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Therapeutic potential of chalcones as cardiovascular agents

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ABSTRACT

Cardiovascular diseases are the leading cause of death affecting 17.3 million people across the globe and are estimated to affect 23.3 million people by year 2030. In recent years, about 7.3 million people died due to coronary heart disease, 9.4 million deaths due to high blood pressure and 6.2 million due to stroke, where obesity and atherosclerotic progression remain the chief pathological factors. The search for newer and better cardiovascular agents is the foremost need to manage cardiac patient population across the world. Several natural and (semi) synthetic chalcones deserve the credit of being potential candidates to inhibit various cardiovascular, hematological and anti-obesity targets like angiotensin converting enzyme (ACE), cholesteryl ester transfer protein (CETP), diacylglycerol acyltransferase (DGAT), acyl-coenzyme A: cholesterol acyltransferase (ACAT), pancreatic lipase (PL), lipoprotein lipase (LPL), calcium (Ca^{2+})/potassium (K^{+}) channel, COX-1, TXA_2 and TXB_2. In this review, a comprehensive study of chalcones, their therapeutic targets, structure activity relationships (SARs), mechanisms of actions (MOAs) have been discussed. Chemically diverse chalcone scaffolds, their derivatives including structural manipulation of both aryl rings, replacement with heteroaryl scaffold(s) and hybridization through conjugation with other pharmacologically active scaffold have been highlighted. Chalcones which showed promising activity and have a well-defined MOAs, SARs must be considered as prototype for the design and development of potential anti-hypertensive, anti-anginal, anti-arrhythmic and cardioprotective agents. With the knowledge of these molecular targets, structural insights and SARs, this review may be helpful for (medicinal) chemists to design more potent, safe, selective and cost effective chalcone derivatives as potential cardiovascular agents.

Contents

Abbreviations: 1,4-DHP, 1,4-dihydropyridyl; 4-HD, 4-hydroxyderricin; AA, arachidonic acid; ACAT, acyl-coenzyme A: cholesterol acyltransferase; ACE, angiotensin converting enzyme; ADP, adenosine 5′-diphosphate; AngI, angiotensin I; AngII, angiotensin II; BP, blood pressure; CETP, cholesteryl ester transfer protein; CHD, coronary heart disease; COX-1, cyclooxygenase-1; CVDs, cardiovascular diseases; DGAT, diacylglycerol acyltransferase; DRC, derricin; ET, essential thrombocythemia; HC, hepatic cholesterol; HDL, high-density lipoprotein; HFD, high fat diet; HSYA, hydroxysafflor yellow A; HT, hypertension; IHD, ischemic heart diseases; LCC, lonchocarpin; LDL, low density lipoprotein; LPL, lipoprotein lipase; MBHC, mannich bases of heterocyclic chalcones; MDRC, multi-drug resistance channels; MI, myocardial infarction; MTP, microsomal triglyceride transfer protein; PE, phenylephrine; PL, pancreatic lipase; PLs, phospholipids; PPAR, peroxisome proliferator-activated receptor; PTX, pentoxifylline; SAR, structure activity relationship; SHRSP, stroke-prone spontaneously hypertensive rats; TC, total cholesterol; TG, triglycerides; TXA_2, thromboxane A_2; TXB_2, thromboxane B_2; VLDL, very low density lipoprotein; WRP, washed rabbit platelet; YLSC, 17-methoxyl-7-hydroxyl-benzofuran chalcone; YOH, yohimbine.

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1. Introduction

Cardiovascular diseases (CVDs) are the leading cause of death across the globe. About 17.3 million people died from CVDs in 2008 which represents 30% of all global deaths. Of these 7.3 million people died due to coronary heart disease, 9.4 million deaths were due to high blood pressure and 6.2 million died due to stroke. It is estimated that the death toll may reach 23.3 million by 2030. Most CVDs are caused by risk factors such as tobacco use, unhealthy diet, physical inactivity, high blood pressure, obesity, diabetes and elevated lipids. Lower and middle income countries are disproportionately affected by CVDs (~75%) and death toll occurs almost equally in men and women. The reason for reduced CVDs in developed nations may be improved health care facilities and better access to newer drugs [1]. Still, the search for newer therapeutic agents with improved pharmacokinetic and pharmacodynamic profile and low toxicity is the foremost need to manage cardiovascular complications.

