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Mini-Reviews in Medicinal Chemistry, 2013, *13*, 87-94

Anti-Inflammatory Trends of 1, 3-Diphenyl-2-propen-1-one Derivatives

Syed Nasir Abbas Bukhari*, Ibrahim Jantan and Malina Jasamai

Drug and Herbal Research Centre, Faculty of Pharmacy, Universiti Kebangsaan Malaysia, Kuala Lumpur, 50300, Malaysia

Abstract: Chalcones (1, 3-Diphenyl-2-propen-1-one) are constituted by a three carbon α, β-unsaturated carbonyl system. The biosynthesis of flavonoids and isoflavonoids is initiated by chalcones. Notable pharmacological activities of chalcones and its derivatives include anti-inflammatory, antifungal, antibacterial, antimalarial, antituberculosis, antitumor, antimicrobial and antiviral effects respectively. Owing to simplicity of the chemical structures and a huge variety of pharmacological actions exhibited, the entities derived from chalcones are subjected to extensive consideration. This review article is an effort to sum up the anti-inflammatory activities of chalcone derived chemical entities. Effect of chalcones on lipid peroxidation, heme oxygenase 1(HO-1), cyclooxygenase (COX), interleukin 5 (IL-5), nitric oxide (NO) and expression of cell adhesion molecules (CAM) is summarized stepwise.

Keywords: Chalcones, Anti-inflammatory, Lipid peroxidation, Heme oxygenase1(HO-1), Cyclooxygenase (COX), Interleukin 5 (IL-5), Nitric oxide (NO).

INTRODUCTION

The inception of flavonoids and isoflavonoids is instigated by Chalcones [1]. Flavonoids are found in usual dietary intake of humans. Chemically, a three carbon α, β-unsaturated carbonyl system enacts chalcone (1,3-Diphenyl-2-propen-1-one). These are synthesized by the condensation reaction of aromatic aldehydes with acetophenones in the presence of alkali [2]. They take part in an assortment of chemical reactions and prove to be of value in the synthesis of isoxazole, pyrazoline and a variety of heterocyclic compounds as hexanones. Chalcones have a pivotal role in the synthesis of potentially therapeutic entities. Due to the simplicity of chemical structures and a variety of pharmacological actions shown, the entities derived from chalcones are under extensive studies. Among the documented pharmacological activities of chalcones and derivatives, those which abound are anti-inflammatory [2, 3], antifungal [4], antibacterial [5], antimalarial [6], antituberculosis [11], antitumor [7], antimicrobial [8,9] and antiviral activities[10], yet other effects observed include antioxidant [12,13], antimitotic [14], antileishmanial [15], antiplatelet [16] and anticancer activities [17,18]. This review article is an effort to abstract the anti-inflammatory activity of chalcone derivatives.

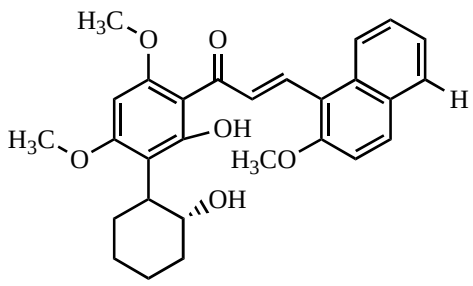
ANTI-INFLAMMATORY TRENDS OF CHALCONES

Inflammation is a protective response intended to eliminate the initial cause of cell injury as well as the necrotic cells and tissues resulting from the original affront. It is one of the basic pathologic processes found in many disorders and consists of complex cytological and chemical reactions in response to the stimuli. Various chalcone compounds have been shown to annul inflammatory stimuli and abate the effect of inflammation. Exclusive consideration has been given to chalcones due to their simple structures and assorted pharmacological activities. Anti-inflammatory activities of chalcones in terms of responsible functional groups are reported in Table **1**.

LIPID PEROXIDATION

A pro-inflammatory antecedent event produced by oxidative stress or as an outcome of tissue damage is lipid peroxidation. Phenolic antioxidants and chalcones work by donating electron to the intermediate radicals to inhibit lipid peroxidation. The medicinal chemistry study using computer software showed that chalcones with high energy of lowest unoccupied molecular orbital (LUMO) and small ionization potential are cogent inhibitors of hydroperoxides.

