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REVIEW ARTICLE

Pancreatic Lipase Inhibitors from Plant Sources for Possible use as Antiobesity Drugs

[1]Rinkey R Shahu, [2]Sveeta Mhatre, [3]Priyanka Rathod, [4]Chandana Kulkarni, [5]Raman P Yadav

ABSTRACT

Pancreatic lipase inhibitors prevent the breakdown of dietary fat into fatty acids, thereby reducing their absorption in the gut. This action makes them attractive for use as antiobesity drugs. Currently, a few drugs have been approved by the Food and Drug Administration (FDA) for long-term use in the management of obesity. Over the last decades, studies have shown that many plants exhibit pancreatic lipase inhibitor activity in their extracts. The present review highlights the current status of our knowledge about lipase inhibitory activity in molecules derived from plant sources. We could possibly have a range of natural products derived from plants that could be of use in the treatment of obesity.

Keywords: Aquatic plants, Edible plants, Medicinal plants, Pancreatic lipase inhibitors.

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INTRODUCTION

Obesity is recognized as a major public health concern at the global level by the World Health Organization. It is related to a number of serious and potentially fatal diseases (Fig. 1).[1,2] A number of drugs for the treatment of obesity have been tried with varying results and adverse side effects (Table 1). Inhibition of dietary triglyceride absorption by inhibiting pancreatic lipase is an effective approach for the management of obesity (Fig. 2). Tetrahydrolipstatin (orlistat), a saturated derivative of lipstatin, which is a potent inhibitor of gastrointestinal lipase, has been approved by the FDA. However, it has severe side effects. So, discovery of other lipase inhibitors from natural sources, namely plants, which could have minimal side effects, is an attractive area of research. A number of plants have been reported as sources of pancreatic lipase inhibitory molecules (Fig. 3). Our present knowledge about plants as sources of lipase inhibitors, which could be used as antiobesity agents after proper clinical trials, is summarized in the following paragraphs.

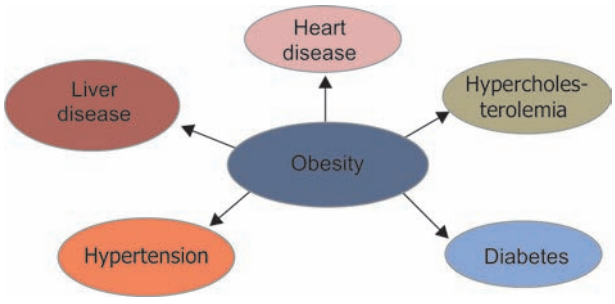


Fig. 1: Obesity and related complications (Adapted and derived from)[1,2]

Table 1: Name of drugs for obesity management and their side effects[3,4]

Name of medicine	*Side effects*
Dinitrophenol	High blood pressure, faster heart rate, palpitations, closed angle glaucoma, drug additions, restlessness, agitations, insomnia
Orlistat	Oily spotting bowel movement, oily stools
Sibutramine	Increase blood pressure, dry mouth, constipation, headache, insomnia
Rimonabant	Cause psychiatric problems
Phentermine/topiramate	Long-term effect on heart and blood vessels, mental health, cognitive side effects
Redux	Abnormal Heart rhythm, heart valve damage
Exenatide/Liraglutide	Severe nausea

GENERAL PLANTS

Various herbs and plants have been reported as having pancreatic lipase inhibitory activity (Fig. 4). Ado et al[5]

[1]Postgraduate Student, [2-4]PhD Student, [5]Professor and Technical Director

[1-4]Department of Medical Biotechnology, MGM School of Biomedical Sciences, MGM Institute of Health Sciences, Navi Mumbai, Maharashtra, India

[5]Department of Medical Biotechnology, MGM School of Biomedical Sciences, MGM Institute of Health Sciences, Navi Mumbai, Maharashtra, India and MGM Central Research Laboratory, MGM Medical College & Hospital, MGM Institute of Health Sciences, Navi Mumbai, Maharashtra, India

