

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, Noemí Boque, Javier Campión, J.Alfredo
Martínez

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)

(figure 1). 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 steatorrhea, 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 tested 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*, *albolongus*, *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 ($83\% \pm 5\%$, $96\% \pm 3\%$ and $97\% \pm 5\%$, respectively), even higher than Orlistat. *Pleurotus eryngii* 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 tociformis*, 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 derivatives 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 (chlorogenic 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*

(SRHW) 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 IC₅₀ 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 IC₅₀ 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 IC₅₀ 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 IC₅₀ 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, anti-allergy, 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 *K_i* 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 three floratheasaponins (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 1 Plant extracts that showed over 40% inhibitory activity *in vitro* of pancreatic lipase and part of the plant from which the extract has been isolated.

Family	Scientific name	Common name	Part of plant	Ref	Family	Scientific name	Common name	Part of plant	Ref
Aeraceae	<i>Acer pseudosieboldianum</i>	Korean maple	Whole	[138]	Lamiaceae	<i>Spirodela polyrhiza</i>	Common duckmeat	Whole	[138]
Anacardiaceae	<i>Pistacia vera</i>	Pistachio	Fruits hull	[52]	Lamiaceae	<i>Thymus pulegoides</i>	Lemon thyme	Whole	[22]
Apiaceae	<i>Levisticum officinale</i>	Garden lovage	Whole	[52]	Lauraceae	<i>Cinnamomum zeylanicum</i>	Cinnamon	Derm	[52]
Apiaceae	<i>Sanicula chinensis</i>	Bian Dou Cai	Whole	[138]	Lauraceae	<i>Lindera glauca</i>	Grayblue spicebush	Whole	[138]
Araliaceae	<i>Eleutherococcus senticosus</i>	Siberian ginseng	Leaves	[114]	Liliaceae	<i>Asparagus cochinchinensis</i>	Shiny asparagus	Radix	[138]
Aspidiaceae	<i>Cyrtomium falcatum</i>	Japanese holly fern	Whole	[138]	Liliaceae	<i>Scilla scilloides</i>	Chinese scilla	Whole	[138]
Asteraceae	<i>Artemisia scoparia</i>	Redstem wormwood	Whole	[138]	Linaceae	<i>Linum usitatissimum</i>	Oil flax	Seed	[139]
Asteraceae	<i>Helianthus annuus</i>	Common sunflower	Seed	[139]	Lythraceae	<i>Lythrum salicaria</i>	Purple loosestrife	Whole	[138]
Brassicaceae	<i>Brassica nigra</i>	Black mustard	Radix	[22]	Musaceae	<i>Musa sapientum</i>	French plantain	Fructus	[22]
Brassicaceae	<i>Brassica oleracea capitata</i>	Cabbage	Folium	[22]	Myricaceae	<i>Myrika spp</i>	Bayberry	Bark	[140]
Brassicaceae	<i>Raphanus sativus</i>	Radish	Radix	[22]	Myrtaceae	<i>Myrtus communis</i>	True myrtle	Leaves	[52]
Caprifoliaceae	<i>Lonicera japonica</i>	Japanese honeysuckle	Whole	[138]	Myrtaceae	<i>Solanum tuberosum</i>	Potato	Flowers	[22]
Celastraceae	<i>Euonymus sachalinensis</i>	Spindletree	Whole	[138]	Oleaceae	<i>Olea europaea</i>	Olive	Folium	[22]
Crassulaceae	<i>Rhodiola rosea</i>	Roseroot stonecrop	Whole	[141]	Orchidaceae	<i>Gastrodia elata</i>	Tien Ma	Whole	[138]
Cucurbitaceae	<i>Cucurbita pepo</i>	Field pumpkin	Whole	[138]	Oxalidaceae	<i>Oxalis corniculata</i>	Sleeping beauty	Whole	[138]
Cucurbitaceae	<i>Momordica cochinchinensis</i>	Spiny bittergourd	Whole	[138]	Poaceae	<i>Eriochloa villosa</i>	Hairy cupgrass	Whole	[138]
Cyperaceae	<i>Bulbostylis barbata</i>	Watergrass	Whole	[138]	Poaceae	<i>Hemarthria sibirica</i>	Weed	Whole	[138]
Cyperaceae	<i>Carex kobomugi</i>	Japanese sedge	Whole	[138]	Poaceae	<i>Panicum dichotomiflorum</i>	Fall panicgrass	Whole	[138]
Cyperaceae	<i>Cyperus amuricus</i>	Asian flatsedge	Whole	[138]	Poaceae	<i>Setaria italica</i>	Foxtail bristlegrass	Whole	[138]
Eleagnaceae	<i>Elaeagnus macrophylla</i>	Oleaster	Whole	[138]	Polygalaceae	<i>Polygala tenuifolia</i>	Yuan Zhi	Whole	[138]
Ericaceae	<i>Arctostaphylos uva-ursi</i>	Bear berry	Folium	[22]	Polygonaceae	<i>Reynoutria elliptica</i>	Black bindweed	Whole	[138]
Ericaceae	<i>Vaccinium myrtillus</i>	Bilberry	Fructus	[22]	Polygonaceae	<i>Rheum ribes</i>	Rhubarb	Rhizomes	[52]
Eriocaulaceae	<i>Eriocaulon sieboldianum</i>	Flattened pipewort	Whole	[138]	Potamogetonaceae	<i>Potamogeton distinctus</i>	Pondweed	Whole	[138]
Fabaceae	<i>Alhagi camelorum</i>	Camelthorn	Aerial parts	[52]	Rosaceae	<i>Rosa damascene</i>	Damask rose	Floret	[52]
Fabaceae	<i>Glycyrrhiza uralensis</i>	Gan Cao	Whole	[138]	Rosaceae	<i>Rubus idaeus</i>	Raspberry	Fructus	[22]
Fabaceae	<i>Lespedeza cuneata</i>	Chinese bush clover	Whole	[138]	Rosaceae	<i>Malus domestica</i>	Apple	Fructus	[22]
Fabaceae	<i>Phaseolus vulgaris</i>	Common bean	Whole	[22]	Rubiaceae	<i>Gardenia jasminoides</i>	Cape jasmine	Whole	[138]
Fabaceae	<i>Pisum sativum</i>	Garden pea	Fructus	[22]	Rubiaceae	<i>Rubia akane</i>	Asian madder	Whole	[138]
Fabaceae	<i>Pueraria thunbergiana</i>	Kudzu	Whole	[138]	Rutaceae	<i>Citrus aurantifolium</i>	Lime	Whole	[138]
Fabaceae	<i>Quercus infectoria</i>	Aleppo oak	Galls	[52]	Rutaceae	<i>Murraya koeningii</i>	Curryleaf tree	Leaves	[142]
Juncaceae	<i>Juncus effusus</i>	Soft rush	Whole	[138]	Rutaceae	<i>Oriza japonica</i>	Pearl frost	Whole	[138]
Lamiaceae	<i>Agastache rugosa</i>	Purple giant hyssop	Whole	[138]	Saxifragaceae	<i>Chrysosplenium grayanum</i>	Golden saxifrage	Whole	[138]
Lamiaceae	<i>Origanum vulgare</i>	Oregano	Herba	[22]	Simaroubaceae	<i>Ailanthus altissima</i>	Tree of heaven	Whole	[138]
Lamiaceae	<i>Prunella vulgaris</i>	Common selfheal	Whole	[73]	Tiliaceae	<i>Tilia platyphyllos</i>	Largeleaf linden	Whole	[22]
Lamiaceae	<i>Rosmarinus officinalis</i>	Rosemary	Folium	[22]	Urticaceae	<i>Urtica urens</i>	Dwarf nettle	Aerial parts	[52]
Lamiaceae	<i>Salvia officinalis</i>	Salvia	Folium	[22]	Zingiberaceae	<i>Afromomum meleguetta</i>	Meleguetta pepper	Seed	[143]