The synthetic chalcone (**1**) proved to be an accomplished inhibitor in the formation of hydroperoxides, as exhibited by 63% as compared to aspirin (66%) [19]. The semi-synthetic chalcone (**2**) inhibited human neutrophils bound pro-inflammatory responses, including respiratory burst, degranulation, and calcium mobilization.



(**1**)

*Address correspondence to this author at the Faculty of pharmacy, Universiti Kebangsaan Malaysia, Jalan Raja Muda Abdul Aziz, 50300, Kuala Lumpur, Malaysia; Tel: 006014276573;
E-mail: snab_hussaini@yahoo.com

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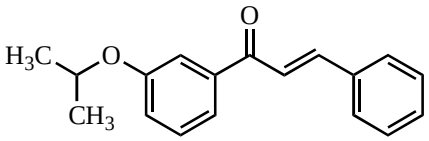
Table 1. Anti-Inflammatory Properties of Chalcone Derivatives

Sr. No.	Biological Activity	Functional Groups Promoting the Biological Activity	References (Number)
1	Anti- Inflammatory	Methoxy groups at 3,4,5- and/or 3',4',5'-positions	Sawle *et al.* 2008 [45]
		2′-Hydrophobic group (benzyloxy or cyclohexylmethoxy) in ring A; 6′ hydroxyl group in ring A	Yang *et al.* 2007 [46]
		2′-Hydroxyl group in ring A	Jin *et al.* 2007 [47]
		4′-Azide group in ring A; 4-methyl group in ring B	Chiaradia *et al.* 2008 [48]
		EW groups in ring B, mainly at C-2	Zarghi *et al.* 2006 [49]

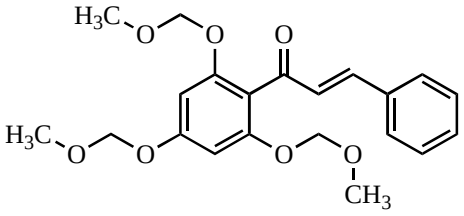


(**2**)

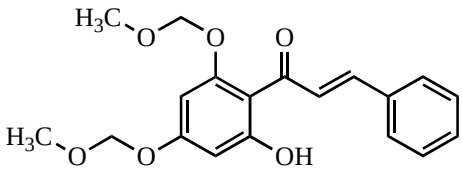
The raised levels of cellular cyclic adenosine monophosphate (cAMP) through the inhibition of cAMP specific phosphodiesterase were underlying these responses [20]. Various chalcones were proved to be active against one or more inflammatory mediators.

HEME OXYGENASE 1 INDUCERS

Heme oxygenase 1 (HO-1) is an essential analytical anti-inflammatory enzyme and the stimuli are oxidative stress and cytokines. Sawle *et al.* reported the correlation of anti-inflammatory activity of several methoxychalcones with their potency as HO-1 inducers. A gradual increase in HO-1 activity was observed along with sequential increase in the number of methoxy substituents in the 3, 4, 5- and 3′, 4′, 5′-positions of the aryl rings. The methoxy groups placed either together in the *ortho* positions or alone in the 4- or 4′-position were abortive. Reduction or protection of α, β-double bond and carbonyl group led to the loss of increased HO-1 activity by methoxychalcones. Chalcone mediated HO-1 induction was decreased by inhibitors of phosphatidylinositol-3 kinase pathway or Thiols [21]. Jin *et al.* reported the depletion of GSH to abet the induction of HO-1 and caused potent anti-inflammatory activity by 2′,4′,6′- tris(methoxymethoxy) chalcone (**3**). Chemical transformations of (**3**) on the basis of SAR led to the synthesis of two potent synthetic derivatives (**4**), (**5**) and the naturally occurring cardamonin (**6**).