Corresponding Author: Raman P Yadav, Professor and Technical Director, Department of Medical Biotechnology, MGM School of Biomedical Sciences, MGM Institute of Health Sciences Navi Mumbai, Maharashtra, India and MGM Central Research Laboratory, MGM Medical College & Hospital, MGM Institute of Health Sciences, Navi Mumbai, Maharashtra, India, Phone: +912227432890, e-mail: raman.yadav@mgmmumbai.ac.in

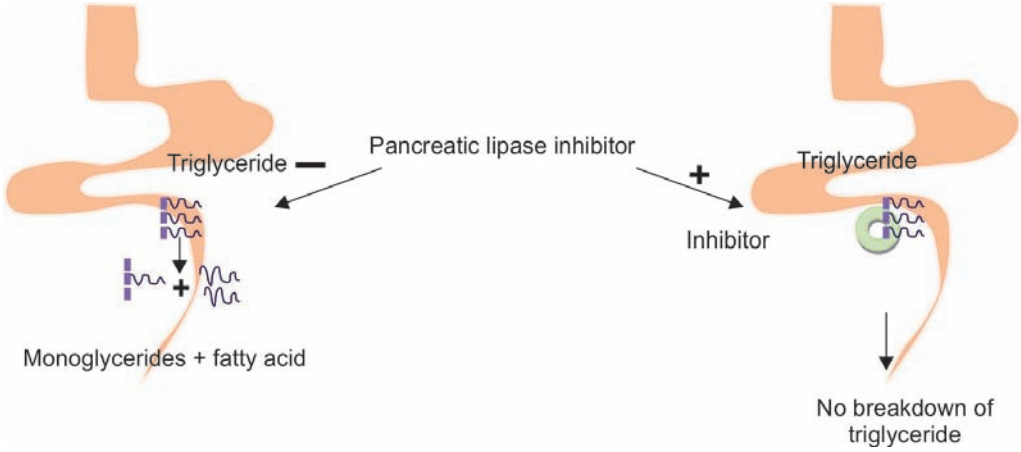


Fig. 2: Pancreatic lipase inhibition

evaluated the antilipase activity of the crude methanolic extract of different parts, such as leaves, stem, roots flower, and fruits of 98 plants collected from Malaysia. They concluded that 19.4% of extract exhibited antilipase activity more than 80%. Kim et al[6] screened 115 herbal ethanolic extracts for porcine pancreatic lipase inhibitory activity *in vitro*. Among the 115 plant extracts, 18 extracts showed an half maximal inhibitory concentration (IC_{50}) value <50 µg/mL. *Cudrania tricuspidata* showed an IC_{50} value of 9.91 µg/mL. *Cudrania tricuspidata* decreased the plasma triglycerol levels; however, these effects were weaker than that of orlistat (positive control). Teixeira et al[7]

