DESIGN SYSTHESIS AND EVALUATION OF ANTI BACTERIAL ACTIVITY FOR CHALCONE AND IT'S DERIVATIVE

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ABSTRACT:
Chalcones, a subclass of flavonoid-based phenolic compounds, represent one of the most abundant families of bioactive natural products. Their distinctive chemical architecture and broad pharmacological spectrum—including anticancer, anti-inflammatory, antimicrobial, antioxidant, and antiparasitic activities—have sparked significant interest in the synthesis of chalcone derivatives. Owing to their straightforward construction from simple aromatic precursors, chalcones offer a flexible platform for structural modification, enabling the generation of diverse functionalized analogues. These synthetic derivatives often mirror the bioactivity of their natural counterparts, with many exhibiting superior potency and reduced toxicity. This review highlights the potential of bioinspired chalcone synthesis to expand chemical space for drug discovery. Emphasis is placed on evaluating the biological activities of synthesized chalcones and their derivatives, exploring their molecular interactions, and elucidating possible mechanisms of action.

Keywords: *chalcones, biomolecular interactions, synthesis, natural products, bioactivities, mechanisms, anticancer, antimicrobial, phenolics.*

INTRODUCTION:

Chalcone is as flavonoid, are considered as intermediate in the flavonoids biosynthesis, and are widespread in plants. The existence of the α,β-unsaturated ketone moiety in chalcones is a common part found in a large number of biological active compounds. Therefore, chalcone derivatives from nature or synthetic origin exhibit diverse pharmacological activities, such as antimicrobial [1], antitumor [2], anticancer [3,4], radical scavenger [5], and inhibitor of topoisomerase I [6]. However, isolation of chalcone derivatives from nature requires a long and usually complicated procedure which does not comparable to the yield obtained. Due to time consuming and intensive process in the isolation procedure, and to their diverse pharmacological activities, the development of an efficient synthetic protocol of chalcone derivatives attracts many researchers. A good synthetic method gives us advantages to obtain chalcone derivatives attaching various substituents in excellent yield which possibly do not exist in nature. Furthermore, chalcones are known as the key intermediate in the synthesis of various biologically important heterocyclic compounds. In this article, the preparation methods of chalcones, structure diversity, role of chalcone as synthon for the synthesis of diverse heterocyclic compounds, and their biological activity are review Chalcone (1) and its derivatives are primarily synthesized in the laboratory using Claisen-Schmidt reaction, in which acetophenone (2) or its derivative is reacted with benzaldehyde (3) or its derivative using strong base, such as NaOH, KOH, or NaH as catalyst in a polar solvent as shown in the following reaction [7]. Other catalysts are also used, such as sodium phosphate doped sodium nitrite [8] and aluminium-magnesium hydroxide hydrate [9]. First, the hydroxy-acetophenone (4) derivatives was bounded to the resin, and then treated with derivatives of benzaldehydes using NaOH as catalyst in methanol. The formed hydroxychalcones (5) were then released by the addition of trichloro acetic acid. -Cl = trityl-chloride resin Solid phase cross aldol condensation employing magnesium hydrogen sulphate was used to synthesize chalcone in good yield and self-condensation products were not observed.[10] Chalcones belong to the flavonoid family and consist of two aromatic rings with different substitutions, connected by α, β-unsaturated carbonyl moiety [11, 12]. This core structure can be found in various naturally occurring, synthetic and semisynthetic molecules [13]. Chalcone and its derivatives are present in a wide range of foods and plants, including tea, vegetables, fruits, soy and spices [14]. These natural sources continue to inspire the discovery and design of new potential drugs [15,16]. Chalcones are widely distributed in plants and serve as precursors for the synthesis of flavanols and other flavonoids. They have diverse biological activities and are of medicinal significance. The classic method for synthesizing chalcones is the base-catalyzed Claisen–Schmidt condensation reaction [17,18]. Numerous studies have shown that

chalcones possess various bioactivities, such as antibacterial, antimalarial, anticancer, antifibrogenic, immunomodulatory, antileishmanial, anti-inflammatory, cytotoxic, analgesic, and antioxidant properties [19-28].

ACTIVITIES OF CHALCONE:
Chalcones and their derivatives are the most active compounds that are known for their broad spectrum of activity. Antioxidant, Antimicrobial, Anti-inflammatory, Anticancer etc.

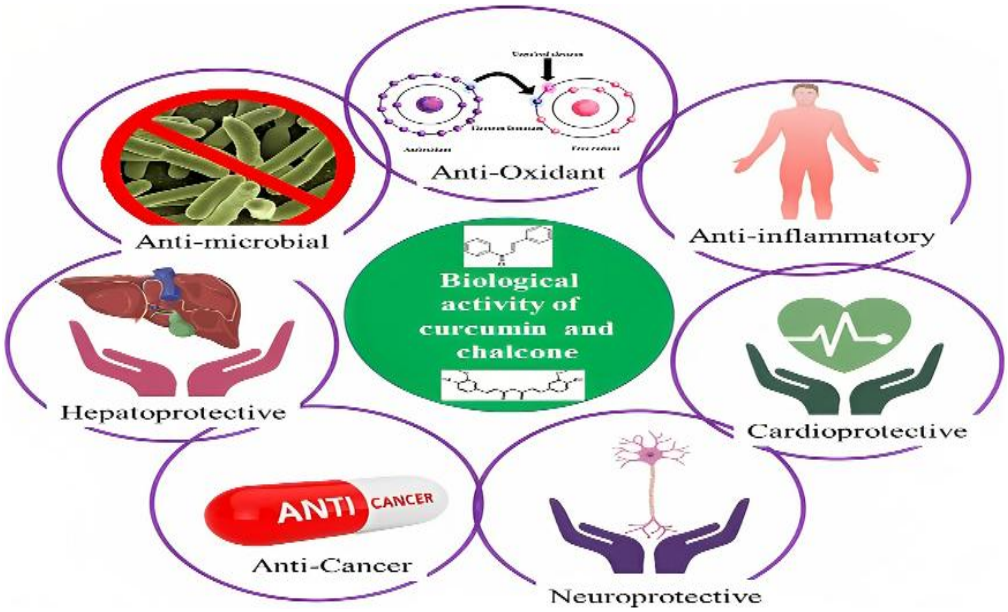

Figure no:1-Biological activities of chalcone

Antioxidant:
Antioxidants are the compounds that inhibit the oxidation process. This substance can prevent or slow damage to cells caused by free radicals. Oxidation is a chemical reaction that generates free radicals, thereby leading to chain reactions that may damage the cells of organisms and hence responsible for oxidative stress resulting in chronic diseases such as heart diseases, stroke, cancer, arthritis, respiratory diseases, Parkinson's disease, and other inflammatory conditions. [29]

Antimicrobial:
Antimicrobial agents are the drugs used to treat infectious diseases caused by different types of bacteria and fungi. The use of these drugs is now common, and continuous efforts are put in by the scientific community to search for newer antimicrobial agents due to antimicrobial resistance shown by the microbes.[30] nticancer: Cancer is a widely spreading disease all over the world, necessitating the need to develop new anticancer agents. Anticancer or antineoplastic drugs are those that are effective in the treatment of malignant or cancerous diseases. The design, synthesis, and antitumor potential of chalcones were studied against human breast adenocarcinoma MCF-7 cells in a concentration-dependent manner. Leo et al. reported the chalcone derivatives for cytotoxicity against human tumour cells.[31] Anti-inflammatory: Anti-inflammatory drugs are the drugs that are used to reduce pain and inflammation. In other words, these are pain-relieving drugs. These drugs work mainly by inhibiting the cyclooxygenase enzymes, COX-1 and COX-2, that produce prostaglandins. [32]

SYNTHETICALLY EVOLUTION OF CHALCONE:
Classical Claisen Schmidt condensation: First introduced in the late 19th century, the most common and straightforward method. [33]
•Process: Aldol condensation between Acetophenone derivatives and benzaldehyde derivatives under basic or acidic conditions. [34]
•Base-catalysis (NaoH, KoH, NaOet) or acid catalysis (Hcl, Lewis acid).
• Example: 2- hydroxy acetophenone + Benzaldehyde = 2- hydroxy chalcone.

