morbidities. The most commonly reported adverse effects of Orlistat are a range of gastrointestinal side effects, including steathorrhea, bloating, oily spotting, faecal urgency and faecal incontinence, as well as hepatic adverse effects [19,38]. These adverse effects are similar to those observed for other lipase inhibitors tasted in phase II studies, such as Cetilistat (ATL-962) [39].

On the other hand the inhibition of fat absorption could be accompanied by liposoluble vitamin deficiencies, which could be prevented by the vitamin supplementation
strategy, as other authors have recommended when vitamin deficiency occur in patients undergoing Orlistat therapy [40].

Hence the interest in the search for new natural substances that show potent inhibitory activity against PL and have fewer side effects than the current ones.

**Natural inhibitors of pancreatic lipase**

In the continued search of effective antiobesity agents, several bacterial, fungal and marine species have been screened to find new compounds with PL inhibitory activity. Many metabolic products from microorganisms, such as different kinds of *Streptomyces* (toxytricini, sp.NR 0619, abolongus, aburaviensis and lavendulae) have a potent inhibitory activity of PL [9]. Lipstatin was isolated from an actinobacterium, *Streptomyces toxytricini*, and the catalytic hydrogenation product of lipstatin is the approved antiobesity drug tetrahydrolipstatin (Orlistat; marketed by Roche as Xenical™) [18]. Panclicins, analogs of tetrahydrolipstatin isolated from *Streptomyces* sp. NR0619, also present strong anti-lipase activity [41]. Other compounds which act also as potent inhibitors of PL, at least in vitro, are ebelactones A and B, isolated from *Streptomyces aburaviensis* [42], and vibralactone, isolated from the culture broth of the polypore *Boreostereum vibrans* [43]. Finally, other examples of lipase inhibitors have been obtained from yeasts and fungi such as *Candida antarctica, Candida rugosa, Gestrichum candidum, Humicola lanuginose, and Pseudomonas glumae*, which have received special attention and are widely used in the pharmaceutical industry [44].

Due to the biodiversity and unexplored resources, the fungal kingdom has been particularly searched to find new substances with lipase inhibitory activity. In a thorough screening of lipase inhibitors of fungal origin in Slovenia [23], extracts obtained from three species, *Laetiporus sulphureus, Tylopilus felleus* and *Hygrocybe*
conica, exhibited very high lipase inhibitory activities (83% ± 5%, 96% ± 3% and 97% ± 5%, respectively), even higher than Orlistat. Pleurotus eringii water extract also shows a significant inhibitory activity against PL, preventing postprandial hyperlipidemia through low intestinal absorption of dietary fat [45]. Finally, the water and ethanol extracts from fruiting bodies of Phellinus linteus show a potent lipase inhibitory and anti-obesity effect [46]. A special case is that of monascus pigments from Monascus sp., which have been used for many years as natural colorants and as a healthy food in East Asia, being used in the production of certain fermented foods. Various monascus derivatives with incorporated unnatural amino acids show inhibitory activities against lipase [47].

In the same way, marine products are an especially rich source on bioactive compounds [48]. In a milestone study, Bitou et al. [24] screened the lipase inhibitory activities of methanol and ethyl acetate extracts from 54 species of marine algae. These investigations observed a very high activity (almost 100% inhibition) in the methanol extracts from Caulerpa taxifolia and Asparagopsis tociiformis, although the methanolic extracts of other Chlorophyta (i.e., Caulerpa okamurae or Codium latum) Rhodophyta (i.e., Gloiopeltis tenax or Hypnea charoides) and Phaeophyta (i.e., Sargassum muticum, Dictyopteris latiuscula or Cutleria cylindrica), were also very promising. In this sense, Phaeophyta generally contains large amounts of polyphenols such as tannins, with lipase-inhibiting activity. In fact, most compounds with a porphyrin structure are able to inhibit lipase activity [49]. Two algae whose extract inhibits gastric and pancreatic lipases are Caulerpa prolifera, which may be a source of a potential antiobesity agent [50], and Caulerpa taxifolia that synthesizes the toxin caulerpenyne [24]. On the other hand, carotenoids from Undaria pinnatifida and Sargassum fulvellum, specifically
fucoxanthin that is in vivo metabolised to fucoxanthinol, suppress triglyceride absorption via the inhibition of PL in the intestinal lumen [51].

Medicinal plants have been used as dietary supplements for body weight management and control in many countries. In this sense, presence of PL inhibitors has been demonstrated in different plant species (table 1), although more research is needed for identifying and characterizing effective lipase inhibitors [52]. Lipase inhibitors of plant origin include certain proteins, such as those from soybean [53] and from wheat bran and germ [54]. Other proteins that strongly inhibit hydrolysis of triglycerides are the basic protein protamine [55] and ε-polylysine [56], which could act, as several amphiphilic proteins like ovoalbumin and β-lactoglobulin [57], by the desorption of lipase from its substrate due to a change in interfacial quality [58].

Other lipase inhibitors from plant origin are basic polysaccharides, especially chitosan oligosaccharides, water-soluble chitosan (46 kDa) and polydextrose when a basic group is introduced [59,60], phytic acid and other myo-inositol phosphate esters [61], phenylboronic acid, a potent inhibitor of lipase from Oryza sativa [62] and carnosic acid, a diterpene isolated from the methanolic extract of the leaves of sage (Salvia officinalis) and rosemary [63]. Korean and Chinese researchers have been very active in the search of new lipase inhibitors of herbal origin. Among the most promising compounds there are platycodin D, isolated from the fresh roots of Platycodon grandiflorum [64,65], dioscin, from Dioscorea nipponica [66], licochalcone A, from the roots of Glycyrrhiza uralensis [67], phenolic constituents from the leaves of Nelumbo nucifera [68], the aqueous ethanol extracts of Juniperus communis or common juniper (bark) and Illicium religiosum (wood) [69], the ethanol extract from stem bark and leaves from mango tree (Mangifera indica), which is able to prevent weight gain induced by feeding a high-fat diet to Wistar rats [70], a pomegranate leaf extract rich in
ellagic acid and tannins [71], Rhei rhizoma (rhubarb) and the combinatorial drug Chunghyuldan [72], Prunella vulgaris, Rheum palmatum and other herbs [73]. Most of the common compounds that are found in different plant species are polyphenols, saponins and terpenes (table 2). In the following chapters we will present those compounds with more information available classified according to the biochemical structure.

**Polyphenols**

A number of studies have revealed various health benefits of plant polyphenols and their importance in foods, beverages and natural medicine. In this context, polyphenols have some potential efficacy for preventing obesity. They inhibit enzymes related to fat metabolism including PL, lipoprotein lipase, and glycerophosphate dehydrogenase [74]. Polyphenol extracts are able to decrease the blood levels of glucose, triglycerides and LDL cholesterol, increase energy expenditure and fat oxidation, and reduce body weight and adiposity [75,76]. In fact, many polyphenols, including flavones, flavonols, tannins and chalcones, have shown an inhibitory activity of PL [9,22].

