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BIOLOGICAL ACTIVITY OF CHALCONES AS CARBONYL COMPOUND DERIVATIVES

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Abstract. Microbial infections remain serious diseases and their frequency continues to increase. It is therefore essential to find effective therapeutic agents with the least side effects. Chalcones, as derivatives of carbonyl compounds, have shown very interesting antimicrobial and pharmaceutical activities, because of their synthetic chemical structures.

Keywords: *Chalcones, new chemical synthesis, antimicrobial and pharmaceutical activities.*

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1. Introduction

The excessive and inappropriate use of antibiotics has led to the selection and expansion of multi-resistant microorganisms, and to a dramatic increase in the rate of treatment failure. Thus, bacteria have evolved many different resistance mechanisms such as: (1) modification of antibiotic binding site; (2) production of enzymes which can degrade or modify the structure of antibiotic; (3) mutations in genes encoding transporter proteins leading to disruptions in cell wall permeability; (4) active pumping of antibiotic molecules (Miklasińska-Majdanik *et al*., 2018). Therefore, the search for new active, effective antimicrobial compounds with fewer side effects remains an emergency to fight against these multi-resistant pathogens. It is in this context that chalcones, derivatives of carbonyl compounds (aldehydes and ketones) have been chosen (Xu *et al*., 2019). Many studies have shown different therapeutic properties of chalcone derivatives. Chalcones possess a wide range of activities due to the presence of α,β-unsaturated group in their structure (Chavan *et al*., 2016; Deepa & Jain, 2022). A detailed evaluation of chalcones mechanism action and their derivatives is important, for synthesis of new chemical molecules for pharmacological purposes. This review summarize the potential health benefits of chalcone derivatives, particularly biological activity, for the development of new agents that could be a useful reference for pharmaceutical scientists (Dhaliwal *et al*., 2022).

2. Definition and chemical synthesis

Chalcone is a unique, α, β-unsaturated carbonyl with biologically active properties and is a precursor of various heterocyclic compounds. Chalcones are considered as

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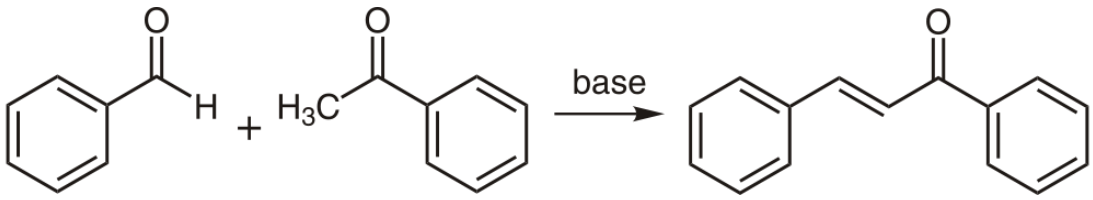
mediators for various synthesis of therapeutic compounds. For decades, chalcones have attracted special attentions among researchers due to their pharmaceutical properties and easy preparation (Farooq & Ngaini, 2019).

Chalcones are generally prepared by condensation reactions via base or acid catalysis. Although chalcones are a type of easily synthesized α,β-unsaturated ketone, an increasing number of new techniques and procedures have recently been reported due to their interesting biological activities and the development of various catalysts or reaction conditions (Zhuang *et al*., 2017). Among different methods, we have: Cross Aldol Condensation (Claisen-Schmidt), Meyer-Schuster Rearrangement, Deamination of Aziridine, Debromination of Vicinal Dibromides, Oxidation of Benzylic Alcohols, Wittig Reaction, Coupling Reactions, Dehydrogenation and Deoxygenation. However, the Claisen-Schmidt condensation remains the best known as it offers preparations of chalcones by reaction of acetophenone and benzaldehyde (Zhuang *et al*., 2017; Farooq & Ngaini, 2019).



Benzaldehyde **Acetophenone** **Chalcone**

Scheme 1. Claisen-Schmidt condensation [11].

3. Chalcones biological activities

Antibacterial activity

A series of chalcones were synthesized and evaluated for antibacterial. The results of antibacterial studies have shown that compounds N_1 and N_6 were active against *Staphylococcus aureus* and *Escherichia coli*. Compounds N_5 and N_9 were active against *Staphylococcus aureus* and P. putida. Compound N_2 has shown antibacterial activity against *Escherichia coli* only whereas compound N_8 was found to be active against *Staphylococcus aureus* only. Compounds N_1, N_5, N_6 and N_9 were further subjected to MIC_{50} value determination. The results have shown that only compound N_1 i.e. 3-(4-nitrophenyl)-1-phenyl prop-2-en-1-one emerged as the most active compound with MIC_{50} value of 471µg/ml against *Staphylococcus aureus* (Kumar *et al*., 2009).

