Chalcones: Chemistry, Biological Activities, and Pharmacological Potential

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Abstract :

Flavonoids constitute a structurally diverse class of naturally occurring polyphenols that play crucial roles in human health and disease prevention. Among them, chalcones—characterized by an α,β-unsaturated carbonyl system linking two aromatic rings—have emerged as privileged scaffolds owing to their remarkable biological versatility and synthetic accessibility. While antioxidant and anticancer properties of chalcones have been extensively explored, growing evidence highlights their broader biological significance. This short communication provides a focused overview of the diverse biological roles of chalcones beyond their classical activities, including anti-inflammatory, antimicrobial, antiviral, antidiabetic, neuroprotective, cardioprotective, immunomodulatory, and enzyme-inhibitory effects. The molecular basis of these activities is discussed in relation to their structural features, target diversity, and modulation of key cellular signaling pathways such as NF-κB, MAPK, AMPK, and Nrf2. Additionally, the pharmacological relevance of chalcones as multifunctional bioactive molecules and their potential as lead compounds in drug discovery are highlighted. Owing to their simple molecular framework, tunable reactivity, and broad therapeutic applicability, chalcones continue to attract significant attention in medicinal chemistry and chemical biology. This review underscores the importance of chalcones as small molecules with major biological impact and emphasizes future opportunities for their rational design and clinical translation.

Keywards: Chalcones, Anti-oxidants, Anticancer, Biological Activities

Introduction :

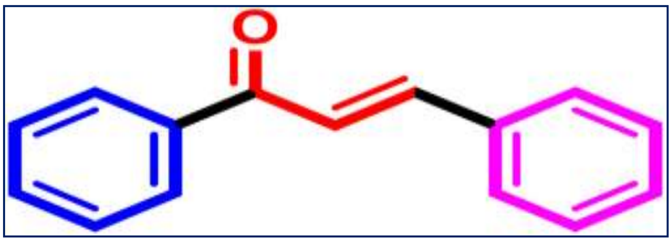

Figure 1: Chalcone

Chalcones are simple open-chain flavonoids (C_6–C_3–C_6 scaffold), chemically known as 1,3-diaryl-2-propen-1-ones [1,2]. This scaffold consists of two aromatic rings (A and B) connected by a three-carbon α,β-unsaturated carbonyl bridge [1]. The trans (E) isomer is thermodynamically favored in nature [3]. Chalcones are widely distributed throughout the plant kingdom, occurring in fruits, vegetables, teas, and many medicinal herbs [4]. The aromatic rings can accommodate a variety of substituents (phenolic –OH, $–OCH_3$, halogens, prenyl groups, etc.), leading to extensive structural diversity [5]. In general, chalcones are classified as simple (unaltered C_6–C_3–C_6) or hybrid derivatives (e.g., fused with heterocycles) [6]. The conjugated enone moiety renders the β-carbon electrophilic (a Michael acceptor), which is crucial for their reactivity in biological systems [7].

Chalcones (1,3-diphenyl-2-propen-1-ones) represent a privileged and highly tunable scaffold in natural product chemistry. Their simple α,β-unsaturated carbonyl core (a conjugated enone) imparts both chemical reactivity and the ability to interact with diverse biological targets. Beyond the widely reported antioxidant and anticancer activities, chalcones exhibit a remarkable spectrum of additional biological effects, including anti-inflammatory activity; antimicrobial actions (antibacterial, antifungal, antiviral, and antiprotozoal); enzyme modulation (e.g., kinases, phosphodiesterases, xanthine oxidase); antidiabetic and metabolic regulation; neuroprotective and cognitive benefits; cardioprotective and vasoactive effects; immunomodulatory and wound-healing properties; anti-angiogenic and anti-metastatic adjunct effects; and chemosensitization. Each major biological role is discussed below with mechanistic insights, representative examples, and translational considerations.