NATURALLY EVOLUTION OF CHALCONE:
Origin in Plant Secondary Metabolism:
• Chalcones are considered the central intermediates in flavonoid Biosynthesis.
• They are produced from phenylpropanoid metabolism, which starts with phenylalanine.[35]
• Enzyme: Chalcone synthase catalyses the consideration of p- coumaroyl- coA and three malonyl - coA units to yield a chalcone.

• These chalcones then undergo Isomerization to flavanones- further diversified into flavones, flavanols, anthocyanins and isoflavonoids. [36]

Physicochemical Properties of Synthetic Chalcones:

1. General Physical Characteristics:

Appearance: Most chalcones are yellow to orange crystalline solids due to extended conjugation.

Melting Point: Typically ranges from 100–200 °C depending on substituents.

Solubility: Soluble in organic solvents like ethanol, methanol, chloroform, and DMSO; poor aqueous solubility unless ionizable groups are present.[37]

2. Spectroscopic Properties:

UV-Vis Absorption: Exhibits strong absorption in the 280–400 nm range due to $\pi \rightarrow \pi^*$ transitions in the α, β-unsaturated carbonyl system.

IR Spectroscopy: Characteristic C=O stretching around 1660–1680 cm^{-1}; aromatic C=C and C-H stretch also prominent.

NMR Spectroscopy:

^1H NMR: Deshielded α, β-unsaturated protons (δ ~7.5–8.0 ppm).

^{13}C NMR: Carbonyl carbon appears around δ ~190–195 ppm.[38]

3. Chemical Reactivity:

Isomerization: Trans-isomers are thermodynamically favoured; cis-isomers may form under photochemical or acidic conditions.

Cyclization: Chalcones readily cyclize to flavanones or aurones under acidic or oxidative conditions.[39]

4. Thermodynamic and Solution Properties:

Partition Coefficient (Log P): Typically ranges from 2.5–4.5, indicating moderate lipophilicity.

pKa Values: Phenolic chalcones show pKa ~8–10, influencing ionization and solubility.

Stability: Stable under ambient conditions; sensitive to strong acids, bases, and light.[40]

5. Colorimetric Reactions:

Wilson's Test: Pink coloration with conc. H_2SO_4 confirms chalcone presence.

$FeCl_3$ Test: Blue-violet coloration indicates phenolic OH groups.[41]

Physicochemical Properties of Naturally Evolved Chalcones:

1. General Physical Characteristics:

Appearance: Crystalline solids, typically yellow, orange, or brown due to extended conjugation.

Melting Point: Varies with substitution; generally, between 100–200 °C.

Solubility: Soluble in organic solvents (ethanol, methanol, chloroform); also soluble in aqueous acidic and alkaline media. In alkaline solution, they form deep red or orange-red colors.[42]

2. Spectroscopic Properties:

UV-Vis Absorption:

Band I (340–390 nm): $\pi \rightarrow \pi^*$ transitions in the enone system.

Band II (200–270 nm): $n \rightarrow \pi^*$ transitions.

IR Spectroscopy:

C=O stretch: 1660–1680 cm^{-1}.

Aromatic C=C and phenolic OH stretches are prominent.

NMR Spectroscopy:

^1H NMR: α, β-unsaturated protons appear at δ ~7.5–8.0 ppm.

^{13}C NMR: Carbonyl carbon appears at δ ~190–195 ppm.[43]

3. Chemical Reactivity:

Isomerization: Trans-isomers are thermodynamically stable; cis-isomers may form under acidic or photochemical conditions.

Cyclization: Natural chalcones can cyclize enzymatically to flavanones via chalcone isomerase in plants.

Color Reactions:

Wilson's Test: Pink coloration with conc. H_2SO_4.

$FeCl_3$ Test: Blue-violet colour if phenolic OH groups are present.[44]

4.Thermodynamic and Solution Properties:

Partition Coefficient (Log P): Typically, 2.5–4.5, indicating moderate lipophilicity.

pKa Values: Phenolic chalcones show pKa ~8–10, affecting solubility and ionization.

Stability: Stable under ambient conditions; sensitive to strong acids, bases, and light.[45]

5. Biological and Structural Relevance:

Found in plants like *Angelica keiskei*, *Glycyrrhiza glabra*, *Humulus lupulus*.

Serve as biosynthetic precursors to flavonoids and isoflavonoids via chalcone isomerase.[46]

