

LIPASE INHIBITORS FROM PLANTS AND THEIR MEDICAL APPLICATIONS

GURMEET SINGH¹, SUKRUTHA SURESH¹, VENKATA KRISHNA BAYINENI, RAVI KUMAR KADEPPAGARI*

Food Science and Technology Division, Centre for Emerging Technologies, Jain University, Jain Global Campus, Jakkasandra, Kanakapura
Main Road, Ramanagara Dist., Karnataka, India, 562112
Email: k.ravikumar@jainuniversity.ac.in

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ABSTRACT

Obesity and its related disorders have become a major concern across the world. However, there are only few medications for treating obesity. Reducing the fat absorption through the inhibition of pancreatic lipase has become most favorable strategy for treating obesity since pancreatic lipase is a safe target and its inhibition does not alter the central pathways. However, the only available pancreatic lipase inhibitor for the treatment of obesity is orlistat and it is derived from lipstatin which is produced by a microbe, *Streptomyces toxytricini*. Many pancreatic lipase inhibitors are reported from the plant sources and they can be classified in to saponins, phenols, terpenes, glycosides, alkaloids, carotenoids and polysaccharides. Plant pancreatic lipase inhibitors are reported to show the antiobesity effects in the animal models. However, there is no plant inhibitor in the clinical use. This review describes the different lipase inhibitors from plant sources and their effects on the obesity and its related parameters.

Keywords: Obesity, Pancreatic lipase inhibitor, Orlistat, Saponins, Phenols, Terpenes, Glycosides, Alkaloids, Carotenoids, Polysaccharides.

INTRODUCTION

Obesity is becoming a major concern even in the developing countries due to the improved economic conditions and it is not confined to the developed world. Hence, studies focusing on the regulation of body weight are getting more attention and there is a vital scope for the drugs that control the obesity. Obesity is primarily related to the lipid metabolism and the enzymes involved with this metabolism can be selectively targeted for developing anti obesity drugs. Lipases (E. C. 3.1.1.3) are the enzymes that catalyze the hydrolysis of triacylglycerols (TAGs) to glycerol & fatty acids (FAs) and these enzymes play an important role in the metabolism of lipids. Recent approaches for the treatment of obesity focused on the inhibition of dietary triglyceride absorption via pancreatic lipase inhibition. Lipase inhibitors will also be helpful in treating atherosclerosis.

Despite various studies on the obesity there are only few drugs approved for the treatment of obesity and they are orlistat, sibutramine, lorcaserin and remonabant [1-4]. Orlistat is a tetrahydrolipstatin and it was shown to inhibit the activity of lipases, gastric lipase, pancreatic lipase and cholesterol ester hydrolase [5, 6]. Orlistat will be derived from the lipstatin (obtained from *Streptomyces toxytricini*) by hydrogenation and it reduces the intestinal fat absorption by inhibiting pancreatic lipase. Hence, it is available as anti obesity drug [7, 8]. Whereas other approved anti obesity drugs act through central pathways. The problem with the approved anti obesity drugs is their hazardous side-effects like blood pressure, dry mouth, gastrointestinal problems, headache, insomnia, acute kidney injury and oxalate nephropathy [9-11]. Hence, demand has been increasing for the molecules that have no or reduced side effects. In this context, compounds from the natural sources are promising. Currently, the natural products for the treatment of obesity are not explored to the complete extent and they could become promising alternatives for the development of safe anti obesity drugs. The present review covers the different lipase inhibitors from plant sources and their medical applications.

Plant sources and types of lipase inhibitors

Different plants have been screened for the lipase inhibitors in a thrust for the search of bioactive anti obesity molecules from the natural resources. The lipase inhibitors from the plants can be grouped in to the following classes based on their chemical structures. They are saponins, phenols, terpenes, glycosides, alkaloids, carotenoids and polysaccharides.

