INHIBITORY ACTIVITY OF CHALCONE MOETIES ON PANCREATIC LIPASE ENZYME: A REVIEW

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ABSTRACT
The main challenge of today’s research is to design a novel drug for the treatment of ailments with lesser side effects. Obesity derives from Latin word obesities which means tout, fat, or plump. Medically, obesity is a condition in which excess body fat has been accumulated to the extent that it may have an adverse effect on health, leading to reduced life expectancy or increased health problems. Improper lipid metabolism adds other disorders like diabetes, musculoskeletal, cardiovascular and leads to cancer. Improper balance between energy intake and energy expenditure leads to obesity. The major target for the development of antiobesity drug is to inhibit the action of pancreatic lipase enzyme. Chalcones and their heterocyclic analogues, belong to the flavanoid family, which possess a number of interesting biological properties such as antioxidant, cytotoxic, anticancer, antimicrobial, antiprotozoal, antiulcer, antihistaminic and anti-inflammatory activities. In this review, an attempt is made to present a current scenario of the bioactive compounds from chalcone moieties possessing diverse electron-donating and -withdrawing groups were prepared that have been investigated for their pancreatic lipase inhibition. The purpose of this review is to provide an overview of the inhibitory activity of naturally occurring and synthetic chalcones on pancreatic lipase enzyme.

KEYWORDS: Pancreatic lipase inhibitors, chalcones, antiobesity activity.

INTRODUCTION
Obesity is defined as an abnormal or excessive fat accumulation that may impair health. According to WHO global estimates of obesity in 2016 about 600 million adults and 41 million children were found to be obese and it has achieved more than doubled since 1980. Obesity may be considered as no cause if it was not having any risk for non-communicable
diseases. The fundamental cause of obesity is an energy imbalance between calories consumed and calories expended. Raised BMI is a major risk for non communicable diseases such as cardiovascular diseases, diabetes, musculoskeletal disorders some cancers (including endometrial, breast, ovarian, prostate, liver, gallbladder, kidney, and colon). however fewer active substances has been approved by FDA for treating raised BMI.

Pancreatic lipase inhibitor plays a vital role in depletion of excessive fat deposit. Pancreatic lipase is a common target for antiobesity activity. Pancreatic lipase isolated from fermented broth of the Streptomyces toytricini bacterium in 1981 and named lipstatin.\textsuperscript{[1]} It is a selective and potent irreversible inhibitor of human gastric and pancreatic lipases. Lipase inhibitors mechanism based on fat digestion. These inhibitors bind covalently as an ester to the serine hydroxyl group at the active site on pancreatic and gastric lipases and form a stable complex.\textsuperscript{[2,3,4]} This results in a conformational change in the enzyme which causes exposing of the catalytic active site. When the active site is exposed, the hydroxyl group on the serine residue is acylated. This leads to irreversible inactivation of the enzyme. The inactive lipase is incapable of hydrolysing fats into absorbable fatty acids and monoglycerides, therefore triglycerides are excreted undigested with faeces.\textsuperscript{[5]} With this mode of action calorie uptake from fat in food is limited, hence body weight is reduced.\textsuperscript{[6,7]} The main role of lipase inhibitors is therefore to inhibit lipases in the gastrointestinal tract, but they do not have significant activity against proteases, amylases or other digestive enzymes. Several classes of compounds shows profound pancreatic lipase inhibitory activity such as flavanoids, saponins and substance of microbial source such as lipstatin and panclicins. Chalcones are chemically trans-1, 3-diaryl-2-propen-1-ones\textsuperscript{[8]}, a biosynthetic product belonging to flavanoid family. Chalcones are precursors in the synthesis of many biologically important heterocycles such as benzothiazepine, pyrazolines, 1, 4-diketones, and flavones. Thus the synthesis of chalcones has generated vast interest to organic as well as for medicinal chemists. The traditional methods for the synthesis of 1, 3-diaryl-2-propenones involves the use of strong bases such as sodium hydroxide and potassium hydroxides. Chalcones and its derivatives have attracted increasing attention due to numerous pharmacological applications. Chalcones are α, β-unsaturated ketones consisting of two aromatic rings (ring A and B) having diverse array of substituent. Rings are interconnected by a highly electrophilic three carbon α, β-unsaturated carbonyl system that assumes linear or nearly planar structure.\textsuperscript{[9]} They contain the ketoethylenic group (–CO–CH=CH–). Chalcones possess conjugated double bonds and a completely delocalized π-electron system on both benzene rings. The dihedral angle between
the two phenyl rings is 13.0(1)°, and the dihedral angle from the plane of C7/C8/C9 to the
phenyl rings (C1 to C6 and C10 to C15) are 13.8(1)° and 2.6(1)°, respectively, indicating that
the central C7-C8-C9 fragment lies nearly in the phenyl ring plane of C10 to C15, but rather
more displaced out of the other benzene ring of C1 to C6. The molecule forms a zigzag chain
by C-H π (arene) hydrogen bonds along the c axis. There also exist intermolecular hydrogen
bonding interactions involving C11 acting as H-bond donor, via H11, to O in the adjacent
molecules at 1-x, 1-y, 1-z, resulting in a three-dimensional network. They can be readily
synthesized in laboratory by the Claisen-Schmidt reaction which is very easy and simple to
conduct as well as inexpensive.

