REVIEW ARTICLE

A Comprehensive Review on Chalcone Analogues-versatile Scaffold with Medicinal and Biological Potential

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Abstract

This review's main focus is on the most recent synthesis of chalcones with N, O, or S heterocycles, highlighting their biological potential. Chalcone derivatives are considered in beneficial species because they possess a keto-ethylenic moiety, CO–CH=CH–. Due to the existence of a reactive α, β-unsaturated carbonyl group, the synthesis of chalcone derivatives, which have been physiologically explored for use against specific disease targets, has been made possible by recent advances in heterocyclic chemistry. The need for novel drugs that are effective against multidrug-resistant pathogens has been driven by the growth in antibiotic resistance brought on by a variety of reasons. Chalcones are phenolic compounds that fall within the flavonoids category. They are a part of a large category of naturally occurring bioactive substances. During this review we have gone through a number of studies where chalcones were created via Claisen Schmidt condensation of suitable acetophenone with suitable aromatic aldehydes in the presence of an aqueous solution of potassium hydroxide and ethanol at room temperature in an effort to create antibacterial agents. The review content have been obtained through web browsing on various scientific databases and search engines like Science Direct, Pub Med, Research Gate, Google Scholar, etc. The synthesis of diverse chalcone derivatives was motivated by the potential activity of naturally occurring chalcones as anticancer, anti-inflammatory, antibacterial, antioxidant, and antiparasitic characteristics, as well as by their unique chemical structural structure. Flavonoids and isoflavonoids, which are frequent chemical building blocks found in a variety of naturally derived compounds, are enhanced by chalcone. This review may prove to be helpful for the creation and design of new powerful therapeutic medications.

Keywords: Chalcones analogs, Biological properties, Flavonoids, Claisen Schmidt.

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Introduction

Chalcone is a compound consisting of two aromatic rings linked by an unsaturated alpha, beta-ketone, with various substituents on the two aromatic rings. Chalcone can be easily found in most of plants naturally and is an intermediate precursor of flavonoids and isoflavonoids. It was reported to have a wide range of applications in the fields of biology and biochemistry such as antitumor, anti-inflammatory, and antimalarial agents.[1] Chalcones are the natural phytoconstituents having functional groups in an aromatic ketone and an enone that forms important moiety for a variety important for biological significance, which are jointly known as chalcone.[2] Chalcones are natural phytoconstituents widely distributed in plants that originate in the flavonoid family including chalcones, which are secondary metabolites of edible or medicinal plants.[3] The foundation of chalcone 1, 3-diphenyl-2-propen-1-ones is two aryl moieties connected by an alpha, beta-unsaturated carbonyl group. The structure of these compounds has a -C=O-CH=CH- keto-ethylenic moiety.[5] They have an order that contains delocalized pi electrons in their aromatic rings. Chalcones, which greatly contribute to the coloration of the corolla of various plants, are mostly composed of polyphenolic compounds with hues ranging from yellow to orange. Chalcones occur naturally in a variety of foods, including fruits, vegetables, cereals, flowers, tea, roots, stems, and wine.[8]

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Clinical Significance of Chalcone Analogs

Chalcones are - unsaturated ketones containing the reactive keto-ethylenic group –CO-CH=CH-. (Figure 1). The presence of a double bond in conjugation with carbonyl functionality is believed to be responsible for the biological activities of chalcones, as the removal of this functionality makes them inactive.[9] The conjugated double bond produces the delocalization of π electrons which reduces its electrophilic character and makes it an intermediate for the synthesis of various biologically important heterocycles such as pyrazoline, oxazoline, thiazine, oxazine, pyrimidine, etc.[10]

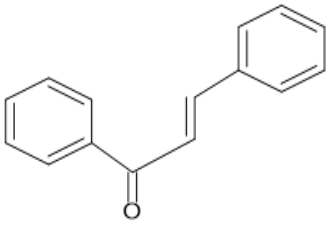

Figure 1: Structure of chalcone

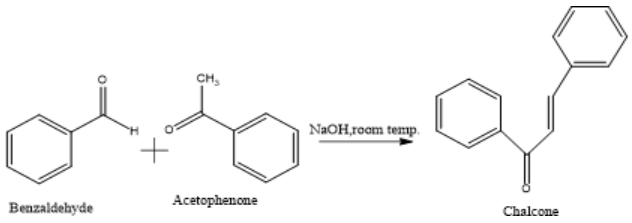

Figure 2: Claisen schmidt condensation of suitable acetophenone with suitable aromatic aldehydes

Methodology

A number of chalcones were created via Claisen Schmidt condensation of suitable acetophenone with suitable aromatic aldehydes in the presence of an aqueous solution of potassium hydroxide and ethanol at room temperature in an effort to create antibacterial agents. IR and NMR spectrum data were used to describe the produced molecules.

