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AN OVERVIEW OF CHALCONES AS ANTINOCICEPTIVE AGENTS

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ABSTRACT

Pain pathophysiological mechanisms are highly complex and heterogeneous. Progress in the area of pain suggests the involvement of classical and emerging inflammatory mediators such as prostaglandins, bradykinin, bacterial N-formylated peptides and microRNAs in the induction and processing of pain. Research in neurobiology and pathophysiology of pain led to several new drug targets and novel strategies for the antinociceptive drug development. Current analgesic drugs are effective in the treatment of pain but are associated with several side effects and hence there is a need to search better drugs. The extensive synthesis and therapeutic utility of chalcones always invigorate interest of medicinal chemists. This review is an attempt to focus on chalcones that exhibit antinociceptive activities over the past two decades. The literature on chalcones is presented as xanthoxyline derived, ring substituted, heteroaryl and naturally occurring chalcones along with their antinociceptive activities.

INTRODUCTION

Pain is a major global public health issue, as over one third of world's population suffers from persistent pain[1]. Pain is subjective and the translation of nociception into pain perception can be altered by several factors such as stress and anticipation. Nociceptors, specialized peripheral sensory neurons, mediates pain perception and alert us to potentially damaging stimuli at the skin by transuding these stimuli into electrical signals that are relayed to higher brain centers[2-3].

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Within the presently available analgesics, NSAIDs, opioids and triptans are the largest groups, which were specifically developed as analgesics whereas anticonvulsants and antidepressants are main drug classes which were developed for non pain indications, but their effectiveness in pain was later confirmed FDA review [4].

Opioid drugs are very effective in severe pain conditions but are associated with serious side effects upon acute administration such as respiratory depression and pruritus and repeated use of these drugs can lead to tolerance, opioid-induced hyperalgesia, constipation, and the potential of addiction. NSAIDs act peripherally and untoward side effects of NSAIDs include gastric ulcers, renal failure, allergic conditions, and hemorrhage by inhibiting platelet aggregation. Because of these significant side effects, there are many drug classes under investigation for alleviating pain.

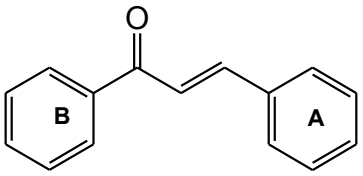


Fig.1 General Structure of chalcone

Chalcones (*trans*-1, 3-diaryl-2-propen-1-one) are natural precursors of flavonoids and isoflavonoids with widespread distribution in plants[5]. Chalcones, flavanones, dihydrochalcones, and aurones are categorized into minor flavonoids. Chalcones exhibit a variety of pharmacological activities such as vasorelaxant, antitubercular, anticancer, antimalarial, antidiabetic, antiniflammatory, antifungal activities[6-14]. Several chalcones such as metochalcone **(1)** and Sofalcone **(2)** have been approved for clinical use and clinical trials have shown that these compounds reached reasonable plasma concentration and are well tolerated in humans[13]. Chalcones and their derivatives such as 2′, 4′-dihydroxychalcone, 1-(4-hydroxyphenyl)-3-m-tolyl-propenone (HPTP) and quinoline-chalcone hybrids exhibit antiulcer activities and in particular, chalcones possessing isoprenyloxyl group show gastroprotective effects[15-17]. Antiulcerogenic activity of chalcones may be due to increase in the mucosal blood flow, stimulation of gastric mucosa synthesis or by increased prostaglandin (PGs) levels. Chalcones have therapeutic potential for the treatment of ulcer and Sofalcone, a synthetic analogue of Sophoradin (*Sophora tonkinensis*) is used in the treatment of gastritis and peptic ulcer disease[18].