Saponins

Rhizomes and roots of different plants contain these compounds. They are comprised of steroid or triterpene and sugar. There are various saponins that inhibit pancreatic lipase. Saponins isolated from the roots of *Platycodon grandiflorum* were shown to inhibit pancreatic lipase and have anti obesity effect [12, 13]. Platycodin D inhibited the lipase inhibitor in a competitive manner with K_i of 0.18 ± 0.03 mM. Chikusetsusaponin III, IV, 28-deglucosyl-chikusetsusaponin IV and V isolated from *Panax japonicas* were reported to inhibit the pancreatic lipase activity [14]. This plant was used for treating hyperlipidemia, hypertension, arteriosclerosis and diabetes mellitus in the folk medicine of Japan and China. In another study saponins, ginsenosides Rb1, Rb2, Rc and Rd isolated from *Panax quinquefolium* inhibited the pancreatic lipase [15]. Ginseng saponin isolated from *Panax ginseng* inhibited the pancreatic lipase activity with an apparent IC_{50} value of 500 μ g/ml [16]. Lupane kind of saponins, sessiloside and chiisanoside were isolated from the leaves of *Accanthopanax sessiliflorum* [17]. Both compounds inhibited the lipase activity in a dose dependent manner and sessiloside (0.36 mg/ml) showed better IC_{50} value compared to that of chiisanoside (0.75 mg/ml). About 16 triterpenoid saponins were reported from *Acanthopanax senticosus*. Among the isolated molecules, copteroside B, hederagenin 3-O-b-D-glucuronopyranoside 6-O-methyl ester, silphioside F and gypsogenin 3-O-b-D-glucuronopyranoside inhibited the pancreatic lipase with the IC_{50} values of 0.25, 0.26, 0.22 and 0.29 mM respectively [18].

Dioscin, diosgenin, prosapogenin A, C and gracillin isolated from *Dioscorea nipponica* showed the lipase inhibition activity with the IC_{50} values of 20, 28, 1.8, 42.2, and 28.9 μ g/ml, respectively [19]. Scabiosaponins, a kind of triterpenoid saponins isolated from *Scabiosa tschiliensis* showed strong inhibitory activity on pancreatic lipase. They are scabiosaponin E, scabiosaponin F, scabiosaponin G, scabiosaponin I, hookeroside A, hookeroside B and prosapogenin 1b. Among these scabiosaponins prosapogenin 1b showed the best inhibitory activity on pancreatic lipase [20]. Another kind of saponins, escins was reported from *Aesculus spp.* These compounds are triterpene oligoglycosides and they were found to inhibit the pancreatic lipase. Escins Ia and IIa that contain triglycol moieties were reported to be less potent than the escins Ib and IIb that contain angeloyl moieties [21]. Dammarane kind of triterpene saponins, cyclocariosides (A, II and III) were isolated from *Cyclocarea paliurus*. Cyclocariosides were attributed to be responsible for the pancreatic lipase inhibitory activity of *C. paliurus* extract [22]. Tea saponins (E1 and E2) were reported to inhibit the

pancreatic lipase activity in a competitive manner [3, 23]. Three acylated oleanane type triterpene oligoglycosides, chakasaponins I, II and III isolated from *Camellia sinensis* (Chinese tea plant) could able to inhibit the porcine pancreatic lipase [24]. Gypsosaponins A-C, new triterpenoid saponins purified from *Gypsophila oldhamiana* reported to show pancreatic lipase inhibition activity and they inhibited 58.2%, 99.2% and 50.3% of the activity respectively at the concentration of 1 mg/ml [25]. Three triterpene saponins and one monoterpenic oligoglycoside that inhibit the lipase activity was reported from *Ilex paraguariensis* [26]. Saponins, rarasaponins I, II and rarasoside A isolated from *Sapindus rarak* showed the IC₅₀ values of 131,172 and 151 μM respectively on the pancreatic lipase and they were more potent than the saponin E₁ (IC₅₀ =270 μM) [27].

Terpenes

This class of natural compounds consists of 5 carbon isoprene units. Majority of the terpenoids have multi cyclic structures and they differ from each other by their basic carbon skeleton and functional groups. Terpenoids reported to show the pancreatic lipase inhibitory effect, hypotriglyceridemic and hypocholesterolemic effects. Terpenes, 3-*O*-trans-*p*-coumaroyl actinidic acid, ursolic acid, 23-hydroxyursolic acid, corosolic acid, asiatic acid and betulinic acid purified from *Actinidia arguta* reported to show pancreatic lipase inhibitory activity with the IC₅₀ values of 14.95, 15.83, 41.67, 20.42, 76.45 and 21.10 μM respectively [28].

