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Mini-Review

Recent Advances in Chalcone Derivatives as Promising Antimicrobial Agents: A Mini Review

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Abstract

The rapid emergence of antimicrobial resistance (AMR) has created an urgent need for the development of novel antimicrobial agents with improved efficacy and reduced susceptibility to resistance. Among various bioactive scaffolds, chalcone derivatives have attracted considerable attention because of their structural diversity, synthetic accessibility, and broad-spectrum antimicrobial properties. This mini review summarizes recent advances in the biosynthesis and synthetic approaches of chalcone derivatives, highlighting their applications as promising antimicrobial agents. In addition, recent findings on the antimicrobial activities of chalcone derivatives against Gram-positive bacteria, Gram-negative bacteria, mycobacteria, and pathogenic fungi are discussed, with particular emphasis on structure–activity relationships that govern their biological performance. The review further describes the diverse mechanisms underlying their antimicrobial activity, including membrane disruption, inhibition of essential bacterial enzymes, interference with nucleic acid and protein synthesis, suppression of biofilm formation, and attenuation of bacterial virulence. Collectively, these complementary mechanisms contribute to the broad-spectrum antimicrobial activity of chalcone derivatives and provide a promising strategy for addressing antimicrobial resistance. Although substantial progress has been achieved, further studies focusing on rational structural optimization, comprehensive biological evaluation, pharmacokinetic characterization, and in vivo validation are required to facilitate the translation of chalcone derivatives into clinically relevant antimicrobial agents.

Keywords: Chalcone, Antimicrobial, Synthetic, Antibacterial, Antifungal

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1 Introduction

The rapid global emergence of antimicrobial resistance has become a major public health concern, creating an urgent demand for antimicrobial agents with alternative molecular structures and mechanisms of action that differ from conventional antibiotics such as β-lactams, quinolones, and glycopeptides[1], [2], [3]. In particular, the increasing prevalence of multidrug-resistant (MDR) Gram-positive and Gram-negative pathogens has severely compromised the effectiveness of last-line therapeutic interventions and contributed substantially to morbidity, mortality, and economic burden worldwide[1], [2], [4]. These pathogens utilize diverse resistance mechanisms, including enzymatic antibiotic inactivation, efflux pump activity, target-site modification, biofilm formation, and membrane-associated permeability barriers[4], [5]. Consequently, considerable research efforts have focused on identifying compounds capable not only of eliminating bacterial pathogens but also of overcoming antimicrobial resistance mechanisms. Among the various molecular frameworks being studied for the development of antimicrobial drugs, chalcones have attracted considerable attention due to their structural simplicity, ease of synthesis, and broad-spectrum biological activity[5], [6], [7].

Chalcones are aromatic ketones characterized by a conjugated 1,3-diphenyl-2-propen-1-one framework containing an α,β-unsaturated carbonyl moiety (Figure 1). This open-chain enone structure provides remarkable conformational and electronic flexibility, allowing extensive structural modification and functionalization[8]. Moreover, chalcones can be readily synthesized through straightforward and efficient synthetic approaches, particularly Claisen–Schmidt condensation, enabling the rapid generation of structurally diverse derivatives and hybrid molecules[6], [8], [9]. The incorporation of various pharmacophores, including heterocycles, thiazoles, pyrans, and prenylated substituents, has further expanded their pharmacological potential and antibacterial spectrum[7].

Both natural and synthetic chalcone derivatives have demonstrated broad-spectrum antimicrobial activities against bacteria, fungi, protozoa, and viruses[5], [10], [11]. Recent studies have increasingly focused on the rational design of chalcone-based antibacterial agents with enhanced potency and selectivity Structure–activity relationship (SAR) investigations have revealed that the introduction of electron-withdrawing substituents, such as halogens and nitro groups, as well as specific hydroxylation patterns, often enhances antibacterial activity[5], [12]. In addition, chalcones exhibit multitarget antibacterial mechanisms by inhibiting essential bacterial enzymes and processes, including DNA gyrase, MurA, penicillin-binding proteins, efflux pumps, membrane integrity, and biofilm formation[13], [14], [15]. Overall, these properties highlight chalcones as versatile and attractive scaffolds for the development of next-generation antibacterial agents and antimicrobial resistance modulators.