(**3**)



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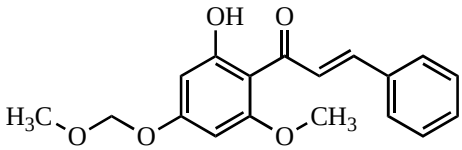

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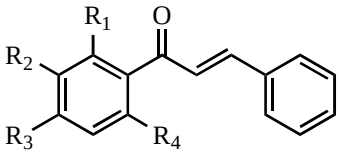
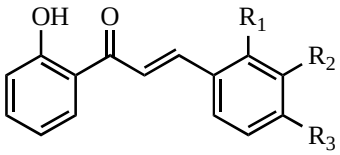


(**6**)

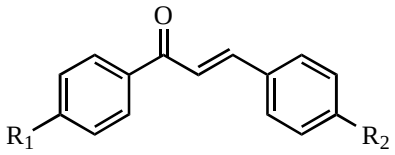
It was observed that alterations in the α,β- unsaturated ketone caused a significant decrease or even loss of anti-inflammatory activity, which supports the affiance of α, β-unsaturated ketone group which acts as a Michael acceptor of nucleophillic species like reduced glutathione (GSH) or cysteine residues on proteins. The presence of 2′-hydroxy group elicited remarkable anti-inflammatory effects by increasing the electrophilic properties of α,β-unsaturated ketones due to hydrogen bonding imparted to the ketone moiety [22]. Foresti *et al.* incubated endothelial cells of aorta with hydroxychalcones (**7–9**) (5-50 μM), which culminated in enhanced HO-1 activity. The compound (**7**) was found non toxic after sustained exposure (24 or 48 h). It is noteworthy that the extracellular signal regulated kinase (ERK), p38, and c-Jun NH_2-terminal protein kinase pathways played insignificant role in the induction of HO-1 by (**7**) [23].



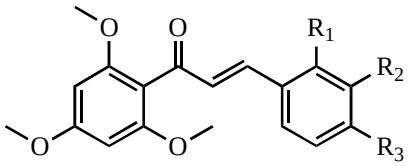
(**7**)**:** R_1 = H, R_2 = H, R_3 = H (**8**)**:** R_1 = OH, R_2 = H, R_3 = H
(**9**)**:** R_1 = H, R_2 = OH, R_3 = OH

INHIBITION OF CYCLOOXYGENASE

The prime strategies to have an appropriate anti-inflammatory agent include inhibition of cyclooxygenase (COX) and production of nitric oxide (NO). Zarghi *et al.* determined *in vitro* COX-1/ COX-2 SARs by using different substituents on ring B of chalcones, possessing a methanesulfonamide (MeSONH) or on an azide (N_3) COX-2 pharmacophore at *p*-position on ring A. Chalcone (**10**) was identified as a selective COX-2 inhibitor (IC_{50} = 1.0 μM; selectivity index (SI)>100), but it was less active as compared with reference drug rofecoxib (IC_{50} = 0.50 μM; SI>200). Chalcone (**11**) elicited potent but selective COX-2 inhibition (IC_{50} = 0.3 μM; SI = 60). Several synthetic chalcones (1**2-17**) were evaluated for their efficacy to check the production of NO in murine macrophages of the line RAW 246.7 induced by bacterial lipopolysaccharides (LPSs). They gave mean IC_{50} values less than or equal to those obtained for 1400W, a highly selective inhibitor of induced nitric oxide synthase (*i*NOS). This outcome implies that the tested compounds can act as inhibitors of inflammatory processes. The quantitative SAR (QSAR) study unveiled that electron withdrawing (EW) substituents in ring B (chlorine and nitro groups) increased the inhibition of NO production, especially when in position C-2 [24].



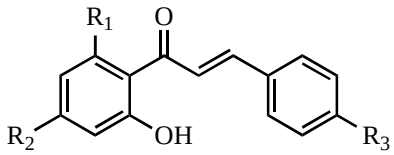
(**10**): $R_1 = NHSO_2CH_3$, $R_2 = CH_3$
(**11**): $R_1 = N_3$, $R_2 = CH_3$



(**12**): R_1 = Cl, R_2 = H, R_3 = H
(**13**): R_1 = H, R_2 =Cl, R_3 = H
(**14**): R_1 = H, R_2 =Cl, R_3 = Cl
(**15**): $R_1 = NO_2$, R_2 =H, R_3 = H
(**16**): R_1 = H, $R_2 = NO_2$, R_3 = H
(**17**): R_1 = H, R_2 =H, $R_3 = NO_2$

INTERLEUKIN 5 (IL-5)

