Decades of Structural Innovations in Chalcone Derivatives and Their Pharmacological Profiling

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***Abstract*—Chalcones, recognized as compounds derived from 1,3-diphenyl-2-propen-1-one, are a fundamental framework in medicinal chemistry because of their unique α,β-unsaturated ketone structure, which leads to a broad range of biological functions. These compounds, which occur naturally and synthetically, possess diverse pharmacological capabilities, acting as anticancer, antibacterial, anti-inflammatory, and antioxidant substances. Due to their straightforward synthesis, primarily through the Claisen-schmidt condensation, extensive structural modifications can allow the optimization of their pharmacological profile. Comprehensive spectral analysis using FT-IR and NMR techniques has been crucial for identifying and confirming the structural characteristics of these compounds.The therapeutic significance of chalcone is highlighted by the clinical use of chalcone- based medications like sofalcone and metochalcone, as well as various derivatives undergoing advanced preclinical investigations. This review focuses on a systematic summary of recent development in the chemistry, synthesis, spectral analysis, and multifaceted biological activities of chalcones and their continued importance as one of the most promising scaffolds in the search for new therapeutic agents.**

***Index Terms*—Chalcone, Anti microbial, Anti oxidant, Anti bacterial, Anti cancer**

I. INTRODUCTION

Chalcones, also known as 1,3-diphenyl-2-propen-1-one derivatives, are open chain unsaturated carbonyl systems with α, β-unsaturated systems that have three carbons joining two aromatic rings[1]. Most naturally occurring chalcones are polyhydroxylated aromatic compounds, which are secondary metabolites of terrestrial plants with a variety of biological activities[1] and are thought to be the bioprecursors of open chain flavonoids, flavonoids, and isoflavanoids[2]. The word "Chalcone" is derived from the Greek word "Chalcos", which means "bronze", due to the colours of most natural chalcones.[3]. It was kostanecki and tambor who came up with the name "Chalcones". Benzyl acetaphenone and benzylideneacetaphenone are other names for chalcones[4]. Numerous biological and pharmacological activities, such as antimicrobial, anti-inflammatory, analgesic, cytotoxic, antitumor, antimalarial, antitubercular, antiviral, anti-HIV, antiulcerative, Antileishmanial, antioxidant, antiprotozoal, antihistaminic, antifedent, immunomodulatory, anticonvulsant, antihyperglycemic, antihyperlipidemic, and antiplatelet activities, have been reported for compounds with chalcone as their backbone[5].

Chalcone, also known as chalconoid, is an enone and an aromatic ketone that serves as the fundamental building block of a number of significant biological compounds[2]. 1,3-diphenyl-2-propen-1-one, which is regarded as phenyl styryl ketone, is the common IUPAC Acceptable consistent naming of chalcone. The chalcone nucleus's numbering is significantly different from that of the flavonoid structure. The aryl rings that are present in chalcone are called rings A and B. As seen in figure 1, ring A is identified by primed numbers, while ring B is identified by primed numbers, while ring B is identified by non-primed numbers[6]. Chalcones are small, non-chiral molecules with a low molecular weight (between 300 and 600 g/mol) and a comparatively high lipophilicity (Log P 5-7)[2].

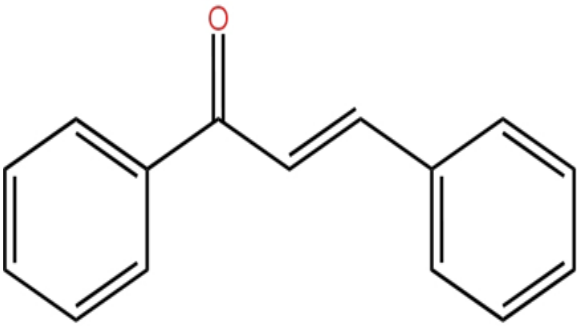
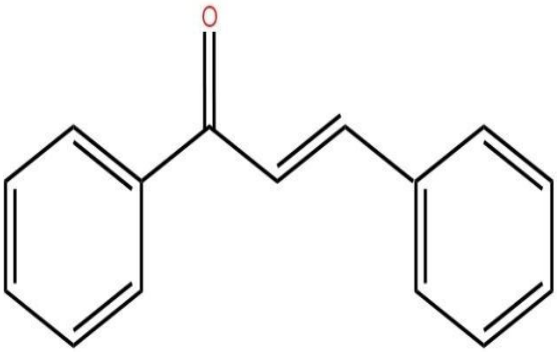
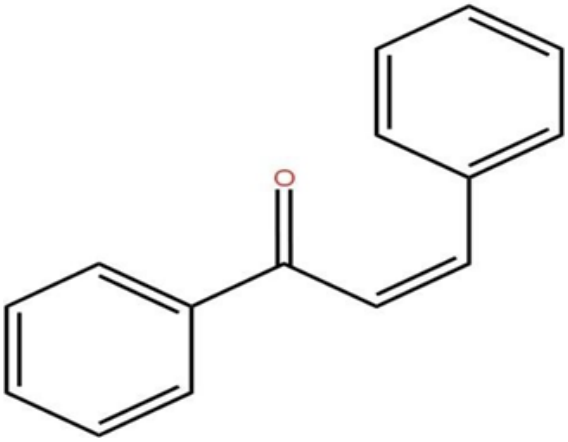


Fig 1: General structure of chalcone[12].

Chalcones come in two forms: cis and trans. The trans isomer is more thermodynamically stable than the cis form[7]. However, because there is no steric crowding between the carbonyl group and ring B, the trans (E) isomer has superior thermodynamic stability. The two aromatic rings of chalcones with a π-electron system delocalize with the conjugated double bonds, resulting in a negligible redox potential and a better chance of enduring electron transfer[8].



(1) E-Chalcone (trans)

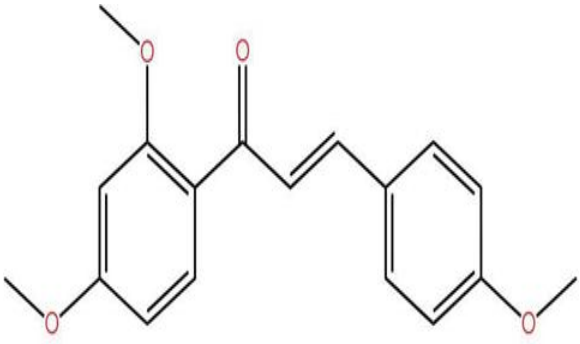


(2) Z-Chalcone (Cis) Fig 2: Cis and Trans isomer of chalcone[11].

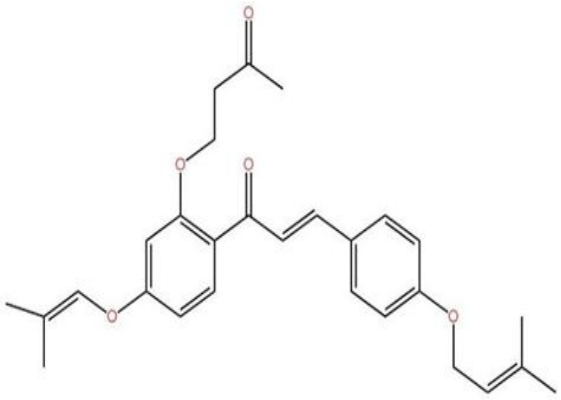
1.2 Physicochemical properties of chalcones

Naturally occurring chalcones are usually crystalline solids with a range of hues, such as orange, yellow, and brown. Chalcones are more stable than isoflavanoids and relative flavonoids. Chalcones are soluble in both acidic and alkaline aqueous solutions in addition to organic solvents. In an aqueous alkaline medium, a deep red or orange color develops. Chalcones that have been treated with concentrated sulfuric acid turn pink, i.e. The e. wilson test results are positive. When chalcones with free phenolic hydroxyl groups are exposed to an alcoholic ferric chloride solution, they change color, i.e., shades such as blue wine red, blue black, violet, or green are produced[9]. According to Go et al. (2005) and colleagues, X-ray structures of chalcones from the Cambridge database are consistent with the general planarity and rigidity of the extended p-system in chalcones. Chalcone's enone moiety's Cα-Cβ double bond can take on either an E or Z configuration. Thermodynamically, The E-isomer is more stable[10].

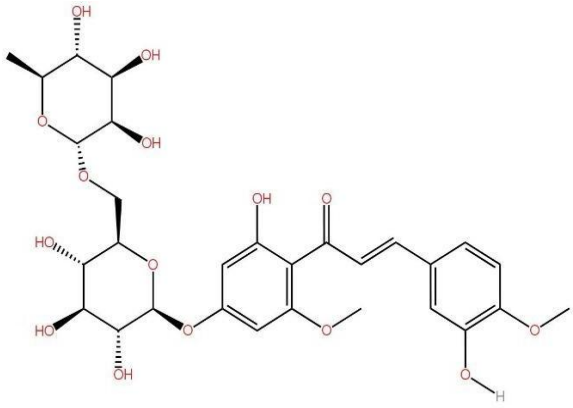
1.3 FDA Approved Marketed drugs and its application



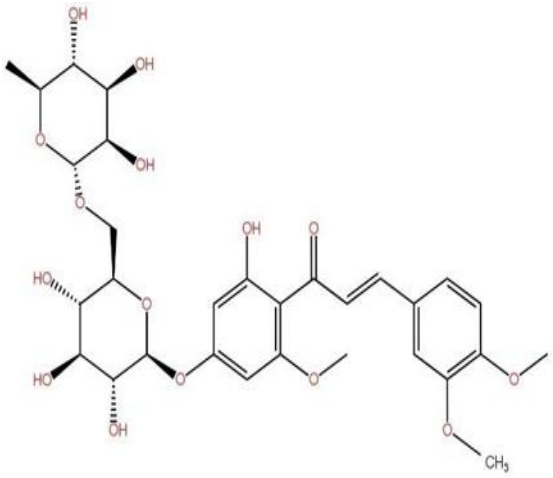
(3) Metochalcone



(4) Sofalcone



(5) Hesperidin methylchalcone



(6)Hesperidin trimethylchalcone Fig 3 : FDA approved marketed drugs of chalcones[11].

Natural metabolites or their synthetic analogs have been used to create more than half of the clinical drugs approved by the US Food and Drug Administration (FDA). For many years, traditional medicine has also made use of plants that contain chalcones, which are straightforward pharmacological scaffolds of a number of naturally occurring metabolites[8]. Sofalcone was marketed as an anti-ulcer, mucoprotective medication, while metochalcone was marketed as a choleretic[12]. With just three recycling steps, the medication metochalcone, which was produced in our solvent- free environment, had a 92 percent isolated yield[13]. The metochalcone compound suppressed the multiplication of cells, their movement, advancement through the cells lifecycle, the increase in tumor size and triggered the characterisctic secretion linked to cellular aging. Metochalcone, a compound belonging to the chalcone group, shows promise as a possible treatment for breast and lung malignancies through its influence on the JAK2/STAT3 signaling route. It could also aim at STAT3, triggering the creation of a senescence-linked secretory characteristic[14]. Tanaka & Co. For over 20 years, the Japanese have been using the 2009 sofalcone drug to treat gastritis or gastric ulcers. It significantly inhibits the inflammatory crosstalk between RAW264.7 macrophages and 3T3F442A adipocytes. Sofalcone has also been shown to be effective in preventing 3T3-F442A cells from differentiating into adipocytes from preadipocytes[15]. Furthermore, clinical trials have demonstrated that hesperidin trimethylchalcone (assessed for trunk or branch varicosis) and hesperidin methylchalcone (tested for chronic venous lymphatic insufficiency) were well-tolerated, reached acceptable plasma concentrations, and relieved symptoms[11]. The use of HMC as a treatment led to a noticeable decline in neutrophil presence, swelling, visible and cellular harm to the colon, reduction in colon size, oxidative tension, and the creation of pro-inflammatory cytokine through the reduction of NF-κB activity within the colon[16].

1.4 Pharmacological profiling of chalcone

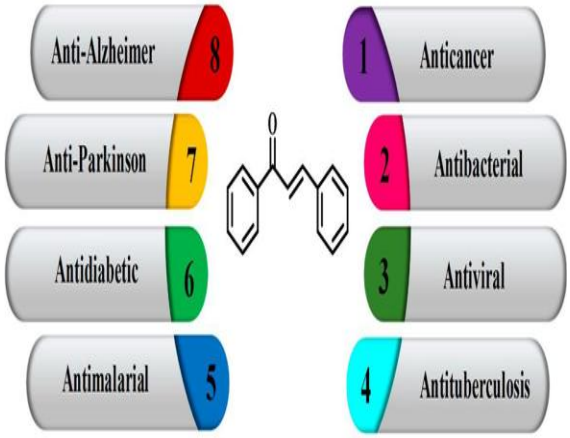


Fig 4: Diverse pharmacological activities of chalcones[17].