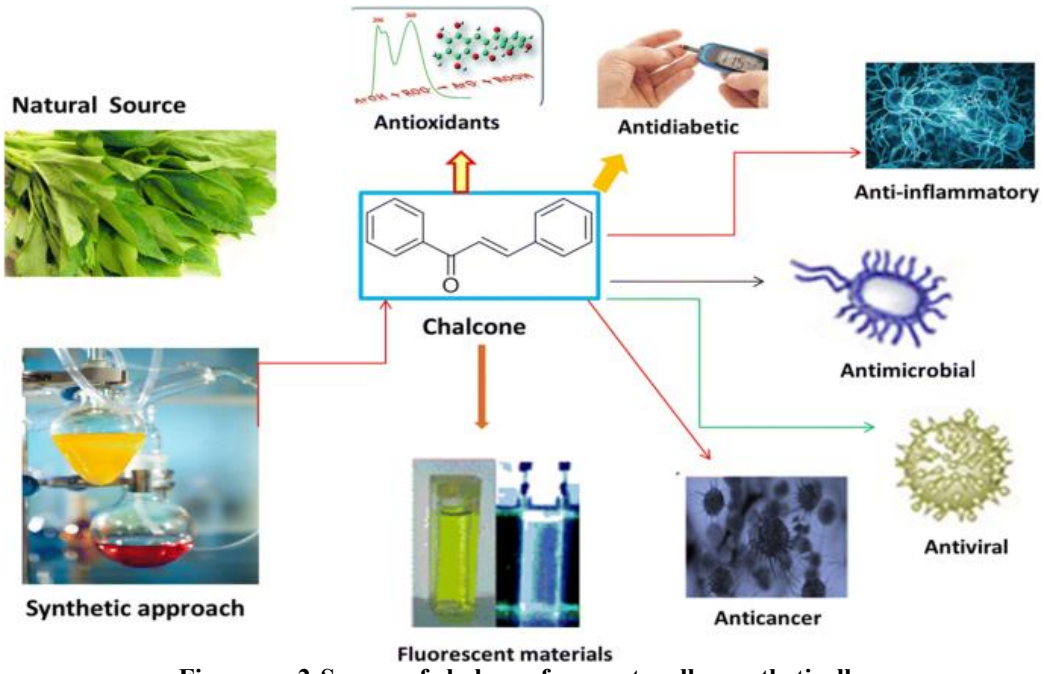

Figure no:2-Source of chalcone from naturally, synthetically

CLASSIFICATION OF CHALCONE

Table1: Classification of Chalcone

Class	Basic Moiety	Substitution Type	Representative Examples
Simple Chalcones	1,3-Diphenyl-2-propen-1-one	No substituents	Chalcone, Benza acetophenone
Substituted Chalcones	1,3-Diphenyl-2-propen-1-one	–OH, –OCH_3, –NO_2, –Cl, etc.	4-Methoxychalcone, 3-Nitrochalcone, 4-Chlorochalcone
Hydroxychalcones	1,3-Diphenyl-2-propen-1-one	Hydroxyl groups on rings	Butein, Isoliquiritigenin, Cardamonin
Amino Chalcones	1,3-Diphenyl-2-propen-1-one	–NH_2 group on ring	2'-Aminochalcone, 4-Amino-4'-methoxychalcone
Halogenated Chalcones	1,3-Diphenyl-2-propen-1-one	Cl, Br, F on rings	3-Bromo-4'-methoxychalcone, 4-Fluorochalcone
Heterocyclic Chalcones	Heteroaryl–CO–CH=CH–Aryl	Furan, thiophene, pyridine rings	2-Furylchalcone, 2-Thienylchalcone, 2-Pyridylchalcone
Dihydrochalcones	1,3-Diphenylpropan-1-one	Saturated alkene (no C=C bond)	Neohesperidin dihydrochalcone, Phloretin
Natural Chalcones	Polyhydroxylated chalcone backbone	Often glycosylated or prenylated	Licochalcone A, B, C; Xanthohumol; Echinchalcone

1**. Isoliquiritigenin**
Source: Glycyrrhiza glabra (Liquorice)
Activity: Antioxidant, anti-inflammatory, anticancer
Structure: 4,2′,4′-Trihydroxychalcone

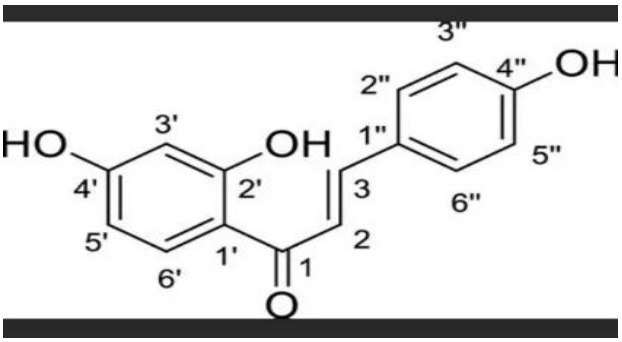

Figure no :3 Isoliquiritigenin

2. **Butein**
Source: Butea monospermic (Flame of the forest)
Activity: Anti-inflammatory, anticancer, tyrosinase inhibitor (used in skin whitening)
Structure: 3,4,2′,4′-Tetrahydroxychalcone

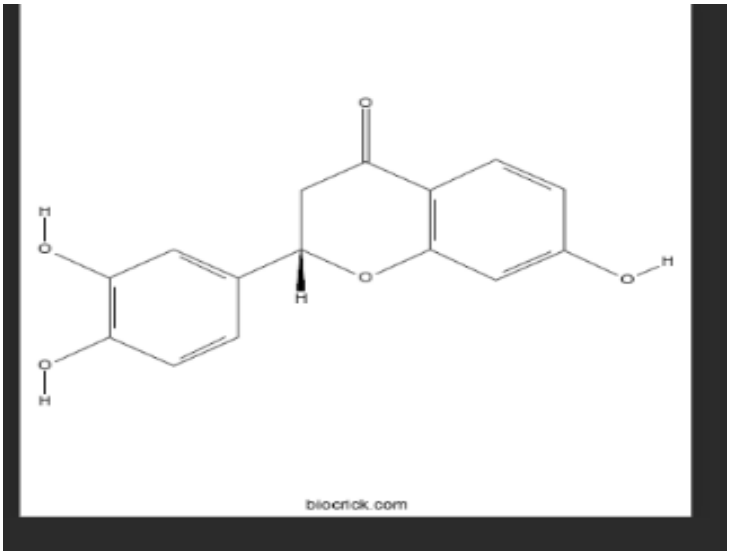

Figure no:4 Butein

3**. Cardamonin**
Source: Alpinia katsu Madai and Boesenbergia rotunda
Activity: Anti-inflammatory, anticancer, antioxidant
Structure: 2′,4′-Dihydroxy-6′-methoxychalcone

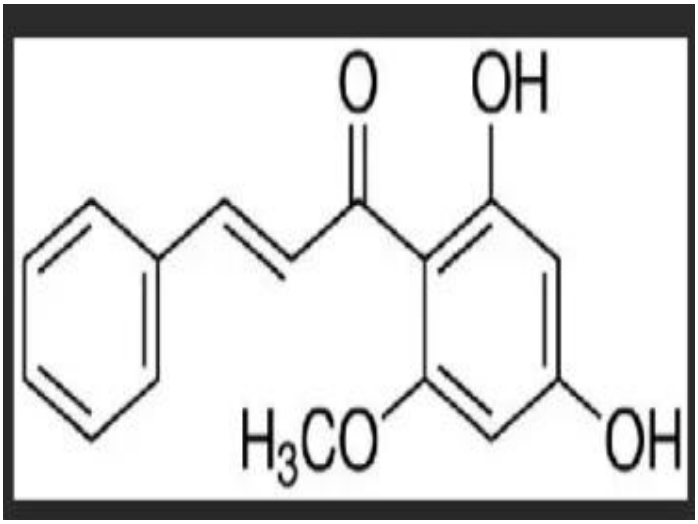

Figure no:5 Cardamonin

4. **Xanthoangelol**
Source: Angelica keiskei (Ashitaba)

Activity: Antibacterial, antiangiogenic, anticancer
Note: Found in the yellow sap of the plant

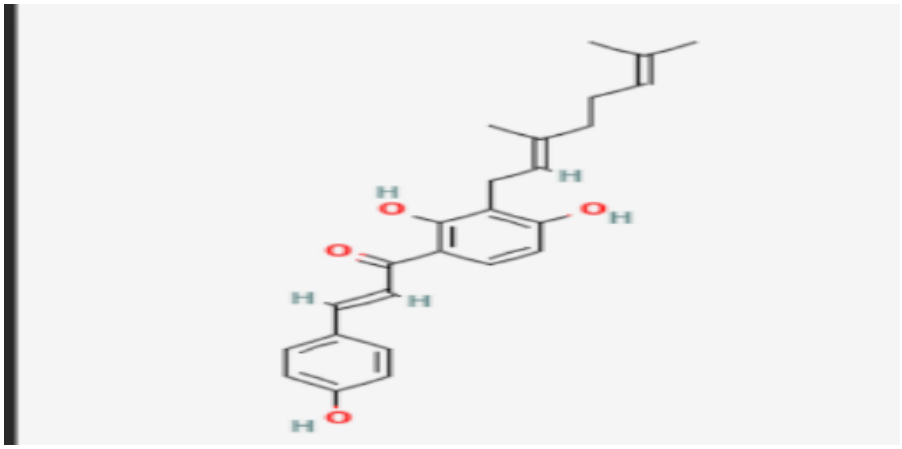

Figure no:6 Xanthoangelol

5. **Flavokawain A, B, C**
Source: Piper methysticum (Kava plant)
Activity: Anticancer, anti-inflammatory
Note: Flavokawains are a subclass of chalcones