Thirteen chalcones synthesized have shown variable antibacterial activity against *Staphylococcus aureus, Bacillus subtilis* and *Escherichia coli* (Kumbhar *et al*., 2014). Based on zone of inhibition, chalcones N_1, ($C_{16}H_{14}O_2$) **: (Z) -1- (2- hydroxy phenol) – 3 – *p* – tolyl prop – 2 – en - 1- one** and N_7, ($C_{15}H_{12}O_2$) **: (Z) -1- (2 – hydroxy phenyl) - 3- phenyl prop-2-en-1-one** have been shown to be effective against *Escherichia coli.* Compound N_{11}, ($C_{15}H_{11}NO_3$) **: (Z) -3- (3 – nitro phenyl) – 1 - phenyl prop-2-en-1-one** has been shown to be effective against *Staphylococcus aureus*. Chalcones N_4, ($C_{15}H_{11}ClO$) **: (Z) – 3 - (4 – chloro phenyl) -1- phenyl prop – 2 – en - 1- one**, N_8, ($C_{16}H_{14}O_3$) **: (Z) -1- (2 – hydroxy phenyl) – 3 - (4-methoxy phenyl) prop-2-en-1-one** and N_9, ($C_{16}H_{12}Cl_2O_3$) **: (Z) -1- (3, 5-dichloro-2- hydroxy phenyl) – 3 - (4-**

methoxyphenyl) prop-2-en-1-one have been shown to be effective against *Bacillus subtilis*. Compound N_9, showed the highest activity (17 mm) among all chalcones.

In a wide search program towards new and efficient antimicrobial agents, substituted chalcones have been synthesized. Compound **$C_{16}H_{13}IO_2$**, *3-(4-methoxy phenyl)-1-(4-iodophenyl) 2-propen-1-one* showed excellent activity against *Staphylococcus aureus* at both concentration i.e. 500 µg/ml and 1000 µg/ml. However, no activity was observed for compounds against *P. aeruginosa*, a Gram negative organism. It is widely known that Gram positive and negative organisms have significantly different membrane compositions and architecture, which would explain the selective activity of the present compounds against Gram positive *Staphylococcus aureus* (Choudhary & Juyal, 2011).

Antifungal activity

Ten chalcone derivatives were synthesized and screened biologically for antifungal activity. Infact, two compounds, *2‑benzylidene‑3,4‑dihydronaphthalen‑1(2H)‑one* and *2‑(4‑chlorobenzylidene)‑3,4‑dihydronaphthalen‑1 (2H)‑one* among the 10 compounds showed antifungal activity against *Microsporum gypseum*. The results so obtained were superior or comparable to ketoconazole. It was observed that none of compounds tested showed positive results for *Candida albicans* and *Aspergillus niger* (Deepa & Jain, 2022).

The antifungal activity of different synthetic hydroxychalcones was determined against *Candida* species. It was revealed that the presence of hydroxyl groups at C-2, C-4, and C-2' in chalcone was essential to inhibit *Candida* growth. Among chalcone derivatives examined, 2,4,2'-trihydroxy-5'-methylchalcone showed the most intensive anti-Candida activity, suggesting that it could be a potential therapeutic agent for candidosis (Dhaliwal et al., 2022; Tsuchiya *et al*., 1994).

Antimalarial activity

Twenty-seven novel chalcone derivatives were synthesized using Claisen-Schmidt condensation and their antimalarial activity against asexual blood stages of *Plasmodium falciparum* was determined. Antiplasmodial IC(50) (half-maximal inhibitory concentration) activity of a compound against malaria parasites in vitro provides a good first screen for identifying the antimalarial potential of the compound. The most active compound was 1-(4-benzimidazol-1-yl-phenyl)-3-(2, 4-dimethoxy-phenyl)-propen-1-one with IC (50) of 1.1 µg/mL. The presence of methoxy groups at position 2 and 4 in chalcone derivatives appeared to be favorable for antimalarial activity as compared to other methoxy-substituted chalcones (Awasthi *et al*., 2009).

Among the 27 novel chalcone derivatives synthesized, only one compound was found to be the most antimalarial active (Yadav *et al*., 2012). Chalcone derivatives administrated intraperitoneally to the *Plasmodium yoelii* infected mice model showed significant inhibition of these strains (Tomar *et al*., 2010).

Antiviral activity

Various studies have reported that different types of chalcones can act on important targets in diseases caused by viral infections (Elkhalifa *et al*., 2021; Malbari *et al*., 2018; Patil *et al*., 2019).

Anti-coronavirus

Two viral proteases of severe acute respiratory syndrome coronavirus (SARS-CoV), a chymotrypsin-like protease ($3CL^{pro}$) and a papain-like protease (PL^{pro}) are attractive targets for the development of anti-SARS drugs. In this study, nine alkylated chalcones (1–9) and four coumarins (10–13) were isolated from *Angelica keiskei*, and the inhibitory activities of these constituents against SARS-CoV proteases ($3CL^{pro}$ and PL^{pro}) were determined (cell-free/based). Of isolated alkylated chalcones, chalcone 6, containing the perhydroxyl group, exhibited the most potent $3CL^{pro}$ and PL^{pro} inhibitory activity with IC_{50} values of 11.4 and 1.2 μM. Our detailed protein-inhibitor mechanistic analysis of these species indicated that chalcones exhibited competitive inhibition characteristics to the SARS-CoV $3CL^{pro}$, whereas noncompetitive inhibition was observed with the SARS-CoV PL^{pro} (Park *et al*., 2016).

