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INSIGHTS INTO THE POTENTIAL PHARMACOLOGICAL PRACTICES OF CHALCONES: A SHORT REVIEW

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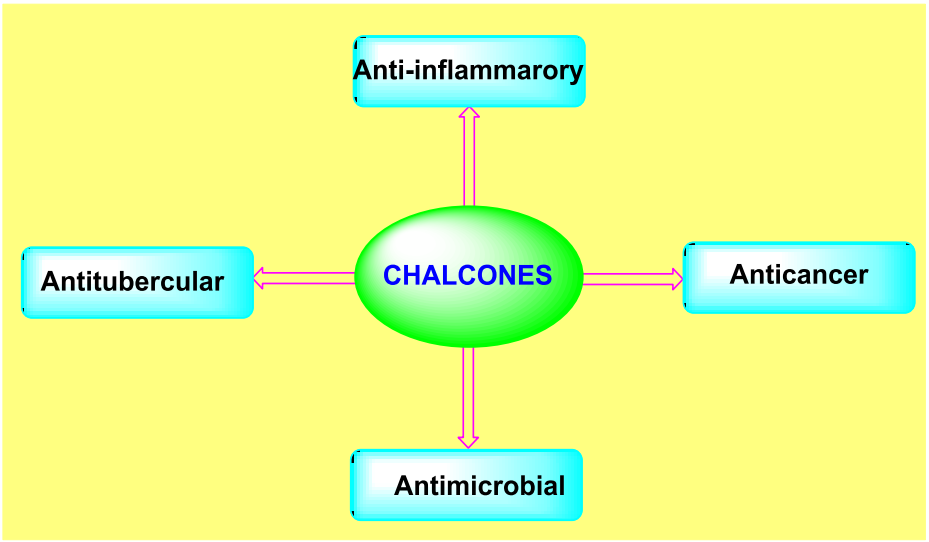
ABSTRACT

Chalcone is a unique class of organic compounds of great medicinal value since it contains the flavonoids' reactive enone moiety. Chalcone and its derivatives have medicinal properties due to the existence of an unsaturated carbonyl component. Anticancer, antibacterial, Antifungal, Antioxidant, anthelmintic, antiulcer, antiviral, insecticidal, antiprotozoal, anticancer, anti-inflammatory, antihypertensive, antidiabetic, etc, are the pharmacological activities shown by the chalcones. In the present review, antibacterial, antifungal, anticancer, anti-tubercular, and anti-inflammatory properties have been addressed.

KEYWORDS: Chalcone, Claisen-Schmidt, Green chemistry, antibacterial, antifungal, anticancer, anti-tubercular, and anti-inflammatory.

GRAPHICAL ABSTRACT



INTRODUCTION

Chalcone is a basically a 1,3-diphenyl-2-propen-1-one (**Figure1**) framework and are often considered as open-chain flavonoids.[1,2] Chalcones have a have a huge variety of biological functions.[3-6] The chalcone nucleus is one of the most widespread and well-known intermediates, appearing in a wide variety of flavonoids and medicinal agents. Chalcones have a wide spectrum of biological properties, owing to their small structures and Michael acceptor attributes, which encourage them to accommodate a wide range of biomolecules and react or interact with them. The Michael acceptor site can be tweaked to improve chalcones' biological efficiency. Chalcones are robust mediators that can be used to make a number of heterocyclic structures. Chalcones are useful intermediates in the synthesis of a wide range of heterocyclic compounds with various pharmacological properties.[7,8] The chalcone route is the most popular way to produce important pharmacological motifs such as pyrazolines[9-11], benzodiazepines[12], pyrimidines[13] and so on. Natural and synthetic analogues of chalcone have a wide variety of pharmacological and biological effects. Anticancer[14], antimycobacterial[15], antibacterial[16], antifungal[17], antiviral[18], anti-inflammatory[19], antitumour[20], antihypertensive[21], antioxidant[22], etc, properties have been explored in the past. Variety of green chemistry approaches like ultrasound[23-25], water mediated[26], microwave methods[27], PEG-400 mediated[28], solvent-free methods[29], etc have been employed in the past for the synthesis of wide range of chalcone motifs. In the present review, antibacterial, antifungal, anticancer, anti-tubercular, and anti-inflammatory properties have been addressed.

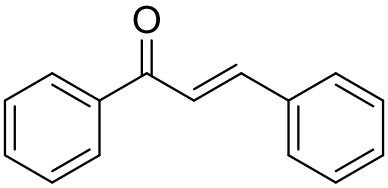


Figure 1: 1,3-diphenyl-2-propen-1-one (Chalcone).