Chalcone is an aromatic ketone that serves as the basis for numerous significant pharmacological applications in drug development. Chalcones have been shown to exhibit pharmacological activity, and various substituted derivatives, including heterocyclic analogs, have been found to possess potent biological properties that inhibit the growth of

microorganisms[18]. Chalcones found in nature are categorized as phenolic compounds and often have one or more phenolic hydroxyl groups in their structures. These groups usually give them the ability to scavenge free radicals, that can be beneficial in combating oxidative stress. The connection between oxidative stress and inflammatory reactions is well known. Thus, it is expected that any reduction in oxidative stress will reduce inflammatory reactions. It has also been shown that chalcones with the capacity to scavenge free radicals have anti-inflammatory properties. [19]. Numerous chalcone derivatives have been shown to have antiviral qualities, with notable and substantial effect on the modulation of different anti-infective molecular targets. Chalcone derivatives are thus positioned as potentially safe and potent broad-spectrum antiviral drugs.Chalcones have been utilized in the creation of innovative therapies that exhibit strong activity against 5 lipoxygenase and amyloid-β aggregation, indicating that chalcone derivatives may serve as a promising multifunctional candidate in the fight against multi-resistant Alzheimer's disease[20]. Chalcones and their derivatives are regarded as potential future antidiabetic medications. The antidiabetic effects of both synthetic and natural chalcones have demonstrated encouraging results on various target sites[21]. Licochalcone A is currently regarded as the most promising antimalarial compound identified to date. Natural chalcones have demonstrated the ability to inhibit the growth of both chloroquine-susceptible and chloroquine-resistant strains of Plasmodium falciparum[22]. Both natural and synthetic chalcones exhibit antitumor properties both in vivo and in vitro, and they also demonstrate efficacy against drug-resistant cancers. A key mechanism underlying the antiproliferative effects of chalcones is their ability to inhibit tubulin and disrupt the assembly of microtubules[23]. Chalcone derivatives, including Licochalcone A, which is isolated from Glycyrrhiza inflata, demonstrated significant antitubercular activity[24].

Numerous chalcones are recognized for demonstrating significant antimicrobial and antifungal activity attributed to the presence of α,β-unsaturated carbonyl groups that may augment the activity[25].Furthermore, chalcones can serve as foundational structures for the synthesis of various heterocyclic compounds that exhibit diverse pharmacological activities[26]. Chalcones can be readily modified and synthesized to produce a diverse range of compounds with varying structures. These properties make such compounds highly appealing as fundamental building blocks for the creation of molecule-targeting agents[27].

II. GLOBAL IMPACT OF CHALCONE ON INDIA

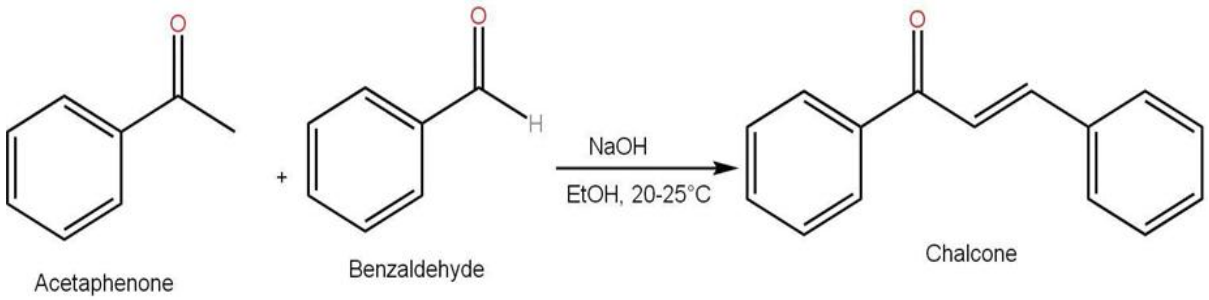
Chalcones are incredibly prevalent biologically active substances found in natural products. Chalcone's natural isolates and synthetic modifications are being investigated worldwide in an effort to create more effective compounds for a range of illness. They are widely found in fruits, vegetables, tea, and spices and are among the most popular categories of natural products. Chalcones have shown a low toxicity profile and impressive biological properties. Chalcones have attracted attention because of their ability to supress phenolic groups, which is useful for both food preservation and drug development. Drug discovery using chalcone frameworks may be significantly impacted by strategic chemical modifications of natural chalcones that are necessary to produce new flavonoid molecules[28].

III. SYNTHESIS OF CHALCONE

Chalcones possess simple yet advantageous structure, often employed as a fundamental framework in drug development due to their straightforward synthesis process which permits numerous modifications, making them valuable for finding new medicines. Typically, chalcones are created via condensation reactions, facilitated by either acidic or basic catalysts[6].

3.1 Clasein-Schmidt condensation reaction :

Chalcone derivations, or α,β-unsaturated ketones, can be obtained through the C-C valuable bond formation reaction known as the Claisen-Schmidt condensation reaction between acetophenone and benzaldehyde[29].



Scheme 1 : Synthesis of chalcone[27]

General Method of Preparation of Chalcones

Choudhary et al (2012)., described a general process for making chalcones. A 250 ml round-bottomed flask fitted with a magnetic stirrer was used to dissolve a mixture of acetophenone and benzaldehyde derivatives (0.01 mol) in 10 ml of rectified spirit. After 30 minutes of vigorous stirring, 10 ml of sodium hydroxide solution (1g in 10 ml H2O) was added dropwise to the reaction mixture until the solution turned turbid. A cold water bath on the magnetic stirrer was used to keep the reaction temperature between 20 and 25˚ C. The precipitation happened after the reaction mixture was neutralized by 0.1-0.2N HCl following vigorous stirring for four to five hours. The crude chalcones were filtered off, dried in the air, and then recrystallized using rectified spirit[30] (scheme 1).

IV. SPECTRAL CHARACTERIZATION

As far as their synthesis, structure, and photochemical behavior are concerned, chalcones are an intriguing class of molecules. Few studies have examined the spectral behavior of these compounds, despite the fact that numerous investigations have dealt with them[31].

4.1 Infrared and FTIR Spectroscopy

For the description of inorganic and organic compounds., FT-IR spectroscopy can be a useful fundamental tool. Jagadeesh M. and others. stated that The overlapping bands that occur at particular wavenumbers are clearly visible in the specified vibrations that occur at similar wavenumbers/range; for example, the aromatic C=C bond vibrations overlap with the hydrogen bonded carbonyl group, and the aromatic C-H stretching vibrations overlap with the hydrogen bonded OH functional group. 2'-hydroxychalcones exhibit cis-to-trans isomerization due to intramolecular hydrogen bonding, which further affects their spectroscopic characteristics. The vibrational frequencies in the IR and Raman experimental spectra are notably red-shifted in comparison to those in the DFT-calculated spectra of the hydroxy chalcones optimized structures; this suggests that the 2'-hydroxy functional group plays a significant role in intramolecular hydrogen bonding in the hydroxy chalcone[32]. All of the chalcones' FT-IR spectra displayed a peak at 1640cm^{-1}, which is indicative of a conjugated ketone group. At 1580cm^{-1}, the double bond peak emerged. Chalcones with nitrogen substituents peaked at 3300cm^{-1}, while the aromatic regions were visible at 1000cm^{-1}[33].

In the IR spectrum of chalcone, the unsaturated carbonyl group usually appears as a prominent band in between 1625 and 1650 cm^{-1}. The region where other absorption bands appear is determined by the substituents present on aromatic / heteroaromatic rings as well as the type of rings[34]. According to IR studies, the C=O stretching mode has two peaks that suggest a second isomer, trans-(s-trans)-chalcone, coexists in solution with trans-(s-cis)-chalcone. In the 1600-1700 cm^{-1} range, these conformers are observed as doublets[35]. The asymmetrical and symmetrical stretching vibrations of the aromatic C-H bonds are represented by the two low intensity bands in the 3120-3080 cm^{-1} ranges, respectively. The =C-H group 12's C-H stretching is attributed to the band at 3030-3010 cm^{-1}. The stretching mode of the C=O linkage is responsible for the bands that appear to be intense within the 1685–1650 cm^{-1} range. As the acceptor character of the substituent on the arylidenering increases, this band typically shifts to a higher wavenumber. The aromatic ring's vibrations are attributed to the three intense to medium bands with the 1610–1570 cm^{-1} range. The wide weak band at 1460–1430 cm^{-1} is caused by the inplane deformation

of the =C–H bond. As the arylidene system's acceptor character rises, the band typically shifts to higher values. The aromatic C-H groups inplane bend results in a collection of three to five distinct medium intensity bands close to 1180, 1150, 1100, 1020, and 880 cm^{-1}. The more the electronic character differences, the more bands there are. This is because the altered charge density on the rings causes the two molecules' energy states to differ more. The type of substitution of the aromatic rings is characterized by the medium or high intensity bands below 900 cm^{-1}. The bands resulting from the monosubstituted ring for series I appear as a medium band at 710-690 cm^{-1} and a strong band at 755-735 cm^{-1}. The p-disubstituted rings of a, b, d, f, and g have bands located at 800-820 and 790-780 cm^{-1}[31]. While the C=O stretching mode of the s-cis conformer is detected at a higher frequency, the C=O stretching mode of the s-trans conformer is detected at a lower frequency The splitting of the carbonyl in the IR spectra disappeared when only trans- (s-cis)-chalcone was present in the solid state[35].

4.2 NMR spectroscopy of chalcones :

NMR spectroscopy has surpassed even the most optimistic predictions, offering a remarkably broad range of remarkable applications that extend beyond chemistry to physics, biology, medicine, other related fields[31]. The number of protons and carbons that each molecule contains determines how the molecules are characterized by nuclear magnetic resonance spectroscopy[36]. A unique experimental method known as STD NMR (Saturation Transfer Difference Nuclear Magnetic Resonance) was used to uncover the interactions of chalcone compounds at the smallest scales[37].

Chalcones exhibit three distinctive signals in the carbon nuclear magnetic resonance (13C NMR) spectrum: a typical signal for carbonyl in the range δ 188.6–194.4 and two additional prominent signal for Cα and Cβ in the range 116.1-128.1 and 136.9-145.4 ppm, respectively[6]. These signals can also be easily recognized by their characteristic appearance as a six line multiplet in the half resonance decoupled spectrum 24. In comparison to corresponding acetoxy and methoxy compounds, the presence of a 2'-hydroxy group causes the carbonyl carbon shift to shift downfield by 3 ppm, most likely due to hydrogen bonding. A comparatively small class of chalcones known as β-hydroxy chalcones can occasionally be found in nature as the enol-tautomers of dibenzoylmethane derivatives. Nuclear magnetic resonance spectroscopy (NMR) offers one of the best ways to ascertain the ratio of the tautomers present. The degree of ketoenol tautomerism is mainly solvent dependent. The exchangeable proton of the enol tautomer's β-OH appears as a 1H singlet at δ 16.0 in the 1 H NMR spectra recorded in CDCl3, while the α-CH2 protons of the keto tautomer appear as a 2H singlet at δ 4.50. The 1H methine. singlet of the enol tautomer (α-CH), located at δ 6.5, and its corresponding C-α resonance at δ 90 to 92 in the 13C NMR spectra, is another diagnostic resonance[34].

Ha protons are ethylenic protons that are closer to the carbonyl group, and Hb protons are those that are next to Ha protons (figure). Compared to Hb protons, chalcone Ha protons exhibited a chemical shift at higher fields. This could be because the carbonyl group in the system is primarily responsible for the polarization of the C=C double bond, which results in a higher electron density at position a than at position b[35].

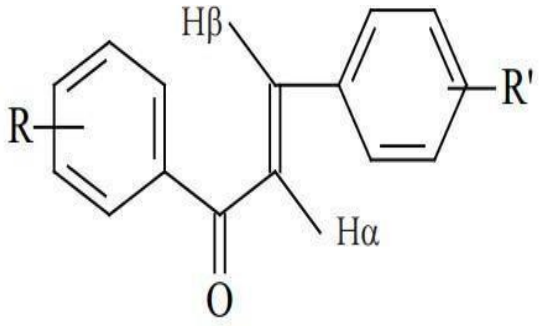
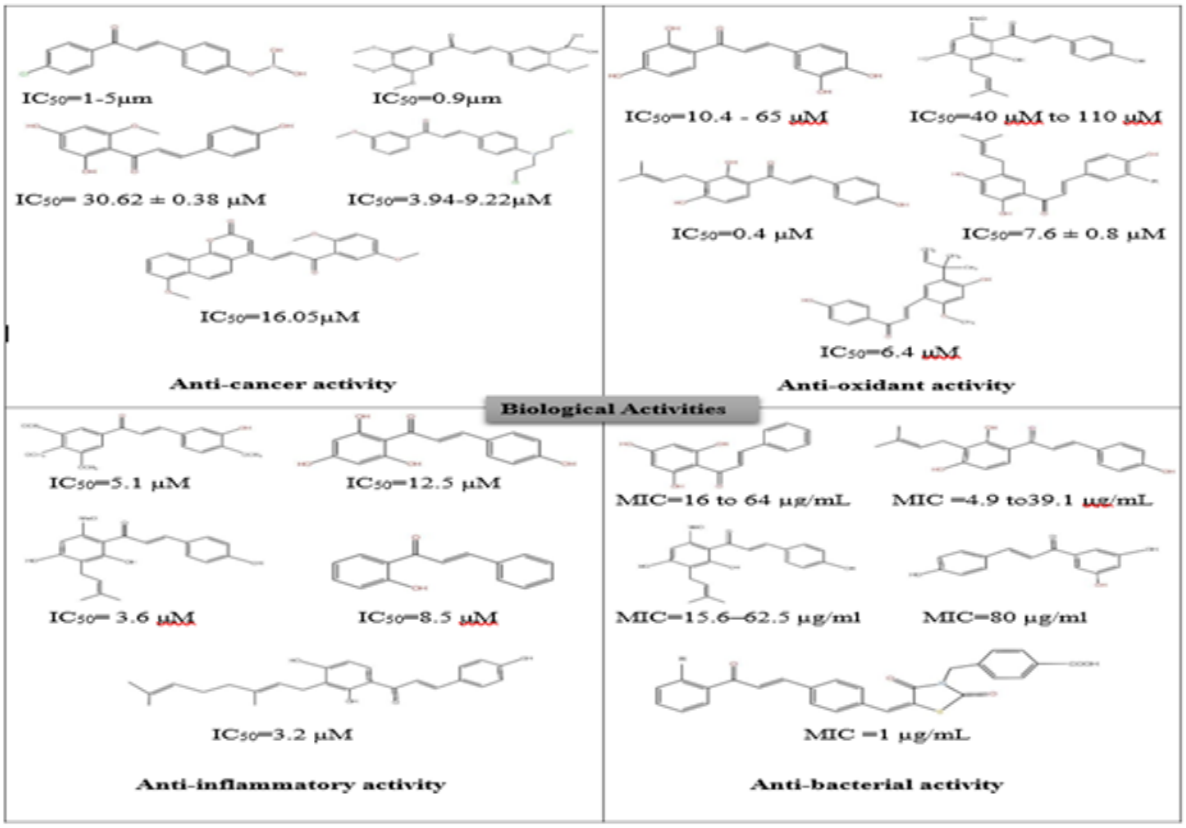


Fig 4: General presentation of chalcone protons which have enone structure[35].

