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Chalcones and Their Biological Applications: A Review of Therapeutic Potential

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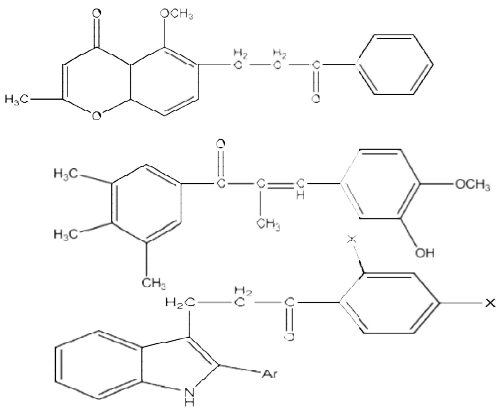
Abstract: *A class of naturally occurring flavonoids known as chalcones has attracted a lot of interest because of its wide range of pharmacological characteristics. Chalcones have a unique chemical structure made up of two aromatic rings joined by a three-carbon α,β-unsaturated carbonyl system. They are thought to be the biogenetic progenitors of flavonoids and isoflavonoids, which are plentiful in plants, and they form the core of many significant biological molecules. Chalcones and their derivatives have drawn a lot of interest in medicinal chemistry because of their structural diversity and bioactivity. Numerous biological activity, such as antioxidant, antibacterial, amoebicidal, antiulcer, antiviral, insecticidal, antiprotozoal, anticancer, cytotoxic, and immunosuppressive properties, are possessed by chalcones. This review provides a comprehensive analysis of the biological applications of chalcones, with a focus on their mechanisms of action and therapeutic implications. Furthermore, it discusses recent advancements in chalcone-based drug development and their potential for clinical translation. Understanding the pharmacological effects of chalcones could pave the way for the development of novel therapeutic agents, making them valuable in addressing various human health challenges.*

Keywords: Chalcones, medicinal chemistry, antioxidant, bioactivity, antimicrobial, anticancer

Graphical Abstract



Several chalcones with an indole moiety were created and their antibacterial and antifungal properties were examined.

The α- to methyl compound was found be the most active and tested for the chemotherapy of leukemias.

Heterocyclic substituted chalcones were introduced for the treatment of breast cancer, menopausal disorders and osteoporosis.

I. INTRODUCTION

1,3-diaryl-2-propen-1-ones, another name for chalcones, are a significant class of naturally occurring substances that are members of the flavonoid family. They have a broad spectrum of pharmacological effects and are important intermediates in the production of flavones and flavonols. Because of their open-chain flavonoid backbone and structural simplicity, they are easily modified chemically, which increases their biological efficacy. They are very reactive and effective in biology because of the α,β-unsaturated carbonyl system that is part of their structure. The

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therapeutic potential of chalcones in a variety of diseases, including as cancer, bacterial and viral infections, and inflammatory disorders, has been thoroughly investigated due to their broad range of medical applications.[1]

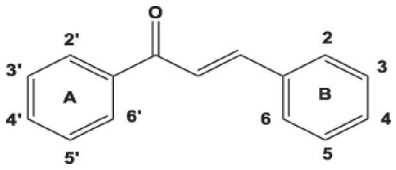
The therapeutic potential of chalcones spans several areas, including anti-inflammatory, antioxidant, anticancer, antimicrobial, antiviral, and antidiabetic effects. Research has shown that chalcones possess the ability to modulate various signaling pathways, inhibit key enzymes, and interact with cellular targets that play critical roles in disease mechanisms. In cancer research, for example, chalcones have been identified as potent inhibitors of tumor growth, promoting apoptosis (programmed cell death) and reducing metastasis in various cancer types.

Additionally, chalcones have demonstrated antimicrobial properties, offering promise in combating resistant bacterial and viral infections. Their antioxidant activities help protect cells from oxidative stress, potentially reducing the risk of degenerative diseases like Alzheimer's and cardiovascular disorders.

Given their diverse biological activities, chalcones are being explored in drug design and development, either as standalone compounds or as templates for synthetic modifications to improve efficacy and bioavailability. This review highlights the therapeutic potential of chalcones, summarizing current findings on their biological effects, mechanisms of action, and the promise they hold in advancing medical and pharmaceutical applications.[2]

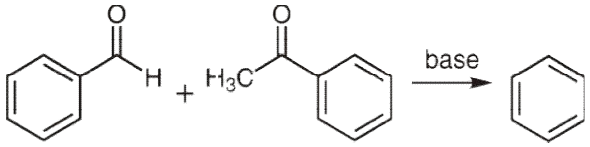
Chalcone Structure in General

Two aromatic rings (A and B) are joined by a three-carbon α,β-unsaturated carbonyl system to form chalcones. These rings' biological activity is influenced by the hydroxyl, methoxy, halogen, and other substituents that are present on them. Their therapeutic efficacy can be optimized through structural alterations, which makes them appealing scaffolds for drug design.



Chalcone Synthesis

The primary method of creating chalcones is the Claisen–Schmidt condensation reaction, which occurs when an aromatic aldehyde and an acetophenone are combined with an acid or basic catalyst (such as NaOH or KOH). Improved bioactivity is made possible by changes to the core structure.



