Pancreatic Lipase Inhibitor from Food Plant: Potential Molecule for Development of Safe Anti-obesity Drug

Sveeta V Mhatre, Amita A Bhagit, Raman P Yadav

ABSTRACT

Obesity is a global health concern, widely recognized as the largest and fastest growing public health problem in the developed and developing countries associated with high morbidity and mortality. It is a multifactorial disease resulting in significant impairment of health. The strategies used for the treatment of obesity generally comprise of prescription of drugs and surgery. Number of basic mechanisms has been considered for obesity management but these entail serious complexities. In recent year’s pancreatic lipase, a principal lipolytic enzyme secreted by the pancreas has gained importance as -obesity target. As the PL acts in the duodenum it has least involvement with the blood or brain, avoiding a lot of drug related side effects. Although PL has been considered as good target for obesity management, the drug discovery and development in this section is not abundantly explored. Numerous natural molecules have been established for pancreatic lipase inhibitory activity but only orlistat (tetrahydrolipstatin), a saturated derivative of lipstatin designed to inhibit the action of gastrointestinal lipase approved by Food and Drug Administration (FDA) for long-term usage. However, it has severe side effects. Therefore, the possible treatment of obesity using natural products is an extensive field to be explored. Several plant derived molecules including medicinal plants have been reported for their pancreatic lipase inhibitory activity. In particular pancreatic lipase inhibitor from food plants can be considered as a good source for the discovery of a safe anti-obesity agent due to possible active principle as edible component. Present review mainly focuses on the pancreatic lipase inhibitor from food plants and its potential in the development of safe anti-obesity drug.

Keywords: Obesity, Pancreatic lipase inhibitor (PL inhibitor), Plant derived.

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INTRODUCTION

Obesity is generally caused by an imbalance between energy intake and expenditure which can be most often defined as a body mass index (≥30 kg/m²). Obesity is still an exciting crossroad in reference to pharmacological management. Number of synthetic drugs came into market but could not make high impact on obesity management. Now the use of natural molecule is gaining renewed interest as potential source of new anti-obesity drugs. Natural products extracted from traditional plant and microbial sources have always displayed an opportunity for the development of new therapeutic agents. Lipids in diet serve as the major source of undesirable calories; the inhibition of fat digestion is a good approach for reducing fat absorption. Many researchers are involved in the molecular regulation of triglyceride synthesis and in pharmaceutical approaches to reduce the fat absorption and storage for the discovery of new anti-obesity agents. Natural products provide an ample scope for the discovery of pancreatic lipase inhibitors that can be developed into anti-obesity clinical products. Currently, natural products for the safe management of obesity is largely unexplored. Therefore; search of new, effective and safe anti-obesity phytochemical particularly from food stuff would provide an excellent opportunity in obesity management.

Obesity and Related Complications

Obesity is a metabolic disorder caused because of the imbalance between energy intake and expenditure in which excess body fat has accumulated to the extent that it may cause adverse effect on health, leading to reduced life expectancy and/or increased health related problems. People are classified as different class of obese on the basis of their body mass index. In the late 1930’s the medical profession made a change in opinion on the desirability of surplus “fats” and accepted it as a health problem. This field was relatively unexplored till leptin was discovered. Leptin plays an important role in regulating energy absorption and energy expense, including appetite and metabolism. It circulates at levels proportional to body fat. It regulates the amount of food taken and energy spends by acting on receptors in the mediobasal hypothalamus. Therefore, overweight and obesity can be described as an abnormal fat accumulation that display or alarm...
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Pancreatic Lipase Inhibition in Obesity Management

Among all the targets used for the treatment of obesity, altering metabolism of lipids by inhibition of dietary fat absorption using pancreatic lipase is an interesting and comparatively safe approach toward the development of an anti-obesity drug. Pancreatic lipase is a principal lipolytic enzyme secreted by the pancreas and plays a pivotal role in the digestion of fats (Fig. 1). As the pancreatic lipase acts in the duodenum and it has least involvement with the blood or brain avoiding a lot of drug related side effects and development of other complications.

In view of search for a better and comparatively safer drug target for pancreatic lipase inhibition, large number of synthetic as well as natural molecules/extracts has been investigated for pancreatic lipase inhibitory activity. However orlistat (also known as tetrahydrolipstatin), designed and developed as anti-obesity drug is the only widely available and approved anti-obesity drug for long term use a saturated derivative of lipstatin inhibits the action of gastrointestinal lipase and thus reduces absorption of dietary fat. However, it displays severe side effects with various complications which are now a major concern of its long term use. It is the only weight loss medication of its kind that has been approved by the FDA. It basically blocks the digestion and absorption of fat in stomach and intestines. The fat that remains unabsorbed is excreted in the stool.