V. BIOLOGICAL ACTIVITIES

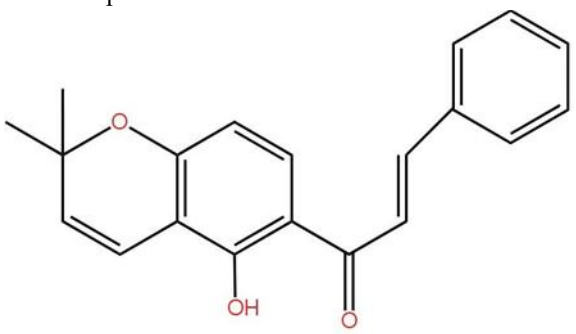
The wide range of pharmacological and therapeutic potential of chalcones and their derivatives makes them extremely important in medicinal chemistry, even in the twenty-first century. Anticancer, Antibacterial, Anticonvulsant, antiHIV, antihyperglycemic, anti-inflammatory, antileishmanial, antimicrobial, antioxidant, antiprotozoal, antitubercular, antiviral and anti-ulcerative properties are among the many biological activites exhibited by the chalcone derivatives[6].



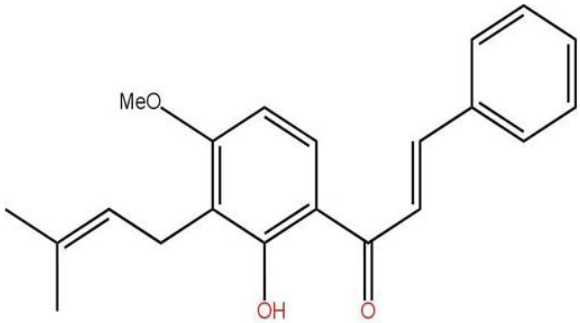
5.1 Anticancer Activity

Uncontrolled cell growth, which is the result of regulatory dysfunction and can be brought on by a number of environmental and genetic factors, is the hallmark of cancer. Despite having a challenging prognosis, it still requires very aggressive treatment and has a high death rate, which is brought on by the illness itself as well as the side effects of treatment. Research on treating this disease has focused on natural products like chalcones of the type (1,3-diaryl-2-propen-1-ones), which have a conjugated carbonyl system that acts by preventing tubulin polymerization in tumor cells, thereby stopping its abnormal reproduction cycle[39].

5.1.1 M.L. Go et al (2005)., reported that A leukemic cell line was cytotoxically affected by a hexane extract made from the roots of Lonchocarpus sericeus, a common plant in northeastern brazil (IC50: 17.6 µg /ml). Four lonchocarpin and five derricin, which were present in about equal amounts, were the extract's primary constituents[10]. Derricin and lonchocorpin were cytotoxic to the CEM leukemic cell line, preventing cell growth with an IC50 of less than 20 g/mL. Tumor cells were cytotoxically affected by lonchocarpin[40].



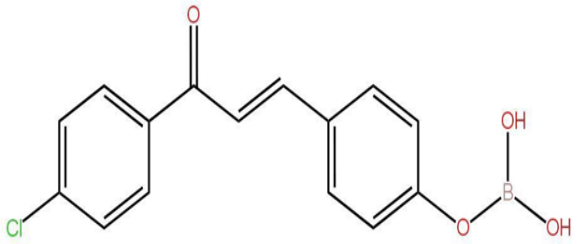
(7) Lonchocarpin



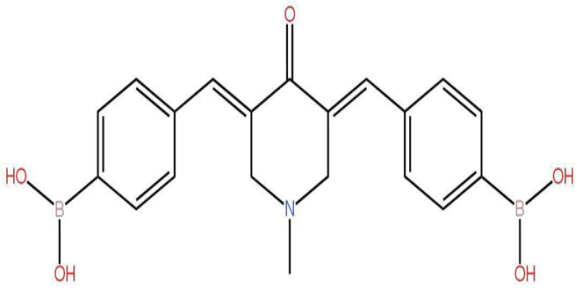
(8) Derricin

Figure 6

5.1.2 Achanta et al (2006)., evaluated a series of boronic chalcone derivatives for their growth inhibitory activity in the colon carcinoma call line 3,5bis-(4-boronic acidbenzylidene)-1 methyl-piperidin-4-one showed strong cytotoxic activity against p53-/- cells using apoptosis assays with IC_{50} values of 1 to 5 µM, and 3(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium
bromide showed strong activity against p53+/+ cells in colony formation assay, with an IC_{50} value of 0 to 6 µM. For cells with wt p53 function, boric chalcone derivatives might be more effective. When compared to normal breast epithelial cells, boronic chalcone derivatives have a much stronger growth inhibitory effect on human breast cancer cell lines and cause an accumulation of p53 and p21 proteins[41].

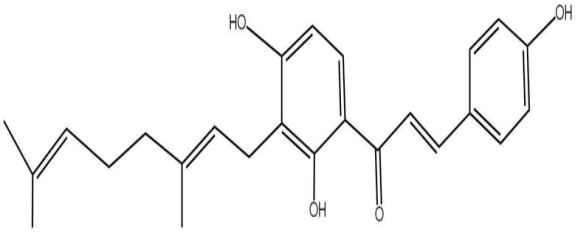


(9) 3(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide



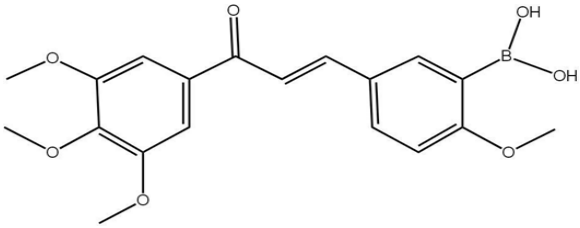
(10) 3,5bis-(4-boronic acidbenzylidene)-1 methyl-piperidin-4-one
Figure 7

5.1.3 Motani et al (2008)., demonstrated that xanthoangelol, a representative chalcone constituent, has a cytotoxic effect on drug-resistant neuroblastoma and causes the tumor cells to undergo apoptosis. In neuroblastoma, xanthoangelol exhibited strong cytotoxicity and caused apoptosis through caspase-3 activation. In the mechanism of xanthoangelol-induced apoptosis, the mitochondrial pathway is more significant than the death receptor pathway[42].



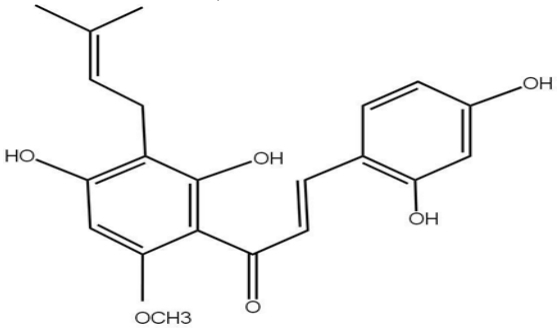
(11) xanthoangelol
Figure 8

5.1.4 Kong Y et al (2010)., demonstrated that the effects of boronic acid analog include disruption of A-10 cells' microtubule network, suppression of human MCF-7 breast cancer cell growth, and inhibition of [3 H] colchicine binding to tubulin. Boronic acid chalcone exhibited strong cytotoxic activity against MCF-7 cnacer cells (IC_{50} = 0.9 µM), but it was only marginally effective as an inhibitor of tubulin polymerization and colchicine binding[43].



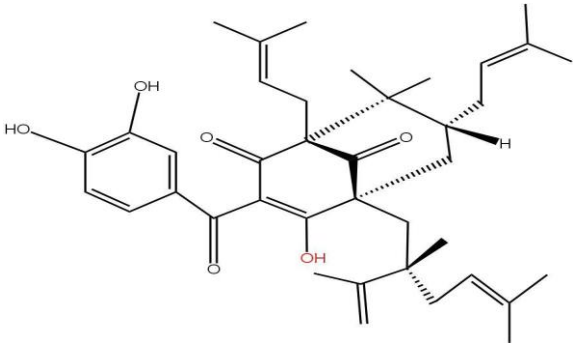
(12) A boronic acid chalcone
Figure 9

5.1.5 orlikova B et al (2011)., reported that By increasing Heme oxygenase-1 (HO-1) activity the prenylated chalcone 7,9,2',4-tetrahydroxy-8-methoxychalcone from Sophora flavescenes effectively suppressed the expression of interferon (INF)c and tumour necrosis factor alpha (TNF-a)-induced chemokines (TARC/CCL17,MDC/CCI22, and CTACK/CCI27)[44].



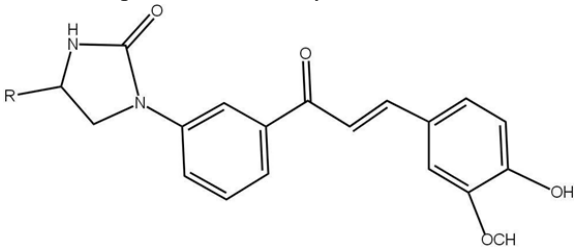
(13) 7,9,2′,4′-tetrahydroxy-8-isopentenyl-5-methoxychalcone
Figure 10

5.1.6 Saadat N et al (2012a)., reported that In human leukemia HL-60 cells, garcinol showed more apoptosis induction than curcumin . The activation of caspase-3 was made possible by the release of caspase-3 was made possible by the release of cytochrome c from the mitochondria . Additionally, apoptosis was accompanied by a marked upregulation of the well-known proapoptotic proteins Bad and Bax and a downregulation of the antiapoptotic protein Bcl-2, According to the findings, cytochrome c release into the cytosol triggers garcinol-induced apoptosis, which is then followed by procaspase-9 processing, caspase-3 and caspase-2 activation , PARP degradation , and DNA fragmentation[45].



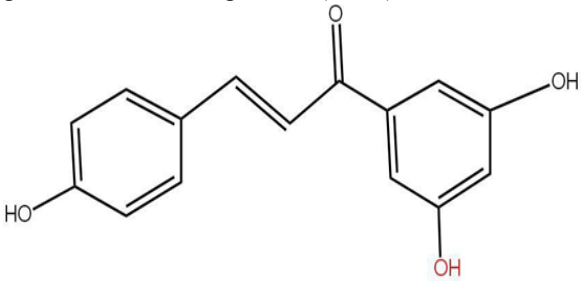
(14) Garcinol
Figure 11.

5.1.7 K Sahu N et al (2012b)., reported that When 10M concentrations of hybrid compounds 15a, 15b, and 15c were applied to breast carcinoma cells (MCF-7), the compounds showed good anticancer activity with GI_{50} values ranging from 1.26 to 13.9 Mdot. A panel of 53 human tumor cell lines from nine different cancer types were used to test the anti-cancer potential of a number of novel chalcone linked imidazolones. Interestingly, when the concentration of the same compounds was increased to 30 M, cells in the G0/G1 phase of the cell cycle accumulated. [12].



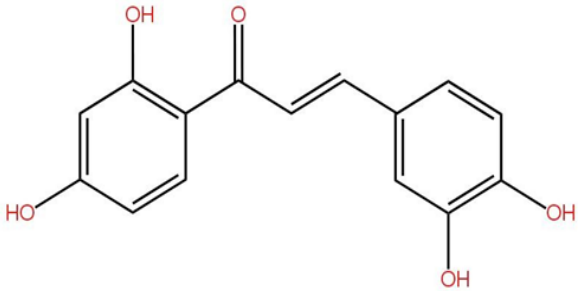
(15) coumarin–chalcone hybrids
(15) a: R= Phenyl ;(15) b: R=4-Methoxy Phenyl ;
(15) c: R=4-Chloro Phenyl
Figure 12

5.1.8 Jung et al (2014a)., has been reported that Isoliquiritigenin causes apoptosis and inhibits the growth of different cancer cell types in culture. Additionally, it has been demonstrated to inhibit tumor angiogenesis, reduce cancer cell migration, invasion, and metastasis, and suppress the growth of xenograft tumors created from human cancer cells in athymic nude mice. By stopping cells at the G1 and G2/M phases of the cell cycle and causing p53- and Fas-FasL-mediated apoptosis in these cells, ILQ prevents the growth of human lung cancer (A549) cells[46].