Crocin and crocetin isolated from *Gardenia jasminoides* were reported to have pancreatic lipase inhibitory activity with the IC₅₀ values of 2.1 and 2.6 mg/ml respectively [29]. Terpenoids i.e. carnosic acid, carnosol, royleneic acid, 7-methoxyrosmanol and oleanolic acid isolated from *Salvia officinalis* were found to inhibit the pancreatic lipase with the IC₅₀ values of 12, 4.4, 35, 32 and 83 μg/ml respectively [30]. Trilactone terpenes, ginkgolides A, B, and bilobalide isolated from *Ginkgo biloba* were found to inhibit the pancreatic lipase activity with the IC₅₀ values of 22.9, 90.0 and 60.1 μg/ml respectively [31]. Secoiridoids, ligstroside, oleuropein, 2"-hydroxyoleuropein and hydroxyframoside B isolated from *Fraxinus rhynchophylla* reported to show the inhibitory effect on the pancreatic lipase [32]. Carvacrol isolated from the *Monarda punctata* inhibited the lipase activity with the IC₅₀ value of 4.07 mM [33]. A new endoperoxysesquiterpene lactone, 10α-hydroxy-1α,4α-endoperoxy-guaia-2-en-12,6α-olide purified from *Chrysanthemum morifolium* reported to show the lipase inhibitory activity with the IC₅₀ values of 161.0 μM [34].

Phenolics

In these compounds hydroxyl group is directly bonded to aromatic hydrocarbon. These compounds are usually large and have complex chemical structure and important phenolic compounds are flavonoids, phenolic acids, polyphenols and tannins. Phenolic compounds were reported to show lipase inhibition activity in addition to antioxidant, anti-inflammatory and anti microbial activities. Flavonoids, hesperidin and neohesperidin purified from *Citrus unshiu* reported to inhibit the 50 % of porcine pancreatic lipase activity at the concentration of 32 and 46 μg/ml, respectively [35]. However, other flavonoids, narirutin and naringin didn't inhibit the lipase. Galangin, a flavonol purified from *Alpinia galanga* was reported to inhibit the pancreatic lipase with the IC₅₀ value of 48.20 mg/ml [36]. Licochalcone A, a pancreatic lipase inhibitor from *Glycyrrhiza uralensis* was reported to inhibit the 50 % of activity at the concentration of 35 μg/ml [37]. Isoliquiritigenin and 3,3',4'-tetrahydroxy-2-methoxychalcone isolated from *Glycyrrhiza glabra* inhibited the pancreatic lipase with the IC₅₀ values of 7.3 and 35.5 μM respectively [38]. Methyl chlorogenate purified from *Eremochloa ophiuroides* inhibited the 50 % of pancreatic lipase activity at 33.6 μM [39] and 3-*O*-caffeoyl-4-*O*-galloyl-L-threonine acid isolated from *Filipendula kamschatica* inhibited pancreatic lipase with half maximal concentration of 26 μM [40]. A flavan dimer, (2S)-3,4,7-trihydroxyflavan-(4α→8)-catechin isolated from *Cassia nomame* was reported to inhibit the pancreatic lipase with the IC₅₀ value of 5.5 μM [41]. A phlorotannin, 7-phloroecol isolated from *Eisenia bicyclis* (a brown algae) inhibited the pancreatic lipase with the IC₅₀ value of 12.7±1.0 μM [42]. Flavonoids, eriodictyol and sigmoidin A isolated

from *Erythrina abyssinica* were reported to show pancreatic lipase inhibitory activity with the IC₅₀ values of 134±19.39 and 4.5±0.87 μM respectively [43]. IC₅₀ value of sigmoidin A was around 30 times more than that of eriodictyol.

