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Chalcones: Multifunctional And Potential Aldose Reductase Inhibitors & Sensitizers

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ABSTRACT

Around 400 million individuals worldwide already have diabetes mellitus (DM), which is expected to impact 600 million people by the year 2030. DM is the metabolic condition with the highest rate of growth. The most important necessity to manage the growing diabetes population is the quest for novel anti-diabetic medications. The fact that several natural chalcones have the ability to function via regulating aldose reductase should be acknowledged. This review paper details a thorough investigation of anti-diabetic chalcones as aldose reductase inhibitors. The review will undoubtedly enthuse experts throughout the world working on pharmacological, novel medication, and natural product research. The investigations will show how to investigate and create new, secure, and effective pharmaceutically active treatments for diabetes and its consequences.

Keywords: Chalcone; Diabetes; Inhibitors; Antihyperglycemic; Aldose reductase; Insulin sensitizers

1. INTRODUCTION

Insulin is known to regulate the blood glucose levels and maintains the homeostasis by regulating the uptake by the muscles, liver, etc. and the endogenous production. It plays a pivotal role in the glycogen formation, protein synthesis, triglycerides formation from glucose, nucleic acid synthesis, energy metabolism, and transport of biomolecules across the cellular membranes [1]. An alteration in the glucose homeostasis by inconsistent insulin secretion, reduced cellular uptake, and hepatic gluconeogenesis leads to precipitation of hyperglycemic condition which is termed as Diabetes Mellitus (DM) [2]. DM is a metabolic disorder not only limited to the carbohydrate metabolism but also the chronic metabolic disorder of fat and protein which is often characterized by high blood sugar levels [3]. The probable reason behind the pathophysiological symptom may be either because the insulin-secreting cells of the body do not have

the ability to produce insulin in the necessary quantity required to convert sugar and other aldose materials into energy, which is often termed as Diabetes Mellitus Type-1 (DMT1) [4]. The other form is referred to as Diabetes Mellitus Type-2 (DMT2) where the body has enough amount of insulin, however, the body does not use the insulin properly as a result of acquired resistance in the cellular level that prevents internalization of the ligand through transporter system [5].

2. CHALCONES

Modern researchers continue to be drawn to the chemistry of chalcones because of their small size, which makes synthesis simple, their large replaceable hydrogen, which can be used to create a number of derivatives with therapeutic potential, and technological advancements that have allowed them to explore new biological targets for the benzylideneacetophenone scaffold [6,7]. Kostanecki and Tambor were the first to synthesize these naturally occurring chromophores, and they also gave them the name "Chalcones" [8]. Numerous conjugated variants of the scaffold 1,3-diphenyl-2-propene-1 occur in nature [9]. The benzylideneacetophenone scaffold, which consists of two aromatic nuclei connected by a three-carbon, unsaturated carbonyl bridge, is used to synthesize isoflavonoids, flavonoids, and aurones, which are the building blocks of flavones [10]. As isomeric compounds, chalcones and flavonones easily interconvert in the presence of acids and bases, with the former serving as a catalyst for chalcone synthesis and the latter as an aid for flavonone creation [11]. Additionally, in Michael addition reactions, these palatable chalcones serve as Michael acceptors [12]. Numerous chalcones, both naturally occurring and synthesized, have been reported to have a wide range of pharmacological potentials, including antihistaminic, antineoplastic properties that include ovarian cancer cell proliferation inhibitors; pulmonary cancer; anti-inflammatory; antifungal; antiplatelet; antimalarial; antioxidant; antimicrobial; hypolipidemic; antileishmanial; antitubercular; antihypertensive; antiinvasive; osteogenic; hypnotic, antinociceptive, antiprotozal, antifibrinogenic, antiulcer, immunosuppressive, antidiabetic, antimetastatic, free radical scavenging, anxiolytic, and antiretroviral activity [13-21].