A series of chalcones prepared by Claisen Schmidt condensation of suitable acetophenone with suitable aromatic aldehydes in the presence of an aqueous solution of potassium hydroxide and ethanol at room temperature (Figure 2) in an effort to create antibacterial agents.[11]

Anticancer

A complex illness that kills millions of people every year globally, cancer is brought on by unchecked cell growth. The potential for chalcone compounds to have anticancer activity through a variety of physiological mechanisms has been studied. The developed chalcone compound with a novel anticancer-related mode of action, diverse chalcone derivatives are designed and synthesized. Variously substituted poly-methoxy chalcone components were prepared. Anticancer therapies employ a number of methods, such as surgery, chemotherapy, and radiation, either alone or in combination.[12] Major obstacles to effective cancer therapy include side effects and multidrug resistance. Chalcones are one example of a phytochemical that has been found to be affordable, accessible, and comparatively harmless.[18] Chalcones have the ability to target important molecular processes that may contribute to the genesis and spread of cancer. Scientists are utilizing several molecular pathways to create novel, more potent, and effective therapeutic anticancer medications by utilizing traditional knowledge of medicinal plants and the sustainable use of marine natural goods.[20]

Antimalarial

Malaria is a major parasitic infection disease in the world, caused by *Plasmodium falciparum*. Chalcones are precursors of numerous plant metabolites with distinctive scaffolds owing to exceptional biological properties. The main structure is 1,3-diphenyl-2-propene-1-oness, the two benzene rings are associated by highly electrophilic three-carbon alpha, beta-unsaturated carbonyl configuration. Chalcone derivatives have been tested for its antimalarial activity against *P. falciparum*. Chalcone drugs are used by the treatment of malaria. The available medicines such as chloroquine is no longer effective in the treatment of malaria, due to the increasing of multiple drug resistance. *P. falciparum* and *P. vivax* are the two major human malaria parasites. The majority of deaths are caused by *P. falciparum*, which has become resistant to almost all treatments. It is understandable why chalcones' antimalarial action has attracted so much attention. A Michael addition of nucleophilic species to the double bond of the enone is likely the cause of the strong antimalarial activity of several chalcones.[30-34]

Antiviral

The chalcone derivatives mainly, nucleosides have generated widespread interest due to their antiviral properties. An example of a chalcone analog that is utilized as an antiviral. Since the dawn of time, several viral epidemics have wracked the globe, including the most recent COVID-19 pandemic. The ongoing appearance and spread of new viral illnesses have compelled researchers to look for fresh therapeutic approaches that can get beyond the drawbacks of antiviral medications that are already on the market. Chalcone are natural studies on the suppression of plant viruses and human rhinoviruses led researchers to the discovery of chalcones' antiviral capabilities. Chalcones have varying antiviral activity, which implies that the antiviral activity of each chalcone is dependent on certain patterns of substitution. Onyilagha *et al.* looked into hydroxy and methoxy-modified chalcone compounds. Antiviral activity of chalcones on nepoviral infectivity in tomato ringspots.[35-40]

Antibacterial

More and more research are being done on chalcones' antibacterial properties. Many research teams have either synthesized or altered naturally occurring chalcones or have isolated and characterized the structure of chalcones with antibacterial activity. The capacity of the, -unsaturated ketone to undergo a conjugated addition to a nucleophilic group, such as a thiol group in an important protein, has been linked to bactericidal effects. A number of a-triazolyl chalcones were created, and the created substances showed strong antibacterial and antifungal activity. In a different investigation into the antibacterial action of three chalcones, diuvaretin, uvaretin, and isouvaretin, it was shown that

only gram-positive bacteria were inhibited from growing in culture.[41]

Antileishmanial

A set of common illnesses known as leishmaniasis are brought on by parasitic protozoans of the genus *Leishmania*. A variety of *in-vitro* and *in-vivo* experiments have recently revealed a number of synthesized and naturally occurring chalcone derivatives to be promising *Leishmania* inhibitors. Despite extensive testing of synthetic materials, licochalcone A is still one of the few naturally occurring chalcones that is being studied. There are several protozoan parasite species. A set of common illnesses known as leishmaniasis are brought on by parasitic protozoans of the genus *Leishmania*. A variety of *in-vitro* and *in-vivo* experiments have recently revealed a number of synthesized and naturally occurring chalcone derivatives to be promising *Leishmania* inhibitors. Despite extensive testing of synthetic materials, licochalcone A is still one of the few naturally occurring chalcones that is being studied. The protozoan parasite comes in several species.[41]

