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CHALCONES IN MEDICINAL CHEMISTRY: AN IN-DEPTH ANALYSIS OF STRUCTURE-ACTIVITY RELATIONSHIPS AND PHARMACOLOGICAL SIGNIFICANCE

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ABSTRACT

Background: Chalcones are among the leading categories of flavonoids across the entire kingdom of plant, The term chalcone is originated from the Greek name chalcos which means bronze. Chalcones were initially manufactured in the research lab in late 1800s Naturally existing chalcones were not separated till the year 1910. Chalcones possess a broad spectrum of biological activities including antioxidative, antibacterial, antihelmintic, amoebicidal, antiulcer, antiviral, insecticidal, antiprotozoal, anticancer, cytotoxic and immunosuppressive. Changes in their structure have offered a high degree of diversity that has proven useful for the development of new medicinal agents having improved potency and lesser toxicity and good pharmacological actions. **Objectives:**

- To Study in detail about Chalcones
- To Evaluate the Presence of Chalcones as a Potential API
- To Know about the Possible Applications and the Effects of Chalcones.
- To Draw Conclusions About the Anti-Inflammatory Activities of Chalcones.

- To Analyze the Possible Advantages and Risks associated with the Use of Chalcones as an API.

KeyFindings: Chalcones and Chalcone Derivatives, Pharmacological Activities of Chalcones, Anti-Inflammatory Activities of Chalcones, Sources and Synthesis of Chalcones.

Conclusion: The purpose of this review is to summarize the most important pharmacological activities highlighting the cellular and molecular mechanisms of action of natural and synthetic chalcones, to better understand their therapeutic potential in the future while specifically focusing on their Anti-Inflammatory Activities.

1. INTRODUCTION

The chemistry of chalcones has generated intensive scientific studies throughout the world. The name "Chalcones" was given by Kostanecki and Tambor.[1]

Chalcones are also known as benzyl acetophenone or benzylidene acetophenone. In chalcones, two aromatic rings are linked by an aliphatic three carbon chain. Chalcones (trans-1, 3-diaryl-2-propen-1-ones) are α, β-unsaturated ketones consisting of two aromatic rings (ring A and B) having diverse array of substituents.

Rings are interconnected by a highly electrophonic three carbon α, β-unsaturated carbonyl system that assumes linear or nearly planar structure.[2] They contain the ketoethylenic group (–CO–CH=CH-). Chalcones possess conjugated double bonds and a completely delocalized π-electron system on both benzene rings.

Chalcones have been used as intermediate for the preparations of compounds having therapeutic value.[3] Chalcones have been identified as interesting compounds that are associated with several biological activities. The most common chalcones found in foods are phloretin and its glucoside phloridzin (phloretin 2′-0-β-glucopyranoside), and chalconaringenin.

Chalcone bears a very good synthon so that variety of novel heterocycles with good pharmaceutical profile can be designed.

Therapeutic applications of chalcones trace back thousands of years through the use of plants and herbs for the treatment of different medical disorders, such as cancer, inflammation, and diabetes. Several chalcone-based compounds have been approved for clinical use.

For example, metochalcone was once marketed as a choleretic drug, while sofalcone was previously used as an antiulcer and mucoprotective drug.[4]

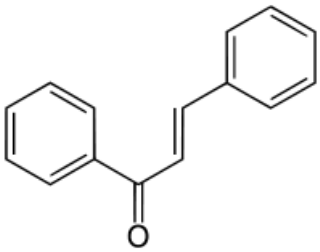

Figure 1: Chalcone Basic Structure.

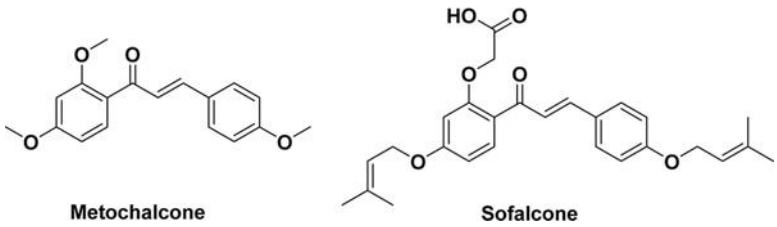

Figure 2: Structure of Chalcone Derivatives.

2. Sources of Chalcones

Chalcones are occurrs not only in flowers but also in leaves, fruits, roots, stems and all parts of the plant kingdom. The naturally occurring chalcones are generally crystalline solids and they possesses different colors including yellow, orange, and brown. The largest number of natural chalcones has been isolated from species of the Leguminosae, Asteraceae and Moraceae families.[5]

Chalcones constitute an important group of natural compounds that are especially abundant in fruits (e.g., citruses, apples), vegetables (e.g., tomatoes, shallots, bean sprouts, potatoes) and various plants and spices (e.g., licorice), many of which have been used for centuries in traditional herbal medicine.

The majority of the content of chalcones in citrus fruits and various plants is mediated through the formation of 4,2′,4′,6′-tetrahydroxychalcone also known as naringenin chalcone by chalcone synthase. Naringenin chalcone also plays an essential role in the flavonoid biosynthetic pathway and contributes significantly to the total amount of plant flavonoids.[6]

Chalcones are the key compounds in many species of plants in plant metabolism, through where they can be extracted, isolated, purified and converted into a viable from of dosage form.

Apart from these biological sources many chalcones are synthesized by artificial chemical reactions such as Claisen-Schmidt condensation, Aldol condensation.

There have been various successful attempts of biological Synthesis of chalcones and their extraction from their natural counterparts.