Side effects associated with orlistat include allergic reactions like hives, difficulty in breathing and swelling of face, throat, tongue, etc. Oily and frequent bowel movements, bowel urgency and gas stomach pain, nausea, vomiting, diarrhea, rectal pain are main side effects of orlistat. Respiratory side effects have included

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Decreasing absorption of lipids</th>
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<tr>
<td>Stimulating thermogenesis</td>
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<td>Lowering lipogenesis</td>
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<td>Enhancing lipolysis</td>
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<td>Suppressing appetite</td>
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Table 1: Basic mechanisms used for anti-obesity medication strategy

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Table 2: Some commonly used anti-obesity medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse effects</th>
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<tbody>
<tr>
<td>Phentermine#</td>
<td>Insomnia, tremor, ↑blood pressure and pulse rate, headache, palpitation, constipation</td>
</tr>
<tr>
<td>Diethylpropion#</td>
<td>As above</td>
</tr>
<tr>
<td>Topiramate#</td>
<td>Paraesthesia, dizziness, altered taste, fatigue, memory impairment, somnolence, anorexia, and abdominal pain</td>
</tr>
<tr>
<td>Zonisamide#</td>
<td>↑Nervousness, sweating, tremors, gastrointestinal adverse effects, hypersonnia, fatigue, and insomnia</td>
</tr>
<tr>
<td>Orlistat*</td>
<td>Abdominal pain, bloating, flatulence, oily stools, diarrhea, ↓absorption of fat soluble vitamins</td>
</tr>
</tbody>
</table>

#Medications for short-term weight management or selected medications used off-label to promote weight loss; *Medication for long-term weight management; ↑Increasing; ↓Decreasing

Obesity is a multifarious disorder of heterogeneous group of conditions with multiple causes and effects. It has serious effects linked to it including coronary heart disease, high blood pressure, diabetes-2 and stroke. Obesity is also linked to higher rates of certain types of cancer, i.e., colon, rectum or prostate cancer in men and gallbladder, uterus, cervix, or ovarian cancer in women. Other obesity linkages include high cholesterol, depression, gastroesophageal heartburn, infertility, etc.

Medication and their Adverse Effects

Drug treatment of obesity is generally focused at reducing energy/food intake either by an action mainly on the gastrointestinal system or via an action through the central nervous system control of appetite and feeding (Table 1). In certain situations, there may be a necessity of prescription weight loss medication. Lot of side effects may occur due to these medicines, such as allergic reactions; respiratory, gastrointestinal, psychological, musculoskeletal and cardiovascular side effects; nervous system related side effects. Obesity is a multifarious disorder of heterogeneous group of conditions with multiple causes.

A number of drugs have been used for the treatment of obesity; though most of them have been discontinued from the market because of their adverse effects. In fact, amphetamine, rimonabant and sibutramine licenses have been withdrawn due to an increased risk of psychiatric disorders and non-fatal myocardial infarction or stroke. At present for the treatment of obesity orlistat is the only available choice. Hopefully, better anti-obesity drugs will be developed with lesser side effects in future.

The anti-obesity drugs currently approved by Food and Drug Administration (FDA) for treatment against obesity exhibit a series of side effects and need additional supplements to be taken along with the drug. Elevated side effects of marketed anti-obesity drug is now major concern in obesity management (Table 2).
influenza, upper respiratory infections of ear, nose, throat and lower respiratory infection symptoms. Musculoskeletal side effects have noted back pain, pain in the lower extremities, arthritis, myalgia, joint disorder and tendonitis. Headache and dizziness are major nervous system side effects. Psychiatric side effects have included psychiatric anxiety and depression. This is the prime reason for researcher as they are looking for new plant derived pancreatic lipase inhibitor especially from food plant for development of safe anti-obesity drug. Natural products serve as tremendous source for pancreatic lipase inhibitors.