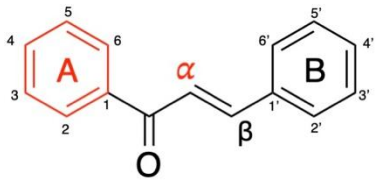

Figure 1. Structure Chalcone

Although numerous studies have highlighted the antimicrobial potential of chalcone derivatives, a comprehensive and systematic discussion integrating their synthetic strategies, structural diversification, and antimicrobial mechanisms remains limited. Previous reports have primarily focused on the general biological activities of chalcones, while recent advances in rational molecular design, hybrid scaffold development, and structure–activity relationship (SAR) optimization for antimicrobial applications have not been extensively summarized. In addition, the increasing recognition of chalcone derivatives as multitarget antimicrobial scaffolds with the potential to address antimicrobial resistance further highlights the need for an updated and focused review in this field. Therefore, this mini review summarizes recent advances in the biosynthesis, synthetic strategies, and antimicrobial activities of chalcone derivatives, with

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particular emphasis on the relationship between structural modification and biological activity. The review further discusses the multitarget mechanisms underlying their antimicrobial effects, including membrane disruption, inhibition of essential bacterial enzymes, interference with nucleic acid and protein synthesis, suppression of biofilm formation, and attenuation of bacterial virulence. Finally, current challenges and future perspectives are highlighted to provide insights into the rational development of next-generation chalcone-based antimicrobial agents.

2 Method

This mini review was conducted through a literature search using Google Scholar, PubMed, ScienceDirect, and Scopus databases. Articles published in English between 2014 and 2026 were retrieved using the keywords chalcone, chalcone derivatives, antimicrobial activity, antibacterial, antifungal, and synthesis. Original research articles and review papers relevant to the synthesis and antimicrobial activities of chalcone derivatives were included, while duplicate publications, conference abstracts, non-English articles, and studies unrelated to the scope of this review were excluded. The selected literature was analysed to summarize recent advances in the synthesis and antimicrobial potential of chalcone derivatives.

3 Result and Discussion

3.1 Biosynthesis Chalcones

Chalcones are early and important intermediates in the flavonoid biosynthetic pathway, originating from the general phenylpropanoid pathways in plants. Their biosynthesis starts with the amino acid phenylalanine, which is transformed through several steps into *p*-coumaroyl-CoA[16]. Phenylalanine is deaminated by phenylalanine ammonia-lyase, converted to *p*-coumaric acid through hydroxylation, and finally activated to *p*-coumaroyl-CoA by CoA ligase. A crucial stage in this biosynthetic route is mediated by chalcone synthase (CHS), a plant type III polyketide synthase recognized as the key regulatory enzyme in flavonoid biosynthesis. Initially, CHS binds a molecule of *p*-coumaroyl-CoA to the catalytic cysteine residue located within its active site, followed by the stepwise addition of three malonyl-CoA units [17], [18]. These successive condensations form a tetraketide intermediate, which then undergoes Claisen-type cyclization to yield naringenin chalcone (2′,4,4′,6′-tetrahydroxychalcone) (Scheme 1)[19], [20].

Naringenin chalcone is rapidly isomerized by chalcone isomerase (CHI) to form the flavanone naringenin, a central intermediate in the biosynthesis of diverse flavonoid subclasses, including flavonols, anthocyanins, and isoflavonoids. Despite the relatively broad substrate specificity of chalcone synthase (CHS), which may lead to the formation of side products such as *p*-coumaroyltriacetic acid lactone[19]. Chalcone isomerase-like proteins (CHILs) interact with CHS to facilitate chalcone production, minimize byproduct formation, and improve metabolic flux within the flavonoid biosynthetic pathway[19], [21].