Polyphenols isolated from oolong tea were reported to show potent pancreatic lipase inhibitory activities [44]. The compounds and their IC₅₀ values are listed in the table 1. Among this compounds oolonghomobisflavan A showed the best IC₅₀ value. Procyanidin fraction of the apple polyphenol extract showed the strong pancreatic lipase inhibition activity, whereas polyphenols present in the polyphenol fraction showed relatively lower inhibition [45]. IC₅₀ values of these compounds were listed in the table 2. A pancreatic lipase inhibitor, 3-methylethergalangin isolated from *Alpinia officinarum* showed the IC₅₀ value of 1.3 mg/ml on triolein [46]. Another pancreatic lipase inhibitor, 5-hydroxy-7-(4'-hydroxy-3'-methoxyphenyl)-1-phenyl-3-heptanone with the IC₅₀ value of 1.5 mg/ml on triolein was isolated from the same plant [47]. In addition, extracts of peanut (*Arachis hypogaea*) shell [48], *Mangifera indica* [49], grape seed extract [50] and *Salacia reticulata* [51] were reported to show the lipase inhibition activity and this activity was attributed to the polyphenolic compounds present in those extracts. Recently, a stilbenoid, wilsonol C isolated from *Vitis vinifera* was reported to show the potent pancreatic lipase inhibitory effect with the IC₅₀ value of 6.7 ± 0.7 μM [52]. Phenolic extracts of *Vigna* species were reported to show the inhibitory activities on pancreatic lipase with IC₅₀ values of 7.32 to 9.85 mg/ml [53]. Three flavonoids, quercetin-3-*O*-β-D-arabinopyranosyl-(1→2)-β-D-galactopyranoside, quercetin-3-*O*-β-D-glucuronide and kaempferol-3-*O*-β-D-glucuronide from *Nelumbo nucifera* (Lotus) leaf extracts were identified as lipase inhibitors [54]. A new phenolic compound, broussonone A purified from *Broussonetia kanzinoki* reported to inhibit the pancreatic lipase in a noncompetitive manner with the IC₅₀ value of 28.4 μM [55].

Phenolic compounds, protoaphin-fb, 2-*O*-digalloyl-1,3,4,6-tetra-*O*-galloyl-β-D-glucose, 1,2,3,4,6-penta-*O*-galloyl-β-D-glucose, 1,2,4,6-tetra-*O*-galloyl-β-D-glucose, 3-hydroxy-5-methoxy-phenol 1-*O*-β-D-glucoside, methylgallate and gallic acid isolated from *Galla Rhois* reported to show the pancreatic lipase inhibitory activity with the IC₅₀ values in the range from 30.6±2.4 to 3.5±0.5 mM [56]. A phloroacetophenone, 2',4',6'-trihydroxyacetophenone purified from *Myrcia multiflora* showed the inhibition of pancreatic lipase activity [57]. Hydroxy-chavicol isolated from *Eugenia polyantha* reported to show the inhibitory effect on the pancreatic lipase [58]. Anthocyanin, Cyanidin-3-glucoside isolated from *Aronia melanocarpa* was reported to inhibit the pancreatic lipase with the IC₅₀ value of 1.17±0.05 mg/ml [59]. Polyphenols from different berries were reported to show the pancreatic lipase inhibitory activity *in vitro* [60]. In another study, transformates of curcumin, erythro-1-(3-methoxy-4-hydroxy-phenyl)-propan-1,2-diol and threo-1-(3-methoxy-4-hydroxy-phenyl)-propan-1,2-diol were reported to show the better pancreatic lipase inhibitory activity compared to the parent compound, curcumin [61].

Glycosides

A glycoside is a compound in which sugar is bound to another functional group through glycosidic bond. Glycosides were reported to show pancreatic lipase inhibitory activity. Kaempferol 3-*O*-rutinoside isolated from *Cassia auriculata* was found to inhibit the pancreatic lipase with the IC₅₀ value of 2.9 μM, whereas rutin, quercetin and luteolin isolated from the same plant showed the weak inhibition with the IC₅₀ values greater than 100μM and kaempferol isolated from the same plant showed almost no inhibition of pancreatic lipase [62]. Glycosides, 1,4,8-trihydroxynaphthalene-1-*O*-β-D-[6'-*O*-(3'',4'',5''-trihydroxybenzoyl)] glucopyranoside isolated from *Juglans mandshurica* [63] and acteoside isolated from *Ligustrum purpurascens* (kudingcha tea) [64] were reported to show the pancreatic lipase inhibition. Luteolin-6-*C*-β-D-boivinopyranoside, orientin, isoorientin, derhamnosylmaysin and isoorientin-2-*O*-α-L-rhamnoside isolated from *Eremochloa ophiuroides* showed the pancreatic lipase inhibitory activity with the IC₅₀ values of 50.5, 31.6, 44.6, 25.9 and 18.5 μM respectively [65]. Licuroside and