**Plant Derived Pancreatic Lipase Inhibitor**

Search of potent lipase inhibitors from plant extracts is among the various strategies employed for the discovery of anti-obesity drugs. The formative variance of natural products combined with the fact that they were elaborated within the living systems provides a more sustainable choice to completely synthetic molecules. Potential of natural products for the management of obesity is still broadly unexplored. Natural products provide an ample scope for the discovery of pancreatic lipase inhibitors that can possibly be developed into clinical products. Hence, the focus is also on plant derived pancreatic lipase inhibitor as a potential molecule for preparing for an anti-obesity drug. Large number of plant derived components including various types extracts, phytochemicals, processed plant have been reported for inhibition of pancreatic lipase inhibitory activity. Long list of plants extracts have been investigated for lipase inhibitory activity and good number of plant extracts have been reported for lipase inhibitory activity. Inhibitory effect of some plant extracts on pancreatic lipase was presented by Cholamhoseinian and co-worker, 2010 where they have shown the percent (%) inhibition of pancreatic lipase. According to the data given in a research paper percent inhibition of various plants against pancreatic lipase are as follows, Quercus infectoria, galls (85.0%), Eucalyptus alba, leaves (64.0%), Rosa damascena, floret (57.0%) (Fig. 2A), Levisticum officinale, roots (55.0%), Urtica urens, aerial parts (44.7%), Alhagi camelorum, aerial parts (44.5%), Otostea persica, aerial parts (44.0%), Rheum ribes, rhizomes (43.0%), Pistacia vera, fruit hull (42.0%), Myrtus communis, leaves (40.0%) (Fig. 2B), Cinnamomum Zeylanicum, derrm (39.0%), Ficus caria, leaves (34.2%), Nigella sativa, seeds (31.4%), Pimpinella anisum, seeds (31.0%), Trigonella foenum-graecum, seeds (30.0%), Banium persicum, seeds (28.0%), Carthamus oxyacantha, aerial parts (28.0%), Arctium lappa, roots (26.8%), Zingiber officinale, rhizomes (23.4%), Convolvulux pilosellaefolius, aerial parts (23.3%), Origanum majorana, plant (23.0%), Rubia tinctorum, roots (23.0%), Camellia sinensis, leaves (22.0%), Peucedanum aucheri, roots (22.0%), Outreya carduiformis, aerial parts (21.3%), Cordial mixa, fruits (21.0%), Ocimum basilicum, seeds (21.0%) inhibition, Olea europaea, leaves (21.0%), Punica granatum, fruits hull (21.0%), Laurus nobilis, leaves (20.5%), Dacrusia assadi, aerial parts (20.0%), Ferula oopoda, aerial parts (20.0%), Teucrium scordium, aerial parts (20.0%). Quercus infectoria showed the highest percent inhibition while Ferula oopoda and Teucrium scordium showed lowest percent inhibition. A plant benzoquinone embelin (2,5-dihydroxy-3-undecyl-1,4-benzoquinone) obtained from the dried fruit of Embelia ribes has been investigated for pancreatic lipase inhibitory activity. In addition, dried berries are also

Figs 2A and B: (A) *Rosa damascene* (floret), and (B) *Myrtus communis* (leaves) with pancreatic lipase inhibitory activity

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reported to inhibit enzymes, such as pancreatic lipase. In view of search for pancreatic lipase inhibitors, the methanol extract of *Dioscorea nipponica* makino powder was also evaluated which showed potent inhibitory activity against porcine pancreatic lipase with an IC\textsubscript{50} value of 5 to 10 µg/mL, with 4-methylumbelliferyl oleate as a substrate.\textsuperscript{12} *D. nipponica* active components dioscin and its aglycone, diosgenin, prevented the increase of blood triglyceride level when administered orally with corn oil to mice, suggesting it appeared to have a potent inhibitor against fat absorption.

**Food Plant Derived Pancreatic Lipase Inhibitor**

Phytochemicals screening for anti-obesity activity particularly from edible plant would provide an excellent new strategy for addressing the issues of obesity and its complications.\textsuperscript{3} Food plant derived lipase inhibitory molecule may be of therapeutic interest with respect to the treatment of obesity. Extracts from various selected food plants have been screened for potential lipase inhibitory activity.\textsuperscript{13} Food plants, such as cabbage (Fig. 3A), garden pea, parsley, celery and nettle which are used in food preparations have been explored to study pancreatic lipase inhibitory activity.\textsuperscript{14} Extracts from Bearberry, pear prepared from fruit plants have also been reported as pancreatic lipase inhibitors. Recently lipase inhibitory activity of some food stuff extracts, such as apple, yerba mate (Fig. 4A), grapevine, soybean, oolong tea (Fig. 4B), ginseng and peanut, cinnamon (Fig. 5A) have been reported.\textsuperscript{15-16}

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Figs 3A and B: (A) *Brassica oleracea* var. *Capitata*-Cabbage (bulb), and (B) *Magnifera indica* (stem, bark, leaves) with pancreatic lipase inhibitory activity

Figs 4A and B: (A) Yerba mate plant (leaves), and (B) Oolong tea (leaves)

Some of the phytochemicals identified are polyphenols and saponins which inhibit pancreatic lipase activity, which could be applied in the management of the obesity epidemic. Lipase inhibitors of plant origin generally include various phytochemicals, proteins and others.