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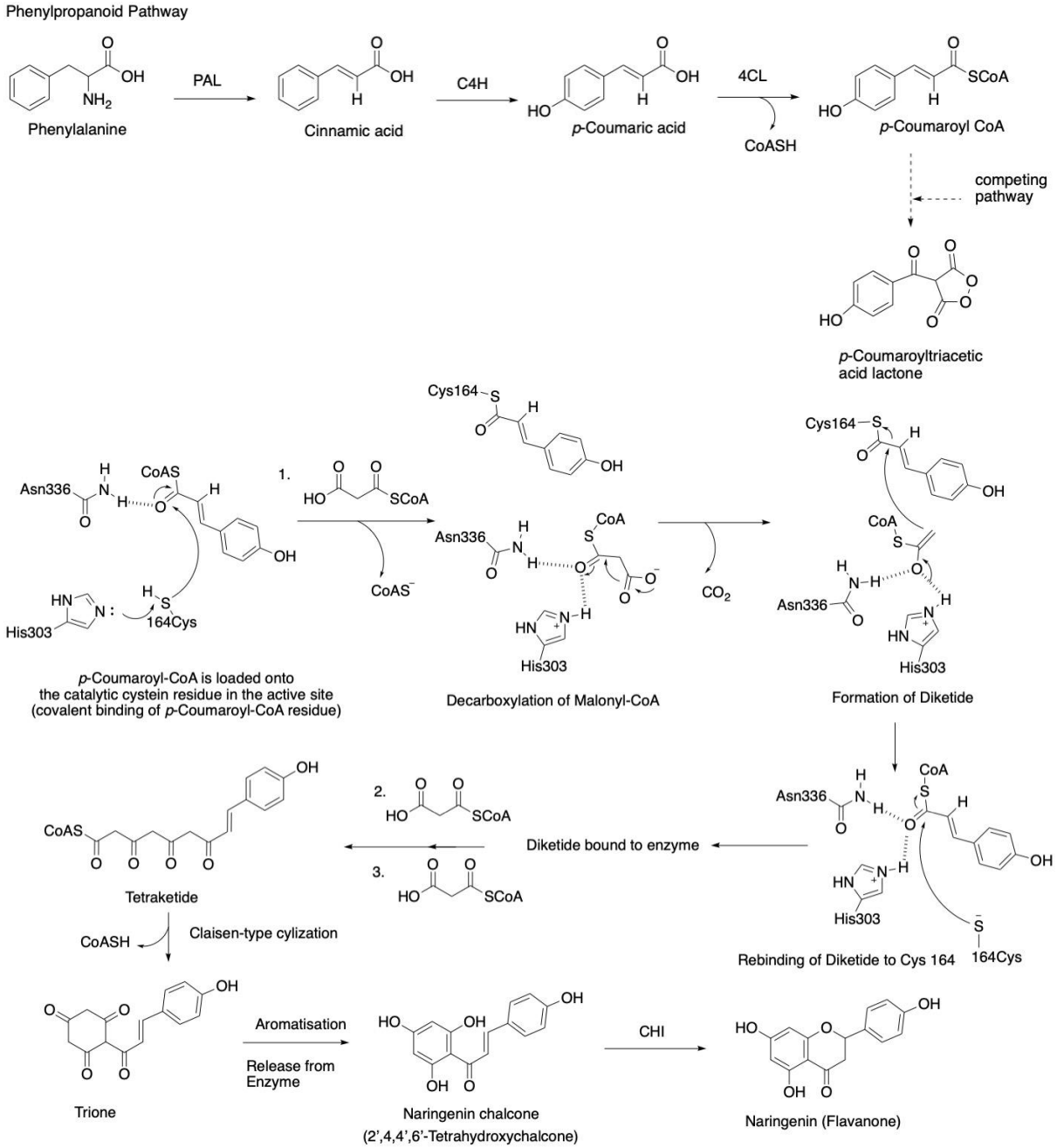

Scheme 1. Biosynthesis pathway and mechanism of chalcone synthase[19], [20].

3.2 Recent Advance in Synthesis Chalcone

A variety of synthetic methodologies have been reported for the preparation of chalcone derivatives, highlighting the synthetic flexibility of this scaffold for medicinal and pharmaceutical applications. Among the available approaches, condensation-based strategies are the most widely utilized, particularly the acid- or base-catalysed reaction between aromatic aldehydes and ketones[22]. The Claisen–Schmidt condensation is considered the conventional and most established method owing to its straightforward procedure, mild reaction conditions, and ability to afford chalcone derivatives in relatively high yields [5], [6], [23]. In addition to this classical approach, several alternative reaction pathways have been explored to facilitate structural diversification and improve synthetic efficiency. These methods include transition metal-catalysed cross-coupling reactions such as Suzuki and Heck coupling, Wittig reactions, Friedel–Crafts acylation employing cinnamoyl chloride, and photochemical approaches including the Photo-Fries rearrangement of phenyl cinnamates [11], [24], [25]. Collectively,

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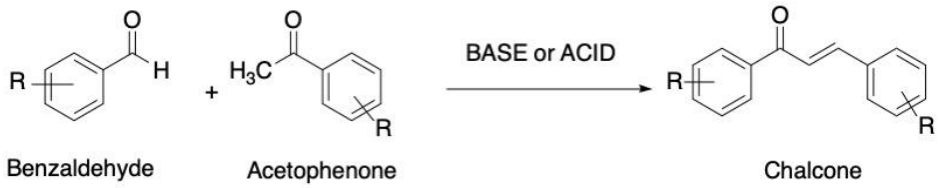
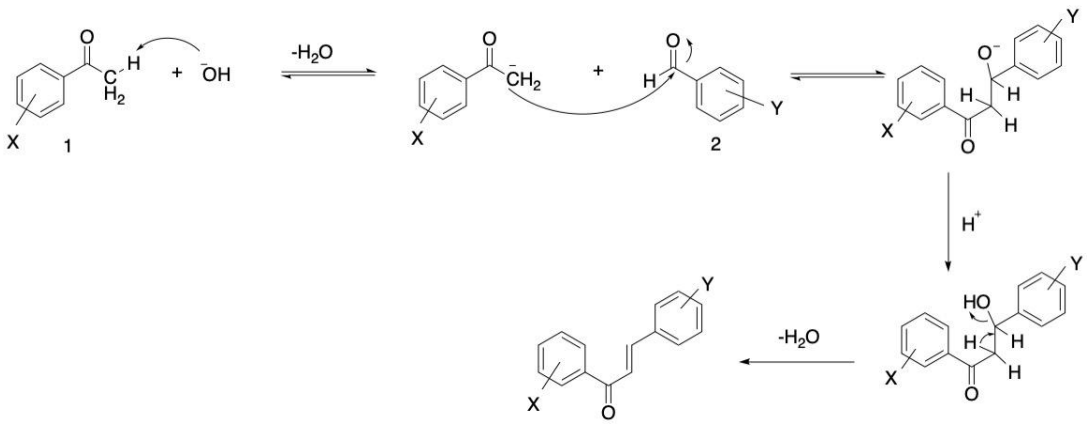
these synthetic routes provide versatile platforms for the development of structurally diverse chalcone analogues with potential biological and pharmacological activities.

