Plant Archives Vol. 20, Supplement 1, 2020 pp. 3812-3819 **e-ISSN:2581-6063 (online), ISSN:0972-5210**

REVIEW ARTICLE
CHALCONES: A PRIVILEGED SCAFFOLD WITH DIVERSE BIOLOGICAL ACTIVITIES

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Abstract

This review article provides information on the biological activities of chalcone whether natural or synthetics derivatives. Chalcone (1,3-diaryl-2-propen-1-ones) derivatives are widely found naturally (pteridophytes to multicellular organism). Chemically it consist of open-chain flavonoids in which the two aromatic rings are joined by a three-carbon α,β-unsaturated carbonyl system. Chalcones have been reported to possess many pharmacological activities, including anti-inflammatory, antimicrobial, antifungal, antiviral antioxidant, hepato-protective, anti-cancer activities and also have been reported to manage cardiovascular system disorders. Chalcones are secondary metabolites found in plants. Some natural flavonoids also help in hostility oxidative stress and play vital role as growth regulators, chalcones may exist in cis or trans form and trans form is more favorable. Some chalcones are isolated naturally from different plants, and have been approved for clinical trials in the treatment of cancer, cardiovascular disorders, viral diseases and have extensively shown one or more pharmacological activities. The main objective of this review article is that to summarize the recent development in the pharmacological or biological activities of natural or synthetic chalcone.

Key words: Chalcones, Flavonoids, Anti-cancer, Antioxidant, Claisen-schmidt.

Introduction

Chalcones are considered to be precursors of flavonoids and isoflavonoids which are one of the major classes of natural products such as vegetables, fruits, spices, tea and soya. The naturally occurring chalcones and its synthetic analogues exhibit a wide spectrum of biological activities (Dimmock *et al*., 1999; Go *et al.,* 2005; Carlo *et al*., 1999). The flavonoids are hydroxylated phenolic substances and are synthesized by plants in response to microbial infection (Dixon *et al*., 1983). Their activities are structure dependent, and the chemical nature of flavonoids depending on their structural class, degree of hydroxylation, other substitutions and conjugations, and degree of polymerization (Hemi *et al*., 2002). Chemically it is defined as an- α,β -unsaturated ketone having core scaffold of 1,3-diaryl-2-propen-1-one. The phenyl ring when attached to the carbonyl group is defined as A ring and the other benzene ring is named as the B ring as shown in (Fig 1).

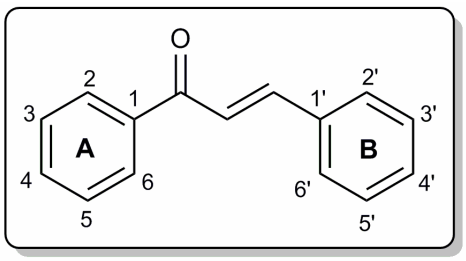


Fig. 1: Basic structure of Chalcone

Generally these are chemically synthesized by claisen-schmidt condensation reaction of aldehyde and ketone as depicted in (Fig. 2) which shows base catalyzation or acid catalyzation leads to dehydration that yields chalcones (Guida *et al*., 1997; Romanelli *et al*., 2011).