Table 2 Some classes of natural compounds that have been reported to *in vitro* inhibit pancreatic lipase activity and species from which the compound has been obtained.

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

Table 3 Plant extracts that showed *in vivo* inhibitory activity of pancreatic lipase, doses and effects.

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

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

- 1 *Drew B, Dixon A, Dixon J.* Obesity management: update on orlistat. *Vasc Health Risk Manag* 2007; 3: 817-821
- 2 *Brug J, Crawford D.* The obesity pandemic. Is it bad or worse? *Eur J Public Health* 2009; 19: 570-571
- 3 *Schrauwen P, Westerterp KR.* The role of high-fat diets and physical activity in the regulation of body weight. *Br J Nutr.* 2000; 84: 417-427
- 4 *Voshol P, Rensen PCN, van Dijk K, Romijn J, Havekes L.* Effect of plasma triglyceride metabolism on lipid storage in adipose tissue: studies using genetically engineered mouse models. *Biochim Biophys Acta* 2009; 1791: 479-485
- 5 *Abete I, Astrup A, Martinez JA, Thorsdottir I, Zulet M.* Obesity and the metabolic syndrome: role of different dietary macronutrient distribution patterns and specific nutritional components on weight loss and maintenance. *Nutr Rev* 2010; 68: 214-231
- 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
- 7 *Rubio M, Gargallo M, Millán A, Moreno B.* Drugs in the treatment of obesity: sibutramine, orlistat and rimonabant. *Public Health Nutr* 2007; 10: 1200-1205
- 8 *Moreno D, Ilic N, Poulev A, Brasaemle D, Fried S, Raskin I.* Inhibitory effects of grape seed extract on lipases. *Nutrition* 2003; 19: 876-879
- 9 *Birari R, Bhutani K.* Pancreatic lipase inhibitors from natural sources: unexplored potential. *Drug Discov Today* 2007; 12: 879-889
- 10 *Sumantran V.* Experimental approaches for studying uptake and action of herbal medicines. *Phytother Res* 2007; 21: 210-214
- 11 *Yamagishi S, Matsui T, Ueda S, Fukami K, Okuda S.* Clinical utility of acarbose, an alpha-glucosidase inhibitor in cardiometabolic disorders. *Curr Drug Metab* 2009; 10: 159-163
- 12 *Raz I, Eldor R, Cernea S, Shafir E.* Diabetes: insulin resistance and derangements in lipid metabolism. Cure through intervention in fat transport and storage. *Diabetes Metab Res* 2005; 21:3-14
- 13 *Hosoyama H, Sugimoto A, Suzuki Y, Sakane I, Kakuda T.* [Isolation and quantitative analysis of the alpha-amylase inhibitor in *Lagerstroemia speciosa* (L.) Pers. (Banaba)]. 2003; 123: 599-605
- 14 *Tsujita T, Takaku T, Suzuki T.* Chestnut astringent skin extract, an alpha-amylase inhibitor, retards carbohydrate absorption in rats and humans. *J Nutr Sci Vitaminol* 2008; 54: 82-88