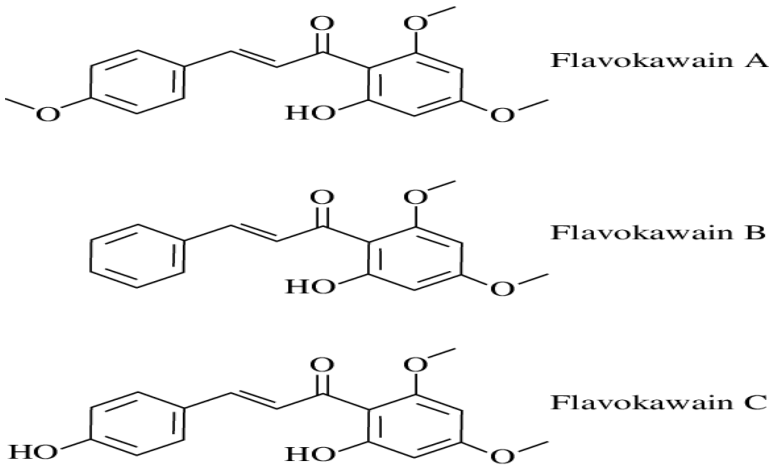

Figure no:7 Flavokawain A, B, C

6. **Licochalcone A**
Source: Glycyrrhiza inflate (Chinese licorice)
Activity: Antimicrobial, anticancer, antimalarial.[47]

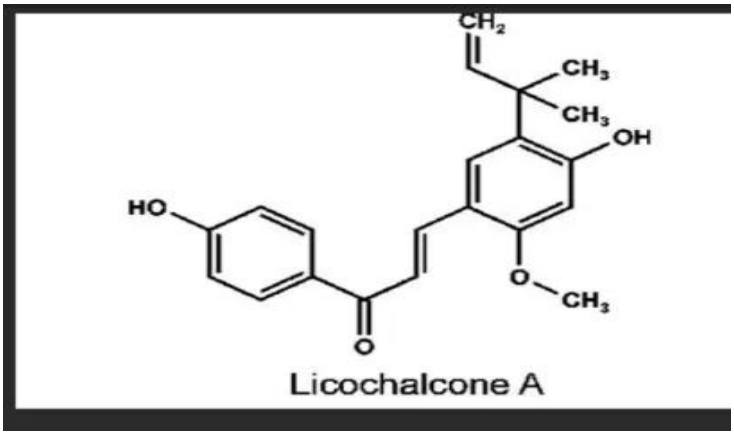

Figure no:8 Licochalcone A

ADVANTAGES/USES OF CHALCONE:

1.Medical uses:
a) Anti-cancer: Chalcones block tubulin polymerization, induce apoptosis and arrest the cell cycle.
Example: Synthetic chalcones derivatives active against breast and colon cancer [48].
b) Antimicrobial: Effective against staphylococcus aureus, Escherichia coli and candida albicans [49].
c) Anti - inflammatory: Inhibit nitric oxide (NO), prostaglandins and NF- kB signaling [50].
d) Antioxidant: Neutralize reactive oxygen species due to phenolic groups [51].
e) Anti-malarial: Chalcones inhibits parasitic enzymes and the growth of plasmodium & leishmania [52].
f) Neuroprotective: Some chalcones inhibit acetylcholinesterase and reduce amyloid- beta aggregation [53].
2.Pharmaceutical uses:
a) Lead scaffold: Chalcone is consider a "privileged structure" in medicinal chemistry for designing multifunctional groups [54].
3.Industrial uses:
a) Chemical intermediates: used in synthesis of flavonoids, heterocycles and dyes [55].
b) Material science: some Chalcone derivatives act as liquid crystal materials, corrosion inhibitors and fluorescent probes.[56]
4.Agricultural uses:
a) Plant defence compounds:
Naturally occurring chalcones protects plant against microbial infection [57].
b) Potential pesticides and herbicides: synthetic chalcones tested as agrochemicals due to enzyme inhibition properties [58].

BIOAVAILABILITY OF CHALCONE:
1.General bioavailability:
• Chalcones are lipophilic but often have poor aqueous solubility.
• They undergo extensive first pass metabolism leading to low oral bioavailability.
• Many natural chalcones show high biological activity in vitro, but there in vivo is limited because of rapid metabolism [59,60].
2.Absorption and metabolism:
• Absorption: chalcones are moderately absorbed in the intestine but show poor systemic exposure due to metabolism.
• Metabolic pathways: phase I and phase II reactions.
• Example: Xanthohumol is rapidly converted into isoxanthohumol and other metabolites, reducing its bioavailability [61,62].
3.Strategies to improve bioavailability:
a) Structural modification: Adding hydrophilic substituents increases solubility.
• Hydro molecules with heterocycles enhance stability and pharmacokinetics [63].
b) Nano-formulations & drug delivery systems:
• Liposomes, nanoparticles, micelles solid lipid nanoparticles can improve solubility, absorption and circulation time.
• Example: Nanosuspensions of xanthohumol showed improved oral bioavailability [64].
c) Prodrug approach: • Conjugating chalcones with amino acids, sugars, or phosphates can enhance water solubility and bioavailability [65].

DRUG PROFILE

CHALCONE
Chalcone is the organic compound C 6 H 5 C (O)CH=CHC 6 H 5. It is an α,β-unsaturated ketone. A variety of important biological compounds are known collectively as chalcones or chalconoids They are widely known bioactive substances, fluorescent materials, and chemical intermediates.

PHYSICAL PROPERTIES
STRUCTURE: -

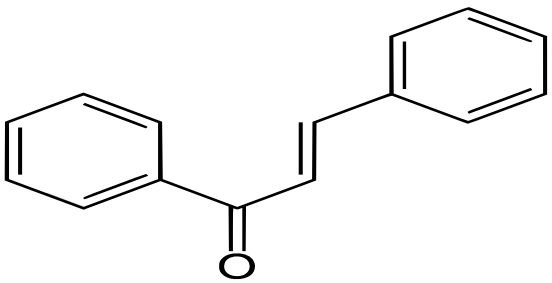

Figure no:9 - Chalcone (1,3-Diphenylprop-2-en-1-one)

IUPAC NAME: 1,3-Diphenylprop-2-en-1-one

Chemical formula	$C_{15}H_{12}O$
Molar mass	208.260 g·mol^{-1}
Appearance	pale yellow solid
Density	1.071 g/cm^3
Melting point	55 to 57 °C (131 to 135 °F; 328 to 330 K)
Boiling point	345 to 348 °C (653 to 658 °F; 618 to 621 K)
Magnetic susceptibility (χ)	−125.7·10^{-6} cm^3/m [76]

