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Chemical and Biological Potential of Chalcones as a Source of Drug: A Review

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ABSTRACT

Chalcone and its derivatives are known for their bioactive properties either natural or synthetic. Chalcones and its derivatives possess a broad spectrum of biological activities including antioxidative, antibacterial, antifungal, antiprotozoal, antihelmintic, antiviral, insecticidal, anticancer, antidiabetic, cytotoxic and immunosuppressive. Infectious diseases caused by bacteria, fungi, viruses and parasites such as malaria, tuberculosis, AIDS etc. are still a major threat to public health in developing as well as in developed countries, despite tremendous progress in medicinal chemistry. The impact is more acute in developing countries due to non-availability of desired medicines and emergence of widespread drug resistance. This review is an effort to study pharmacological screening of natural and synthetic chalcones, studying importance of chalcones and synthesis of pharmacologically active chalcones with reference to chemical and biological potential as drug.

INTRODUCTION

Since the age's human being are dependent on nature for all needs. The plants are valuable source of a wide range of secondary metabolites, which are used as pharmaceuticals, agrochemicals, flavors, fragrances, colours, biopesticides and food additives. With the presence of a wide variety of secondary metabolites, plants have formed the basis of the traditional medicine systems that have been in existence for thousands of years in many countries.

When the era of synthetic drugs began, it opened thousand doors for the development of various natural, semisynthetic and synthetic molecules with potential action. Chalcones, considered to be the precursor of flavonoids and isoflavonoids, are abundant in edible plants. They consist of open-chain flavonoids in which the two aromatic rings are joined by a three-carbon α, β-unsaturated carbonyl system. Chalcones, one of the major classes of natural products with widespread distribution in fruits, vegetables, spices, tea and soy based foodstuff have been subject of great interest for their interesting pharmacological activities. Chalcones (1,3-diaryl-2-propen -1-ones) belong to the flavonoid family. Chalcones have been reported to possess many useful properties, including antibacterial, antimalarial, antifungal, antiviral and anti-inflammatory, antidiabetic, anticancer cytotoxic, antiprotozoal, antihistaminic, antiulcer activities which makes these compounds as a special attraction for investigation.

This review paper is an effort to put forward all the recent investigations by researcher throughout the world with respect to chalcones and its derivatives potential as drug.

ANTIMICROBIAL ACTIVITY

Microorganisms may cause number of deadly diseases like tuberculosis, typhoid, syphilis, meningitis, leprosy, pneumonia, common cold, tetanus, whooping cough, chick pox, diphtheria and anthrax etc. Bacteria are further classified as Gram-positive bacteria and Gram-negative bacteria. Fungi as *Candida albicans*, *Aspergillus niger* etc. may cause diseases called mycoses which can affect skin, nails, body hair and internal organs such as lungs and body systems such as nervous system for example candidiasis, Oral candidiasis and Cryptococcus meningitis etc. Viruses are amongst the smallest microbes which may either consist of DNA or RNA. Human Immune Deficiency Virus (HIV) causes deadly disease

AIDS which is a leading cause of deaths globally whereas hepatitis B and hepatitis C viruses are associated with liver cancer.

Chalcones either naturally or synthetic derivatives are noted antimicrobial agents herein we through some light on antimicrobial properties of chalcones in brief.

Synthesized chalcones **1a**–**e**, hydrazones **2a**–**e**, pyrazoles **3a**–**e**, and dihydropyrazoles **4a**–**e** and **5a**–**e** were tested for their antimicrobial activity against four test organisms, namely *Staphylococcus aureus* ATCC6538P, *Escherichia coli* ATCC8739, *Pseudomonas aeruginosa* ATCC9027, and *Candida albicans* ATCC2091 using rifampicin (5 μg/disc) and ampicillin (10 μg/disc) as standard drugs. Except Pyrazoles **3a**–**e** all other compounds showed potent activity only against *Staphylococcus aureus* and *Candida albicans* in the order of inhibition **2a**–**e** > **4a**–**e** > **1a**–**e** ≥ **5a**–**e**. minimum inhibitory concentration (MIC) values for the individual compounds that showed inhibition zones > 10 mm were determined by means of the agar well-diffusion method in DMSO. The trend of activity was observed as follows: X > H > OMe > NO2 where X = Cl, Br. It is obvious that the presence of pharmacophores such as chloro and bromo substituents with lipophilic properties increases the antimicrobial activity.[1]