- 15 *Tormo MA, Gil-Exojo I, de Tejada AR, Campillo JE*. White bean amylase inhibitor administered orally reduces glycaemia in type 2 diabetic rats. *Br J Nutr* 2006; 96: 539-544
- 16 *Bray G, Ryan D*. Drug treatment of the overweight patient. *Gastroenterol* 2007; 132: 2239-2252
- 17 *McClendon K, Riche D, Uwaifo G*. Orlistat: current status in clinical therapeutics. *Expert Opin Drug Saf* 2009; 8: 727-744
- 18 *Weibel EK, Hadvary P, Hochuli E, Kupfer E, Lengsfeld H*. Lipstatin, an inhibitor of pancreatic lipase, produced by *Streptomyces toxytricini*. I. Producing organism, fermentation, isolation and biological activity. *J Antibiot* 1987; 40: 1081-1085
- 19 *Viner RM, Hsia Y, Tomsic T, Wong ICK*. Efficacy and safety of anti-obesity drugs in children and adolescents: systematic review and meta-analysis. *Obes Revs* 2010; 11: 593-602
- 20 *Heymsfield SB, Segal KR, Hauptman J, Lucas CP, Boldrin MN, Rissanen A*. Effects of weight loss with orlistat on glucose tolerance and progression to type 2 diabetes in obese adults. *Arch Intern Med* 2000; 160: 1321-1326
- 21 *Torgerson J, Hauptman J, Boldrin M, Sjstrm L*. Xenical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care* 2004; 27: 155-161
- 22 *Slanc P, Doljak B, Kreft S, Lunder M, Janes D, Strukelj B*. Screening of selected food and medicinal plant extracts for pancreatic lipase inhibition. *Phytother Res* 2009; 23: 874-877
- 23 *Slanc P, Doljak B, Mlinaric A, Strukelj B*. Screening of wood damaging fungi and macrofungi for inhibitors of pancreatic lipase. *Phytother Res* 2004; 18: 758-762
- 24 *Bitou N, Ninomiya M, Tsujita T, Okuda H*. Screening of lipase inhibitors from marine algae. *Lipids* 1999; 34: 441-445
- 25 *Abete I, Parra MD, Zulet MA, Martinez JA*. Different dietary strategies for weight loss in obesity: role of energy and macronutrient content. *Nutr Rev* 2006; 19:5-17
- 26 *Astrup A*. The role of dietary fat in the prevention and treatment of obesity. Efficacy and safety of low-fat diets. *Int J Obes* 2001; 25: 46-50
- 27 *Lomba A, Martinez JA, Garcia-Daz D, Paternain L, Marti A, Campion J, Milagro FI*. Weight gain induced by an isocaloric pair-fed high fat diet: A nutriepigenetic study on FASN and NDUF6 gene promoters. *Mol Genet Metab* 2010; 101: 273-278
- 28 *Lomba A, Milagro FI, Garcia-Daz DF, Campion J, Marzo F, Martinez JA*. A high-sucrose isocaloric pair-fed model induces obesity and impairs NDUF6 gene function in rat adipose tissue. *J Nutrigenet Nutrigenomics* 2009; 2: 267-272
- 29 *Hermisdorff HHM, Volp ACP, Bressan J*. [Macronutrient profile affects diet-induced thermogenesis and energy intake]. *Arch Latinoam Nutr* 2007; 57: 33-42

- 30 *Mobbs C, Mastaitis J, Yen K, Schwartz J, Mohan V, Poplawski M.* Low-carbohydrate diets cause obesity, low-carbohydrate diets reverse obesity: a metabolic mechanism resolving the paradox. *Appetite* 2007; 48: 135-138
- 31 *Rolls BJ.* The role of energy density in the overconsumption of fat. *J Nutr* 2000; 130: 268-271
- 32 *Jäger S, Trojan H, Kopp T, Laszczyk M, Scheffler A.* Pentacyclic triterpene distribution in various plants - rich sources for a new group of multi-potent plant extracts. *Molecules* 2009; 14: 2016-2031
- 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
- 34 *Armand M.* Lipases and lipolysis in the human digestive tract: where do we stand? *Curr Opin Clin Nutr Metab Care* 2007; 10: 156-164
- 35 *Lowe M.* The triglyceride lipases of the pancreas. *J Lipid Res* 2002; 43: 2007-2016
- 36 *Sugiyama H, Akazome Y, Shoji T, Yamaguchi A, Yasue M, Kanda T.* Oligomeric procyanidins in apple polyphenol are main active components for inhibition of pancreatic lipase and triglyceride absorption. *J Agric Food Chem* 2007; 55: 4604-4609
- 37 *Neovius M, Johansson K, Rssner S.* Head-to-head studies evaluating efficacy of pharmacotherapy for obesity: a systematic review and meta-analysis. *Obes Rev* 2008; 9: 420-427
- 38 *Filippatos T, Derdemezis C, Gazi I, Nakou E, Mikhailidis D, Elisaf M.* Orlistat-associated adverse effects and drug interactions: a critical review. *Drug Saf* 2008; 31: 53-65
- 39 *Kopelman P, Bryson A, Hickling R, Rissanen A, Rossner S, Toubro S.* Cetilistat (ATL-962), a novel lipase inhibitor: a 12-week randomized, placebo-controlled study of weight reduction in obese patients. *Int J Obes* 2007; 31: 494-499
- 40 *Melia AT, Koss-Twardy SG, Zhi J.* The effect of orlistat, an inhibitor of dietary fat absorption, on the absorption of vitamins A and E in healthy volunteers. *J Clin Pharmacol* 1996; 36: 647-653
- 41 *Mutoh M, Nakada N, Matsukuma S, Ohshima S, Yoshinari K, Watanabe J.* Panclitics, novel pancreatic lipase inhibitors. I. Taxonomy, fermentation, isolation and biological activity. *J Antibiot* 1994; 47: 1369-1375
- 42 *Nonaka Y, Ohtaki H, Ohtsuka E, Kocha T, Fukuda T, Takeuchi T.* Effects of ebelactone B, a lipase inhibitor, on intestinal fat absorption in the rat. *J Enzym Inhib* 1996; 10: 57-63
- 43 *Liu D, Wang F, Liao T, Tang J, Steglich W, Zhu H.* Vibralactone: a lipase inhibitor with an unusual fused beta-lactone produced by cultures of the basidiomycete *Boreostereum vibrans*. *Org Lett* 2006; 8: 5749-5752
- 44 *Weber HK, Zuegg J, Faber K, Pleiss J.* Molecular reasons for lipase-sensitivity against acetaldehyde. *J Mol Catal B* 1997: 131-138