(16) Isoliquiritigenin
Figure 13

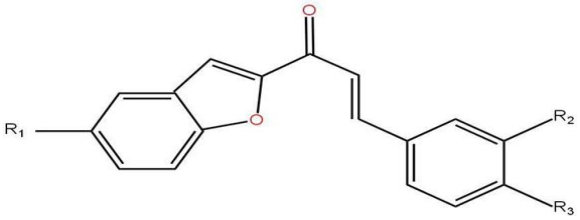
5.1.9 Yang et al (2014b)., reported that in both in vitro and in vivo investigations, butein has been demonstrated to inhibit the growth and induce apoptosis in a number of human cancer cells, such as melanoma, prostatic, breast, hepatocellular, bladder, and colon cancer. Furthermore, it is either completely safe or very mildly harmful to healthy cells. Butein has the ability to stop cancer cells from growing and cause apoptosis. It dramatically reduced the viability of ovarian cancer cells TOV21G and ES-2 in a dose-and time-dependent manner[34]. et al. Michalkova R (2023). Butein directly affects breast cancer cell proliferation by modifying the impact of various cellular proteins. According to some theories, cyclooxygenase (COX) inhibitors may be employed in the chemoprevention of breast cancer[42].



Butein Figure 14

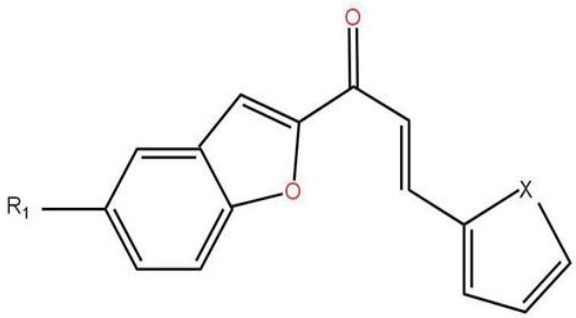
5.1.10 Coşkun D et al (2016)., demonstrated

that the anticancer activity of synthetic benzofuran chalcone compounds (18)a, (18)b, and (19)a was assessed in vitro using the MTT test. On PC3 and MCF-7 cell lines, the benzofuran-substituted chalcones exhibited anticancer action ($p < 0.05$). The viability percentage of PC-3 and MCF-7 cells was drastically decreased by all of the substances at 100 μM concentrations ($p < 0.001$). Benzofuran-substituted chalcone compounds were investigated, and their cell survival percentages were calculated. Compounds a, b, and c were determined to be the most effective against MCF-7 and PC-3 cell lines. Their log IC_{50} values were computed using the computer application GraphPad Prism 6 and the inhibition percentage values[48].



(18) a) R1 = Br, R2 = H, R3 = H (log IC50 = 1.89 μM)

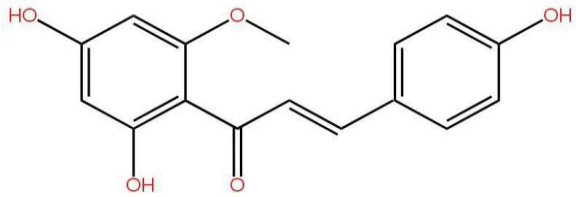
(18) b) R1 = H, R2 = H, R3 = H (log IC50 = 6.28 μM)



(19)a) R1 = H, X = S (log IC50 = 2.55 μM)

Figure 15

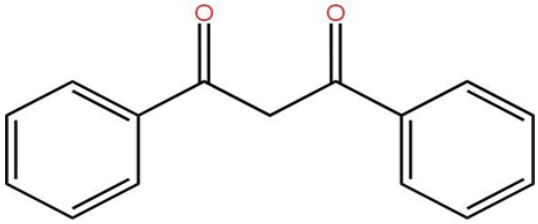
5.1.11 Fong HY et al (2017)., has been reported that Helichrysetin inhibits the growth of colorectal, lung, and breast cancer cells, making it physiologicall y active against these cancer cells.Helichrysetin lowers the viability of Ca Ski cells and prevents their multiplication.An IC_{50} of <50 µM indicates that a chemical is active against cancer cells.Therefore, helichrysetin's IC_{50} value of 30.62 ± 0.38 µM suggests that it is effective against Ca Ski cells.In additi on to acting as a possible agent that damages DNA, helichrysetin can also kill human cervical cancer cells by activating JNK[49].



(20) Helichrysetin

Figure 16

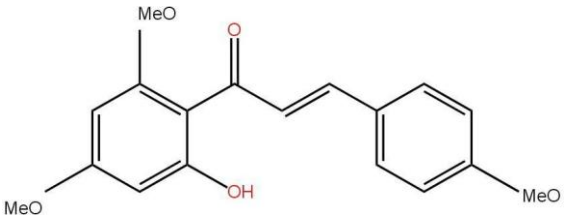
5.1.12 Nascimento et al (2018)., reported that Dibenzoylmethane (DBM) has a variety of anticancer properties.DBM has been demonstrated to trig ger cell cycle arrest and apoptosis in human prostate and colon cancer cells, as well as to stop the pro duction of carcinogen-induced DNA adducts in mammary glands ,the lungs and the Nrf2 detoxification pathway bot in vitro and in vivo[36]. DBM successfully decreased the activity of NFκB, the nuclear factor Kappa light chain enhancer of activated B cells, by 65%.This transcription fact or's decreased DNA binding was the cause of this activity decline.The transcription factor NF-kB is known to initiate the growth and survival of cancer, hence this result is important[50].



(21) Dibenzoylmethane (DBM)

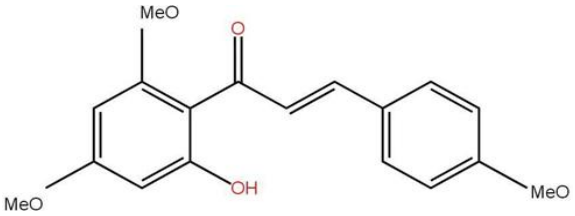
Figure 17

5.1.13 Juan li et al (2019)., reported that A unique chalcone from the kava plant called flavokawain A (FKA) caused G2/M arrest and death in several tumor cells[90].Abu et al. (2014),Flavokawain A was also demonstrated to suppress bladder cancer cell line proliferation in vitro.The fact that FKA exclusively causes G2/M arrest in MDA MB 231 suggests that its anticancer effects are selective and contingent on the p53 state.Therefore, FKA s hows promise in treating triple negative breast cancer that is more aggressive and has a p53 mutation[52].



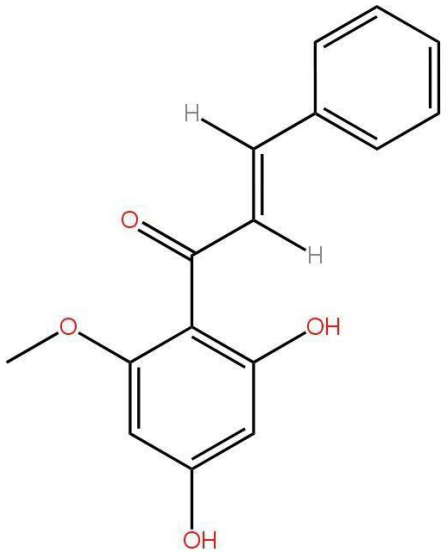
(22) Flavokawain A
Figure 18

5.1.14 Hseu et al (2020a)., reported that Melanoma cell shape was dramatically altered by flavokawain B (FKB), suggesting that it has antitumor capabilities. Oncogenesis has been connected with a number of constitutive active kinase mutat ions in the microtubuleassociated protein (MAP) kinase pathway.BRAF (V600E) is among the most common oncogenic genotypes.BRAF is endogenously expressed by the A375, which also inhibits E RK phosphorylation in the absence of ligands and causes constitutive activation of the MAP kinase p athway.FKB plays a crucial role in preventing oncogenesis in melanoma cells, as evidenced by the n otable dose-dependent downregulation of the BRAF protein linked to oncogenesis in BRAFexpressing A375 cells, along with its downstream phosphorylated ERK1/2 proteins [53].



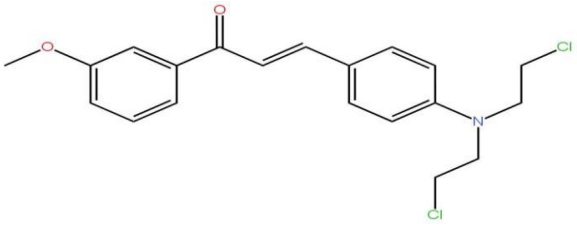
(23) Flavokawain B
Figure 18

5.1.15 Ramchandani et al (2020b).,was reported that Cardamonin is useful in treating a variety of human diseases, such as multiple myeloma, glioblastom a, leukemia, melanoma, breast, cervical, colon, stomach, lung, ovarian, and prostate cancers. The main mechanism of cardamonin is the mammalian target of rapamycin (mTOR) signaling pathway, which is essential for autophagy (the elimination of damaged cells), cell metabolic regulation, a nd proliferation inhibition.Cardamonin can induce apoptosis in a variety of cells by upregulating proapoptotic proteins including caspase-3 and Bcl2 associated X protein (Bax) and downregulating antiapoptotic molecules like B-cell lymphoma 2 (Bcl-2)[54].



(24) Cardamonin
Figure 20

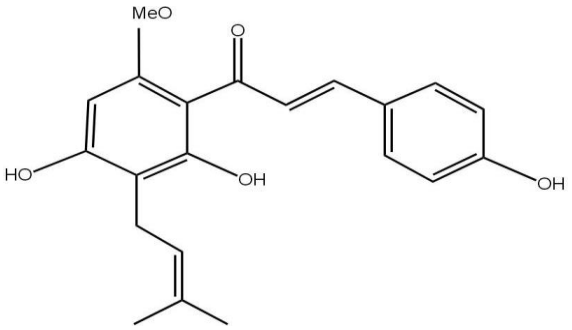
5.1.16 Elkhalifa et al (2020c)., demonstrated that (E)-3-(4-(Bis(2-chloroethyl) amino) phenyl)1(3methoxyphenyl) prop-2-en-1-one) was found to be particularly effective against TNBC and other BC phenotypes. It caused considerable cell cycle arrest of TNBC cells at the G2/M phase and had antiproliferative action (IC_{50}=3.94-9.22μM) against tumor invasion and migration in triple-negative breast cancer (TNBC) call lines[55].



(25)((E)-3-(4-(Bis(2-chloroethyl) amino) phenyl)-1-(3- methoxyphenyl) prop-2-en-1one)
Figure 21

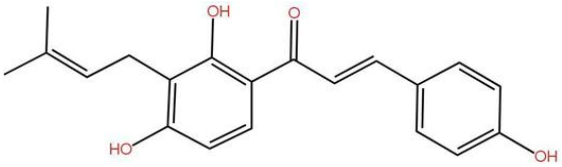
5.1.17 Girisa et al (2021a).,reported that xanthohumol (XN) protected hepatocellular carcinoma and melanoma cells against metastasis and cell division. Additionally, by altering the phosphatase and tensin homolog (PTEN)/Akt/mammalian target of rapamycin (mTOR) pathway, XN prevented the proliferation, differentiation, and overproduction of cardiac fibroblasts brought on by TGF-β1. FOSrelated

antigen 1 (Fra1) and the extracellular signal-regulated kinase ½ (ERK1/2) pathway have also been shown to be inhibited by XN. This results in a decrease in cyclin D1 and an inhibition of activator protein-1 (AP-1) transcription in non-small cell lung cancer (NSCLC) cells[56].



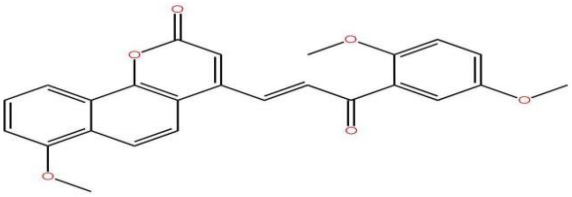
(26) Xanthohumol
Figure 22

5.1.18 Gao et al (2021b) ., reported that 4-Hydeoxyderricin (4-HD) is a significant natural chalcone that was extracted from A. keiskei and has a number of useful qualities, including anticancer effects. Morever, HD inhibited proliferation and metastasis and caused exceptional cell cycle arrest and death. In order to have an anti-HCC cell proliferation impact, it may cause mitochondrial apoptopic cell death and increase apoptosis and cell cycle arrest of the HCC cells via modifying the PI3K/AKT/mTOR signaling pathway[57].

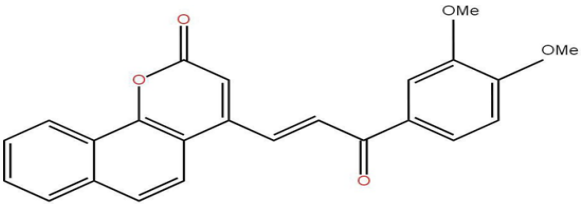


(27) 4-Hydeoxyderricin or isobavachalcone
Figure 23

5.1.19 Saquib M et al (2021c)., reported that Using the MTT assay, benzocoumarinchalcone hybrid compounds 28 and 29 were tested for antiproliferative activity against a panel of four different human cancer cell lines: MCF-7 (ER+ ve) and MDA-MB-231 (ER-ve) cell lines from breast cancer, Ishikawa cell line from endometrial cancer, and Hela cells from cervical cancer. Raloxifen (RAL) and tamoxifen (TAM) served as controls. Containing IC_{50} values of 16.05µM and 24.10µM, repectively, another benzocoumarin chalcone hybrid compound containing methoxy groups at positions 3 and 4 of the aroyl ring demonstrated antiproliferative action against MCF-7 and MDAMB-231 cell lines[58].