Flavonoids are a type of plant secondary metabolites which are characterized as containing two or more aromatic rings, each bearing at least one aromatic hydroxyl and connected with a carbon bridge [76]. Some of them are polymerized into large molecules, either by the plants themselves or as a result of food processing. These polymers are called tannins and three subclasses (condensed tannins, derived tannins and hydrolysable tannins) exhibit a variety of beneficial effects on health [76]. For example, hesperidin, a flavonoid obtained from the peels of Citrus unshiu shows a PL inhibitory activity [77].
Proanthocyanidins (PA), also known as condensed tannins, are the most common group of flavonoids in the Western diet. They consist of monomeric units of flavans linked through carbon-carbon and ether linkages, which are considered the second most abundant group of natural phenolics after lignins [78]. PA can be found in such common foodstuffs as cereals, legumes, fruits, vegetables and beverages (red wine and tea in particular) [75,79]. They have a putative role as antioxidants, showing beneficial effects on inflammatory processes, cardiovascular diseases and other pathological conditions [80,81]. For example, these compounds actively reduce plasma triglycerides by inhibiting the absorption of dietary lipids [79] and possess inhibitory effects on different digestive enzymes, such as trypsin, amylase, and lipase [36].

Some examples of polyphenols with inhibitory action on PL are proanthocyanidins from edible herbs, such as those from Cassia mimosoides [82], and tea catechins, especially (−)-catechin gallate and (-)-gallocatechin gallate, [83]. Some of the most thoroughly studied polyphenol extracts in relation to PL inhibition are the following:

1. *Arachis hypogaea*

2. Peanut (*Arachis hypogaea*) shells (hulls, seed coats), which are by-products of the peanut industry, provide several compounds showing PL inhibitory activity in a dose dependent manner (1 mg/ml = 42% inhibitory effect) that are able to reduce body weight gain in rats fed a high-fat diet [84]. This plant contains several bioactive molecules, such as luteolin (figure 2), certain fatty acids, caffeic, ferulic and benzoic acids, all of which are able to inhibit lipases [9]. Coumarin derivates and phenolic acids were assumed to be the major active constituents. However the authors have not examined the individual effects of each compound. *Camellia sinensis*
*Camellia sinensis* or tea plant (green tea, black tea or oolong tea) contains over 60 polyphenols, some of them with a potent PL inhibitory activity. It is likely the plant whose extracts have been more thoroughly used for searching new PL inhibitors. The major polyphenols are catechins (figure2), which constitute about one third of its total dry weight. A serving of tea is moderate to high in flavonoid and/or tannin content [85-89]. Nakai et al. [90] found that the polyphenols with more potent PL inhibitory effect were flavan-3-ol digallate esters isolated from oolong tea, such as (-)-epigallocatechin-3,5-digallate. Oolong tea-polymerized polyphenols reduced postprandial hypertriglyceridemia in olive oil loaded in rats and mice [91]. Also (-)-epigallocatechin, abundant in the green tea extract, is a weak inhibitor of PL and is able to decrease the postprandial hypertriglyceridemia in rodents [92]. The administration of black-tea polyphenols suppressed postprandial hypertriglyceridemia in a dose-dependent manner in rats, with theaflavin-3,3'-digallate as the most effective PL inhibitor [93], whereas other authors point out to thearubigins [94]. These extracts are able to prevent increases in body weight and adiposity in mice fed a high-fat diet [95]. The PL inhibitory and hypotriglyceridemic effects of tea extracts were corroborated by Tanaka et al. [96], who orally administered mixed fermented tea extracts and Loquat tea extracts to rats with a 10% soybean oil emulsion. Finally, cocoa tea extract (*Camellia sinensis var. ptilophylla*) is rich in polyphenols with PL inhibitory effect. A single oral administration of this extract produces an inhibition of plasma triglyceride levels in olive oil-loaded ICR mice and triolein-loaded rats [97].

3. *Glycine max*

Daidzein (figure2) belongs to the group of isoflavones and is produced almost exclusively by the members of the fabaceae/leguminosae (bean) family such as soybean. In one study, Guo et al. [98] investigated the effects of daidzein on body weight,
adipose tissue, blood and liver lipid levels in obese mice fed a high-fat diet, finding that daidzein reduced body and white adipose tissue weights in obese mice and ameliorated the hyperlipidemia induced by the high fat diet. The authors attributed this effect to the inhibition of PL activity and fat digestion.

4. *Ilex paraguariensis*

Yerba mate (MT) is a plant from the subtropical region of South America that is widely consumed in Brazil, Argentina, Paraguay, and Uruguay. Yerba mate contains polyphenols, such as flavonoids (quercetin and rutin) (figure2) and phenolic acids (chlorogenic and caffeic acids) and is also rich in caffeine and saponins [99]. These substances act on the lipid metabolism by inhibiting PL activity in a concentration value of 1.5 mg/mL [99]. Several triterpene saponins and monoterpene oligoglycosides from the leaves of Yerba mate were found to exhibit potent inhibitory activity on porcine PL [100].

5. *Malus domestica*

Apples (*Malus domestica*) belong to the Rosaceae family whose fruits contain several phenolic substances (cholorogenic acid, catechin, epicatechin, phloridzin and procyanins). Procyanidins in apples are mainly composed of various polymerized catechins, with some of them showing a PL inhibitory activity and reducing triglyceride absorption [36]. In corn oil-loaded mice, a single oral administration of apple polyphenols reduced plasma triglyceride levels, and a test diet containing 600 mg of apple polyphenols significantly inhibited triglyceride elevation at 6 h after ingestion, indicating an inhibition of triglyceride absorption [36].

6. *Salacia reticulata*

*Salacia reticulata* contains a high concentration of polyphenols, including catechins and condensed tannins. In hot water-soluble extract from the roots of *Salacia reticulata*
The concentration is about 24% polyphenols [74]. The polyphenols from Salacia reticulata inhibit enzymes related to fat metabolism including PL, lipoprotein lipase, and glycerophosphate dehydrogenase, and are effective in preventing obesity [101]. In fact, Salacia extract markedly improved metabolic syndrome symptoms (including body weight, adiposity, glucose intolerance, hypertension and peripheral neuropathy) in TSOD mice [102].

7. Taraxacum officinale

Dandelion (Taraxacum officinale) is a perennial herbaceous plant of the family Asteraceae that has been used as a phytomedicine due to its choleric, antirheumatic, diuretic, and anti-inflammatory properties [103]. Extracts from this plant have shown hypolipidemic effects and an inhibitory activity of PL, decreasing AUC (area under curve) for the postprandial triglyceride response curve [103].