The Extraction of pure chalcones have made it possible for its approval in clinical trials as a possible remedy for the treatment of various diseases.

3. Importance of Chalcones

1) They have close relationship with flavones, aurones, tetralones and aziridines.

2) Chalcones and their derivatives find application as artificial sweeteners, scintillator, polymerization catalyst, fluorescent whitening agent, organic brightening agent, stabilizer against heat, visible light, ultraviolet light and aging.[7]

3) 3, 2', 4', 6'-tetrahydroxy-4-propoxy-dihydrochalcone-4-β'-neohesperdoside[8] has been used as synthetic sweetener and is 2200 times sweeter than glucose.

4) They contain a keto-ethylenic group and are therefore reactive towards several reagents e.g. (a) phenyl hydrazine, (b) 2-amino thiophenol etc.

5) The chalcones have been found useful in elucidating structure of natural products like hemlock tannin, cyanomaclurin, ploretin, eriodictyol and homo eriodictyol, naringenin etc.

6) The synthesis and structural studies of complexes of Co (II), Ni (II), Cu (II), Zn (II) and Cd (II) with substituted chalcones has been reported.[9] In general, for metal Complexation reactions, the Schiff derivatives of the chalcones are preferred which not only offer selectivity in metal Complexation reactions but also an enhancement in biological activities.

7) The presence of α,β-unsaturated carbonyl system of chalcone makes it biologically active. They have shown antibacterial activity against S. aureus, E. coli, C. albicans, T. utilis, S. sake, W. anomalaand some other organisms.

8) The Liquorice extracts contains a chalcone, viz. Isoliquritigenin, which is currently in use as a phosphodiesterase III inhibitor for the treatment of cardiovascular diseases.[10] In the Far East countries such as Korea, Japan, and China, another chalcone compound called 'Butein'

has also been traditionally used for treatment of pain, thrombotic disease, stomach cancer, and parasitic infection as well as a food additive.

9) Liquorice has been used in China for the treatment of gastric and duodenal ulcers, bronchial asthma, Addison's disease, poisoning by food and drugs and skin disease such as eczema and urticaria. It still finds medicinal application because of its wide-ranging therapeutic properties, including relief from rheumatic and other types of pain and healing effect on ulcers.

10) Saxena and co-workers grafted chalcone derivatives on estradiol framework some of which showed potent anticancer activity against some human cancer cell lines.[11]

4. Chemistry

The Physical Characteristics associated with Chalcones Include a Molecular Weight of 208.26 gm/mol, A Density of 1.071 g/cm^3, A Melting Point that ranges from 55^{0C} to 57^{0C}, and a Boiling Point that Ranges from 345$^{\circ C}$ to 348$^{\circ C}$. Chemical formula is Written as $C_{15}H_{12}O$.

The chemistry of chalcones has generated intensive scientific studies throughout the world. Chalcones are open chain flavonoids whose basic structure includes two aromatic rings bound by a three carbon α, β-saturated carbonyl group. Chalcones are polyhydroxylated in the aryl ring and phenolic group present in basic structure shows redical quenching properties.

Chalcone are important intermediates in the synthesis of many pharmaceuticals and utilization of heterogeneous catalyst for the production of chalcones can also been used but there are studies which state that the use of activated carbon as catalyst in the combination with ultrasounds, because their extended surface area, micro porous structure and high degree of surface activity.

Chalcones, dihydrochalcones and aurones are composed of pigments whose colour changes from yellow to orange in some Coreopsis and Asteraceae taxa species. These compounds are found not only in flowers but also in lots of different tissues of the plants. Free radical scavenging properties of phenol groups of chalcones increased the interest in consumption of plants that included chalcones.[12]

Chalcones are included dimer, oligomer, Diels-Alder adducts and different conjugates. At the same time because of being precursors of all of other flavonoid groups, chalcones are very

important biosynthetic compounds. Essential property that separates chalcones and dihydrochalcones from the other Flavonoids is that an open chain with three carbon molecules binds to A and B ring instead of C ring of Flavonoids (Figure 1).

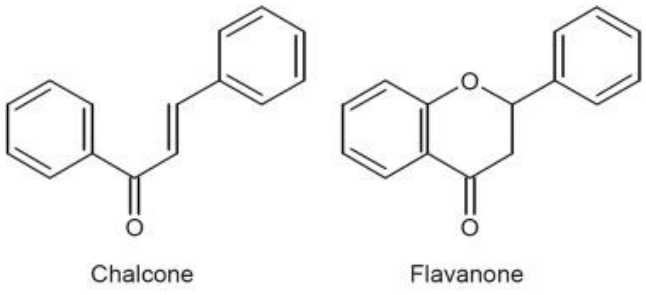

Figure 3: Chalcone and Flavanone.