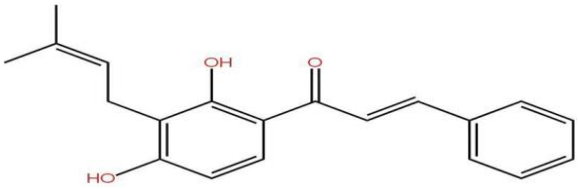


(28) The benzocoumarin-chalcones



(29) Benzocoumarin-chalcone hybrid having methoxy group
Figure 24

5.1.20 Silva et al (2025)., reported that in cell lines of prostate and oral-laryngeal malignancies, isocordoin also has cytotoxic action.Furthermore, it has been demonstrated t hat isocordoin analogues stimulate apoptosis in human melanoma cells via Hsp70[42]. It was discovered that discovered that isocordoin may stop the cancer prostate cell P-3's call cycle. The percentages of cells in G1, G2, and S phases were 26.0, 53.3, and 20.5, respectively[42]. At an IC_{50} of 27.2 µM, isocordoin demonstrated a mild cytotoxic effect on HT-29 cells[59].



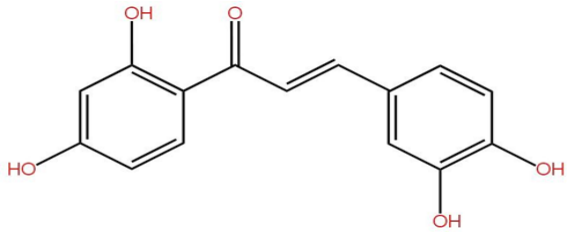
(30) Isocordoin
Figure 25

5.2 Anti-Oxidant activity

Antioxidants are widely used, notably in the care of stroke and neurodegenerative diseases. The antiaging process seen among many antioxidants is the ability to fix cellular damage and suppress the permanent creation of free radicals. Furthermore, antioxidants

have been introduced into dietary supplements, helping people get enough nutrients in order to have a healthy body and avoid illnesses like cancer and coronary heart disease[60]. Antioxidants can also be defined as substances that can prevent or retard the oxidation of an oxidizable substrate during a chemical reaction. The antioxidant properties of natural compounds such as chalcones are associated with various mechanisms, including the scavenging of free radicals[61].

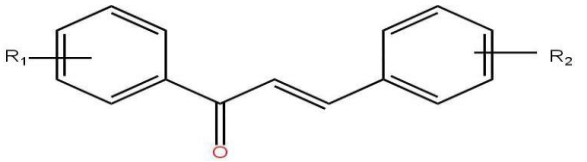
5.2.1 Chen et al (2005)., reported that The mechanism of butein favors H-atom transfer over electron transfer, with the B-ring exhibiting a strong ability to donate hydrogen, (IC_{50}=10.4 μM to 65 μM) and the 4-OH showing the lowest bond dissociation energy (BDE). As a result, butein can act as a potent antioxidant against the DPPH radical; a potential mechanism involves the initial abstraction of the Hatom from the 4-OH by the DPPH radical, followed by the abstraction of another H-atom from the 3OH position, leading to the formation of a quinone structure[62].



(31) Butein

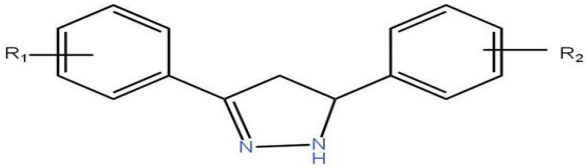
Figure 26

5.2.2 Doan TN et al (2011)., was tested Compounds 32a, 32b, 33a were evaluated for their antioxidant properties using the DPPH radical scavenging method. The nitrogen-centered stable free radical DPPH is commonly utilized in spectrophotometric studies to assess antioxidants. This method relies on the presence of an unpaired electron in the DPPH free radical, which exhibits a strong absorption peak at 517 nm and appears purple in color. An antioxidant that scavenges radicals interacts with the DPPH stable free radical, leading to decolorization that corresponds stoichiometrically to the number of electrons it captures. The change in absorbance resulting from this interaction is used to quantify antioxidant activity[63].



(32) a. R_1 = 2'-OH , 4'-OCH_3 ; R2= 3-OCH_3, 4-OCH_3

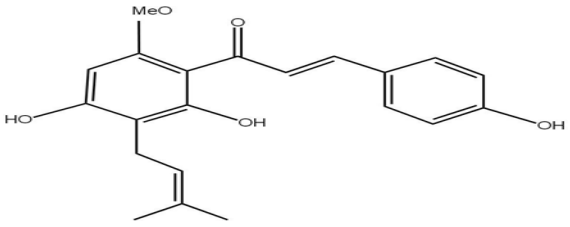
(32) b.R_1 = 2'-OH ; R2= 2-OCH_3, 4-OCH_3



(33)a.R_1 = 4'-NO_2 ; R2= 4-$N(CH_3)_2$

Figure 27

5.2.3 Zhang et al (2014)., reported that Xanthohumol (XN) demonstrated significant antioxidant effects by preventing the oxidation of LDL, effectively scavenging reactive radicals such as hydroxyl and peroxyl radicals, and suppressing the production of superoxide anions and nitric oxide (IC_{50}=40 μM to 110 μM). Nonetheless, there have been reports indicating that XN can also act as a prooxidant, capable of quickly generating O_2[64].

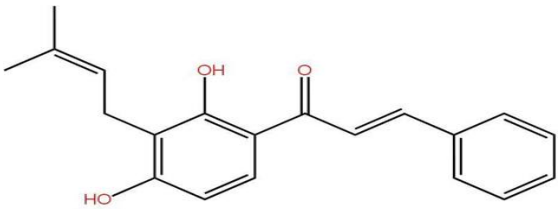


34) Xanthohumol

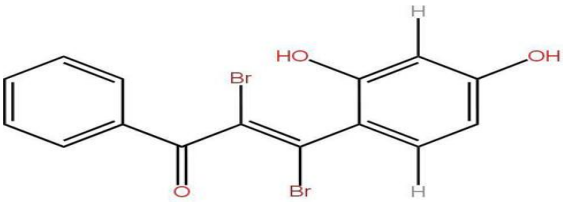
Figure 28

5.2.4 M. S. Alam et al (2015)., reported that The DPPH method was used to assess the free radicalscavenging activities of twenty compounds, all of which demonstrated considerable DPPH radicalscavenging effects. Among the compounds evaluated, compounds a and b exhibited the strongest activity out of the twenty. Additionally, the IC_{50} values for compounds

35) a (1.44 M) and (35)b (1.68 M) were similar to that of the standard antioxidant ascorbic acid (1.03 M). It is well established that polyphenolic compounds with multiple hydroxyl groups, like a or b, display outstanding antioxidant properties[65].



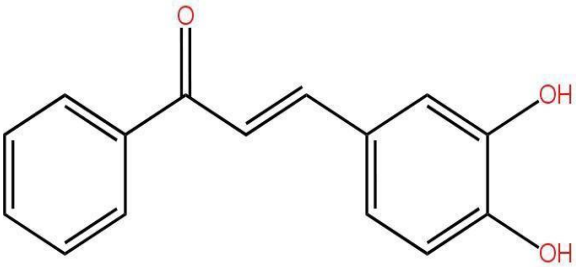
(35)



(36)

Figure 29

5.2.5 Díaz-Carrillo JT et al (2018a)., Demonstrated that Chalcones with two hydroxyl groups demonstrated increased antioxidant activity in the DPPH assay; compounds 36a and 36b performed the best (91 percent and 90 percent inhibition, respectively). In the ABTS method (33 and 35, respectively) and FRAP method (2.4 and 2.7, respectively), the antioxidant activities measured as µmol TE/µmol compound for 36a and 36b were likewise the highest. Chalcones' capacity to scavenge DPPH radicals has been shown to positively correlate with their ability to transfer hydrogen atoms. Chalcones' hydroxyl groups are essential for capturing radicals, and the number, polarity, hydrophobicity, and substitution pattern of the compounds all influence their antiradical activity.. The superior antioxidant values for compounds 36a and 36b have been attributed to the presence of a 3,4hydroxycinnamoyl group (catechol) in their molecular structures[66].



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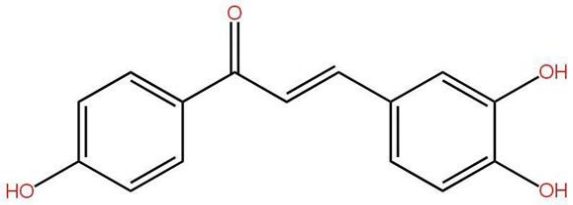
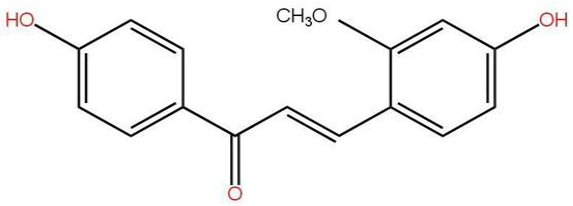


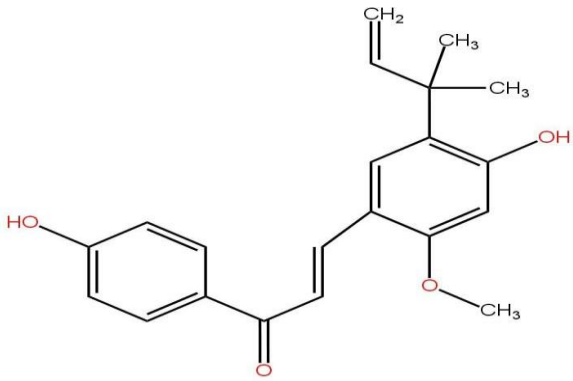
(38)

Figure 30.

5.2.6 Hongming Lv et al (2018b)., reported that Licochalcone A may activate Nrf2-driven protective mechanisms that help alleviate oxidative stress-related cellular damage in RAW 264.7 cells[56]. According to Liang et al. (2018), licochalcone A is a derivative of echinatin, featuring a 1,1-dimethyl-2-propenyl side group (also known as α,α-dimethyl-β-propenyl). The antioxidant activities of echinatin and licochalcone A were compared quantitatively using their IC50 values, with echinatin consistently presenting higher IC50 values than licochalcone A (IC50=6.4 µm). This variation can likely be linked to the 1,1dimethyl-2-propenyl group located at the 5-position of licochalcone A. Consequently, it was posited that this substituent enhances the antioxidant properties of chalcones, potentially due to its electrondonating inductive effect (+I)[68].



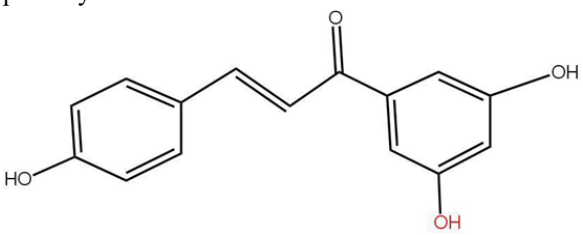
(39) Echinatin



(40) Licochalcone A

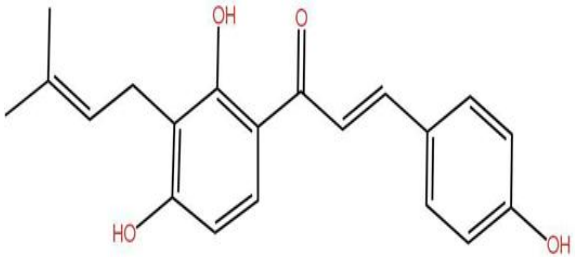
Figure 31

5.2.7 Dingding Shi et al (2020)., reported that Isoliquiritigenin is widely acknowledged as safe and serves as a powerful source of nutraceuticals. It has demonstrated effective radical scavenging capabilities in neutralizing free radicals such as O2, H2O2, and OH. Furthermore, isoliquiritigenin may function as an indirect antioxidant by stimulating the Keap1-Nrf2 pathway[69].



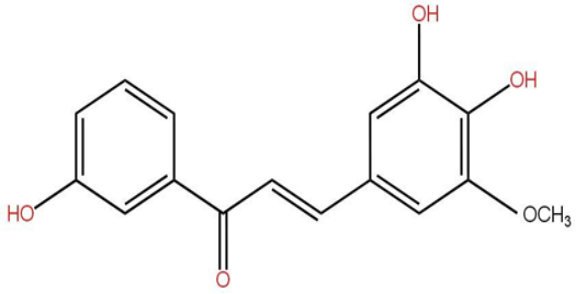
(41) Isoliquritigenin
Figure 32

5.2.8 Wang M et al (2021)., reported that Isobavachalcone (IBC) exhibits the ability to directly scavenge free radicals. In the ferric reducing antioxidant potential (FRAP) assay, it demonstrated an IC50 value of 0.4 μM. Additionally, IBC displayed strong peroxyl radical-scavenging capabilities, evidenced by an oxygen radical absorbance capacity (ORAC) value of
24.83 μM. The presence of hydroxyl groups in its molecular structure may play a role in the scavenging activity of IBC. During its antioxidant function, the primary mechanisms involved are hydrogen atom transfer and single electron transfer. Treatment with IBC led to an increase
in the activity of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px), while also reducing the malondialdehyde (MDA) level, a marker of peroxidation, in rats subjected to Sephadex-induced lung injury[70].

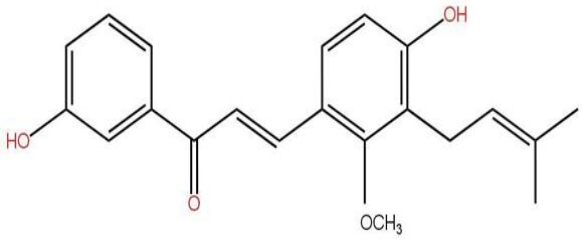


(42) Isobavachalcone Figure 33.