Studies based on the potentially active chalcone skeleton,[2] have pointed out the importance of the positions of the electron releasing groups (such as the methoxy and hydroxy groups or compounds 2 and 4) in the B ring in obtaining a better antibacterial activity than others when compared with the reference standard amoxicillin at both 0.5 ml (500 μ g) and 1 ml (1000 μ g) concentration levels. Fungicidal screening data revealed that chalcone having a pharmacophore such as a nitro group has exhibited more antifungal activity than other chalcones when compared with the reference standard fluconazole at both 0.1 ml (10 0 μ g), 0.5 ml (500 μ g), and 1 ml (1000 μ g) concentration levels.

The synthesized compounds showed potential anti-bacterial effects. Barbuceanu *et al.* [3] developed a series of thiazolo[3,2-b][1,2,4]triazole incorporating diphenylsulfone moieties starting from 5-[4-(4-X-ph enylsulfonyl)pheny l]-4 H -1,2,4-triazole-3 -thioles and evaluated them for antibacterial activity against *Acinetobacter baumannii, Citrobacter freundii, E. coli , P. aeruginosa , Enterococus faecalis,* and *S. aureus*. Tetracycline and ampicillin were used as control. In an extensive investigation by Venkatesh *et al.* [4], they found that the compounds 5a (5-[3-(4-Chlorophenyl)-1-phenylprop-2-en-1-ylidene]-2- thioxodihydropyrimidine-4,6(1H,5H)-dione), 5e (5-[3-(4-Chlorophenyl)-1-(4-methoxyphenyl) prop-2-en-1- ylidene]-2-

thioxodihydropyrimidine-4,6(1H,5H)-dione) and 5k (5-[1,3-Bis(4-chlorophenyl)prop-2-en-1-ylidene]-2- thioxodihydropyrimidine-4,6(1H,5H)-dione) having Cl substituents on para position of phenyl ring were found to exhibit good antibacterial activity against *Staphylococcus aureus* and *Bacillus subtilis* with MIC value 27.72-37.42 µg/mL. Compounds 5i and 5j showed very good activity against *Pseudomonas aeruginosa* with MIC value 28.11 µg/mL and 29.86 µg/mL respectively; Compound 5c (5-[3-(4-Methoxyphenyl)-1-phenylprop-2-en-1-ylidene]-2- thioxodihydropyrimidine-4,6(1H,5H)-dione) is inactive against the *Staphylococcus aureus* and remaining compounds showed considerable activity against all tested strains. The MIC of antifungal activity of title compounds indicated that, the compound 5e was found to exhibit good activity against all the tested fungal strains with MIC value 23.50- 28.00 µg/mL. Compounds 5i (5-[3-(4-Methoxyphenyl)-1-(4-nitrophenyl) prop-2-en-1-ylidene] pyrimidine-2,4,6(1H,3H,5H)-trione) and 5j (5-[3-[4-(Dimethylamino)phenyl]-1-(4-nitro)prop-2-en-1- ylidene]-2-thioxodihydropyrimidine-4,6(1H,5H)-dione) showed moderate activity against the tested fungi *Aspergillus niger* and *Alternaria alternata* with MIC value 22.66-36.49 µg/mL.

Thiazolidine derivatives from 2-amino-4-phenyl-1,3thiazole synthesized by Verma *et al.* [5] and evaluated them for antimicrobial activity against *Bacillus subtilis*, *Escherichia coli*, *Staphylococcus aureus*, *Aspergillus niger*, *Aspergillus flavus*, and *Candida albicans* using ampicillin as standard. Some of the synthesized compounds displayed good activities (Scheme 7) Dawane *et al.* [6] synthesized 1-(4-(40 -chlorophenyl)- 2-thiazolyl)-3-aryl-5-(2-butyl-4-chloro-1H-imidazol-5yl)- 2-pyrazoline derivatives by base catalyzed treatment of suitable chalcones with 4(40 -chlorophenyl)-2-hydrazino-thiazole in polyethylene glycol as reaction solvent (Scheme 15) and tested them for antibacterial and antifungal activity using tetracycline as standard. Compounds exhibited stronger antifungal and antibacterial activities.