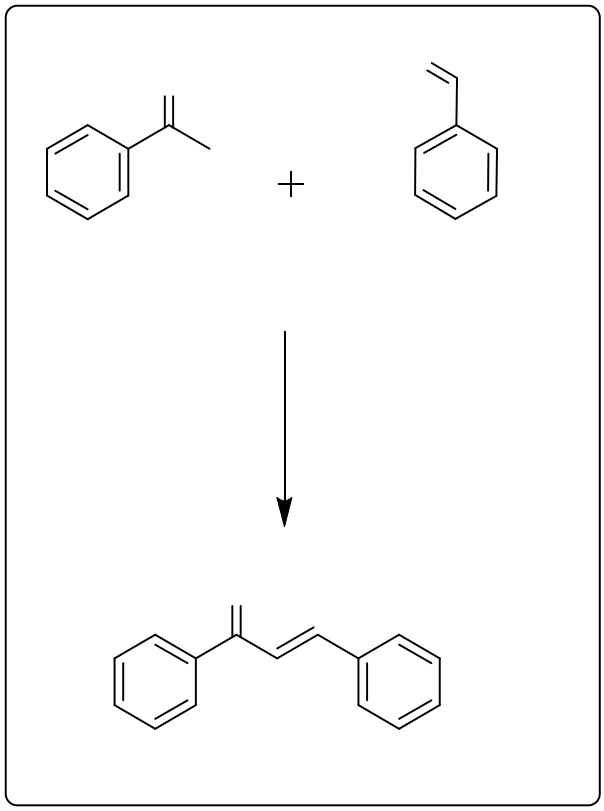


Fig. 2: General scheme for synthesis of chalcones

Pharmacological Profiling of Chalcones

Chalcones have been studied and reported to acquire pharmacological activities that includes anti-microbial, anti-inflammatory, antivral, antifungal, hepato-protective, antioxidant, anti-cancer activities and cardiovascular system disorders as shown in (Fig. 3).

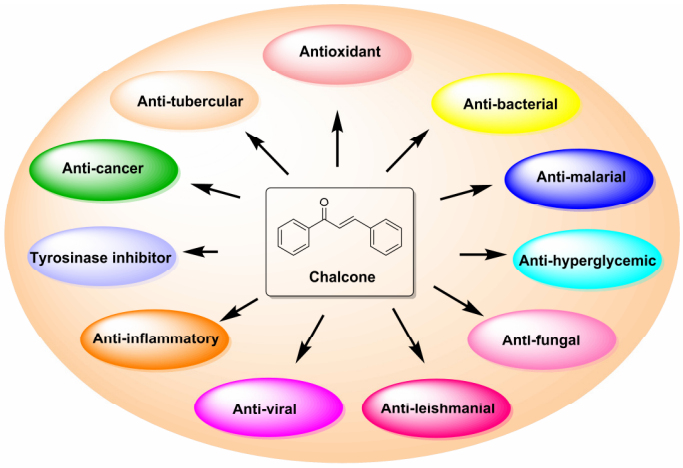
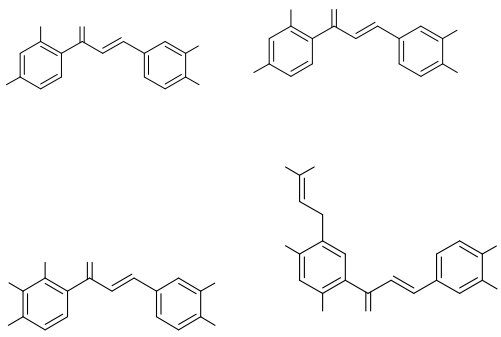


Fig. 3: Pharmacological Activities of Chalcones

Antioxidant Activity

Plants produce numerous antioxidants that protect against molecular damage from reactive oxygen species (ROS), and phenolics which composed to be the major class of plant-derived antioxidants. They have the property to forage the free radicals and prevent from lipid peroxidation (Morel *et al.,* 1993). The hydroxychalcones having isoprenyl substituents on their phenyl rings mainly possess antioxidant activity, and the 3,4-dihydoxy chalcones, for example sappanchalcone, butein and okanin, are known to be effective antioxidants having the concentration ranging 0.025–0.1%, as resulted by induction time measurements (Dziedzic *et al.,* 1983). The presence of a hydroxyl group and a catechol group resulted in antiradical activity, the hydroxyl group is present at C-2' in ring A, and of a catechol group in ring B which appears to be favourable for antiradical activity, while lack of -double bond leads to decrease in the efficacy (Cai *et al.,* 2006).

Brousso chalcone A (BCA) is isolated from *Broussonetia papyrifera Vent*. The reported chalcone have iron-induced lipid peroxidation inhibitory activity in rat brain homogenate with an IC_{50} of 0.63 ± 0.03 µM which indicates that BCA is a powerful antioxidant with versatile free radical-scavenging activity. It was as potent as butylated hydroxyl toluene (BHT). In the 2,2-diphenyl-1picrylhydrazyl (DPPH) assay, BCA shows the radical-scavensing which is more potent than that of tocopherol (vitamin E). On the other hand, BCA suppressed NO production concentration dependently, with an IC_{50} of 11.3 µM in LPS- activated macrophages (Cheng *et al.,* 2001). Despite these various natural occurring anti-oxidantchalcones are in Fig 4.



