RECENT DEVELOPMENTS IN SYNTHESIS AND APPLICATION OF MULTIFACETED CHALCONE COMPOUNDS

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ABSTRACT
Chalcone, a biosynthetic product of shikimate pathway, is abundant in edible plants. It is also found in number of biologically active molecules. In recent times, there has been phenomenal increase in number of publications on versatile chalcone compounds which reflects the interest in this field throughout the world. This review article presents compilation of novel techniques for synthesis of chalcone compounds which are focussed on green chemistry and report more recent efforts made on this pharmacophore. It also highlights the important application of chalcones for synthesis of pharmacologically interesting heterocyclic compound and pharmacological diversity of chalcones.

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INTRODUCTION

Chalcone (1,3-diarylmethanone) which possesses the α, β – unsaturated carbonyl systems, is one of the most ubiquitously found secondary metabolites in the plant kingdom. This structure has always been considered as privileged pharmacophore because of its application in synthesis of various five and six member heterocyclic compounds as well as its therapeutic activity against a wide spectrum of diseases. ‘Chalcone’, this common name has been given by Kostanecki. He was the first one to report chalcone synthesis [1].

![General structure of chalcone (1)](image)

Figure 1: General structure of chalcone (1)

Despite wealth of research has been done on chalcone molecules; still, there is continued plethora of growth in publication on chalcone motif due to its significant applications at academia and industry. Chalcone, three carbon open chain flavonoids, are generally colored compounds due to presence of reactive α, β – unsaturated carbonyl pharmacophore. Interestingly, this ketoethylenic group in chalcone has been reported to be responsible for remarkable biological potential of chalcone. Cis and trans isomer forms of chalcones can be possible. Among which trans chalcone is thermodynamically stable. Some pure extracts of chalcones from plants or crude extracts of plants which contain chalcone, like liquorice, are available commercially due to its pharmacological applications. Some of the previously synthesized chalcone analogues have been selected for clinical trials. Isoliquiritigenin, liquorice chalcone, is used for the treatment of cardiovascular diseases because of its phosphodiesterase III inhibitor property [2]. Some Eastern countries use liquorice chalcone traditionally for treatment of pain, thrombotic diseases, gastritis, stomach cancer and parasitic infection as well as food additives [3-5].

True importance of chalcone is extended into two branches, One is biological activity associated with them which includes antimalarial [6-8], anticancer [9-11], anti-inflammatory [12,13], antimicrobial [14-18] anticonvulsant [19], antioxidant [20-22], xanthine oxidase inhibitor, aldo reductase inhibitor, epoxide hydrolase inhibitor [23-25], etc. and other one is its use as a template for synthesis of various heterocyclic compounds such as pyrimidine, pyrazoline, benzofurans, thiadiazines, isoxazole, quinolinones, benzodiazepine, etc. Some of these synthesized compounds show significant therapeutic activity [26-29].

There are different methods reported for synthesis of chalcone analogues, most commonly used one is Claisen-Schmidt condensation reaction. They can be synthesized conventionally by acid or base catalyzed method. However, Green chemistry approaches are more beneficiary to synthesize chalcone derivatives so as to avoid pollution, use of toxic reagents and strong acidic or basic condition [30]. Based on above mentioned application of chalcones, this review has focused on the different strategies for easy production of chalcone analogues considering green chemistry approaches. Moreover, it also covers its application for synthesis of various heterocyclic compounds and recently reported pharmacological activities of chalcone.

**Strategies for synthesis of chalcone analogues**

Chalcones are conventionally synthesized by base catalyzed Claisen-Schmidt condensation reaction of appropriate aldehyde and ketone. There are several drawbacks of conventional method for synthesis of chalcone such as harsh reaction condition, mixture of products, pollution due to toxic reagents. In an endeavor to prevent these difficulties, recently more focus is given towards green chemistry approaches where chalcones are synthesized by methods which are eco-friendly, simple, require less time, products are obtained in excellent purity with good yield, mild reaction condition.