Preliminary investigation of antimicrobial activity of chalcones was performed with 13 newly-synthesized chalcones with diverse chemical structure, against seven laboratory control strains of Gram-positive and Gram-negative bacteria and two laboratory control strains of yeasts. Three of the tested compounds (1,3- Bis-(2-hydroxy-phenyl)-propenone, 3-(3-hydroxy-phenyl)-1-(2-hydroxy-phenyl)-propenone and 3-(4-hydroxy-phenyl)-1-(2-hydroxy-phenyl)-propenone) exerted most prominent antistaphylococcal activity and were chosen for further investigation of antimicrobial activity against clinical isolates of MRSA (Methicillin resistant Staphylococcus aureus)[7].

Sivakumar *et al.* [8] have synthesized 25 chalcone derivatives and performed QSAR studies of their antimycobacterial activity. According to their results introduction of -NMe_2, -OMe, -SMe groups in different positions of the ring B led to the increase of anti-tuberculosis activity as compared to unsubstituted chalcone. At the same time, introduction of the hydrophilic groups -OH and -NO_2 in the ring A also enhances anti-mycobacterial activity. Halogen substitution in positions R1 and R3 of the ring A reduces the activity of the resulted derivatives. Nitro- and methoxy-substitution in position R3 also has negative effect on antituberculosis activity.

A reduced number of studies have been done on the anti-infective activity of chalcones against plant viruses, though the antiviral activity of chalcones against the tomato ringspot virus (ToRSV) has been reported. In a first study, the 2-hydroxychalcone was found to weakly inhibit ToRSV infectivity on *Chenopodium quinoa* [9]. However, in 1997, [10] Onyilagha and collaborators found higher antiviral activities after testing 21 chalcones. This study demonstrated that antiviral activity is activated by hydroxylation of the A-ring at 2',3',4' positions and B-ring at C-4', suppressed by hydroxylation at C-5', and reduced by methoxylation of the B-ring. In fact, 2',3',4',4-tetrahydroxychalcone inhibited ToRSV infectivity in a 69%, while many other chalcones induced around a 50% inhibition.

Asquith *et al.* [11] developed thiazine derivatives and checked for their antiviral properties using the nucleocapsid protein of the feline immunodeficiency virus (FIV) in-vitro cell culture that showed activity in nanomolar concentration and low toxicity thus these thiazine analogues may be suitable candidates for HIV treatment and could be tested further to check for potency in mice and human HIV infected tissues. Glycycoumarin, glycerin, glycerol and liquiritigenin isolated from *Glycyrrhiza uralensis*, as well as isoliquiritigenin, licochalcone A and glabridin, develop antivirals activity against hepatitis C virus (HCV) infection[12].

Licochalcone G, licochalcone A, echinantin, 5-prenylbutein, licochalcone D, isoliquiritigenin, licoagrochalcone A, and kanzonol C were isolated from the acetone extract of the *Glycyrrhiza nflata.* All the isolated compounds showed activity against NAs from influenza viruses. The non-prenylated chalcones echinantin and isoliquiritigenin (IC 50 5.80 ± 0.30 and 8.41, 0.39 µg ml-1 , respectively) exhibited higher activity than the prenylated compounds 5-prenylbutein, the C-5 hydroxy derivative of licoagrochalcone A (IC 50 25.87 ± 2.03 µg ml-1) [13].

In an report by Govindan *et al.*[14] the substituted forms of 1,4-benzothiazines and 1,5-benzothiazepines and their annelated derivatives are pharmacologically very important as some of them can be used as antimicrobials, antiviral, antibacterial and antifungal drugs. The 1,4-thiazines are toxic to the two fungal species of *Aspergillus niger* and *Aspergillus fumigatus.*

Antimicrobial activity also can be studied by developing an *Insilico* drug molecule and then its effect is assessed as it do not need wet lab experimentation which are time consuming and expensive as well.