- 45 Mizutani T, Inatomi S, Inazu A, Kawahara E. Hypolipidemic effect of *Pleurotus eryngii* extract in fat-loaded mice. *J Nutr Sci Vitaminol* 2010; 56: 48-53
- 46 Lee J, Song J, Lee J. Optimal Extraction Conditions of Anti-obesity Lipase Inhibitor from *Phellinus linteus* and Nutritional Characteristics of the Extracts. *Mycobiol* 2010; 38: 58-61
- 47 Kim J, Kim H, Park H, Youn S, Choi D, Shin C. Development of inhibitors against lipase and alpha-glucosidase from derivatives of monascus pigment. *FEMS Microbiol Lett* 2007; 276: 93-98
- 48 Jones A, Gu L, Sorrels C, Sherman D, Gerwick W. New tricks from ancient algae: natural products biosynthesis in marine cyanobacteria. *Curr Opin Chem Biol* 2009; 13: 216-223
- 49 Bitou N, Ninomiya M, Tsujita T, Okuda H. Screening of lipase inhibitors from marine algae. *Lipids* 1999; 34: 441-445
- 50 Ben Rebah F, Smaoui S, Frikha F, Gargouri Y, Miled N. Inhibitory effects of tunisian marine algal extracts on digestive lipases. *Appl Biochem Biotechnol* 2008; 151: 71-79
- 51 Matsumoto M, Hosokawa M, Matsukawa N, Hagio M, Shinoki A, Nishimukai M. Suppressive effects of the marine carotenoids, fucoxanthin and fucoxanthinol on triglyceride absorption in lymph duct-cannulated rats. *Eur J Nutr* 2010; 49: 243-249
- 52 Gholamhoseinian A, Shahouzehi, B. and Sharifi-far, F. Inhibitory Effect of Some Plant Extracts on Pancreatic Lipase. *Int J Pharmacol* 2010; 6: 18-24
- 53 Gargouri Y, Julien R, Pieroni G, Verger R, Sarda L. Studies on the inhibition of pancreatic and microbial lipases by soybean proteins. *J Lipid Res* 1984; 25: 1214-1221
- 54 Lairon D, Lafont H, Vigne JL, Nalbone G, Lonardi J, Hauton JC. Effects of dietary fibers and cholestyramine on the activity of pancreatic lipase in vitro. *Am J Clin Nutr* 1985; 42: 629-638
- 55 Tsujita T, Matsuura Y, Okuda H. Studies on the inhibition of pancreatic and carboxylester lipases by protamine. *J Lipid Res* 1996; 37: 1481-1487
- 56 Tsujita T, Sumiyoshi M, Takaku T, Momsen W, Lowe M, Brockman H. Inhibition of lipases by epsilon-polylysine. *J Lipid Res* 2003; 44: 2278-2286
- 57 Ivanova M, Panaiotov I, Bois A, GArgouri Y, Verger R. Inhibition of pancreatic lipase by ovalbumin and -lactoglobulin A at the air-water interface. *J Colloid Interface Sci* 1990; 136: 363-374
- 58 Gargouri Y, Julien R, Sugihara A, Verger R, Sarda L. Inhibition of pancreatic and microbial lipases by proteins. *Biochim Biophys Acta* 1984; 795: 326-331
- 59 Han LK, Kimura Y, Okuda H. Reduction in fat storage during chitin-chitosan treatment in mice fed a high-fat diet. *Int J Obes* 1999; 23: 174-179
- 60 Tsujita T, Takaichi H, Takaku T, Sawai T, Yoshida N, Hiraki J. Inhibition of lipase activities by basic polysaccharide. *J Lipid Res* 2007; 48: 358-365