Conventionally, condensation of hydroxyl substituted aryl carbonyl is very difficult as side products can be formed. Approaches in green chemistry have excellent feature that polyhydroxyl chalcones can be obtained in good yield and purity. Different strategies reported for synthesis of chalcones include microwave assisted synthesis [30-32], using PEG-400 [33], grinding technique [34], small molecule microarray platform technique [26], using ionic liquids [35], Suzuki reaction [36]. These approaches have reported as most suitable method for synthesis of various chalcone analogues. Solvent free method synthesis is especially suitable for microwave assisted synthesis which includes anhydrous K$_2$CO$_3$ as a condensing agent [37], heterogeneous catalyst like I$_2$- Al$_2$O$_3$ [38]. These methods are more promising towards synthesis of hydroxyl or methoxy group substituent chalcones.
Applications of chalcones
Application of chalcones associated with its pharmacological actions

Anticancer activity
Ketoethylenic group is mild electophilic in nature. Mild electrophiles (thiol) can be more attracted by α, β – unsaturated carbonyl system of chalcone than strong electrophiles (amino, hydroxyl groups). Thus there is less possibility of chalcone to interact with amino or hydroxyl groups of nucleic acid, which in turn, would unlikely lead to mutagenicity or carcinogenicity which are major side effects of generally used cytotoxic drugs. This favorable low toxicological profile of chalcone has attracted many scientists to perform extensive research of chalcone for developing safe anticancer drugs [39, 40]. There are several modes of actions reported by which chalcone analogues show anticancer activity. Due to complex, multimodal pharmacological action and various structural requirements of chalcone, it is difficult to specifically state the structural activity relationship for various chalcone derivatives [41-44].

Vineet Kumar et al. [45] synthesized a series of chalcones and evaluated them for their in vitro and in vivo cytotoxic activity by determining potency of chalcone derivatives to activate the expression of Nrf2 regulated cytoprotective agents in Human Lung Epithelial Cells. A total of twenty chalcones shows higher induction of Nrf2 regulated transcriptional targets than the positive control that is sulforphane. Among them, compound 2 (Figure 2) was found to be more active and showed high solubility and nontoxicity. It was observed that presence of trifluoromethyl (–CF₃) substitution on ring B enhance the activity dramatically. The position of –CF₃ substitution was important for activity and cytotoxicity of these compounds. Chalcone analogues with –CF₃ substitution at ortho position on ring B were most active compounds, followed by para, meta substitution. This indicates four bond separations between carbonyl and -CF₃ plays important role for exhibiting anticancer activity.

Even if there is profound of research in the area of chalcone has been done, very few chalcone hybrids which possess simple chalcone scaffold combined with N- methyl urocanic ester side chain present in sarcodictyin family of compound have been reported. A.Ciupa et al. [46] synthesized hybrid chalcones and evaluated them for antiproliferative activity against HT29 and MDA-MB-231 cell lines. Among series of synthesized urocanic chalcone hybrid compounds, compound 3 (Figure 2) is most active and selective compound.

![Figure 2: Chalcone analogues showing anticancer activity.](image)

Antibacterial activity
Nowadays, there is emergence of multi drug resistance bacteria, toxicity and side effects of drugs make the treatment of infection difficult. There is continuous need to discover novel antibacterial drugs which do not produce resistance against bacteria and should be safe.

In an attempt to solve the above mentioned problem, A.N. Mayekar et al. [47] Synthesized and evaluated a series of cyclohexenone derivatives for antibacterial activity against Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella pneumoniae bacterial strains by serial plate dilution method. Compounds 4 and 5 (Figure 3) showed comparatively good activity against all bacterial strains. These results show that presence of arylo moiety bearing bromo and dichloro groups enhance antibacterial activity compared to standard, Ampicillin, against all mentioned bacterial strains.
A new concept of coumarin-chalcone hybrid. Compound 6, (Figure 3) had been invented. This hybrid possesses two compounds which show antibacterial activity synergistically due to combination of chalcone and coumarin.

Chalcone compounds 7, 8, 9 (Figure 3) compared to standard, benzylpenicillin, showed antibacterial activity against Bacillus subtilis, Bacillus pumilis, Staphylococcus aureus, Escherichia coli and Pseudomonas vulgaris [48]. Heterocyclic chalcone analogues bearing pyrimidine moiety showed better antibacterial activity than thiophene or furan substituted chalcone analogues against Pseudomonas aeruginosa, Escherichia coli, Staphylococcus aureus, and staphylococcus methicillin. However, furan bearing chalcone analogue 10 (Figure 3) reported better activity as compared to thiophene and quinoline [49].