1. Chalcones derived from xanthoxyline

Xanthoxyline (2-hydroxy-4, 6-dimethoxy acetophenone; **3**) is an interesting active component isolated from the leaves and stems of *Sebastiania schottiana* which exhibit antispasmodic activity against acetylcholine-induced contraction of the guinea pig ileum. Xanthoxyline derived chalcones were synthesized using xanthoxyline and various ring substituted aromatic aldehydes which showed antinociceptive activity in acetic acid and formalin induced pain models. In this study, compound containing bromine atom at 4-positionof the ring A **(4)** exhibited dose dependent inhibition in the acetic acid induced writhing assay and the chalcone containing methylenedioxy group in position 3 and 4 of the ring A **(5)** produced graded inhibition in acetic acid induced writhing model and against both phases of formalin-induced licking test, comparable to that of standard drugs acetaminophen and aspirin[19]. Introduction of different substituent groups on ring A of xanthoxyline derived chalcones **(6a-g)** led to chalcones with moderate to good activity. It was demonstrated that the compound with carboxylic moiety at 2nd position **(6d)** exhibited promising activity when given orally at 100mg/kg body weight which caused a 92.2% reduction in abdominal constrictions[20]. A benzofuranone **(7)** was synthesized from the carboxylic derivative which was potent and caused dose related inhibition against the writhing test with ID $_{50}$ of 6.1 when given intraperitonially. It was also effective in reducing the painful stimulus in both phases of formalin, in the capsaicin and in the glutamate tests with ID $_{50}$ of 27.3, 18.9, 12.6 and 24.5 µmol/kg respectively [21].

2. Chalcones isolated from plants

2′, 4′-Dihydroxy-4-prenyloxy chalcone (8) obtained from the methanolic extract of *Indigofera pulchra* exhibited good analgesic effect in the acetic acid induced writhing suggesting that it has peripheral analgesic activity[22]. Chalcones isolated from the kawa plant (*Piper methysticum*) are known as flavokawins (Flavokawin A, B and C; **9-11**). Flavokawin B (6′-hydroxy-2′, 4′-dimethoxychalcone) inhibits nitric oxide (NO) and prostaglandin (PG) production in lipopolysaccharide (LPS)-stimulated murine monocytic macrophages (RAW264.7 cell line) [23]. It was found to be 68 fold more effective than acetyl salicylic acid in acetic acid induced writhing test when administered intraperitonially and it was suggested that this may involve inhibition of cyclooxygenases and lipooxygenases. Further the involvement of flavokawin B in the activation of NO-cGMP-PKC-ATP sensitive k+ channels pathway for its antinociceptive activity has been investigated [24-25]. 2′-Hydroxy-4′,6′-dimethoxy-chalcone-4-*O*-β-D-glucopyranoside (12) and 2′-hydroxy-4′,6′-dimethoxy-chalcone-4-O-[2′′-*O*-(5′′′-*O*-*trans* cinnamoyl)- β-D-apifuranosyl] β-D- glucopyranoside (13) were isolated from the ethyl acetate fraction of *Viscum album* which showed remarkable antinociceptive activity in the p-

benzoquinone-induced writhing test without inducing any apparent acute toxicity as well as gastric damage[26].

3) Ring substituted chalcones

Chalcones substituted with different groups on ring A or B (15a-d) exhibited peripheral antinociceptive activity in acetic acid induced writhing and formalin induced pain assays. The parent unsubstituted chalcone exhibited good peripheral antinociceptive activity with calculated ID_{50} value of 99.7 µmol/kg in acetic acid induced writhing test, being equipotent to aspirin and paracetamol when administered intraperitonially indicating that the chalcone or 1,3-diaryl-2-propen-1-one has essential pharmacophoric features to exhibit antinociceptive activity. Among the synthesized compounds, derivative bearing chlorine atoms at 3rd and 4th positions of ring B was found to be the most active compound with ID_{50} value of 9.07 µmol/kg and 91% of maximum inhibition. This compound was found to be active in the late phase of formalin test with ID_{50} value of 111.5µ mol/kg with 82% of maximum inhibition. The incorporation of methyl group decreased the activity, suggesting that the electron releasing groups are not favourable. This series of chalcones became the basis for an extensive evaluation of chalcones as antinociceptive agents [27]. Introduction of acetamido group at 4th position of ring B (16a-i) significantly improved antinociceptive effects in different peripheral and central nociception models. All the synthesized derivatives exhibited moderate to good activity, nitro derivative being most potent than the standard drugs when administered intraperitonially (3.93µmol/kg). This compound was found to be effective in the second phase of the formalin test and capsaicin test. Chalcone containing furan ring also exhibited good activity in acetic acid induced writhing assay [28].