Carpestemon from ripen fruits of Solanum stramonifolium has been identified and investigated for pancreatic lipase inhibitory activity.\(^\text{17}\) Carpestem showed moderate lipase inhibitory activity with IC\(_{50}\) value of 56 µg/mL. Water extract of Juglans mandshurica fruit also showed strong pancreatic lipase inhibitory activity in vitro.\(^\text{18}\)

The extract also inhibited the normal elevation in the level of plasma triacylglycerol in rats 2 to 4 hours after oral administration of lipid emulsion. Fourteen compounds have been isolated from J. mandshurica fruit were subjected for their pancreatic lipase inhibitory activity. One of which showed the strongest pancreatic lipase inhibitory activity. An investigation carried out on the inhibitory effect of Cyclocarya paliurus extract on postprandial hyperlipemia in mice showed single dose of C. paliurus extract with 5 mL/kg of lard and olive oil suppressed the plasma triacylglycerol (TG) levels and prevented its rise. C. paliurus extract showed pancreatic lipase inhibitory activity with an IC\(_{50}\) of 9.1 µg/mL in vitro.\(^\text{19}\) A study on triterpenoid saponins isolated from the fruits of Acanthopanax senticosus showed pancreatic lipase inhibitory activity.\(^\text{20}\) Among the isolated compounds, silphioside F, copteroside B, hederagenin 3-O-b-D-glucuronopyranoside 6-O-methyl ester and gypsogenin 3-O-b-D-glucuronopyranoside showed inhibitory activity toward pancreatic lipase. Effects of ethanol extract of Mangifera indica L. (stem bark and leaves, Fig. 3B) on lipases (pancreatic lipase, lipoprotein lipase and hormone-sensitive lipase) as well as for the inhibition of lipolysis of 3T3-L1 adipocytes were carried.\(^\text{21}\) Extract of stem bark and leaves of Mangifera indica L. inhibited pancreatic lipase and lipoprotein lipase. Methanolic extract from the leaves of Salvia officinalis L. was also investigated for lipase inhibition showed considerable amount of inhibitory effect on serum triglyceride elevation in olive oil loaded mice (500 and 1000 mg/kg, orally) and pancreatic lipase inhibitory activity with IC\(_{50}\) of 94 mg/mL.\(^\text{22}\) In an interesting experimentation pancreatic lipase inhibitory activity of the rhizome of Alpinia officinarum (AO) and its anti-hyperlipidemic activity were investigated and measured.\(^\text{23}\) The ethyl acetate fraction exhibited the most potent inhibition. 3-methylethergalangin was isolated from that fraction as an inhibitor of pancreatic lipase with an IC\(_{50}\) value of 1.3 mg/mL. The results suggested pancreatic lipase inhibition was responsible for the hypolipidemic activity of AO and 3-methylethergalangin. Tannin-rich extract obtained from the Araucaria angustifolia seed coat is also reported as an effective pancreatic lipase inhibitor.\(^\text{24}\) Inhibition was of the parabolic non-competitive type. This interesting result was most probably due to the indirect inhibition of triglyceride absorption by inhibition of pancreatic lipase.

In past some beverage plants have also been investigated for pancreatic lipase inhibitory activity. Anti-obesity effects of oolong tea in high-fat diet-treated mice were also investigated by some research group.\(^\text{15}\) Interestingly, they found the pancreatic lipase inhibitory activity actions of substance present in oolong tea. The results also suggested that oolong tea may be an effective crude drug for the treatment of obesity and fat liver caused by a high-fat diet. Methanolic extract of Ilex paraguariensis leaves was also demonstrated for porcine pancreatic lipase inhibitory activity.\(^\text{25}\) From the methanolic extract, three new triterpene oligoglycosides, mataglycosides A, B, and C, were isolated together with eighteen known compounds. Several constituents showed inhibitory activities on pancreatic lipase. In an investigation carried out on Cassia auriculata a traditional medicine used for the treatment of diseases, such as hyperlipidemia, diabetes and some other disease conditions.\(^\text{26}\) The crude extract of cassia auriculata exhibited pancreatic lipase inhibitory activity with an IC\(_{50}\) of 6.0 ± 1.0 µg/mL suggesting that anti-hyperlipidemic effect of the extract might be responsible for the anti-lipase activity.