- 61 *Knuckles B.* Effect of phytate and other myo-inositol phosphate esters on lipase activity. *J Food Sci* 1988; 53: 250-252
- 62 *Raghavendra MP, Prakash V.* Phenylboronic acid--a potent inhibitor of lipase from *Oryza sativa*. *J Agric Food Chem* 2002; 50: 6037-6041
- 63 *Ninomiya K, Matsuda H, Shimoda H, Nishida N, Kasajima N, Yoshino T.* Carnosic acid, a new class of lipid absorption inhibitor from sage. *Bioorg Med Chem Lett* 2004; 14: 1943-1946
- 64 *Zhao HL, Sim J, Shim SH, Ha YW, Kang SS, Kim YS.* Antiobese and hypolipidemic effects of platycodin saponins in diet-induced obese rats: evidences for lipase inhibition and calorie intake restriction. *Int J Obes* 2005; 29: 983-990
- 65 *Zhao H, Kim Y.* Determination of the kinetic properties of platycodin D for the inhibition of pancreatic lipase using a 1,2-diglyceride-based colorimetric assay. *Arch Pharm Res* 2004; 27: 1048-1052
- 66 *Kwon C, Sohn H, Kim S, Kim J, Son K, Lee J.* Anti-obesity effect of *Dioscorea nipponica* Makino with lipase-inhibitory activity in rodents. *Biosci Biotechnol Biochem* 2003; 67: 1451-1456.
- 67 *Won S, Kim S, Kim Y, Lee P, Ryu J, Kim J.* Licochalcone A: a lipase inhibitor from the roots of *Glycyrrhiza uralensis*. *Food Res Intern* 2007; 40: 1046-1050
- 68 *Ono Y, Hattori E, Fukaya Y, Imai S, Ohizumi Y.* Anti-obesity effect of *Nelumbo nucifera* leaves extract in mice and rats. *J Ethnopharmacol* 2006; 106: 238-244
- 69 *Kim H, Kang M.* Screening of Korean medicinal plants for lipase inhibitory activity. *PTR. Phytother Res* 2005; 19: 359-361
- 70 *Moreno D, Ripoll C, Ilic N, Poulev A, Aubin C, Raskin I.* Inhibition of lipid metabolic enzymes using *Mangifera indica* extracts. *J Food Agric Environ* 2006; 4: 21-26
- 71 *Lei F, Zhang XN, Wang W, Xing DM, Xie WD, Su H.* Evidence of anti-obesity effects of the pomegranate leaf extract in high-fat diet induced obese mice. *Int J Obes* 2007; 31: 1023-1029
- 72 *Yang H, Kim Y, Bae H, Cho, Ki-Ho, Shin, Ji-Eun, Kim N, Kim Dong-Hyun.* Rhei Rhizoma and *Chunghyuldan* inhibit pancreatic lipase. *Nat Product Sci* 2003; 9: 38-43
- 73 *Zheng C, Duan Y, Gao J, Ruan Z.* Screening for anti-lipase properties of 37 traditional Chinese medicinal herbs. *J Chin Med Assoc* 2010; 73: 319-324
- 74 *Yoshikawa M, Shimoda H, Nishida N, Takada M, Matsuda H.* *Salacia reticulata* and its polyphenolic constituents with lipase inhibitory and lipolytic activities have mild antiobesity effects in rats. *J Nutr* 2002; 132: 1819-1824
- 75 *Terra X, Montagut G, Bustos M, Llopiz N, Ardvoll A, Blad C.* Grape-seed procyanidins prevent low-grade inflammation by modulating cytokine expression in rats fed a high-fat diet. *J Nutr Biochem* 2009; 20: 210-218

- 76 *García-Lafuente A, Guillamón E, Villares A, Rostagno M, Martínez J.* Flavonoids as anti-inflammatory agents: implications in cancer and cardiovascular disease. *Inflammation Res* 2009; 58: 537-552
- 77 *Kawaguchi K, Mizuno T, Aida K, Uchino K.* Hesperidin as an inhibitor of lipases from porcine pancreas and *Pseudomonas*. *Biosci Biotechnol Biochem* 1997; 61: 102-104
- 78 *He F, Pan Q, Shi Y, Duan C.* Biosynthesis and genetic regulation of proanthocyanidins in plants. *Molecules* 2008; 13: 2674-2692
- 79 *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
- 80 *Lee Y, Cho E, Tanaka T, Yokozawa T.* Inhibitory activities of proanthocyanidins from persimmon against oxidative stress and digestive enzymes related to diabetes. *J Nutr Sci Vitaminol* 2007; 53: 287-292
- 81 *de la Iglesia R, Milagro FI, Campion J, Boque N, Martinez JA.* Healthy properties of proanthocyanidins. *Biofactors* 2010; 36: 159-168
- 82 *Yamamoto M, Shimura S, Itoh Y, Ohsaka T, Egawa M, Inoue S.* Anti-obesity effects of lipase inhibitor CT-II, an extract from edible herbs, *Nomame Herba*, on rats fed a high-fat diet. *Int J Obes* 2000; 24: 758-764
- 83 *Ikeda I, Tsuda K, Suzuki Y, Kobayashi M, Unno T, Tomoyori H.* Tea catechins with a galloyl moiety suppress postprandial hypertriacylglycerolemia by delaying lymphatic transport of dietary fat in rats. *J Nutr* 2005; 135: 155-159
- 84 *Moreno D, Ilic N, Poulev A, Raskin I.* Effects of *Arachis hypogaea* nutshell extract on lipid metabolic enzymes and obesity parameters. *Life Sci.* 2006; 78: 2797-2803
- 85 *Han LK, Kimura Y, Kawashima M, Takaku T, Taniyama T, Hayashi T.* Anti-obesity effects in rodents of dietary teasaponin, a lipase inhibitor. *Int J Obes* 2001; 25: 1459-1464
- 86 *Tanaka T, Matsuo Y, Kouno I.* Chemistry of Secondary Polyphenols Produced during Processing of Tea and Selected Foods. *Int J Mol Sci* 2009; 11: 14-34
- 87 *Koo S, Noh S.* Green tea as inhibitor of the intestinal absorption of lipids: potential mechanism for its lipid-lowering effect. *J Nutr Biochem* 2007; 18: 179-183
- 88 *Juhel C, Armand M, Pafumi Y, Rosier C, Vandermander J, Lairon D.* Green tea extract (AR25) inhibits lipolysis of triglycerides in gastric and duodenal medium in vitro. *J Nutr Biochem* 2000; 11: 45-51
- 89 *Bose M, Lambert J, Ju J, Reuhl K, Shapses S, Yang C.* The major green tea polyphenol, (-)-epigallocatechin-3-gallate, inhibits obesity, metabolic syndrome, and fatty liver disease in high-fat-fed mice. *J Nutr* 2008; 138: 1677-1683

