Review Article

A Review of Microwave-Assisted Chalcone Synthesis: Advancements Over Conventional Methods and their Pharmacological Actions

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ABSTRACT

The review explores the microwave-assisted synthesis of biologically active chalcones, underscoring its benefits compared to traditional synthesis techniques. Chalcones, which naturally occur in various plant-based foods and beverages, possess an α, β-unsaturated carbonyl system and polyhydroxylated aryl rings, contributing to their wide-ranging biological effects including antioxidant, antimicrobial, anti-inflammatory, and anticancer activities. Conventional synthesis methods typically require 24 hours of heating, making them time-intensive and less productive. In contrast, microwave-assisted synthesis dramatically shortens reaction times to mere minutes while enhancing yield and consistency. By comparing these two approaches, this review emphasizes the improved efficiency and biological potential of chalcones created through microwave irradiation, offering insights into their expanded applications in the field of medicinal chemistry.

Keywords: Chalcones, Claisen Schmidt condensation, microwave assisted method, conventional method, antiviral activity, anti-inflammatory activity.

INTRODUCTION

Chalcones are 1,3-diphenyl-2-propene-1-one1,2, in which two aromatic rings are linked by a three carbon α, β-unsaturated carbonyl system. These are abundant in edible plants and are considered to be the precursors of flavonoids and iso flavonoids. Chalcones are synthesized by Claisen-Schmidt condensation, which involves cross-aldol condensation of appropriate aldehydes and ketones by base catalysed or acid catalysed reaction followed by dehydration.[1] Chalcone is a common natural pigment and one of the important intermediate in the biosynthesis of flavonoids.[2] The synthesized compounds were purified by recrystallization and chromatography. The compounds were characterized by H NMR and IR analysis. The compounds were tested for their antibacterial and antioxidant activities by standard methods.[3]

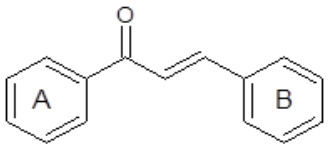


Figure 1: Basic structure of chalcone

Microwave radiation is characterized by its relatively long wavelength, ranging from 1 mm to 1 m, and occupies the electromagnetic spectrum between radio waves and infrared radiation. For the past 50 years, microwave energy has been primarily used for heating food. However, its applications have now expanded to include organic synthesis.[4] In 1855, Robert Bunsen created a burner that served as a heat source for reaction vessels, establishing a conventional method for synthesizing organic compounds through heating. Technological innovations have recently enhanced the efficiency of microwave energy for heating chemical reactions. Organic processes that previously required hours or even days to complete can now be finished within minutes using this advanced method.[5]

Organic compounds can be synthesized through two distinct approaches.

Conventional Method

In this process, energy is transferred to the reactant molecules from an external source through the walls of the reaction vessel. After the vessel is heated, thermal energy is conventionally transmitted to the solvent and reacting molecules. Consequently, this method is extremely slow and time-intensive. The method is also dependent on the use of solvents, which can be costly and not always environmentally friendly. Additionally, the prolonged reaction times and potential for reduced yields due to inefficient heating make this technique less favourable compared to newer methods like microwave-assisted synthesis.

Microwave or non-conventional method

This method is not limited by thermal conductivity of the reacting vessel. Microwaves directly reaches to the reacting mixture and rises the temperature of the system by coupling of microwave to dipole rotation or ionic conductivity of molecule. Only polar molecule can interact with the microwave radiation die to high dipole moment for example, water, ethanol, dichloromethane, chloroform, acetonitrile, DMF, etc. absorb radiation rapidly but nonpolar substances like aromatic and aliphatic hydrocarbon with no dipole moment cannot reacts to microwaves.[6]

The main advantages of microwave assisted organic synthesis are speed up reaction the microwave can use higher temperatures than conventional heating system and consequently the reactions are completed in few minutes instead of hours.[7] Better productivity in which less formation of side product is observed using microwave irradiation, and the product is recovered in higher yield. Consequently, also the purification step is faster and easier. Easy handling availability of high technology and large range of reactor vessels, allows easy handling from few millilitres to one litre without changing reaction parameters. Reproducibility is good due to closed reacting system control the various reaction parameters, such as temperature, pressure and power, always reproduces the same reaction conditions. It is very simple to save and use an optimized synthesis method.[8] Due to various advantages of nonconventional heating over the conventional heating recently the microwave has become the useful nonconventional source for the organic synthesis. [9-12]

Microwave assisted with synthesis of chalcones.