Antifungal

It is intriguing to note that chalcone derivatives only displayed activity against dermatophytes and not other types of fungi, as dermatophytes are a group of fungi that typically infect the keratinized areas of the body and dermatomycoses are very challenging to treat. Using the agar dilution technique, Lopez *et al*. investigated chalcones against a panel of human opportunistic pathogenic fungi. An intriguing has been published on the effect of the substituents on ring A. A number of chalcones were created in an effort to create antimicrobial agents using the Claisen-Schmidt condensation of suitable acetophenones with suitable aromatic aldehydes in the presence of an ethanol and potassium hydroxide aqueous solution at room temperature. By using their IR, ^{1}H-NMR spectrum data, and elemental analyses, the produced substances were identified. The cup plate technique was used to evaluate each compound's antibacterial and antifungal properties. Crotmadine, a compound that displayed antifungal action, was isolated from the leaves and stems of *Crotalaria* madarosis Wight & Arn. An ethanol extract of the leaves of *Maclure tinctoria* (L.) D. Don ex stead yielded five prenylated flavonoids, including one novel natural substance. All of the identified compounds were tested for effectiveness against *Cryptococcus neoformans* and *Candida albicans*. The most effective compound against both yeasts was discovered to be compound 3 (isobavachalcone). By using assay-guided fractionation, the crude methanolic extract of *Zuccagnia angulate* Hook. and Arn. allowed the separation of two chalcones as the components in charge of the antifungal activity. The chalcones isolated from the methanol extract of *Artocarpus nobilis* Thwaites' leaves shown strong fungicidal action when used as an antifungal agent. The antifungal susceptibility of a novel dimeric chalcone isolated from the fresh entire uncrushed fruits of *Mallotus philippensis*'s var. *pallidus* airy shaw was successfully tested.[42-44]

Anti-inflammatory

Numerous chalcones and their derivatives have been mentioned in the literature as having potential to inhibit cyclooxygenase (COX). The results of a study using a carrageenan-induced hind paw edoema model to evaluate the anti-inflammatory effects of new chalcone derivatives revealed that the 5′-chloro-2′-hydroxy-4′6′-dimethyl-3, 4, 5-trimethoxy chalcone exhibited the most potent anti-inflammatory activity with a 90% inhibition of edoema]. Another research examined the inhibitory effects of a new family of indole-based chalcones on COX-1 and COX-2, and found that COX-1 was remarkably inhibited. The nitrogen-containing chalcone derivatives demonstrated inhibition of certain inflammatory process-related enzymes, including trypsin, COX-2, and -glucuronidase. In a different study, it was found that artificial fluoro-hydroxy substituted pyrazole chalcones had a selective inhibitory effect against the COX-2 enzyme and a moderate effect against the COX-1 enzyme. The suppression of COX-2 was related to the activity. Nitric oxide (NO) and prostaglandin E2 (PGE2) production suppression has been suggested as a possible treatment for a variety of inflammatory illnesses. Damage to tissues might result from high NO levels. It has been shown that activated macrophages produce an excessive amount of NO in inflammatory disorders like rheumatoid arthritis. Therefore, it would be intriguing to create NO inhibitors that are strong and focused for possible therapeutic applications[45-52]

Antimicrobial

Chalcones are well-known chemical building blocks used to create a variety of heterocyclic compounds. According to reports, chalcone-based compounds contain a variety of biological properties, including antibacterial properties. release of chemical mediators, leukotriene B4 production, tyrosinase activity, and aldose reductase activity are all inhibited. The antibacterial action of chalcones is discovered to be caused by the presence of a reactive, -unsaturated keto function. Ten fresh chalcones based on thiazoles were created and there *in-vitro* antifungal capabilities were examined as part of ongoing research into the development of novel antimicrobials. These had little antifungal efficacy against all of the investigated fungi and were less potent than ketoconazole and bifonazole. The antibacterial activity of the produced compounds was examined *in-vitro* using the agar cup-plate technique. The outcomes showed good antibacterial and antifungal activity.[53]

Antidiabetic

According to reports, chalcones may have an inhibitory effect against alpha-glucosidase or alpha-amylase.[54]

Result and Discussion

The synthesis of diverse chalcone derivatives was motivated by the potential activity of naturally occurring chalcones as anticancer, anti-inflammatory, antibacterial, antioxidant, and antiparasitic characteristics, as well as by their unique

chemical structural structure. Flavonoids and isoflavonoids, which are frequent chemical building blocks found in a variety of naturally derived compounds, are enhanced by chalcone

Conclusions

A special template called a chalcone is connected to several biological processes. The compounds or extracts of chalcone-rich plants may be used as medications or food preservatives due to the phenolic groups' radical quenching characteristics. This review article has listed the anti-infective and anti-inflammatory properties of several chalcones. The literature is analyzed to provide a meaningful overview of the structural requirements.

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