Interleukin 5 (IL-5) has been found to govern several allergic diseases including allergic rhinitis and asthma. Yang *et al*. observed chalcone (**18**) as an exhilarating inhibitor of IL-5 (79% at 50 μM, IC_{50} = 25.3 μM). The activity of this compound was compatible with that of budenoside (70% at 50 μM, IC_{50} = 26.8 μM), which is being used for the treatment of chronic asthma. Twenty six chalcones were synthesized to identify their structural requirements. Out of those, 14 compounds (**19–31**) inhibited IL-5 with more than 95% at 50 μM and had IC_{50} values ranging between 1.8 and 14.3 μM, giving chalcone (**30**) as the most active compound. The structural requirements of chalcone analogs which hold the potent inhibitory activity against IL-5 were summarized as follows: 1) a lyophilic group such as benzyloxy or cyclohexylmethoxy at C-2′ on ring A is obligatory; 2) the existence of phenolic hydroxyl at C-6′ on ring A is critical; 3) propenone motif as α,β-unsaturated ketone is essential; 4) EW groups with hydrogen acceptor property at C-4 on ring B as small as three atom size enhance the activity [25].

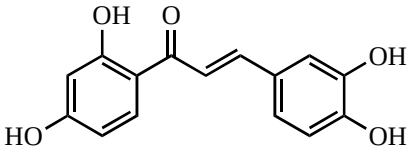


(**18**): R_1 = BNO, R_2 = H, R_3 = OH
(**19**): R_1 = CHMO, R_2 = H, R_3 = OH
(**20**): R_1 = BNO, R_2 =H, R_3 = COOH
(**21**): R_1 = H, R_2 = BNO, R_3 = COOH
(**22**): R_1 = CHMO, R_2 =H, R_3 = COOH
(**23**): R_1 = CHMO, R_2 =H, $R_3 = COOCH_3$
(**24**): R_1 = H, R_2 = CHMO, R_3 = COOH
(**25**): R_1 = CHMO, R_2 = H, R_3 = H
(**26**): R_1 = CHMO, R_2 = H, R_3 = Cl
(**27**): R_1 = CHMO, R_2 = H, $R_3 = NHCOCH_3$
(**28**): R_1 = CHMO, R_2 = H, $R_3 = CH_2OH$
(**29**): R_1 = CHMO, R_2 = H, R_3 = CHO
(**30**): R_1 = CHMO, R_2 = H, $R_3 = SO_2NH_2$
(**31**): R_1 = BNO, R_2 = H, $R_3 = SO_2NH_2$

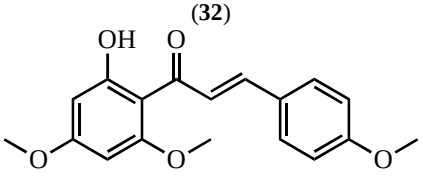
NF-κB

NF-κB is a transcription factor involved in several inflammatory and neoplastic diseases and is a major target in drug discovery. Folmer *et al.* demonstrated that flavokawin A (**33**) and flavokawin B (**34**), isolated from *Piper methysticum*, inhibited tumor necrosis factor (TNF)-α-induced IκBα degradation on one hand and translocation of p50 and p65 NF-κB subunits from the cytoplasm to the nucleus, on the other. Compound (**33**) also inhibited important inflammation related proteins such as Iκβ kinase, p38-regulated/activated kinase, mitogen-activated protein kinase 3, dual specificity tyrosine-phosphorylated and regulated kinase 1A, and Aurora B kinase [27]. Pandey *et al.* found that anti-inflammatory and antitumor activities of butein (**32**) culminated in the suppression of the NF-κB activation pathway partly through the direct inhibition of IκBα kinase (IKK) [26]. Cho *et al.* demonstrated that xanthohumol (**36**) could down regulate the inflammatory mediators by inhibiting NF-κB trans-activation in LPS-activated macrophages and also by inhibiting STAT-1α and IRF-1 activation in interferon (IFN)-γ-induced macrophages. The macrophages play a critical role in the pathogenesis of many inflammatory diseases and therefore (**36**) may be a potential therapeutic target against inflammatory and/or autoimmune diseases [28]. Kim *et al*. observed that the anti-inflammatory activity of isoliquiritigenin (**37**)**,** isolated from *Glycyrrhyza uralensis*, initiated *via* the suppression of IKK, ERK1/2 and p38 phosphorylation in RAW 264.7 cells going through NF-κB inhibition reached *i*NOS, COX-2, TNF-α and IL-6 down-regulation. These results concluded that (**37**) can be considered as a potential agent for treatment of