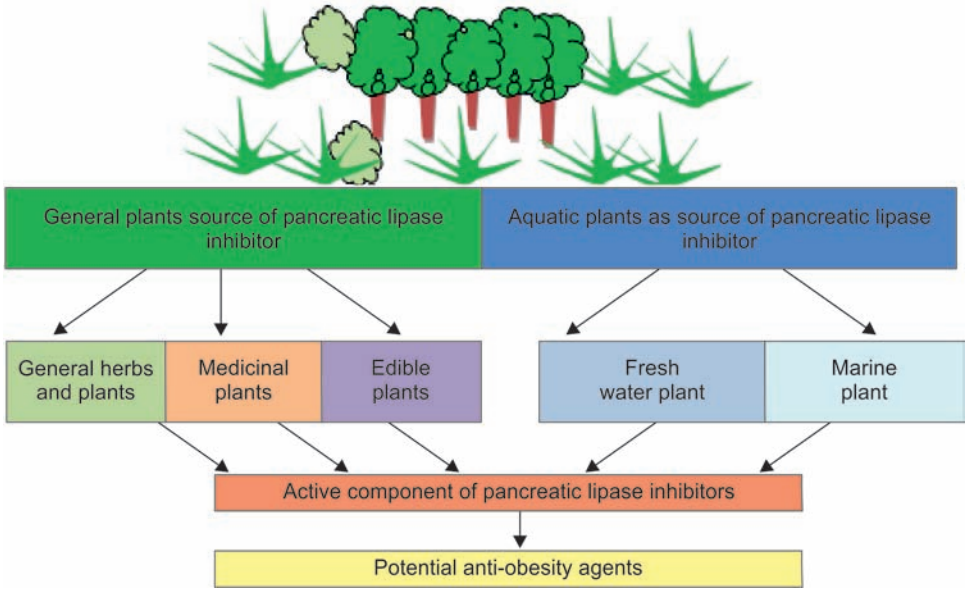
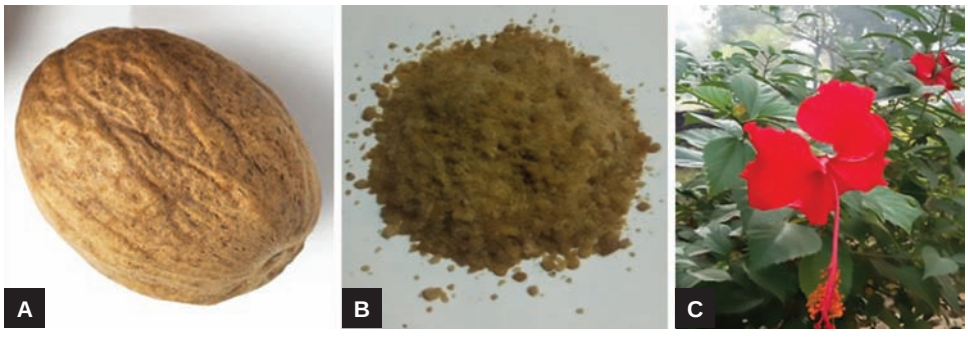


Fig. 3: Plant as source of inhibitor of pancreatic lipase



Figs 4A to C: (A) *Myristica seed*, (B) *Ferula asafoetida resin*, (C) *Hibiscus rosa-sinensis*

studied the effects of *Passiflora nitida Kunth* leaf extract on digestive enzymes and high caloric diet in rats on pancreatic lipase by using a spectrophotometric assay. The *Passiflora nitida* extract at a high concentration showed the inhibition against pancreatic lipase. Ekanem et al[8] found the inhibition activity of the pancreatic lipase of ethanolic extract of *Aframomum melegueta* (seeds) and *Spilanthes acmella* (flower buds) using the *in vitro* assay.

Roh and Jung[9] screened 400 crude plant extracts for their antiobesity activity. Among 400 plants examined, 44 extracts from plants showed a high antilipase activity using 2,4-dinitrophenylbutyrate as a substrate in porcine pancreatic lipase assay. Among 44 extracts, *Salicis radicis* cortex had the highest lipase inhibitory activity. Chompoo et al[10] screened the antiatherogenic properties of acetone extract of *Alpinia zerumbet* seeds. In this, they studied several methods to find the ability of acetone extract from pericarps, leaves, rhizomes, flowers, stem, and seed of *A. zerumbet*. Only seed showed the highest activity against the pancreatic lipase. Moreno et al[11] studied the effect of peanut shell extract on obesity. The plant extract exhibited inhibitory activity in pancreatic lipase. The concentration of 1 mg/mL showed the inhibitory effect against the pancreatic lipase. These plant extracts could prevent weight gain induced by feeding a high-fat diet to rats. Adnyana et al[12] studied the ethanolic extract of pomegranate (*Punica granatum*) leaves and found that they inhibited pancreatic lipase activity significantly. Habtemariam[13] investigated the inhibitory activity of ethanolic extract of *Cassia auriculata* (aerial part) on pancreatic lipase. The extract showed the lipase inhibitory activity which was dose-dependent. Kurihara et al[14] studied the inhibitory effect of *Cyclocarya paliurus* water extract of leaves against pancreatic lipase activity. These extracts reduced the plasma triacylglycerol level in mice when fed with lard and olive oil.

