

# Chalcones: Beyond Bioactive Properties - Exploring Their Potential as Polymeric Materials

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## Abstract

*Chalcones, a class of natural compounds characterized by their unique chemical structure, have garnered significant attention in recent years for their diverse pharmacological and biological activities. This review aims to comprehensively assess and summarize the latest research spanning the last five years. By synthesizing findings from a plethora of studies, this retrospective analysis elucidates the evolving landscape of chalcone research, shedding light on their therapeutic potential and biological effects. The primary objective of this review is to identify and analyse the gaps in current knowledge regarding the toxicological, pharmacological and biological activities of chalcones. By critically evaluating the existing literature, we aim to pinpoint areas where further investigation is needed, thereby guiding future research endeavours. Central topics addressed in this review encompass the wide-ranging chemical benefits and biological activities exhibited by chalcones, including their anti-inflammatory, antioxidant, anticancer, and biochemical repairing attributes. By identifying gaps in our understanding and emphasizing potential avenues for exploration, this retrospective analysis aims to inspire and guide researchers in harnessing the full pharmacological and polymeric potential of chalcones in the years to come.*

**Keywords:** Chalcones, anti-inflammatory, pharmacological, biochemical, synthetic compounds, polymer

## INTRODUCTION

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Chalcones represent a group of natural compounds distinguished by their unique open-chain structure, comprising two aromatic rings linked by a three-carbon  $\alpha$ ,  $\beta$ -unsaturated carbonyl framework, [1]. have emerged as a fascinating area of study in the field of pharmacology and biology. Over the past many years, research on chalcones has witnessed a surge in interest, driven by their diverse range of pharmacological and biological activities. This period has been marked by significant strides in unravelling the therapeutic potential of chalcones, shedding light on their multifaceted roles in human health. The unique chemical structure of chalcones imparts them with a broad spectrum of biological activities, making them intriguing candidates for therapeutic interventions [2]. These compounds are ubiquitously distributed in the plant kingdom, where they serve various functions, including defence mechanisms against pathogens and environmental stressors. However, beyond their ecological roles, chalcones have demonstrated remarkable interactions with biological systems,

prompting extensive exploration into their potential applications in medicine [3]. One of the key driving forces behind the heightened interest in chalcones is their demonstrated anti-inflammatory properties [4]. Inflammation is a multifaceted physiological reaction that holds a pivotal role in the body's defense mechanisms. Nevertheless, dysregulated, or persistent inflammation is associated with the onset of various diseases, including cancer, cardiovascular disorders, and neurodegenerative conditions. The anti-inflammatory capabilities of chalcones have been the focus of extensive research, with numerous studies focusing on elucidating the molecular mechanisms through which these compounds modulate inflammatory pathways [5]. In addition to their anti-inflammatory effects, chalcones exhibit notable antioxidant activity [6]. The aging process and the development of various diseases are associated with oxidative stress, this imbalance emerges from the interaction between the generation of reactive oxygen species (ROS) and the organism's capacity to counteract them. Chalcones, with their ability to scavenge free radicals and mitigate oxidative damage, have garnered attention as potential therapeutic agents in conditions associated with increased oxidative stress. The anticancer properties of chalcones represent another facet of their pharmacological profile that has been extensively explored in recent years [7]. Cancer, characterized by uncontrolled cell growth, represents a multifaceted and diverse array of diseases, posing a significant global health challenge. Chalcones have demonstrated anti-proliferative, pro-apoptotic, and anti-angiogenic effects across various cancer types, making them attractive candidates for further anticancer drug development [8]. Moreover, the antimicrobial potential of chalcones has been a subject of growing interest, particularly in the context of combating drug-resistant microbial strains. The emergence of antibiotic resistance presents a grave concern for public health, highlighting the need to investigate alternative antimicrobial agents. Chalcones have shown promising antimicrobial, antifungal, and antiviral activities, opening new avenues for the development of novel antimicrobial agents [9]. While the past five years have witnessed significant advancements in understanding the pharmacological and biological activities of chalcones, there remains a need for a comprehensive retrospective analysis to synthesize and thoroughly assess the current state of knowledge. This review seeks to address this void by thoroughly examining recent literature, highlighting significant discoveries, and evaluating the constraints and difficulties present in ongoing research. As we embark on this journey through the realms of chalcone research, our overarching goal is to not only present a comprehensive overview of the recent studies done, but also to critically analyse the existing knowledge to identify gaps and potential avenues for future exploration of chemical advancements and industrial achievements. By doing so, we aspire to contribute to the ongoing dialogue surrounding the therapeutic potential of chalcones and inspire further research that may unlock new dimensions of their pharmacological and biological significance.