Chemical structures of few chalcone scaffold-based drugs/clinically implemented chalcones as follows:

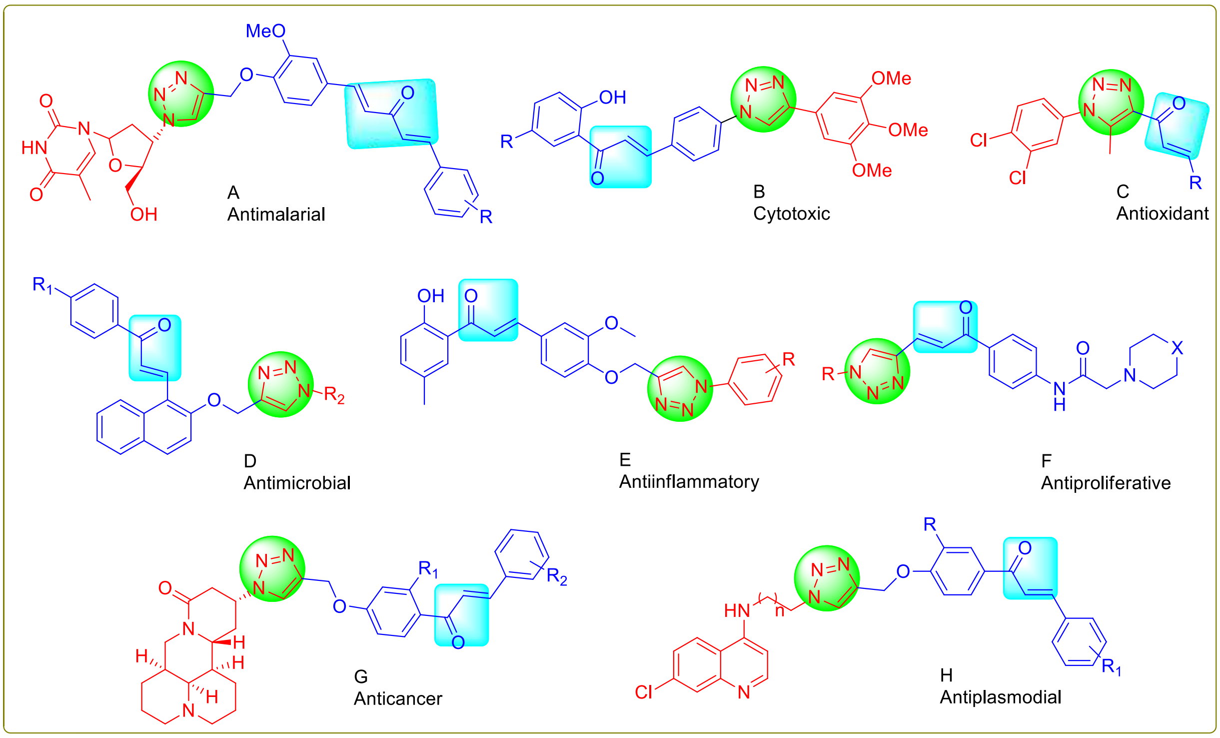

Figure 2: Reported Biological Active chalcone derivatives

Natural Sources of Chalcones:

a. **Common foods:** Chalcones are found in many edible plants (fruits, vegetables, spices, and teas)[4]. For example, apples and berries contain dihydrochalcone and chalcone derivatives that contribute to dietary antioxidant intake[8].

b. **Leguminosae (Fabaceae):** Many legumes produce potent chalcones. Licorice (*Glycyrrhiza* spp.) yields isoliquiritigenin and licochalcones (e.g. licochalcone A)[9][10]. Sophora and related genera also contain bioactive chalcones.

c. **Moraceae:** Mulberry (*Morus*) and jackfruit (*Artocarpus*) species are rich in butein and other polyhydroxychalcones[9]. These compounds have been isolated from Moraceae plants used in traditional remedies.

d. **Asteraceae and others:** Species in the daisy family (e.g. *Helichrysum*, *Dorstenia*) and various medicinal herbs (e.g. *Angelica*, *Scutellaria*, *Tarenna*) produce unique chalcones[11][9]. Broadly, plants historically used in ethnomedicine – such as licorice (Glycyrrhiza), pepperwort (Piper), and broom (Ruscus) – have been shown to contain chalcone-like metabolites[10].