ANTICANCER ACTIVITY

The major challenges associated with currently available anticancer agents include lack of selectivity, toxicity, resistance and development of secondary malignancy. These drawbacks have motivated the search for newer, more efficacious and better tolerated antitumor drugs, with natural products especially plants offering an inexhaustible reservoir for new drug discovery and development. Chalcones are widely present in edible plants. Chalcones and their derivatives are reported to exhibit promising anticancer activity.[15] Synthesized chalcone hybrids are active against various cancer cell lines such as human breast adenocarcinoma cell line MCF-7, human prostate cancer cell line PC3, human lung adenocarcinoma cell line A549 and human adenocarcinoma cell line HT-29 (colorectal cancer).

Mondhe *et al.*[15] synthesized 2-Methyl-3-(3-((E)-3-(3,4,5-trimethoxyphenyl)-2-propenoyl)phenyl)-3,4-dihydro-4 quinazolinone (8b) and its cytotoxic effect was explored using a panel of cancer cell lines of different human tissue origin and it inhibited the proliferation of cells with IC50 values ranging from 5.5 to 17 μ M The results thus depict a better cytotoxic profile of 8b. In vivo anticancer potential of 8b was studied in four murine tumors viz., Ehrlich Ascites Carcinoma, Ehrlich Tumor (solid), Sarcoma-180 (Ascites) and Sarcoma-180 (solid). Compound 8b showed a significant tumor growth inhibition against all the four murine tumor models.

Coumarins are an interesting class of compounds endowed with broad spectrum antitumor activities, hence chalcones employing coumarinyl moiety as a substitute for ring A or B have been reported in literature for anticancer properties. Sashidhara *et al* [16] synthesized and evaluated a series of coumarin-chalcone hybrids for their *in vitro* cytotoxicity against a panel of four human cancer cell lines and normal fibroblasts (NIH_3T_3). Compound 53 was found to

be the most promising in the series with 30-fold more selectivity towards C33A (cervical carcinoma) cells over normal fibroblast NIH3T3 cells with an IC50 value of 3.59 µM.

A series of novel 1-adamantyl chalcones (Fig.1)) was reported for treatment of breast cancer and/or other proliferating disorders by Anderson *et al.*[17]. These 1-adamantyl chalcones have been tested for growth inhibitory activity against two different types of breast cancer cell lines (MCF-7 and MDA-MB435) and a non-cancerous breast epithelial cell line (MCF-10).

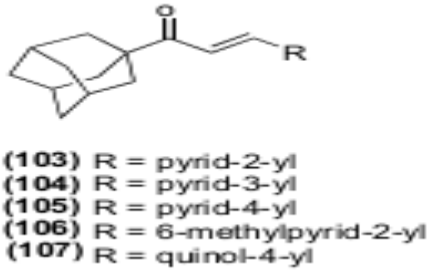

Fig 1: Structure of Adamantyl chalcones.

Bertl *et al.* [18] studied the potential antiangiogenic effects of xanthohumol and isoxanthohumol, chalcones isolated from *Humulus lupulus* (hopse). In *in vitro* conditions, they observed a reduction of newly formed capillary growth by xanthohumol at a concentration range of 0.5 to 10 µM (lC $_{50}$value of 2.2 µM). The inhibitory effect of isoxanthohumol was weaker. Furthermore, xanthohumol effectively blocked tumor angiogenesis and tumor growth *in vivo* and interferes with several steps in the angiogenic process. Xanthohumol also reduced Vascular Endothelial Growth Factor (VEGF) secretion, decreased cell invasion and metalloprotease production in acute and chronic myelogenous leukemia cell lines[19]. Moreover, licochalcone E ,a retrochalcone isolated from the roots of *Glycyrrhiza inflata*, was found to be an inducer of apoptosis in endothelial cells by modulating NFKB and members of the Bcl-2 family [20]. Several lines of investigation suggest that by replacing the original phenyl ring of chalcones by heteroaryl moieties, resulting heterocyclic chalcone compounds may be effective anticancer agents. The study by Thanh-Dao Tran *et al.*[21] presented herein demonstrated that some representative heterocyclic chalcones, namely, phenothiazinyl chalcones and pyridinyl 2 1 -hydroxychalcones exhibit promising anticancer properties. Thus, these classes of chalcones, whose structures are far different from anticancer drugs currently on the market, exhibit potential cytotoxicity. In study by Severi F *et.al.* [22] a series of boronic chalcones were evaluated for anti-cancer