8. Vitis vinifera

Grapevine (Vitis vinifera) has become a model plant for studying proanthocyanidin biosynthesis. Grapevine proanthocyanidins (figure2) consist of two major flavan 3-ol monomers, catechin and epicatechin, that have inhibitory activity on PL [79,104]. Polyphenol-rich extracts from a range of berries, particularly cloudberry, are able to inhibit PL activity in vitro, which has been attributed to their content in ellagitannins and proanthocyanidins [105].

Saponins

Saponins are a major family of secondary metabolites that occur in a wide range of plants species [106]. These compounds have been isolated from different parts of the plants, including the roots, rhizomes, stems, bark, leaves, seeds and fruits. Occasionally, the whole plant has been used [107].
Saponins are categorized into two major classes, the triterpenoid and the steroid saponins, which are both derived from the 30 carbon atoms-containing precursor oxidosqualene [107,108]. Some of the triterpene-rich plant materials are common foodstuffs consumed in large amounts in Mediterranean countries. Therefore, the correlation of a triterpene-rich diet and the beneficial effects of consuming a Mediterranean diet should be investigated in more detail [32]. These types of plant secondary metabolites are found to inhibit PL and, thus, may represent potential effective treatments for obesity and related disorders [9,22]. One example are different saponins isolated from tea [85] or ginseng [109].

1. *Aesculus turbinata*

The Japanese horse chestnut (*Aesculus turbinata*) is a medicinal plant widely used in East Asia. The saponin mixture extracted from the seeds is called escins and has a strong inhibitory activity on PL [110]. In mice fed a high-fat diet, total escins suppressed the increase in body weight, adiposity and liver fat, and increased triglyceride level in the feces, whereas it decreased plasma triglycerides after the oral administration of a lipid emulsion [111,112].

2. *Dioscorea nipponica*

The methanol extract of *Dioscorea nipponica* Makino powder has a potent inhibitory activity against porcine PL, with an IC\textsubscript{50} value of 5-10 μg/mL [66]. In fact, the saponin dioscin and its aglycone, diosgenin, both suppressed the increase of blood triacylglycerols when orally injected with corn oil to mice. Rats fed a high-fat diet containing 5% *Dioscorea nipponica* Makino gained significantly less body weight and adipose tissue than control animals [66], and a similar result has been observed after administering the aqueous extract of this rhizome to mice fed a high-fat diet [113].

3. *Eleutherococcus senticosus*
*Eleutherococcus senticosus* is a shrub, belonging to the family Araliaceae, which is commonly distributed in north-eastern Asia. It is used as a traditional Chinese medicine against ischemic heart diseases, neurasthenia, hypertension, arthritis, and tumors [114]. At least fifteen triterpenoid saponins (figure3) with *in vitro* PL inhibitory activity have been isolated from the fruits of *Eleutherococcus senticosus* [115]. The total saponin fraction obtained from the fruits of *Eleutherococcus senticosus* exhibits inhibitory activity on PL with an IC$_{50}$ value of 3.63 mg/mL [114].

4. *Eleutherococcus sessiliflorus*

Different lupine-type triterpene triglycosides isolated from a hot water extract of *Eleutherococcus sessiliflorus* leaves are able to inhibit PL activity *in vitro*, and to suppress the body weight gain of mice fed a high-fat diet [116].

5. *Gardenia jasminoides*

Crocin is a glycosylated carotenoid extracted from the fructus of *Gardenia jasminoides* (figure3). Gardeniae fructus is used in Asian countries as a natural colorant, and in Chinese traditional medicine for its antioxidant, cytotoxic, antitumor and neuroprotective effects. Crocin and crocetin are effective hypolipidemic agents that act by reducing the absorption of fat and cholesterol through inhibition of PL activity [117]. Sheng et al. demonstrated that crocin selectively inhibited the activity of PL as a competitive inhibitor [118].

6. *Gypsophila oldhamiana*

*Gypsophila oldhamiana* (Caryophyllaceae) is a plant distributed in the north of China whose roots have high amounts of saponins, sterols and fatty acids. The extract from this plant shows a potent inhibitory activity of PL with an IC$_{50}$ value of 0.54 mg/ml [118,119], with different triterpenoid saponins, gypsosaponins A-C as the more efficient compounds [119].
7. *Panax ginseng*

Ginseng is one of the most popular medicinal herbs and is commonly consumed as powder, a beverage or a food supplement. Roots of *Panax ginseng* contain high levels of ginsenosides (figure3), which are steroidal saponins that show beneficial effects on lipid metabolism. Saponins from ginseng roots suppress the expected increase in body weight and plasma triacylglycerols in mice following a high-fat diet, which was probably mediated by inhibiting PL with an IC$_{50}$ value of 500 μg/mL [109].

8. *Panax japonicus*

The rhizomes of *Panax japonicus* (Japanese ginseng) are used in folk medicine for the treatment of arteriosclerosis, hyperlipidemia, hypertension and diabetes mellitus. Chikusetsusaponins prevent the increase in body weight and parametrial adipose tissue weight induced by a high-fat diet and inhibited the elevation of postprandial plasma triacylglycerols due to their inhibitory action of PL on dietary fat [120]. The delay in intestinal fat absorption was also behind the antiobesity effects observed for Korean white ginseng extract in high-fat diet-induced obese mice [121].

9. *Panax quinquefolium*

American ginseng (*Panax quinquefolium*) is a native plant from North America. The saponins isolated from stems and leaves of *Panax quinquefolium* may prevent fat storage in adipose tissue and postprandial elevations of plasma triacylglycerols by inhibiting the intestinal absorption of dietary fat through the inhibition of PL activity [122].

10. *Platycodi grandiflorum*

*Platycodi radix*, widely used in traditional Oriental medicines as a remedy for respiratory disorders, is rich in saponins, which are responsible for a diversity of effects including antiinflammation, antiallergy, antitumor, and immunostimulation [64]. Given
its inhibitory action on PL [123], with platycodin D as the most efficient compound [124], it ameliorated high fat-induced obesity in mice [125] and rats [64]. SK1 is an edible saponin-rich compound from Platycodi radix that is able to reduce body weight and fat accumulation by increasing fecal lipid outputs in high-fat-fed mice [126].

11. *Sapindus rarak*

The methanolic extract from the pericarps of *Sapindus rarak* (Lerak) shows a PL inhibitory activity that is probably due to diverse saponins and sesquiterpene glycosides [127].

12. *Scabiosa tschiliensis*

Different triterpenoid saponins isolated from the Mongol and Chinese traditional medicinal herb *Scabiosa tschiliensis* have shown strong inhibition of PL in vitro [128]. Due to the difficult task of isolating scabiosaponins and the scarceness of this type of saponins in nature, some of them have been successfully synthesized in the laboratory [129].