Chalcones turn to flavanones with a stereospecific reaction catalyzed by chalcone isomerase enzyme in plants. Close biogenetic and structural relation between chalcones and flavanones is the reason for these compounds usually found together in natural products. This is the cause of the identification of chalcone, dihydrochalcone and aurones together with flavanone and dihydroflavonol generally. Chalcones are called as minor flavonoids. But using name of minor flavonoids for chalcones doesn't seem appropriate because of increasing of new species of flavonoids.[13]

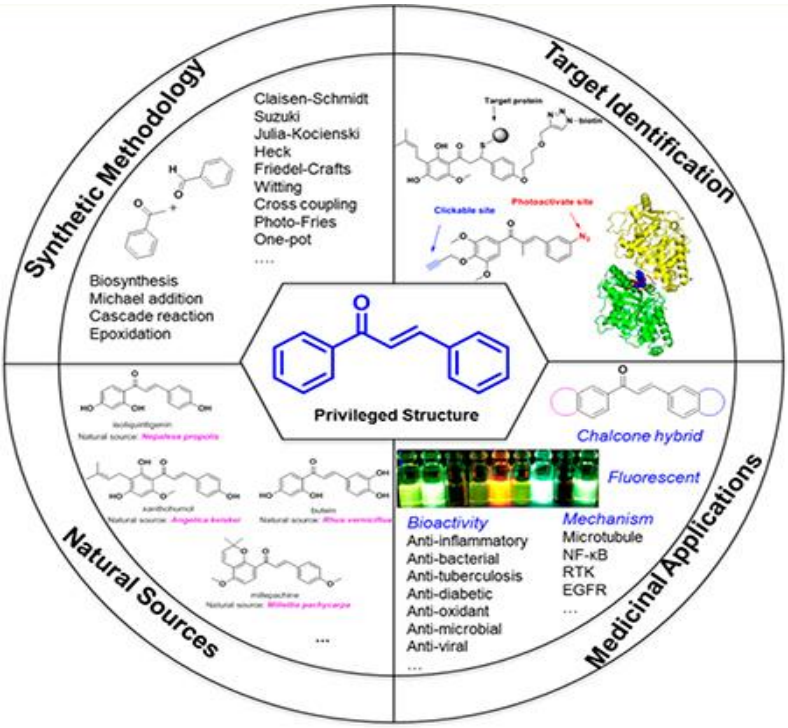

Figure 4: Chemistry of Chalcones.

Hence, chemically chalcones have an unprecedented potential to tap into the drug development sector. Which could have immense capability for chalcones other than its inherited pharmacological abilities to make a dent in the chemical world. As it could also serve as a precursor for flavanoids as well as a variety of other molecues for their synthesis.

5. Identification Tests for Chalcones[14]

Table no 1: Identification Tests for Chalcones.

Test	Observation	Inference	Result
Solubility Tests: 1)Compound + Alcohol (Methanol, Ethanol)	Soluble	Presence of chalcone group	Chalcones present
2)Compound + Alkaline Solution (NaOH, KOH,$CaCO_3$)	Deep red/ orange red color	Presence of chalcone group	Chalcones present
Wilson Test: Compound + H_2SO_4	Pink color	Presence of chalcone group	Chalcone present
Confirmation Test: 1)Compound + Alcoholic ferric chloride solution	Violet color	Presence of free phenolic hydroxyl groups	Chalcones Confirmed
2)Compound + Dil.Acetic Acid + 1-2 drops of H_2SO_4	Orange/ Purple Color	Liberation of carbonium ion	Chalcones Confirmed

6. Synthesis of Chalcones

Synthetic method of preparing chalcones

The most convenient method is the Claisen- Schimdt condensation of equimolar quantities of aryl methyl ketone with aryl aldehyde in the presence of alcoholic alkali.

6.1 Claisen-Schmidt Reaction

A variety of methods are available for the synthesis of chalcones, the most convenient method is the one that involves the Claisen- Schmidt condensation of equimolar quantities of a substituted acetophenone with substituted aldehydes in the presence of aqueous alcoholic alkali.

In the Claisen-Schmidt reaction, the concentration of alkali used, usually ranges between 10 and 60 %. The reaction is carried out at about 50°C for 12-15 hours or at room temperature for one week. Under these conditions, the Cannizaro reaction also takes place and thereby

decreases the yield of the desired product. To avoid the disproportionation of aldehyde in the above reaction, the use of benzylidene-diacetate in place of aldehyde has been recommended.

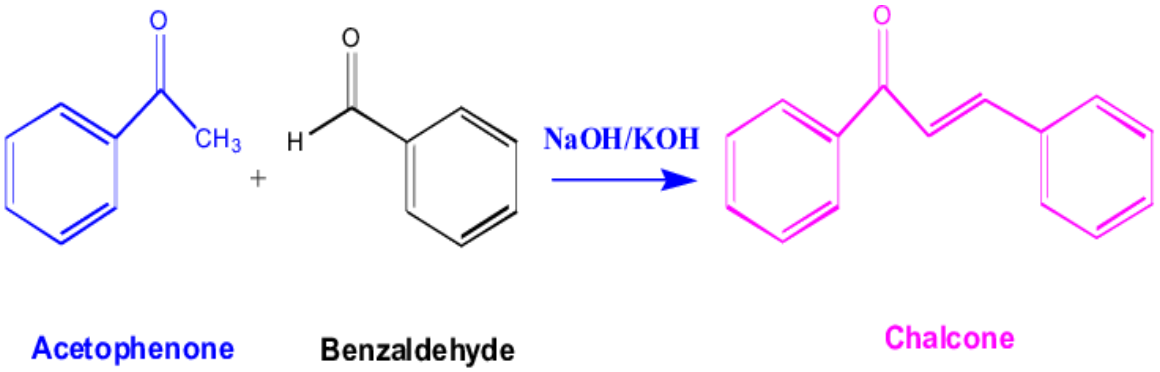

Figure 5: Claisen-Schmidt Reaction of Chalcones.