Chalcone are widely distributed in nature like fruits, vegetables, tea and spices.[12] Naturally occurring chalcones are polyhydroxylated in the aryl ring due to phenolic group and due to presence of α, β unsaturated carbonyl group it shows various biological activities, such as antioxidant, antimicrobial, anti-inflammatory, anticancer, etc. Chalcones being natural precursors are obviously important intermediates for the synthesis of flavones[11.] They are easily prepared by Claisen schmidth reaction of acetophenone with benzaldehyde in ethanol or methanol in basic condition by using sodium or potassium hydroxide (figure 2). The author Mauricio Cabrera et al. has reported the synthesis of substituted chalcone from 2-hydroxy acetophenone and substituted benzaldehyde in methanol and potassium hydroxide by stirring at room temperature for 24 hours.[13]

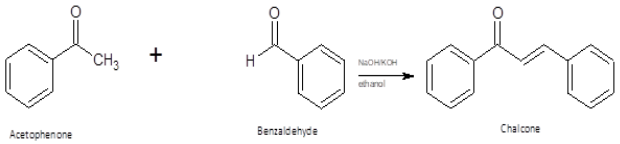


Figure 2: Claisen-Schmidt condensation for the synthesis of chalcones

The synthesis of chalcone by conventional heating take longer time to complete so, microwave irradiation procedure for the synthesis of chalcone has been reported recently by researchers to minimize the time and to improve the yield. G. Thirunarayanan et al. in 2012 reported the synthesis of chalcone from aryl methyl ketone and substituted benzaldehyde in green catalyst flyash: H2SO4 by microwave irradiation at 160-800 watt, total 38 compounds were synthesized in which compound 30 had more yield (Figure 3)[14] Same chalcone were synthesized by microwave irradiation in 40% sodium hydroxide at 160-320 watt and time required was 60-120 sec.[15]

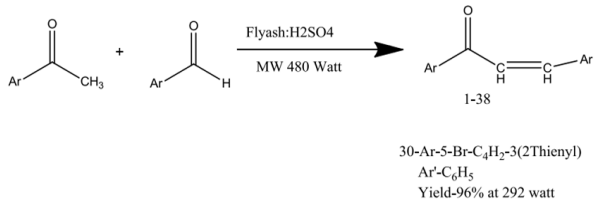


Figure 3: Synthesis of chalcone by microwave Irradiation with Flyash: H_2SO_4.

Novel chalcone was prepared from 2-acetyl hetero cyclic derivatives and respective aldehyde in aqueous potassium hydroxide solution by microwave irradiation for about 2–6 min at 180 watts (Figure 4) and also synthesized this chalcone conventionally at room temperature reaction was completed in 24 hours.[16]

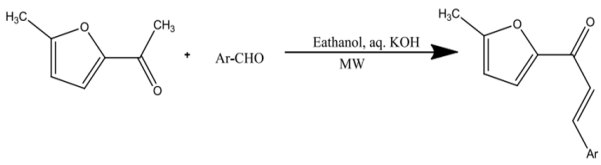


Figure 4: Chalcone with heterocyclic ring

In Green chemistry as like microwave radiation the concentrated solar radiation (CSR) is better as a non-conventional technique for the organic synthesis. Solar energy is available free of cost and it is a renewable source of energy. Solar energy is the unique clean, nontoxic and easily available source. The solar radiations emit a large number of ultraviolet as well as infrared radiations between the range of 280–4000 nm which serves both photochemical and thermal energy respectively. In this regards, solar energy is an able tool for the reaction and offers some advantageous. The usage of solar energy to execute the organic reactions has been reported by Jadhav et al. the green solar assisted synthesis of chalcone (3-(4-fluorophenyl)-1-(4-m ethoxyphenyl)-prop-2-en-1-one) [17-19] Janaki et al. in 2016 reported synthesis of benzimidazole chalcone by fly-ash: H2SO4 catalysed aldol condensation from 2-benzimidazole methyl ketone and various substituted benzaldehydes in microwave oven. The yields of these chalcones were more than 70%.[20](Figure 5)

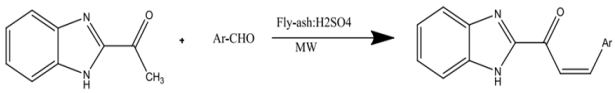


Figure 5: Synthesis of benzimidazole chalcone

Pharmacological activities of chalcones:

Chalcones against infectious diseases:

1. Anti-Tubercular Activity:

Tuberculosis (TB) is a contagious illness that primarily affects the lungs. Many chalcone analogues have been tested for anti-tubercular activity, and there have been reports of chalcones with intense anti-tubercular activity. [21-23] Chalcones with extended phenyl skeletons showed good activity against Mycobacterium tuberculosis, with MIC values almost equal to those of standard drugs such as

rifampicin and streptomycin. The docking and QSAR study results of these conformationally restricted chalcones also matched the MABA assay results. [24,25] The spirochrone chalcones were tested for inhibitory activity against M. tuberculosis. Moreover, their docking studies were performed with protein phosphotyrosinase phosphatase B. Docking studies indicated that one of the spirochrome chalcones was bound to the protein at the same pocket region as the natural ligand, and the MIC value indicated that it was more active than the standard drug used in the MABA assay.[25]

Table 1: Key differences and advantages between conventional and microwave assisted method of synthesis:

	Conventional method	Microwave assisted method
Reaction time	Requires several hours (up to 24 hours).	Reaction time reduced to minutes (seconds to a few minutes).
Energy efficiency	Energy is transferred slowly, resulting in inefficiency.	Rapid and uniform heating, reducing energy consumption and time
Solvent usage	Often requires solvents, which may not be environmentally friendly.	Can be carried out with little to no solvent, offering a greener alternative.
Reaction yield	Longer reaction times may lead to lower yields due to side reactions or incomplete reactions.	Faster reactions generally lead to higher yields and fewer side products.
Product purity	Purification may be more challenging due to impurities or incomplete reactions.	Higher purity of the product is often achieved due to better control over reaction conditions.

2. Antiviral Activity:

Numerous viral infections, including HIV and coronaviruses, cause serious health problems in people all over the world. Numerous plants that naturally contain chalcones have been used to treat viral infections since time immemorial. [26-29]Chalcone derivatives with the purine derivative showed a better EC50 value than the standard drug ribavirin in inhibiting the tobacco mosaic virus. Some natural chalcone derivatives were screened for their activity against SARS-CoV-2, with satisfactory EC50 values. The results matched the molecular docking studies with the protein RdRp, and the threshold values were calculated.[30]

3. Antimalarial Activity:

Malaria is caused by a parasite called Plasmodium falciparum, which is transmitted by mosquitoes. Antimalarial medications such as chloroquine and artemisinin are readily available. However, modern P. falciparum strains are resistant to available medications. Many chalcones that occur naturally have been used to treat malaria. [31,32] A sulfonyl-based 4-methoxychalcone could be used as an efficient oral drug against malaria, with an IC50 value of 2.06 µM; furthermore, the docking study indicated a comparatively high binding score of −7.3 Kcal/mol.[33]As expected, the imidazole group contributes to the activity, which showed potent antimalarial activity, with an IC50 value of 1.1 µM. The docking results proved that the molecule shows H-bonding and aromatic interactions with the proteins 1J2I and 1J3K.[34]. An azide–alkyne coupling can produce a triazole-bearing chalcone from the combination of quinolone and natural moieties.

4. Antibacterial Activity:

Pathogens becoming more resistant to antibiotics have caused the effectiveness of current antibiotics to decline. Both natural and artificial chalcones have demonstrated activity against some Gram-positive and Gram-negative strains.[35,36] Biofouling is one of the significant problems in marine-based product development. In one of the studies, the organism V. natriegens (MD6) and other marine strains (P. fluorescens and B. flexus) were taken for antibacterial studies. The extensive analysis of bacterial studies proves that heterocyclic chalcones are superior to homocyclic chalcones. The trans-chalcone containing a difurano ring (28 µM) potentially better inhibits the activity of S. aureus compared to the standard drug amoxicillin.[36]

Chalcones for non-infectious diseases:

5. Anti-Alzheimer's Activity:

Alzheimer's disease is a neurological condition that causes memory loss in people especially those over 65 years old. It also results in other behavioral problems and a decline in language and orientation abilities. The factors vital to its cause are oxidative stress, acetylcholinesterase (AChE), and Aβ1-42 (amyloid beta) aggregation. [37-42] The docking studies on newly synthesized chalcone-O-alkylamine analogues were performed with acetylcholinesterase, butyrylcholinesterase (BuChE), and Aβ1-42. It was found that a compound was bound to the same pocket region as the natural ligand. Moreover, the in vitro analysis showed that it could cross the BBB and inhibit MAO-B and BACE-1 in the treatment of neurodegenerative disorders.[43]

