IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Nuclear Factor-Kappa Beta Inhibitory Potential Of Chalcones: Advancing Anti-Inflammatory Drug Discovery

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ABSTRACT

Inflammation remained a key concern among human civilization for centuries. Inflammation can be both external as well as internal in response to immunological and nonimmunological stimuli. It is a process in which white blood cells and some important chemical mediators are produced which protect us from pathogenic organisms such as bacteria and virus. It is a vital part of the body's immune response which is caused by a number of physical reactions triggered by the immune system in response to a physical injury or an infection. It's generally seen as the body's way of protecting itself by getting rid of potentially damaging stimuli and getting the healing process under way. Two primary enzymes, cyclooxygenase and lipoxygenase, play a large role in mediating inflammation, a crucial function in the human body. The former plays a crucial role in the biosynthesis of prostanoids like Thromboxanes and prostacyclins; while the later play a vital role in the biosynthesis of leukotrienes. Attenuating inflammatory responses by the inhibition of the pro-inflammatory cytokines and its symptoms may have an insightful role towards the treatment of chronic inflammatory diseases. The suppression of inflammation based on the molecular targets remained an emerging perspective. NF-κB is a pro-inflammatory target, its activation, NF-κB-luciferase activity, NF-κB target genes, κBα, κB kinase-α/β, NF-κB p65, etc. aggravates serious inflammatory conditions. Chalcones of both natural (hesperidin, isoliquiritigenin, butein, and xanthohumol) and synthetic (dihydrotriazine-chalcones, carboxamide linked chalcone, E-α-p-OMe-C_6H_4-TMC, and L6H9) origin have been found to profoundly inhibit the above targets associated with the NF-κB pathway.

Keywords: Anti-inflammatory, Chalcone, Inflammation, Inhibitor, Molecular Target, NF-κB

1. INTRODUCTION

Inflammation remained a key concern among human civilization for centuries. Inflammation can be both external as well as internal in response to immunological and nonimmunological stimuli [1]. It is a process in which white blood cells and some important chemical mediators are produced which protect us from pathogenic organisms such as bacteria and virus. It is a vital part of the body's immune response which is caused by a number of physical reactions triggered by the immune system in response to a physical injury or an infection [2]. It's generally seen as the body's way of protecting itself by getting rid of potentially damaging stimuli and getting the healing process under way. Although, the process is necessary for survival and has its own importance in biology, however, the aggravation of this biological process leads to extreme conditions of discomfort, pain, and suffering [3]. Because inflammation might last longer than required, researchers claimed that it does more damage than good. It has been dated back in several civilizations about the etiology and treatment approaches, which reveals the prevailing continuous obstacles to mankind [5]. It is often characterized by redness, swelling, warmth, and sometimes pain and some immobility. Inflammatory diseases involve a series of disorders which leads to edema, granuloma formation, respiratory conditions, leukocyte infiltration, etc [6]. As the body's own tissue is being attacked by an autoimmune illness like arthritis, the anguish experienced by sufferers is magnified many times over. Consequently, anti-inflammatory drugs are seldom used to alleviate pain and subsequent reactions [7].

2. CHALCONES

Chalcone is a natural product present abundantly in Nature. It comprises of a benzylideneacetophenone component, often referred to as prop-2-ene-1-one in which an, unsaturated carbonyl bridge connects two aromatic nuclei [8]. The term “chalcone” was first termed by Tambor and Kostanecki in the year 1899 for designating these natural chromophoric products. Open chain intermediates in the production of aurones, they serve as the building blocks for the production of flavonoids and isoflavonoids, isomeric forms of flavonones, and later interconvert easily into flavonone. They are also Michael acceptors in Michael addition reactions [9]. This scaffold is known to exert multiple pharmacological activities such as anti-fungal, anti-protozal, anti-obesity, hypnotic, anti-diabetic, anti-gout, anti-histaminic, hepatoprotective, antioxidant, anti-invasive, anti-platelet, anti-retroviral, anti-arrhythmic, osteogenic, anti-tubercular, anti-metastatic, sedative, hypolipidemic, anti-fibrinogenic, anti-trypanosomal, anti-leishmanial, anti-inflammatory, anti-hypertensive, analgesic, anti-malarial, immunosuppressive, cardioprotective, anxiolytic, anti-ulcer, anti-microbial, anti-nociceptive, artificial sweetener, etc [10-15].