This reaction has been found to work without any solvent at all - a solid-state reaction. In a study investigating green chemistry synthesis, chalcones were also synthesized from the same starting materials in high temperature water (200 to 350 °C). Alternatively, the substituted chalcones were synthesised by piperidine mediated condensation to avoid side reactions such as multiple condensations, polymerizations, and rearrangements. The presence of enone functionality in chalcone moiety confers biological activity upon it, like anti-inflammatoryanti-fungal, anti-oxidant, anti-malarial anti-tuberculosis analgesic anti- HIV and anti-tumor activities.[15]

6.2 Microwave Irradiation Assisted Synthesis

The Claisen–Schmidt condensation stays the most common method in homogeneous phase or in interfacial solid-liquid conditions using barium hydroxide catalyst (C-200). Unfortunately 2’-hydroxychalcones always cyclized to flavanones. One synthetic pathway to avoid this undesirable reaction is using protective group or the Friedel–Crafts reaction of phenols with acyl halides. This method request long reaction time and anhydrous conditions which limits the scope of its application.

By applying successful microwave irradiation for the preparation of target molecules. The reaction took place in well closed pressure tube for 2 min with high yields. It is noteworthy to mention that to carry out the reaction in an open vessel failed. A mixture of two products (3 and 4) and starting compounds was obtained in this case. Obviously, the well closed tube affords to reach temperatures much higher than boiling point of ethanol. The measured temperature in the reaction tube immediately.[16]

6.3 Aldol Condensation

Acetophenone and benzaldehyde are the starting materials for this reaction. First, acetophenone is treated with a base like KOH which converts it into the more active form, its enolate form. It will then react with benzaldehyde to form intermediate. The intermediate will then lose water molecule by heat to form chalcone.[17]

$C_6H_5\,CO\text{-}CH_3 + O{=}CHC_6H_5 \rightarrow C_6H_5CO\text{-}CH{=}CHC_6H_5$

Acetophenone Benzaldehyde Benzalacetophenone.

Figure 6: Aldol Condensation.

7. Structure Activity Relationship Studies of Chalcones

In the past decades, several reports has been published on structure-activity relationship (SAR) studies of chalcones and are more appropriate to recognize the structural signatures for further desing and develepoment of new therapeutic potent molecules.

Chalcones possess broad-spectrum pharmacological activities are believed due to their appropriate structural substitutions in ring A and B.

- Introduction of two strong electron withdrawing halogen groups at 2, 4- positions of aryl ring of chalcone may have possessed potent antibacterial activity while on incorpation of electron donating groups such as p-CH3, 2,4- (CH3)2, p- or m-OCH3 on aryl groups suppress the activity.

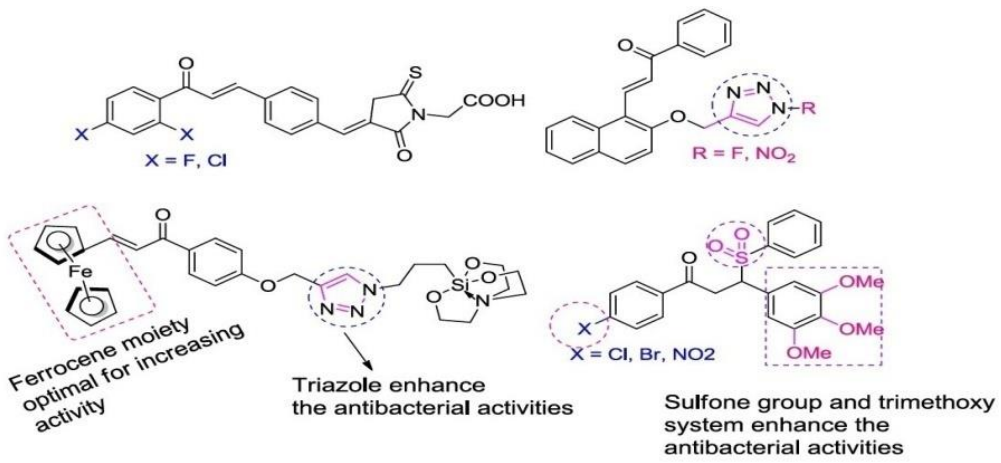

Figure 7: SAR of Antibacterial Chalcones.

- Mahapatra et al. (2015) reported the therapeutic approaches of chalcones and their structural studies in perspective of diabetes. Chalcones having either 2C- and 4C-hydroxyl pattern or more hydroxylation in ring B of chalcones exhibits potent antidiabetic activities.[18]

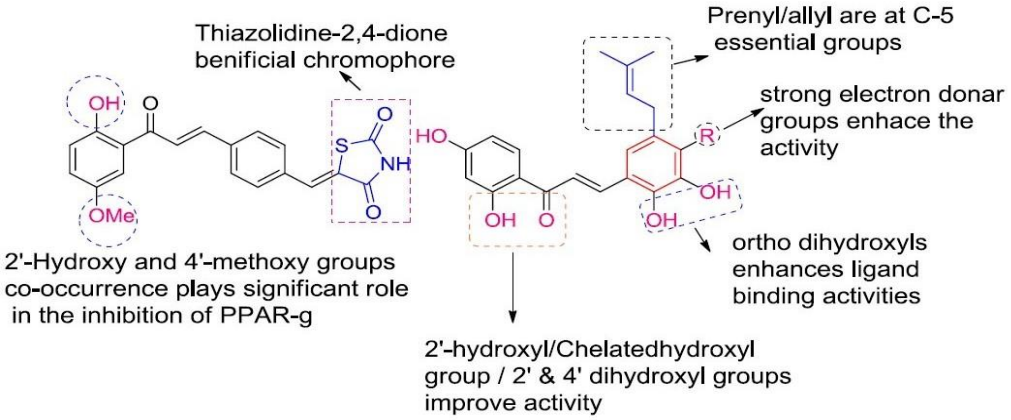

Figure 8: SAR of Antidiabetic Chalcones.