Kim and Kang[15] studied the inhibition of pancreatic lipase activity in aqueous and ethanol extract of 19 selected plants from Korea. Of these, *Illicium religiosum* (wood) and *juniperus communis* (bark) showed the highest pancreatic lipase inhibitory activity. Gholamhoseinian et al[16] measured the antilipase activity of methanolic extract of 100 plants. Among them, several plants showed an inhibitory activity between 25 and 50% on pancreatic lipase. Kwon et al[17] focused on the inhibitory activity of *Dioscorea nipponica* methanol extract on pancreatic lipase. Sahib et al[18] concluded that their pancreatic lipase inhibitory activity could be used for developing antiobesity agents. The antipancreatic lipase activity of ethanolic extract of *Centella asiatica, Morinda citrifolia,* and *Momordica charantia* was studied using different concentrations, using orlistat and epicatechin as synthetic and natural substrate as control respectively. Zhang et al[19] showed that 95% ethanol extract of *Taraxacum officinale* inhibited porcine pancreatic lipase activity. A single oral dose of this extract significantly inhibited an increase in plasma triglyceride levels.

Prashith Kekuda et al[20] studied the pancreatic lipase inhibitory study of *Artocarpus lakoocha* Roxb pericarp. These plants showed the pancreatic lipase inhibition in a dose-dependent manner. de Souza et al[21] investigated the effect of *Baccharis trimera.* They observed that aqueous and infused extract did not exhibit the effect on pancreatic lipase, whereas methanolic extract showed the inhibition activity. Oliveira et al[22] studied the chemical composition and inhibitory activity of pancreatic lipase from Brazilian Savannah *Oxalis cordata A*. leaves. The crude extract, ethyl acetate extract, and water extract of *O. cordata A.* showed an inhibitory activity. Wu et al[23] studied the inhibitory effects of Litchi flower–water extract containing phenolic acids, flavonoids, condensed tannins, anthocyanins, and proanthocyanidins, and found inhibitory effect on lipase *(in vitro).* Morikawa et al[24] studied the pancreatic lipase inhibitory activity in the flowers of *Bellis perennis.* The methanolic extract of the flowers of *B. perennis* displayed the pancreatic-lipase inhibitory activity. Griffiths[25] studied the inhibitory effects of digestive enzyme extracted from field bean (*Vicia faba*) and found that water extracts of testa of *V. faba* (colored-flower variety) were able to inhibit the activity of α-amylase, lipase, and trypsin, whereas no inhibitory activity was observed in similar extracts from white flower. Yoshikawa et al[26] studied the inhibitory activity from the flower bud of Chinese tea plant. The MeOH extract of flower buds of Chinese tea plant (*Camellia sinensis* L.) showed inhibitory effects against pancreatic lipase. Some of the compounds showed promoting effects on gastrointestinal transit in mice and inhibitory effects against porcine pancreatic lipase. Lee et al[27] studied the inhibitory effects of *Gardenia jasminoides* extract on pancreatic lipase and found that it inhibited lipase at a concentration of 2.1 mg/mL. Marrelli et al[28] investigated the potential health benefits of Mediterranean dietary plants as antiobesity agents. The formulation obtained from *Capparis sicula* showed the highest inhibitory effect on pancreatic lipase. Won et al[29] found lipase inhibitor from the roots of *Glycyrrhiza uralensis*.

MEDICINAL PLANTS

Several medicinal plants have been found to possess pancreatic lipase inhibitory activity. Bustanji et al[30] screened the methanolic extract of 23 traditional medicinal plants as antipancreatic lipase activity. These plants were collected from an area in Jordan. The inhibition of pancreatic lipase activity of the plant extract and orlistat was measured using a spectrophotometric assay. Thirteen plant extracts showed the inhibition of pancreatic lipase with an IC_{50}

ranging between 108 and 938 µg/mL. The positive control, orlistat, exhibited an IC_{50} value of 0.65 µg/mL. Ong et al[31] screened the lipase inhibitory activity of methanolic extract of different parts of 32 selected medicinal plants using porcine pancreatic lipase and p-nitrophenyl butyrate and *in vitro* assay. Out of these, a total of 4 crude extracts showed *in vitro* inhibitory activity against the porcine pancreatic lipase. Zheng et al[32] screened 37 traditional Chinese medicinal herbs. Among these, six extracts showed a moderate-to-strong antilipase activity.