This compound was considered more active then vitamin C.ElSayedAly and his co-workers synthesized multiple set of chalcone derivatives and their copper and zinc complexes and subjected to Anti-oxidant screening using 1,1-biphenyl-2-picrylhydrazyl (DPPH) free radical scavenging and the hydroxyl-radical scavenging assays at 30 nM along with their anti-obesity and cytotoxicity evaluation (Aly *et al.,* 2014).

Using claisen–schmidt condensation method, new chalcones and their allylated analogues were synthesized by Doan *et al*. And evaluated for their anti-oxidant activity using DPPD-free radical scavenging mehod in addition to anti-microbial screening (Doan and Tran, 2011).

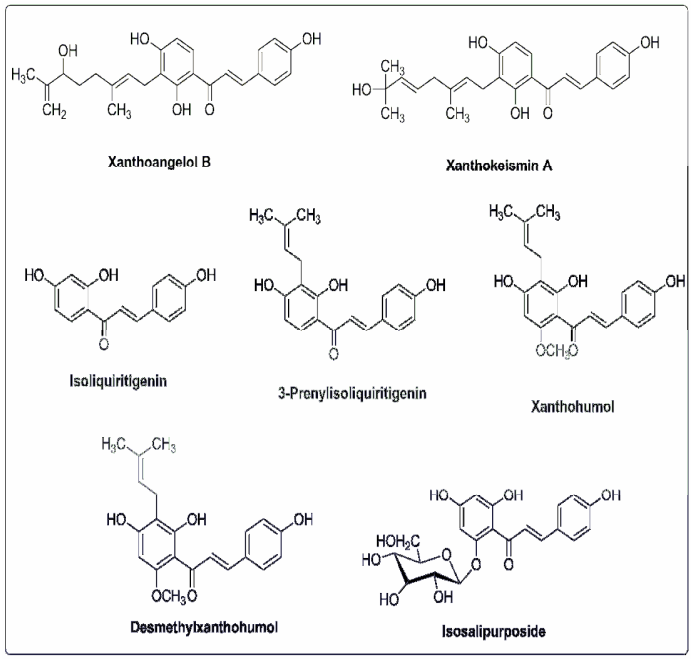
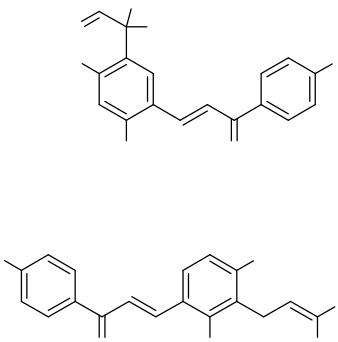


Fig. 4: Chemical structures of natural occurring anti-oxidant chalcones.

Anti-bacterial activity

Liquorice (root and rhizome of Glycyrrhizaspp.) is currently used in the tobacco, confectionery, and pharmaceutical industries. Among the retrochalcones (chalcones which do not have an oxygen-function at the 2-position) isolated from *Glycyrrhiza inflate* licochalcone Aand licochalcone C showed potent antibacterial activity especially to *Bacillus subtilis*, *Staphylococcus aureus* and *Micrococcus luteus***.**



The bacteriostatic effects of licochalcone A 1A tested by Tsukiyama*et al*. (Tsukiyama *et al.,* 2002) were shown by MICs of 2_e15 mg ml^1 for Gram-positive bacteria including

spore-forming bacteria, such as the genera *Bacillus coagulans, B. subtilis* and *Bacillus stearothermophilus* (MIC ¼ 2 mg ml^{1}) as well as *Clostridium sporogenes* (8 mg ml^{1}), and toxin-producing bacteria such as *Bacillus cereus* (3 mg ml^{1}) and *S. aureus* (3 mg ml^{1}). Licochalcone A was also effective when tested against *Lactobacillus acidophilus* and *Lactobacillus plantarum* with MICs of 5 mg ml^{1}, as well as for *Enterococcus faecalis* and *Enterococcus faecium*with MICs of 6 mg ml^{1}, and active against *Streptococcus lactis* and *Staphylococcus mutans*with MICs of 8 and 5 mg ml^{1}, respectively.