PREPARATION:

Chalcone is synthesized through a base - catalysed condensation reaction between benzaldehyde and acetophenone, commonly known as the Claisen-Schmidt condensation. In this method, equal molar amounts of benzaldehyde and acetophenone are dissolved in ethanol, and a dilute sodium hydroxide solution is added gradually while stirring. The reaction mixture is kept cool using an ice bath to control the temperature and minimize side reactions. Over the course of 30 to 45 minutes, a yellow precipitate forms, indicating the production of chalcone. This solid is then filtered, washed with cold water, and purified by recrystallization from ethanol. The final product is a yellow crystalline compound with a melting point around 55–59 °C, and dried then the chalcone was obtained

Figure no:10- Prepared of 1,3-Diphenylprop-2-en-1-one

STRUCTURAL ACTIVITY RELATIONSHIP (SAR):

RING A:

Substitution at C 2

Hydroxy (-OH) Enhances hydrogen bonding and stability, key for anti-diabetic and antioxidants activity [77]

Substitution at C 4

Hydroxy (-OH) Boots anti diabetic and antibacterial activity [78]

Dimethyl amine $N(CH_3)_2$ Strong electron-donating, improves PPAR -y binding and anti -diabetic potential [79]

Methoxy($-OCH_3$) May reduce anti-bacterial activity.[80]

RING B:

Substitution at C 2

Halogens (-Cl, -Br) Electron - withdrawing halogens enhance antibacterial potency.[81]

Substitution at C4

Methyl($-CH_3$) electron-donating may suppress antibacterial activity [82]

Dimethyl amine $N(CH_3)_2$ enhances pharmacological spectrum including antimicrobial and antioxidants activity [83]

Substitution at C 2,3,4

Hydroxy (-OH): Multiple hydroxyls improve antioxidants and anti-diabetic effects.[84]

THERAPUETIC USES:

1. 1.Anticancer Chalcones inhibit various cancer cell lines by modulating apoptosis, cell cycle arrest, and angiogenesis. Derivatives like xanthohumol and iso liquiritigenin show potent activity against breast, colon, and prostate cancers [85]
2. Anti-inflammatory They suppress pro-inflammatory cytokines (e.g., TNF-α, IL-6) and inhibit enzymes like COX-2 and I NOS, making them effective in treating chronic inflammation.
3. Antioxidant Chalcones scavenge free radicals and enhance endogenous antioxidant enzymes (e.g., SOD, catalase), contributing to cellular protection against oxidative stress.[86]
4. Antimicrobial Exhibiting broad-spectrum antibacterial and antifungal activity, chalcones disrupt microbial membranes and inhibit DNA gyrase and topoisomerase enzymes.[87]
5. Antidiabetic Certain chalcones enhance insulin sensitivity and inhibit α-glucosidase and aldose reductase, aiding in glycemic control.[88]
6. Neuroprotective Chalcones modulate neuroinflammation and oxidative stress, showing promise in models of Alzheimer's and Parkinson's diseases.[89]
7. Antiparasitic Some derivatives are active against Plasmodium falciparum and Leishmania species, interfering with parasite metabolism.[90]

4-CHLORO CHALCONE
PHYSICAL PROPERTIES:
STRUCTURE

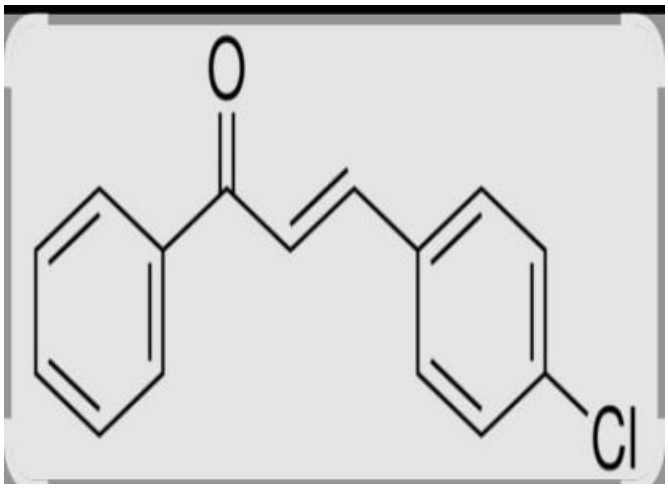

Figure no:11 1-(4-chlorophenyl)-3-phenylprop-2-en-1-one

IUPAC: E)-1-(4-chlorophenyl)-3-phenylprop-2-en-1-one
MOLCULAR FORMULA: $C_{15}H_{11}ClO$.
MOLECULAR WEIGHT: 242.70g/mol
MELTING POINT: ~360.6 °C at 760 mmHg
DENSITY: ~1.2 g/cm³
LogP: ~3.5–4.0 (lipophilic)
SOLUBILITY: Soluble in ethanol, DMSO
INSOLUBILITY: Partially insoluble in water [91]

PREPARATION:
4-Chlorochalcone is prepared by the Claisen-Schmidt condensation of 4-chlorobenzaldehyde with acetophenone in the presence of a base like sodium hydroxide, using ethanol as the solvent. The reaction mixture is stirred at room temperature or slightly heated for a few hours, allowing the formation of the α, β-unsaturated ketone. After completion, the product precipitates upon pouring into ice-cold water, is filtered, washed, and recrystallized to yield pure 4-chlorochalcone.

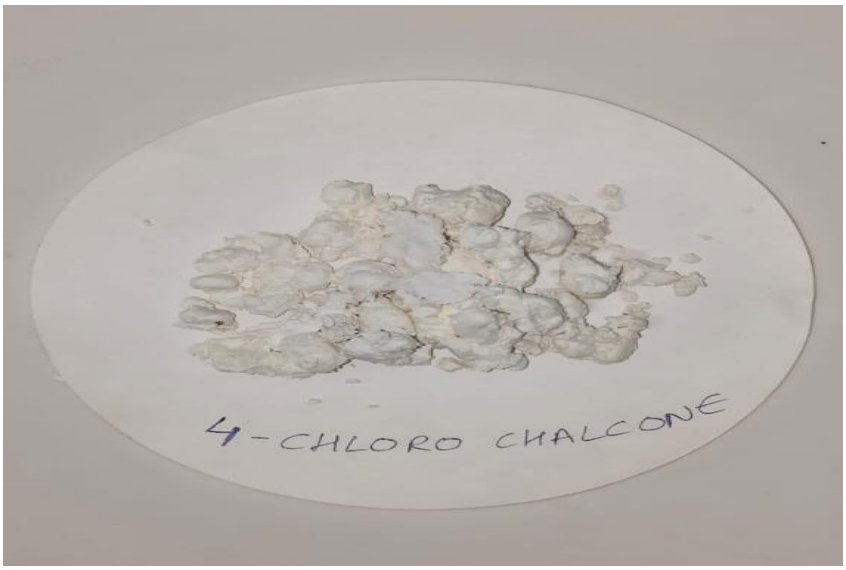

Figure no :12– Prepared of 1-(4-chlorophenyl)-3-phenylprop-2-en-1-one

STRUCTURAL ACTIVITY RELATIONSHIP (SAR):

RING A:

Hydroxy (–OH) and Methoxy (–OCH_3) Groups:
Increase antioxidant and antifungal activity.
Facilitate hydrogen bonding and stabilize free radicals.[92]
Substitution at 4 position: Dimethyl amino (–$N(CH_3)_2$):
Improves DNA intercalation through enhanced planarity and basicity.
Increases anticancer potential by stabilizing interactions with nucleic acids.[93]
Substitution of Nitro (–NO_2) Groups at 3 or 4 position:
Strong electron-withdrawing effects increase cytotoxicity and antibacterial potency.
Enhance electrophilicity of chalcone moiety, aiding target binding.[94]
Heterocyclic A-ring Substituents (e.g., Pyrazole, Thiazole Rings)
Boost selectivity and potency against resistant microbial strains.
Improve binding affinity due to heteroatoms and ring rigidity.[95]
4-Chloro Substitution on B-ring
Enhances lipophilicity and membrane permeability.
Acts as an electron-withdrawing group, improving antimicrobial and anticancer activities.
Provides metabolic stability, improving biological half-life.[96]
B-ring 4-Chloro Combined with Fused Rings on A-ring (e.g., Naphthyl)
Enhance hydrophobic interactions with enzyme binding sites.
Increase anticancer activity by improving molecular recognition.[97]

THERAPUETIC USES

Anticancer Activity: 4-Chloro chalcones inhibit tubulin polymerization and induce apoptosis in cancer cells. [98]
Antimicrobial Activity: Effective against *E. coli*, *S. aureus*, and *Candida albicans* due to membrane disruption and enzyme inhibition.
Halogen substitution improves penetration and resistance profile.[100]
Anti-inflammatory Activity: Inhibits COX-2 and NF-κB pathways, reducing cytokine production and oxidative stress.
Methoxy-substituted 4-chloro chalcones show enhanced selectivity.[101]
Antioxidant Activity: Scavenges free radicals and protects against lipid peroxidation.
Synergistic effect observed with hydroxyl/methoxy groups on A-ring.[102]
Cardioprotective Effects: Reduces infarct size and myocardial damage markers (AST, LDH) in ischemia models.
Halogenated chalcones like 4′-chlorochalcone outperform lovastatin in lipid-lowering studies.[103]
Antidiabetic Potential: Inhibits α-glucosidase and enhances insulin sensitivity.[104]

MECHANISM OF CHALCONE:

1.**The Claisen–Schmidt Condensation**

This is the classical reaction for chalcone synthesis: a crossed aldol condensation between an aldehyde and a ketone.
Mechanistic Steps (Base-Catalyzed Version)
The base-catalyzed mechanism is more common and better studied. Below are the detailed steps:
1. Deprotonation of the ketone (enolate formation)
A base (for example, hydroxide ion, alkoxide) deprotonates an α-hydrogen of the ketone, generating an enolate ion.

The enolate is stabilized by resonance: negative charge shared between α-carbon and carbonyl oxygen.
2. Nucleophilic attack on the aldehyde
The enolate (nucleophile) attacks the carbonyl carbon of the aldehyde (electrophile), forming a β-hydroxy ketone (an "aldol" intermediate).
3. Proton transfers
Protonation of the alkoxide oxygen (if necessary) to produce the neutral β-hydroxy ketone.
4. Dehydration (elimination of water)
Removal of water (–OH from the aldol, –H from the α-carbon) leading to formation of a double bond between α and β carbons of the ketone. This gives the α,β-unsaturated ketone (chalcone).
5. E-/Z stereoselectivity
Usually the thermodynamically more stable E-isomer (trans across the C=C) predominates.[105]
2.Acid-Catalyzed Version
While base catalysis is more common, acid catalysed paths also exist.
Under acidic conditions, the mechanism proceeds via enol rather than enolate (since deprotonation is more difficult under acid).
The aldehyde is protonated to increase electrophilicity. The ketone may tautomerize to the enol form, which attacks the protonated aldehyde. Subsequently dehydration steps occur, etc. [106]
According to this, the mechanism can be divided into two major parts:
Activation of acetophenone (i.e. deprotonation to form enolate) — very fast, single step.
Attack on aromatic aldehyde and dehydration — proceeds through several intermediate complexes and multiple steps.
In the acid-catalysed cyclization of 2-hydroxychalcone to flavanone, studies (DFT with M06-2X) show that the process proceeds via protonation → cyclization → tautomerization, with the tautomerization step being rate determining.
Rate-Determining Step, Energetics, and Roles of Solvent / Water
One key finding: proton transfers (or their assistance by water) are important in lowering energy barriers. The water molecule often acts as a proton shuttle in many steps.
The dehydration (elimination of water) step often has a higher activation energy; in many computational studies this (or some proton transfer / tautomerization after cyclization) is rate limiting.
Solvent effects: Polar solvents stabilize ionic intermediates (enolate, etc.) and can influence the equilibrium between enolate/enol etc. Also, removal of water (by using drying agents or azeotropic removal) pushes equilibrium toward chalcone.
Alternative & Experimental Considerations
Use of different catalysts: strong base (NaOH, KOH, alkoxides), or acid catalysts; also solid base or solid acid supports; ionic liquids etc. Mechanism steps are similar, but catalyst nature can affect rates, side-reactions, selectivity.
Reaction conditions: temperature, solvent polarity, mixing order, concentration, presence of water. These all can alter which step becomes limiting, how pure product is, whether side reactions (self-condensation, overreaction etc.) occur.
Elementary Mechanism (Base-Catalyzed, with Water-Assist) — Step-by-Step

Step 1: Enolate Formation
Base abstracts an α-hydrogen from the ketone, forming the enolate. Water may help by acting as proton acceptor/donor, stabilizing the transition. Low barrier quickly established equilibrium. It is fast compared to subsequent condensation steps in many cases.

Step 2: Aldehyde Activation (Electrophile)
The aldehyde is not strongly activated under base, but its carbonyl carbon is electrophilic enough; if in acidic catalysis, protonation increases electrophilicity. Under base, sometimes the protonated water or solvent molecules can stabilize charges. Affected by substituents on the aromatic ring; electron-withdrawing groups make aldehyde more electrophilic and speed up attack. Electron-donating substituents slow it down.

Step 3: Nucleophilic Attack (Aldol Step):
The enolate attacks aldehyde carbonyl, forming a tetrahedral alkoxide intermediate which becomes β-hydroxy ketone. There is an energetic penalty for forming the alkoxide; solvent stabilization helps. This intermediate can exist in several conformations; also, hydrogen bonding / solvation important. Computational studies show several intermediate complexes in this phase.

Step 4: Protonation of Alkoxide
The alkoxide oxygen obtains a proton (from water, solvent, or the acid formed when base abstracts α-H) to yield the neutral β-hydroxy ketone. This proton transfer is often rapid if proton sources are available. The presence of water helps.

Step 5: Dehydration (Elimination of Water)
Removal of water leads to formation of the double bond between α and β carbons. Mechanism of elimination may proceed through E1cb type pathway (base abstracts α-H first, forming carbanion, then leaving group departs) or via concerted

elimination in some cases. This step often has higher activation energy; sometimes it's the rate-determining step. Also influenced by temperature and base strength.