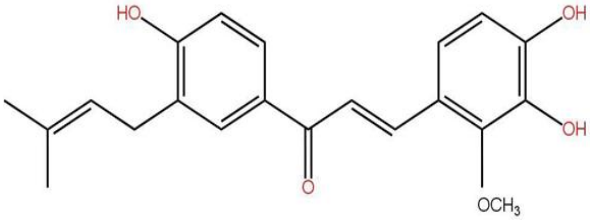
5.2.9 Mittal A et al (2022a)., reported that Both theoretical and experimental results show that licochalcones have important antioxidant qualities. Echinatin's hydroxyl group at position C-3 was changed to produce (43) licochalcone B which had more antioxidant potential than echinatin. On the other hand, (44) licochalcone C, which had a lower scavenging capacity than echinatin, was produced by replacing the prenyl group at the C-3 position of echinatin. Furthermore, compared to the other licochalcones examined, (45) licochalcone D, which has a hydroxyl group at C-3 and a prenyl group at C-30, showed better antioxidant activity. Because of the formation of intramolecular hydrogen bonds with nearby hydroxyl and methoxy groups, 3-OH was found to be the main location for the inactivation of reactive species in licochalcone B and D. Furthermore, licochalcone E (46), which had the lowest antioxidant activity, was produced by adding a 100,200dimethyl-200-propenyl group at C-5. It was widely acknowledged that the scavenging mechanism depends on the retrochalcones' B ring. [71].



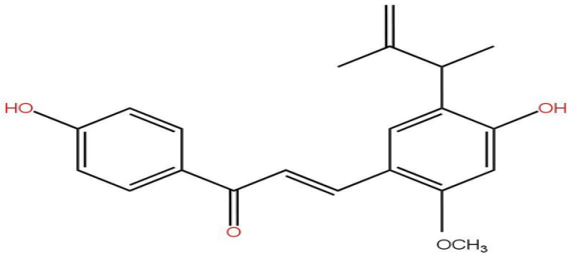
(43) Licochalcone B



(44) Licochalcone C

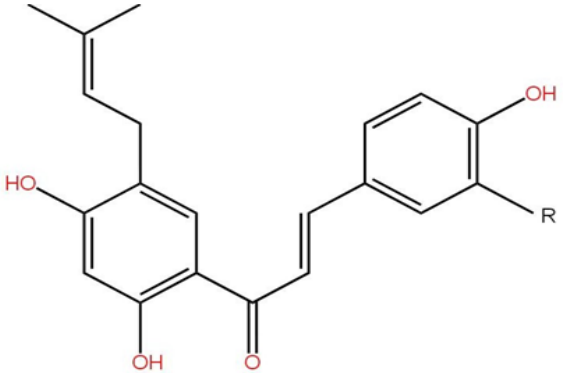


(45) Licochalcone D



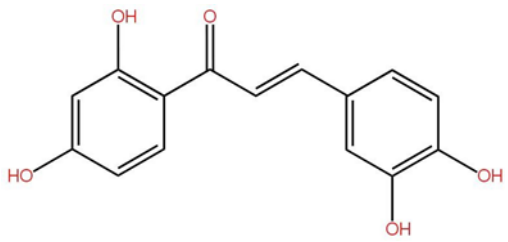
(46) Licochalcone E Figure 34.

5.2.10 Chen Y et al (2022b)., reported that In a diphenyl-2-picrylhydrazyl assay, broussochalcone A demonstrated greater radical scavenging activity at concentrations between 1 and 30 μM compared to α-tocopherol, with IC50.200 values recorded at 7.6 ± 0.8 μM. Broussoflavonol F, broussoflavan A, broussoaurone A, and broussoflavonol G showed a concentration-dependent inhibition of TBARS formation induced by Fe2+, with IC50 values of 2.1, 2.7, 1.0, and 1.2 μM, respectively. Broussochalcone A also exhibited a concentration-dependent inhibition of lipid peroxidation caused by iron in rat brain homogenate[72].

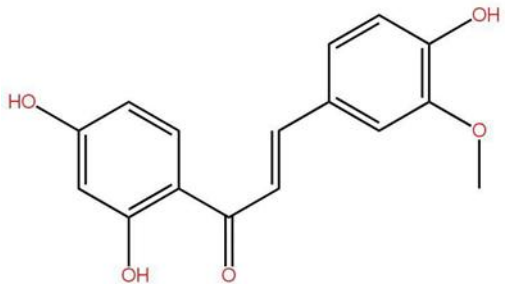


(47) Broussochalcone A Figure 35.

5.2.11 Wenkai Pan et al (2023a)., reported that Butein and homobutein share structural characteristics with the well-known antioxidants caffeic acid and ferulic acid, which are recognized for their ability to hinder lipid peroxidation through a direct chain-breaking mechanism by capturing chain-carrying alkylperoxyl radicals. In addition to their antioxidant properties, both butein and homobutein demonstrate significant effectiveness in inhibiting tyrosinase, exhibiting a dominant competitive mechanism when l-dopa serves as the substrate (diphenolase reaction), with KI values of 3.30 and 2.50 μM, respectively[73].

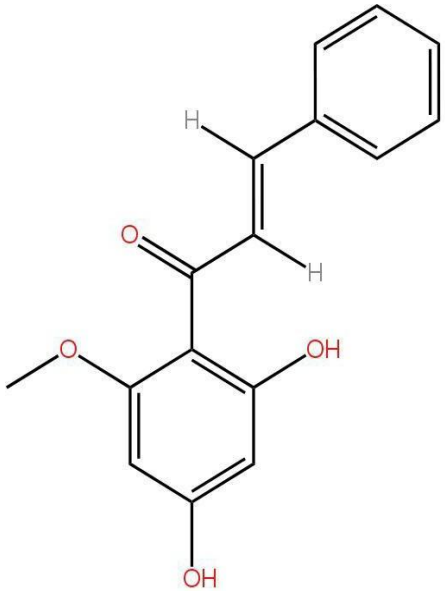


(48) Butein



(49) Homobutein Figure 36.

5.2.12 Barber K et al (2023b)., reported that The antioxidant and anti-inflammatory effects of Cardamonin (CD) involve its interaction with cellular targets like Nrf2. Additionally, CD has demonstrated its ability to halt both the activation and production of matrix metalloproteinases, inhibit the NF-κB signaling pathway, and elevate the levels of antioxidant proteins such as heme oxygenase1 and NADPH quinone oxidoreductase-1, resulting in antioxidant effects[74].



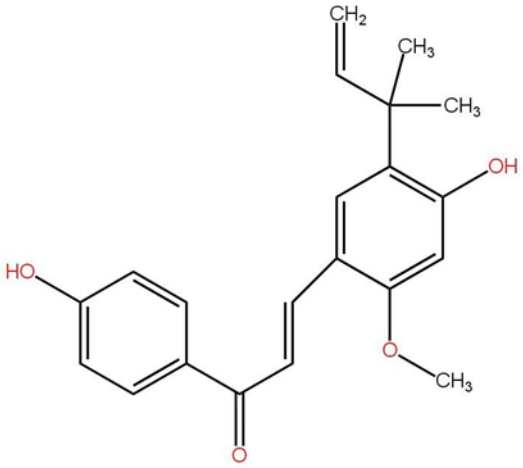
(50) Cardamonin
Figure 37

5.3 Anti-inflammatory activity

Inflammation is a biological process that involves various inflammatory mediators such as PGE2, nitric oxide, and PLA2. Inhibiting these mediators could be beneficial for the design and development of effective anti-inflammatory agents. Non-steroidal anti-inflammatory drugs (NSAIDs) have been utilized to treat inflammatory disorders through several mechanisms, including the inhibition of COX1, COX-2, LOX, and NO. Chalcone derivatives, known for their distinctive chemical structure, have emerged as promising candidates for influencing inflammatory pathways[75]. The anti-inflammatory effects of chalcone derivatives have been studied and seem to be linked to the reduction of inflammatory mediators like nitric oxide (NO) and tumor necrosis factor (TNF) produced by macrophages activated with lipopolysaccharide (LPS). This protective mechanism may result from the concurrent suppression of various inflammatory mediators' production and/or a direct inhibitory effect on the activation of transcription factors (NF-κB, AP-1) that control the inflammatory response[76]. The anti-inflammatory properties of chalcones hold significant interest in the biomedical field[77].

5.3.1 Kolbe L et al (2006a)., demonstrates that Aqueous extracts rich in Licochalcone A from G. inflata, along with synthetic LicA, effectively suppress pro-inflammatory reactions in various skin-related cell types. The in vitro suppression of pro-inflammatory responses by LicA can be observed through fMLP- or zymosan-triggered oxidative bursts in granulocytes, UV-triggered PGE2 release by keratinocytes, LPS-triggered PGE2 release by adult dermal fibroblasts, fMLP-triggered LTB4 release by granulocytes, and LPS-triggered IL-6/TNF-a release by immature dendritic cells. Other researchers have noted the inhibitory effects of LicA on T cell proliferation and cytokine production induced by mitogens, along with its ability to

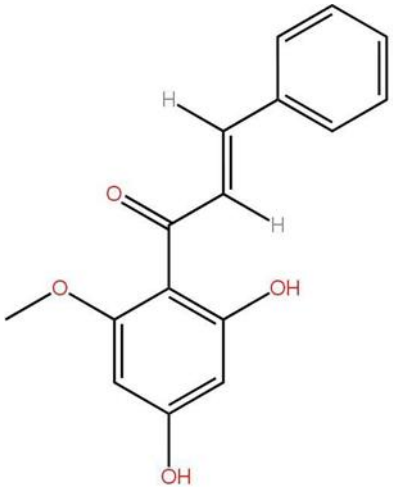
inhibit inflammatory responses driven by phorbol esters. LicA should be regarded as a strong anti-inflammatory agent with a wide range of targets[78].



(50)Licochalcone A Figure 38.

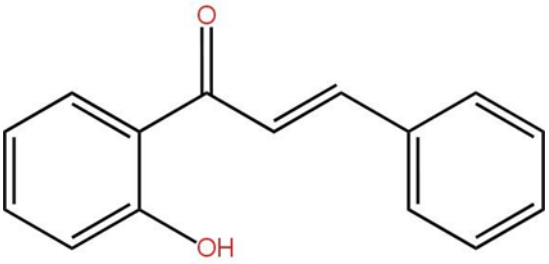
5.3.2 Ahmad S et al (2006b)., reported that Cardamonin exhibits pronounced inhibitory effects

on the release of pro-inflammatory mediators in the tested cellular systems. Thus, it is highly likely that cardamonin is the active component when applied in traditional medicine. Cardamonin may reduce the production of COX and iNOS products, specifically PGE2 and NO, owing to its scavenging properties that result in repression of gene transcription. The impact of cardamonin on prostanoid production was notably significant, with both PGE2 and TxB2 levels decreasing markedly in a dosedependent manner. The primary beneficial outcome of NSAIDs is the inhibition of prostanoid synthesis, which ultimately leads to alleviation of pain and swelling[79].



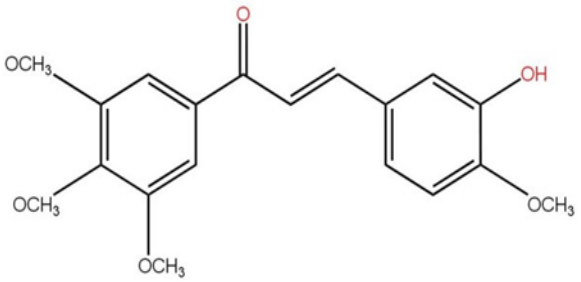
(52) Cardamonin
Fgiure 39

5.3.3 Abuarqoub H et al (2006c)., investigated that 2'-hydroxychalcone activates heme oxygenase activity and enhances HO-1 expression in RAW 264.7 macrophages. The anti-inflammatory effects of 2-HC are assessed by quantifying nitrite levels produced by macrophages exposed to LPS, both with and without the compound (IC50=8.5 μM). 2'-hydroxychalcone reduces TNF- production stimulated by LPS, as TNF- is a key cytokine involved in the inflammatory response initiated by LPS. The presence of 2'-HC is essential for decreasing both nitrite and TNF- production in LPS-activated macrophages[80].



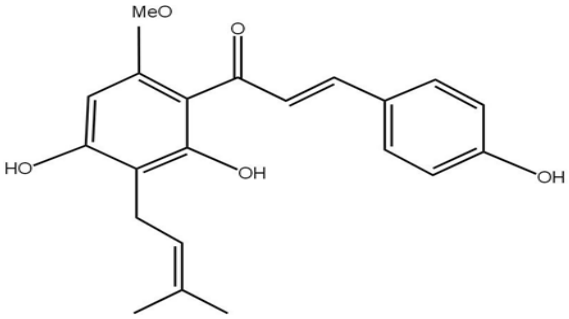
(53) 2'-Hydroxychalcone
Figure 40

5.3.4 Srinivasan et al (2009)., demonstrated Most natural chalcone-based NF-κB inhibitors feature hydroxyl and methoxy functional groups, which determine the necessity of the R,β unsaturated carbonyl group for NF-κB inhibition. The compound 3-Hydroxy-4,3′,4′,5′-tetramethoxychalcone has been shown to effectively inhibit NF-κB activation, displaying an IC50 of 5.1 μM. This compound hinders the kinase activity of IKKβ and/or IRAK4. Furthermore, it exhibits significant cytotoxicity against lung cancer cells in vitro, with most GI50 values falling within the single-digit micromolar range, aligning with its potency as an NF-κB inhibitor[81].



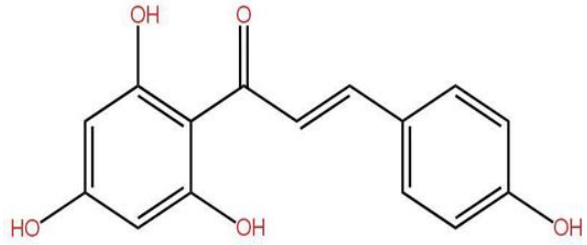
(54) 3-Hydroxy-4,3′,4′,5′-tetramethoxychalcone
Figure 41.