activity and mechanisms of action. Among these 3,5-bis-(4-boronic acid-benzylidene)-1-methyl-piperidin-4-one (AM114) exhibited most potent growth inhibitory activity with IC 50 values of 1.5 and 0.6 μM in 3-(4,5-dimeth -ylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay and colony formation assay, respectively. The cytotoxic activity of AM114 was shown to be associated with the accumulation of p53 and p21 proteins and induction of apoptosis. Mechanistic studies showed that AM114 treatment inhibited the chymotrypsin-like activity of the 20S proteasome in vitro, leading to a significant accumulation of ubiquitinated p53 and other cellular proteins in whole cells.

ANTIDIABETIC PROPERTY

In an exclusive study on antidiabetic effect by Ram Pratap *et.al.* [23] the hybrid congener 3 derived from hydroxychalcone and pharmacophore oxypropanolamine for adrenergic receptor, along with its enantiomers 9a and 9b were selected from a series of compounds for detailed studies of their antidiabetic profile in sucrose-challenged, low-dosed, streptozotocin-induced diabetic rats and in db/db mice, and antidyslipidaemic profile in high fat diet-induced dyslipidaemic hamsters. The test compounds exhibited significant and consistent antidiabetic and antidyslipidaemic activities in the above models. The pharmacodynamic studies of two metabolites, 10 and 11, were undertaken. Metabolite 10 (3-Benzo-(1, 3)-dioxol-5-yl-1-[4-(3-tert-butylamino-2-hydroxy-propoxy)-phenyl]-propan-1-one) having greater bioavailability in plasma was synthesized and found to exhibit significant antidiabetic activity.

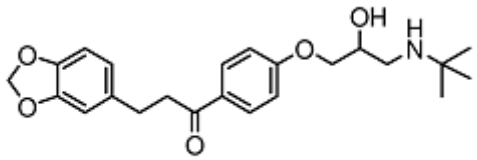

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Fig:2 Metabolite 10 (3-Benzo-(1, 3)-dioxol-5-yl-1-[4-(3-tert-butylamino-2-hydroxy-propoxy)-phenyl]-propan-1-one)

Santhi *et.al* [24] studied that the chalcone reacts with semicarbazide hydrochloride, thiosemicarbazide, phenylhydrazine hydrochloride, benzhydrazide and benzene sulphonylhydrazide to give 4,5- dihydro-3,5-dip-tolylpyrazole-1-carboxamide(2),4,5-dihydro-3,5-dip-tolylpyrazole-1- carbothioamide (3),4,5-dihydro-1-phenyl-3,5-dip-tolyl-1H-pyrazole(4),(4,5-dihydro-3,5-diptolylpyrazol-1-yl)(phenyl)methanone(5),3,5-bis(4-

methylphenyl)-1-(phenylsulfonyl)-4,5- dihydro-1H-pyrazole(6). It is noteworthy to mention that, among all the derivatives, compounds 1,3,4 and 6 were found to be better hypoglycemic agent compare with standard drug insulin in reducing the blood glucose level.