isoliquiritoside isolated from *Glycyrrhiza glabra* showed pancreatic lipase inhibitory activity with the IC₅₀ values of 14.9 and 37.6 µM respectively [38].

Alkaloids

These compounds mostly contain basic nitrogen atoms and some of the alkaloids reported to inhibit the pancreatic lipase activity. Caffeine, theophylline and theobromine were reported to inhibit the human pancreatic lipase activity in a dose dependent manner [66]. Piperazine and piperidine triazole ureas were reported to inhibit the monoacylglycerol lipase selectively [67].

Carotenoids

An important carotenoid, fucoxanthin was isolated from edible seaweeds, *Undaria pinnatifida* and *Sargassum fulvellum* reported to inhibit the pancreatic lipase with the IC₅₀ value of 660 nM and fucoxanthinol, a derivative of fucoxanthin was also shown to inhibit the pancreatic lipase with the IC₅₀ value of 764 nM [68].

Polysaccharide

Low molecular weight chitosan (46 KDa) was reported to inhibit the pancreatic lipase and it could reduce the elevation of plasma triacylglycerol level in the mice [69]. Pectin extracted from the apple (*Malus pumila*) pomace was reported to inhibit the pancreatic lipase (steapsin) [70].

Table 1: Polyphenols isolated from oolong tea

Polyphenol	IC ₅₀ (mM)
(-)-Epigallocatechin 3,5-di-O-gallate	0.098
Prodelfinidin B-2 3,30-di-O-gallate	0.107
Assamicain A	0.120
Oolonghomobisflavan A	0.048
Oolonghomobisflavan B	0.108
Theasinensin D	0.098
Oolongtheanin 30-O-gallate	0.068
Theaflavin	0.106
Theaflavin 3,30-O-gallate	0.092

Table 2: Pancreatic lipase inhibitors isolated from apple

Pancreatic lipase inhibitor	IC ₅₀ (µg/ml)
Dimers to nonamers of procyanidins	>125, 32.9, 6.7, 1.3, 2.3, 0.7, 1.9 & 0.9
Phloridzin	58.7
Phloretin-2'-xyloglucoside	44.6
Chlorogenic acid	59.8
<i>p</i> -Coumaroyl quinic acid	89.0

Medical applications

Pancreatic lipase is a key enzyme for digesting the dietary fats and reduction of fat absorption by inhibiting the pancreatic lipase is suggested to be an important therapeutic strategy for obesity. Inhibitors of pancreatic lipase will play an important role in the treatment of obesity since pancreatic lipase is a safe target and its inhibition will not alter central pathways. Black tea extract containing polyphenols (lipase inhibitors) suppressed the increase of plasma triglyceride levels in the rat and increase in body weight, mass of parametrial adipose tissue and the lipid content of liver in the high fat fed mice [71]. Diets supplemented with green tea (-)-epigallocatechin-3-gallate, a pancreatic lipase inhibitor demonstrated the reduction of body weight and mass of different adipose tissues in a dose dependent manner in the mice and this diet also reduced the triglyceride levels in the plasma and liver lipid [72]. Galangin, pancreatic lipase inhibitor isolated from *Alpinia galanga* lead to the reduction of the body weight and parametrial adipose tissue weight induced by the cafeteria diet in the rats. Galangin also

lead to the reduction of serum lipids, liver weight, lipid peroxidation and hepatic triglyceride accumulation [73].

