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Investigating the Mechanisms and Therapeutic Applications of Chalcones

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ABSTRACT

Introduction: Chalcones, are a group of organic compounds containing two aromatic rings bridged by a three-carbon -α, β; unsaturated carbonyl system. This attracted much attention because of their versatility in pharmacological profiles.
Aims & Objectives: To investigate the therapeutic efficacy of a particular chalcone derivative, namely (E)-1-(4-bromophenyl)-3-(4-chlorophenyl) prop-2-ene-1-one.
Place and Duration of Study: It was conducted in the Pharmacology Laboratory of the Institute of Basic Medical Sciences, Khyber Medical University, Peshawar, and the University of Malakand for about one year.
Materials & Methods: This was a lab-based experimental study. The therapeutic efficacy of a chalcone derivative, (E)-1-(4-bromophenyl)-3-(4-chlorophenyl) prop-2-ene-1-one was assessed through an experiment on pain and inflammation in mice. Claisen-Schmidt condensation reaction and spectroscopic tools were used.
Results: Pharmacological data proved a significant decrease in pain and inflammation with chalcone derivatives as compared to Diclofenac Sodium. Reduction of 75.20% in acetic acid-induced writhing as compared to 84.4% with Diclofenac. After 3 hours, there was 67.08% reduction in edema.
Conclusion: This study provides evidence that chalcone derivatives in moderation may be effective and safer than present-day drugs that address pain and inflammation. This result may need to be further clinically related to potentially translate them in different patient populations in terms of efficacy and safety.

Keywords: Chalcones, therapeutic efficacy, mechanisms, analgesic activity.

INTRODUCTION

Natural products have long been a cornerstone of drug discovery, with many modern pharmaceutical agents tracing their origins to compounds isolated from plants and other organisms. Among these natural products, chalcones—a class of compounds with the general structure of 1,3-diaryl-2-propen-1-one—have garnered significant attention due to their diverse biological activities. Chalcones are intermediates in the biosynthesis of flavonoids and isoflavonoids, both exhibit a wide array of pharmacological properties, including anti-inflammatory, antimicrobial, antitumor, and antioxidant activities.[1-3] The therapeutic potential of chalcones has been increasingly recognized, prompting further investigation into their mechanisms of action and therapeutic applications. The molecular structure of chalcones, characterized by two aromatic rings connected by a three-carbon α, β-unsaturated carbonyl system, allows for interactions with various biological targets. The presence of electron-withdrawing or electron-donating groups on the aromatic rings can modulate their pharmacological properties, leading to the design of chalcone derivatives with enhanced activity[4,5]. Recent studies have focused on optimizing chalcone derivatives through structure-activity relationship (SAR) analyses to improve their efficacy against diseases such as cancer, inflammation, and microbial infections.[6,7]

Despite the promising preliminary data, the specific mechanisms underlying the biological activity of many chalcone derivatives remain largely unexplored. One such compound, (E)-1-(4-bromophenyl)-3-(4-chlorophenyl) prop-2-ene-1-one, has shown considerable promise in early screenings. Its halogenated aromatic rings suggest modifications that may enhance its lipophilicity, metabolic stability, and overall biological activity.[8] However, a comprehensive study investigating its therapeutic efficacy and mechanisms of action is lacking. Understanding the detailed

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pharmacodynamics and pharmacokinetics of this chalcone derivative could reveal its full therapeutic potential and inform further drug development.

Thus, this study aims to investigate the therapeutic efficacy of (E)-1-(4-bromophenyl)-3-(4-chlorophenyl) prop-2-ene-1-one, with a focus on its mechanisms of action and potential therapeutic applications. This study will utilize a multidisciplinary approach, combining in vitro and in vivo models to elucidate the pharmacological profile of the chalcone derivative. Specific aims include exploring its interaction with key biological targets, such as enzymes, receptors, and signaling pathways involved in disease processes, including cancer, inflammation, and microbial infections.[9,10] Additionally, the study will assess the compound's safety profile, including cytotoxicity and off-target effects potential.