Kumar et al[33] screened the lipase activity of different parts of 33 medicinal plants from India *in vitro*. The ethanolic extract of *Cassia siamea* roots showed the highest pancreatic lipase inhibition. Kaewpiboon et al[34] studied the lipase inhibitory activity of 52 plant species of Thai medicinal plant *in vitro*. Compared with all extracts, only the ethanol extract of *Coscinium fenestratum* stem showed a weak lipase inhibitory activity. Sharma et al[35] studied the antilipase activity of different parts of 75 medicinal plants. Among these, only three plants of methanolic extracts showed high antilipase activity above 80%, which were *Setaria italica (L.)* Palib., *Orixa japonica* Thunb., and *Eriochloa villosa* (Thunb.) Kunth. Lee et al[36] screened the inhibitory activity of pancreatic lipase and phosphodiesterase from Korean medicinal plant extracts. Sixty-one plants were screened for their antilipase activity. The lipase activity was determined by measuring the hydrolysis of p-nitrophenyl butyrate to p-nitrophenol and also the inhibitory effects were measured on phosphodiesterase. *Sorbus commixta* (stem, leaf) and *Viscum album* (whole plant) showed antilipase activity with an IC_{50} value of 29.6 and 33.3 µg/mL respectively. Yoshikawa et al[37] investigated some components against the pancreatic lipase and lipoprotein lipase from *Salacia reticulata* adipose tissue *in vitro* and *in vivo*. Soluble extract inhibited pancreatic lipase from the adipose tissue. Chen et al[38] showed various pancreatic lipase inhibitors in *Forsythia suspense* leaves. Sridhar et al[39] have highlighted the pancreatic lipase inhibitory activity of alkaloid-rich *Tabernaemontana divaricata L.* Kasabri et al[40] studied the antiobesity effects of *Adiantum capillus-veneris* extracts *in vivo* and *in vitro. Adiantum capillus-veneris* and its phytoconstituents inhibited the pancreatic lipase activity *in vitro. Adiantum capillus-veneris* showed pancreatic lipase inhibition. Uzun et al[41] studied the antiobesity activity of *Sempervivum davisii. Sempervivum davisii* showed a moderate pancreatic lipase inhibitory activity. Afifi et al[42] studied the biological evaluation of *Arum hygrophilum Boiss.* (Araceae). *Arum hygrophilum* exhibited pancreatic lipase inhibition in a dose-dependent manner.

Jaradat et al[43] evaluated the antilipase potential of ten traditional and medicinal plants of Palestine using organic and aqueous extracts. The inhibitory activity of aqueous extracts of *Vitis vinifera* and *Rhus coriaria* showed against pancreatic lipase. Buchholz and Melzig[44] studied 23 medicinal plants for the treatment of obesity. Methanolic and water extracts of plants were prepared for an *in vitro* study. The methanolic extracts of *Hibiscus sabdariffa L.* showed pancreatic lipase inhibitory activity with IC_{50} of 35.8 ± 0.8 µg/mL, whereas methanolic extracts of *Tamarindus indica L.* showed pancreatic lipase inhibition with the IC_{50} value of 152.0 ± 7.0 µg/mL.