13. *Teasaponins*

At least three kinds of tea (oolong, green and black) have been used as healthy drinks. Teasaponins suppress the increases in body and parametrial adipose tissue weights and adipocyte diameters induced by a high-fat diet in mice by inhibiting PL, and also reduce the elevation in plasma triacylglycerol levels after oral administration of a lipid emulsion. The $Ki$ value of teasaponins was determined to be 0.25 mg/mL [85]. Thus, the crude saponin fraction from the flower buds of Chinese tea plant exhibits accelerating effects on gastrointestinal transit in mice and inhibitory effects against porcine PL, and thee florateasaponins (A-C) showed inhibitory effects on serum triglyceride elevation [130].
**Triterpenes**

Terpenes are the primary constituents of the essential oils of many types of plants and are classified by the number of terpene units in the molecule (diterpenes, triterpenes, among others). The pharmacological relevance of triterpenes has increased during the last two decades demonstrating multi-target properties such as wound healing, anti-inflammatory, anti-bacterial, antiviral, hepatoprotective and anti-tumoral effects, combined with low toxicity [32]. Triterpene extracts are safe and provide high potential for further pharmaceutical and pharmacological research [131], some of them inhibiting PL activity:

1. *Betula alba*

Bark of birch (*Betula alba*) contains pentacyclic triterpenes (figure3). This triterpene extract is safe and provides high potential for further pharmaceutical and pharmacological research [32,131], playing an inhibitory activity on PL [22].

**Clinical studies about pancreatic lipase inhibitors**

A number of plants and natural products have been screened for their PL inhibitory activity but just some of them have gone up to clinical studies. In this line, only one product derived from natural compounds (Orlistat) is currently in clinical use, although others are under investigation. Some of them are *Panax ginseng* [132], *Camellia sinensis* [133], *Eleutherococcus senticosus* [134], *Malus domestica* [135] and *Arachis hypogaea* [136].

In one study [132], the administration of an extract of *Panax ginseng* in humans for 8 weeks decreased circulating cholesterol, triglyceride and low density lipoprotein levels (LDL). Each subject ingested 2 g of *Panax ginseng* extract three times a day.
Lee et al. [134] reported that healthy postmenopausal women treated for 6 months with *Eleutherococcus senticosus* supplementation showed significant decreases in serum LDL levels and LDL/HDL ratios.

In other study, Sugiyama et al. [135] assessed six healthy male volunteers that followed a high fat diet with 40 g of fat with 10 control or 10 apple polyphenol (*Malus domestica*) capsules (600 or 1500 mg, respectively). In this study, they demonstrated that apple polyphenols may prevent obesity in humans by a PL inhibitory mechanism.

Green tea (*Camellia sinensis*) has been extensively studied in relation to obesity and other metabolic disorders. Thus, Chantre et al. [133] showed that green tea consumption may be useful to treat obesity by both, increasing thermogenesis and inhibiting PL. Thus, a green tea extract showed a direct *in vitro* inhibition of gastric and pancreatic lipases [133]. In moderately obese patients, green tea lowered body weight by stimulating thermogenesis and increasing energy expenditure when each subject received 2 times/d a green tea extract (2 capsules morning, 2 capsules midday). Ingestion of 4 capsules containing AR25 (Exolise) provided a daily total intake of 375 mg catechins, of which 270 mg was epigallocatechin gallate. Also, He et al. [137] administered daily 8 g of oolong tea for 6 weeks to 102 obese subjects. As a result, 70% of the obese subjects decreased more than 1 kg in body weight. In *in vitro* studies suggested that the effect of oolong tea on body weight could be partially attributed to the inhibition of PL [68].

According to these data, a number of common herbal products that are being studied in animal (table 3) and human models for obesity treatment contain different metabolites that act on lipid digestion and absorption. However, it is very difficult to establish in *in vivo* studies whether these antiobesity effects are only or mainly due to PL activity.
inhibition. The clinical implications of this therapeutic approach have yet to be
determined.

Conclusions

Orlistat is the only drug authorized and presented in Europe for the treatment of obesity
within an adequate energy intake, which acts by inhibiting the lipolytic activity of PL.
With the aim of finding new compounds more potent or with less secondary effects than
Orlistat, new natural products are being identified and screened for their PL inhibitory
potential. Some of these extracts are obtained from plants that are rich in polyphenols
and saponins and show inhibitory effects on fat digestion, whereas other extracts come
from algae, fungi and microorganisms. Thus, natural products provide an exciting
opportunity and promise for the development of new therapeutic approaches to the
treatment of obesity by blocking the digestion and absorption of dietary lipids, and
constitute a valuable alternative to other pharmacological agents. Some of the products
reviewed in this article show potentially promising effects for weight control. In
particular apple, green tea, soybean and ginseng seem to have great potential as sources
of molecules with PL inhibitory activity. For all of them more data are needed to define
effects, optimal dose required, and mechanism of action, as well as their possible side or
toxic effects.

Thus, there is an urgent need to update the knowledge on the numerous natural sources
that could act as inhibitors of PL in order to screen them as new potential therapeutic
antiobesity agents with low secondary effects.
Acknowledgements