- A structural design like, 2C-hydroxylation or 2C-, 3C-dihydroxylation, 2,3,4-trihydroxylation, and 4-dimethylamino groups in chalcones are more essential and capable to possess a wide range of pharmacological activities including antioxidant activity and antibacterial activities, 2C-hydroxylation is in chelation with carbonyl group is exhibits promising biological activities.

- The presence of strong electron donar groups such as dimethylamino substituents in chalcone, showed potent inhibition of nitirc oxide synthase which is a important step in the inflammatory activity of body. Mono or poly hydroxyls or methoxylated chalcones were displays strong anti-inflammatory activity by inhibiting lipoxygenase.

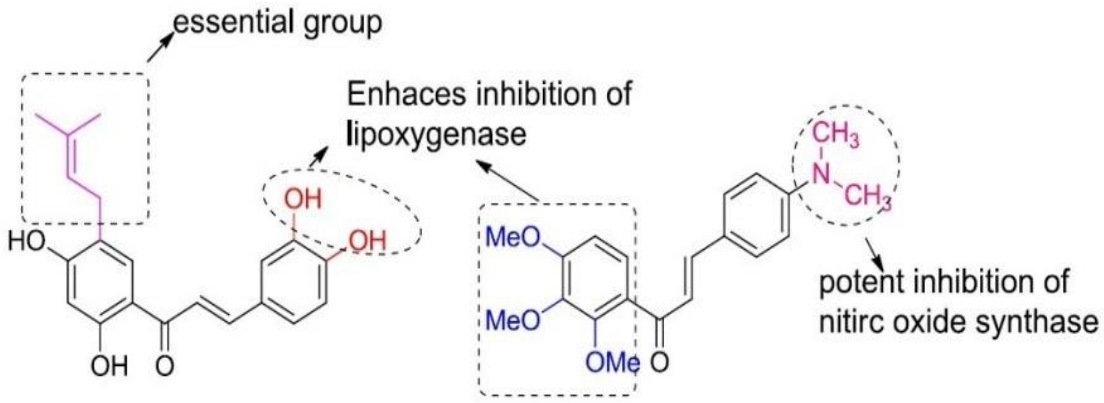

Figure 9: SAR OF Antiinflammatory Chalcones.

8. Pharmacological Activities of Chalcones

8.1 Antimicrobial Chalcones

Antimicrobial agents are the drugs used to treat infectious diseases caused by different types of bacteria and fungi. The use of these drugs is now common, and continuous efforts are put by the scientific community to search for newer antimicrobial agents due to antimicrobial resistance (AMR) shown by the microbes.

Mutation, gene transfer, phenotypic change, and selective pressure are some of the causes behind AMR. Antimicrobial or drug resistance is commonly developed by bacteria, fungi, parasites, and viruses when the microbe no longer responds to a drug that previously treated them effectively.

This AMR can lead to several issues including difficulty in controlling the disease, a longer stay of the microbes in the host, higher risks of spreading, and increase in mortality rates. Infectious diseases are one of the common problems encountered globally.

Although several commercially marketed drugs are available, the search for new drug molecules becomes essential for the treatment of infectious diseases. Consequently, the search for new antimicrobial agents becomes essential.

Herein we discuss the recent updates in the search of chalcones as an attempt to develop antimicrobial agents.

1)Methoxy-4’-amino chalcones showed good in vitro antimicrobial activities against Escherichia coli, Staphylococcus aureus, and Candida albicans. A molecular docking study also supported the observed results showing good interactions with the active sites of dihydropteroate synthase enzyme of E. coli and S. aureus.[19]

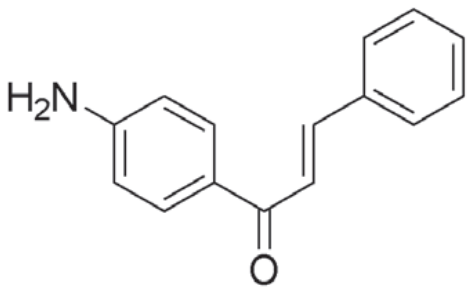

Figure 10: Methoxy-4’-amino Chalcones.

2)The quinoxalinyl chalcones synthesized by the Claisen-Schmidt condensation were found to be good antimicrobial agents. The antimicrobial studies were carried out against Staphylococcus aureus, Escherichia coli, and Candida albicans using the disk diffusion method. The selected chalcones were evaluated for anticancer and cytotoxicity activity against MCF-7 cancer cell lines using the MTT assay method showing good anticancer activity.[20]

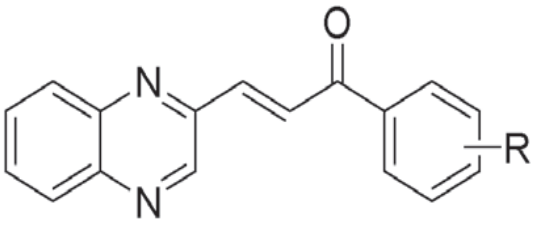

Figure 11: Quinoxalinyl Chalcones.

3)Some fluorinated chalcone-triazole hybrids were studied for antimicrobial activities against S. epidermidis, B. subtilis, E. coli, and P. aeruginosa bacterial and two fungal strains, namely, A. niger and C. albicans, by standard serial dilution method.[21] The results of the in vitro antimicrobial activity were compared with ciprofloxacin and fluconazole standard drugs.