Carvacrol, a lipase inhibitor purified from *Monarda punctata* suppressed the elevation of blood triacylglycerol level in the mice [33]. Ginseng saponin, a pancreatic lipase inhibitor was attributed to be responsible for the antiobesity and hypolipidemic effects in the high fat diet fed mice [16]. Carnosic acid, a potent pancreatic lipase inhibitor inhibited the triglyceride elevation in the olive oil fed mice and lead to the reduction of the body weight gain and the epididymal fat accumulation in the high fat fed mice [30]. Pancreatic lipase inhibitors, 3-methylethergalangin and 5-hydroxy-7-(4'-hydroxy-3'-methoxyphenyl)-1-phenyl-3-heptanone isolated from the *Alpinia officinarum* reduced the serum triglyceride level in the corn oil feeding induced triglyceridemic mice and lowered the serum triglyceride and cholesterol in the triton WR-1339-induced hyperlipidemic mice [46, 47]. Triterpenes isolated from *Abies sibirica* were attributed to inhibit the mouse plasma lipase activity and LDL antioxidative activity which play a role in preventing arteriosclerosis [74]. Flavonoids from *Nelumbo nucifera* demonstrated to reduce the total cholesterol, triglycerides, LDL cholesterol and malondialdehyde in various *in vivo* systems [75]. Ursolic acid stearyl glucoside was demonstrated to prevent high fat diet induced obesity in mice by possibly inhibiting the activity of pancreatic lipase [76].

Marine carotenoids, fucoxanthin and fucoxanthinol reported to reduce the lymphatic triglyceride absorption and systemic blood triglyceride level increase in the lymph duct cannulated rats [68]. Pancreatic lipase inhibiting saponins, sessilioside and chiisanoside isolated from *Acanthopanax sessiliflorus* prevented the weight gain in the high fat diet fed mice [17]. Evidences were shown for the role of platycodin saponins in the lipase inhibition and restriction in the calorie intake [13]. Saponin fraction from *Panax japonicas* reported to inhibit the weight gain, weight of adipose fat pad and rise in the plasma triglyceride content in the high fat fed rodent model [14]. In another study, lipase inhibiting saponins, ginsenosides isolated from stems and leaves of *Panax quinquefolium* inhibited the high fat diet induced obesity in the mice [15]. Pancreatic lipase inhibitors, crocin and crocetin isolated from *Gardenia jasminoides* reported to reduce the increase of serum triglyceride level in the corn oil fed triglyceridemic mice and showed hypolipidemic activity in the high fat or high cholesterol fed hyperlipidemic mice [29].

Though many studies established the indirect link between the pancreatic lipase inhibitory activity and the antiobesity effect there is a need for the more direct studies. It is commonly accepted that material of plant origin is safer than the synthesized equivalent. However, in its purified or enriched form molecule might behave differently and every drug needs to be thoroughly tested for its safety before commercialization. Potential of a compound to be used as a drug depends on many factors in addition to its safe origin. One such factor is stability of the compound. Carnosol shows stronger pancreatic lipase inhibitory activity *in vitro*, but it lacks substantial effects *in vivo* due to its instability in the solvents. One needs to develop suitable systems that deliver the compounds in a stable manner. Nano delivery systems are gaining lot of importance recently, but their safety need to be evaluated thoroughly.

Future perspectives

There is no approved lipase inhibitor from the plant sources for the treatment of obesity despite the isolation of so many lipase inhibitors from plants. The only approved lipase inhibitor available for the treatment obesity is orlistat and it was derived from the lipstatin that was produced from the microbe, *Streptomyces toxytricini*. However, this approved inhibitor has unpleasant side effects. The common plant (tea, peanut, apple, grape etc.) extracts with lipase inhibitory activity might reduce the side effects due to their safety. Hence, plants must be thoroughly explored for developing commercial pancreatic lipase inhibitors for the treatment of obesity. Although, there are many animal studies with respect to the role of lipase inhibitors in the reduction of obesity, there is no single plant pancreatic lipase inhibitor in the clinical use till now. Hence there is a need for the clinical studies that will lead these inhibitors in to the development of anti obesity drugs and such

studies will answer how the compounds of plant origin will have fewer side effects compared to the synthetic candidates. There is no reported protein or peptide based plant lipase inhibitor except the lipoxigenase 1 [77]. One can explore this area and might come up with novel inhibitors by manipulating the protein sequence with the help of molecular tools.

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CONFLICT OF INTERESTS

Declare None

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