In a primary screening by Change *et.al* [25] substitution on A-ring is crucial for promoting cellular glucose consumption. Accordingly, 60 chalcone derivatives with and without substitutions on A-ring were examined in developed model. Two anti-diabetic clinical drugs, pioglitazone and rosiglitazone were used as positive controls with culture medium glucose concentrations of 230 and 263 mg/dl, respectively. Chalcones which lowered glucose level (n = 3) below 240 mg/dl were regarded as active candidates. In an exclusive study 5-(4-fluorobenzyl)-2,4-thiazolidinedione was synthesized by reaction of 4-fluoroaniline with methyl acrylate to give crude 2-Bromo-3-(4-fluoro-phenyl)-propionic acid methyl ester as an oil which was treated with thiourea in presence of sodium acetate and ethanol to give 5-(4-fluoro-benzyl)-2-imino-thiazolidine-4-one which on oxidation gave 5-(4-fluoro-benzyl)-thiazolidine-2,4-dione. This was condensed with the quinoline derivatives in presence of Tetrahydrofuran. Among the synthesized derivatives five of them were screened for oral hypoglycemic activity, the compounds SK, SK-3 were showing significant activity and compound SK- 2 was showing moderate activity and compounds SK-4 and SK-5 were active. Ao *et al*. [26] synthesized N-(4-substituted-1,3-thiazol-2-yl)-2-[4-(methylsulfonyl)phenyl]-3-(tetrahydro-2 H -pyran-4-yl) propanamides as glucokinase activators. The results indicated that the compound N-(4-isopropyl-1, 3-thiazol-2-yl)-2-[4-(methylsulfonyl) phenyl]-3-(tetrahydro-2H-pyran-4-yl) propanamide was potent glucokinase activator. Iino *et al* [27] identified and synthesize d 3-alkoxy -5-phenoxy- N -thiazolyl benzamides modification on derivatives of 2-aminobenzamide as glucokinase activators. Incorporation of an alkoxy or phenoxy substituent results in identification of 3- isopropox y-5-[4-(methylsulfon yl) phenoxy]-N -(4-methyl-1,3-thiazol-2 -yl)benzamide as a potent and orally bioavailable glucokinase activator.

ANTIINFLAMMATORY ACTIVITY

Recent reports indicate the importance of chalcones as anti-inflammatory agents involved in the inhibition of cell migration and the inhibition of TNF-α production in mouse model. Chalcone derivatives have been extensively reported to inhibit NO synthesis, iNOS and cycloxygenase 2 protein expression in lipopolysaccharide (LPS) stimulated cells. The structure-activity analysis demonstrated that chalcones with substituents that reduce the

electronic density in the B ring, such as chlorine atoms or nitro groups, show better biological activity and selectivity in the inhibition of nitrite production, and position 2 in B ring seems to be more important[28]. Six chalcones were isolated from *Angelica keiskei* 2',4',4-trihydroxy-3'-[2-hydroxy-7-methyl-3-methylene-6-octaenyl]chalcone] (1), 2',4',4-trihydroxy-3'-geranylchalcone (2), 2',4',4-trihydroxy-3'-[6-hydroxy-3,7-dimethyl-2,7-octadienyl]chalcone (3), 2',4-dihydroxy-4'-methoxy-3'-[2-hydroperoxy-3-methyl-3-butenyl] chalcone (4), 2',4-dihydroxy-4'-methoxy-3'-geranylchalcone (5), and 2',4-dihydroxy-4'-methoxy-3'-[3-methyl-3-butenyl]chalcone(6). Among them, compounds 1 to 3 showed potent inhibitory activity of IL-6 production in TNF-α-stimulated MG-63 cell, while compounds 4 to 6 did not. The inhibitory activity of IL-6 production in TNF-α-stimulated MG-63 cell is likely to be affected by the presence of C-4' hydroxyl group in the chalcone moiety [29]. In another investigation Won *et al.*[30] synthesized (E)-1(2hydroxyphenyl)-3(thiophen- 2-yl)prop-2-en-1-one, a chalcone derivative which was tested in vitro for its inhibitory activity on chemical mediators released from mast cells, neutrophils, macro -phages and microglial cells with satisfactory results. In this study, (Z)-2-(3,4-dihydroxybenzylidene)-5-me -thoxybenzofuran-3(2 H)-one (compound 5) synthesized and its analgesic and anti-inflammatory effects were estimated by formalin, carrageenan and hot-plate methods in mice.[31] The chalcone derivatives isolated from the fruits of *Malotus philippinensis* called mallotophilippens C (7), D (8) and E (9) xanthohumol (10), and dihydroxanthohumol (11) inhibited the production of NO induced by LPS and IFN-y in murine macrophage-like cell line, RAW 264.7. Furthermore, mallotophilippens inhibited inducible iNOS, COX-2, IL-6 and IL-113 mRNA gene expression[32]. Daikonya and co-workers hypothesized that the main inhibitory mechanism of these compounds may be the inactivation of the nuclear factor KB (NF-KB) [33].