5.3.5 Lee IS et al (2010a)., reported that Xanthohumol exhibits anti-inflammatory effects against inflammatory responses induced by LPS in BV2 microglial cells, a murine cell line that displays both phenotypic and functional characteristics of activated microglial cells(IC50= 3.6 μM). It is essential to determine if XN activates NRF2 signaling and boosts the levels of downstream ARE-responsive proteins, as well as to explore whether the NRF2 signaling
activation triggered by XN could serve as a primary cellular mechanism responsible for its anti-inflammatory properties[82].



(55) Xanthohumol
Figure 42

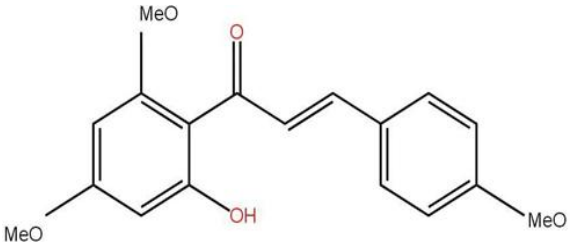
5.3.6 Batovaska DI et al (2010b)., reported that Naringenin chalcone reduced the production of proinflammatory mediators TNF-α, monocyte chemotactic protein-1 (MCP-1), and nitric oxide (NO) in LPS-activated RAW 264 macrophages and/or 3T3-L1 adipocytes that were co-cultured with macrophages (IC50=12.5 μM). Naringenin chalcone may be beneficial for alleviating the inflammatory alterations in adipose tissue associated with obesity[83].



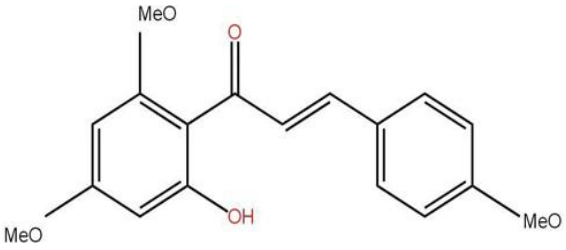
(56) Naringenin chalcone
Figure 43.

5.3.7 Kwon et al. in (2013)., The research was carried out by inducing inflammation in LPS-stimulated RAW 264.7 cells. Flavokawain A

demonstrates its anti-inflammatory properties by inhibiting the expression of iNOS and COX-2 triggered by LPS, along with the subsequent production of NO and PGE2 in murine macrophages. This compound also reduced the expression of other pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6. The protective effects of flavokawain A against inflammatory immune responses are facilitated through the inhibition of the NF-κB-AP-1-JNK/p38 MAPK signaling pathways. Furthermore, flavokawain A was found to hinder both NF-κB- and AP-1DNA binding activity as well as promoter activity in cells stimulated with LPS. Additionally, it has been reported that flavokawain B also prevents the production of pro-inflammatory mediators such as NO and PGE2 in LPS-stimulated macrophages. Moreover, flavokawain B suppressed LPS-induced iNOS and COX-2 expression through downregulation of the NF-κB signaling pathways. This suggests that flavokawains, a type of chalcone, exert their anti-inflammatory effects by inhibiting NF-κB and AP-1 dependent pro-inflammatory gene expression[84].



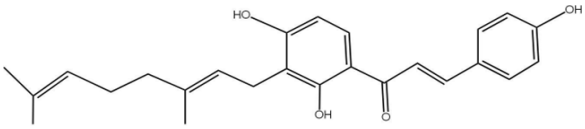
(57) Flawokawain A



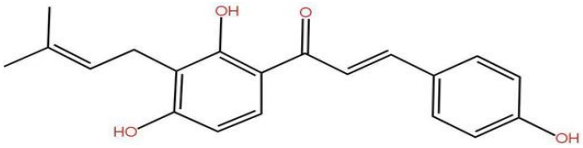
(58) Flawokawain B

Figure 44.

5.3.8 Li Y et al (2016)., Investigated Xanthoangelol (XA) and 4-Hydroxyderrcin (4-HD) are beneficial in reducing inflammation caused by obesity and the inflammation-related decline in UCP1 gene expression, both of which help alleviate disorders associated with obesity. It has been observed that XA and 4-HD lower LPS-induced proinflammatory factors in RAW macrophages by inhibiting the phosphorylation of P65 and c-Jun N-terminal kinase (JNK). Additionally, XA has been noted to prevent the rise of LPS-triggered plasminogen activator inhibitor-1 levels in the plasma of mice (IC_{50}=3.2 μM). Moreover, XA and 4-HD reduce proinflammatory factors in RAW264.7 macrophages activated by L1CM through the suppression of the JNK pathway[85].



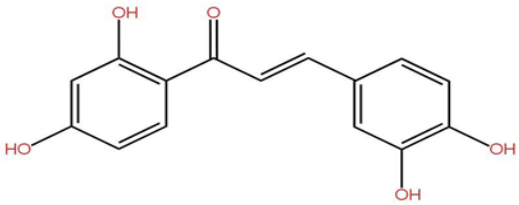
(59) Xanthoangelol



(60) 4-Hydroxyderricin

Figure 45

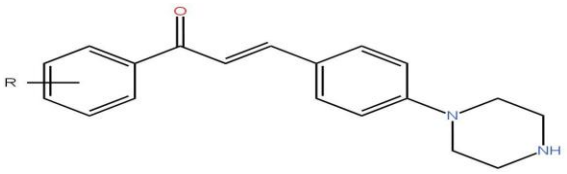
5.3.9 Padmavathi G et al (2017)., reported that Butein, recognized for its significant anti-inflammatory properties, has been identified as a potential treatment option. It was able to eliminate the proinflammatory effects caused by LPS-stimulated macrophages by inhibiting the production of NO from iNOS, diminishing the nuclear localization of NFκB, modulating the Erk1/2 MAPK signaling pathway, and enhancing HO-1 expression. Butein facilitated the suppression of NFκB and AP-1 while also reducing the expression of ICAM1 and E-selectin induced by TNF-α and PMA in human umbilical vein endothelial cells (HUVECs). Interestingly, butein was also shown to inhibit inflammation in adipocytes and macrophage migration, similarly downregulating NF-κB, JNK, MAPK, and the production of NO from iNOS, which supports its capability to mitigate insulin resistance associated with obesity[86].



(61) Butein

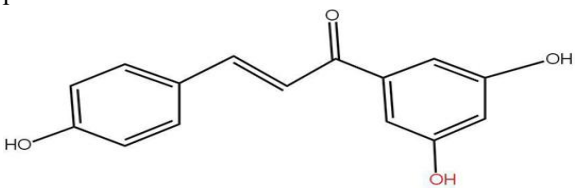
Figure 46

5.3.10 Kar Mahapatra Det al (2019)., Demonstrated that Heterocycle (piperazine)-linked chalcones have been recognized as significant contenders for addressing a range of autoimmune conditions, including rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, and enteritis. The patent CN106008400A demonstrates the anti-inflammatory properties of chalcones in various contexts, including their effects on the mouse macrophage cell line Raw 264.7, an animal model of multiple sclerosis, the experimental autoimmune encephalomyelitis model, and an arthritis model, where a concentration-dependent reduction in T-lymphocyte proliferation and a decrease in cytokine components with minimal cytotoxic effects were noted. These substantiated findings can be related to the immunosuppressive qualities of the analogs[87].



(62) Heterocycle (piperazine)-linked chalcones
Figure 47.

5.3.11 Li M et al (2022)., demonstrated that In vitro studies have shown that Isoliquiritgenin (ISL) reduces the inflammatory response in macrophages by inhibiting the homodimerization of TLR4. In vivo experiments indicated that ISL blocked NF-κB activation in septic mice, leading to a decrease in the levels of IL6, TNF-α, and COX-2. Furthermore, ISL prevented the activation of upstream signaling pathways, including the phosphorylation of p38 within the MAPK pathway and the DNA binding of NF-κB p65[88].

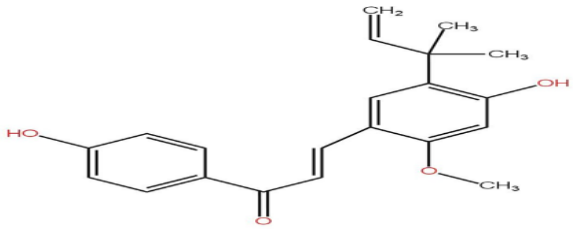


(63) Isoliquiritigenin
Figure 48

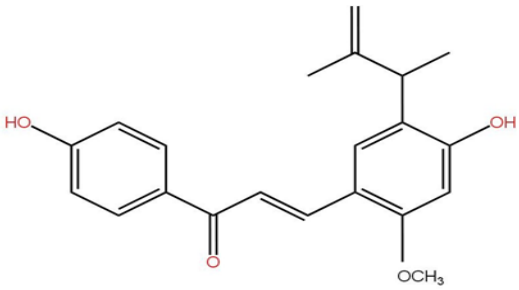
5.4 Anti-Bacterial activity

Chalcone acts as an antibacterial compound with moderate to high efficacy, attributed to the presence of the reactive αβ-unsaturated system. The ability to modify its structure by adding various substituent groups to the aromatic ring may lead to increased potency, reduced toxicity, and a broader range of antibacterial effects[89]. The role of resistance mechanisms and their suppression by Chalcones is frequently referenced in numerous studies within this review. This is a result of the rise of various intricate mechanisms and the swift spread of multidrug-resistant pathogens that are concerning to global health organizations, as these traits create obstacles to current therapies, many of which have experienced reductions in both application and efficacy[90].

5.4.1 Liu XL et al (2008a)., reported that Licochalcone A exhibits activity against various Grampositive bacteria but shows no effectiveness against Gram-negative bacteria or eukaryotic organisms. Its antibacterial properties against MRSA are characterized by minimum inhibitory concentrations (MICs) that range from 18.4 to 47.0 mM, depending on the specific strain being tested. Wu SC et al. (2019) confirmed that licochalcone E also has antibacterial effects against MRSA T144 and MSSA ATCC29213 using the Oxford cup method. Furthermore, licochalcone A could serve as a valuable compound for developing antibacterial agents aimed at preserving foods with high salt content, such as soups, and those with proteases, like fermented foods, where cationic peptides may be less effective[91].

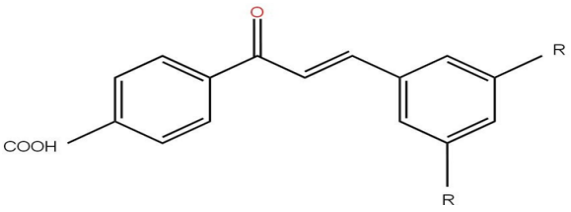


(64) Licochalcone A



(65) Licochalcone E
Figure 49.

5.4.2 X.L. Liu et al (2008b)., observed that compounds designated 66a and 66b exhibited the highest levels of activity, demonstrating a minimum inhibitory concentration (MIC) of 2 mM when tested against S. aureus. The presence of lipophilic constituents, specifically CF3 and Br, on the B ring of these compounds was a major factor in their effectiveness. The compound identified as 67 showed the most promise, displaying a MIC of 2 mM against a strain of S. aureus that showed resistance to methicillin. Differing from other compounds, compound 67 selectively interfered with bacterial membranes without inducing substantial breakdown of red blood cells. The antibacterial capabilities of these compounds were assessed using nonresistant
strains of both S. aureus and E. coli; those that showed good potential were then tested to see if they could damage red blood cells[92].



(66) a) R=Br, (66) b) R=CF3

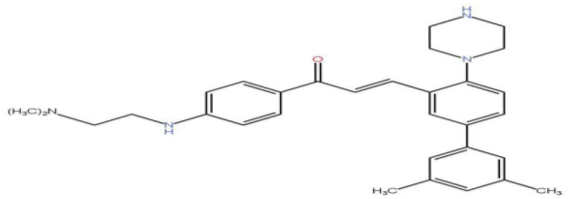
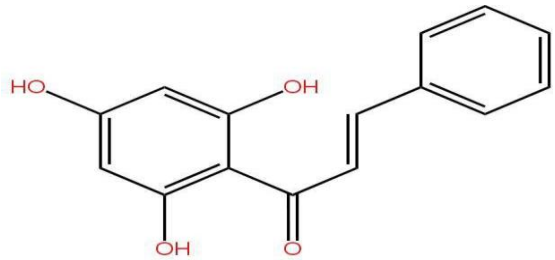


Figure 50

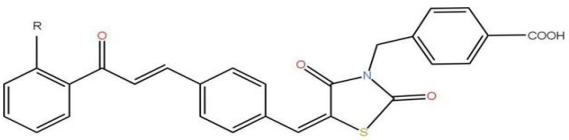
5.4.3 Ruddock PS et al (2011)., demonstrated that Pinocembrin chalcone derived from P. lanceaefolium demonstrates a fairly good antimicrobial effect on both NG strains, whether they are easily treatable or harder to treat. Chalcones typically show stronger effects than flavanones when dealing with methicillin-resistant S. aureus strains, with minimum inhibitory concentrations ranging from 16 to 64 µg/mL. Helichrysum trilineatum has been found to contain pinocembrin chalcone, recognized for its ability to combat microbes. The effectiveness of pinocembrin chalcone is noteworthy because its activity against NG strains displaying varied antimicrobial resistance characteristics implies a wide-ranging, yet possibly new, way of fighting microbes[93].