The scaffold has received global attention in this century owing to the simplicity of the structure, non-complicated synthetic steps, ease of computational studies, the presence of a number of replaceable hydrogen, and a variety of promising biological activities [16]. The scaffold's inhibitory properties play a vital part in the exacerbation of illnesses by blocking the channels, enzymes, receptors, etc., that contribute to hyperactive states along any biomolecular pathway [17-19].

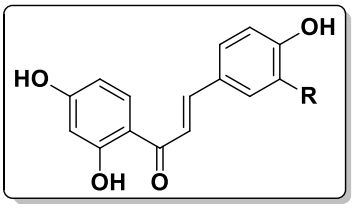
In the due course, numerous non-therapeutic applications are well known. The scaffold played an imperative role in the structural elucidation of a variety of natural products like flavonoid, coumarin, flavanone, chromane, chromanochromane, tannin, etc [20]. The derivatives have been reported to be applied as organic brightening agent, insecticide, scintillator, fluorescent whitening agent, fluorescent polymers, analytical receptor for iron determination, polymerization catalyst, etc [21-22].

3. NF-κβ

NF-κB is a component in a pro-inflammatory signaling pathway which stimulates the release of cytokines, chemokines, and adhesion molecules by promoting the expression of pro-inflammatory genes [23]. The factor is often found to be highly activated in chronic inflammatory diseases [24]. A complex role of this component has been found in the pathogenesis of both inflammation and cancer. The potential role of NF-κB has also been perceived in the immune system [25]. The hyperactive state of NF-κB has been implicated as the expression of IL-1/TNFα signaling pathway and attracted the pharmaceutical scientists towards drugs development [26].

4. CHALCONES AS NF-κβ INHIBITORS

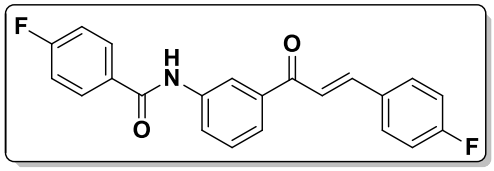
The dose-dependent inhibitory potential of butein **(1)** against TNF-α induced NF-κB activation was studied by Pandey *et al*. The natural product also inhibited the proliferative components such as IκBα kinase (IKK) and NF-κB regulated gene products that are actively involved in the proliferation by directly interacting with the Cys179 residue [27].



(1) R = OH; **(2)** R = H

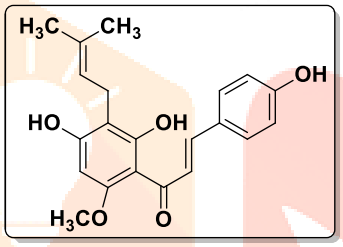
The NF-κB inhibitory attribute of isoliquiritigenin **(2)**, a chalcone isolated from the leaves of *Glycyrrhiza inflate* have been studied by the researchers. The natural chalcone significantly reduced the adipose tissue inflammation by inflammasome-independent and well as inflammasome-dependent pathways which lead to acute suppression of IκBα phosphorylation and also decreased the macrophage stimulation, ultimately leading to enhanced anti-inflammatory response [28].

The inhibitory characteristics of carboxamide linked chalcone **(3)** against LPS stimulated NF-κB activation was studied. The compound suppressed the NF-κB activation with IC_{50} of 1.12 μM along with considerable inhibition of mediators; prostaglandins and interleukins [29].



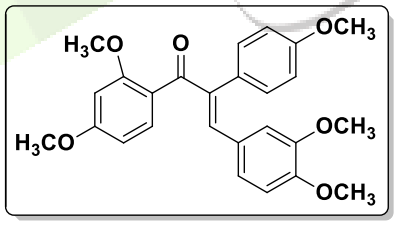
(3)

A prenylated natural chalcone obtained from *Humulus lupus* L., xanthohumol **(4)** have been isolated by Gao *et al*. and found to express a noteworthy immunosuppressive response by profoundly inhibiting the anti-inflammatory target NF-κB as well as interleukins, T-cells, lymphocytes, cytokines, etc. mediated immune responses [30].



