JOURNAL OF PHARMA INSIGHTS AND RESEARCH

SHORT COMMUNICATION

Phytochemical and therapeutic potential of Chalcones in the treatment of Hyperlipidemia

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Publication history**:** Received on 21st October; Revised on 18th November; Accepted on 22nd November

Article DOI: 10.5281/zenodo.10232299

Abstract: Chalcones have been used in the traditional system of medicine from antiquity. These are the polyphenolic flavonoid bioactive constituents known to possess tremendous therapeutic potential in the amelioration of various ailments such as Cancer, Diabetes owing to its antioxidant and anti-inflammatory activities. These were found to be useful in the treatment of Cardiovascular, Haematological and Obesity disorders. Chalcones and their semi-synthetic derivatives received potential attention in this lieu. Metabolic disorders due to the present sedentary lifestyle in practice are the leading cause of mortality and stands as a greatest health challenge globally in this 21st century. The major etiologies of the metabolic disorders include resistance to insulin leading to Diabetes, obesity, hyperlipidemia and hypertension ultimately leading to the cardiovascular disturbances. Hyperlipidemia or Atherosclerosis is a disorder in which level of fat or cholesterol level is enhanced and obstructs the blood vessels leading to heart failure and stroke. The bioactive constituent is associated with decreasing total cholesterol, triglycerides and phospholipids. These Phytochemicals are known to mediate the biological response either by interfering with any one of the following mechanisms viz. Triglycerides synthesis, Transfer and Metabolism of fat such as CETP inhibition, TG inhibition, ACAT inhibition, LPL activators, etc. High levels of cholesterol in blood subsequently gives rise to coronary heart disorders viz. Angina Pectoris, Myocardial Infarction, etc.

Keywords: Chalcones; Polyphenolic; Flavonoid; Triglycerides; Atherosclerosis; Hyperlipidemia

1. Introduction

Chalcones or chalconoids are the polyphenolic secondary metabolites belonging to the class of flavonoids (C6-C3-C6 system). Chemically they contain the aromatic ketonic groups connected by the 3C- α, β- unsaturated carbonyl system (enone) joining two fragrant aryl rings [1]. They can be otherwise named as Benzylacetophenone or benzylidene acetophenone. They are the significant intermediates in the biosynthesis of flavonoids. They are biosynthesised from the phenyl alanine of the shikimic acid pathway through the enzyme chalcone synthase [2]. Some of the important Phytochalcones are naringenin, butein, xanthoangelol, flavokawin, 4-hydroxyderricin, cardamonin, isoliquiritigenin, isosalipurposide and dihydroxychalcone. They are known to possess the following pharmacological activities due to the presence of ketoethylenic moiety containing reactive α, β carbonyl group viz. anti-inflammatory, antimicrobial, antioxidant, anticancer, anti-diabetic, immunomodulation, anti-obesity, Cardiovascular and haematological disorders. Along with the plant derived chalcones semi-synthetic chalcones with slight modifications in the aryl ring also received increasing attention owing to the mediation of various pharmacological responses by a single phytochemical molecule. They are found in various angiosperm families such as Asteraceae, Leguminosae and Moraceae. Some of the chalcones in diet from fruits and vegetables are obtained from citrus fruits, potato, tomato, beans, etc., [3-5]. Chalcones are known exhibit enormous therapeutic potential in the ailment of various diseases viz. anticancer, antidiabetic, antimalarial, anti-tuberculosis, neurodegenerative disorders, antimicrobial, etc.

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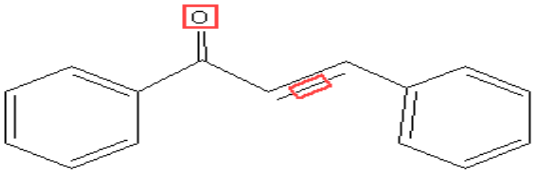

Figure 1 Basic Structure of Chalcone

2. Phytochemical classification of Chalcones

Plant derived chalcones can be categorised as hydroxyl and methoxyl derivatives of Chalcone scaffolds, Trans-Chalcones, Prenylated Chalcones, Chromene based Chalcones, Quinone Chalcones, Cinnamoyl Chalcones and Dihydrochalcones [6, 7].