Karthikeyan [34] synthesized a series of 2, 4-dichloro-5-fluorop henyl containing thiazolotriazoles starting from 3-(2,4-dichloro- 5- fluorophenyl)-4 H -1,2,4-triazole-3-thiol and screened them for anti-inflammatory and analgesic activities. Pethidine and indomethacin were taken as standard. Compounds substituted with electron withdrawing groups presented good activity.

ANTIOXIDANT EFFECT

Eight dihydrochalcones were isolated from the roots of *Anneslea fragrans* var. lanceolata, davidigenin-2'-O-(6"-O-4"'-hydroxybenzoyl)-β-glucoside, davidigenin-2'-O-(2"-O-4"'-hydroxybenzoyL)-β-glucoside, davidigen-2'-O-(3"-O-4"'-hydroxybenzoyl)-β-glucoside (44),

davidigenin-2'-O-(6''-O-syringoyl)-β-glucopyranoside, 1-O-3,4-dimethoxy-5-hydroxyphenyl-6-O-(3,5-di-O-methylgalloyl)-β-gluco-pyranoside (46) davidioside (47), 4'-O-methyldavidioside (48) and davidigenin (49). Compounds 46 to 49 showed weak 2, 2-di phenyl-1 –picryl hydrazyl (DPPH) radical scavenging activity, whereas the other chalcones did not display any DPPH radical scavenging activity. The 2,6-dimethoxy groups of the syringoyl moiety may further stabilize the phenoxyl radicals enhancing the radical scavenging ability of compounds 45 and 46.[35]. Gouda *et al* [36] synthesized thiazole and thiophene derivatives from 3-acetyl coumarin (Scheme 53) and evaluated its antioxidant activity after postulating the structure activity relations hip of them. Ascorbic acid was taken as positive control

In an evaluation study by Venkatachalam *et al.*[37] for anti-oxidant properties of the novel synthesized test compounds of chalcones and flavones when tested using 4 different anti-oxidant evaluating methods it was found that, the ABTS method gave better antioxidant activity for both flavones and chalcones whereas, the DPPH method gave antioxidant profile only for flavones. However, all the four evaluating *in vitro* methods showed that the test compounds such as JVC1(3,4-(methylenedioxy) benzaldehyde) JVC2 (4-benzyloxy benzaldehyde), JVC3(4-[(2-cyanoethyl)methylamino]benzaldehyde), JVC4 (4-[(2-pyridyl)benzaldehyde), JVC5 (4-(methylthio)benzaldehyde) had the maximum antioxidant properties among the test compounds. A series of 2,4-dichlorothiazolyl thiazolidine-2,4-dione and 4-chloro-2-benzylsulfanylthiazolyl-thiazolidin e-2,4-dione derivatives was designed and studied by Bozdag *et al*[38].The synthesized compounds were tested for their antioxidant properties by determining their effects on superoxide anion formation, and the 2, 2-di phenyl-1 –picryl hydrazyl (DPPH) stable free radical using butylated hydroxyl toluene (BHT) as standard. Chlorobenzyl derivative (Scheme 56) exhibited strong superoxide anion scavenging activity.

ANTIMALERIAL ACTIVITY

Worldwide, 300-500 million people are infected with malaria each year. Most cases occur in sub-Saharan Africa, with approximately 2 million people dying there each year. Unfortunately, the emergence of malarial parasite strains resistant to chloroquine has eroded this drug´s efficacy. Extensive programs are underway to screen natural products and synthetic derivatives for new agents to treat chloroquine-resistant malaria. The n-hexane extract of leaves of *Piper hostmannianum* var. berbicense (Miq.) (Piperaeeae) exhibited

interesting activity against *Plasmodium falciparum* (IC_{50} = 8 µg ml^{-1}) [39]. An activity bioassay-guided fractionation led to the isolation of dihydrochalcones hostmanin A (55), hostmanin B (56), hostmanin C (57) hostmanin D (58) and 2',6'-dihydroxy-4'-methoxydihydrochalcone (59), as well as linderatone (60), adunctin E (61) and (-)-methyllinderatin (62). All chalcones were actives in vitro against *Plasmodium falciparum*, whereas linderatone and (-)-methyllinderatin were considered to be potentially interesting. Dominguez *et.al* [40] synthesized two molecules showing antimalarial properties one with sulphonamide moiety and other with phenylurenyl chalcones