When Fukai *et al*. (Fukai *et al.,* 2002) examined licochalcone A, inhibitory activity was detected against the growth of Helicobacter pyroliin vitro (MIC ¼ 25 mg ml^{1}). Kromann *et al*. (Kromann *et al.,* 2014) tested the analogues of licochalcone A against *S. aureus* and showed that the free hydroxyl group in 4^{0}-position of ring B was necessary for the antibacterial activity.

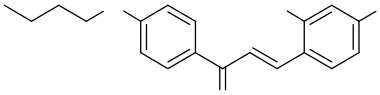
Antibacterial assays of liquoricephenolics for *S. aureus*, including a few strains of methicillin-resistant (MRSA), and methicillin-sensitive S. aureus (MSSA) were examined by Hatano *et al*. (Hatano *et al.,* 2014) and Fukai *et al*. (Fukai *et al.,* 2002). Licochalcone A showed antibacterial effect on the MRSA strains (OM481, OM505) with MIC values of 16 mg ml1 (Hatano *et al.,* 2014) and MRSA strains (K3 and ST28) with MIC ¼ 6.25 mg ml1(Fukai *et al.,* 2002). Chalcone (*Belofsky et al., 2004*) isolated from *Daleaversicolor* exhibited individually and in synergy with known antibiotics (berberin, erythromycin and tetracycline) the activity towards the human pathogen *S. aureus* and the opportunistic pathogen *B. cereus* studied 4´-carboxy chalcones substituted in ring A and showed that many of these compounds were very interesting antibacterial compounds (Nielsen *et al*., 2004). The activity of these chalcones was correlated with the lipophilicity of the substituents in ring A. The lipophilicity of the substituent in ring A is essential for the activity. The lipophilic compounds were very potent and as the substituents become more polar the activity gradually decreased.

Anti-malarial activity

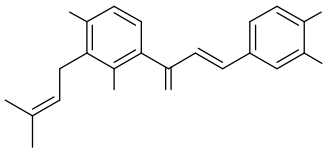
Plasmodium falciparum and *Plasmodium vivax*are the two major human malaria parasites. *P. falciparum*is responsible for most deaths and it has developed resistance to nearly all available drugs. No wonder that the antimalarial activity of chalcones has generated great interest. Many chalcones have been described for their high antimalarial activity, probably as a result of a Michael addition of nucleophilic species to the double bond of the enone (Troeberg *et al.,* 2000*;* Ram *et al.,* 2000). Licochalcone A isolated from Chinese liquorice roots, has been reported (Chen *et al.,* 1994; Kharazmi*et al.,* 1997) as highly effective in an in vitro screen against chloroquine-susceptible (3D7) and chloroquine-resistant (Dd2*) P. falciparum*strains in a [^{3}H] hypoxanthine uptake assay.

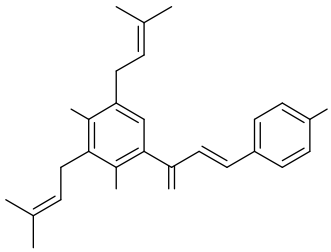
In a detailed study Liu *et al*. (Liu *et al.,* 2001) and Go *et al*. (Go *et al.,* 2004) showed that in vitro antimalarial activity of chalcones against a strain of chloroquine-resistant human malarial parasite, *P. falciparum* (K1)was mainly determined by the properties of ring B. Thesize and hydrophobicity of substituents were identified as critical parameters. Hydroxylated chalcones were less active than the corresponding alkoxylated analogues. A few of the alkoxylated chalcones had IC_{50} values below 6.5 mM.