3. CHALCONES AS ALDOSE REDUCTASE INHIBITORS

Aldose reductase (ALR), an enzyme is primarily responsible for converting glucose into sorbitol in the presence of a co-factor essential for facilitating reduction process known as nicotinamide adenine dinucleotide phosphate (NADPH). This aldo-keto reductase is activated to metabolize the high glucose concentration when the usual glycolytic cycle gets saturated [22]. In the absence of insulin, the sorbitol produced from the glucose gets accumulated in the nerve, retina, lens, etc. and produce oxidative stress, burning sensation, osmotic swelling, neuropathic pain, change in the membrane permeability, renal injury, and several other detrimental effects. Overall, it leads to a decrease in the quality of life, depression, produce a psychological effect, fatigue, etc [23]. Chalcones have been recognized as molecules with ALR inhibitory perspectives.

A noteworthy inhibition of ALR enzyme (53.66-74.39%) and reduction of advanced glycation end products (AGE) have been presented by the three chalcones **(1-3)**, isolated from *Sophora flavescens* at 10 mg/ml concentration. The inhibitory potential of the chalcones was found to be quite comparable with the USFDA approved marketed product epalrestat (55.56%) [24].

The ALR inhibitory potential of isoliquiretigenin **(4)**, isolated from *Glycyrrhizae radix* in rat lens was determined by Aida *et al*. The phytoconstituent also displayed inhibition of hydroxyl radical accumulation in the human red blood cells (RBCs), sciatic nerve, and rat lens **(Figure 1)** [25].

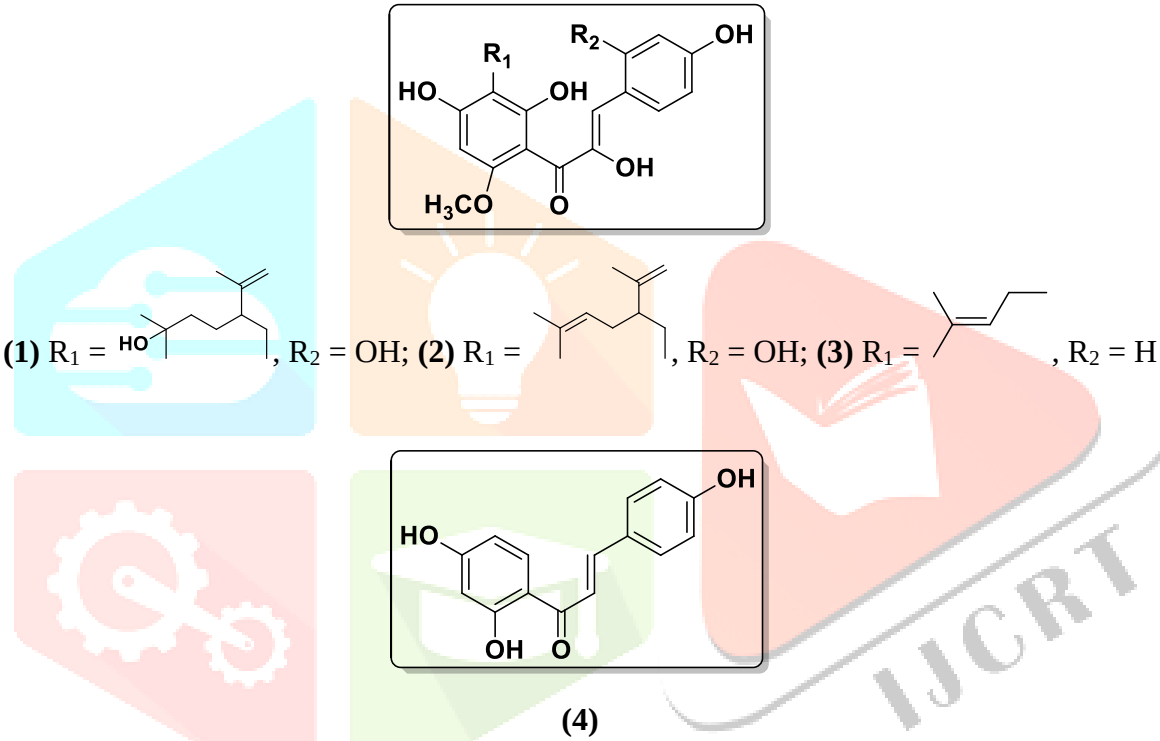

Figure 1. Natural chalcones as ALR inhibitors.