Anti HIV

A series of fourteen (A1 - A14) qunioline based chalcones were screened for reverse transcriptase inhibitors (RT) and found potentially active against RT. Bioassay, theoretical and dockings studies with RT (the enzyme required for reverse transcription of viral RNA) results showed that the type and positions of the substituents seemed to be critical for their inhibition against RT. The bromo and chloro substituted chalcone displayed high degree of inhibition against RT. The A4 and A6 showed high interaction with RT, contributing high free binding energy (ΔG -9.30 and -9.13kcal) and RT inhibition value (IC50 0.10μg/ml and 0.11μg/ml), (Hameed *et al*., 2016; Sharma *et al*., 2011).

Anti-hepatitis B

A bioassay-guided fractionation using different chromatographic techniques of the methanolic extract of D. cinnabari led to the isolation of two chalcone derivatives. Using a variety of spectroscopic techniques, including ^{1}H-, ^{13}C-, and 2D-NMR, these derivatives were identified as 2,4'-dihydroxy-4-methoxydihydrochalcone (compound **1**) and 2,4'-dihydroxy-4-methoxyhydrochalcone (compound **2**). Both compounds were isolated for the first time from the red resin (dragon's blood) of D. cinnabari. The compounds were first evaluated for cytotoxicity on HepG2.2.15 cells and 50% cytotoxicity concentration (CC50) values were determined. They were then evaluated for anti-HBV activity against HepG2.2.15 cells by assessing the suppression of HBsAg and HBeAg production in the culture supernatants and their half maximum inhibitory concentration (IC_{50}) and therapeutic index (TI) values were determined. Compounds **1** and **2** indicated inhibition of HBsAg production in a dose- and time-dependent manner with IC_{50} values of 20.56 and 6.36 μg/mL, respectively (Mothana *et al*., 2022).

Anti-inflammatory activity

Literature reported several chalcones and their derivative that have shown promise to inhibit cyclooxygenase (COX), (Araico *et al*., 2006; Bano *et al*., 2013; Farzaneh *et al*., 2018; Jantan *et al*., 2014; Nyandoro *et al*., 2012; Okuda-Tanino *et al*., 2017; Özdemir *et al*., 2015). In a study to assess the anti-inflammatory effect, new chalcone derivatives using carrageenan-induced hind paw edema model, the results showed that 5′-chloro-2′-hydroxy- 4′6′-dimethyl-3, 4, 5- trimethoxychalcone (1) exhibited the most potent anti-inflammatory activity with a 90% inhibition of edema (Bano *et al*., 2013).

Compounds N_1 to N_{10}, were also evaluated for anti-inflammatory activity in albino rats by Carrageenan induced hind paw edema method. Results obtained have shown that three compounds N_3, N_6 and N_{10} possess significant anti-inflammatory effects. Compound N_6, a chalcone of 4-Hydroxy benzaldehyde with acetophenone was found to be the most active compound and its effects are more potent than standard anti-inflammatory drug, Diclofenac Sodium. It has shown 50% inhibition of edema as compared to 42.30% of Diclofenac Sodium at 1H duration in the dose of 200 mg/kg. However the effect was diminished to 3.33% at 3H duration, indicating shorter duration of action. Compound N10, a chalcone of 4- dimethyl amino benzaldehyde with acetophenone have shown increase in % edema inhibition from 19.23% at 1H to 36.66% at 3H interval, indicating longer duration of action. Thus compounds N_6 and N_{10} could be explored further for development of a potent anti-inflammatory agent (Kumar *et al*., 2009).

Antidiabetic activity

Several synthetic chalcones have been reported in vitro to have potential inhibitory activity against α-glucosidase or α-amylase (Ansari *et al*., 2005; Attarde *et al.*, 2014; Bak *et al*., 2011; Cai *et al.*, 2017).

In Vivo, several authors have evaluated the anti-hyperglycemic activity of synthetic chalcones in streptozotocin-induced diabetic rats (Acharjee *et al*., 2018; Mahapatra *et al.*, 2017; Naidu, 2018; Najafian *et al*., 2010; Raju *et al*., 2018; Rawat *et al*., 2011; Satyanarayana *et al*., 2004; Sengupta *et al*., 2017; Shukla *et al.*, 2007; 2017; Tajammal *et al*., 2017). It was found that these compounds have a moderate to potential ability to reduce blood sugar.

4. Conclusion

This review summarize the recent antimicrobial and other biological activities of carbonyl compound derivatives with their action mode. We have shown different methods of chalcone derivatives synthesis and characterization. Chalcone derivatives potentially inhibit different targets pathway of microbial resistance. Those having a hydroxyl (OH) or nitric oxide (NO) group in their structure are more effective against *Escherichia coli*. Chalcones with an OH or NO or Br or Cl group in their structure are more effective against *Staphylococcus aureus*. Thus, biological properties of chalcone depend on the chemical molecules that are related to its structure.

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