Therapeutic Role of Phytomedicines on Obesity: Importance of Herbal Pancreatic lipase Inhibitors

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Abstract

Obesity has been declared one of the major threats to human health in 21st century. It has become the center of much clinical attention and especially clinical laboratories, whose aim is to reduce this new world syndrome. Dietary fat is associated with well known diseases like diabetes, hypertension and cardio-vascular diseases. Certain long-term medications like use of insulin, sulfonylureas, thiazolidinediones, atypical antipsychotics, antidepressant, steroids, some anticonvulsants (phenytoin and valproate), pizotifen and some forms of hormonal contraception may also cause weight gain or changes in body composition. Retardation of nutrient absorption and digestion may be used as an approach to manage obesity and related diseases. Orlistat is the only approved drug for long-term use and widely accepted also. However, some side effects and complications are also related with this medication. Currently, plant based natural products as anti-obesity therapeutics is largely unexplored and such products may be safer and effective alternative(s) for this ever increasing pandemic. Anti-nutritional factors (ANF) are natural compounds which act to retard nutrient(s) uptake. Phyto-chemicals like kievitone and visoltricine are useful in pharmacological treatments. Phyto-chemicals like flavonoides, saponins, alkaloids and many others are reported as biologically active molecules. Plants may prove to be an alternative source(s) of a variety of anti-lipolytic therapeutic molecule(s) that can either inhibit the pancreatic lipase or the uptake/absorption of fat(s) or both. In this review we emphasize the potential role of these bioactive compounds as pancreatic lipase (PL) inhibitory molecules. Moreover, medicinal plants are promising sources for isolation, identification and characterization of bioactive compounds for developing effective anti-obesetic agents.

Keywords: Obesity, Orlistat, pancreatic lipase inhibitors and phytochemical(s).

Introduction

Obesity, the ‘New World Syndrome’ has been declared a global epidemic by WHO\textsuperscript{1,2} and is now being recognized as a major health concern especially in new world countries. There are over 400 million clinically obese and 1.6 billion overweight adults according to a WHO survey\textsuperscript{3,4}. In developed countries like USA\textsuperscript{5}, Australia and Canada\textsuperscript{6,7} it is increasing at a faster rate. In United States, obesity has been assumed to be an important cause of human deaths\textsuperscript{8}. One in three Americans are obese. In the European Union, half population of adults and approximate 20\% of school-age children are reported as overweight. In England over a quarter of adults (26\%) were reported as obese in 2010\textsuperscript{9}. A statistical study report that in US 35\% of adults and almost 17\% of youth were obese in the year 2009-10\textsuperscript{10}. The Indians are also reported for obesity and their consequences\textsuperscript{11}. There is a constant rise in obesity related deaths each year. Major health consequences associated with overweight and obesity are dyslipidemia, coronary artery disease, type-2 diabetes, reproductive and gastrointestinal cancers, sleep apnea, stroke, fatty liver and osteoarthritis\textsuperscript{12}. Recently, it has been found to promote prostate cancer, too\textsuperscript{13}. Obese patients may lower the risk of cardiovascular diseases and type-2 diabetes by reducing only 5-10\% weight\textsuperscript{14,16}. Medication is also available, as therapeutic compounds that can block/ inhibit fat digestion\textsuperscript{17}. Orlistat which is a saturated derivative of Lipstatin\textsuperscript{18} lowers the body weight when taken under suitable dietary advice\textsuperscript{19,20}. This drug has also been shown to improve OGT (oral glucose tolerance)\textsuperscript{21}.

Natural compounds from plants and microbes can be developed as anti-obesity clinical products\textsuperscript{22}. Retardation of nutrient absorption and digestion may be used as an approach to manage obesity and related diseases. For example, valoneaic acid dilactone from banaba\textsuperscript{23}, chestnut astringent skin extract\textsuperscript{24}, amylase inhibitor from white beans\textsuperscript{25} and acarbose\textsuperscript{26} showed clinical effects against diabetes and cardio-metabolic disorders. Marine algae\textsuperscript{27}, fungi\textsuperscript{28} and some plants have been screened for anti-lipase activity\textsuperscript{29}.