In summary, this research aims to bridge the gap between the preliminary pharmacological potential of (E)-1-(4-bromophenyl)-3-(4-chlorophenyl) prop-2-ene-1-one and its practical therapeutic applications. By systematically investigating its mechanisms of action, efficacy, and safety, the study seeks to establish this chalcone derivative as a viable candidate for further development as a therapeutic agent. The findings could advance the field of chalcone-based drug development, providing new insights into structure-activity relationships and identifying novel therapeutic targets.[2,4,7]

MATERIALS AND METHODS

This was a lab-based experimental study conducted in the Pharmacology Laboratory of the Institute of Basic Medical Sciences, Khyber Medical University, Peshawar, and the University of Malakand for about one year. After obtaining ethical and administrative approvals vide No: DIR/KMU-AS&RB/TE/002081 dated: 01/03/2024 and vide No: Pharm/22/EC/75-01/2 dated: 10/02/2022 respectively, the following methods and techniques were adopted for the study.

Research Design and Synthesis of Chalcone Derivative

The work started with the preparation of the chalcone derivative, which is (E)-1-(4-bromophenyl)-3-(4-chlorophenyl) prop-2-ene-1-one through a Claisen-Schmidt condensation reaction. This involved forming an aldol condensation product where 4-bromoacetophenone was condensed with 4-chlorobensaldehyde using sodium hydroxide (NaOH) as the base catalyst in ethanol solvent. The reaction advancement was followed using Thin Layer Chromatography (TLC), and the product was further purified by Column Chromatography. The assignment of the structure to the synthesized chalcone was evidenced by Fourier-Transform Infra-Red (FT-IR), and Nuclear Magnetic Resonance (NMR) spectroscopy with both ^1H and ^13C NMR.

Table 1: Materials Used for Chalcone Synthesis and Pharmacological Testing

Material	Description	Supplier
4-chlorobens-aldehyde	Chemical reagent for chalcone synthesis	Sigma-Aldrich, Germany
4-bromoaceto-phenone	Chemical reagent for chalcone synthesis	Sigma-Aldrich, Germany
Ethanol	Solvent for the synthesis process	Sigma-Aldrich and Merck, Germany
Sodium hydroxide (NaOH)	The base catalyst for Claisen-Schmidt condensation	Common laboratory supply
Thin-layer chromatography (TLC) plates	For monitoring the progress of the reaction	Merck, Germany
Carrageenan	Used in the pharmacological testing for inducing inflammation	Sigma-Aldrich, Germany
Ethyl acetate	Used in the extraction and purification process	Sigma-Aldrich, Germany

Animal Model and Ethical Considerations

These chalcones were synthesized and tested in BALB/c mice to determine their pharmacological characteristics. The Institutional Animal Care and Use Committee reviewed and approved all the protocols used in the present study to maintain the ethical treatment of animals as dictated by best practice. Mice were kept under standard BIS Ph05 environmental conditions with a twelve-hour light-dark cycle. The control group was administered with 2% normal saline in all the study groups

Pharmacological Evaluations

Analgesic Activity Testing

Acetic Acid-Induced Writhing Test: The chalcone derivative was administered to mice orally at doses of 10 and 20 values in milligrams per kilogram. The intraperitoneal injection was used to induce the pain response, and the injection volume and concentration depended on the size of the mouse, with small mice receiving 0.6% acetic acid, and the number of writhes as an indicator of the response was counted for fifteen- minutes.

Formalin Paw Licking Test: The presence of the chalcone chromophore on the compound might also have contributed to the enhanced anti-OXA-48 activity, particularly after oral administration of the 2.5% formalin was administered intraplanar in the mouse paw, and the time spent at the injected paw was measured for 30 min to evaluate both phases of pain, spinal (acute, due to the action of formalin on peripheral receptors) and tonic (at 24 hours after the treatment).

Tail Immersion Test: After administering the chalcone derivative, the pain threshold response test using heat was performed; the tails of the mice were dipped in water at 55°C.

Anti-inflammatory Activity

Carrageenan-Induced Paw Edema Model: To determine the anti-inflammatory activity, carrageenan was injected into the mice's paws following the administration of chalcone derivatives at doses of 10 and 20 mg/kg. To quantify the edema, paw volume was determined at graduated time intervals using a plethysmometer.

Statistical Analysis

Statistical analysis of the results was performed via one-way analysis of variance (ANOVA) with Dunnett's test as a post-test to compare means between the experimental and control groups. A p-value < 0. 05 was deemed statistically significant, too. All results were analyzed using statistical tests and expressed as mean ± SEM.