Claisen–Schmidt condensation remains the most widely employed route for constructing the chalcone scaffold. It typically involves the reaction of substituted or unsubstituted benzaldehydes with acetophenone derivatives under acidic or basic catalytic conditions (Scheme 2)[23]. Classical protocols are predominantly base-catalysed, with NaOH and KOH being the most commonly used catalysts. However, other inorganic bases such as LiOH and $Ba(OH)_2$, organic bases including piperidine and pyridine, and acidic catalysts such as HCl and $AlCl_3$ have also been reported[26]. These catalysts promote the formation of α,β-unsaturated ketones through aldol condensation followed by dehydration, providing direct access to structurally diverse chalcone derivatives (Scheme 3)[8]. The simplicity of this method, together with the commercial availability of aromatic aldehydes and ketones, makes Claisen–Schmidt condensation particularly suitable for the rapid generation of chalcone libraries for biological evaluation.



Scheme 2. Claisen Schmidt Condensation[23].

Despite its broad applicability, classical acid- or base-catalysed Claisen–Schmidt condensation may suffer from moderate yields, prolonged reaction times, the use of organic solvents, and limited catalyst recovery, depending on the electronic and steric properties of the starting materials. To overcome these limitations, recent methodological developments have focused on improving both the efficiency and sustainability of this transformation. Recyclable SO_3H-functionalized ionic liquids, micellar-mediated systems, solvent-free grinding, microwave-assisted protocols, and heterogeneous catalysts such as MgO and activated biochar have been introduced as greener alternatives to conventional conditions[5], [6], [8], [27], [28], [29], [30], [31]. These strategies offer several advantages, including improved yields, reduced solvent consumption, shorter reaction times, and catalyst reusability. Therefore, Claisen–Schmidt condensation continues to serve not only as a reliable method for chalcone synthesis but also as an adaptable platform for developing environmentally benign routes toward antimicrobial and other bioactive chalcone derivatives.



Scheme 3. Proposed Mechanism of Claisen Schmidt Condensation[8].

In addition, Palladium-catalysed cross-coupling reactions have been explored as alternative strategies for the synthesis and structural diversification of chalcone derivatives, particularly for accessing highly substituted frameworks. da Costa et al. (2018) reported a sequential Heck/Suzuki strategy in

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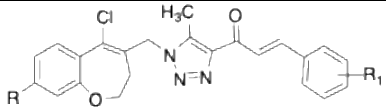
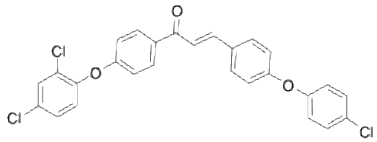
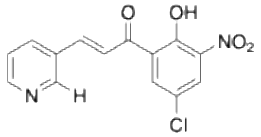
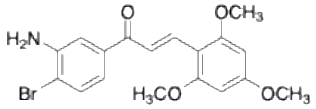
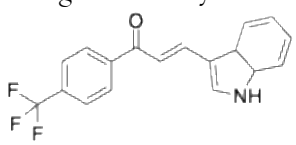
which β-arylated chalcones were converted into α,β-diarylchalcones through bromination followed by Suzuki cross-coupling, affording the products in 60–99% yield over two steps[32]. Similarly, Otte et al. (2024) applied Pd-catalysed Heck-type coupling of arenes diazonium salts with 8-allylcoumarins or allyl-substituted flavonoids, followed by DDQ-mediated allylic oxidation, to generate coumarin– and flavonoid–chalcone hybrids with high regioselectivity[33]. In addition, Vieira et al. (2012) developed a greener Suzuki coupling protocol for biphenyl chalcone and coumarin derivatives using palladium acetate in PEG-400 under microwave irradiation, providing good to excellent yields, short reaction times, and broad functional group tolerance[34]. Overall, these studies highlight the utility of palladium-catalysed coupling reactions for constructing structurally diverse chalcone-based scaffolds beyond conventional Claisen–Schmidt condensation. This work highlights the potential of Suzuki coupling for the structural diversification of chalcone scaffolds.