![Chemical Structures](image)

**Figure 3:** Chalcone analogues showing antibacterial activity.

**Antifungal activity**

Chalcone derivatives generally show antifungal activity against dermatophytes only. They do not active against other type of fungi. Chalcone derivatives 4, 5 (Figure 3) showed significant activity comparable to standard, Fluconazole [48]. This study shows that electron withdrawing group substitution in aromatic ring increases antifungal activity.

**Antimycobacterial activity**

*Mycobacterium tuberculosis*, causing tuberculosis, has developed resistance to several existing drugs. Still now, some chalcone analogues have shown good antimycobacterial activity against *Mycobacterium tuberculosis* and its multi drug resistance strain.

M. S. Yar *et al.* [50] synthesized and evaluated series of chalcones against *Mycobacterium tuberculosis* H37RV strain using microplate alamar blue assay method. Among the synthesized compounds 11, 12 (Figure 4) showed highest efficacy and exhibited > 90% inhibition at ≈ 6.25 µg/mL. This remarkable potency indicates that presence of dimethyl amino phenyl substituted chalcone shows better antitubercular activity.
Chalcone analogues and chalcone like compounds 13, 14, 15, 16, 17, 18 (Figure 4) exhibited > 90% inhibitory activity against *Mycobacterium tuberculosis* H37Rv. Maximal activity of compound 13 (Figure 4) may be due to introduction of –chloro group. But addition of halogen substitution to another B ring, compound 14, reduces activity. It was also noticed that bromo, iodo substitution reduce the antimycobacterial activity. While for chalcone like compounds, hydrophilic substituents such as methoxyl, hydroxyl and amino groups lead to reduction or complete loss of activity. Lipophilic and hydrophilic group on either side 2- propene-1-one of chalcone like analogues play important role for antitubercular activity. Moreover, these chalcones further modified to flavones resulting decrease in antimycobacterial activity [51].

![Chemical structures](image)

**Figure 4:** Chalcone analogues showing antitubercular activity

### Antimalarial activity

Malaria, caused by Plasmodium parasite, is one of the most common infectious diseases in tropical and subtropical countries. Various mechanism of actions of chalcones have been reported which include inhibition of parasitic enzyme i.e. cystein protease [52], inhibition of parasite induced channels [53], facilitating inhibition of hemozoin formation through π-π stacking interaction, inhibitor of falcipain 2 activity [54], inhibition of components of mitochondrial respiratory chain, that is, bc1 complex, cyclic dependent protein kinase [55, 56], plasmepsin [54].

Discovery of licochalcone A, an oxygenated chalcone, as a potent antimalarial agent, has prompted interest in the antimalarial activity of chalcones. Naturally occurring phloretin, aglycone of biflavonoid glycoside phlorizin showed antimalarial activity by inhibition of sorbitol transport in infected cells. In addition, Cajanus cajan, a common food in tropical Africa, identified and used as a part of ethnotherapy for malarial infection in South Western Nigeria [57, 58]. Moreover, cajachalcone (2, 6-Dihydroxy-4-methoxy chalcone),

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19 (Figure 5), had been reported as an active constituent in Cajanus cajan which exhibits significant antimalarial activity with IC\textsubscript{50} of 2.0 µg/ml, 7.4µM which was compared to chloroquine diphosphate (IC\textsubscript{50} of 0.21 µg/ml = 0.66 µM).

S. S. Lim \textit{et. al.} [59] synthesized and evaluated series of chalcone derivatives for determining antimalarial activity against \textit{Plasmodium falciparum} strain FCR-3. Among the synthesized chalcone compounds, chalcone analogue 20 (Figure 5), 4'-methoxy substituted dihydrochalcone, exhibited 100% inhibition against \textit{P. falciparum} at concentration of 5.4 µg/mL [EC\textsubscript{50} = 1.0 µg/mL]. It is also reported that α, β – unsaturated carbonyl system increased the activity when electron withdrawing or donating group was substituted at C-4 position.

![Figure 5: Chalcone analogues showing antimalarial activity.](image)

Chalcone quinoline, compound 21 (Figure 6), is slightly more potent than chloroquine in inhibiting β- hematin formation. Difficulty with this analogue was its poor solubility, which was overcome by piperazine bearing chalcone quinoline analogue. Analogues 22, 23 (Figure 6) were the most active of the all chalcone quinoline analogues. These compounds showed antimalarial activity may be by inhibition of hemazoin formation [60].