Chalcones containing 5, 6, 7, 8-tetrahydronaphthalene (17a-c) as ring B exhibited good central and peripheral antinociceptive activities. Interestingly, these chalcones also demonstrated less gastric ulcerogenic activities. Among the compounds synthesized, naphthalene and indole containing chalcones exhibited significant antinociceptive activities[29]. A series of novel chalcones (18a-g) substituted with phenyl thiourea or phenyl urea at 4th position of ring B were synthesized and evaluated in a number of pain models. In this study, thiourea derivatives were found to be more potent than corresponding urea derivatives. It is also suggested that these chalcones act by other mechanisms which do not involve opioid and vanilloid receptors. The results indicated that thiourea derivative possessing chlorine atom at 4th position of ring A of chalcone showed promising antinociceptive activity compared with some well-known non-steroidal antiinflammatory and analgesic drugs[30].

A. razmi et al synthesized chalcone derivatives possessing a methyl sulphonyl group at the 4th position of ring A or B and different substituent groups (H, Me, F, OMe) and corresponding regioisomers (19a-h) and evaluated them for their antinociceptive activity and antiinflammatory activity. The results demonstrated that the relative position of methyl sulphonyl group has no influence on antinociceptive and antiinflammatory activity and halogens significantly increased the activity of compounds. Introduction of methoxy group reduced the antiinflammatory activity[31].

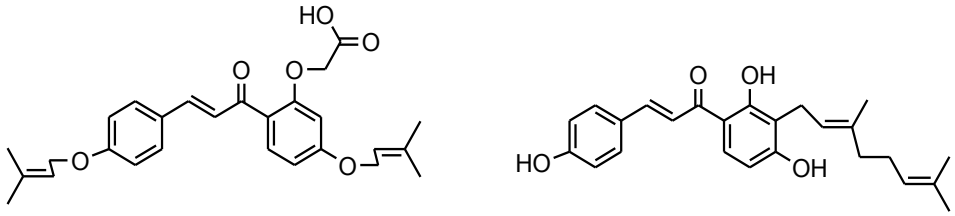
4) Heterocyclic Chalcones

i) Pyridine-based chalcones

To explore the significance of substitution on ring B, researchers further synthesized a number of chalcones (20a-g) using cinnamaldehyde, salicylaldehyde and pyridine carboxaldehyde and evaluated their peripheral antinociceptive activities using acetic acid writhing assay. In case of cinnamaldehyde-derived chalcones, good activity was observed with nitro substitution at 4th position whereas in the other series of chalcones, derivatives bearing chlorine atom at 2nd and 5th positions exhibited promising activity. This study indicated the importance of electronic parameters for peripheral antinociceptive activity[32].

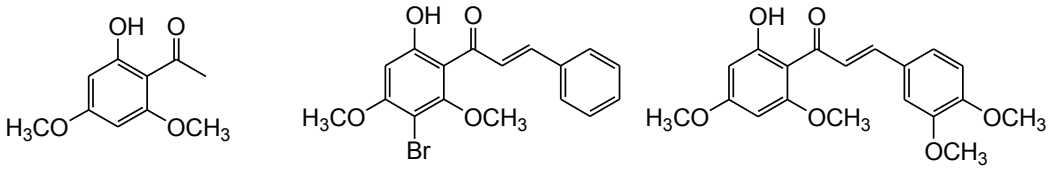
ii) Quinazoline-based chalcones

Various chalcones containing quinazoline moiety (21a-e) exhibited good antiniflammatory and analgesic activities. Substitution by 2-methoxy phenyl or 2-naphthyl increased the activities. In this study, Molecular-docking results revealed that these derivatives have good correlation between their antiniflammatory activities and binding affinity towards COX-2 enzyme. Moreover, quinazoline bearing chalcones have less gastric ulcerogenic activity[33].



(1) (2)