2,4-Dimethoxy-4´-butoxychalcone (Chen *et al.,* 1997) is a novel compound which has outstanding antimalarial activities against both human (*in vitro*) and rodent (*in vivo*) parasites with no observable signs of toxicity. Compound exhibited a concentration-dependent inhibitory effect on the [^{3}H] hypoxanthine uptake of the chloroquine-susceptible (IC_{50} of 3D7 was 8.9 mM) and chloroquine-resistant (IC_{50} of Dd2 was 14.8 mM) strains of *P. falciparum.*



Crotaorixin (Narender *et al.,* 2005) isolated from the aerial parts of the Crotalaria orixensisexhibited 100% inhibition of maturation of *P. falciparum* (strain NF-54) parasites from ring stage to schizont stage both at 50 and 10 mg ml^{1} concentrations. The *in vivo* antimalarial activity of bischalcones (Ram *et al.,* 2000) against chloroquine-sensitive and resistant strains of *P. berghei*in mice revealed that the site of oxygenated substituents in the phenyl ring A greatly influences the activity profile. In general, chalcones with 3-methoxy and 3,4-dimethoxy substituents displayed a significant activity compared to 2,4-dimethoxy substituents. The compound with three-methylene-group chain contributes significantly more to the activity than those with the four- and six-methylene-group chain.



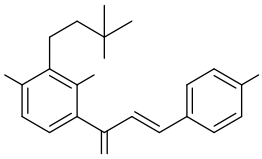


Anti-fungal activity

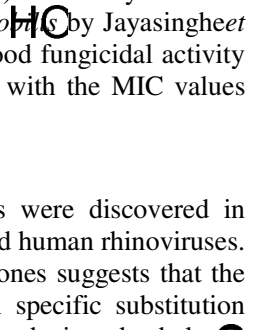
Lopez *et al*. (Lopez *et al.,* 2001) tested chalcones against a panel of human opportunistic pathogenic fungi, using the agar dilution method. Regarding the influence of the substituents on ring A, an interesting structureactivity correlation can be observed. (a) Electrondonating groups tended to weaken the antifungal activity. (b) Electron-withdrawing groups in the para-position increased the potency. The presence of an enone linkage would be a structural requirement necessary but not by itself sufficient for the antifungal activity.

Suman *et al.* in 1995 evaluated some substituted chalcones for their antifungal activity against *Rhizoctoniasolani*, *Fusariumoxysporum* and *Colletotrichum capsicum* strains of phytopathogenic fungi. The study showed that α,β-dibromo-3,3´-dinitrochalcone had the

activity against all three fungi with MIC ¼ 6.25 mg ml^{-1}, and 4,4´-dimethylchalcone showed activity against C. capsicum (MIC ¼ 6.25 mg ml^{1}).



Crotmadine isolated from the leaves and stems of *Crotalaria madurensis* exhibited antifungal activity against *T. mentagrophytes* at a concentration of 62.5 mg ml^{1} (*Bhakuni and Chaturvedi,* 1984). Geranylchalcone derivatives isolated from *Artocarpus nobilis* by Jayasinghe*et al*. (Jayasinghe *et al.,* 2004) showed good fungicidal activity against *Cladosporium cladosporioides* with the MIC values in the range of 2_e15 mg/spot.



Anti-viral activity

Antiviral properties of chalcones were discovered in studies on inhibition of plant viruses and human rhinoviruses. The variable antiviral activity of chalcones suggests that the activity of each chalcone depends on specific substitution patterns. A hydroxy and methoxy substituted chalcone derivatives were investigated by Onyilagha *et al*. (Onyilagha *et al.,* 1997; Malhotra *et al.,* 1996*)* for activity against tomato ringspotnepovirus (ToRSV) infectivity. Acquired immunodeficiency syndrome (AIDS), caused by the human immunodeficiency virus (HIV), has been a life threatening health problem since 1980, and flavonoids have been investigated for anti-HIV activity. Wang *et al*. (Wang *et al.,* 2004) reported that xanthohumol was a selective inhibitor of HIV-1 and may represent a novel therapeutic agent for HIV1 infection. Interestingly, a recent report by Wu and colleagues (Wu *et al.,* 2003) demonstrated that chalcone from the genus Desmos showed potent anti-HIV activity (EC_{50} 0.022 mg ml^{1}) with a good therapeutic index (TI) (489). A C-4 methoxy group in the chalcone skeleton may be critical for anti-HIV activity. On the other hand, Ru(II)/Ru(III) polypyridyl complexes containing 2,6-(2´-benzimidazolyl)-pyridine/chalcone as co-ligand (Mishra *et al.,* 2001) inhibited HIV replication by 50% with a concentration of <0.1 mg ml^{1}.