3.3 Antimicrobial Activities of Chalcone Derivatives

Chalcone derivatives have been widely studied as broad-spectrum antimicrobial agents against Gram-positive bacteria, Gram-negative bacteria, and pathogenic fungi [35], [36]. Their antimicrobial activity strongly influenced by structure–activity relationships (SAR), particularly the nature and position of substituents on the two aromatic rings[37], [38]. Recent studies have shown that the incorporation of hydroxyl, methoxy, halogen, and heterocyclic moieties can enhance antimicrobial potency through various mechanism, including membrane permeabilization or disruption, inhibition of essential microbial enzymes, interference with nucleic-acid–related processes, and biofilm suppression[10], [12], [39]. To highlight the recent development in this field, representative studies reporting the antimicrobial activities of chalcone derivatives against various pathogenic microorganisms are summarized in Table 1.

Table 1. Recent studies on the antimicrobial activities of chalcone derivatives

Chalcone derivatives	Structural modification	Microorganism	Antimicrobial activity	References
 Benzoxepine-1,2,3-triazolyl-chalcone	R: CH_3; OCH_3 R_1: F; OH; OCH_3; Cl; NO_2; CH_3	*S. aureus* *F. oxysporum* *M. tuberculosis* $H_{37}Rv$	1.34-4.32 1.36-2.05 0.90-2.05 MIC (μg/mL)	[40]
 Chalcone-diphenyl ether	Diphenyl ether	*S. aureus* *E. coli,* *Salmonella, and* *P. aeruginosa*	12.50 16.67 MIC (μg/mL)	[41]
 Thiophen-chalcone	NO_2; Cl	*B. cereus* *S. sonnei*	22.3 ± 0.6 mm 43.3 ± 0.6 mm	[42]
 Halogen-methoxy chalcone	NH_2; Br; OCH_3	*S. aureus* *E. coli* *P. aeruginosa*	30 mm 33 mm 34 mm	[8]
 Trifluoromethyl-chalcone	Indole-ring; Trifluoromethyl (CF_3)	*S. aureus* *B. subtilis* *E. coli* *P. vulgaris* *C. albican*	16.18 32.04 7.93 7.93 15.87 MIC	[43]

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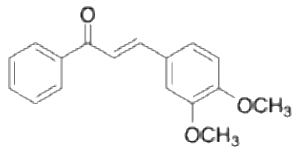
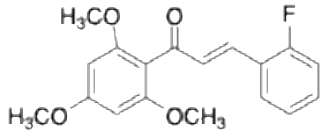
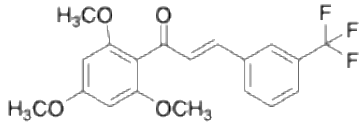
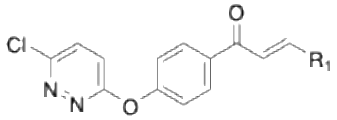
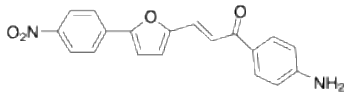
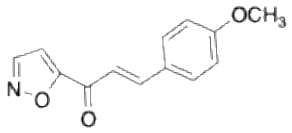
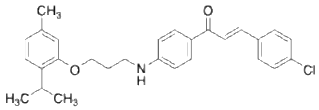
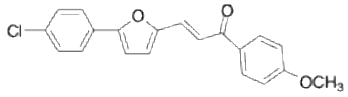
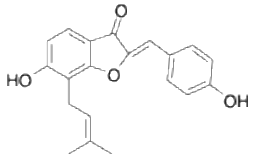
			(μg/mL)	
 Methoxy-chalcone	OCH_3	*E. coli* *S. typhi* *S. aureus* *B. subtilis* *A. niger*	700 700 400 400 900 MIC (μg/mL)	[44]
 Fluoro-substituted chalcone	OCH_3; F	*M. tuberculosis* $H_{37}Rv$	IC_{50} < 16.760 (μg/mL)	[45]
 Trifluoromethyl-chalcone	OCH_3; CF_3	*S. aureus*	7.81 MIC (μg/mL)	[46]
 Pyridazine-chalcone	R_1:4-CH_3-C_6H_4	*R. solani*	EC_{50} 18.10 (μg/mL)	[47]
 Furan-chalcone	4-aminophenyl	*S. aureus* *C. albicans*	12.5 6.25 MIC (μg/mL)	[48]
 Isoxazole-chalcone	Isoxazole; OCH_3	*S. aureus* *P. aeruginosa* *A. niger* *C. tropicalis*	4 8 8 8 MIC (μg/mL)	[49]
 Thymol-chalcone	Thymol *o*-Cl	*E. coli* *S. aureus*	13.5 12.16 MIC (μg/mL)	[50]
 Furan-chalcone	Furan; Cl; OCH_3	*E. coli* *S. epidermis* *C. albicans*	12 10 14 mm	[51]
 Prenylated isobavachalcone derivative	Prenyl; OH	*S. aureus* *E. coli* *P. aeruginosa* *MRSA*	3.22 7.41 7.74 1.93 MIC (μg/mL)	[52]