## RECENT INVESTIGATIONS AND FINDINGS

This comprehensive review delves into the structure and characteristics of bis-chalcones (Figure1), providing an insightful exploration of their physicochemical characteristics [10]. Additionally, the synthesis methodologies employed for these compounds, as documented in the literature, are elucidated, with a focus on the latest advancements in the field. Notably, the review places emphasis on the less-explored aspects of bis-chalcones, shedding light on their chemical intricacies.

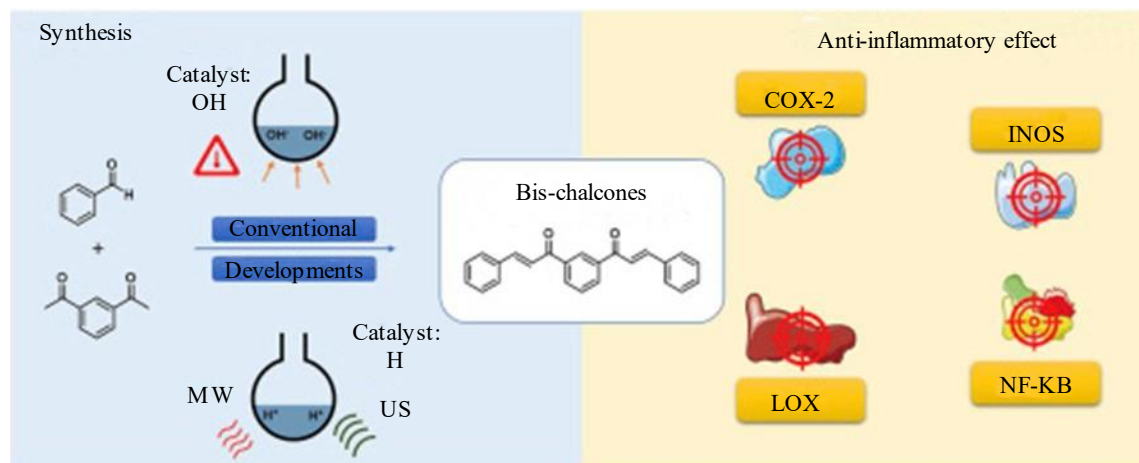
A primary focus of this review centres on the anti-inflammatory properties exhibited by bis-chalcones. The article meticulously outlines the structures responsible for their active anti-inflammatory effects, drawing attention to relevant findings in the existing body of literature. Furthermore, the mechanisms underlying the anti-inflammatory activity of bis-chalcones are thoroughly examined, providing a comprehensive understanding of their potential therapeutic implications. Through this examination, the review aims to bridge the existing knowledge gap and offer valuable insights that may inspire further investigations into the anti-inflammatory potential of bis-chalcones.