Tiruttani Kuppireddy Padmaja et al\textsuperscript{[10]} investigated the ethanolic extract of \textit{Bauhinia
purpurea} on the changes in body weight, insulin resistance as well as on the activity of
amylase; lipase, leptin and adiponectin levels in high caloric diet (HCD) induced obese rats.
These findings suggest that EEB administration suppresses high-caloric-diet-induced obesity
and it can be developed as a potential candidate for the treatment of obesity and associated
complications.

Nitin A et al\textsuperscript{[11]} reviewed an attempt on bioactive compounds possessing from plant and
microbial origin for their pancreatic lipase inhibition. Various natural products such as
alkaloids, carotenoids, glycosides, polyphenols, polysaccharides, saponins and terpenoids are
well studied while lipophilic compounds from microbial sources are the most active against
the pancreatic lipase. Few studies on the synthetic analogues, structurally similar to the
triglycerides have been described further a direction for the development of potential lead(s)
or pharmacophore for pancreatic lipase inhibition in order to treat and/or prevent obesity and
related disorders.

Ryan DH et al\textsuperscript{[12]} reviewed new medications and their important events in the management of
weight reduction and for an eye of interest in the physician who manages hypertension. All
the newer agents are refitting of older targets hence older once are newer again in the
pharmacotherapy of obesity.

El Sayed Aly MR et al\textsuperscript{[13]} rationally designed four sets of chalcones for evaluation of their
antiobesity, antioxidant and cytotoxicity activities. These sets include nine oleoyl chalcones
as mimics of oleoyl estrone, three monohydroroxy chalcones (chalcone ligands), Schiff base-
derived chalcones and four copper as well as zinc complexes. Oleoyl chalcones as an
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isosteric isomer of oleoyl estrone, were as active as Orlistat on weight loss and related metabolic parameters using male SD rats in vivo. Chalcone ligands and Schiff base-derived chalcones were weakly antioxidants, while, the copper and zinc complexes were good antioxidants with zinc chelates being more active than their copper analogues vitro. Chalcones are bifunctional probes for potential investigations in cancer diagnosis and radiotherapy by complexation with Gd(3+) or metal radioisotopes followed by posttranslation of Shiga toxin B-subunits that target globotriosyl ceramide expressing cancer cells.

Poonam Shukla, Amar Bahadur Singh et al\textsuperscript{[14]} synthesised a series of aryloxypropanolamines based chalcone derivatives and evaluated for their antihyperglycemic activity in SLM and STZ rat models. Most of the compounds exhibited moderate to good activity ranging from 6.5% to 31.1% in SLM and 8.3% to 22.6% in STZ models, respectively. The most potent compound 5g exhibited glucose lowering of 26.7% in SLM and 22.6% in STZ models. A definite structure–activity relationship was observed while varying the nature as well as the position of the amine in ring B.

Maria Joao Matos et al\textsuperscript{[15]} review emphasizes the rationale behind the natural sources, the discovery, the design, the synthesis, the biological activities and the study of structure–activity relationships of the new chalcone derivatives.

Liming Ni et al\textsuperscript{[16]} Naturally-occurring and synthetic chalcone compounds have shown promising biological activity and safety profiles and have the potential to be developed as, or more properly, serve as lead compounds for, the discovery of antioxidant, anti-inflammatory, anticancer or anti-infective agents. Mechanisms of the diverse activities observed with chalcone compounds are not well-defined. This review highlights recent developments and patent activities of chalcones with various therapeutic properties.