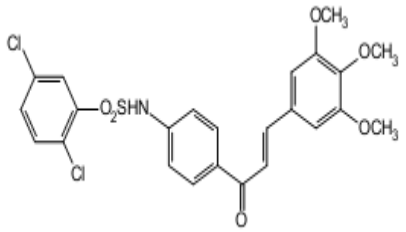

Fig: 3 Sulphonamide moiety

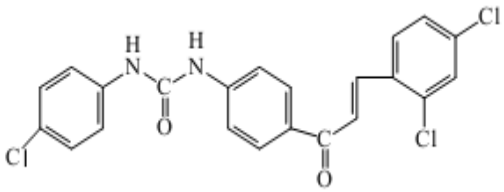

Fig:4 Phenylurenyl chalcones

Yadav *et al.* [41] synthesized 27 derivatives for antimalarial effect and they found that Antiplasmodial IC50 (half-maximal inhibitory concentration) activity of a compound against malaria parasites in vitro provides a good first screen for identifying the antimalarial potential of the compound. The most active compound was 1-(4-benzimidazol-1-yl-phenyl)-3-(2, 4-dimeth-oxy-phenyl)-propen-1-one with IC 50 of 1.1 l g/mL, while that of the natural phytochemical, licochal-cone A is 1.43 lg/mL. The presence of methoxy groups at position 2 and 4 in chalcone derivatives appeared to be favorable for antimalarial activity as compared to other methoxy-substituted chalcones. Furthermore, 3, 4, 5-trimethoxy groups on chalcone derivative probably cause steric hindrance in binding to the active site of cysteine protease enzyme, explaining the relative lower inhibitory activity.

In an another investigation by Sulistyowaty *et al.* [42,] Chalcone gave IC_{50} 0.242 µg/ml, while compound with methoxy group on para position of 3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one gave IC_{50} value 54.316 µg/ml. The presence methoxy group on ortho position of 3-(2-methoxyphenyl)-1-phenylprop-2-en-1-one gave undesired result with IC_{50} value >100 µg/ml, which means it has no antimalarial activity while other chalcone derivative with hydroxyl group on meta position, 3-(3-hydroxyphenyl)-1-phenylprop-2-en-1-one gave IC_{50} value 14.136 µg/ml. In this investigation, the standard antimalarial drug, Chloroquine diphosphate

was also examined and gave IC_{50} value 0.006 µg/ml. From the observation, it can be concluded that chalcone which has no substituent at its both ring gave the greatest IC_{50} value among the tested compounds, also they all have lower antimalarial activity than commercially available antimalarial medicine, Chloroquine.

Bhattacharjee *et al.* [43] have developed a 3D Pharmacophore for antimalarial activity and used it to conduct virtual screening (in silico search) of a chemical library which resulted in identification of several potent chalcone-like antimalarials. The identified compounds were not only found to be potent in vitro against several drug resistant and susceptible strains of *Plasmodium falciparum* and have better metabolic stability but included one with good in-vivo efficacy in a mouse model of malaria.

Chalcones are stable, low molecular weight compounds and easy to prepare in a cost-effective manner, thus attracts attention of different scientists for the synthesis of antimalarial chalcones to find out a novel and efficacious drug. *In-silico* strategies have been of importance in target identification and in prediction of novel drugs by means of bioinformatics tools to analyze possible active sites, drug likeness, molecular docking and ADME/T. The utilization of complementary experimental and informatics methods increases the rate of success in many stages of the drug discovery, by assessing the interactions between the ligands and the binding site of the protein according to their binding affinity and elucidation of their functions to the discovery and development of compounds with desired properties.

This is multidisciplinary aspect by which we can hit the target and utilized the expertise from *In vivo, In vitro* and *In-silico* methods which allows saving of time and funds as well. So, in conclusion, the chalcones and its derivatives potential as bioactive compound as a miracle molecules by exploiting the existing knowledge and its application for betterment of mankind.

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