EDIBLE PLANTS

Edible plants are known to be a source of pancreatic lipase inhibitor (Fig. 5). Adisakwattana et al[45] studied the inhibitory activity of aqueous extract of nine edible plants against the pancreatic lipase using orlistat as the positive control. They concluded that the *Ginkgo biloba* (ginkgo) and *Morus alba* (mulberry) have activity against the pancreatic lipase. Conforti et al[46] studied the pancreatic lipase inhibitory activity of 18 species of edible plants by monitoring the hydrolysis of p-nitrophenyl caprylate, which releases the yellow chromogen, p-nitrophenol. The aqueous extracts of *Silene vulgaris* leaves and *Portulaca oleracea* leaves showed highest pancreatic lipase inhibition. Senapaty et al[47] studied three extracts, namely petroleum ether, chloroform, and ethanolic extracts of fenugreek seeds, which were inhibitory against the porcine pancreatic lipase enzyme using *in vitro* assay. The ethanolic extract showed the highest activity compared with petroleum ether and chloroform extracts. The study showed that ethanolic extract of fenugreek seeds can be used as an antiobesity agent. Marrelli et al[48] screened the lipase inhibitory activity of hydro-alcoholic extracts of five edible plants. *Clematis vitalba L.* and *Lepidium sativum L.* showed the highest IC_{50} value of 0.99 ± 0.18 and 1.28 ± 0.29 mg/mL respectively. Moreno et al[49] assayed the inhibitory effect of grape seed on lipase. The ethanolic plant extract inhibited the pancreatic lipase activity. Han et al[50] studied the pancreatic lipase inhibitory activity of water extract of *Juglans mandshurica* fruit. This extract strongly inhibited pancreatic lipase in a dose-dependent manner. Moreno et al[51] investigated the inhibitory effect of ethanolic extract of *Mangifera indica* on pancreatic lipase. The plant extract showed inhibition against pancreatic lipase. The plant extract reduced the isoproterenol-stimulated lipolysis in 3T3-L1 adipocytes. Deshpande et al[52] investigated the antiobesity activity of *Ziziphus mauritiana Lam* bark powder (ZMBP) on high-fat-diet-induced obesity in a study done on rats. The dual-energy X-ray absorptiometry analysis was carried out for 90 days; at the end of this treatment, it showed a reduction in body weight over the standard drug treatment; it was due to the polyphenolic compound of ZMBP. Morikawa et al[53] investigated the antihyperlipidemic constituents from the

Figs 5A to E: (A) *Cinnamomum zelyanicum (bark)*, (B) *Syzygium aromaticum (bud)*, (C) *Trigonella foenum-graecum (Fenugreek) seeds*, (D) *Mangifera indica,* (E) *Moringa sp. (leaves)*

bark of *Shorea roxburghii*. They were found to suppress the plasma triglyceride elevation in olive oil-treated mice and also inhibited pancreatic lipase activity.

Tsujita et al[54] examined the lipase inhibition activity of citrus pectin. Lower molecular weight pectin strongly inhibited lipase activities. At acidic pH, i.e., below pH 7.0, a strong lipase inhibition was observed in pectin. Mhatre et al[55] studied the *in vitro* pancreatic lipase activity of some edible spices. A number of extracts showed pancreatic lipase inhibitory activity. *Zanthoxylum armatum* extract showed the lowest IC_{50} value of 9.0 µg/mL. Isaksson et al[56] have reported the effects of pH and duodenal juice viscosity on the inhibition of lipase and amylase enzymes. They found that pectin of high methylic etherification and guar gum reduces the lipase and amylase activity by lowering the duodenal juice pH, making it viscous. Lee et al[57] prepared methanolic and ethanolic extracts of *Phellinus linteus*. The methanol extracts of *P. linteus* showed a lipase-inhibiting activity. Toma et al[58] investigated the inhibitory activity of ethanolic extract of leaf *Moringa stenopetala* on pancreatic lipase. These plants showed a slight inhibition against pancreatic lipase. Kaisoon et al[59] studied the edible flowers of Thailand. *Tagetes erecta*, *Cosmos sulphureus,* and *Bougainvillea glabra* extracts inhibited the activity of pancreatic lipase.

AQUATIC PLANTS

Liu et al[60] studied the inhibition of pancreatic lipase in *Nelumbo nucifera* leaves. *In vitro* biochemistry study of *N. nucifera* leaves showed the highest pancreatic lipase inhibitory activity against porcine pancreatic lipase. Ono et al[61] assessed the effects of aqueous and ethanol extracts of *N. nucifera* leaves on pancreatic lipase. The extract showed a lipase inhibition activity and it also promoted lipolysis in 3T3-L1 adipocytes. The *in vivo* results showed the decrease of plasma triacylglycerol level at 1 hour after the oral administration of lipid emulsion in the group treated with the plant extract. Kim et al[62] studied the biological activities of *Lythrum salicaria.* They concluded that ethanolic and water extract of *L. salicaria L* exhibited the antiobesity activity.