The authors thank Línea Especial (LE/97) from the University of Navarra (Spain) and the CENIT PRONAOS Program (MICINN, Spain) for financial support. AL. de la Garza and N. Boqué hold pre-doctoral grants from Ibercaja.
<table>
<thead>
<tr>
<th>Family</th>
<th>Scientific name</th>
<th>Common name</th>
<th>Part of plant</th>
<th>Ref</th>
<th>Family</th>
<th>Scientific name</th>
<th>Common name</th>
<th>Part of plant</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aeraceae</td>
<td><em>Acer pseudosieboldianum</em></td>
<td>Korean maple</td>
<td>Whole</td>
<td>[138]</td>
<td>Lamiaceae</td>
<td><em>Spiridela polyrhiza</em></td>
<td>Common duckmeat</td>
<td>Whole</td>
<td>[138]</td>
</tr>
<tr>
<td>Anacardiaceae</td>
<td><em>Pistacia vera</em></td>
<td>Pistachio</td>
<td>Fruits hull</td>
<td>[52]</td>
<td>Lamiaceae</td>
<td><em>Thymus pulegioides</em></td>
<td>Lemon thyme</td>
<td>Whole</td>
<td>[22]</td>
</tr>
<tr>
<td>Apiaceae</td>
<td><em>Levisticum officinale</em></td>
<td>Garden lovage</td>
<td>Whole</td>
<td>[52]</td>
<td>Lauraceae</td>
<td><em>Cinnamomum zeylanicum</em></td>
<td>Cinnamon</td>
<td>Derm</td>
<td>[52]</td>
</tr>
<tr>
<td>Apiaceae</td>
<td><em>Sanicula chinesis</em></td>
<td>Russian nettle</td>
<td>Whole</td>
<td>[138]</td>
<td>Lauraceae</td>
<td><em>Lindera glauca</em></td>
<td>Grayblue spicebush</td>
<td>Whole</td>
<td>[138]</td>
</tr>
<tr>
<td>Araliaceae</td>
<td><em>Eleutherococcus senticosus</em></td>
<td>Siberian ginseng</td>
<td>Leaves</td>
<td>[114]</td>
<td>Liliaceae</td>
<td><em>Asparagus cochinchesis</em></td>
<td>Shiny asparagus</td>
<td>Radix</td>
<td>[138]</td>
</tr>
<tr>
<td>Aspidiaceae</td>
<td><em>Cystotum falcatum</em></td>
<td>Japanese holly fern</td>
<td>Whole</td>
<td>[138]</td>
<td>Liliaceae</td>
<td><em>Scilla selloides</em></td>
<td>Chinese scilla</td>
<td>Whole</td>
<td>[138]</td>
</tr>
<tr>
<td>Asteraceae</td>
<td><em>Artemisia scoparia</em></td>
<td>Redstem wormwood</td>
<td>Whole</td>
<td>[138]</td>
<td>Linaceae</td>
<td><em>Linum usitatissimum</em></td>
<td>Oil flax</td>
<td>Seed</td>
<td>[139]</td>
</tr>
<tr>
<td>Asteraceae</td>
<td><em>Helianthus annus</em></td>
<td>Common sunflower</td>
<td>Seed</td>
<td>[139]</td>
<td>Lythraceae</td>
<td><em>Lythrum salicaria</em></td>
<td>Purple loosestrife</td>
<td>Whole</td>
<td>[138]</td>
</tr>
<tr>
<td>Brassicaceae</td>
<td><em>Brassica nigra</em></td>
<td>Black mustard</td>
<td>Radix</td>
<td>[22]</td>
<td>Musaeae</td>
<td><em>Musa sapientum</em></td>
<td>French plantain</td>
<td>Fructus</td>
<td>[22]</td>
</tr>
<tr>
<td>Brassicaceae</td>
<td><em>Brassica oleracea capitata</em></td>
<td>Cabbage</td>
<td>Foliolum</td>
<td>[22]</td>
<td>Myricaceae</td>
<td><em>Myrica spp</em></td>
<td>Bayberry</td>
<td>Bark</td>
<td>[140]</td>
</tr>
<tr>
<td>Caprifoliaceae</td>
<td><em>Loniceraja japonica</em></td>
<td>Japanese honeysuckle</td>
<td>Whole</td>
<td>[138]</td>
<td>Myrtaceae</td>
<td><em>Solomonum tuberosum</em></td>
<td>Potato</td>
<td>Flowers</td>
<td>[22]</td>
</tr>
<tr>
<td>Celastraceae</td>
<td><em>Euonymus sachalinensis</em></td>
<td>Spindletree</td>
<td>Whole</td>
<td>[138]</td>
<td>Oleaceae</td>
<td><em>Olea europeae</em></td>
<td>Olive</td>
<td>Foliolum</td>
<td>[22]</td>
</tr>
<tr>
<td>Crassulaceae</td>
<td><em>Rhoiola rosea</em></td>
<td>Roseroot stonecrop</td>
<td>Whole</td>
<td>[141]</td>
<td>Orchidaceae</td>
<td><em>Gastrodia elata</em></td>
<td>Tien Ma</td>
<td>Whole</td>
<td>[138]</td>
</tr>
<tr>
<td>Cucurbitaceae</td>
<td><em>Cucurbita pepo</em></td>
<td>Field pumpkin</td>
<td>Whole</td>
<td>[138]</td>
<td>Oxalidaceae</td>
<td><em>Oxalis corniculata</em></td>
<td>Sleeping beauty</td>
<td>Whole</td>
<td>[138]</td>
</tr>
<tr>
<td>Cucurbitaceae</td>
<td><em>Momordica cochinchinesis</em></td>
<td>Spiny bastardgourd</td>
<td>Whole</td>
<td>[138]</td>
<td>Pooaceae</td>
<td><em>Eriochloa villosa</em></td>
<td>Hairy cupgrass</td>
<td>Whole</td>
<td>[138]</td>
</tr>
<tr>
<td>Cyperaceae</td>
<td><em>Cyperus esculentus</em></td>
<td>Spiny bittergourd</td>
<td>Whole</td>
<td>[138]</td>
<td>Pooaceae</td>
<td><em>Hemarthria sibirica</em></td>
<td>Weed</td>
<td>Whole</td>
<td>[138]</td>
</tr>
<tr>
<td>Cyperaceae</td>
<td><em>Carex kobomugi</em></td>
<td>Japanese sedge</td>
<td>Whole</td>
<td>[138]</td>
<td>Pooaceae</td>
<td><em>Panicum dichotomiflorum</em></td>
<td>Fall panicgrass</td>
<td>Whole</td>
<td>[138]</td>
</tr>
<tr>
<td>Cyperaceae</td>
<td><em>Cyperus amuricus</em></td>
<td>Asian flatsedge</td>
<td>Whole</td>
<td>[138]</td>
<td>Pooaceae</td>
<td><em>Setaria italica</em></td>
<td>Foxtail bristlegrass</td>
<td>Whole</td>
<td>[138]</td>
</tr>
<tr>
<td>Elyagnaceae</td>
<td><em>Elaeagnus macrophylle</em></td>
<td>Olearster</td>
<td>Whole</td>
<td>[138]</td>
<td>Polygalaceae</td>
<td><em>Polygala tenuifolia</em></td>
<td>Yuan Zhi</td>
<td>Whole</td>
<td>[138]</td>
</tr>
<tr>
<td>Ericaceae</td>
<td><em>Arctostaphylus uva-ursi</em></td>
<td>Bear berry</td>
<td>Foliolum</td>
<td>[22]</td>
<td>Polygoneae</td>
<td><em>Reynoutria elliptica</em></td>
<td>Black bindweed</td>
<td>Whole</td>
<td>[138]</td>
</tr>
<tr>
<td>Ericaceae</td>
<td><em>Vaccinium myrtillus</em></td>
<td>Bilberry</td>
<td>Fructus</td>
<td>[22]</td>
<td>Polygoneae</td>
<td><em>Rheum ribes</em></td>
<td>Rhubarb</td>
<td>Rhizomes</td>
<td>[52]</td>
</tr>
<tr>
<td>Ericaulaceae</td>
<td><em>Ericaulon sieboldianum</em></td>
<td>Flattened pipewort</td>
<td>Whole</td>
<td>[138]</td>
<td>Potamogetonaceae</td>
<td><em>Potamogeton distinctus</em></td>
<td>Pondweed</td>
<td>Whole</td>
<td>[138]</td>
</tr>
<tr>
<td>Fabaceae</td>
<td><em>Althae camelorum</em></td>
<td>Cameldhorn</td>
<td>Aerial parts</td>
<td>[52]</td>
<td>Rosaceae</td>
<td><em>Rosa damascene</em></td>
<td>Damask rose</td>
<td>Fioret</td>
<td>[52]</td>
</tr>
<tr>
<td>Fabaceae</td>
<td><em>Glycyrrhiza uralensis</em></td>
<td>Gan Cao</td>
<td>Whole</td>
<td>[138]</td>
<td>Rosaceae</td>
<td><em>Rubus ideus</em></td>
<td>Raspberry</td>
<td>Fructus</td>
<td>[22]</td>
</tr>
<tr>
<td>Fabaceae</td>
<td><em>Lemneseda cuneata</em></td>
<td>Chinese bush clover</td>
<td>Whole</td>
<td>[138]</td>
<td>Rosaceae</td>
<td><em>Malus domestica</em></td>
<td>Apple</td>
<td>Fructus</td>
<td>[22]</td>
</tr>
<tr>
<td>Fabaceae</td>
<td><em>Phaseolus vulgaris</em></td>
<td>Common bean</td>
<td>Foliolium</td>
<td>[22]</td>
<td>Rubiaceae</td>
<td><em>Gardenia jasmoinodes</em></td>
<td>Cape jasmine</td>
<td>Whole</td>
<td>[138]</td>
</tr>
<tr>
<td>Fabaceae</td>
<td><em>Pisum sativum</em></td>
<td>Garden pea</td>
<td>Fructus</td>
<td>[22]</td>
<td>Rubiaceae</td>
<td><em>Rubia akane</em></td>
<td>Asian madder</td>
<td>Whole</td>
<td>[138]</td>
</tr>
<tr>
<td>Fabaceae</td>
<td><em>Quercus variabilis</em></td>
<td>Alkali oak</td>
<td>Galls</td>
<td>[52]</td>
<td>Rutaceae</td>
<td><em>Murraya koeninggi</em></td>
<td>Curlyleaf tree</td>
<td>Leaves</td>
<td>[142]</td>
</tr>
<tr>
<td>Juncaceae</td>
<td><em>Juncus effusus</em></td>
<td>Soft rush</td>
<td>Whole</td>
<td>[138]</td>
<td>Rutaceae</td>
<td><em>Orica japonica</em></td>
<td>Pearl frost</td>
<td>Whole</td>
<td>[138]</td>
</tr>
<tr>
<td>Lamiales</td>
<td><em>Agastache rugosa</em></td>
<td>Purple giant hyssop</td>
<td>Whole</td>
<td>[138]</td>
<td>Saxifragaceae</td>
<td><em>Chrysosplenium grayanum</em></td>
<td>Golden saxifrage</td>
<td>Whole</td>
<td>[138]</td>
</tr>
<tr>
<td>Lamiales</td>
<td><em>Agrostis stolonifera</em></td>
<td>Oregano</td>
<td>Herba</td>
<td>[22]</td>
<td>Simaroubaceae</td>
<td><em>Alanthus altissima</em></td>
<td>Tree of heaven</td>
<td>Whole</td>
<td>[138]</td>
</tr>
<tr>
<td>Lamiales</td>
<td><em>Primula vulgaris</em></td>
<td>Common selfheal</td>
<td>Whole</td>
<td>[73]</td>
<td>Tiliaeae</td>
<td><em>Tilia platyphylos</em></td>
<td>Large leaf linden</td>
<td>Whole</td>
<td>[22]</td>
</tr>
<tr>
<td>Lamiales</td>
<td><em>Rosmarinus officinalis</em></td>
<td>Rosemary</td>
<td>Foliolum</td>
<td>[22]</td>
<td>Urticaeae</td>
<td><em>Urtica urens</em></td>
<td>Dwarf nettle</td>
<td>Aerial parts</td>
<td>[52]</td>
</tr>
<tr>
<td>Lamiales</td>
<td><em>Salvia officinalis</em></td>
<td>Salvia</td>
<td>Foliolum</td>
<td>[22]</td>
<td>Zingiberaeae</td>
<td><em>Afromimum meleguetta</em></td>
<td>Meleguetta pepper</td>
<td>Seed</td>
<td>[143]</td>
</tr>
</tbody>
</table>
Table 2 Some classes of natural compounds that have been reported to \textit{in vitro}\ inhibit pancreatic lipase activity and species from which the compound has been obtained.