RESULTS

Synthesis and Characterisation of Chalcone Derivatives

The Claisen-Schmidt condensation reaction was conducted to synthesize the chalcone derivative, (E)-1-(4-bromophenyl)-3-(4-chlorophenyl) prop-2-ene-1-one, which formed crystals. Spectral analysis also revealed its chemical uniformity and configuration for the same. The IR spectrum of the compound displayed absorption maxima at 1656 cm^-1 for CO stretching and 1604 cm^-1 for C=C stretching in the aromatic moiety of the chalcone system, thereby confirming the chalcone linkage[11]. Additional structural information from the NMR was obtained from distinguishing signals of the protons in aromatic and olefinic regions at the given chemical shift.

Figure 1: Synthesis of Chalcone

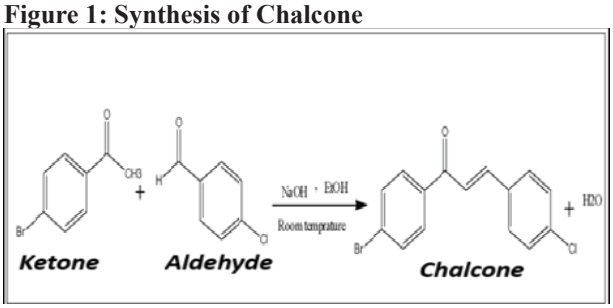


Table 2: Spectral Analysis of Synthesised Chalcone

Technique	Characteristic Observations
FT-IR	Carbonyl stretch at 1656 cm^-1, C=C stretch at 1604 cm^-1
^1H NMR Ppm	Aromatic protons at 7.4-8.2 ppm, Olefinic protons adjacent to ketone at 6.0-6.5
^13C NMR	Carbon signals for aromatic rings at 128-140 ppm, ketone at 190 ppm

This table reveals the information that identifies the synthesized chalcone derivative, which is the spectroscopic data. The absence of any peak in the region 1650-1700 cm-1 implies the lack of functional groups and bonds that are not characteristic of chalcones. Consequently, FT- IR results support the efficiency of the synthesis.

Pharmacological Testing

In this study, the pharmacological effects of the chalcone derivative were determined by different pharmacological tests on mice, specifically concerning its analgesic and anti-inflammatory effects.

Analgesic Activity

Acetic Acid-Induced Writhing Test

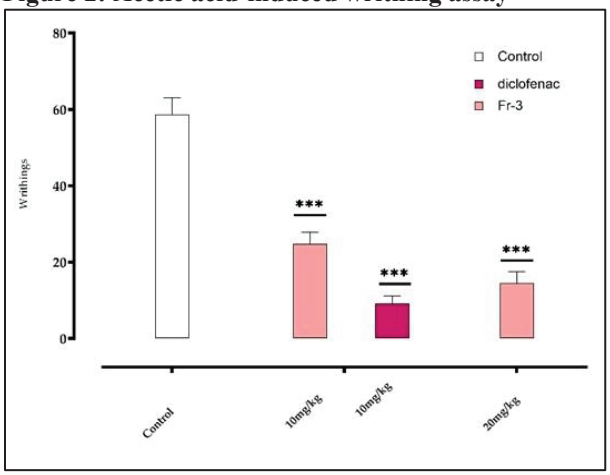
The derivative significantly reduced the number of writhes caused by acetic acid, demonstrating substantial analgesic properties.

Table 3: Results of Acetic Acid-Induced Writhing Test

Treatment	Dose (mg/kg)	Reduction in Writhes (%)	Comparison with Control (%)
Chalcone Derivative	20	75.20	Near to diclofenac (84.43%)

The data presented in this table describes the efficacy of the synthesized chalcone derivative in modulating pain sensations in the acetic acid-induced writhing test. Regarding the analgesic activity, inhibition is nearly equal to that of diclofenac, therefore, the analgesic potential of the chalcone derivative seems promising.[12]

Figure 2: Acetic acid-induced writhing assay



Formalin Paw Licking Test

The test result revealed that the synthesized chalcone derivative also significantly decreased the licking time in neurogenic and inflammatory conditions.