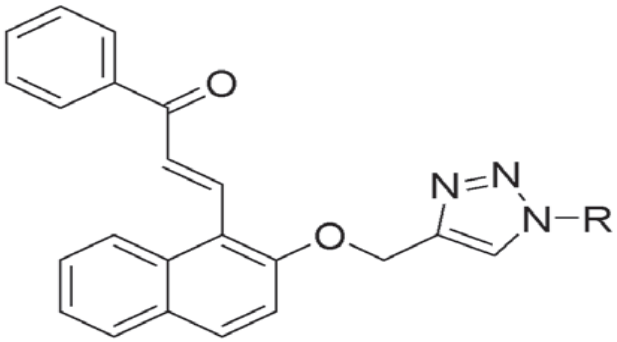

Figure 12: Fluorinated Chalcone-triazole Hybrids.

4) Dehydroacetic acid chalcone-1,2,3-triazole hybrids were shown to possess good in vitro antimicrobial activities against Staphylococcus epidermidis, Bacillus subtilis, Escherichia coli, and Pseudomonas aeruginosa bacteria and two fungal strains, viz., Aspergillus niger and Candida albicans.[22]

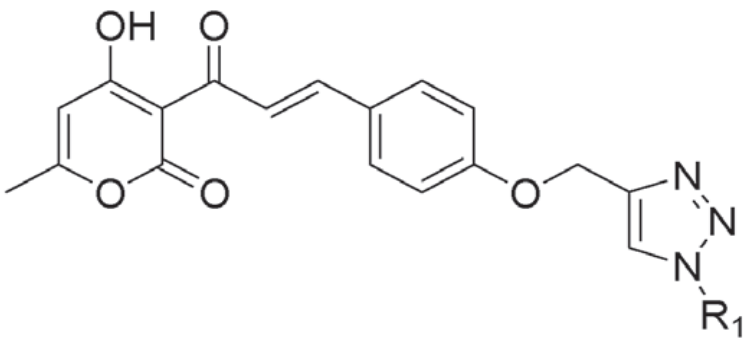

Figure 13: Dehydroacetic acid Chalcone-1,2,3-triazole hybrids.

5)Chalcones incorporated with a piperazine ring exhibited promising antimicrobial activity against Escherichia coli, Aspergillus niger, Salmonella typhi, Penicillium chrysogenum, and Staphylococcus aureus bacterial strains as well as Aspergillus flavus, Bacillus subtilis, and Candida albicans fungi.[23]

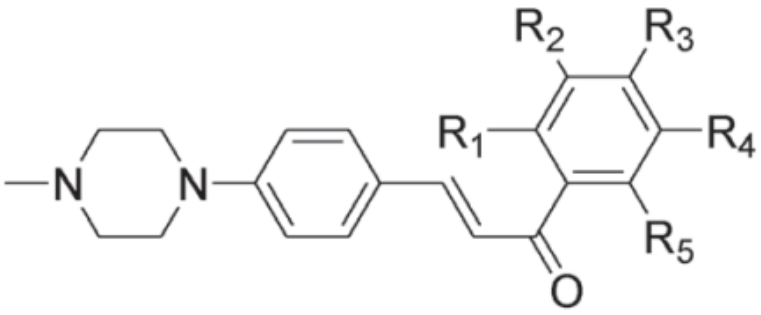

Figure 14: Chalcone with a Piperazine Ring.

8.2 Anti-Diabetic Chalcones

Non-insulin dependent diabetes mellitus (NIDDM, type-II diabetes) is a chronic metabolic disease characterized by insulin resistance, hyperglycemia and hyperinsulinaemia. The disease is often associated with obesity, dyslipidemia and hypertension leading to cardiovascular risks.

β3-adrenergic receptors (β3-AR) are found on the cell surface of both white adipose (WAT) and brown adipose tissue (BAT) where their stimulation promotes lipolysis and thermogenesis respectively. BAT also plays an important role in the maintenance of glucose homeostasis; hence β3-AR agonists are useful for treating diabetes as well as obesity. The aryloxypropanolamines were first described as β3-AR agonists.

Chalcones with proper substitutionmhave recently been isolated from Broussonetia papyrifera Commonly called as Paper Mulberry is known to selectively inhibit enzymes like protein tyrosine phosphatase 1B and aldose reductase. Their antioxidant property attracted to explore hybrid structures as antihyperglycemic agents, because oxidative stress also plays an important role in diabetic patients leading to vascular complications.

3,4-Dimethoxy compound displayed significant antihyperglycemic effect. Mono methoxy series showed blood glucose lowering activity. Compounds vicinally deoxygenated as dimethoxy and methylenedioxy substitution showed the best antihyperglycemic activity when compared to the corresponding monomethoxy compounds. Compounds containing propanolamine chain at para position showed significant activity as compared to meta and ortho substituted compounds.[24]

8.3 Anti-Inflammatory Chalcones

Anti-inflammatory drugs are the drugs which are used to reduce pain and inflammation. In other words, these are pain-relieving drugs. These drugs work mainly by inhibiting the cyclooxygenase enzymes, COX-1 and COX-2, that produce prostaglandins.

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 edema, 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).

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’.[25]

Herein we discuss some of the efforts for the development of chalcone-based heterocycles as effective anti-inflammatory compounds.[26]

1)Indole-based chalcones were synthesized and evaluated for in vitro COX-1 and COX-2 inhibitory activity.