6. Anti-inflammatory:

Activated macrophages play a key role in inflammatory responses and release a variety of mediators, including nitric oxide (NO). NO is a potent vasodilator that facilitates leukocyte migration and formation of oedema, as well as leukocyte activity and cytokine production. NO can also react with superoxide anion to form peroxynitrite, a potent

oxidizing molecule that contributes to tissue injury during inflammatory responses. Nitric oxide is generated from Larginine by nitric oxide synthase (NOS). Compounds that inhibit excess production of NO by macrophages might be of benefit for the prevention and treatment of autoimmune diseases, septic shock and different inflammatory pathologies. Chalcones with substituents that increase the electronic density of the B-ring, such as methoxy, butoxy or dimethylamine groups, did not show significant activity in the inhibition of the nitrite production. Trimethoxy chalcone derivatives with fluoro substitution at C4' are better inhibitors of nitrite production. Trifluoromethyl group at C2' in dimethoxy chalcones as well as trimethoxy chalcones possess very potent inhibition of nitrite accumulation. Trifluoromethyl group at C3' or C4' in dimethoxy chalcone as well as trimethoxy chalcone possess less activity than when it is at C2'. Isoliquiritigenin isolated from Nepalese propolis (Funakoshi et al. 2015) and butein isolated from Rhus verniciflua (Yang et al. 1998) are another significant natural chalcones which exhibit potent anti-inflammatory activity by inhibiting LPS-induced iNOS and COX-2 expression. Zaho et al. (2003) reported a reduced chalcone which identified as anti inflammatory agent by inhibiting the production of NO induced by LPS and INF-γ in murine microphage-like cell lines.[44]

7. Cytotoxic activity:

Mannich bases of phenolic azobenzenes demonstrated cytotoxic activity, and various mannich bases analogues of chalcones exhibited potent cytotoxicity against murine P338 and L1210 leukemia cells as well as several human tumor cell lines. Mannich bases of heterocyclic chalcones are evaluated for cytotoxic activity against four human cancer cell lines (PC-3, MCF-7, KB and KB-VIN). Mannich base of chalcone with morpholine substitution at C3 or C5 and pyridyl or phenyl at C2 substitution are found to possess good cytotoxic activity.[45]

8. Antihepatotoxic activity:

Silymarin isolated from seeds of silybum marianum commonly known as Milk Thistle has been used as a potent Antihepatotoxic agent against a variety of toxicants. It is a mixture of three isomers namely, silybin (1), silydianin (2) and silychristin (3). Silybin is the most active component containing 1,4-dioxane ring system, whereas other isomers do not possess 1,4-dioxane ring, and thus do not display significant activity. Chalcone derivatives possessing 1,4-dioxane ring system exhibiting antihepatotoxic activity. The potent compounds possess 2-hydroxy methyl group at position 2 of the dioxane ring of chalcone derivatives, which has also indicated that the presence of hydroxy methyl group at position 2 in dioxane ring possesses a significant role in exhibiting the antihepatotoxic activity. This is in accordance with the view that silybin too possess the same group at the same position. The substitution in the aromatic ring of chalcones have no significant role in exhibiting antihepatotoxic activity.[46]

9. Antileishmanial activity:

Conventional structure activity relationships show that antileishmanial activity is favoured by chalcones with more hydrophilic character, with the most active members found among 40-hydroxychalcones. The good antileishmanial activities of the naphthalenyl and pyridinyl derivatives suggest that considerable tolerance for the size of ring A exists.[47]

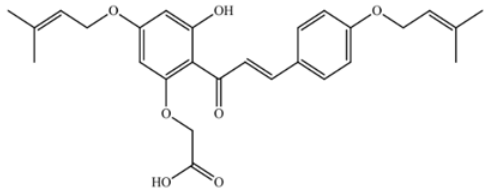
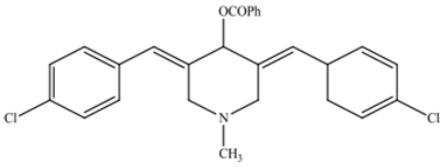
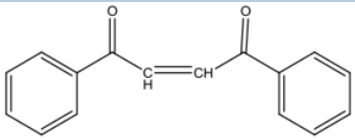
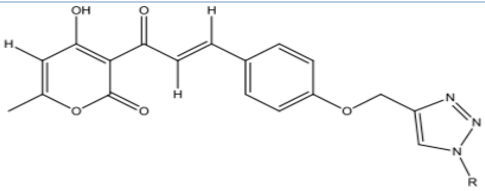
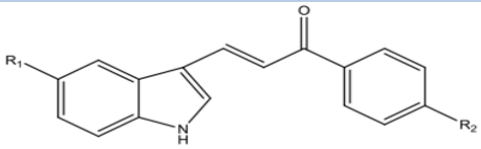
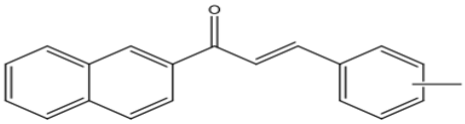
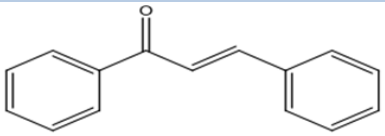
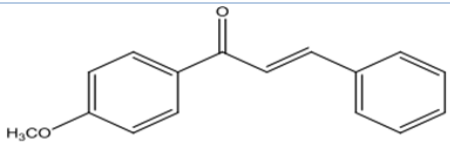
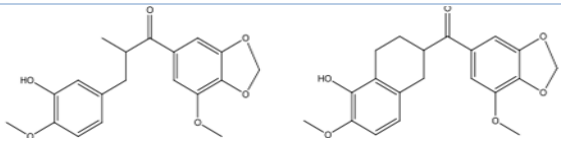
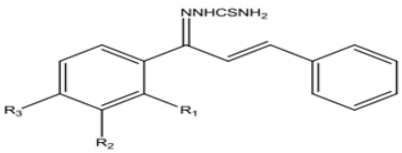
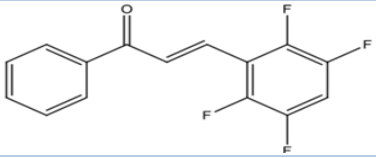
10. Tyrosinase inhibitors:

Tyrosinase (monophenol monooxygenase, E: C: 1.14. 18.1), also known as polyphenol oxidase), is a copper-containing enzyme widely distributed in nature. It catalyses two reactions involving molecular oxygen in the melanin biosynthesis pathway: the hydroxylation of monophenols to o-phenols (monophenolase activity), and the oxidation of the o-phenols to o-quinones (diphenolase activity). These quinones are highly reactive and tend to polymerize spontaneously to form brown pigments of high molecular weight (melanin), which determine the color of mammalian skin and hair. Quinones can also react with amino acids and proteins and thus enhance the development of brown color. The inhibitory activity of a series of chalcones was set against their structure and their antioxidant potency (which can contribute to prevent pigmentation resulting from nonenzymatic oxidation).[48,51]

CONCLUSION

This review has provided a comprehensive analysis of the biological activities of chalcones and highlighted the advantages of non-conventional heating methods over traditional approaches. Specifically, it has explored the effectiveness of microwave-assisted synthesis in the derivatisation of chalcones, emphasizing its ability to enhance reaction efficiency, reduce processing time, and improve overall yield. Compared to conventional heating methods, microwave irradiation offers a more uniform and selective heating mechanism, leading to better reaction control and minimizing unwanted side reactions. This approach not only accelerates the synthesis process but also contributes to the development of biologically active chalcone derivatives with potential pharmaceutical applications. The findings discussed in this review underscore the significance of microwave-assisted techniques in modern organic synthesis, paving the way for further advancements in medicinal chemistry and drug discovery.

Table 2: Chalcone derivatives with various biological activities.

Structure of chalcone	Name and author	Activity
	Di-O-Prenylated Chalcone by Kyogoku et al. [51,52]	Antiulcer
	Benzoic acid 3,5-bis-(4-chlorobenzylidene)-1- methyl-piperidin-4-yl ester by Aneta Modzelewska, et al.[53]	Inhibit Breast Cancer cell line
	Synthetic chalcone by Ruby John Ant.[54]	Antioxidant and Anticancer
	Dehydroacetic acid-chalcone-1,2,3- triazole Kashmiri Lal, et al.[55]	Antimicrobial
	New indole-based chalcones Ahmet Ozdemir et al.[56]	COX1 and COX2 Inhibitor (Anti-inflammatory)
	2-Acetyl naphthalene Chalcone, Varun Arora et al.[57]	Antifungal, Antimicrobial
	Novel Chalcone, Sandip Sen et al.[58], Nasir Tajuddeena, et al.[59]	Antioxidant, Antimicrobial Antileishmanial activity
	Methoxy substituted chalcone Bijo Mathew, et al.[60]	Tyrosinase stimulant activity
	α-methyl chalcone complexed with tubulin to form 1, 2, 3, 4-tetrahydronaphthalen-2-yl aryl ketones as a conformational mimetics.[61]	Anti-proliferative activity against tumor and endothelial cells
	Thiosemicarbazide derivative of chalcone et al. Jinbing Liu.[62]	Tyrosinase Inhibitors
	1-(phenyl)-3-(2,3,5,6-tetrafluorophenyl)-prop-2-en-1-one, Otavio Augusto Chaves, et al.[63]	Tyrosinase stimulant activity

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