<table>
<thead>
<tr>
<th>Metabolites, Scientific name</th>
<th>Common name</th>
<th>Family</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flavonoids, Alpinia officinarum</td>
<td>Lesser galangal</td>
<td>Zingiberaceae</td>
<td>[144,145]</td>
</tr>
<tr>
<td>Flavonoids, Taraxacum officinale</td>
<td>Dandelion</td>
<td>Asteraceae</td>
<td>[103]</td>
</tr>
<tr>
<td>Flavonoids, Actinidia arguta</td>
<td>Kiwi</td>
<td>Actinidiaceae</td>
<td>[146]</td>
</tr>
<tr>
<td>Polyphenols, Arachis hypogaea</td>
<td>Peanut</td>
<td>Fabaceae</td>
<td>[9]</td>
</tr>
<tr>
<td>Polyphenols, Mangifera indica</td>
<td>Mango</td>
<td>Anacardiaceae</td>
<td>[9]</td>
</tr>
<tr>
<td>Polyphenols, Medicago sativa</td>
<td>Alfalfa</td>
<td>Fabaceae</td>
<td>[78]</td>
</tr>
<tr>
<td>Polyphenols, Nelumbo nucifera</td>
<td>Sacred lotus</td>
<td>Nelumbonaceae</td>
<td>[9]</td>
</tr>
<tr>
<td>Polyphenols, Salacia reticulata</td>
<td>Kotala himbutu</td>
<td>Celastraceae</td>
<td>[101]</td>
</tr>
<tr>
<td>Polyphenols, Salix matsudana</td>
<td>Corkscrew willow</td>
<td>Salicaceae</td>
<td>[147]</td>
</tr>
<tr>
<td>Polyphenols, Proanthocyanidins, Camellia sinensis</td>
<td>Green, black, oolong tea</td>
<td>Theaceae</td>
<td>[89]</td>
</tr>
<tr>
<td>Polyphenols, Saponins, Ilex paragauriensis</td>
<td>Yerba mate</td>
<td>Aquifoliaceae</td>
<td>[99]</td>
</tr>
<tr>
<td>Polyphenols, Saponins, Cassia mimosoides</td>
<td>Nomame herba</td>
<td>Fabaceae</td>
<td>[148]</td>
</tr>
<tr>
<td>Polyphenols, Saponins, Cinnamomum sieboldii</td>
<td>Cinnamon</td>
<td>Lauraceae</td>
<td>[86]</td>
</tr>
<tr>
<td>Polyphenols, Theobroma cacao</td>
<td>Cocoa</td>
<td>Malvaceae</td>
<td>[86]</td>
</tr>
<tr>
<td>Polyphenols, Saponins, Vitis vinifera</td>
<td>Grape vine</td>
<td>Vitaceae</td>
<td>[79,104]</td>
</tr>
<tr>
<td>Saponins, Aesculus hippocastanum</td>
<td>Horse chestnut</td>
<td>Sapindaceae</td>
<td>[32]</td>
</tr>
<tr>
<td>Saponins, Aesculus turbinata</td>
<td>Japanese horse chestnut</td>
<td>Hipocastanaceae</td>
<td>[110]</td>
</tr>
<tr>
<td>Saponins, Arctostaphylos uva-ursi</td>
<td>Bearberry</td>
<td>Ericaceae</td>
<td>[32]</td>
</tr>
<tr>
<td>Saponins, Ardisia japonica</td>
<td>Marlberry</td>
<td>Myrsinaceae</td>
<td>[152]</td>
</tr>
<tr>
<td>Saponins, Avena sativa</td>
<td>Oat</td>
<td>Poaceae</td>
<td>[149]</td>
</tr>
<tr>
<td>Saponins, Coffea arabica</td>
<td>Coffee</td>
<td>Rubiaceae</td>
<td>[32]</td>
</tr>
<tr>
<td>Saponins, Cyclacarya paliurus</td>
<td>Wheel wingnut</td>
<td>Juglandaceae</td>
<td>[9]</td>
</tr>
<tr>
<td>Saponins, Dioscorea nipponica</td>
<td>Yam</td>
<td>Dioscoreaceae</td>
<td>[9]</td>
</tr>
<tr>
<td>Saponins, Eleutherococcus senticosus</td>
<td>Siberian ginseng</td>
<td>Araliaceae</td>
<td>[114]</td>
</tr>
<tr>
<td>Saponins, Eleutherococcus sessiliflorus</td>
<td>Sessiliside</td>
<td>Araliaceae</td>
<td>[9]</td>
</tr>
<tr>
<td>Saponins, Gardenia jasminoides</td>
<td>Cape jasmine</td>
<td>Rubiaceae</td>
<td>[118]</td>
</tr>
<tr>
<td>Saponins, Gypsophila oldhamiana</td>
<td>Oldham’s baby’s-breath</td>
<td>Caryophyllaceae</td>
<td>[119]</td>
</tr>
<tr>
<td>Saponins, Kochia scoparia</td>
<td>Burningbush</td>
<td>Chenopodiaceae</td>
<td>[150]</td>
</tr>
<tr>
<td>Saponins, Malus domestica</td>
<td>Apple</td>
<td>Rosaceae</td>
<td>[32]</td>
</tr>
<tr>
<td>Saponins, Momordica charantia</td>
<td>Balsampear</td>
<td>Cucurbitaceae</td>
<td>[151]</td>
</tr>
<tr>
<td>Saponins, Olea europeae</td>
<td>Olive</td>
<td>Oleaceae</td>
<td>[32]</td>
</tr>
<tr>
<td>Saponins, Panax ginseng</td>
<td>Ginseng</td>
<td>Araliaceae</td>
<td>[109]</td>
</tr>
<tr>
<td>Saponins, Panax japonicus</td>
<td>Japanese ginseng</td>
<td>Araliaceae</td>
<td>[120]</td>
</tr>
<tr>
<td>Saponins, Panax quinguefolium</td>
<td>American ginseng</td>
<td>Araliaceae</td>
<td>[122]</td>
</tr>
<tr>
<td>Saponins, Phatodoid radix</td>
<td>Doraji</td>
<td>Campanulaceae</td>
<td>[64]</td>
</tr>
<tr>
<td>Saponins, Phatodon grandiflorum</td>
<td>Balloon flower</td>
<td>Campanulaceae</td>
<td>[103]</td>
</tr>
<tr>
<td>Saponins, Sapindus rarak</td>
<td>Soapberry</td>
<td>Sapindaceae</td>
<td>[127]</td>
</tr>
<tr>
<td>Saponins, Scabiosa tschiliensis</td>
<td>Pincushions</td>
<td>Dipsacaceae</td>
<td>[9]</td>
</tr>
<tr>
<td>Saponins, Solanum lycopersicum</td>
<td>Tomato</td>
<td>Solanaceae</td>
<td>[32]</td>
</tr>
<tr>
<td>Terpenes, Salvia officinalis</td>
<td>Salvia</td>
<td>Lamiaceae</td>
<td>[32]</td>
</tr>
<tr>
<td>Triterpenes, Aloe vera</td>
<td>Aloe vera</td>
<td>Asphodelaceae</td>
<td>[32]</td>
</tr>
<tr>
<td>Triterpenes, Betula alba</td>
<td>Birch</td>
<td>Betulaceae</td>
<td>[32]</td>
</tr>
<tr>
<td>Triterpenes, Calendula officinalis</td>
<td>Pot marigold</td>
<td>Asteraceae</td>
<td>[32]</td>
</tr>
<tr>
<td>Triterpenes, Melissa officinalis</td>
<td>Lemon balm</td>
<td>Lamiaceae</td>
<td>[32]</td>
</tr>
<tr>
<td>Triterpenes, Origanum vulgare</td>
<td>Oregano</td>
<td>Lamiaceae</td>
<td>[32]</td>
</tr>
</tbody>
</table>
Table 3: Plant extracts that showed *in vivo* inhibitory activity of pancreatic lipase, doses and effects.