Nasir AAA & Kamarulzaman et al\textsuperscript{[17]} insilico study was carried out on selected plants to find the lead compounds that can inhibit pancreatic lipase. Malaysian ethno botanical plants that have potential in reducing body weight were selected to be the candidates of pancreatic lipase inhibitors. The chemical structures of the plants were taken from NADI database (www.nadidiscovery.com). The three dimensional structure of pancreatic lipase was obtained from Protein Data Bank (PDB ID: 1LPB) with its inhibitor, MUP. Hydrogen atoms were added to the protein. MUP ligand was re-docked into the active pocket of the macromolecule with 50x50x60 in grid points in x, y, and z coordinates. The RMSD value for control docking is
1.14 Å. Therefore, parameters used for control docking can be further utilized in virtual screening of pancreatic lipase inhibitor.

Sugiyama H, Akazome Y, Shoji T\(^{[18]}\) proved Inhibitory effects of apple polyphenol extract (AP) and procyanidin contained in AP on in vitro pancreatic lipase activity and in vivo triglyceride absorption in mice and humans were examined. AP and procyanidin considerably inhibited in vitro pancreatic lipase activity. However, polyphenols, except for procyanidin, in AP (i.e., catechins, chalcones, and phenol carboxylic acids) showed weak inhibitory activities on pancreatic lipase. Pentamer of procyanidin has proved maximum inhibitory effects on pancreatic lipase enzymes. These results suggested that with respect to in vitro pancreatic lipase inhibition, the degree of polymerization was an important factor and oligomeric procyanidin mainly contributed. Simultaneous ingestion of AP and triglyceride significantly inhibited an increase of plasma triglyceride levels in both models. These results suggested that the oligomeric procyanidins contained in AP inhibited triglyceride absorption by inhibiting pancreatic lipase activity in mice and humans.

He et al.\(^{[19]}\) administered daily 8 In vitro studies suggested that the effect of oolong tea on body weight could be partially attributed to the inhibition of PL.

Mahiti Gupta\(^{[20]}\) Pancreatic lipase (PL) is considered as one of the safest target for diet-induced anti-obesity drug development. Orlistat is the only PL inhibitor approved for anti-obesity treatment till date. In the process of exploration of new PL inhibitors, we have screened culture filtrates of 70 endophytic fungi of medicinal plants using qualitative as well as quantitative in-vitro PL assays. The qualitative assays indicated potential PL inhibition in only three isolates, namely #57 TBBALM, #33 TBBALM and #1 CSSTOT. Only ethyl acetate extracts of the culture filtrates of these isolates exhibited the PL inhibition. #57 TBBLAM ethyl acetate extract of culture filtrate exhibited potential PL inhibition with an IC50 of 3.69mg/ml which was comparable to the positive control, i.e. Orlistat exhibiting IC50 value of 2.73mg/ml. Further molecular phylogenetic tools and morphological studies were used to identify the isolate #57 TBBALM as Penicillium species.

Tina Buchholz, Matthias F. Melzig\(^{[21]}\) Obesity and its associated diseases such as diabetes mellitus and coronary heart diseases are a major challenge for our society. An important target for the treatment of obesity includes the development of inhibitors of nutrient digestion and absorption. Inhibition of pancreatic lipase and the associated reduction of lipid absorption
is an attractive approach for the discovery of potent agents. Currently, the only clinically approved pharmacologic agent as pancreatic lipase inhibitor is Orlistat. However, its usage is compromised by unpleasant gastrointestinal adverse reactions (oily stools, oily spotting, flatulence). The use of botanical materials as a potential source of new drugs is of increasing importance and application. Natural products that are interesting for obesity treatment are generally considered to have less toxic and side effects than totally synthetic drugs. One of the most important sources of potential pancreatic lipase inhibitors represents the class of polyphenols. This article summarizes most studied subclasses of polyphenols including flavonoids, hydroxycinnamic acids, hydroxybenzoic acids and lignans with pancreatic lipase inhibitory effects. A structural comparison of potent inhibitors shows an increased inhibitory effect depending on number and position of phenolic hydroxyl groups, degree of polymerization and elimination of glycosylation during digestion.

Billington CJ, Epstein LH[22] More than half of adult Americans are overweight or obese, and public health recommendations call for weight loss in those who are overweight with associated medical conditions or who are obese. However, some controversy exists in the lay press and in the medical literature about the health risks of obesity. We review briefly the large body of evidence indicating that higher levels of body weight and body fat are associated with an increased risk for the development of numerous adverse health consequences. Efforts to prevent further weight gain in adults at risk for overweight and obesity are essential. For those whose present or future health is at risk because of their obesity and who are motivated to make lifestyle changes, a recommendation for weight loss is appropriate.

Diana Rucker, 1 Raj Padwal,1 Stephanie K Li,[23] summarise the long term efficacy of antiobesity drugs in reducing weight and improving health status.