Fig. 3 Natural Sources of Chalcones

Structural Diversity of Chalcones

Chalcones exhibit considerable chemical diversity. The core 1,3-diaryl-2-propenone can carry multiple substituents: common patterns include phenolic –OH (often at the 2′, 4′, 4 positions), –OCH_3, –O-prenyl, or halogens on either ring[5]. These substitutions modulate lipophilicity and reactivity. Chalcones can be converted to related flavonoids by cyclization (e.g. to flavanones or aurones), and some naturally occurring derivatives include dihydrochalcones (saturated bridge) or bis-chalcones (two chalcone units linked)[12][6]. In fact, chalcone derivatives can be further hybridized with other pharmacophores (e.g. indoles, azoles, coumarins) to form novel fused frameworks[6][7]. This versatility underlies why over 90,000 chalcone structures are listed in chemical databases, many with reported bioactivity[12]z.

Biological Activities:

A) Antioxidant Effect:

Chalcones are powerful antioxidants due to their polyphenolic character. The phenolic –OH groups readily donate hydrogen to quench free radicals, and chalcone-containing extracts can inhibit lipid peroxidation[13]. For example, naturally occurring chalcones such as xanthohumol (from hops) and isoliquiritigenin (licorice) show strong DPPH and cell-based antioxidant activity[14][8]. Structure–activity relationships indicate that an –OH on the B-ring and a para $–OCH_3$ on ring A often enhance radical-scavenging power[14]. These antioxidant effects also contribute to anti-inflammatory actions: chalcones can suppress inflammatory cytokine release and inhibit COX-2/5-LOX enzymes, in part by activating Nrf2–ARE pathways to upregulate cellular defenses[14][15].

B) Anticancer Effects

Chalcones are likewise noted for anticancer properties. They induce cytotoxicity through multiple mechanisms – for instance, many chalcones trigger apoptosis and cell-cycle arrest in cancer cells[16][17]. The conjugated enone can form covalent adducts with nucleophilic protein thiols, disrupting redox signaling and depleting antioxidant enzymes in tumor cells. Natural chalcones like butein and isoliquiritigenin have demonstrated potent antiproliferative effects: butein induces G_2/M arrest and caspase-3-mediated apoptosis in various carcinoma lines[17][18]. Chalcones can also inhibit angiogenesis and metastasis by blocking key signaling (e.g. NF-κB, MAPK)[18]. In summary, the chalcone scaffold "possesses strong biological activities, viz. anti-tumor activity and anticancer potency"[16], making it a promising lead in cancer chemotherapy research.

Pharmacological Relevance and Therapeutic Potential

Because of their diverse bioactivities, chalcones have significant pharmacological relevance. Some derivatives are already used as drugs: for example, metochalcone (a bile-stimulating agent) and sofalcone (a gastroprotective anti-ulcerant) are synthetic chalcone drugs approved for clinical use[19][20]. The figure above illustrates their core chalcone structures. Hesperidin methylchalcone is another chalcone derivative prescribed for chronic venous insufficiency.

Likewise, licorice-derived chalcones have been developed therapeutically: isoliquiritigenin functions as a phosphodiesterase III inhibitor for cardiovascular disease[21]. In addition, many chalcones demonstrate good drug-like properties – for example, preliminary trials show generally low toxicity and acceptable bioavailability[22].

Beyond anticancer and antioxidant uses, chalcones also exhibit antimicrobial, antidiabetic, and neuroprotective actions[15][22]. Their capacity to inhibit enzymes (xanthine oxidase, epoxide hydrolase, kinases, etc.) makes them versatile pharmacological tools[23][22]. Taken together, chalcones are viewed as "leading bioactive flavonoids" with therapeutic potential against cancers, inflammation, metabolic and cardiovascular diseases[15][22]. Their simple scaffold and synthetic accessibility continue to inspire drug design: researchers routinely "introduce chalcone derivatives to achieve enhanced anticancer activity" in conventional chemotherapy[16][22].

Biological Roles of Chalcones Beyond Antioxidant and Anticancer Activities

Chalcones, characterized by the α,β-unsaturated carbonyl framework linking two aromatic rings, represent a versatile and biologically privileged class of flavonoids. While antioxidant and anticancer activities dominate early investigations, accumulating evidence demonstrates that chalcones exert a wide spectrum of biological effects extending far beyond these roles [1,5,18]. Their planar structure, electrophilic enone moiety, and substituent flexibility enable interactions with multiple cellular targets, positioning chalcones as multifunctional bioactive molecules of pharmacological significance.