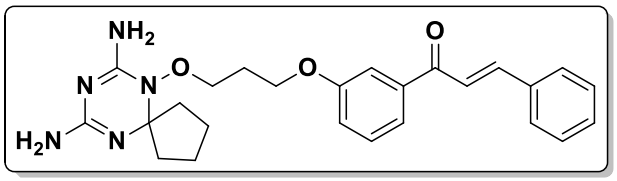
(4)

E-α-p-OMe-C_6H_4-TMC **(5)**, a novel compound has been screened for the dose-dependent NF-κB suppression in LPS-treated RAW264.7 macrophages and the suppression of pro-inflammatory factors in HK-2 and Jurkat cells without significant toxicity [31].



(5)

The synthetically hybridized dihydrotriazine-chalcones **(6-7)** scaffold have been screened for antiinflammatory prospective by Gan and co-workers. The hybrid compounds inhibited the NF-κB pathway in a dose-dependent manner by targeting the cysteine residue in IKKa/β along with LPS-induced iNOS suppression. The hybrids were found to be much more active than the parent compounds; chalcone and dihydrotriazine [32].



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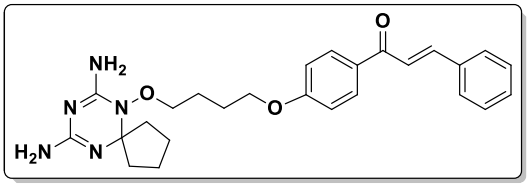
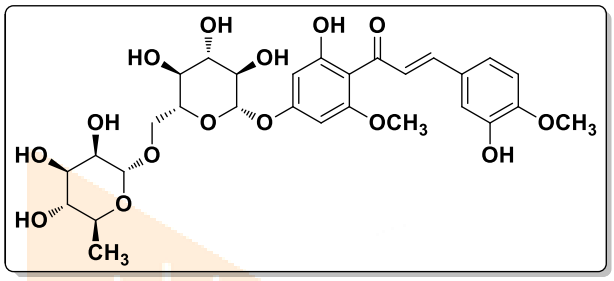


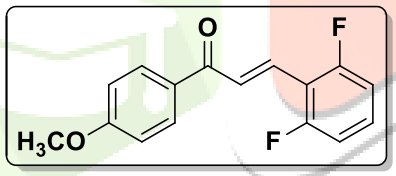
(7)

Interestingly, Felipe *et al*. presented the anti-inflammatory potential of water-soluble hesperidin methyl chalcone **(8)** in Swiss albino rats in the dose of 30 mg/kg b.w. The chalcone compound suppressed the edema by the mixed mechanism (TRPV1 and NF-κB inhibition) along with prevention of carrageenan-induced cytokine release [33].



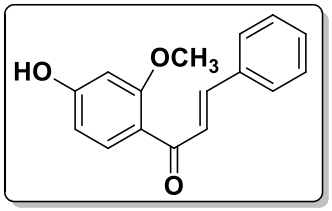
(8)

A noteworthy NF-κB blockade has been produced by a novel fluorinated chalcone derivative L6H9 **(9)** which led to a tremendous protection against the high glucose-induced anti-inflammatory activity. The chalcone drastically reduced the cardiac cytokine expression, Nrf2 levels, and decrease diabetes-induced inflammation [34].



(9)

Ren *et al*. reported the potential of cardamonin **(10)** in mediating blockade of NF-κB p65, exhibiting the NF-κB-luciferase inhibition activity, downregulating NF-κB target genes, κBα inhibition, and suppression of κB kinase-α/β activity in dextran sulfate sodium-induced mouse which marked improved the anti-inflammatory conditions [35].



(10)

5. CONCLUSION

The discovery and rational development of new anti-inflammatory drugs based on molecular targets represent a rising approach. Attenuating inflammatory responses and its symptoms by the suppression of NF-κB activation, NF-κB-luciferase activity, NF-κB target genes, κBα, κB kinase-α/β, NF-κB p65, etc. remained an emerging perspective. Chalcones of both natural (hesperidin, isoliquiritigenin, butein, and xanthohumol) and synthetic (dihydrotriazine-chalcones, carboxamide linked chalcone, E-α-p-OMe-C_6H_4-TMC, and L6H9) origin have been found to profoundly inhibit the above targets associated with the NF-κB pathway. The inhibition of the pro-inflammatory cytokines by the repression of NF-κB may have an insightful role towards the treatment of chronic inflammatory diseases.

CONFLICT OF INTEREST

No conflict of interest is declared.

FUNDING INFORMATION

No agency provided any funds.

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