- 90 Nakai M, Fukui Y, Asami S, Toyoda-Ono Y, Iwashita T, Shibata H. Inhibitory effects of oolong tea polyphenols on pancreatic lipase in vitro. *J Agric Food Chem* 2005; 53):4593-4598
- 91 Toyoda-Ono Y, Yoshimura M, Nakai M, Fukui Y, Asami S, Shibata H. Suppression of postprandial hypertriglyceridemia in rats and mice by oolong tea polymerized polyphenols. *Biosci Biotechnol Biochem* 2007; 71: 971-976
- 92 Ikeda I. Multifunctional effects of green tea catechins on prevention of the metabolic syndrome. *Asia Pac J Clin Nutr* 2008; 17: 273-274
- 93 Kobayashi M, Ichitani M, Suzuki Y, Unno T, Sugawara T, Yamahira T. Black-tea polyphenols suppress postprandial hypertriacylglycerolemia by suppressing lymphatic transport of dietary fat in rats. *J Agric Food Chem* 2009; 57: 7131-7136
- 94 Kusano R, Andou H, Fujieda M, Tanaka T, Matsuo Y, Kouno I. Polymer-like polyphenols of black tea and their lipase and amylase inhibitory activities. *Chem Pharm Bull* 2008; 56: 266-272
- 95 Uchiyama S, Taniguchi Y, Saka A, Yoshida A, Yajima H. Prevention of diet-induced obesity by dietary black tea polyphenols extract in vitro and in vivo. *Nutrition* 2010. In Press
- 96 Tanaka K, Tamaru S, Nishizono S, Miyata Y, Tamaya K, Matsui T. Hypotriacylglycerolemic and antiobesity properties of a new fermented tea product obtained by tea-rolling processing of third-crop green tea (*Camellia sinensis*) leaves and Loquat (*Eriobotrya japonica*) leaves. *Biosci Biotechnol Biochem* 2010; 74: 1606-1612
- 97 Kurihara H, Shibata H, Fukui Y, Kiso Y, Xu J, Yao X. Evaluation of the hypolipemic property of *Camellia sinensis* Var. *ptilophylla* on postprandial hypertriglyceridemia. *J Agric Food Chem* 2006; 54: 4977-4981
- 98 Guo Y, Wu G, Su X, Yang H, Zhang J. Antiobesity action of a daidzein derivative on male obese mice induced by a high-fat diet. *Nutr Res* 2009; 29: 656-663
- 99 Martins F, Noso T, Porto V, Curiel A, Gambero A, Bastos DHM. Maté tea inhibits in vitro pancreatic lipase activity and has hypolipidemic effect on high-fat diet-induced obese mice. *Obesity* 2010; 18: 42-47
- 100 Sugimoto S, Nakamura S, Yamamoto S, Yamashita C, Oda Y, Matsuda H. Brazilian natural medicines. III. structures of triterpene oligoglycosides and lipase inhibitors from mate, leaves of *ilex paraguariensis*. *Chem Pharm Bull* 2009; 57: 257-261
- 101 Yoshikawa M, Shimoda H, Nishida N, Takada M, Matsuda H. *Salacia reticulata* and its polyphenolic constituents with lipase inhibitory and lipolytic activities have mild antiobesity effects in rats. *J Nutr* 2002; 132: 1819-1824
- 102 Akase T, Shimada T, Harasawa Y, Akase T, Ikeya Y, Nagai E. Preventive Effects of *Salacia reticulata* on Obesity and Metabolic Disorders in TSOD Mice. *Evid Based Complement Alternat Med* 2009. In Press

- 103 Zhang J, Kang M, Kim M, Kim M, Song J, Lee Y. Pancreatic lipase inhibitory activity of taraxacum officinale in vitro and in vivo. *Nutr Res Pract* 2008; 2: 200-203
- 104 Zhao J, Pang Y, Dixon R. The mysteries of proanthocyanidin transport and polymerization. *Plant Physiol.* 2010; 153: 1-18
- 105 McDougall GJ, Kulkarni NN, Stewart D. Berry polyphenols inhibit pancreatic lipase activity *in vitro*. *J Food Chem* 2009; 115: 193-199
- 106 Sparg SG, Light ME, van Staden J. Biological activities and distribution of plant saponins. *J Ethnopharmacol* 2004; 94: 219-243
- 107 Vincken J, Heng L, de Groot A, Gruppen H. Saponins, classification and occurrence in the plant kingdom. *Phytochemistry* 2007; 68: 275-297
- 108 Haralampidis K, Trojanowska M, Osbourn A. Biosynthesis of triterpenoid saponins in plants. *Adv Biochem Eng Biotechnol* 2002; 75:31
- 109 Karu N, Reifen R, Kerem Z. Weight gain reduction in mice fed Panax ginseng saponin, a pancreatic lipase inhibitor. *J Agric Food Chem* 2007; 55: 2824-2828
- 110 Kimura H, Ogawa S, Jisaka M, Kimura Y, Katsube T, Yokota K. Identification of novel saponins from edible seeds of Japanese horse chestnut (*Aesculus turbinata* Blume) after treatment with wooden ashes and their nutraceutical activity. *J Pharm Biomed Anal* 2006; 41: 1657-1665
- 111 Hu J, Zhu X, Han L, Saito M, Sun Y, Yoshikawa M. Anti-obesity effects of escins extracted from the seeds of *Aesculus turbinata* BLUME (Hippocastanaceae). *Chem Pharm Bull* 2008; 56: 12-16
- 112 Kimura H, Ogawa S, Katsube T, Jisaka M, Yokota K. Antiobese effects of novel saponins from edible seeds of Japanese horse chestnut (*Aesculus turbinata* BLUME) after treatment with wood ashes. *J Agric Food Chem* 2008; 56: 4783-4788
- 113 Song M, Lv N, Kim E, Kwon K, Yoo Y, Kim J. Antiobesity activity of aqueous extracts of *Rhizoma Dioscoreae Tokoronis* on high-fat diet-induced obesity in mice. *J Med Food* 2009; 12: 304-309
- 114 Li F, Li W, Fu H, Zhang Q, Koike K. Pancreatic lipase-inhibiting triterpenoid saponins from fruits of *Acanthopanax senticosus*. *Chem Pharm Bull* 2007; 55: 1087-1089
- 115 Jiang W, Li W, Han L, Liu L, Zhang Q, Zhang S. Biologically active triterpenoid saponins from *Acanthopanax senticosus*. *J Nat Prod* 2006; 69: 1577-1581
- 116 Yoshizumi K, Hirano K, Ando H, Hirai Y, Ida Y, Tsuji T. Lupane-type saponins from leaves of *Acanthopanax sessiliflorus* and their inhibitory activity on pancreatic lipase. *J Agric Food Chem* 2006; 54: 335-341
- 117 Lee I, Lee J, Baek N, Kim D. Antihyperlipidemic effect of crocin isolated from the fructus of *Gardenia jasminoides* and its metabolite Crocetin. *Biol Pharm Bull* 2005; 28: 2106-2110