As shown in Table 1, recent studies demonstrate that antimicrobial activity is markedly affected by both the type of substituent and scaffold modification. Electron-donating groups, such as methoxy and

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hydroxyl substituents, as well as electron-withdrawing groups including halogens, nitro, and trifluoromethyl moieties, were frequently associated with enhanced antimicrobial activity [12], [48], [53]. These structural modifications are thought to improve lipophilicity, electronic properties, and intermolecular interactions with microbial targets, thereby increasing biological potency [5], [53], [54].

Another notable trend is the increasing development of hybrid chalcone derivatives, in which the chalcone scaffold is combined with pharmacologically active heterocyclic moieties such as triazole, thiophene, furan, isoxazole, and pyridazine[47], [48]. This molecular hybridization strategy has been widely employed to broaden the antimicrobial spectrum and enhance biological activity by integrating multiple pharmacophoric features into a single molecule.

Collectively, the studies summarized in Table 1 suggest that rational structural modification is a key determinant of the antimicrobial activity of chalcone derivatives. Optimization of both substituent patterns and scaffold architecture has consistently improved antimicrobial potency, supporting the continued development of chalcone-based molecules as promising candidates for combating microbial infections, including drug-resistant pathogens.

3.4 Proposed Mechanisms Underlying the Antimicrobial Activity of Chalcone Derivatives

The antimicrobial activity of chalcone derivatives is mediated through multiple mechanisms of action, making these compounds attractive candidates for overcoming microbial resistance. Unlike conventional antimicrobial agents that often target a single biological pathway, chalcone derivatives exhibit multitarget effects by interacting with microbial membranes, essential enzymes, nucleic acid synthesis, and biofilm formation (Figure 2) [55], [56], [57], [58], [59]. The α,β-unsaturated carbonyl moiety of chalcones, together with appropriate structural modifications, plays a crucial role in facilitating these interactions and contributes to their broad-spectrum antimicrobial activity.

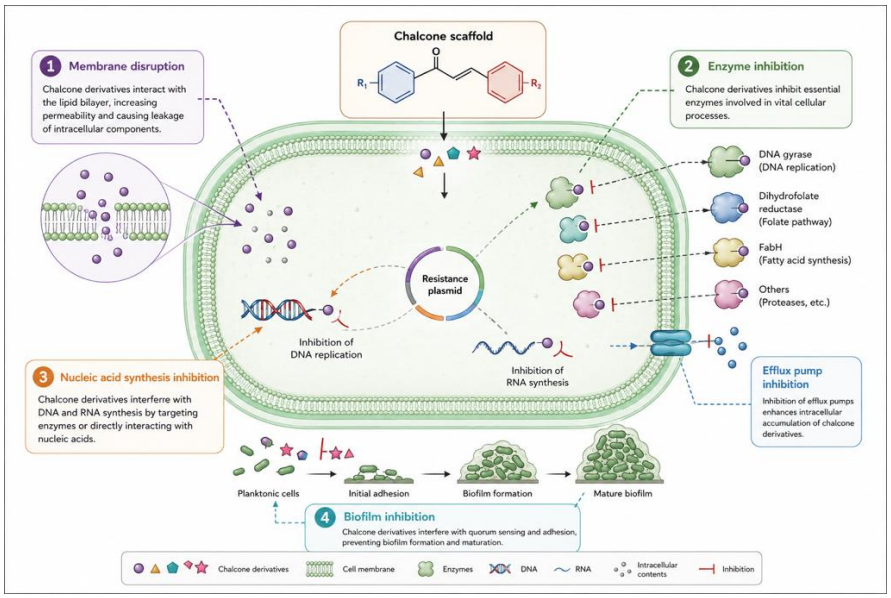

Figure 2. Schematic representation of the proposed mechanisms of antimicrobial action of chalcone derivatives [38].