<table>
<thead>
<tr>
<th>Scientific name</th>
<th>Common name</th>
<th>Doses</th>
<th>Model</th>
<th>Effects</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Aesculus turbinata</em></td>
<td>Japanese horse chestnut</td>
<td>0.1 – 0.5% of diet</td>
<td>DIO mice</td>
<td>↓ TG plasma levels and ▼ body weight gain</td>
<td>[153]</td>
</tr>
<tr>
<td><em>Arachis hypogaea</em></td>
<td>Peanut</td>
<td>1% of diet</td>
<td>DIO rats</td>
<td>▼ Body weight gain</td>
<td>[136]</td>
</tr>
<tr>
<td><em>Camellia sinensis</em></td>
<td>Green, black, oolong tea</td>
<td>3% of HFD</td>
<td>Rats</td>
<td>Body weight gain and ▼ visceral fat</td>
<td>[89]</td>
</tr>
<tr>
<td><em>Cassia mimosoides</em></td>
<td>Nomame herba</td>
<td>1 – 3.5% of diet</td>
<td>DIO rats</td>
<td>▼ Body weight gain</td>
<td>[154]</td>
</tr>
<tr>
<td><em>Coffea arabica</em></td>
<td>Coffee</td>
<td>0.5% of standard diet</td>
<td>Mice</td>
<td>▼ Body weight gain</td>
<td>[155]</td>
</tr>
<tr>
<td><em>Cyclocarya paliurus</em></td>
<td>Wheel wingnut</td>
<td>250 mg/kg; VO</td>
<td>Mice</td>
<td>▼ TG plasma levels and blood glucose levels</td>
<td>[156]</td>
</tr>
<tr>
<td><em>Dioscorea nipponica</em></td>
<td>Yam</td>
<td>5% of HFD</td>
<td>Rats</td>
<td>▼ TG plasma levels and ▼ body weight gain</td>
<td>[157]</td>
</tr>
<tr>
<td><em>Eleutherococcus senticosus</em></td>
<td>Siberian ginseng</td>
<td>12 mg/kg</td>
<td>DIO rats</td>
<td>▼ Abdominal fat, TG in liver and serum and LDL in serum</td>
<td>[158]</td>
</tr>
<tr>
<td><em>Eleutherococcus sessiliflorus</em></td>
<td>Sessiloside</td>
<td>100-300 mg/kg; VO</td>
<td>Mice</td>
<td>▼ TG plasma levels</td>
<td>[159]</td>
</tr>
<tr>
<td><em>Gardenia jasminoides</em></td>
<td>Cape jasmine</td>
<td>50 mg/kg/d</td>
<td>Mice</td>
<td>▼ Body weight gain</td>
<td>[118]</td>
</tr>
<tr>
<td><em>Humulus lupulus</em></td>
<td>Common hop</td>
<td>0.2 – 1.2% (w/w) of extract</td>
<td>Mice</td>
<td>▼ Body weight gain and ▼ blood glucose levels</td>
<td>[160]</td>
</tr>
<tr>
<td><em>Ilex paraguariensis</em></td>
<td>Yerba mate</td>
<td>0.24% of HFD</td>
<td>Rats</td>
<td>▼ Body weight gain</td>
<td>[99]</td>
</tr>
<tr>
<td><em>Kochia scoparia</em></td>
<td>Burningbush</td>
<td>3% of HFD</td>
<td>Mice</td>
<td>▼ Body weight gain</td>
<td>[150]</td>
</tr>
<tr>
<td><em>Malus domestica</em></td>
<td>Apple</td>
<td>200 mg/kg; VO</td>
<td>Mice</td>
<td>▼ TG plasma levels</td>
<td>[161]</td>
</tr>
<tr>
<td><em>Myrica spp</em></td>
<td>Bayberry</td>
<td>-----</td>
<td>-----</td>
<td>▼ TG plasma levels</td>
<td>[140]</td>
</tr>
<tr>
<td><em>Nelumbo nucifera</em></td>
<td>Sacred lotus</td>
<td>5% of diet</td>
<td>Mice</td>
<td>▼ TG plasma levels and ▼ body weight gain</td>
<td>[162]</td>
</tr>
<tr>
<td><em>Panax ginseng</em></td>
<td>Ginseng</td>
<td>200 mg/kg with HFD</td>
<td>Rats</td>
<td>▼ Body weight gain</td>
<td>[109]</td>
</tr>
<tr>
<td><em>Panax japonicus</em></td>
<td>Japanese ginseng</td>
<td>1 – 3% of diet</td>
<td>DIO mice</td>
<td>▼ Body weight gain</td>
<td>[120]</td>
</tr>
<tr>
<td><em>Platycodi radix</em></td>
<td>Doraji</td>
<td>70 mg/kg, with HFD</td>
<td>Sprague Dawly rats</td>
<td>▼ Body weight gain</td>
<td>[64]</td>
</tr>
<tr>
<td><em>Rhodiola rosea</em></td>
<td>Roseroot stonecrop</td>
<td>150 mg/kg</td>
<td>Mice</td>
<td>▼ TG plasma levels</td>
<td>[141]</td>
</tr>
<tr>
<td><em>Rosmarinus officinalis</em></td>
<td>Rosemary</td>
<td>200 mg/kg HFD</td>
<td>Mice</td>
<td>▼ Body weight and fat mass</td>
<td>[163]</td>
</tr>
<tr>
<td><em>Salacia reticulata</em></td>
<td>Kotala himbutu</td>
<td>125 mg/kg; VO HFD</td>
<td>Rats</td>
<td>▼ Body weight gain</td>
<td>[101]</td>
</tr>
<tr>
<td><em>Salix matsudana</em></td>
<td>Corkscrew willow</td>
<td>5% of HFD</td>
<td>Wistar rats</td>
<td>▼ Body weight gain</td>
<td>[147]</td>
</tr>
</tbody>
</table>