Imbalance between energy intake and energy expenditure leads to over-weight and Obesity\textsuperscript{30}. High intake of dietary fat, overeating and reduced physical activity together lead to obesity\textsuperscript{31} that are main causes of prevalence of obesity in westernized societies. Normally, man and woman have 18-23\% and 25-30\% of body fat in average. Women with over 30\% and men with over 25\% body fat are considered obese. Overweight and obesity are determined by using weight and height to
calculate a number called the ‘Body Mass Index’ (BMI). The formula for calculating BMI was given by a Belgian scientist Adolphe Quetelet in 1830 to assess the body fat. BMI equals a person’s weight in kilograms (kg) divided by his/ her height in meters (m) squared. But recently a modified Quetelet’s BMI formula that has been proposed and it is gaining good acceptance.

Quetelet’s BMI= Weight (kg)/ Height (m²) = 703 X weight (lb)/ height (in²)
New formula BMI= 1.3 X Weight (kg)/ Height (m²) = 5734 X weight (lb)/ height (in²)

An adult is considered overweight if he/ she has a BMI between 25 and 29.9 and is considered obese if BMI of 30 or higher (table 1).

In some cases, such as athletes, may be identified as overweight according to BMI even though they do not have excess body fat. So BMI calculation does not take into account the muscular mass (i.e. heavy weight lifters) or the stage of development (i.e. when our body is still developing). A few other methods that may be useful to diagnose the level/ grade of obesity include; i. Waist circumference, sagittal diameter and waist-to-hip ratio: 102 cm (40 inches) for a man and 88 cm (35 inches) for a woman is currently recommended upper limit for waist circumference in the United States. Waist-to-hip ratio greater than 1 in men or greater than 0.85 in women is considered obese. ii. Skin fold caliper: This test measures fat beneath the skin, but cannot measure fat accumulated inside the abdomen. iii. Water displacement test: Determining how well we float provides an estimated ratio of fat to body mass. iv. Blood tests: To assess other medical conditions in which body weight increases (like thyroid disorder), some blood tests can also be performed.

Alimentary obesity makes up most of obesity cases and results when a person consumes more calories than he/ she can burn. Some cases of secondary obesity results in disorders like Cushing's syndrome, polycystic ovary syndrome (PCOS) and insulin tumors. Childhood obesity occurs when children and adolescents are above the normal body weight for their age and height. A limited number of cases are primarily due to genetics, medical reasons or psychiatric illness.

Sometimes weight excess is also a major feature in some syndromes, such as Prader-Willi syndrome, Bardet-Biedl syndrome, Cohen syndrome and MOMO syndrome. A few cases are also reported with single point DNA mutation. Some cases like hypothyroidism, Cushing’s syndrome and growth hormone deficiency also reported to weight gain. Some long-term medications may also cause weight gain or changes in body composition; these include insulin, sulfonlyureas, thiazolidinediones, atypical antipsychotics, antidepressants, steroids, some anticonvulsants (phenytoin and valproate), pizotifen and some forms of hormonal contraception. Some other factors, which also play a role in obesity may include;

Age: At older age body’s ability to metabolize food slows down and there is less requirement of calories to maintain body weight. So at age of 40 or after we tend to gain weight. There's some evidence that when an older a woman gives birth, there is a higher child's risk of obesity.

Gender: Women tend to be more overweight than men due to difference in resting metabolic rate. Additionally, women tend to gain weight after menopause.

Environmental factors: Environmental factors unknowingly affect our metabolism. We know hormones regulate body weight and many of today's pollutants affect our hormones. For convenience we are living in temperature-controlled rooms/ office. Moreover, smoking also reduces weight.

Psychological factors: Many persons eat in response to boredom, sadness or anger. Too little sleep may also result in gain of body weight.

Genetic factors: Some of the genetic factors predispose us to obesity. Some reports evidencing fertility of obese people than leaner ones. If obesity has a genetic component, the percentage of obese people in the population will increase. Moreover, union of obese spouses also promotes the chances to have obese child in generation.