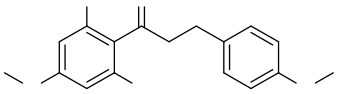
Anti-inflammatory activity

The prostaglandin E_2 (PGE_2) inhibition and production nitric oxide (NO) has been demonstrated as an effective therapy for inflammatory disorders. Tissue damage may occur by consumption of large amount of NO. In inflammatory diseases (*i.e.* rheumatoid arthritis,) the activated macrophages cause excessive NO production which has been observed. Therefore potent and selective inhibitors of NO are interesting to develop.

Herencia *et al*, (Herencia *et al.,* 1998; Herencia *et al.,* 2002) tested a series chalcone derivative for possible anti-inflammatory effect. The inhibition of production of prostaglandin E_2 (PGE_2) and nitric oxide (NO) is potential therapy for different inflammatory disorders. Large amounts of NO may lead to tissue damage. In inflammatory diseases such as rheumatoid arthritis, excessive NO production by activated macrophages has been observed. Therefore, it would be interesting to develop potent and selective inhibitors of NO for potential therapeutic use. Trimethoxychalcone derivatives, with various patterns of fluorination, were evaluated by Rojas *et al*. for their influence on nitric oxide production. 2,4,6-Trimethoxy-20-trifluoromethylchalcone inhibited the production of NO and prostaglandin E2 in lipopolysaccharaide-stimulated RAW 264.7 macrophage cells. PGE_2 accumulation. In the 24-h zymosan-stimulated mouse air pouch reduced nitrite and prostaglandin E_2 levels as well as in the rat adjuvant arthritis.

Anti-Cancer activity

Recent reports have focused on the anti-proliferative and tumorreducing activities of some chalcones and observation that even a high intake of plant based dietary flavonoids is safe and not associated with any adverse health effect causing renewed interest in this class of molecules (*Dinkova-Kostova et al.,* 1998). Among currently identified antitumor agents, chalcones represent an important class of natural small molecules useful in cancer chemotherapy (*Modzelewska et al., 2006*). Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a naturally occurring anticancer agent that induces apoptosis in cancer cells and is not toxic to normal cells. TRAIL induces programmed death in various cancer cells through its interaction with the death receptor TRAIL-R1 and/or TRAIL-R2 (Lopez *et al.,* 2001). Szliszka *et al*reported that chalcones (chalcone, licochalcone-A, isoliquiritigenin, xanthohumol, butein) and dihydrochalcones (2'6'-dihydroxy-4'-metoxydihydro-chalcone 1a, 2'6'-dihydroxy-4,4'-dimetoxydihydrochalcone 1b, 4,2',4',6'-tetrahydroxydihydrochalcone, called phloretin markedly augmented TRAIL-mediated apoptosis and cytotoxicity in prostate cancer cells (Szliszka *et al.,* 2010). These results confirmed the significant role of chalcones and dihydrochalcones in prostate cancer chemoprevention through sensitization of cancer cells to TRAIL-induced programmed death.



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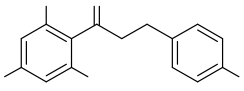

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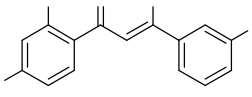
Bandgar *et al.* (Bandgar *et al.,* 2010; Bandgar *et al.,* 2010) synthesized combinatorial library of chlorovinyl chalcones and screened for anticancer, anti-inflammatory and antimicrobial activities in which chalcone 2 was the most potent compound for anticancer activity.