DIO: Diet-induced obesity; HFD: High-fat diet; VO: Via oral. (Daily food intake is approximately rats: 20 g/day; mice: 4.5 g/day)
References


6 Little T, Horowitz M, Feinle-Bisset C. Modulation by high-fat diets of gastrointestinal function and hormones associated with the regulation of energy intake: implications for the pathophysiology of obesity. Am J Clin Nutr 2007; 86: 531-541


29 Hermsdorff HHM, Volp ACP, Bressan J. [Macronutrient profile affects diet-induced thermogenesis and energy intake]. Arch Latinoam Nutr 2007; 57: 33-42

31 Rolls BJ. The role of energy density in the overconsumption of fat. J Nutr 2000; 130: 268-271


33 Stevenson E, Astbury N, Simpson E, Taylor M, Macdonald I. Fat oxidation during exercise and satiety during recovery are increased following a low-glycemic index breakfast in sedentary women. J Nutr 2009; 139: 890-897


49 Bitou N, Ninomiya M, Tsujita T, Okuda H. Screening of lipase inhibitors from marine algae. Lipids 1999; 34: 441-445


He F, Pan Q, Shi Y, Duan C. Biosynthesis and genetic regulation of proanthocyanidins in plants. Molecules 2008; 13: 2674-2692

Quesada H, del Bas JM, Pajuelo D, Daz S, Fernandez-Larrea J, Pinent M. Grape seed proanthocyanidins correct dyslipidemia associated with a high-fat diet in rats and repress genes controlling lipogenesis and VLDL assembling in liver. Int J Obes 2009; 33: 1007-1012


de la Iglesia R, Milagro FI, Campion J, Boque N, Martinez JA. Healthy properties of proanthocyanidins. Biofactors 2010; 36: 159-168


92 Ikeda I. Multifunctional effects of green tea catechins on prevention of the metabolic syndrome. Asia Pac J Clin Nutr 2008; 17: 273-274


121 Lee Y, Cha B, Yamaguchi K, Choi S, Yonezawa T, Teruya T. Effects of Korean white ginseng extracts on obesity in high-fat diet-induced obese mice. Cytotechnology 2010


131 Jäger S, Laszczyk M, Scheffler A. A preliminary pharmacokinetic study of betulin, the main pentacyclic triterpene from extract of outer bark of birch (Betulae alba cortex). Molecules 2008; 13: 3224-3235

133 Chantre P, Lairon D. Recent findings of green tea extract AR25 (Exolise) and its activity for the treatment of obesity. Phytomedicine 2002; 9: 3-8


149 Osbourn A. Saponins in cereals. Phytochemistry 2003; 62: 1-4


158 Cha Y, Rhee S, Heo Y. Acanthopanax senticosus extract prepared from cultured cells decreases adiposity and obesity indices in C57BL/6J mice fed a high fat diet. J Med Food 2004; 7: 422-429