Table 4: Formalin Paw Licking Test Results

Phase	Treatment	Dose (mg/kg)	Reduction in Licking Time (%)
1	**Chalcone Derivative**	20	57.05
2	**Chalcone Derivative**	20	69.93

This table shows a substantial reduction in pain response during both periods of the formalin paw-licking test of the chalcone derivative, which means it targets both neurogenic and inflammatory pains.

Figure 3: Phase 1- Formalin Paw licking test

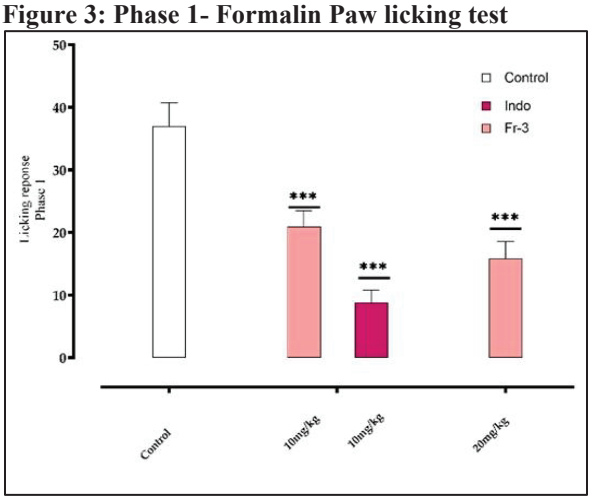
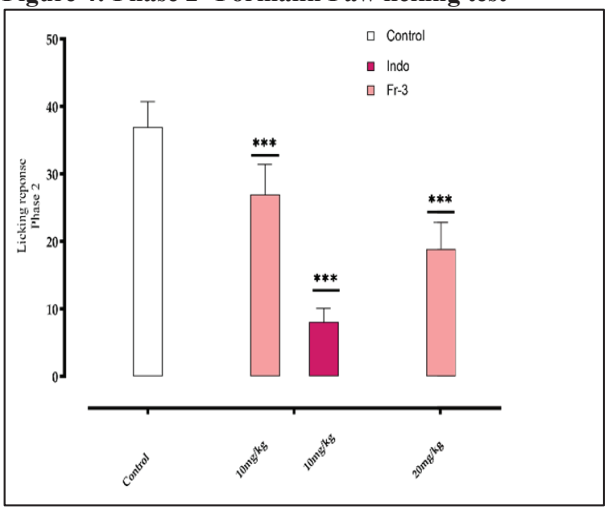


Figure 4: Phase 2- Formalin Paw licking test



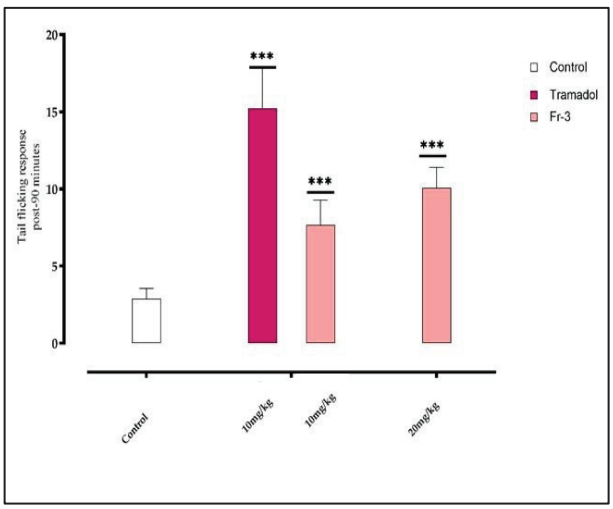
A higher potency for pain threshold was observed, reflecting the chalcone derivative's central analgesic efficacy.

Table 5: Tail Immersion Test Results

Treatment	Dose(mg/kg)	Increase in Pain Threshold (%)
Chalcone Derivative	20	71.52

This table reiterates the superior analgesic effect elicited by the chalcone derivative, as evidenced by the high pain threshold recorded in the tail immersion test, which suggests a possibility of effectively managing neuropathic pain.