Mechanisms of Action

There are several ways that chalcones influence biology, including:

Enzyme inhibition: Chalcones affect the activity of enzymes such tyrosinase, lipoxygenase, and cyclooxygenase (COX).

Numerous chalcones target mitochondrial pathways to cause cell cycle arrest and induce apoptosis in cancer cells.

Modulation of oxidative stress: Their antioxidant qualities aid in scavenging free radicals and minimizing oxidative damage.

Some chalcones exhibit antibacterial action through the breakdown of fungal and bacterial cell membranes.

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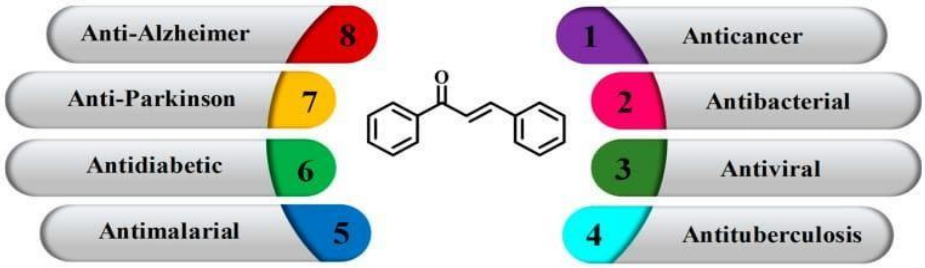
Biological Applications of Chalcones



Structure of chalcone and its bioactivities

Anti-Cancer Action

By focusing on several cellular pathways, chalcones have shown strong anticancer effects. They have the ability to restrict the growth of cancer cells, prevent angiogenesis, and trigger apoptosis. Certain chalcone derivatives interfere with microtubule dynamics, which are necessary for cell division, by acting as inhibitors of tubulin polymerization. Furthermore, they are intriguing candidates for cancer therapy due to their capacity to modify important signaling pathways like PI3K/Akt and NF-κB.[3]

Antimicrobial Characteristics

Chalcones have antibacterial, antifungal, and antiviral properties that are broad-spectrum. They work by interfering with the formation of nucleic acids, disrupting the membranes of microorganisms, and inhibiting enzyme function. Notably, chalcones have been studied as possible substitutes for traditional antibiotics, particularly in the fight against bacteria that are resistant to drugs.

Reduced Inflammation

By blocking important inflammatory mediators including the enzymes lipoxygenase (LOX) and cyclooxygenase (COX), a number of chalcone derivatives have strong anti-inflammatory effects. They also reduce inflammation- related conditions like arthritis and neuroinflammation by modifying transcription factors like NF-κB and pro- inflammatory cytokines.

Antioxidant Activity

Chalcones are known for their strong antioxidant properties, attributed to their ability to scavenge free radicals and enhance endogenous antioxidant defense systems. These properties contribute to their potential in preventing oxidative stress-related diseases, including cardiovascular disorders and neurodegenerative diseases like Alzheimer's and Parkinson's biological activity is influenced by the hydroxyl, methoxy, halogen, and other substituents that are present on them. Their therapeutic efficacy can be optimized through structural alterations, which makes them appealing scaffolds for drug design.

• Potential to Prevent Diabetes

Chalcones have been shown to have hypoglycemic effects, mainly via inhibiting important enzymes including dipeptidyl peptidase-4 (DPP-4) and α-glucosidase. Certain compounds are potential options for managing diabetes because they also improve glucose absorption and insulin sensitivity.

• Neuroprotective Impacts

By lowering oxidative stress, regulating neurotransmitter levels, and avoiding neuronal death, chalcones demonstrate neuroprotective qualities. Because of these effects, they may be used to treat neurological diseases such multiple

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sclerosis, Parkinson's disease, and Alzheimer's disease.4

Chalcone has also been shown to have several biological activities, including antiviral, prostaglandin binding, antiulcer, anti-parkinson, antimalarial, anti-tumor, and cardiovascular.

All things considered, chalcones are a broad class of bioactive substances with a variety of therapeutic applications. They are important for drug development because of their capacity to interact with a variety of biological targets. New therapeutic medicines made from chalcone scaffolds will be made possible by ongoing research that attempts to improve their pharmacokinetic characteristics and clinical usefulness.

II. METHODOLOGY

Chalcones are a class of compounds characterized by a distinctive structure comprising a benzene ring connected to a conjugated enone group. They are widely studied due to their biological activities, including antimicrobial, anticancer, anti- inflammatory, and antioxidant properties. Several synthetic methods have been developed for the preparation of chalcones, including:

1. Aldol Condensation (Base-Catalyzed)

• This is one of the most common and simple methods to synthesize chalcones.

• Mechanism: An aromatic aldehyde reacts with an α,β-unsaturated ketone (usually acetophenone) under basic conditions (e.g., sodium hydroxide or potassium hydroxide). The base deprotonates the α-position of the ketone, leading to the formation of an enolate ion, which attacks the carbonyl group of the aldehyde to form the chalcone.