C) Anti-inflammatory activity

Chalcones exhibit pronounced anti-inflammatory activity by modulating key inflammatory signaling pathways. Numerous chalcone derivatives suppress the production of pro-inflammatory mediators such as nitric oxide, prostaglandins, tumor necrosis factor-α, and interleukins by inhibiting inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) expression [4,10,11]. At the molecular level, chalcones inhibit nuclear factor-κB (NF-κB) activation by preventing IκB phosphorylation and nuclear translocation of NF-κB subunits, thereby downregulating inflammatory gene transcription [8,26]. In addition, chalcones interfere with mitogen-activated protein kinase (MAPK) signaling pathways, including p38, JNK, and ERK, resulting in reduced cytokine production [27].

Several chalcones also activate the Nrf2/HO-1 pathway, enhancing cellular defense mechanisms and attenuating inflammation-induced oxidative damage [21,29]. In vivo studies demonstrate that chalcone derivatives significantly reduce carrageenan-induced paw edema and lipopolysaccharide-induced systemic inflammation, highlighting their potential as anti-inflammatory agents [30].

D) Antimicrobial and antiparasitic activity

Chalcones display broad-spectrum antimicrobial activity against bacteria, fungi, and protozoan parasites. Their antibacterial effects are attributed to membrane disruption, inhibition of cell wall biosynthesis, and suppression of essential bacterial enzymes such as enoyl-ACP reductase [15,31]. Chalcones exhibit notable activity against Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus*, and certain Gram-negative strains [32].

Antifungal chalcones inhibit ergosterol biosynthesis and compromise fungal membrane integrity, resulting in growth inhibition of *Candida* species and other pathogenic fungi [33]. Furthermore, chalcones demonstrate antiparasitic activity against *Leishmania*, *Plasmodium*, and *Trypanosoma* species by disrupting mitochondrial function and redox homeostasis in parasites [34,35]. These properties underscore the potential of chalcones as lead compounds in the development of new antimicrobial and antiparasitic therapies.

E) Antiviral activity

Several chalcone derivatives have been reported to exhibit antiviral activity by targeting viral entry, replication, or host-virus interactions. Chalcones inhibit viral proteases and polymerases, thereby suppressing viral replication in infected cells [19,36]. In vitro studies have demonstrated the efficacy of chalcone-based inhibitors against human immunodeficiency virus, influenza virus, and dengue virus, highlighting their potential as antiviral scaffolds [37,38]. Additionally, modulation of host inflammatory responses by chalcones may contribute to reduced viral pathogenesis.

F) Antidiabetic and metabolic regulatory effects

Chalcones play an important role in metabolic regulation and glucose homeostasis. Numerous chalcone derivatives inhibit α-glucosidase and α-amylase enzymes, leading to reduced postprandial hyperglycemia [20,39]. Beyond enzyme inhibition, chalcones modulate insulin signaling pathways by activating AMP-activated protein kinase (AMPK) and enhancing glucose transporter-4 translocation, thereby improving insulin sensitivity [40].

Some chalcones also protect pancreatic β-cells from glucotoxicity and inflammation-induced apoptosis, contributing to preservation of insulin secretion capacity [41]. Moreover, chalcones influence lipid metabolism through modulation of peroxisome proliferator-activated receptors, offering additional benefits in metabolic syndrome and type 2 diabetes management [16].

G) Neuroprotective effects

Chalcones exhibit neuroprotective activity by attenuating neuroinflammation and preserving neuronal integrity. They suppress microglial activation and reduce the release of pro-inflammatory mediators in the central nervous system through inhibition of NF-κB and MAPK pathways [42]. Certain chalcone derivatives inhibit acetylcholinesterase and butyrylcholinesterase, thereby enhancing cholinergic neurotransmission relevant to cognitive function [44].

Additionally, chalcones interfere with β-amyloid aggregation and protect neurons from amyloid-induced toxicity in experimental models of Alzheimer's disease [43]. Their ability to stabilize mitochondrial function and reduce neuronal apoptosis further supports their potential in neurodegenerative disorder research [17].

H) Cardiovascular and vasoprotective effects

Chalcones contribute to cardiovascular protection by improving endothelial function and vascular tone. Several derivatives promote vasodilation through enhanced nitric oxide bioavailability and inhibition of calcium influx in vascular smooth muscle cells [45]. Chalcones also inhibit platelet aggregation and thrombus formation, reducing cardiovascular risk [46]. Lipid-lowering effects observed in preclinical studies further support their cardioprotective potential [13].