Natural products have been reported to exhibit promising therapeutic activities. Various naturally derived scaffolds have gained significant importance in modern day research where more than half of therapeutic agents bear skeletons derived exclusively from nature [2]. Natural products, both in forms of pharmaceuticals and nutraceuticals (or functional foods) are widely accepted across the globe and are considered relatively safe among the majority of population [3]. The natural constituents have been the mainstay of various biological activities, of them, flavonoids class remained the principal candidate. Flavonoids are a group of heterogeneous heat stable polyphenols with various health benefits [4]. There are more than 4000 polyphenolic compounds known in the plant kingdom for over one billion years. They are ubiquitously found in fruits, vegetables, tea, wine, and are usually subdivided into nine sub-classes including flavonols, flavones, flavanones, flavanols, isoflavones, anthocyanidins, proanthocyanidins, aurones and chalcones, which have promising cardioprotective activities [5]. Various studies have suggested that dietary intake of natural flavonoids displayed protective, modulatory, and mimetic properties that reduce the risk of atherosclerotic progression, weight control, etc. These beneficial effects on the cardiovascular system are exhibited mainly by anti-oxidant activity [6]. Recently, anti-hypertensive, anti-atherosclerotic, anti-platelet, cardioprotective and anti-endothelial dysfunction activities have also been identified. Some of the well-known chalcones such as tinctormine, lonchocarpin, xanthohumol, xanthohumol B, desmethylxanthohumol, xanthoangelol, xanthoangelol E, isobavachalcone, derricin, safflower yellow, hydroxysafflor yellow A, 4-hydroxyderricin, hydroxylated chalcones, substituted chalcone fibrates, sulfonamide substituted chalcones and lupeol-based chalcones have been reported to act on cardiovascular targets. A list of chalcones, their cardiovascular targets and physicochemical properties have been presented in Table 1.

2. Chalcone

Chalcone (**1**) or 1,3-diphenyl-2E-propene-1-one is an open chain intermediate in aurones synthesis of flavones that exists in many conjugated forms in nature. They are the precursors of flavonoids and isoflavonoids containing benzylideneacetophenone scaffold, where the two aromatic nuclei are joined by a three carbon α,β unsaturated carbonyl bridge [7]. Kostanecki and Tambor synthesized a series of natural chromophoric products comprising of α,β unsaturated carbonyl bridge and termed them "chalcone" [8]. Chalcones and their derivatives are usually synthesized by Claisen-Schmidt condensation, however, irradiation with domestic microwave is often employed [9].

Chalcones attracted attention among researchers in this century as compared to other scaffolds due to its simple chemistry, easy synthetic procedures, multiplicity of substitutions and diverse pharmacological potentials such as MDRC inhibition [10], anti-arrhythmic [11], anti-platelet [12], anti-diabetic [13], anti-neoplastic [14], anti-angiogenic [15], anti-retroviral [16], anti-inflammatory [17], anti-gout [18], anti-histaminic [19], anti-oxidant [20], anti-obesity [21], hypolipidemic [22], anti-tubercular [23], anti-filarial [24], anti-invasive [25], anti-malarial [26], anti-protozoal [27], anti-bacterial [28], anti-fungal [29], anti-ulcer [30], anti-steroidal [31], immunosuppressant [32], hypnotic [33], anxiolytic [34], anti-spasmodic [35], anti-nociceptive [36], and osteogenic [37].

3. Molecular targets of chalcone based inhibitors

Various chemically diverse chalcone scaffolds have been reported to inhibit various cardiovascular targets such as angiotensin converting enzyme (ACE) [38], calcium/potassium channels [39], TG synthesis [40], diacylglycerol acyltransferase (DGAT) [41], cholesteryl ester transfer protein (CETP) [42], pancreatic lipase (PL) [43], acyl-coenzyme A: cholesterol acyltransferase (ACAT) [44], and lipoprotein lipase (LPL) [45]. A comprehensive chalcone-target interaction network has been prepared which depicts the therapeutic targets of various chalcones (Fig. 1). Many more derivatives are being developed rationally by structural manipulation of both aryl rings, replacement with heteroaryl scaffold(s) and/or hybridization through conjugation with other pharmacologically active scaffold which showed promising therapeutic potential in the management of hypertension, arrhythmia, thrombosis, obesity and related CVDs.

4. Chalcones as anti-hypertensive agents

Hypertension (HT) or arterial hypertension is a condition characterized by chronically elevated arterial blood pressure (BP). The Hypertension Society has a definite range of BP, which is considered normal, beyond that chance of stroke, MI, arrhythmia and related circumstances develop. HT causes severe damage to human body by affecting different organs of the body. HT promotes thickening of lamina, hypertrophy of smooth muscles and deposition of fibrous tissues in blood vessels. In hypertensive retina, arteriolar thickening, tortuosity and refractiveness occur which eventually results in central retinal vein thrombosis. Hypertensive encephalopathy, subarachnoid hemorrhage, etc. are hypertensive complications in CNS [46]. HT is classified into primary and secondary types as per the reason of disease precipitation. The cause of primary HT is still idiopathic, although secondary HT originates from various endocrine and renal disorders [47]. Though both of them can be managed effectively by pharmacotherapy that modulate/block the hypertensive role of α/β receptors, ACE, calcium channels, electrolyte level, etc., but need of safe, long acting, high therapeutic efficacy, multi-targeted and economic depressor agents is the foremost need