Atefehalsadat Seyedan,1 Mohammed Abdullah Alshawsh,1 Mustafa Ahmed Alshagga,1,2 Sanaz Koosha,1 and Zahurin Mohamed[24] Obesity is recognized as a major life style disorder especially in developing countries and it is prevailing at an alarming speed in new world countries due to fast food intake, industrialization, and reduction of physical activity. Furthermore, it is associated with a vast number of chronic diseases and disabilities. To date, relatively effective drugs, from either natural or synthetic sources, are generally associated with serious side effects, often leading to cessation of clinical trials or even withdrawal from the market. In order to find new compounds which are more effective or with less adverse
effects compared to orlistat, the drug that has been approved for obesity, new compounds isolated from natural products are being identified and screened for antiobesity effects, in particular, for their pancreatic lipase inhibitory effect. Pancreatic lipase inhibitory activity has been extensively used for the determination of potential efficacy of natural products as antiobesity agents. In attempts to identify natural products for overcoming obesity, more researches have been focused on the identification of newer pancreatic lipase inhibitors with less unpleasant adverse effect Drew B, Dixon A, Dixon J. Obesity management 31

Phenolic compounds comprise a broad class of natural products formed mainly by plants, but also microorganisms and marine organisms that have the capacity to form them. Nowadays the interest in these compounds has increased mainly due to their diverse chemical structure and wide biological activity valuable in the prevention of some chronic or degenerative diseases. The functional foods are a rich source of these phytochemicals, and this is the starting point for this book, which shows the state of the art of the phenolic compounds and their biological activity. This book integrates eleven chapters that show the state of the art of diverse biological activity of the phenolic compounds, present in some crops or fruits.

Garza Al, Milagro FI et al.[26] Obesity is a multifactorial disease characterized by an excessive weight for height due to an enlarged fat deposition such as adipose tissue, which is attributed to a higher calorie intake than the energy expenditure. The key strategy to combat obesity is to prevent chronic positive impairments in the energy equation. However, it is often difficult to maintain energy balance, because many available foods are high-energy yielding, which is usually accompanied by low levels of physical activity. The pharmaceutical industry has invested many efforts in producing antiobesity drugs; but only a lipid digestion inhibitor obtained from an actinobacterium is currently approved and authorized in Europe for obesity treatment. This compound inhibits the activity of pancreatic lipase, which is one of the enzymes involved in fat digestion. In a similar way, hundreds of extracts are currently being isolated from plants, fungi, algae, or bacteria and screened for their potential inhibition of pancreatic lipase.

CONCLUSION
Chalcones are an excellent scaffolds for synthetic manipulations and also possess multiple biological and Clinical studies have proven their excellent bioavailability and maximum tolerance in the human body. Therefore, research laboratories worldwide were focussed on synthesis of different chalcone analogues for the development of novel and more potent
drugs. Currently, several drugs containing chalcone nucleus are in either in market or under trial. This review article is complementary to the previous reviews and has been focused on the latest pharmacological activities displayed by different chalcone analogues. The present survey indicate that chalcones have largely been targeted for their anti-cancer, anti-microbial, antimalarial and anti-oxidant properties, although, their potential as anti-HIV, anti-inflammatory and anti/protozoal has also been investigated. It is believed that the information compiled in this mini-review article will not only update scientists with recent findings of biological activities of chalcones but also encourage them to use this promising moiety for the design of novel chalcone molecules with enhanced medicinal properties which possesses antiobesity activity. Orlistat is the only drug authorized and presented in Europe for the treatment of obesity within an adequate energy intake, which acts by inhibiting the lipolytic activity of PL. With the aim of finding new compounds more potent or with less secondary effects than Orlistat, new natural products are being identified and screened for their PL inhibitory potential. Some of these extracts are obtained from plants that are rich in polyphenols and saponins and show inhibitory effects on fat digestion, whereas other extracts come from algae, fungi and microorganisms. Thus, natural products provide an exciting opportunity and promise for the development of new therapeutic approaches to the treatment of obesity by blocking the digestion and absorption of dietary lipids, and constitute a valuable alternative to other pharmacological agents. Some of the products reviewed in this article show potentially promising effects for weight control. In particular apple, green tea, soybean and ginseng seem to have great potential as sources of molecules with PL inhibitory activity. For all of them more data are needed to define effects, optimal dose required, and mechanism of action, as well as their possible side or toxic effects. Thus, there is an urgent need to update the knowledge on the numerous natural sources that could act as inhibitors of PL in order to screen them as new potential therapeutic antiobesity agents with low secondary is an excy effects. Chalcone is an excellent template for designing of drugs.

REFERENCES