I) Immunomodulatory and wound-healing properties

Chalcones modulate immune responses by regulating macrophage polarization and T-cell-mediated cytokine production, thereby maintaining immune homeostasis [47]. Topical application of chalcone-based formulations accelerates wound healing by enhancing collagen deposition, angiogenesis, and re-epithelialization while suppressing excessive inflammation [48]. These properties highlight their potential utility in dermatological and regenerative medicine applications.

J) Enzyme inhibition and molecular target diversity

The chalcone scaffold exhibits remarkable molecular target diversity. Chalcones act as inhibitors of kinases, phosphodiesterases, tyrosinase, xanthine oxidase, and aldose reductase, among others [12,49]. This broad enzyme inhibitory profile underscores the privileged nature of chalcones in medicinal chemistry and explains their wide pharmacological spectrum [18,50].

Fig. 4 Biological Activities of Chalcones

Integrative Perspective: Why Chalcones Matter Pharmacologically?

The pharmacological relevance of chalcones lies not merely in the number of biological activities they exhibit, but in their capacity to modulate complex disease networks through a single, adaptable molecular framework [1–3,18]. Unlike highly specific single-target drugs, chalcones function as multi-target modulators, influencing interconnected signaling pathways that collectively drive disease progression [5,7,50]. This characteristic is particularly advantageous in multifactorial disorders such as chronic inflammation, metabolic syndrome, neurodegeneration, and cardiovascular disease, where pathway redundancy often limits therapeutic efficacy [3,16,17,45].

From a medicinal chemistry standpoint, chalcones represent a rare convergence of synthetic simplicity and biological complexity. Their α,β-unsaturated carbonyl system enables rational tuning of reactivity, selectivity, and target engagement, while their amenability to structural hybridization allows integration with other pharmacophores [18,49,50]. This has led to the development of chalcone-based hybrids with enhanced potency, selectivity, and pharmacokinetic profiles, reinforcing their value as lead compounds rather than merely bioactive curiosities [12,18,49].

Importantly, the therapeutic promise of chalcones is already supported by clinical precedents, with certain derivatives approved or utilized in vascular and gastrointestinal disorders [45,46]. These examples validate chalcones as translatable scaffolds, not just preclinical entities. Continued advances in drug-delivery strategies, prodrug approaches, and structure–activity relationship optimization are expected to overcome remaining limitations related to bioavailability and metabolic stability [18,40,50].

In summary, chalcones exemplify how small molecules can exert major biological and pharmacological impact. Their broad therapeutic scope, mechanistic diversity, and drug-likeness position them as valuable contributors to future drug discovery efforts [1,18,22,50]. Ongoing research aimed at refining their safety and efficacy is likely to further expand the clinical relevance of this versatile flavonoid subclass [18,24,50].

Conclusion :

From my perspective, chalcones clearly emerge as a class of small molecules with disproportionately large biological significance. Beyond their well-established antioxidant and anticancer roles, the breadth of their pharmacological profile—spanning anti-inflammatory, antimicrobial, antiviral, antidiabetic, neuroprotective, cardiovascular, immunomodulatory, and enzyme-inhibitory activities—highlights their status as truly multifunctional bioactive scaffolds. This versatility, combined with their relatively simple chemical framework, positions chalcones as attractive candidates for rational drug design and molecular hybridization strategies.

Chalcones may be regarded as a privileged subclass of flavonoids, in which modest structural modifications at the aromatic rings lead to pronounced changes in biological response. Their widespread natural occurrence in plants and dietary sources, coupled with remarkable structural diversity arising from aromatic substitution patterns [5][6], provides a strong foundation for both safety and efficacy. The consistently reported antioxidant potential and broad-spectrum anticancer activities [14][16], along with the advancement of several chalcone derivatives into clinical use or trials [24][22], further underscore their translational relevance.

In my view, the future of chalcone-based therapeutics lies in systematic structure–activity relationship optimization, precise molecular target identification, and pharmacokinetic refinement. Continued integration of medicinal chemistry, computational modeling, and biological validation is expected to accelerate the development of chalcone-derived agents with improved selectivity and clinical applicability. Overall, chalcones remain a highly promising molecular framework in medicinal chemistry, offering significant opportunities for the development of novel therapeutic agents against cancer, inflammatory disorders, metabolic diseases, and beyond.

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