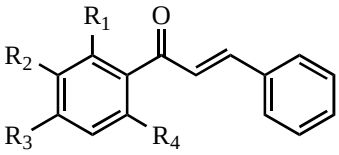
inflammatory diseases [29]. The synthetic chalcone (**38**), which is an anti-inflammatory compound i.e. able to reduce NO production by inhibition of *i*NOS, was shown to prevent the overproduction of NO in LPS-stimulated RAW 246.7 macrophages due to the inhibition of NF-κB activation. This compound also diminished degradation of the NF-κB-IκB complex leading to inhibition of NF-κB translocation into the nucleus, DNA binding and transcriptional activity. Chalcone (**38**) activated NfE2-related factor and provoked a cyto-protective response [30]. Cardamonin (**35**), isolated from *Alpinia rafflesiana*, inhibited NO and prostaglandin E_2 (PGE_2) production from LPS- and IFN-γ-activated RAW 264.7 cells and whole blood with IC_{50} values of 11.4 and 26.8 μM, respectively [31]. The anti-inflammatory mechanism of cardamonin was shown to involve the inhibition of p65NF-κB nuclear translocation due to prevention of I-κBα phosphorylation, which subsequently caused the accumulation of I-κBα [32]. This chalcone also inhibited the generation of the stable thromboxane metabolite, thromboxane B_2 (TxB_2), *via* both COX-1 and COX-2 pathways with IC_{50} values of 2.9 and 1.1 μM, respectively, generation of intracellular ROS, and secretion of TNF-α from RAW 264.7 [31].



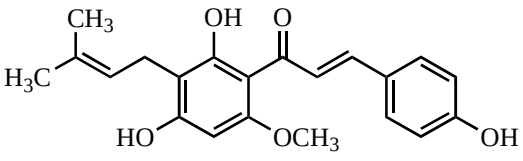
(**32**)



(**33**)



(**34**): R_1 = OH, R_2 = H, R_3 = OCH_3, R_4 = OCH_3
(**35**): R_1 = OH, R_2 = H, R_3 = OH, R_4 = OCH_3



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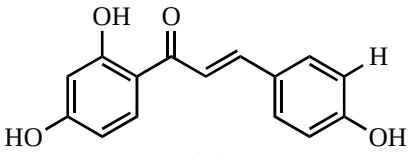

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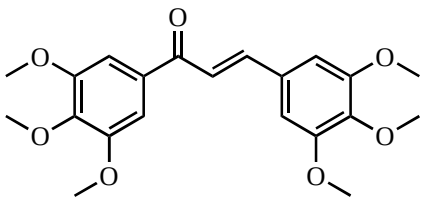

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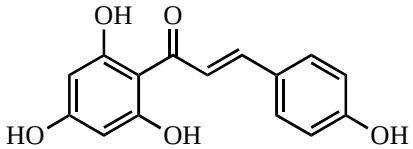


(**39**)

Hatziieremia *et al.* reported that (**35**), separated from *Artemisia absinthium* strongly inhibited LPS induced *i*NOS expression and TNF-α production in both RAW 264.7 and human monocytic THP-1 cells. These are the results of nuclear effect which included inhibition of transcription factor binding to DNA [33]. Naringenin chalcone (**39**) suppressed the production of the pro-inflammatory mediators TNF-α, monocyte chemotactic protein-1 (MCP-1), and NO by LPS-stimulated RAW 264 macrophages and/or 3T3-L1 adipocytes co cultured with macrophages. Naringenin chalcone may be useful for ameliorating the inflammatory changes in obese adipose tissue [34].