- 118 *Sheng L, Qian Z, Zheng S, Xi L*. Mechanism of hypolipidemic effect of crocin in rats: crocin inhibits pancreatic lipase. *Eur J Pharmacol* 2006; 543: 116-122
- 119 *Zheng Q, Li W, Han L, Koike K*. Pancreatic lipase-inhibiting triterpenoid saponins from *Gypsophila oldhamiana*. *Chem Pharm Bull* 2007; 55: 646-650
- 120 *Han L, Zheng Y, Yoshikawa M, Okuda H, Kimura Y*. Anti-obesity effects of chikusetsusaponins isolated from *Panax japonicus* rhizomes. *BMC Complement Altern Med* 2005; 5: 9-9
- 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
- 122 *Liu W, Zheng Y, Han L, Wang H, Saito M, Ling M*. Saponins (Ginsenosides) from stems and leaves of *Panax quinquefolium* prevented high-fat diet-induced obesity in mice. *Phytomedicine* 2008; 15: 1140-1145
- 123 *Xu B, Han L, Zheng Y, Lee J, Sung C*. In vitro inhibitory effect of triterpenoidal saponins from *Platycodi Radix* on pancreatic lipase. *Arch Pharm Res* 2005; 28: 180-185
- 124 *Zhao H, Kim Y*. Determination of the kinetic properties of platycodin D for the inhibition of pancreatic lipase using a 1,2-diglyceride-based colorimetric assay. *Arch Pharm Res* 2004; 27: 968-972
- 125 *Han L, Zheng Y, Xu B, Okuda H, Kimura Y*. Saponins from *platycodi radix* ameliorate high fat diet-induced obesity in mice. *J Nutr* 2002; 132: 2241-2245
- 126 *Kim J, Moon K, Seo K, Park K, Choi M, Do G*. Supplementation of SK1 from *Platycodi radix* ameliorates obesity and glucose intolerance in mice fed a high-fat diet. *J Med Food* 2009; 12(3):629-636
- 127 *Morikawa T, Xie Y, Asao Y, Okamoto M, Yamashita C, Muraoka O*. Oleanane-type triterpene oligoglycosides with pancreatic lipase inhibitory activity from the pericarps of *Sapindus rarak*. *Phytochemistry* 2009; 70: 1166-1172
- 128 *Zheng Q, Koike K, Han L, Okuda H, Nikaido T*. New biologically active triterpenoid saponins from *Scabiosa tschiliensis*. *J Nat Prod* 2004; 67: 604-613
- 129 *Guo T, Liu Q, Wang P, Zhang L, Zhang W, Li Y*. Facile synthesis of three bidesmosidic oleanolic acid saponins with strong inhibitory activity on pancreatic lipase. *Carbohydr Res* 2009; 344: 1167-1174
- 130 *Yoshikawa M, Morikawa T, Yamamoto K, Kato Y, Nagatomo A, Matsuda H*. Floratheasaponins A-C, acylated oleanane-type triterpene oligoglycosides with anti-hyperlipidemic activities from flowers of the tea plant (*Camellia sinensis*). *J Nat Prod* 2005; 68: 1360-1365
- 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

- 132 *Kim S, Park K.* Effects of Panax ginseng extract on lipid metabolism in humans. *Pharmacol Res* 2003; 48: 511-513
- 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
- 134 *Lee Y, Chung H, Kwak H, Yoon S.* The effects of *A. senticosus* supplementation on serum lipid profiles, biomarkers of oxidative stress, and lymphocyte DNA damage in postmenopausal women. *Biochem Biophys Res Commun* 2008; 375: 44-48
- 135 *Sugiyama H, Akazome Y, Shoji T, Yamaguchi A, Yasue M, Kanda T.* Oligomeric procyanidins in apple polyphenol are main active components for inhibition of pancreatic lipase and triglyceride absorption. *J Agric Food Chem* 2007; 55: 4604-4609
- 136 *Moreno D, Ilic N, Poulev A, Raskin I.* Effects of *Arachis hypogaea* nutshell extract on lipid metabolic enzymes and obesity parameters. *Life Sci* 2006; 78: 2797-2803
- 137 *He R, Chen L, Lin B, Matsui Y, Yao X, Kurihara H.* Beneficial effects of oolong tea consumption on diet-induced overweight and obese subjects. *Chin J Int Med* 2009; 15: 34-41
- 138 *Sharma N, Sharma V, Seo S.* Screening of some medicinal plants for anti-lipase activity. *J Ethnopharmacol* 2005; 97: 453-456
- 139 *Möller N, Roos N, Schrezenmeir J.* Lipase inhibitory activity in alcohol extracts of worldwide occurring plants and propolis. *Phytother Res* 2009; 23: 585-586
- 140 *Kobayashi K, Ihara S, Kobata A, Itoh K, Kusunoki N, Yoshizaki F.* Inhibitory effect of Myrica bark on lipase activity in mouse plasma and gastrointestinal tract. *J Med Food* 2008; 11: 289-293
- 141 *Kobayashi K, Yamada K, Murata T, Hasegawa T, Takano F, Koga K.* Constituents of *Rhodiola rosea* showing inhibitory effect on lipase activity in mouse plasma and alimentary canal. *Planta Med* 2008; 74: 1716-1719
- 142 *Birari R, Roy S, Singh A, Bhutani K.* Pancreatic lipase inhibitory alkaloids of *Murraya koenigii* leaves. *Nat Prod Commun* 2009; 4: 1089-1092
- 143 *Ekanem AP, Wang M, Simon JE, Moreno DA.* Antiobesity properties of two African plants (*Aframomum melegueta* and *Spilanthes acmella*) by pancreatic lipase inhibition. *Phytother Res* 2007; 21: 1253-1255
- 144 *Shin J, Han M, Song M, Baek N, Kim D.* 5-Hydroxy-7-(4'-hydroxy-3'-methoxyphenyl)-1-phenyl-3-heptanone: a pancreatic lipase inhibitor isolated from *Alpinia officinarum*. *Biol Pharm Bull* 2004; 27: 138-140
- 145 *Shin J, Han M, Kim D.* 3-Methylethergalangin isolated from *Alpinia officinarum* inhibits pancreatic lipase. *Biol Pharm Bull* 2003; 26: 854-857