4. CHALCONES AS INSULIN SENSITIZERS

Irrespective to the chalcones inhibiting molecular targets, few chalcones have been recently identified as insulin sensitizers. In an imperative report, 4-Hydroxyderricin **(5)**, xanthoangelol **(6)**, cardamonin **(7)**, and flavokawain B **(8)** have been known to exhibit anti-hyperglycemic effect by inhibition of sterol regulatory element-binding protein-1 (SREBP-1) which also played a key function in weight reduction by lipogenesis [26].

Kawabata *et al*. supported the anti-diabetic potentials of the prenylated chalcones **(5-6)** by the ability to enhance the glucose uptake by nearly twice in L6 cells at a concentration of 10 μM. The author concluded that glucose uptake occurred through the glucose transporter-4 (GLUT-4) translocation [27].

The plasma glucose reducing potential of the chalcones **(5-6)** by peroxisome proliferator-activated receptor-γ (PPAR- γ) activation independent pathway has been reported by Enoki *et al* [28].

Nozawa *et al*. studied the plasma glucose lowering potential of xanthohumol **(9)** by modulating the gluconeogenetic gene and farnesoid X receptor (FXR) in KK-Ay mice which is generally associated with hepatic triglyceride **(Figure 2)** [29].

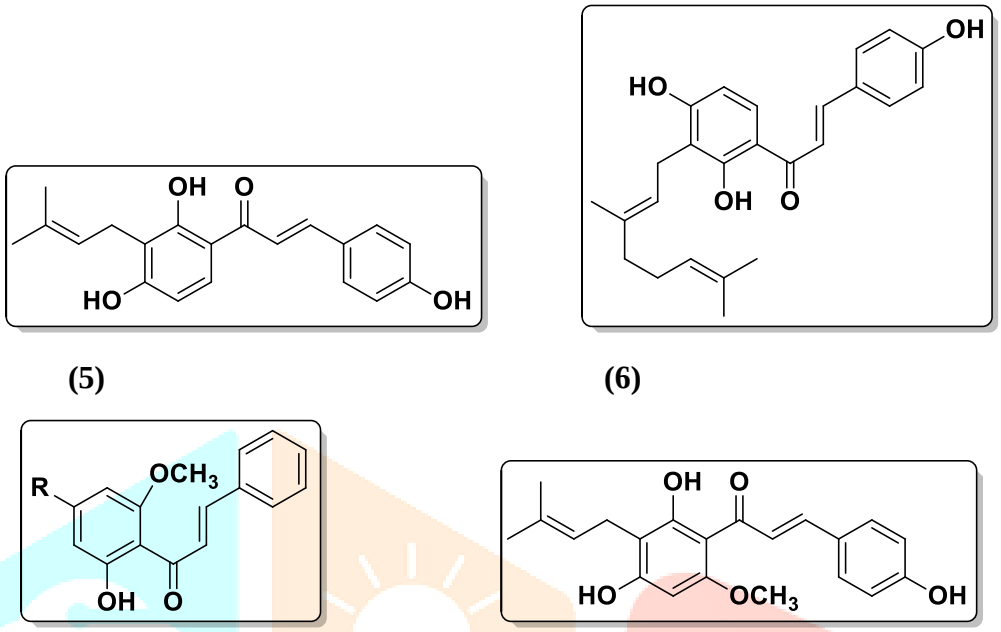

Figure 2. Natural chalcones as insulin sensitizers.

5. CONCLUSION

This article has emphasized a number of crucial studies on chalcones, natural products with tremendous potential to display anti-hyperglycemic effects by regulating the target aldose reductase. The review study will undoubtedly motivate scholars throughout the world working on pharmacological, novel medication, and natural product research. The research will provide a route for investigating and creating new, secure, and powerful pharmaceutically active treatments for diabetes and its consequences.

CONFLICT OF INTEREST

No conflict of interest regarding the publication of this article is declared.

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