This another review delves into diverse aspects of chalcones, exploring their biological sources, pathway inhibition mechanisms, and pharmacological activities [11]. The main aim of this study is to conduct a comprehensive investigation into chalcones as a source of ethnopharmacological wisdom, emphasizing their broad spectrum of pharmacological effects. These activities span a wide range,

including but not limited to anti-cancer, antimicrobial, antioxidative, anti-acne, liver-protective, neuroprotective, and various other properties. Chalcones have exhibited their ability to reduce inflammation by inhibiting essential mediators such as COX-2, NO synthase, and TNF- $\alpha$ . This study will comprehensively discuss these mechanisms, shedding light on the role of chalcones in alleviating inflammation. Current developments in the clinical application of chalcones for addressing inflammation, anti-aging, minimizing oxidative stress, and influencing processes such as autophagy and apoptosis will also be examined. This article consolidates existing insights into the molecular development of inflammation and highlights the crucial contribution of chalcones in counteracting inflammation through the targeting of inflammatory mediators and pathways. By examining the multifaceted pharmacological activities of chalcones, this research enhances our comprehension of their therapeutic possibilities and lays the groundwork for subsequent explorations. into the diverse applications of these secondary metabolites.

This extensive review by Wang et al. centers on the antimicrobial properties and processes of seventeen chalcones obtained from natural sources. Initially, the classification of these chalcones is presented, emphasizing distinctions in their antimicrobial mechanisms [12]. Subsequently, the review provides a concise overview of the extraction procedure and biological impacts of the seventeen naturally derived chalcones, focusing specifically on their antimicrobial efficacy. In conclusion, a detailed summary elucidates the antimicrobial mechanisms intrinsic to these natural chalcones, encompassing actions Focusing on bacterial cell membranes, interactions with biological macromolecules, impacts on biofilms, and regulation of quorum sensing systems. This review article provides a comprehensive exploration of bis-chalcones, detailing their chemical structure and properties. Additionally, the review delves into the methodologies documented in the literature for synthesizing these molecules, with a specific focus on the most recent advancements in the field. Through this thorough analysis, the article aims to contribute to a deeper understanding of bis-chalcones, particularly in the context of their anti-inflammatory properties.

The mechanisms via which chalcones inhibit cancer cell proliferation and cancer formation in both in vitro and in vivo situations are thoroughly examined in this study [13]. Notably, attention is given to gastric cancer (GC) and colorectal cancer (CRC), These are acknowledged as prevalent cancers affecting the digestive tract, exhibiting a high global incidence rate. The review highlights how difficult it is to find treatments for GC and CRC that are both safe and effective at the same time. Chalcones, which are plant-derived polyphenols, have attracted a lot of attention because of their inherent biological activity in tackling this problem. Furthermore, their attractiveness as possible agents in the search for novel and secure therapeutic approaches for stomach and the development of new chalcone derivatives and their comparatively straightforward structural modifications contribute to the improvement of colorectal cancer treatments.



**Figure 1.** Structure and characteristics of bis-chalcones [10].

In their study, Olender et al. aimed to formulate and produce a range of curcuminoid chalcones, the researchers conducted the synthesis of twelve distinct curcuminoid chalcones, validated their structures using spectral techniques, and assessed the biological efficacy of three synthesized compounds across multiple assays, with a focus on toxicity and anticancer properties [14]. The suggested derivatives were produced by the Claisen-Schmidt reaction, which involved reacting particular acetophenones and aldehydes under different circumstances using solvent-free microwave or ultrasonic variations in addition to conventional techniques. The experiments comprised tests for resazurin reduction, caspase-3 activity, and RT-qPCR. Furthermore, the assessment involved measuring intracellular reactive oxygen species (ROS) levels and lactate dehydrogenase (LDH) release [15].

The analysis of the results indicates that compound 3a stimulated the metabolism and/or proliferation of the human colon carcinoma (Caco-2) cell line. In contrast, compounds 3b and 3f displayed considerable toxicity against the Caco-2 cell line. Generally, the initial findings suggest that compound 3b displayed the most promising anticancer activity.

The research conducted by Sharma et al. aims to investigate multifunctional chalcone derivatives capable of targeting multiple aspects implicated in Alzheimer's disease [16]. They created a set of innovative aminoethyl-substituted chalcones utilizing *in silico* methods, which encompassed scaffold morphing, molecular docking, and ADME considerations, in addition to traditional synthetic methods. The synthesized analogs underwent comprehensive characterization, followed by biological assessments using various *in vitro* assays targeting acetylcholinesterase (AChE), advanced glycation end products (AGEs), and radical generation.