Clinical management of obesity: drugs and surgery

In most cases patients who lose weight, regain the weight in subsequent years suggesting obesity has a high relapse rate making difficulty in treatment. So the treatment has to be a lifelong commitment with proper dietary habits and increased physical activities. Pathetically obese patients may lower the risk of cardiovascular diseases and type-2 diabetes by reducing only 5-10% weight. Therapeutic treatment of overweight patients has been reviewed. Leptin, a peptide hormone, was discovered to regulate body weight. Details and additional guidance for the medications to treat overweight patients have been published time-to-time. Currently, the options of medications available to treat overweight patients are quite limited. Additionally, the side effects of these medications are also major concerns to clinicians, particularly for appetite-suppressant drugs. Fenfluramine was withdrawn from market after reports of cardiac fibrosis and pulmonary hypertension.
Pharmaceutical potential of phyto-chemicals

Plants are in use since several years as traditional and natural pharmaceutical aids.\(^{23,74}\) They have been proved to be effective for treating obese patients.\(^{87}\) Gastric bypass surgery causes permanent changes in gastrointestinal tract and its effects cannot be reversed.\(^{78}\)

Surgery may help patients who are in pathetic condition. Two bariatric surgical procedures: gastric bypass and Lap-Band have proved to be effective for treating obese patients.\(^{80}\) Gastric bypass surgery causes permanent changes in gastrointestinal tract and its effects cannot be reversed.\(^{78}\)

Pharmacological studies\(^{91,92}\) have also been reported for their insecticidal properties. Flavonoids particularly genistein have been shown as anti-cancerous phyto-molecule.\(^{109,111}\) Flavonoids\(^{86,87}\) are also used in food processing industries\(^{113}\) and they also have insecticidal properties.\(^{114}\) Tannins\(^{115}\) are also considered as anti-tumor agents,\(^{116}\) antimicrobial agents\(^{117}\) and as anti-helmintic agents\(^{118-120}\) Condensed tannins are reported to be beneficial in agriculture, in nutrition and health of ruminants.\(^{121}\) Alkaloids are known as strong anti-inflammatory agents.\(^{122}\) Protease inhibitors have also been reported for their insecticidal properties.\(^{123-125}\)

Therapeutic interventions to manage obesity using phytomolecules

Phytomolecules may play the key role as an anti-obesic agent via distinct mechanisms. They may reduce lipid absorption from food, reduce energy intake from diet, enhance energy expenditure by degrading stored fat, decrease pre-adipocyte differentiation and proliferation and boost up the lipolysis of accumulated fat in our body (figure 1). As dietary fat is responsible for adiposity so to develop lipid digestion and absorption inhibitors, pancreatic lipase may be targeted for drug development as it is the key component in fat digestion. To develop novel inhibitors those lack unpleasant side effects, phyto-chemicals and secondary metabolites from plants and microbial sources can be focused for antiobesity medication development programme.

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**Figure-1**

Antiobesic medication strategies

1. Pancreatic lipase inhibitory molecules eg. Lipstatin, licochalcone A, chitosan, panchelins, vaillactone and hesperidine
2. Enhancement of energy expenditure eg. EGCG, β-conglycinin, EPA and DHA
3. Appetite suppressants eg. Sibutramine, hydroxyecitric acid, oleoyl-estrone and EGCG
4. Adipogenesis inhibition and apoptotic effect on adipocytes eg. Curcumine, genistein, carnosic acid, sporamine, isorhamnatin and capsicain
Many phytochemicals and metabolites that possess pancreatic lipase inhibitory actions have been reported (table 2, 3 and 4). Energy intake reduction via appetite suppression also provides an option for obesity treatment. Sibutramine is an appetite suppressant that acts by controlling noradrenaline, serotonin, hydroxytryptamine and dopamine. Some herbal appetite suppressants have also been discovered like Hoodia gordoni, Pinellia ternate, and Panax ginseng. Some phytochemical compounds like quercetin, esculetin, genistein, resveratrol and capsaicin shown as antiobesity agents act via adipogenesis inhibitors and apoptotic on adipocytes.

**Anti-obesetic phyto-molecules as pancreatic lipase inhibitors**

The main issue, need to be kept in mind before any effective drug widely accepted, is the toxicity of therapeutic and of course it must also not be addictive. In this concern plants may prove to be an alternative source(s) of a variety of anti-lipolytic molecules(s) that can either inhibit the pancreatic lipase or the uptake/absorption of fat(s) or both. Phytochemicals present in plants offer us the safer natural products that can be developed in the form of therapeutics (table 2). These bioactive compounds can be extracted and purified in many ways. For the pandemic cases these bioactive compounds can be targeted on lipid metabolic pathways. A very large pool of enzymes related to fat digestion has been discovered and can be targeted for development of therapeutics for obesity and related diseases.