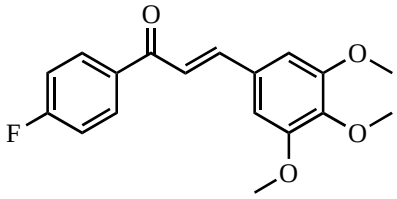
Some chalcone compounds were disclosed in a patent application of Statens Serum Institut (Denmark) to potently inhibit the production of the pro-inflammatory cytokine TNF-α in human peripheral blood mononuclear cells stimulated either with a malarial exoantigen serum-pleural fluid albumin gradient (SPAG) or bacterial lipopolysaccharide (LPS) [35]. At a concentration of 10 μg/mL, licochalcone inhibited 40% of LPS-induced TNF-α [35]. Other compounds that potently inhibited the production of TNF-α include 3′-butoxy-2,4-dimethoxychal-cone, 2′-butoxy-2,4-dimethoxychalcone and 2′-fluoro-3,5-dimethoxychalcone, whereas 4′-dimethyl amino-3,5-dimethoxychalcone and 4′-nitro-3,5- dimethoxychalcone had very little inhibitory effect. Experimental results suggested that the inhibitory effects of these compounds were not due to direct binding to TNF, rather were at the level of synthesis or processing of TNF. It was also depicted that the inhibition of TNF-α production was not due to any toxic effect on cells as shown by tryphan blue dye exclusion, lymphocyte proliferation and monocyte chemiluminescence assays. Interestingly, 4′-cyclohexyl-3,4-dimethoxychalcone and 2′-fluoro-3,5-dimethoxychalcone were substantiated to inhibit TNF-α production in and outside the cell.

Statens Serum Institute further reported in a patent application regarding posology of chalcones and revealed that oral and intraperitoneal administration of chalcone compounds at a dose of 50 mg/kg and 10 mg/kg respectively reduced serum levels of TNF-α by almost 50% in an LPS-induced septic shock model of mice [35]. Some of the compounds fore fended the mice from septic shock death at an oral dose of 50 mg/kg or at an intraperitoneal dose of

2.5 mg/kg. Moreover, the administration of the compounds either before, at the time of or after LPS injection led to the said protection.

NITRIC OXIDE (NO)

Nitric oxide (NO) is a key inflammatory mediator in carcinogenesis. The inhibition of both the formation of NO and the expression of inducible enzyme NO synthase (*i*NOS), by extracts from hops (*Humulus lupulus*) in mouse macrophage RAW 264.7 cells was reported by Zhao *et al.* LPS/IFN-γ-induced production of NO and expression of *i*NOS were suggestively held in check by the ethyl acetate-soluble fraction of *H. lupus*. 3,4,5-trimethoxy-4′-fluorochalcone was reported by Rojas *et al.* to counteract concentration dependent NO production in the mouse macrophage cell line RAW 264.7, with an IC_{50} value in the nanomolar range, and reduced prostaglandin E_2(PGE_2) levels by 58% at a concentration of 10 μM. Moreover, it was observed that it was the expression of *i*NOS rather than its activity which was inhibited.



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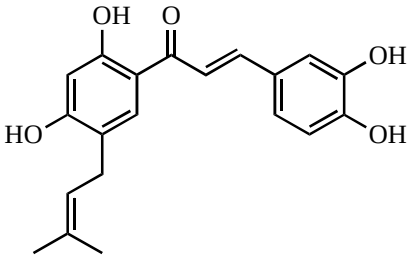
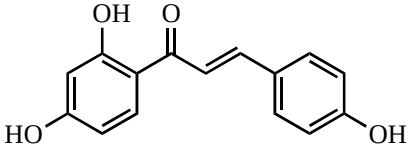


(**41**)



(**42**)