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A series of biphenyl based chalcones was prepared and evaluated for cytotoxicity against human breast cancer cell lines in which two compounds proved to be better anticancer

agents than the standard drug tamoxifen (Sharma *et al.,* 2010).

A series of novel chalcone linked imidazolones was prepared and evaluated for their anti-cancer activity against panel of 53 human tumour cell lines derived from nine different cancer types: leukemia, lung, colon, CNS, melanoma, ovarian, renal, prostate and breast, in which hybrid compounds showed good anti-cancer activity with GI_{50} value ranging from 1.26 to 13.9 M. When breast carcinoma cells (MCF-7) were treated with 10 M concentration of compounds and cell cycle arrest was observed in G2/M phase. Surprisingly, the increased concentration of the same compounds to 30 M caused accumulation of cells in G0/G1 phase of the cell cycle (Kamal *et al.,* 2010). A new series of indolylchalcones were synthesized and evaluated *in vitro* for their anticancer activity against human cancer cell lines in which indolylchalcone was identified as the most potent and selective anticancer agent with IC_{50} value 0.03 M (Kumar *et al.,* 2010). A series of novel chalconethiosemicarbazide derivatives was designed, synthesized and evaluated as potential epidermal growth factor receptor (EGFR) kinase inhibitors (Zhang *et al.,* 2011). Among the compounds, some showed the most potent biological activity (IC50= 0.78 ± 0.05 M for HepG2 and IC_{50}=0.35 M for EGFR), which is comparable to the positive control (Erlotinilb).

Anti-tubercular activity

Tuberculosis (TB) is by far the most frequently encountered mycobacterial disease in the world. Among infectious diseases, TB is the number one killer, with more than 2 million casualties annually worldwide. *Mycobacterium tuberculosis, M. bovis, M. kansasii, M. xenophii* and *M. marinum* were inhibited by Lic A (15) (MIC 20 mg/L) (*Friis-Moller et al., 2002*). A series of flavonoids, chalcones and chalcone-like compounds for inhibitory activity against *M. tuberculosis* H37Rv was evaluated and chalcone-like compound exhibited 96% inhibition at a drug concentration of 12.5 g/ml (Lin *et al.,* 2002). Sivakumar *et al.* screened 25 synthetic chalcones for their activity against *M. tuberculosis* H37Rv at two concentrations (50 and 100 μg/mL). However, it was revealed that antimycobacterial activity totally depends on the substituents in ring B (such as the hydrophilic nitro or hydroxyl groups). Compound was found to be the most active (~99%) based on the % reduction in Relative Light Units at both concentrations (Sivakumar *et al.,* 2007). A series of 4-alkylamino chalcones was synthesized and screened for their *in vitro* anti-tubercular and antimalarial activities.

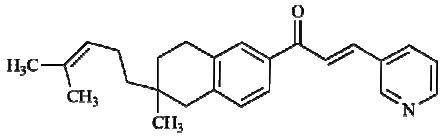
Anti-leishmanial activity

Leishmaniasis is a vector-borne disease caused by protozoan parasites of the genus *Leishmania*. Though a large number of synthetic compounds have been tested, Lic A still remains one of the few naturally occurring chalcones under investigation. Lic A, efficiently inhibited the proliferation of *Leishmaniadonovani* and *L. major* promastigotes and amastigotes *in vitro* by inhibiting fumarate reductase, a selective target present in the parasite mitochondria *(*Kayser *et al.,* 2001; Chen *et al.,* 1993). The Lic C inhibited the growth of the *L. major* parasite to the same extent as Lic A (15) (Nielsen *et al.,* 1995). Liu *et al*. (Liu *et al.,* 2003) synthesized a series of oxygenated chalcones and tested for Leishmanial against *L. donovaniamastigotes*. A comparison of structure–activity relationships revealed that antileishmanial activity was associated with less lipophilic chalcones, in particular those with 4'-hydroxyl-substituted A rings and hetero/polyaromatic B rings and chalcones with good antimalarial activity had alkoxylated A rings and electron-deficient B rings.