Fig.2 Commercially available chalcones

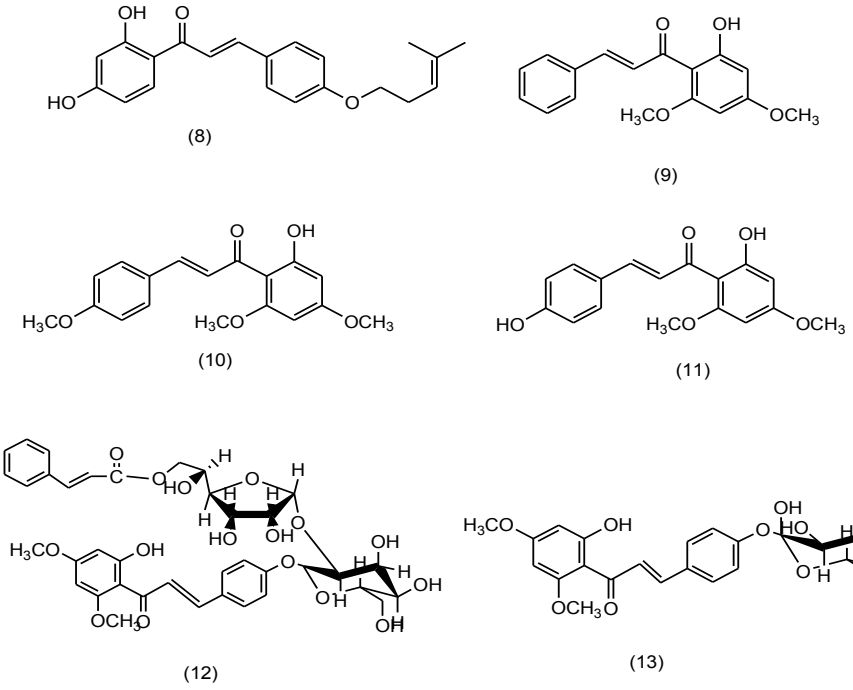


(3) (4) (5)

R= 4-OCH_3, 2-Cl , 4 -Cl, 2-COOH , 4 -Br, 4 -NO_2, 4-C_6H_5

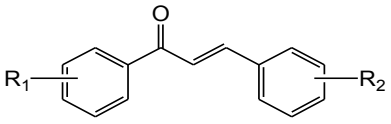
(6a-g) (7)

Fig.3 Xanthoxyline derived chalcones



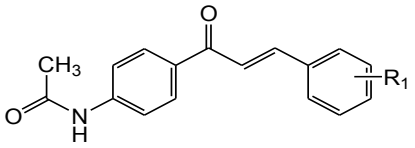
(8) (9) (10) (11) (12) (13)

Fig.4 - Chalcones isolated from plants



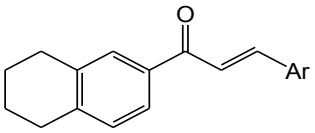
R_1 = H, 4-Br , 3 ,4-Cl, 3 ,4-Cl
R_2 =H, 4-$N(CH_3)_2$

(15 a-d)



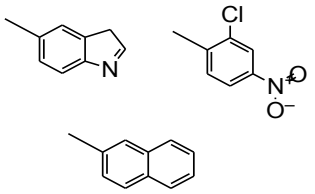
R_1=-H ; 4-OCH_3 ; 4-CH_3 ; 4-Cl; 3,4-Cl_2 ; 4-NO_2; -$N(CH_3)_2$; -C_5H_3S ; -C_5H_3O

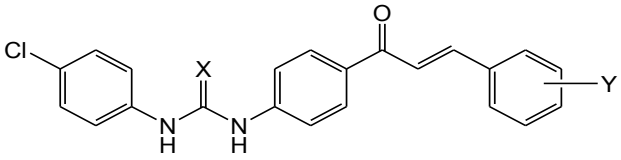
(16 a-i)



(17 a-c)

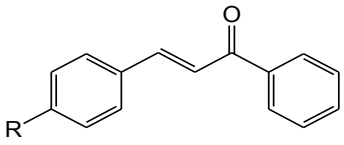
Ar=





X=S,O Y= 4-H, 4-Cl,3,4-$(Cl)_2$,4-OCH_3,4-CH_3

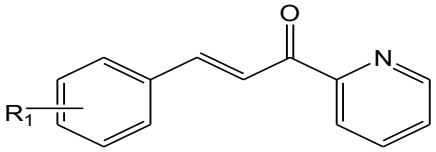
(18a-g)



R=-SO_2Me,-H,-Me,-F,-Cl

(19 a-h)