In *in-vitro* experiments compound (**40**), was pointed out to be an inhibitor of the NF-κB pathway of cellular activation in macrophages. A therapeutic oral administration of compound **40** (25 mg/kg) on days 17 – 24 after adjuvant injection, in the rat adjuvant-induced arthritis model, gave a multitude of effects including significant inhibition of paw oedema, protection from weight loss and reduction of the levels of inflammatory mediators i.e. nitrites and PGE_2 in paw homogenates, without affecting PGE_2 levels in stomach homogenates [36]. The suggestive inhibition of the production of NO through the suppression of the expression of *i*NOS was observed to be done by xanthohumol; a chalcone obtained by bioactivity guided fractionation [37]. Cheng *et al*. reported that broussochalcone A (**41**) hushed up concentration-dependent production of NO, with an IC_{50} value of 11.3 μM in LPS-activated macrophages. The experimental data suggested that compound **41** exerted potent inhibitory effects on NO production mediated by its suppression of IκBα phosphorylation, IκBα degradation, NF-κB activation and *i*NOS expression rather than directly on the enzymatic activity of *i*NOS [38]. Ko *et al.* reported that 2′, 5′-dialkoxychalcone compounds exhibited heady inhibitory effects on NO production in RAW 264.7 macrophages and microglial cells [39]. Rojas *et al.* screened a series of dimethylamino chalcone derivatives as potential inhibitors of NO and PGE_2 production in the RAW 264.7 macrophage cell line. Barfod *et al.* reported the effects of licochalcone and four synthetic analogues on the activity of human peripheral blood monomorphonuclear cell proliferation and cytokine production. Four out of five chalcones tested impeded the proliferation of lymphocytes, measured by thymidine incorporation and by flow cytometry. Furthermore, intracellular target of Chalcones was the production rather than the release of the cytokines, when observed for their inhibitory effects. Collectively, these results reveal that some analogues may have immunomodulatory effects [40]. The Walter and Eliza Hall Institute of Medical Research (Australia) unveiled chalcone compounds as cell proliferation inhibitors for autoimmune disorders and inflammatory diseases. NO scavenging capacity of chalcone derivatives was also demonstrated by Herencia *et al.* in a competitive assay with HbO_2, a physiologically relevant NO scavenger [41].

INHIBITION OF EXPRESSION OF CELL ADHESION MOLECULES (CAM)

Inhibition of expression of cell adhesion molecules (CAM), including CAM-1 of the Vascular type (VCAM-1) and intercellular type (ICAM-1) and E-selectin, has been shown to be important in controlling various inflammatory diseases. Tanaka *et al.* reported that isoliquiritigenin (**16**) possessed ability to decrease the levels of cell surface expression of VCAM-1 and ICAM-1 [39]. (Fig. **2**) shows anti-inflammatory features of isoliquiritigenin in TNF-a-induced endothelial CAM expression.

SAR studies on Chalcone derivatives related to compound **42** demonstrated that the inhibitory activity of the chalcone derivatives was due to the 4-hydroxy group and the possible co-planarity between the phenyl rings and the adjacent conjugated ketone [42]. Madan *et al.* reported that 2′-hydroxychalcone caused the inhibition of the expression of ICAM-1, VCAM-1 and E-selectin in a concentration-dependent manner and so it checked the adhesion of peripheral neutrophils to the endothelial cell monolayers reversibly. It inhibited the induction of steady-state transcript levels of ICAM-1, VCAM-1, and E-selectin through TNF-α as determined by reverse transcription polymerase chain reaction (rT-PCR), and therefore it may mess up with the transcription of their genes. It was demonstrated that 2′-hydroxychalcone also inhibited the drive of NF-κB [43].