Figure 5: The analgesic effect of chalcone using tail immersion test



Anti-Inflammatory Activity

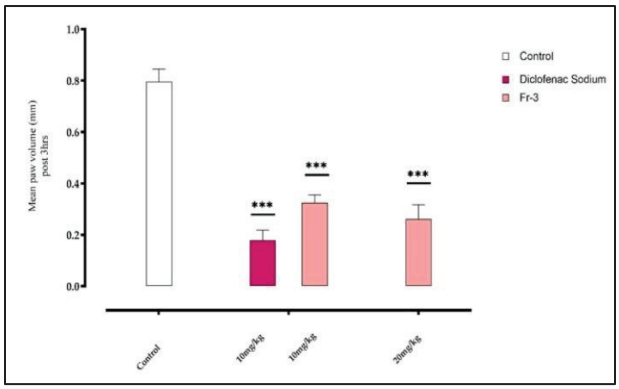
Derivatives also indicated a significant decrease in paw edema, which confirmed good anti-inflammatory activity.

Table 6: Carrageenan-Induced Paw Edema Results

Time post-administration (hrs)	Treatment	Dose (mg/kg)	Reduction in Edema (%)
3	Chalcone Derivative	20	67.08

This table depicts the time-reliant effectiveness of the chalcone derivative in reducing inflammation in the carrageenan-induced paw edema model. Thus, establishing its possibility as an anti-inflammatory drug.

Figure:6: Carrageenan-induced edema



Toxicity Studies

Lack of mortality and minimal alteration in behavioral patterns established in the acute toxicity outcomes demonstrated that the chalcone derivative possessed a higher level of safety and bioavailable in rodents at doses up to 1000 mg/kg.

Mechanistic Insights and Comparative Analysis

The chalcone derivative might work by modifying the peripheral nociceptive receptors and changes in the central sensitization through opioid and serotonin receptors for its analgesic effect and acting through cytokines and enzymes to exert an anti-inflammatory effect. Hence, it has better therapeutic benefits when compared to standard therapies such as diclofenac and tramadol[13]. Chalcone derivative can act as a better therapy because it seems to be at least as effective and has significantly fewer disadvantages.

DISCUSSION

Based on the analysis of the study conducted, it is noted that the synthesized compound (E)-1-(4-bromophenyl)-3-(4-chlorophenyl) prop-2-ene-1-one may also be effective in paw withdrawal as an analgesic and anti-inflammatory agent.[14] The discussion section aims to relate the findings reviewed under the pharmacological evaluations to the general medical usage of chalcone derivatives as well as to other drugs and to compare the latter to the mechanistic profiles highlighted in the study.[15]

Acetic acid-induced writhing was reduced by 75.20% at 20mg/kg, which implies that the treatment was effective in relieving pain in this study, thus effects are strong peripheral analgesic effects. This is the case because these drugs may exert their effect through the inhibition of cyclooxygenase enzymes in the prostaglandin synthesis cascade which as noted is always activated in pain and inflammation. According to the study conducted by Hoxha these are the cyclooxygenase enzymes or COX-1 and the other one is COX-2 they are the chief enzymes that are produced to convert arachidonic acid into prostaglandin products that include pain, fever, and inflammation.[16] This means that these pathways can be stopped to reduce prostaglandin production and hence pain and inflammation. The efficacy of the tail immersion test pointing at the activity of the central pain pathways suggested that chalcones may interfere with the central neurotransmitter systems. The amount of improvement found in the pain threshold was 71.52%, which means that changes in the intensity of the signal or the structure of the central receptors or pathways can interfere with the opioidergic signal. These opiates are principally located in the CNS, and their activation markedly influences the pain threshold.[17]

The profound decreases that have been discussed in this study, both on the neurogenic and the inflammatory phases of the formalin test, again recommend the chalcone in its effectiveness in not only the acute phase (neurogenic) but also the time-delayed phase (inflammatory) pain-relief propensity.[18] Formalin test, for the first phase, is primarily related to direct stimulation of the nociceptors by formalin. While the second phase is more or less related to the perforation induced by the release of inflammatory mediators. Another essential aspect that can be attributed to the chalcone derivative is its broad-spectrum analgesic activity. This may be suitable when dealing with several types of pains, especially neuropathic and chronic pains.[19]