Notably, among all the compounds examined, PS-10 emerged as remarkable, demonstrating potent AChE inhibitory activity with an IC<sub>50</sub> of 15.3 nM—outperforming the standard drug with an IC<sub>50</sub> of 15.68 nM. Additional examinations expanded to *in vivo* assessments of PS-10 against streptozotocin (STZ)-induced dementia in rats, demonstrating memory enhancement as observed in the Morris Water Maze test. To enhance comprehension of the interaction between PS-10 and AChE, molecular dynamic simulation studies were carried out, revealing the stability of the PS-10 and AChE complex. The findings from this study provide valuable insights into the potential of chalcone derivatives, particularly PS-10, as versatile agents for addressing various aspects of Alzheimer's disease, from AChE inhibition to ameliorating oxidative stress.

This study (Sabarathinam & Ganamurali, focuses on the assessment of structurally modified chalcones (SMC) for their potential in managing diabetes [17]. Fourteen structurally modified chalcones, validated both structurally and biologically through original research articles, were systematically screened and included in this investigation. Employing network pharmacology analysis, the study aimed to evaluate the impact of these SMC on diabetes, with a specific emphasis on their interaction with relevant targets. The network pharmacology analysis indicated that compounds S2, S3, S5, S9, and S12 showed significant affinities for targets related to diabetes. To gain a deeper insight into the protein-ligand interaction, a molecular docking complex (ERK2 kinase-S5) underwent molecular dynamics at 300K for 100 ns. The findings collectively suggest that structurally modified compounds, particularly compound S9, exhibit effectiveness and hold promise in identifying lead compounds for glycemic control. This research contributes valuable insights into the potential therapeutic applications of structurally modified chalcones in the context of diabetes management.

In this research study (Kumar et al. the inhibitory potential of thirteen isopropyl chalcones (CA1-CA13) against monoamine oxidase (MAO) was systematically evaluated, specifically targeting the inhibition of MAO for potential applications in Parkinson's Disease (PD) [18]. The synthesis of these isopropyl chalcones was a key initial step, paving the way for their comprehensive assessment. Notably, all thirteen compounds demonstrated a more potent inhibition of MAO-B compared to MAO-A. Compound CA4 emerged as the most potent MAO-B inhibitor, with an impressive IC<sub>50</sub> value of 0.032  $\mu$ M, closely followed by CA3 with an IC<sub>50</sub> of 0.035  $\mu$ M. A selectivity index (SI) study revealed high SI values for MAO-B over MAO-A, with SI values of 49.75 and 353.23, respectively.

This review by Birsa & Sarbu goal is to emphasize the chemopreventive properties linked to hydroxy-substituted natural and synthetic chalcones, along with several analogues, as these compounds exhibit diverse biological activities with potential applications against various diseases [19]. In particular, the focus is on investigating the antioxidant and anti-inflammatory properties demonstrated by chalcones with hydroxy substituents. Hydroxy substituents are crucial in influencing the biological properties of chalcones, and the review systematically categorizes this impact depending on the positioning of hydroxy substituents on either ring A, B, or both. By providing a comprehensive overview of the various biological activities associated with hydroxy-substituted chalcones, the review seeks to provide valuable insights into the potential chemopreventive applications of these compounds, particularly in the realm of disease prevention and management.

In their study, Pojtanadithee et al. concentrate on identifying sulfonamide chalcones with potential as inhibitors of the SARS-CoV-2 main protease (3CLpro), a pivotal target for the development of antiviral treatments against the coronavirus [20]. The research adopted a systematic methodology, integrating structure-based virtual screening with experimental techniques, to identify compounds exhibiting favourable drug-like characteristics. Out of an in-house library containing 1052 natural product-based compounds, 75 pharmacologically active compounds were identified. These analyses indicated the potential of SWC423 as a 3CLpro inhibitor, thereby suggesting its candidacy for further research in the development of therapeutic interventions for COVID-19. In summary, this research highlights the potential of inhibiting 3CLpro with sulfonamide chalcones, exemplified by SWC423, as a promising avenue for the development of effective treatments for COVID-19.