B. S. Sisodia \textit{et. al.} [61] synthesized and evaluated series of steroidal chalcones for determining antiplasmodial activity by evaluation of their effect on hemazoin synthesis and permeation pathway of \textit{Plasmodium falciparum} infected erythrocyte membrane. Gallic acid based chalcone derivative 24 (Figure 6) exhibited best activity among all steroidal chalcones which is comparable to licochalcone A. Derivatives 24, 25 (Figure 6) also showed potency to completely inhibit in vitro parasite development to schizont with MIC ≤ 10 µM. Structure activity relationship indicates that trimethoxylated derivatives 24, 25 exhibited better activity than dimethoxylated derivatives.
In 2, 4-Dimethoxy substituted aromatic ring series of chalcone, analogue 26 (Figure 7) with benzimidazole substituent was found to be most active with IC₅₀ 1.1 µg/mL. Moreover, in the same series, analogues 27, 28, 29 (Figure 7) having pyrrolidine, morpholine, and 1, 2, 4-triazole substituent showed better effect on parasite with IC₅₀ 2.35, 2.95, 3.38 µg/mL respectively. It was also reported that in the chalcone analogues series, two methoxy substitutions at 2 and 4 was optimum for antimalarial activity followed by 3 and 4 and then 2 and 5 which showed moderate activity [62].
Chorovinyl sulfones, analogues of chalcone, 30 and 31 (Figure 8) were found to be potent antimalarial activity against *P. falciparum* with IC₅₀ value of 0.053 µM and 0.025 µM respectively. This study also suggests that 3, 4-Methylenedioxy substituted derivatives located in aromatic ring of α, β – unsaturated chlorophenyl sulfone, 2-chloroquinolinyl group that form part of aromatic system play important role for activity against *Plasmodium falciparum*. 32, 33 (Figure 8) also exhibited moderate activity in *P. berghei* mouse model with 50 and 72% inhibition [63].

**Figure 7:** Chalcone analogues showing antimalarial activity.

**Figure 8:** Chalcone analogues showing antimalarial activity.

**Anti-inflammatory activity**

Different mode of actions has been reported by which chalcone analogues show anti-inflammatory activity. It includes suppression of inflammatory mediators such as nitric oxide (NO) and tumor necrosis factor (TNF), which are generated by macrophages stimulated with lipopolysaccharide (LPS) [64]. Chalcones inhibit production of various inflammatory mediators by a direct inhibitory action of activation of transcription factors (NF-KB, AP-1) that regulate inflammatory process [65].

K. Maria *et. al.* [66] synthesized and evaluated series of chalcones and related manich bases for determining anti-inflammatory activity by evaluating its antioxidant, free radical scavenging activity and lipoxygenase inhibition activity using appropriate in vitro and in vivo models. Results showed that chalcone compound 34 (Figure 9) was most potent (80%) followed by corresponding manich base 35 (77%). Compounds 34, 35 (Figure 9) were found to possess promising anti-inflammatory profile while compound 36 (Figure 9) exhibited high lipoxygenase activity.
Moreover, chalcone semicarbazone compound 37 (Figure 10) reported more anti-inflammatory activity as compared to standard diclofenac using in vivo carrageenan-induced rat paw edema test [67-71]. It was also found that halo substituted aniline chalcone semicarbazone more potent, which may be due to its lipophilicity. But in case of bulky group substituted compounds 38, 39 (Figure 10) decrease in activity was seen which may be due to improper attachment with receptor. This indicates substitution plays important role in improving activity of these compounds [72].

Application of chalcones for the synthesis of heterocyclic compounds
Chalcone possesses α, β – unsaturated carbonyl system, which is one of the most useful Michael acceptors. It undergoes Michael type nucleophilic addition, followed by intramolecular cyclization and aromatization, leading to various five or six membered heterocyclic or cyclic compounds. Interestingly, some of these synthesized compounds show good pharmacological activities. It includes pyrazole [73], pyrazoline [74], thiazine [73], oxazine [73], isoxazole [73], pyrimidine [73] and benzodiazepine [75].

Figure 9: Chalcones showing anti-inflammatory activity.

Figure 10: Chalcone analogues showing anti-inflammatory activity.
CONCLUSION
Chalcone compounds have importance since past time because of its multifaceted applications as demonstrated above. Thus chalcones should be studied for different activities in order to find out pharmacological active compound.

Authors’ Statements

Competing Interests
The authors declare no conflict of interest.

REFERENCES

Figure 11: Application of chalcones for the synthesis of heterocyclic compounds.