The best chalcone derivative significantly reduced carrageenan-induced paw edema enhancement due to its competent control of the core inflammatory process. This can be attributed mainly to the attainment of its principal goal of inhibiting the NF-κB pathway, a chronic inflammation promoter

responsible for regulating DNA transcription, cytokine synthesis, and cell survival. NF-κB is activated to respond to numerous inflammatory stimuli and contributes to activating genes involved in inflammatory processes.[20] Therefore, chalcones were observed to act on this aliphatic pathway and prevent the formation of protruding symbols of inflammation, such as cytokines and mediators that manifest inflammation, symptoms, and tissue damage. In addition, the study suggests that chalcones hinder the migration of inflammatory cells to the site of inflammation.[21] This is important because macrophages and neutrophils intensify at the locality where inflammation is required or at the tissue/pathogens' invasion site. Chalcones may block receptors that dictate the movement and location of these cells to regions of inflammation, hence minimizing inflammation.

The results obtained from the present study and the reported work from the literature indicate that chalcones possess potent anti-inflammatory activity in the context of acute and chronic models of inflammation, such as carrageenan-induced paw edema. Therefore, they may apply to a variety of inflammatory diseases. This ranges from acute inflammation to chronic inflammatory diseases, among other things, rheumatoid arthritis and inflamed bowel syndrome (IBD). In an ailment such as arthritis, individuals are plagued by constant inflammation of the joints and recurrent complaints of severe morbidity.[22] It also improves neuroinflammatory diseases followed by cognitive dysfunction such as dementia and Alzheimer's disease. Chalcones might directly influence the inflammatory process; thus, chalcones is a new therapeutic approach with fewer side effects than current drugs, such as NSAIDs or corticosteroids.[23] In the case of diseases such as IBD, which is an inflammatory bowel disease in which the digestive tract gets irritated for an extended period, chalcones may provide the body with a two-pronged solution where it can help to decrease inflammation as well as provide adequate protection to the damage primarily observed in the epithelial cells underlying the digestive tract. This dual action is critical in chronic processes, where low-intensity inflammation within tissues destroys tissue and their failure.

Comparative Analysis with Standard Treatments

The assessment of the chalcone derivative with standard analgesics and anti-inflammatory drugs, such as diclofenac and tramadol, shows that it has at least the same therapeutic potential, possibly a greater one.[24] These outcomes are significant given the multiple side effects tied to conventional drugs, such as gastrointestinal and cardiovascular issues linked to NSAIDs or potential opioid addiction. The chalcone derivative's favorable toxicity value, also depicted in terms of LD50, indicates a wide safety margin, corroborating its development as a safer drug.[25]

The observed analgesic and anti-inflammatory effects can be attributed to the impact of the discussed compound on the molecular targets generating pain and inflammation signals. They can alter the biochemical activity in several ways; they may hinder the action of cyclooxygenase enzymes, cause a decline in prostaglandin synthesis, and influence other inflammatory mediators like TNF- α and interleukins. Based on the mechanistic information and separate inflammatory targets, chalcones could be examined in other fields that contain inflammation.[26] Autoimmune diseases, subsets of neurodegenerative diseases and even adjuvant treatments for diseases such as cancer where inflammation is known to contribute to tumor growth.

CONCLUSION

In conclusion, the findings of this study portray the chalcone derivative, (E)-1-(4-bromophenyl)-3-(4-chlorophenyl) prop-2-ene-1-one as a potent analgesic and anti-inflammatory compound. The synthesis of the compound shown in the study proved to have an anti-inflammatory and analgesic effect in different in vivo models, being as potent as diclofenac and tramadol but with lower side effects. This can be attributed to the fact that the compound exerts its effect by modulating the activities of cyclooxygenase enzymes and inhibiting pro-inflammatory cytokines. Thus, suggesting its potential usefulness in both peripheral and central nervous system pathways for the treatment of inflammatory responses. This study provides further evidence for the potential utility of chalcone derivatives, including in the treatment of more chronic inflammatory conditions than has currently been addressed with both NSAIDs and opioids, making chalcone derivatives a safer possibility for pain medication. These findings suggest more comprehensive clinical investigations to confirm the effectiveness and safety of chalcone derivatives when applied in various patient pools, expecting to create this group of compounds as an innovative class of pharmacology drugs.

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