Chalcone as antibacterial agents

X. Tang et al[30] synthesised and evaluated a series of novel chalcone derivatives containing the 1,2,4-triazine moiety for antibacterial activities. Using a turbidimeter, the antibacterial activities of the title compounds against *Xoo, R. solanacearum,* and *Xac* were assessed at 100 mg/mL. The commercial bactericide, bismerthiazol and thiadiazole-copper were tested as a control under the same conditions. The majority of the target compounds had significant

antibacterial effects against tested bacterial agents. The results of the bioassays showed that some of the synthesized compounds had exemplary antibacterial properties. Krishna Reddy V et al[31] have synthesized library of benzo[*b*]furan chalcone derivatives derived from 1-(7-methoxy-2-(2,4,6-trimethoxyphenyl)benzofuran-5-yl)ethanone and examined for antibacterial activity against *E. coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Streptococus pyogenes*, with Norfloxacin as the standard drug. Some of the compounds showed excellent to equipotent activity, whereas those with the alkoxy substituent in the sequence showed good to moderate activity. Claisen–Schmidt condensation was used by Z. Ngaini et al[32] to successfully synthesise a sequence of (*E*)-1-(4-alkyloxyphenyl)-3-(hydroxyphenyl)-prop-2-en-1-one derivatives. The hydroxyl groups in the synthesised chalcone derivatives were in the ortho, meta, or para positions, and the length of the alkyl groups varied. To evaluate the influence of the hydroxyl and alkyl groups of the synthesised chalcones on wild-type Escherichia coli American Type Culture Collection 8739, antibacteial analyses were performed. Antibacterial activity was observed in all of the synthesised compounds. The position of the hydroxyl group as well as the length of the alkyl chains were factors in determining the best inhibition. Elecia J. Henry et al[33] aimed at ten chalcones with a ferrocenyl moiety and alkyl chain lengths ranging from one to ten carbons. These ferrocenyl chalcone compounds were found to be effective against three forms of drug-resistant S. aureus, including an MRSA, as well as non-resistant clinically isolated and laboratory-adapted Gram-positive bacteria.

Chalcone as antifungal agents

L.S. Ming et al[34] synthesised heterocyclic chalcones containing the thiophene moiety and examined in vitro for antifungal activity against Candida albicans (MTCC 3958) and Aspergillus niger (MTCC 9933), with promising results. The aminolysis reaction of acyl chloride was used by T.I.A.N. Jia-yuan[35] to design and synthesise chalcone analogues using benzoyl chloride compounds and amines as the starting materials. The antifungal rate of 2-chloro-N-phenyl benzamide at 100 mg/L was 90.27 % against Rhizoctonia solani and 92.56 percent against Sclerotiua sclerotiorum, respectively. Aijaz Ahmad et al[36] synthesised various azole and non-azole derivatives of mono-(M) and bis-(B) chalcones and tested their antifungal activity profile against seven FLC susceptible and three FLC resistant clinically isolated Candida albicans strains alone and in combination with the most widely used antifungal drug fluconazole (FLC). The bis-derivatives had lower MIC values than their mono-analogues based on the minimum inhibitory concentration data. Yuanyuan Shan et

al[37] in order to develop novel anti-candidal agents, twenty chalcone derivatives were designed and synthesised. The antifungal activity of all of the compounds was tested against Candida albicans (ATCC 10231 and ten clinical isolates). With MIC values ranging from 2.0 to 32.0 g/mL, the majority of them had moderate anti-candidal potency. Additionally, they have attempted to link anti-candidal activity to physicochemical properties. The findings showed that including a halogen on the benzene ring improves anti-candidal activity.

Chalcone as anticancer agents

Jiong Zhang et al[38] reported on the synthesis and anticancer activity of a series of chalcone–benzoxaborole hybrid molecules. Three human cancer cell lines and two normal cell lines were used to monitor their anticancer efficacy and toxicity. On SKOV3 cells, the 4-fluoro compound was found to be the most active, with an IC50 of 1.4 µM, while the 4-iodo compound and 3-methyloxy-4-amino compound showed good potency on SKOV3 cells and low toxicity on normal cells. A series of ten novel quinazoline derivatives with chalcone incorporation were designed and synthesised by S. Madhavi et al.[39] The anticancer properties of all the synthesised compounds were tested against four human cancer cell lines (A549, HT-29, MCF-7 and A375). Four of them outperformed the control drug, Combretastatin – A4, in terms of anticancer activity. S. Madhavi et al[40] synthesised novel pyridine-based chalcones and tested them against three human cancer cell lines for anticancer activity (ACHN, MCF-7 and A-549). Five of the compounds were found to have higher potency than the control drug. MTT (3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide) reduction assay. was used to evaluate the anticancer activity of the compounds. Bonakdar et al[41] designed and synthesised five hybrid compounds with chalcone and sulfonamide moieties in three stages. On the human breast cancer cell line MCF-7, the synthesised compounds were tested for anticancer activity in vitro. The most potent anticancer activity against MCF-7 cell line was found in (E)–2–methoxy–N–(4–methoxyphenyl)–5–(3–(4–nitrophenyl) acryloyl) benzene sulfonamide.