**Table-2**

<table>
<thead>
<tr>
<th>Source</th>
<th>Family</th>
<th>Antiobesetic agent</th>
<th>Ref. (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Oryza sativa</em></td>
<td>Poaceae</td>
<td>Phenylboronic acid</td>
<td>137</td>
</tr>
<tr>
<td><em>Salvia officinalis</em></td>
<td>Lamiaceae</td>
<td>Carnosic acid (Diterpene)</td>
<td>138</td>
</tr>
<tr>
<td><em>Platycodon grandiflorus</em></td>
<td>Campanulaceae</td>
<td>Platycodin D (Saponin)</td>
<td>139-141</td>
</tr>
<tr>
<td><em>Glycyrrhiza aurantii</em></td>
<td>Fabaceae</td>
<td>Licochalcone A (Polyphenol)</td>
<td>142</td>
</tr>
<tr>
<td><em>Scabiosa tschilensis</em></td>
<td>Caprifoliaceae</td>
<td>Prosapogenin (Saponin)</td>
<td>143</td>
</tr>
<tr>
<td><em>Acanthopanax sessiliflorus</em></td>
<td>Araliaceae</td>
<td>Sessiloside and chisanoside (Saponins)</td>
<td>144</td>
</tr>
<tr>
<td><em>Panax japonicas</em></td>
<td>Araliaceae</td>
<td>Chikusetsusaponins (Saponin)</td>
<td>145</td>
</tr>
<tr>
<td><em>Dioscorea nipponica</em></td>
<td>Dioscoreaceae</td>
<td>Dioscin (Saponin)</td>
<td>146</td>
</tr>
<tr>
<td><em>Aesculus turbinata</em></td>
<td>Sapindaceae</td>
<td>Escins (Saponin)</td>
<td>147</td>
</tr>
<tr>
<td><em>Cyclocarya paliuris</em></td>
<td>Juglandaceae</td>
<td>Cyclocariosides (Saponin)</td>
<td>148</td>
</tr>
<tr>
<td><em>Gardenia jasminoides</em></td>
<td>Rubiaceae</td>
<td>Crocin (Terpene)</td>
<td>149</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Source</th>
<th>Phytochemical(s)</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Camellia sinensis</em></td>
<td>Proanthocyanidins</td>
<td>167</td>
</tr>
<tr>
<td></td>
<td>and catechins</td>
<td></td>
</tr>
<tr>
<td><em>Cassia mimosoides</em></td>
<td>Proanthocyanidins</td>
<td>168</td>
</tr>
<tr>
<td><em>Malus domestica</em></td>
<td>Procyanidins</td>
<td>169</td>
</tr>
<tr>
<td><em>Coffee arabica</em></td>
<td>Saponins</td>
<td>170, 171</td>
</tr>
<tr>
<td><em>Cyclocarya paliuris</em></td>
<td>Saponins</td>
<td>148</td>
</tr>
<tr>
<td><em>Dioscorea nipponica</em></td>
<td>Saponins</td>
<td>146</td>
</tr>
<tr>
<td><em>Eleutherooccus senticosus</em></td>
<td>Saponins</td>
<td>172, 173</td>
</tr>
<tr>
<td><em>Eleutherooccus sessiliflorus</em></td>
<td>Saponins</td>
<td>174</td>
</tr>
<tr>
<td><em>Gardenia jasminoides</em></td>
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<td>149</td>
</tr>
<tr>
<td><em>Aesculus turbinata</em></td>
<td>Saponins</td>
<td>147, 175</td>
</tr>
<tr>
<td><em>Kochia scoparia</em></td>
<td>Saponins</td>
<td>176</td>
</tr>
<tr>
<td><em>Malus domestica</em></td>
<td>Saponins</td>
<td>169</td>
</tr>
<tr>
<td><em>Panax ginseng</em></td>
<td>Saponins</td>
<td>177</td>
</tr>
<tr>
<td><em>Panax japonicas</em></td>
<td>Saponins</td>
<td>145</td>
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<tr>
<td><em>Platycodin grandiflorum</em></td>
<td>Saponins</td>
<td>140, 141</td>
</tr>
<tr>
<td><em>Ilex paraguariensis</em></td>
<td>Polyphenols and saponins</td>
<td>178</td>
</tr>
<tr>
<td><em>Arachis hypogaea</em></td>
<td>Polyphenols</td>
<td>153, 154</td>
</tr>
<tr>
<td><em>Camellia sinensis</em></td>
<td>Theasaponins and polyphenols</td>
<td>179, 180</td>
</tr>
<tr>
<td><em>Nelumbo nucifera</em></td>
<td>Polyphenols</td>
<td>181</td>
</tr>
<tr>
<td><em>Mangifera indica</em></td>
<td>Polyphenols</td>
<td>153, 154</td>
</tr>
<tr>
<td><em>Cassia nomame</em></td>
<td>Condensed tannins</td>
<td>168</td>
</tr>
<tr>
<td><em>Salacia reticulata</em></td>
<td>Polyphenols</td>
<td>182</td>
</tr>
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</table>