• Advantages: Simple, cost-effective, and gives good yields.

2. Aldol Condensation (Acid-Catalyzed)

• In this method, the reaction proceeds under acidic conditions, using an acid like HCl, H2SO4, or p-toluenesulfonic acid.

• Mechanism: In the presence of acid, an α,β-unsaturated ketone undergoes condensation with an aldehyde to form a chalcone.

• Disadvantages: This method may require higher temperatures and longer reaction times.

3. Michael Addition

• The Michael addition is another synthetic route where an α,β-unsaturated carbonyl compound (such as an enone or enal) reacts with a nucleophile (typically an aromatic compound).

• Mechanism: A nucleophile, such as an aromatic compound (benzene or substituted benzene), attacks the β-carbon of an α,β-unsaturated carbonyl compound (such as methyl vinyl ketone or ethyl vinyl ketone), leading to the formation of chalcones.

• Advantages: This method is versatile and can be applied to a wide range of substrates.

4. Suzuki-Miyaura Coupling

• This is a palladium-catalyzed cross-coupling reaction used to synthesize chalcones.

• Mechanism: An aryl halide (such as aryl iodide or bromide) undergoes a palladium-catalyzed reaction with a boronic acid or boronate ester, leading to the formation of chalcones. This is particularly useful for introducing different aromatic rings into the chalcone structure.

• Advantages: It allows the introduction of different substituents on the aromatic rings and provides high yields.

5. Wittig Reaction

• The Wittig reaction involves the reaction of a phosphonium ylide with a carbonyl compound to form an alkene.

• Mechanism: A phosphonium salt reacts with a strong base to form a ylide, which then reacts with an aldehyde to produce a chalcone.

• Advantages: Provides good control over the geometry of the alkene (E or Z configuration).

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6. Vilsmeier-Haack Reaction

• This is a formylation reaction where an aromatic compound is treated with a reagent such as DMF (dimethylformamide) and POCl3 (phosphorus oxychloride) to generate an aromatic aldehyde, which can then undergo an aldol condensation to form the chalcone.

• Advantages: Useful for the synthesis of formylated chalcones.

7. Cyclization of 1,3-Dicarbonyl Compounds

• In this method, a 1,3-dicarbonyl compound (such as acetylacetone) can undergo cyclization, often in the presence of a base or acid, to form a chalcone structure.

• Advantages: This method offers a straightforward way of creating the chalcone skeleton.

8. Electrophilic Aromatic Substitution

• This method is less common but involves electrophilic substitution reactions on an aromatic ring to introduce a β-carbonyl group, leading to chalcone formation. The reaction can be carried out using a Lewis acid catalyst, such as AlCl3.

9. Condensation of α,β-Unsaturated Ketones with Aromatic Aldehydes

• This method typically involves the reaction of α,β-unsaturated ketones (such as acetophenone derivatives) with aromatic aldehydes under basic or neutral conditions. It is very similar to the aldol condensation but without the strong base.

• Example: Condensation of benzaldehyde with acetophenone derivatives to form chalcones.

III. LITERATURE REVIEW

Chalcones, a class of naturally occurring compounds with a characteristic α,β-unsaturated carbonyl system, have drawn significant attention in recent years for their broad spectrum of biological activities and therapeutic potential. These compounds are found in various plants and are considered precursors to flavonoids. Research has demonstrated that chalcones exhibit a variety of bioactivities, including anticancer, antimicrobial, anti-inflammatory, antioxidant, and antidiabetic effects. For instance, chalcones have shown potent anticancer properties by inducing apoptosis, arresting the cell cycle, and inhibiting metastasis in cancer cells. Studies have highlighted their ability to target critical signaling pathways involved in cancer progression, such as the PI3K/Akt/mTOR and MAPK pathways. Additionally, chalcones have been found effective against a range of pathogens, including bacteria, fungi, and viruses, contributing to their role as potential antimicrobial agents. Their anti-inflammatory and antioxidant properties also play a crucial role in mitigating chronic diseases associated with oxidative stress, such as cardiovascular and neurodegenerative disorders. Moreover, chalcones have demonstrated antidiabetic potential by improving insulin sensitivity and reducing blood glucose levels. The neuroprotective effects of chalcones are also notable, as they have been shown to reduce amyloid plaque formation and tau phosphorylation, both key features of Alzheimer's disease. Despite their promising therapeutic activities, chalcones face challenges such as poor bioavailability and metabolic instability, which hinder their clinical application. However, recent advancements in the synthesis of chalcone derivatives aim to overcome these limitations, offering hope for the development of new therapeutic agents. Continued research is necessary to optimize chalcones for clinical use and further explore their mechanisms of action. Conclusion:

A broad range of pharmacological activities, including antimalarial, anticancer, antiprotozoal (antileishmanial and antitrypanosomal), anti-inflammatory, antibacterial, antifilarial, antifungal, antimicrobial, anticonvulsant, and antioxidant properties, can be attributed to chalcones and their derivatives. As a result, scientists are paying more and more attention to chalcones and their derivatives to find novel, powerful pharmacological activity in them

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