ACTIVE COMPONENT AND POTENTIAL ANTIOBESITY AGENTS

A wide range of plants have been reported for pancreatic lipase inhibitory activity and, in some cases, active components have been identified (Table 2). Nakai et al[63]

Table 2: Some active components of plants for pancreatic lipase inhibition

Active components		
Polyphenols	Flavan-3-ol	Phenol
Saponin	Flavonol	Anthocyanidins
Ellagitannins	Flavonoids	Hydroxycinnamic acid
Hydroxybenzonic acids	Ligans	Proanthocyanidins
Alkaloids	Triterpenoidal saponin	Sessiloside saponin
Chiisanoside saponin	Benzylisoquinoline	Procyanidin

studied the inhibitory effects of oolong tea polyphenols on pancreatic lipase *in vitro. Epigallocatechin 3-O-gallate*, one of the major polyphenols in green tea, showed lipase inhibition with an IC_{50} 0.349 µM, whereas *flavan-3-ol digallate* esters showed higher activities of lipase inhibition with an IC_{50} of 0.098 µM. Sugiyama et al[64] studied the oligomeric procyanidins in apple polyphenol. The oligomeric procyanidins contained in apple polyphenols inhibited the triglyceride level by inhibiting the pancreatic lipase in both mice and humans. Buchholz and Melzig[65] showed the pancreatic lipase inhibitory activity in polyphenolic compounds. The class of polyphenols is an important source for the pancreatic lipase inhibitors. Phenols, saponin, flavonols, anthocyanidins, ellagitannins, flavonoids, hydroxycinnamic acids, hydroxybenzoic acids, lignans, and proanthocyanidins were different phytochemicals, which have been found as components of pancreatic lipase inhibition. Karu et al[66] isolated saponins from *ginseng* root powder and studied their inhibitory activity on the absorption of dietary fat in mice. Consumption of *ginseng* saponins suppressed the expected increase of body weight and plasma triglyceride level. *Ginseng* saponin inhibited the pancreatic lipase activity. Lee et al[67] studied the pancreatic lipase inhibition by c-glycosidic flavones isolated from methanolic extract from the leaves of *Eremochloa ophiuroides*. It showed potent inhibitory effects on pancreatic lipase with an IC_{50} value ranging from 18.5 ± 2.6 to 50.5 ± 3.9 µM.

Ivanov et al[68] isolated the novel catechin from *Bergenia rhizomes* that has pronounced lipase-inhibition activity. An aqueous ethanol extract of *Bergenia crassifolia* rhizomes strongly inhibited the pancreatic lipase *in vitro*. The hydrolysable tannins (+)-catechin 3, 5-di-O-gallate compound strongly inhibited HPL. Birari et al[69] found pancreatic lipase inhibitory alkaloids from *Murraya koenigii* leaves. Twenty-one different plants were screened against pancreatic lipase inhibition. Only *M. koenigii* leaves showed antilipase activity greater than 80%. Four different alkaloids were isolated from the ethanolic extracts of *M. koenigii.* Xu et al[70] studied the *in vitro* inhibitory effects of triterpenoidal saponin on pancreatic lipase. The water extracts of *Platycodi radix* were prepared. All fractions of saponin showed a pancreatic lipase inhibitory activity *in vitro.* Based on further purification of active compound triterpenoid saponin showed the highest pancreatic lipase inhibitory activity. Yoshizumi et al[71] studied the pancreatic lipase inhibitory activity of *Acanthopanax sessiliflorus* leaves. Using a hot water extract of *A. sessiliflorus* leaves, saponins were isolated. From these saponins, only sessiloside and chiisanoside inhibited the pancreatic lipase activity *in vitro.* The lupane-type saponins from *A. sessiliflorus* can be used for the treatment of obesity. Upadhyay et al[72] studied the inhibitory activity of *Moringa* seed protein and found that it inhibited the pancreatic lipase activity.

CONCLUSION

An overview of current literature about the plant sources of pancreatic lipase inhibitors has been presented. So far, the results have been very encouraging. In due course of time, lot of new antiobesity drugs derived from plant sources, which are potent and safe pancreatic lipase inhibitors, are likely to be found and after due clinical trials, these will be put into clinical practice. Hopefully, they will be effective and free of serious side effects.

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