(66) Pinocembrin chalcone

Figure 51

5.4.4 K Sahu N et al (2012)., reported that A novel set of chalcone variants, incorporating both 2,4 thiazolidinedione and benzoic acid elements, were created and assessed for their capacity to combat Gram-positive and Gram-negative bacteria. Within the synthesized collection, compounds 69a and 69b demonstrated notable antibacterial effects, registering a MIC of 1 µg/mL against Gram-positive bacterial types like S. aureus RN 4220 and S. aureus KCTC 503, an efficacy similar to that of the standard medications, Norfloxacin (MIC=2µg/mL) and Oxacillin (MIC=1µg/mL). The examined substances did not show any inhibitory action against Gramnegative bacteria, specifically E. coli 1356 and E. coli 1682, even at a concentration of 64 mg/mL[12].

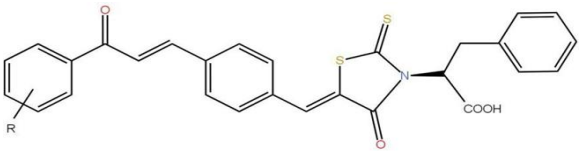


(69) a) R=H; (69) b) R=2-Cl

Figre 52

5.4.5 Ritter et al. (2014)., demonstrated that The antimicrobial capabilities of all the created substances (70) (a-q) were tested in a laboratory setting against a variety of Gram-positive and Gramnegative bacteria, as well as bacteria that are resistant to multiple drugs. These substances' antibacterial effects were contrasted with those of recognized antibacterial medications, specifically oxacillin and norfloxacin, which acted as benchmark controls. The compounds labeled a-q demonstrated notable effectiveness against S. aureus strains resistant to multiple drugs (MRSA CCARM 3167 and MRSA CCARM 3506) and S. aureus strains resistant to quinolone (QRSA CCARM

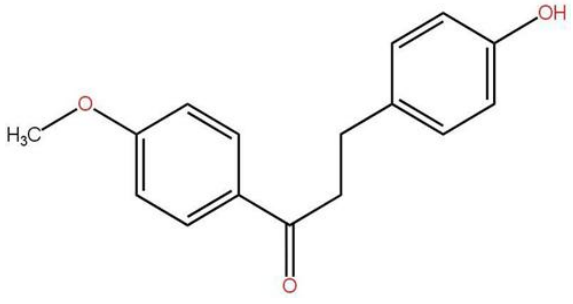
3505 and QRSA CCARM 3519), displaying minimum inhibitory
concentration (MIC) values ranging from 2 to 8 g mL-1. Considering the entirety of this information pertaining to antibacterial activity, the rhodanines (a-q) derived from L-phenylalanine with C5-substitution displayed substantial effectiveness in combating Gram-positive bacteria and bacteria exhibiting resistance to multiple drugs[94].



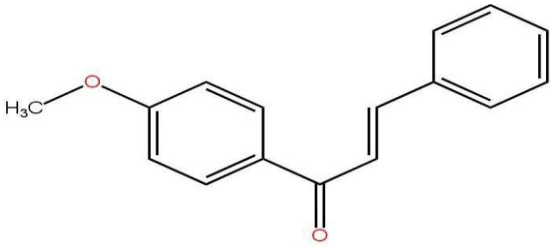
Compound (70) R: (a) 2-F; (b) 4-F; (c) 2-Cl; (d) 3-Cl; (e) 4-Cl; (f) 2,4-(Cl); (g) 2-Br; (h) 3-Br;
(i) 4Br; (j) 4CH3; (k) 2,4-(Cl)2; (l) 2-OCH3; (m) 3-OCH3; (n) 4-OCH3; (o) 4-NHCOCH3;
(p) H; (q) C6H6(3,4-fused)

Figure 53

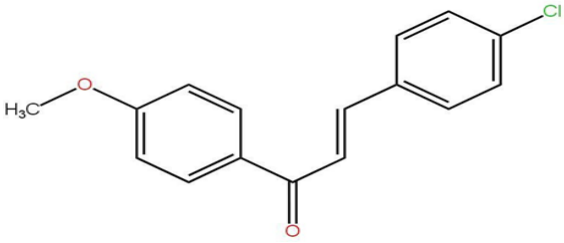
5.4.6 Stompor M et al (2016)., reported that Bacteria with a Gram-positive nature like S. aureus, Staphylococcus epidermidis, Enterococcus faecalis, and Enetrococcus faecium, exhibited a higher level of resistance to 4-hydroxy- 4′-methoxychalcone when compared to those with a Gramnegative nature such as E. coli, Klebsiella pneumonia, and Pseudomonas aeruginosa. The effects of both 4'-methoxychalcone and 4-chloro-4′-methoxychalcone on Streptomyces pyogenes ATCC 176 showed similarities, with inhibition zone diameters measuring 9 and 10 mm correspondingly. However, the presence of a chlorine atom in 4chloro-4′methoxychalcone notably enhanced its antimicrobial capabilities against the anaerobic streptococcus E. faecalis ATCC 29122 (dinh = 10 mm), which demonstrated resistance to 4′methoxychalcone that was not substituted[95].



(71) 4-hydroxy-4'methoxychalcone



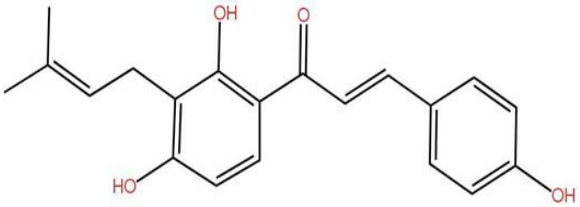
(72) 4-chloro-4'-methoxychalcone



(73) 4'-methoxychalcone

Figure 53

5.4.7 Park S et al (2019a)., reported that 4-Hydroxyderricin, a chalcone, represents a phytochemical element found in Angelica keiskei. Its roles span a range of biological activities, demonstrating capabilities such as reducing inflammation, combatting diabetes, fighting bacteria, and hindering tumor development. The compound 4hydroxyderricin limited the proliferation of Staphylococcus aureus by disrupting the function of seryltRNA synthetase. Notably, 4-Hydroxyderricin hindered the development of the fungi Asc. apis and R. oryzae selectively (showing a MIC of 0.78 mg/L in both 24-hour and 48-hour treatments)[96].

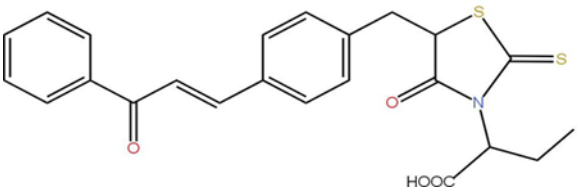


(74) 4-Hydroxyderricin

Figure 55

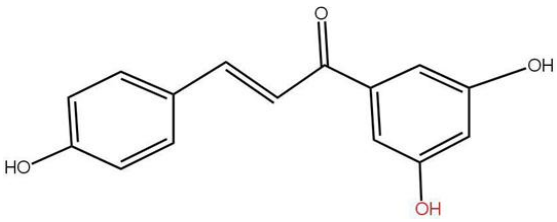
5.4.8 Mousavi SM et al (2019b)., reported that Rhodamine-based substances have been examined for their potential to combat bacteria like Staphylococcus aureus and exhibit
moderate effectiveness against Escherichia coli, leading to diverse uses [66]. A. Mobeen et al. (2019) revealed that titanium molybdate displays exceptional photocatalytic capabilities concerning Rhodamine-B

and exhibits beneficial antibacterial properties, potentially inhibiting bacterial proliferation for use in real-world scenarios[97].



(75) Rhodamine
Figure 56

5.4.9 Qu Q et al (2019c)., demonstrated that Isoliquiritigenin (ISL), a biologically active substance, demonstrates various medicinal properties, notably its capacity to combat bacteria. Research has indicated that ISL exhibits substantial biological effects against Staphylococcus xylosus, showing a minimum inhibitory concentration (MIC) of 80 μg/mL. Furthermore, it has been observed that ISL can impede the multiplication of S. xylosus, where even quantities below the MIC level can disrupt the development of its biofilm. The antibacterial efficacy of Isoliquiritigenin in combating S. xylosus involves modulation of IGPD expression, shedding light on how ISL diminishes the infectious capacity of S.xylosus[98].



(76) Isoliquiritigenin
Figure 57

5.4.10 Jasim HA et al (2021)., In a recent endeavor, a set of chalcone derivatives were created using different substituted amines through the Claisen-Schmidt condensation reaction under alkaline conditions, and their antibacterial properties were tested on different types of bacteria, such as Enterococcus faecalis, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella enterica, and Staphylococcus pneumoniae. Of all the manufactured chalcone derivatives, compound 82 was identified as the strongest antibacterial substance, displaying considerable efficacy against E. coli (MIC = 125 g/mL). Computational investigations confirmed that these compounds bind to DNA and exhibit effective molecular docking[99].

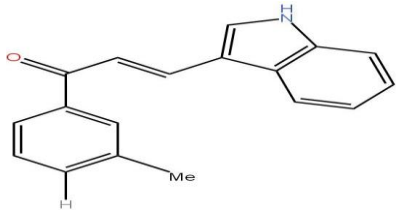
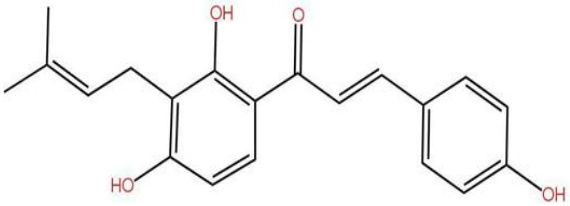


Figure 58.

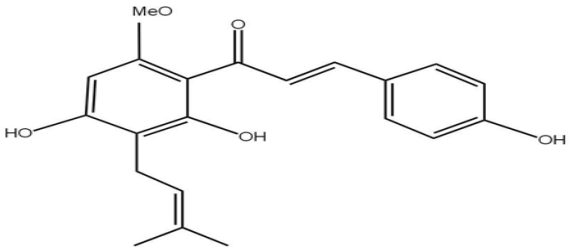
5.4.11 Assis et al (2022)., reported that Isobavachalcone's capability to combat bacteria was tested on biofilms formed by both Methicillin-susceptible Staphylococcus aureus (MSSA) and Methicillin-resistant Staphylococcus aureus (MRSA)[61]. The study revealed that IBC exhibited antibacterial effects on a diverse range of bacteria, including Gram-positive, Gram-negative, and mycobacteria types. These effects were documented against bacteria like Bacillus cereus, Bacillus megaterium, Bacillus stearothermophilus, Bacillus subtilis, Staphylococcus aureus, and Streptococcus faecalis, all of which are Gram-positive; also, against Escherichia coli, Shigella dysenteriae, Proteus vulgaris, Proteus mirabilis, Shigella flexneri, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhi, Morganella morganii, Enterobacter aerogenes, Citrobacter freundii, and Enterobacter cloacae, which are Gram-negative, where the Minimum Inhibitory Concentration (MIC) values typically fluctuated from 4.9 to 39.1 μg/mL[100].



(77) Isobavachalcone
Figure 59

5.4.12 Kołodziejczak A et al (2024)., reported that It has been demonstrated that xanthohumol (XN) can suppress the proliferation of viruses, fungi, and bacteria. The anti-biofilm capabilities and antibiotic

characteristics of xanthohumol have been documented in numerous research papers. Studies into the antibacterial effects of XN provide evidence of its ability to impede the multiplication of Gram-positive bacteria, including Staphylococcus aureus, Staphylococcus pyogenes, and Staphylococcus epidermidis, in addition to Propioni bacterium acnes, a skin pathogen, and Streptococcus mutans, which leads to tooth decay. When tested against S. aureus strains, pure xanthohumol exhibited marginally stronger efficacy (MIC range of 15.6–62.5 μg/mL) compared to an extract derived from hop cones with a 51% xanthohumol concentration (MIC range of 31.2–125.0 μg/mL). The antifungal characteristics of XN encompass the suppression of two varieties of Trichophyton spp. Fungi[101].



(80) Xanthohumol
Figure 60

VI. CONCLUSION

In conclusion, the comprehensive research of chalcones and their numerous derivatives over the last decades marks their deep and far-reaching importance in research field. Among the wide range of pharmacological activities explored, anticancer, antioxidant, anti-inflammatory, and antibacterial are the most widely studied, a fact which indicates therapeutic urgency and the feasibility of the experimental evaluation process. This review consolidates years of research into the systematic exploration of structural modifications such as hydroxylation, methoxylation, prenylation, and hybridization with other pharmacophores and their direct impact on enhancing biological activity and selectivity. The compiled data together highlight that the chalcone nucleus, characterized by its α,β-unsaturated ketone system, represents a privileged, robust, and highly flexible scaffold for rational drug design. Beyond intrinsic activity, chalcones exhibit remarkable adaptability, showing promising effects on many targets covering a wide range of therapeutic aspects antidiabetic, antimalarial, antiviral, and neuroprotective domains. Strategic modification of the chalcone core, including the development of synthetic analogs such as FDA-approved drugs Sofalcone and Metochalcone, proved to be greatly effective in enhancing the pharmacological profile of interest, offering a valuable template for future drug discovery. The versatility, structural simplicity, and tunability of these scaffolds make them key valuable in the development of novel therapeutics. In the future, the combination of innovative synthetic methodologies, structure-based rational design, and focused in vitro and in vivo pharmacological testing will further speed up the translation of chalcone-based molecules into clinically useful applications. Overall, the overview provided in this review reinforces not only the immense therapeutic potential of chalcones but also forms a sound basis for guiding future research at fully harnessing their broad pharmacological spectrum.

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