- 146 Jang D, Lee G, Kim J, Lee Y, Kim J, Kim Y. A new pancreatic lipase inhibitor isolated from the roots of *Actinidia arguta*. *Arch Pharm Res* 2008; 31: 666-670
- 147 Han L, Sumiyoshi M, Zhang J, Liu M, Zhang X, Zheng Y. Anti-obesity action of *Salix matsudana* leaves (Part 1). Anti-obesity action by polyphenols of *Salix matsudana* in high fat-diet treated rodent animals. *Phytother Res* 2003; 17: 1188-1194
- 148 Tucci SA, Boyland EJ, Halford JC. The role of lipid and carbohydrate digestive enzyme inhibitors in the management of obesity: a review of current and emerging therapeutic agents. *Diabetes Metab Syn Obes Targ Ther* 2010; 3: 125-143
- 149 Osbourn A. Saponins in cereals. *Phytochemistry* 2003; 62: 1-4
- 150 Han L, Nose R, Li W, Gong X, Zheng Y, Yoshikawa M. Reduction of fat storage in mice fed a high-fat diet long term by treatment with saponins prepared from *Kochia scoparia* fruit. *Phytother Res* 2006; 20: 877-882
- 151 Oishi Y, Sakamoto T, Udagawa H, Taniguchi H, Kobayashi-Hattori K, Ozawa Y. Inhibition of increases in blood glucose and serum neutral fat by *Momordica charantia* saponin fraction. *Biosci Biotechnol Biochem* 2007; 71: 735-740
- 152 Chang X, Li W, Jia Z, Satou T, Fushiya S, Koike K. Biologically active triterpenoid saponins from *Ardisia japonica*. *J Nat Prod* 2007; 70: 179-187
- 153 Kimura H, Ogawa S, Katsube T, Jisaka M, Yokota K. Antiobese effects of novel saponins from edible seeds of Japanese horse chestnut (*Aesculus turbinata* BLUME) after treatment with wood ashes. *J Agric Food Chem* 2008; 56: 4783-4788
- 154 Yamamoto M, Shimura S, Itoh Y, Ohsaka T, Egawa M, Inoue S. Anti-obesity effects of lipase inhibitor CT-II, an extract from edible herbs, *Nomame Herba*, on rats fed a high-fat diet. *Int J Obes* 2000; 24: 758-764
- 155 Shimoda H, Seki E, Aitani M. Inhibitory effect of green coffee bean extract on fat accumulation and body weight gain in mice. *BMC Complement Altern Med* 2006; 6: 9-9
- 156 Kurihara H, Asami S, Shibata H, Fukami H, Tanaka T. Hypolipemic effect of *Cyclocarya paliurus* (Batal) Iljinskaja in lipid-loaded mice. *Biol Pharm Bull* 2003; 26: 383-385
- 157 Kwon C, Sohn H, Kim S, Kim J, Son K, Lee J. Anti-obesity effect of *Dioscorea nipponica* Makino with lipase-inhibitory activity in rodents. *Biosci Biotechnol Biochem* 2003; 67: 1451-1456
- 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
- 159 Yoshizumi K, Murota K, Watanabe S, Tomi H, Tsuji T, Terao J. Chiisanoside is not absorbed but inhibits oil absorption in the small intestine of rodents. *Biosci Biotechnol Biochem* 2008; 72: 1126-1129

- 160 *Yajima H, Noguchi T, Ikeshima E, Shiraki M, Kanaya T, Tsuboyama-Kasaoka N.* Prevention of diet-induced obesity by dietary isomerized hop extract containing isohumulones, in rodents. *Int J Obes* 2005; 29: 991-997
- 161 *Sugiyama H, Akazome Y, Shoji T, Yamaguchi A, Yasue M, Kanda T.* Oligomeric procyanidins in apple polyphenol are main active components for inhibition of pancreatic lipase and triglyceride absorption. *J Agric Food Chem* 2007; 55: 4604-4609
- 162 *Ono Y, Hattori E, Fukaya Y, Imai S, Ohizumi Y.* Anti-obesity effect of *Nelumbo nucifera* leaves extract in mice and rats. *J Ethnopharmacol* 2006; 106: 238-244
- 163 *Harach T, Aprikian O, Monnard I, Moulin J, Membrez M, Bolor J.* Rosemary (*Rosmarinus officinalis* L.) leaf extract limits weight gain and liver steatosis in mice fed a high-fat diet. *Planta Med* 2010; 76: 566-571