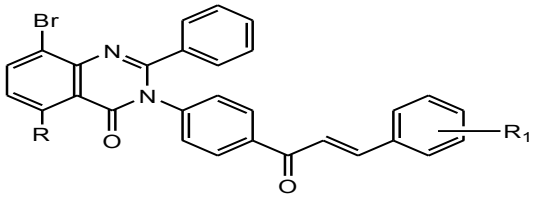
Fig.5. Ring substituted chalcones



R_1= 4-CH_3,OCH_3,NO_2,Br,Cl

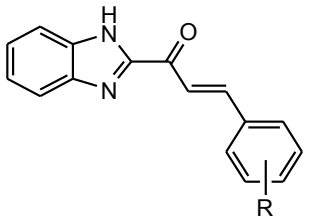
(20a-g)

Fig.6 Pyridine-based chalcones



(21a-e) R= H,Br
R1= naphthyl, p-methoxy phenyl

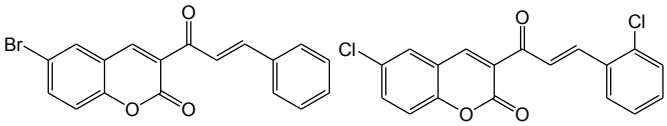
Fig. 7 Quinazoline-based chalcones



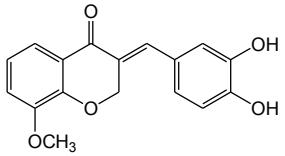
R= 4-F,4-Cl, 4-NO_2, 4-OCH_3,-$N(CH_3)_2$

(22 a-i)

Fig.8 Benzimidazole-based chalcones

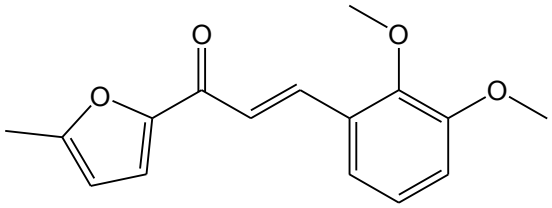


(23a-b)



(24)

Fig.9 Coumarinyl chalcones



(25)

Fig.10 Furan-based chalcones

iii) Benzimidazole-based chalcones

Chalcones having benzimidazole ring (22a-i) demonstrated good antinociceptive, antiniflammatory, CNS locomotor activity and *in vitro* anthelmintics activity. Among the synthesized compounds, derivatives containing halogen atoms such as fluorine or chlorine and derivatives containing electron withdrawing nitro group exhibited good CNS depressant activity. Good antinociceptive activity was observed with 2-chloro or 2-hydroxy derivatives comparable to that of standard drug diclofenac[34].

iv) Coumarinyl chalcones

Coumarinyl chalcones (23a-b) demonstrated good analgesic and anti-inflammatory activities. Among the synthesized chalcones, derivatives substituted with halogen at the 6-position (chlorine/bromine) on coumarinyl ring exhibited good analgesic activity in acetic acid induced writhing test with 92.30% inhibition[35]. Several di hydroxy chalcones exhibit potent lipooxygenase and cyclooxygenase inhibitory activity and dimethylamino chalcones, in particular 3, 4-dimethoxy dimethylamino chalcone

reported to downregulate iNOS expression and showed significant antiniflammatory activities[36-37]. Keeping in view these important structural features, RDHC, a rigid 3, 4-dihydroxy chalcone (24) was synthesized which showed good peripheral and central antinociceptive activity[38].

v) Furan-based chalcones:

Chalcone bearing substituted furanyl group (25) showed remarkable antiinflammatory and peripheral antinociceptive activity and it was suggested that this activity is associated with the inhibition of production of NO and various pro-inflammatory mediators. This particular chalcone was found to be centrally active probably by interacting with the inhibition of capsaicin-sensitive fibers and the glutamatergic system[39]. Mechanisms of the antinociceptive activities observed with chalcones are not well defined and it is proposed that inhibition of iNOS and COX-2 enzymes are responsible for the antinociceptive activity. Recently, we have performed molecular docking studies of ring substituted chalcones on iNOS and COX-2 enzymes and reported that these molecules have good binding affinity for both the enzymes. Molecular docking revealed that electronic effects and hydrogen bonding ability have profound influence on the binding interactions. Pharmacokinetic properties prediction showed that these chalcones have good CNS permeability[40].

The present review reveals the potentiality of chalcones as promising antinociceptive agents. Further, structure modifications on chalcone moiety may provide molecules of high therapeutic potential. There are many other possible targets and strategies available for the development of chalcones as antinociceptive agents.

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