2.1. Drug Developmental of synthetic Chalcones

With the extensive literature search it has been found that there has been tremendous development in this phytoscaffold molecule in the past decade owing to its enormous therapeutic potential. It was evident from the literature that inserting the Heterocyclic rings in the chalcone moiety will further increase the bioactivity of Chalcones. Chalcones with the following Heterocyclic rings have been reported in the literature- Pyrrole [8], Quinoline [9], Pyridine [10], Indole [11], coumarin [12], pyrazole [13], benzofuran [14], isoxazole [15], etc.,

2.2 Therapeutic potential of Chalcones in Hyperlipidemia

One of the derivative of Chalcones, 1m-6 was found to be effective against Hyperlipidemia owing to the stimulation of cholesterol efflux thus reducing the lipid levels in the bloodstream [16]. Table below summarises the various classes of chalcones derived from plant sources acting on various molecular targets to treat Hyperlipidemia.

Table 1 Biological sources of Chalcones with their MOA

Plant source	Chalcone	Chalcone chemical class	MOA of Hyperlipidemic activity
Humulus lupulus	Xanthohumol	Prenyated Chalcones	CETP inhibitor [17], TG inhibitor [18]
Citrus fruits	Naringenin	Hydroxyl derivative of Chalcone/Trans-Chalcone	TG inhibitor [19]
Malus pumila and Prunus mandshurica	Phloretin	Dihydrochalcones	Increase in fatty acid oxidation by PPAR γ2 receptor [20, 21]
Glycyrrihiza glabra	Isoliquiritigenin	Hydroxyl derivative of Chalcone/Trans-Chalcone	NPC1L1 (protein for cholesterol uptake) Inhibitor [22]
Alpinia katsumadai , Alpinia conchigera [23]	cardomonin	Hydroxyl and Methoxyl derivatives of Chalcone	CETP inhibitor [24]

3. Mechanism of action

Hyperlipidemia or Atherosclerosis is the formation of Atheromatous Plaque that is the deposition of fat in the lumen of the blood vessels or arteries that becomes fibrous and thus obstructs the blood flow leading to conditions like Angina pectoris, followed by Myocardial Infarction or stroke. It is characterised by the presence of excessive intracellular and extracellular cholesterol. As the lipid concentration increases the risk of Hyperlipidemia enhances. Some of the Molecular targets for the mediation of pharmacological response are DGAT, CETP, PL, etc.,[25]

Biological fats otherwise called Triglycerides are synthesised in the adipose cells from glycolysis and acetate pathways by DGAT enzyme, hence inhibition of this enzyme can be one of the promising therapeutic target. Chalcones as Inhibitors of TG synthesis can also be the potential leads fo\r the treatment of the ailment [26,27].

Another potent Target for the treatment of Atherosclerosis can be CETP inhibitors. CETP is a plasma protein which takes the fats from either VLDL or LDL and transfer them for Cholesteryl esters from HDL. The inhibition of this protein raises the levels of HDL which is known to reduce the levels of atherosclerosis and thus can be an important anti-atherosclerotic agent [28].

One more target in this scenario can be a Pancreatic Lipase Inhibitor. Pancreatic lipase is a lipolytic enzyme in pancreas known for hydrolysing triglycerides to monoglycerides and free fatty acids. This enzyme has a significant role in fat absorption from the food. Hence inhibition of this enzyme leads to decreased absorption of triglycerides[29]. Other targets include ACAT inhibitors, LPL activators mediating various physiological responses [30, 31].