Step 6: Proton Transfers / Tautomerization (if needed)
After elimination, there may be proton shifts or tautomerization in case enol/enone equilibria need settling, etc.
Self-condensation of ketone (if aldehyde has no or low reactivity) can compete.
Cannizzaro reaction (for non-enolizable aldehydes under strong base) sometimes occurs.
Polymerization / resinification under strongly basic or high temperature conditions.[107]

OTHER MECHANISM OF ACTION OF CHALCONE:
1.Membrane Disruption
Chalcones can integrate into microbial lipid bilayers due to their lipophilic nature, disrupting membrane integrity.
This leads to leakage of cellular contents and eventual cell death.
2. Enzyme Inhibition
The α, β-unsaturated carbonyl group acts as a Michael acceptor, forming covalent bonds with nucleophilic residues in microbial enzymes.
This inhibits key enzymes like DNA gyrase, dihydrofolate reductase, and β-lactamase, impairing DNA replication and cell wall synthesis2.
3. ROS Generation
Chalcones can induce oxidative stress by generating reactive oxygen species (ROS), damaging microbial proteins, lipids, and DNA.
4. Efflux Pump Inhibition
Certain chalcone derivatives inhibit bacterial efflux pumps, enhancing intracellular retention of antibiotics and antimicrobial agents.
5. Quorum Sensing Interference
Chalcones may interfere with microbial communication systems (quorum sensing), reducing virulence and biofilm formation. [108,109]

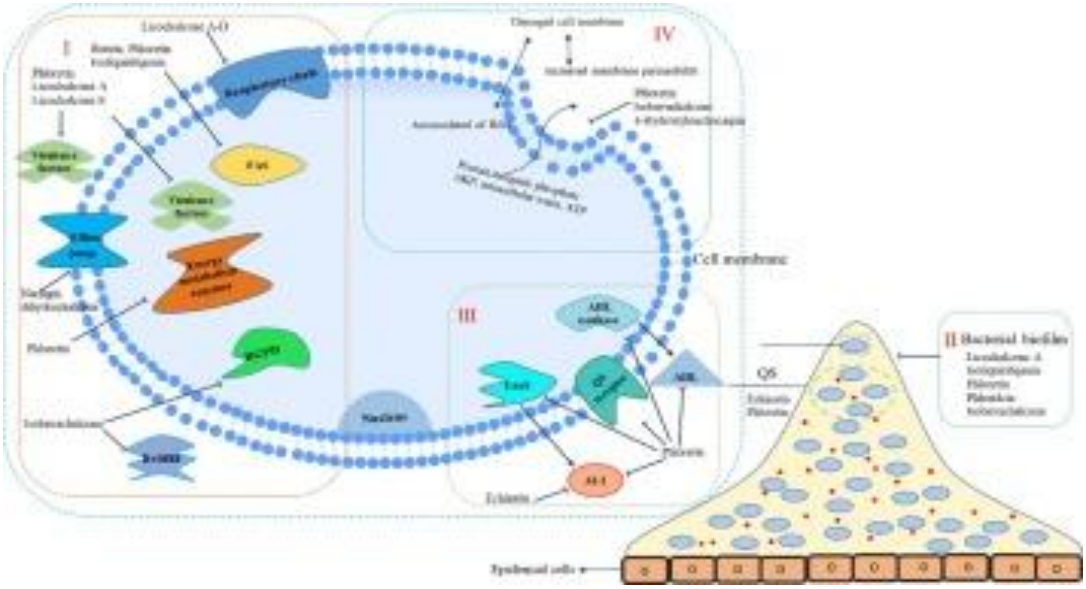

Figure no:13 : Microbial activity of chalcone

PREPARATION OF NUTRIENT BROTH:
CHEMICALS REQUIRED:
Beef extract (0.6g), Peptone(1g), Sodium chloride(1g), Distilled water(200ml)
APPARATUS REQUIRED:
Conical flask, test tube, cotton, measuring cylinder, glass stirrer, autoclave, Bunsen burner.

PROCEDURE:
Weigh all ingredients separately by physical balance. Take a 1000ml conical flask to this add 200ml distilled water and weigh amount of beef extract, peptone, sodium chloride. Heat the mixture and agitate the mixture to dissolve the ingredients and add the distilled water and makeup the final volume. Adjust the pH of the medium to 7. Pour 5ml of the medium in each test tube and plug the tubes with cotton. These medium containing tubes are sterilized in an autoclave at 121ºC under `15lb pressure for 15 minutes. Allow the autoclave to cool and remove the broth tubes [110,111,112]

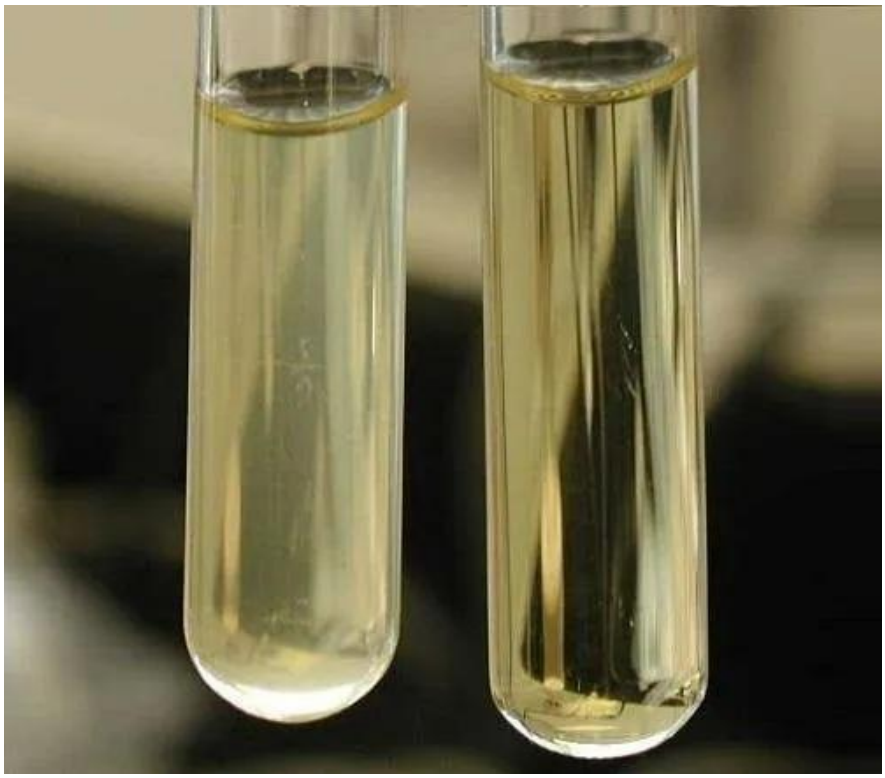

Figure no : 14 Nutrient broth

PREPARATION OF NUTRIENT AGAR
CHEMICALS REQUIRED:
Beef extract (0.6g), peptone(1g), sodium chloride(1g), and distilled water(200ml)
APPARATUS REQUIRED:
Conical flask, test tubes, cotton, measuring cylinder, glass stirrer, autoclave, pH matter and burner
PROCEDURE:
Weigh all ingredients separately by physical balance. Take a 1000ml conical flask to this add appropriate volume of distilled water and weigh amount of ingredients accept agar. Adjust the pH of the medium to 7. Heat the mixture and add agar to the flask and is heated until the agar completely dissolve and makeup the volume up to required quantity. [113,114]