3.4.1 Membrane Disruption

One of the primary antimicrobial mechanisms of chalcone derivatives involves disruption of microbial cell membrane integrity. Many antimicrobial chalcones increase membrane permeability and cause leakage of intracellular contents such as ions, nucleic acids, proteins, or cytoplasmic material in bacteria and yeasts ([37], [60], [61], [62]. This membrane targeting activity is strongly influenced by chemical features such as amphiphilicity, lipophilicity, phenolic substitution, cationic design, and

prenylation, which enhance interaction with the phospholipid bilayer and improve antimicrobial selectivity [63]. The mechanistic step, chalcones first encounter the cell membrane as a barrier, and active compounds often make it more permeable. In Gram-positive bacteria, phenolic chalcones caused detectable ion leakage at concentrations below MIC, and that leakage preceded membrane deformation and cell death, supporting membrane permeabilization as an early antibacterial event [61]. More potent membrane-active designs go beyond ion leakage. Amphiphilic chalcone derivative destroyed transmembrane potential, increased permeability, and caused leakage of DNA and proteins together with intracellular ROS generation, ending in bacterial death [56]. Isobavachalcone disrupted bacterial membranes by PI/SYTO9 staining, while other work linked it to phospholipid binding, proton motive force dissipation, and inhibition of macromolecular biosynthesis [63].

3.4.2 Enzyme Inhibition

Chalcone derivatives exert antibacterial activity by targeting multiple essential bacterial proteins involved in cell survival and proliferation. Several studies have reported their ability to inhibit DNA replication enzymes, including DNA gyrase and GyrB, as well as enzymes responsible for cell wall biosynthesis, such as MurA and glucosamine-6-phosphate synthase (GlcN-6-P synthase). In addition, chalcone derivatives have been shown to interfere with bacterial cell division through inhibition of the FtsZ protein [15], [38]. This multitarget mode of action has been consistently highlighted as one of the key advantages of chalcone derivatives, particularly for overcoming antimicrobial resistance. Zhang et al. 2017 demonstrated that chalcone exerts anti-virulence activity by targeting Sortase A (SrtA) in *Staphylococcus aureus*. Binding of chalcone to the catalytic pocket of enzyme prevented substrate recognition, resulting in impaired SrtA-mediated functions, reduced biofilm formation, and attenuated bacterial invasion. The inhibitory activity against SrtA was reported with an IC_{50} value of 53.15 μM[64]. While DNA gyrase and FtsZ, have been recognized as important antibacterial targets, current evidence supporting MurA and GlcN-6-P synthase remains largely based on molecular docking analyses and antimicrobial phenotypic assays rather than direct enzymatic inhibition studies. Therefore, additional biochemical validation is still required to confirm these proposed mechanisms [10], [38], [51]. Another recently identified mechanism involves inhibition of bacterial protein synthesis. Ahsan et al. (2025) reported that 4-hydroxyderricin suppresses protein biosynthesis by covalently binding to seryl-tRNA synthetase in *Staphylococcus aureus*, revealing a novel antibacterial target for chalcone derivatives[5]. Together with their ability to modulate multiple bacterial pathways, these findings further support the potential of chalcone derivatives for combating antimicrobial resistance[13], [38].

3.4.3 Inhibition of nucleic acid synthesis

Chalcone derivatives inhibit nucleic acid synthesis primarily by targeting bacterial DNA replication enzymes, particularly DNA gyrase and topoisomerase IV, which play essential roles in DNA supercoiling, replication, and chromosome segregation [38]. Molecular docking studies consistently demonstrate favourable interactions between chalcone derivatives and the active sites of these enzymes, while experimental evidence has shown that certain chalcone-related compounds inhibit the gyrases of *Escherichia coli* and *Staphylococcus aureus*, block DNA relaxation, and consequently suppress bacterial growth [65], [66]. These findings indicate that inhibition of bacterial topoisomerases represents one of the best-supported mechanisms underlying the antimicrobial activity of chalcone derivatives.

In addition to enzyme inhibition, several chalcone derivatives have been reported to interact directly with DNA through intercalation or groove binding, potentially disrupting nucleic acid function [9], [67], [68]. However, most of these observations were obtained using model DNA systems rather than microbial replication assays, and therefore provide indirect evidence of antimicrobial activity. Another proposed mechanism involves inhibition of dihydropteroate synthase (DHPS), which disrupts folate biosynthesis and limits the production of DNA and RNA precursors [69]. Together, these findings suggest that nucleic acid inhibition contributes to the multitarget antimicrobial mechanism of chalcone derivatives, although further experimental validation is still required for several proposed targets.

3.4.4 Inhibition of Biofilm Formation and Bacterial Virulence

Chalcones are small aromatic compounds that can both kill microbes and specifically disrupt how bacteria and fungi form and maintain biofilms-protective communities that strongly resist antibiotics. Biofilm formation is a major contributor to persistent infections and antimicrobial resistance because the extracellular matrix protects microbial cells from antibiotics and host immune responses. Chalcone derivatives exhibit potent antibiofilm activity against a broad spectrum of Gram-positive and Gram-negative bacteria, as well as Candida species, with several compounds reducing biofilm biomass or viability by more than 50–95% [70], [71], [72]. Depending on their structural characteristics, chalcone derivatives may function either as biofilm modulators, preventing biofilm establishment, or as biofilm-disrupting agents capable of eradicating mature biofilms[44], [56], [73], [74].