Anti-obesity effect of Platycodi radix, aqueous extract is also investigated and interestingly it was observed that P. radix inhibited intestinal absorption of dietary fat by inhibiting pancreatic lipase activity.\(^\text{27}\) Toward the search of anti-obesity mechanism of P. radix, experiments were performed on activity guided isolation to find active components. The entire saponin fraction of P. radix appeared to have a potent pancreatic lipase inhibitory activity during hydrolysis of triolein emulsified with phosphatidycholine in vitro. Lee et al, 2005 have demonstrated the lipid-lowering potential of aqueous extract of Gardenia jasminoides Ellis (GF) fruits, showed inhibition of pancreatic lipase.\(^\text{28}\) The two components isolated from G. jasminoides showed an IC\(_{50}\) value of 2.1 mg/mL for crocetin and 2.6 mg/mL for crocin on triolein substrate. These compounds efficiently inhibited the increase of serum Triglyceride level, LDL cholesterol levels in hyperlipidemic mice. The results showed that the lipid lowering activity of GF and crocin was due to the inhibition of pancreatic lipase and crocin, while the metabolite crocetin, improved hyperlipidemia. Flavonoids isolated from the leaves of Nelumbo nucifera leaf (NLF) were examined for its in vitro inhibitory potential against lipase. Experiments revealed that NLF displayed high pancreatic lipase inhibitory activity with IC\(_{50}\) value of 0.38 ± 0.022 mg/mL.\(^\text{29}\) The results suggested that NLFs could be thought of as a possible treatment
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In an investigation Salacia reticulata, a plant found in Indian forests, had been examined for its anti-obesity effects. Boiled extract from the roots of S. reticulata were used for in vitro study on rats. Salacia reticulata hot water (SRHW) soluble extract seemed to suppress the body weight with oral administration and also showed pancreatic lipase inhibitory activity thereby ceasing that polyphenolic compound of SRHW might be responsible for anti-obesity effects in rats due to the inhibition of fat metabolizing enzymes. According to a study three triterpenoid saponins, gypsosaponins were isolated from the roots of Gypsophila oldhamiana. These showed pancreatic lipase inhibitory activity. A study on the inhibitory activities of Taraxacum officinale extract against pancreatic lipase in vitro and in vivo was also evaluated to determine its potential use as a natural agent for the management of obesity. Taraxacum officinale extract were measured using 4-MU olate as a substrate at different concentrations. Taraxacum officinale extract showed good inhibitory activities against pancreatic lipase. However researchers stated that further studies are needed to discover the active components involved in pancreatic lipase inhibition and evaluate the effects of continuous usage of T. Officinale as an anti-obesity agent. A study carried out to evaluate the pancreatic lipase inhibitory activity of the extract of Actinidia arguta root triterpenes. Coumaroyl triterpene, 3-O-trans-p-coumaroyl actinidic acid, ursolic acid, 23-hydroxysorolic acid, corosolic acid, asiatic acid, and betulinic acid assessed in vitro showed that coumaroyl triterpene had highest pancreatic lipase inhibitory activity with an IC50 of 14.95 µm. Another study on 3T3-L1 adipocytes, other proteins that strongly inhibit hydrolysis of triglycerides are the basic protein protamine and ε-polysylne. Proteins isolated from the seeds of Moringa have also been reported for pancreatic lipase inhibitory activity. Researchers have also evaluated the potential inhibitory activities of spices. According to research carried out by Etoundi et al., on 19 commonly used Cameroonian spices for their polyphenol content, as well as their in vitro anti-lipase activities indicated that the Xylopia aethiopica (92.25%) and Scorodophloeus zenkeri (with husk) (56.39%) were most effective in inhibiting the activity of pancreatic lipase. A research study carried out to check the pancreatic lipase inhibitory activity of Illicium verum (Fig. 5B) showed an inhibition of 22.7%. Under in vitro conditions ethanolic extracts of seeds of Aframomum melegueta presented pancreatic lipase inhibitory activity in a concentration-dependent manner. Lipase inhibitory activities of 90% was observed in A. meleguetta at certain concentration.

CONCLUSION

As pancreatic lipase inhibition is considered as good drug target for obesity management, molecule from natural origin can be a good drug candidate for designing of safe anti-obesity drug particularly those derived from edible food plant. Voluminous scientific reports are available in...
public domain on various plant including food plant and their products for its anti-obesity and pancreatic lipase inhibitory activity. Pancreatic lipase inhibitors especially from food plant can be explored for development of safe anti-obesity drug for long term use due to possible active principle as edible component.

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