Anti-hyperglycemic activity

It has been also shown that chalcones isolated from plants have insulin-like activities and improve the glucose uptake in adipocytes (Enoki *et al.,* 2007). These studies showed that chalcones are effective antihyperglycemic or hypoglycemic agents as much *in vitro* as *in vivo* experimental models. It has been reported that sulfonamide chalcones act as a potent new class of glucosidase inhibitors. Amongst them, 68a (IC_{50} = 0.98 μM) and 68b (IC_{50} = 0.40 μM) were the most potent inhibitors (*Seo et al.,* 2005).

A series of chalcone derivatives having 3,4-methylenedioxysubstituted ring B and variously substituted ring A was prepared and investigated by Albert*on et al.* as anti-hyperglycemic agents in a glucose loaded animal model (Alberton *et al.,* 2008). Compounds 3 and 4 (methoxy substituent) inhibited the hyperglycemia induced by glucose around 96% similar to that demonstrated for lispro insulin and tolbutamide at 60 min. The naphthyl-chalcones were found to have an acute serum glucoselowering effect in hyperglycemic normal rats specially, chalcone (5) stimulated significantly the insulin secretion induced by glucose and found that the presence of nitro group and their position in the phenyl rings are responsible for the antihyperglycemic activity of chalcones (Seo *et al.,* 2003).



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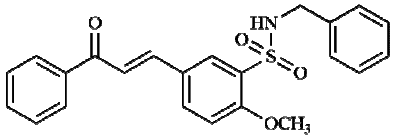

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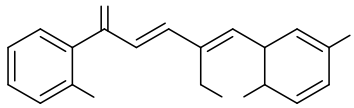

5

Tyrosinase inhibitor

Tyrosinase (monophenolmonooxygenase), also known as polyphenol oxidase, is a copper-containing enzyme widely distributed in nature. It catalyzes 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). Isoliquiritigenin can inhibit both mono- and diphenolase tyrosinase activities with IC_{50} of 8.1 M, when tyrosine was used as substrate, suggesting that chalcones may serve as candidates for skin-lightening agents (Nerya *et al., 2003*). Different tetrahydroxychalcones, the

commercially available Butein and other three which were synthesized and evaluated for the contribution of the different functional groups of the tetrahydroxychalcones to their inhibitory potency on tyrosinase, with a view to optimize the design of whitening agents and showed that a 2,4-substituted resorcinol subunit on ring B contributed the most to inhibitory potency and found two very active tyrosinase inhibitors, with IC_{50} of 0.2 and 0.02M, respectively (Khatib *et al.,* 2005). Hydroxychalcones exhibited high inhibitory effects on tyrosinase with respect to L-tyrosine as a substrate. Kinetic study revealed that competitive inhibitor of tyrosinase has Ki value of 3.1 µM (Jun *et al.,* 2007)

Conclusions

In conclusion, we have described the biological applications of 1,3-diaryl α,β-unsaturated derivatives. From this review article we analyzed that chalcone shows wide variety of application in various diseases. Chalcones are lipophilic as well as hydrophilic, having polar functionalities in different positions, and the skeleton itself is amenable for the generation of functionalities for selective modulation of different enzymes. Hence further research on chalcone may form a compound or derivative which could be useful in treatment of various other hamful diseases. Recent studies in various disease areas have shown that many diseases, specifically those that are metabolic, multi-factorial and are best treated with combinations of drugs acting either with different mechanisms or with a drug exhibiting multiple pharmacological actions. In spite of exhibiting a wide range of biological activities, chalcones are yet to achieve the status of promising drug candidates.

The present review gives detail about the structural requirement of chalcone derivatives for various pharmacological activities. This information may provide an opportunity to scientists of medicinal chemistry discipline to design selective, optimize chalcone derivatives for the treatment of complex diseases.

Conflict of Interest

The authors declare that they have no conflict of interests.

Acknowledgements

I am thankful to all my colleagues and elective students of Chitkara College of Pharmacy, Chitkara University, Punjab Campus, who have been constant source of moral support and inspiration during my research.

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