Mechanistically, chalcone derivatives inhibit biofilm development by targeting multiple stages of the biofilm life cycle. These compounds suppress bacterial adhesion through inhibition of adhesion-associated proteins, including OmpA and Sortase A, reduce extracellular polysaccharide production by inhibiting enzymes such as glucosyltransferase C (GtfC) and neuraminidase, and interfere with intracellular regulatory pathways involving c-di-GMP, quorum sensing, and efflux pumps. Together, these mechanisms impair biofilm establishment, maturation, and persistence, while membrane disruption further contributes to the eradication of established biofilms[57], [70], [72], [73], [75], [76]. Overall, the ability of chalcone derivatives to target multiple stages of biofilm development highlights their potential for combating biofilm-associated and antimicrobial-resistant infections.

Overall, the antimicrobial activity of chalcone derivatives is mediated by multiple complementary mechanisms rather than a single molecular target. Their multitarget mode of action underpins broad-spectrum antimicrobial activity and may reduce the likelihood of resistance development by simultaneously disrupting multiple bacterial pathways. Continued rational structural optimization, together with comprehensive biological validation, is expected to further improve the therapeutic potential of chalcone-based antimicrobial agents.

3.5 Future Perspective and Challenges

Despite the remarkable antimicrobial potential of chalcone derivatives, several challenges remain before these compounds can be translated into clinically useful antimicrobial agents. Most published studies are still limited to in vitro antimicrobial evaluation and computational analyses, whereas comprehensive in vivo, pharmacokinetic, and toxicity studies remain relatively scarce. In addition, several proposed molecular targets have been supported primarily by molecular docking, emphasizing the need for further biochemical and mechanistic validation [11], [77].

Future research should focus on rational structural optimization guided by structure–activity relationship (SAR) studies to improve antimicrobial potency, selectivity, and pharmacokinetic properties. Increasing attention has also been directed toward molecular hybridization, in which the chalcone scaffold is combined with other bioactive pharmacophores to achieve multitarget activity and overcome antimicrobial resistance [77]. Furthermore, advanced drug delivery systems, synergistic combination therapy with conventional antibiotics, and well-designed in vivo studies are expected to accelerate the clinical translation of chalcone-based antimicrobial agents.

Overall, the accumulated evidence indicates that the chalcone scaffold remains a versatile platform for antimicrobial drug discovery. Advances in synthetic strategies have enabled extensive structural diversification, while SAR studies have identified key substituents associated with enhanced antimicrobial activity. Together with their multitarget mechanisms of action, these findings provide a strong foundation for the rational design of next-generation chalcone derivatives. Nevertheless, successful clinical translation will require further optimization of pharmacokinetic properties, comprehensive biological validation, and robust in vivo investigations.

4 Conclusion

Chalcone derivatives have emerged as a versatile class of antimicrobial compounds owing to their structural diversity, synthetic accessibility, and broad-spectrum activity against Gram-positive bacteria,

Gram-negative bacteria, mycobacteria, and pathogenic fungi. Recent advances in synthetic strategies have enabled the development of structurally diverse chalcone derivatives with improved antimicrobial potency and selectivity, while structure–activity relationship studies have highlighted the importance of rational structural modification and molecular hybridization in enhancing biological activity. Current evidence further demonstrates that chalcone derivatives exert antimicrobial effects through multiple complementary mechanisms, including membrane disruption, inhibition of essential bacterial enzymes, interference with nucleic acid and protein synthesis, suppression of biofilm formation, and attenuation of bacterial virulence. This multitarget mode of action contributes to their broad-spectrum antimicrobial activity and may reduce the likelihood of resistance development.

Despite these promising findings, the majority of available studies remain limited to in vitro investigations and computational analyses, with relatively few reports providing comprehensive in vivo, pharmacokinetic, toxicity, and mechanistic validation. Therefore, future research should focus on rational structural optimization guided by structure–activity relationship studies, together with comprehensive biological evaluation and translational research to facilitate the development of clinically relevant antimicrobial agents. Overall, the accumulated evidence supports chalcone derivatives as valuable scaffolds for the rational design of next-generation antimicrobial agents capable of addressing the growing challenge of antimicrobial resistance.

5 Declarations

5.1 Acknowledgements

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5.2 Author contributions

Conceptualization, H.I.F.; literature search, H.I.F., N.M.Z., D.R., and S.A.R.; writing—original draft preparation, H.I.F.; writing—review and editing, H.I.F., N.M.Z., D.R., and S.A.R.; visualization, H.I.F. All authors have read and agreed to the published version of the manuscript.

5.3 Ethics

Ethical approval was not required for this study because it is based exclusively on published literature and does not involve human participants, animals, or primary experimental data.

5.4 Conflict of Interest

The authors declare no conflict of interest.

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