In a thorough review conducted by Hadi Nematollahi et al. a detailed examination is undertaken on the multifaceted pharmacological and biological effects of chalcones and their derivatives, with a particular emphasis on their utilization within antiviral and antimicrobial contexts [21]. Chalcones have garnered significant attention for their diverse effects, including anti-inflammatory, antimicrobial, antiviral, and antitumor properties. The review highlights the suitability of chalcones for antiviral applications, showcasing their effectiveness in selectively targeting various viral enzymes. Furthermore, these compounds have shown significant potential in addressing pathogenic bacteria and fungi, notably strains resistant to multiple drugs. Mechanisms such as the inhibition of DNA gyrase B, UDP-N-acetylglucosamine enol-pyruvyl transferase (MurA), and efflux pumps (e.g., NorA) have demonstrated significance in their antimicrobial efficacy, while antifungal and antiparasitic activities have prompted further exploration, including antitrypanosomal and antileishmanial properties. However, despite these encouraging results, the review emphasizes the necessity for systematic analysis concerning mechanisms, biosafety considerations, pharmacological attributes, and clinical translation studies to support practical applications. Additionally, acknowledging the significance of environmentally friendly and sustainable synthesis methods, particularly concerning industrial applications, the review briefly addresses advancements in this area. In conclusion, the review expresses the aspiration that it will motivate researchers to investigate and develop innovative chalcone compounds possessing medicinal attributes, thus tackling major health challenges like pathogenic viruses and multidrug-resistant bacteria.

Chalcones persist as revered scaffolds for constructing diverse heterocyclic molecules acclaimed for their medicinal and industrial applications. Particularly noteworthy are hybrid chalcones that integrate heteroaromatic components, and the methods employed in their synthesis, especially those adhering to green chemistry principles. This review (Mallia & Sloop, sheds light on the recent advances made in incorporating heteroaromatic elements into the construction of hybrid chalcones, emphasizing environmentally responsible processes utilized in their preparation [22]. The comprehensive examination covers the past few decades, providing insights into the innovative strategies and techniques employed to enhance the synthesis of heteroaromatic hybrid chalcones. By focusing on green chemistry principles, the review underscores the significance of sustainable and environmentally friendly approaches in the preparation of this valuable class of molecules. The outlined advancements aim to contribute to a deeper understanding of the synthetic methodologies involved, offering valuable insights for researchers engaged in the development of novel heteroaromatic hybrid chalcones with diverse applications.

## CONCLUSION

This comprehensive review examines the wide range of pharmacological, polymeric and biological activities associated with chalcones and their derivatives. The review encompasses various applications, including anti-inflammatory and antimicrobial effects, as well as exploring their potential in antiviral therapies. The versatility of chalcones, both natural and synthetic, has been showcased in their ability to target various enzymes and pathways, making them promising candidates for the development of therapeutic interventions against a multitude of diseases. The chemopreventive properties of hydroxy-substituted chalcones, the inhibitory potential against SARS-CoV-2 3CLpro, and the multifunctional aspects of chalcone derivatives in Alzheimer's disease underscore the wide-ranging impact of these compounds in the realm of medicinal research. The synthesis and evaluation of chalcones with isopropyl or curcuminoid moieties further exemplify the continuous exploration of novel derivatives with enhanced activities, providing avenues for potential drug development. Our examination of the structure-activity relationships of bis-chalcones, coupled with our efforts to understand the mechanisms underlying the anti-inflammatory properties of chalcones, has deepened our understanding of their therapeutic effectiveness. The review has not only delved into the biological aspects but also considered the environmentally responsible synthesis of chalcones, emphasizing the importance of green chemistry principles and underscore the remarkable potential of chemically enhanced chalcones across a spectrum of applications. Further investigations and innovations in chalcone research are poised to contribute significantly to the development of new therapeutic agents, providing solutions to emerging health challenges and advancing the field of medicinal chemistry

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