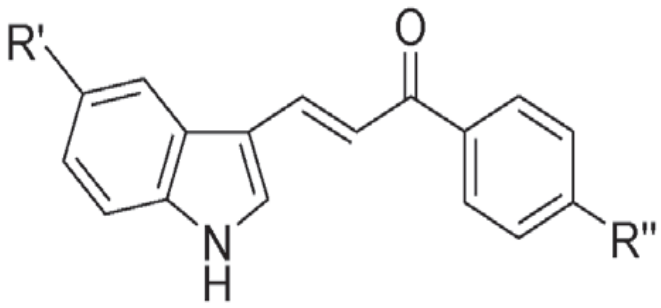

Figure 15: Indole Based Chalcones.

2)α-Substituted 20,3,4,40-tetramethoxychalcones and were evaluated for their ability to modulate inflammatory responses to influence on heme oxygenase-1, nitric oxide synthase, and cytokine expression levels. Anti-inflammatoryactivity was correlated with thiol-alkylating activity, i.e., stronger electrophilessubstituted with CF3, Br, and Cl were found to be more potent than the remaining derivatives.

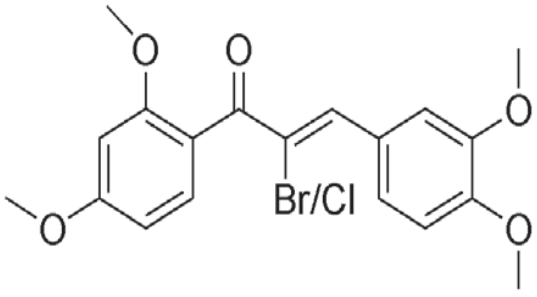

Figure 16: α-Substituted 20,3,4,40-tetramethoxychalcones.

3)Zhang et al. identified methoxy chalcones as a potential candidate for treating acute inflammatory diseases.[27]

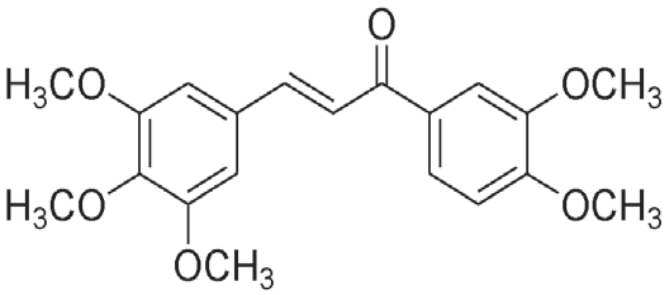

Figure 17: Methoxy Chalcones.

4) Pyrazole- and morpholine-containing chalcones were reported for anti-inflammatory activity by Gadhave and Uphade. The anti-inflammatory activity performed by carrageenan-induced rat paw edema method showed good potency of some of the tested compounds as compared with the standard diclofenac drug.[28]

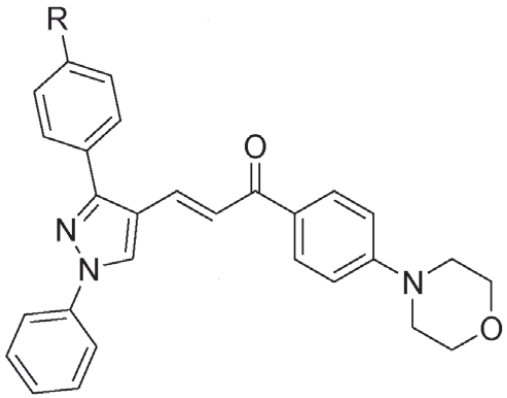

Figure 18: Pyrazole- and morpholine-containing chalcones.

5)Nurkenov et al. studied the in vitro anti-inflammatory effect of chalcones to inhibit the lipopolysaccharide-induced production of anti-inflammatory cytokine interleukin-6 and tumor necrosis factor.[29]

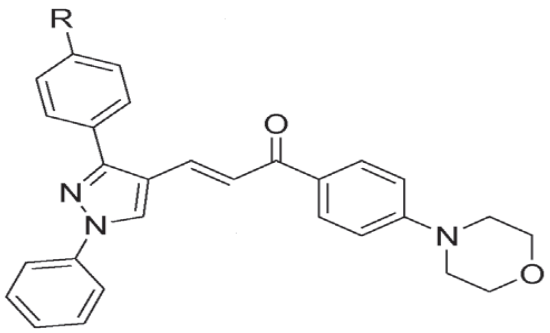

Figure 19: Lipopolysaccharide-induced Chalcones.

6)The imidazole containing chalcone molecule demonstrated noteworthy anti-inflammatory activity as compared with the standard drug, indomethacin.

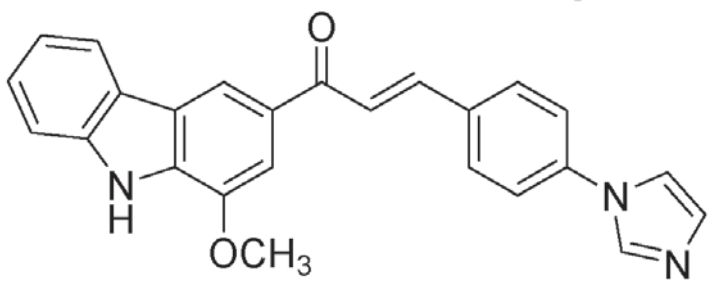

Figure 20: Imidazole containing Chalcone.

Naturally occurring chalcones are phenolic compounds, and often possess one or more phenolic hydroxyl functionality in their structures, which generally offer them with the inherent free-radical-scavenging properties that can be useful against oxidative stress.

It is known that oxidative stress is associated with inflammatory responses.