Chalcone as anti-tubercular agents

M. Mujahid et al[42] synthesised a series of spirochromone annulated chalcone conjugates and tested them for antitubercular activity against the Mycobacterium tuberculosis H37Rv strain of Mycobacterium tuberculosis. Molecular simulation experiments were performed on these compounds using docking and chemoinformatics strategies. Based on the high binding affinity scores, docking simulations were performed against a number of known receptors for

chalcone derived compounds, revealing MTB phosphotyrosine phosphatase B [MtbPtpB] protein as the most likely goal. Five compounds demonstrated strong inhibition with minimum inhibitory concentrations (MICs) ranging from 3.13–12.5 μg mL^{-1}. Rambabu Anandam et al[43] described the synthesis of a series of C-dimethylated-chalcones (9a–q) using a key intermediate of 2-hydroxy-3,5-dimethyl-4,6-dimethoxy acetophenone. The compounds were tested for anti-tubercular activity using the Microplate Alamar Blue assay (MABA) method at concentrations of 100–0.8 g/mL against Mycobacterium tuberculosis strain (H37Rv). Six chalcones were found to have higher antitubercular activity than standard drugs in the experiments, while the remaining compounds had moderate activity. Molecular docking experiments using Mycobacterium tuberculosis protein tyrosine phosphatase (MtbPtp) were also conducted to determine docking ratings. A series of piperazylalkylether related 7chloroquinolinechalcone/ferrocenyl chalcone conjugates were synthesised and tested for antimycobacterial activity and cytotoxicity against the Vero cell line using the mc26230 strain of Mycobacterium tuberculosis by Amandeep Singh et al[44] With a Minimum Inhibitory Concentration (MIC) of 14 g/mL, the ferrocenylchalcone conjugate with pentyl chain as spacer proved to be the most potent among the series in their studies.

Chalcone as anti-inflammatory agents

Jianzhang Wu et al[45] synthesised a series of chalcone derivatives with diverse substitution pattern and evaluated them for anti-inflammatory properties. The existence of electron-withdrawing groups in the B-ring and electron-donating groups in the A-ring of their synthesized chalcones was found to be significant for inhibiting LPS-induced IL-6 expression in a QSAR study. Jingfen Li et al[46] reported the synthesis of two series of 35 chalcone derivatives containing aryl-piperazine or aryl-sulfonyl-piperazine components, and the anti-inflammatory properties of the active compounds were assessed *in vivo* and *in vitro* using the classic para-xylene-induced mice ear-swelling model and ELISA assays. Besides that, in their docking experiments in COX-2 were carried out (4PH9). Most of the synthesized compounds displayed strong anti-inflammatory activity in in vivo anti-inflammatory assays. The anti-inflammatory function of a series of newly synthesised biscoumarin–chalcone hybrids was investigated by Koneni V. Sashidhara et al[47] The compounds examined showed substantial inhibition of carrageenin-induced pawoedema in albino rats, as well as significant scavenging activity. As a result, according to their research these compounds provide an intriguing blueprint for the development of new anti-inflammatory therapeutics. Yan-Ling Tang et al[48] synthesized library of novel chalcone derivatives with a bispiperazine linker and their anti-

inflammatory, cytotoxic, and anti-inflammatory mechanisms were tested in vitro. Their findings showed that most bispiperazinochalcone derivatives had strong NO inhibition (IC50 20 M) and low cytotoxicity (CC50 > 40 M), and selectively inhibited the development of IL-1 by inhibiting NLRP3 inflammasome activation, indicating that they could be used to treat NLRP3 inflammasome-driven diseases.

CONCLUSION

In the conclusion, antibacterial, antifungal, anticancer, anti-tubercular, and anti-inflammatory properties are addressed. The present review shall provide great tool for the investigation of pharmacological profile of new chalcone structures.

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CONFLICT OF INTEREST

The author declares that he do not have any conflict of interest.

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