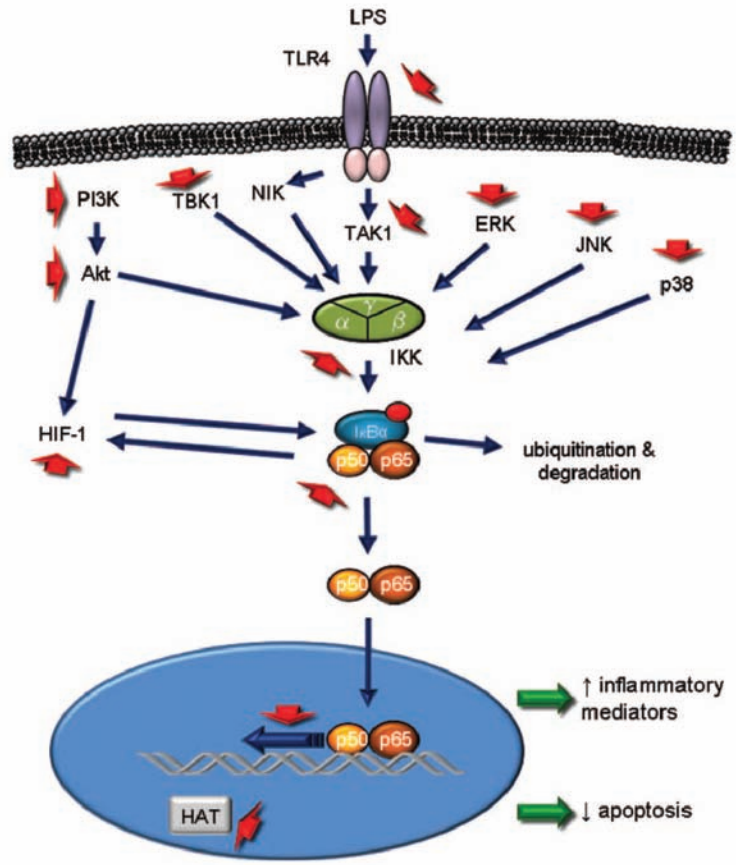


Fig. (1). Diagram above represents NF-κB pathway showing chalcones/flavonoid targets. The canonical pathway within the NF-κB pathway (represented here in central axis) has been shown to be affected by Chalcones/flavonoids at multiple steps. Chalcones/flavonoids can modify the function of the IKK complex and subsequently phosphorylation steps of IκB-α and p65 in this pathway. Chalcones/flavonoids affect: receptor modulation; binding to gene promoters and eventually histone acetylation by HAT. In addition, many other targets which interact with the NF-κB pathway have also been established (all designated by the arrow). This scheme is a simplification of the multiple interactions that have been established [44].

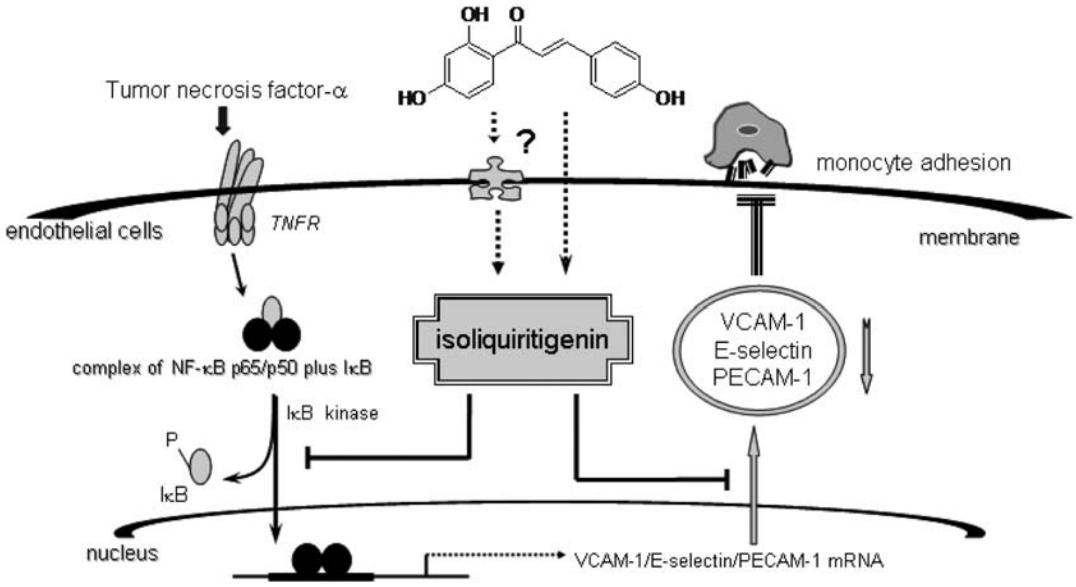


Fig. (2). Schematic diagram showing anti-inflammatory features of isoliquiritigenin in TNF-a-induced endothelial CAM expression. The symbol indicates inhibition or blockade.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENTS

Special thanks to Dr. Ferm´ın S´anchez de Medina for providing us a part of his work (Fig. **1**) as a reference in our article. Furthermore, the authors are thankful to Dr.Wahab Bin Amjad, Dr.Adeel Masood Butt and Dr.Mustafa Abeer for their kind support in the preparation of manuscript.

FUNDING

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. Library access was provided by the Universiti Kebangsaan Malaysia (UKM).

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Received: June 29, 2012 Revised: July 24, 2012 Accepted: July 29, 2012