Pancreatic lipase, a key enzyme, which is responsible for hydrolysis of a majority of dietary fats, may be targeted for the concerned obesity pandemic. Like, Orlistat and Cetilistat acts by inhibiting gastro-intestinal and pancreatic lipases but have side effects including greasy stools, and faecal spotting. And also, it needs supplementation of fat soluble vitamins in diet. So in search of safer anti-obesetic therapeutic several efforts have been made and still going on as pancreatic lipase (PL) inhibitory agents. Many bioactive phyto-chemicals have been screened for their anti-obesetic potential (table 3). Some anti-lipolytic metabolites have been discovered from a variety of microbial and other sources (table 4). Many plant extracts, fungal extracts and chemical compounds like polysaccharides, e-polylysine, protamines, cholestyramine and soya proteins have been shown to possess anti-lipolytic function(s) against pancreatic lipase.
Acknowledgements

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Abbreviations: ANF: Anti nutritional factors; PL: Pancreatic lipase; WHO: World Health Organisation; USA: United States of America; BMI: Body Mass Index; MOMO: Macrosomia; Obesity Macrocephaly Ocular syndrome; DNA: Deoxyribose nucleic acid; EPA: Eicosapentaenoic acid; DHA: Docosahexenoic acid; EGCG: Epigallocatechin gallate; OGT: Oral glucose tolerance; PCOS: Poly cystic ovary syndrome.

Table-4

<table>
<thead>
<tr>
<th>Source</th>
<th>Kingdom</th>
<th>Antiobesetic metabolite</th>
<th>Reference(s)</th>
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</thead>
<tbody>
<tr>
<td>Streptomyces toxytricii</td>
<td>Bacterium</td>
<td>Lipstatin</td>
<td>18</td>
</tr>
<tr>
<td>Streptomyces sp. NR0619</td>
<td>Bacterium</td>
<td>Pancilicins</td>
<td>183, 184</td>
</tr>
<tr>
<td>Streptomyces aburaviensis</td>
<td>Bacterium</td>
<td>Ebelactones</td>
<td>185</td>
</tr>
<tr>
<td>Boreostereum vibrans</td>
<td>Fungus</td>
<td>Vibralactone</td>
<td>186</td>
</tr>
<tr>
<td>Monascus sp.</td>
<td>Fungus</td>
<td>Penicillamine Derivative</td>
<td>187</td>
</tr>
<tr>
<td>Caulerpa taxifolia</td>
<td>Algae</td>
<td>Caulerpenyne</td>
<td>27, 188</td>
</tr>
<tr>
<td>Streptomyces albolongus</td>
<td>Bacterium</td>
<td>Valilactone</td>
<td>189</td>
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<tr>
<td>Streptomyces lavendulae strain MD4-C1</td>
<td>Bacterium</td>
<td>Esterastin</td>
<td>190</td>
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<tr>
<td>Stereum complicatum, ST 001837</td>
<td>Fungus</td>
<td>Percyquinin</td>
<td>191</td>
</tr>
</tbody>
</table>

See weeds

Algae

Fucoxanthinol (carotenoid) 192

Conclusion

Complete understanding of metabolites involved in fat metabolism in our body will open the ways to develop the therapeutics to combat obesity. Pancreatic lipase, a key lipolytic enzyme, is a most attractive target for this purpose. In brief, efforts should be made to develop safer medication to counter the gigantic problem of ever increasing obesity. None of the drugs has been established for long time to cure obesity. The only approved drug, Orlistat, has non ignorable side effects. So in search of nontoxic therapeutic, plant based clinical products are a good option. Pancreatic lipase can be targeted for the concerned pandemic. Pancreatic lipase inhibitors form plant sources as anti-obesetic metabolites has been discovered but none of them reached up to clinical level. Hence concerted efforts are required to explore plants as important natural resources for their therapeutic potential, not only for obesity but for other diseases, too.

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