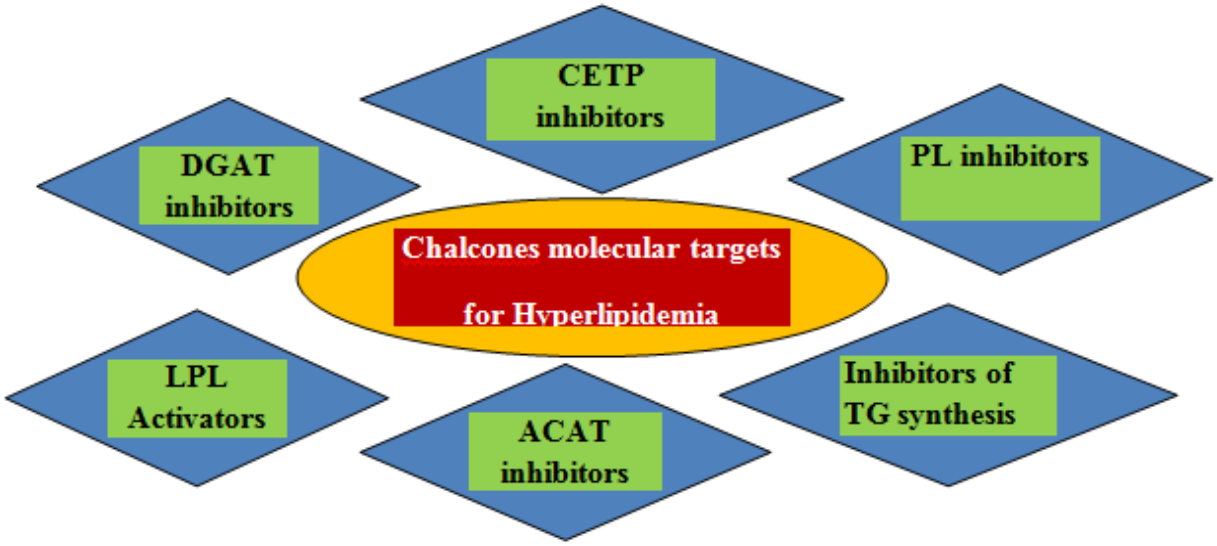

Figure 2 Chalcone based inhibitors for Hyperlipidemia

4. Conclusion

Chalcones can be the most promising option for the treatment of hyperlipidemia owing to their tremendous pharmacological potential in the amelioration of the disease thus paving the way for the rational identification of the most promising scaffolds in the natural products drug discovery and development for the treatment of atheromatous plaque. There is a need for the systematic thorough screening of the compounds for their therapeutic potential by studying their mechanism of action on multiple signaling targets, establishing the structure activity relationship of the novel molecule in order to establish various safety parameters of the phytochemical before it is released for use in the market. Furthermore it is suggested that the synthetic chalcones containing the natural chalcone moiety may exhibit fewer adverse effects when compared to their synthetic equivalents thus Chalcones can be a promising novel phytochemical for the development of chalcone based inhibitors in the management of Hyperlipidemia.

Abbreviations

ACAT: Acyl Coenzyme A-Cholesterol Acyl Transferase

CETP: Cholesterol Ester Transfer Protein

DGAT: Diacyl Glycerol Acyl Transferase

HDL: High Density Lipoprotein

LDL: Low Density Lipoprotein

LPL: Lipoprotein Lipase

MOA: Mechanism of action

NPC1L1: Niemann-Pick1 C1-Like 1

PL: Pancreatic Lipase

VLDL: Very Low Density Lipoprotein

PPAR: Peroxisome Proliferator Activated Receptor

Compliance with ethical standards

Conflict of interest statement

Authors declare no conflict of interest.

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Author's short biography

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Area of Research interest include Drug discovery and development from natural products. Completed my M.Pharm in the Dept. of Phytopharmacy and Phytomedicine, TIFAC CORE in Herbal Drugs, JSS college of Pharmacy,thOoty. My Research area includes extraction, isolation, purification and characterisation of the isolated compounds from natural sources. Completed my internship at The Himalaya Drug company, Bangalore and later on worked as trainer in different US Healthcare MNC'S at Bangalore and Chennai. Right now serving as Assistant Professor in the Department of Pharmacognosy, Narayana Pharmacy College, Nellore, Andhra Pradesh, India.