Thus, any reduction in oxidative stress is expected to inhibit inflammatory responses. Chalcones with free-radical-scavenging properties were shown to also possess anti-inflammatory properties.

8.4 Anti-Malarial Chalcones

Malaria is serious problems for recent era because of the number of antimalarial drug present has developed resistance to nearly all available drugs. No wonder that the antimalarial activity of chalcone has generated great interest. Michael addition of nucleophilic species to the double bond of the enone is probably the reason for the antimalarial activity.

Antimalarial property of some chalcone derivatives is derived from their ability to inhibit the parasitic enzyme, cysteine protease. The enzyme catabolizes globin into small peptides within the acidic food vacuole of the intra-erythrocytic malaria parasite. Without cysteine protease action osmotic swelling occurs, food vacuolar functions are impaired, and parasite death ensues. Malaria blood stage cysteine protease as the most likely target enzyme of chalcones.[30]

The chalcones are conjugates of α, ß-unsaturated ketones that assume linear or near planar structure. This structure is stable in acidic food vacuolar environment where malarial cysteine

protease acts, and structural conformation may fit well into the long cleft of the active site of the enzyme.

Recently, licochalconeA, isolated from chinise liquorice root has been reported highly effective in an in vitro screen against chloroquine sensitive and chloroquine resistance isolated of plasmodium falciparum.[31]

The chloro-series compounds showed marked antiplasmodial activity. Compound, a triazole substituted chalcone was found to be the most effective against the parasites, and pyrrole and benzotriazole showed comparable activities. The morpholine substituents in chloroseries was found to be the least active. Compound, containing triazole and chloro substituents, was found to be the most potent antiplasmodial derivative evaluated, suggesting that small lipophilic groups containing single or multiple nitrogen can enhance antimalarial activity in vitro.

In vitro antiplasmodial results of 4- chloro, 4-methoxy and 3,4,5- trimethoxy series suggested that small or medium sized but highly lipophilic groups containing multiple nitrogen or amine in acetophenone moiety impart antiplasmodial potential. Such compounds may provide additional hydrogen bonding with histidine residue present at the active site of the enzyme, cysteine protease. This is the first report in which chalcones containing small highly polar, lipophilic cyclic amines are showing antimalarial potential.[32]

8.5 Anti-Oxidant Chalcones

Free radicals, including the superoxide radical (O2), hydroxyl radical (OH), hydrogen peroxide (H2O2), and lipid peroxide radicals have been implicated in a number of disease processes, including asthma, cancer, cardiovascular disease, cataracts, diabetes, gastrointestinal inflammatory diseases, liver disease, mascular degeneration, periodontal disease and other inflammatory processes. These radical oxygen species (ROS) are produced as a normal consequence of biochemical processes in the body and as a result of increased exposure to environmental and/or dietary xenobiotics.

Antioxidants are the agents, which can inhibit or delay the oxidation of an oxidisable substrate in a chain reaction.

Chalcones belongs to the largest class of plant secondary metabolites. Which, in many cases, serve in plant defense mechanisms to counteract reactive oxygen species (ROS) in order to

survive and prevent molecular damage and damage by microorganisms, insects, and herbivores. They are known to possess antioxidant character at various extents. The antioxidant activity of natural compounds like chalconoids is related to a number of different mechanisms such as free radical scavenging, hydrogen donation singlet oxygen quenching, metal ion chelation and acting as a substrate for free radicals such as superoxide and hydroxide.

When the chalcone molecules react with the radicals, they are readily converted to the phenoxy radicals due to the high reactivity of hydroxyl groups of chalcones. The ortho (i.e.catechol structure) and paradihydroxylated benzene ring system are generally known to delocalize electrons.[33] As the phenoxy radicals occurring at the ortho- (i.e. catechol structure) or para-dihydroxylated benzene ring system are much more readily converted to a fairly stable semiquinone radicals while, meta dihydroxylated benzene ring system is comparatively less efficient to delocalize electrons as the phenoxy radicals occurring at the meta dihydroxylated ring system is converted to quinone structure which is not much stable.

9. CONCLUSION

From the above review it can be said that chalcones and their derivatives display a wide range of Pharmacological activities, such as antimalarial, anticancer, antiprotozoal (antileishmanial and antitrypanosomal), anti-inflammatory, antibacterial, antifilarial, antifungal, antimicrobial, anticonvulsant and anti-oxidant activities.

Furthermore, this comprehensive review describes the synthesis of chalcones, importance of chalcones therapeutic applications and their structure activity relationship studies. It is an interesting note to mention that the chalcone have a privileged template with an α,β-unsaturated carbonyl system and easily allow for the structural modifications.

For this reason, the researchers make much attention on skeletal modification of chalcones in the design of new and novel materials with diverse applications. Hence, chalcone is an innovative scaffold and plays a significant role in the drug discovery.

10. DISCUSSION

Through this comprehensive and comparative review about chalcones, we have learned that chalcones are not only a simple bridge compounds but they have many useful therapeutic

applications related directly to their pharmacological activities or their tendency to act a precursor for the synthesis of many drug compounds.

Upon further work in the field of chalcones they can be established as a good source of dyes, drug intermediates or as a replacement for higher grade more expensive experimental studies involving plant enzymes or also could prove to be a solution for new sources of antibiotics to combat the grave problem of antibiotic resistance.

Their availability is abundant as they're basically available from any plant source which makes their availability pretty easy and cheap.

Further exploration of derivatives of chalcones may open a huge gate of possibilities to entire class of chalcones-derived drugs, which may be applicable for the therapy of diseases beyond those mentioned in this review.

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