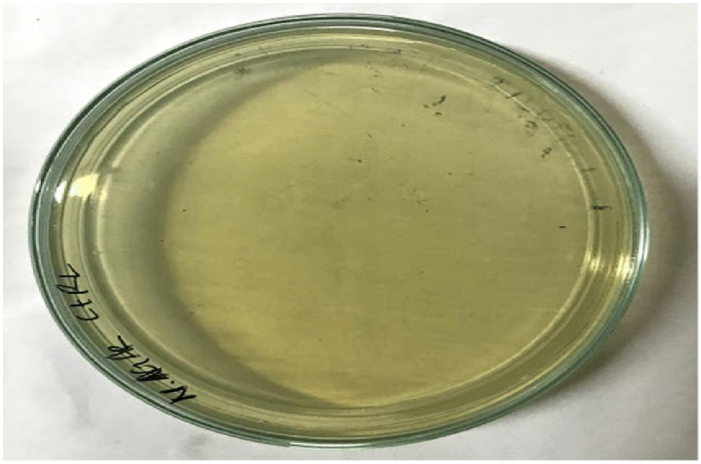

Figure no:15 Nutrient agar

STANDARD DRUG DILUTIONS OF AMIKACIN SULPHATE
PREPARING A STOCK SOLUTION:
Amikacin sulphate injection contains 100mg of amikacin in 2 ml and 1ml contains -50mg of amikacin. Take 1 ml from the standard sample and dilute 50ml with water gives 1mg/ml. From stock 1, 1ml is taken and diluted to 10 ml which gives stock 2,100µg/ml. From stock 2, take 1ml and dilute to 10ml with water which gives10µg/ml. From stock 2 take 2 ml and dilute to 10ml with water which gives 20µg/ml. From stock 2, take 4ml and dilute with water which gives 40µg/ml. Stock 2, take 6 ml and dilute to 10ml with water which gives 60µg/ml. And in the same way of 80µg/ml.

AMIKACIN SULPHATE BY CUP PLATE METHOD:

PROCEDURE:

Inoculate a previously liquefied medium appropriate to assay with requisite quantity of suspension of the microorganism. Add the suspension to the medium at a temperature between 40º and 50º and immediately pour the inoculated medium into the petri dishes, to give a depth of 3 to 4mm, put the plate on a level surface. Store the prepared dishes to manner so as to ensure that no significant growth of the test organism occurs before the dishes or plates are used and the surface of the agar layer is dry at the time of use. Prepare solution of known concentration of the standard preparation and solution of corresponding concentration of antibiotic to be examined in an appropriate buffer solution. Add solutions of antibiotic in the cavities prepared in the agar medium in a sufficient volume almost to fill the holes. Arrange the solution of the standard preparation and the antibiotic under examination on each dish so that they alternate around the dish, henceforth the highest concentration of standard and test preparation are not adjacent. Leave the dishes for 1 to 4 hours at room temperature at 4ºc as appropriate as a period of pre incubation diffusion to minimize the effects of variation in time between the applications of the different solutions. Incubate them for 18 hours at the temperature of 37ºc. accurately measure the diameters or areas of circular inhibition zones and calculate the results.[115]

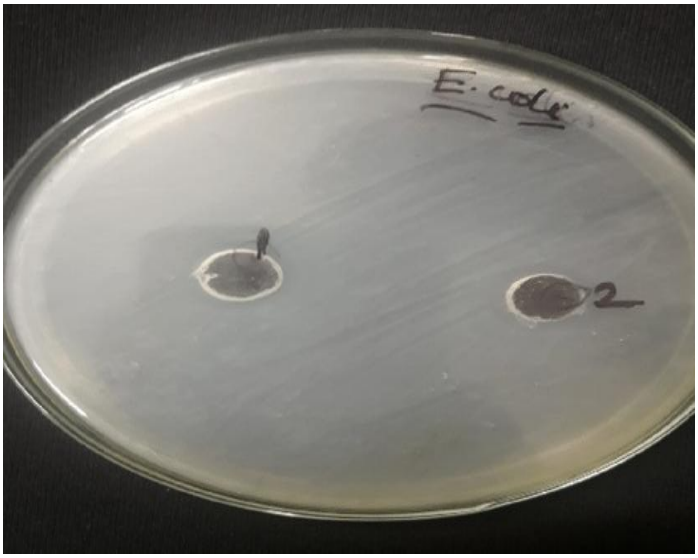

Figure no:16 Cup plate method

INSTRUMENTS USED:

AUTOCLAVE:

Autoclaves are used to sterilize equipment and supplies by subjecting to pressurized saturated steam at 121ºc for around 15-20 minutes depending upon the size of the load and contents. The autoclave was invented by Charles chamber land in 1884.Although precusor known as the steam digester was created by Denis papin in 1679. The name comes from greek autoclave ultimately meaning itself and latin calvis meaning keys, Thus a self-locking device.

Figure no: 17 Autoclave

INCUBATOR:
An incubator is a device or equipment designed to provide a controlled environment for the growth and development of living organisms, such as bacteria, cells or plants. It maintains optimal conditions like temperature, humidity, and light to support the growth and cultivation of microorganisms, cells or plants.

Figure no:18 - Incubator

FOURIER TRANSFORM INFRARED (FTIR) SPECTROSCOPY:
FTIR (Fourier Transform InfraRed) spectroscopy is a widely used analytical technique for identifying and characterizing materials. Here's an overview:

DEFINITION:
FTIR is a non-destructive technique that measures the absorption of infrared radiation by molecules. It provides information about the molecular structure, functional groups, and chemical bonding of a sample.

PRINCIPLE:
FTIR is based on the principle that molecules vibrate at specific frequencies when exposed to infrared radiation. These vibrations cause the molecules to absorb radiation at specific wavelengths, resulting in a unique spectral fingerprint.

INSTRUMENTATION:
A typical FTIR instrument consists of:
1. IR source: Emits infrared radiation
2. Interferometer: Divides the radiation into two beams and recombines them to create an interference pattern
3. Detector: Measures the intensity of the interference pattern
4. Computer: Processes the data and generates a spectrum.

WORKING:
1. Sample Preparation: A sample is prepared by grinding or dissolving it in a suitable solvent.
2. IR Radiation: The sample is exposed to infrared radiation, which is emitted by a broad-spectrum IR source.
3. Interferometer: The IR radiation is directed into an interferometer, which splits the radiation into two beams.
4. Interference Pattern: The two beams are recombined to create an interference pattern, which is measured by a detector.
5. Fourier Transform: The interference pattern is converted into a spectrum using a Fourier transform algorithm.
6. Spectral Analysis: The resulting spectrum is analyzed to identify the characteristic absorption peaks of the sample.

APPILCATIONS:
1. Pharmaceutical analysis: Identification of active pharmaceutical ingredients and detection of impurities
2. Polymer characterization: Analysis of polymer structure, composition, and properties
3. Food analysis: Detection of adulteration, identification of food components, and monitoring of food quality
4. Environmental monitoring: Detection of pollutants, analysis of soil and water samples, and monitoring of air quality
5. Biomedical research: Analysis of biological tissues, cells, and fluids.

RESULTS AND DISCUSSION
IR (INFRA RED) SPECTROSCOPY
CHALCONE:

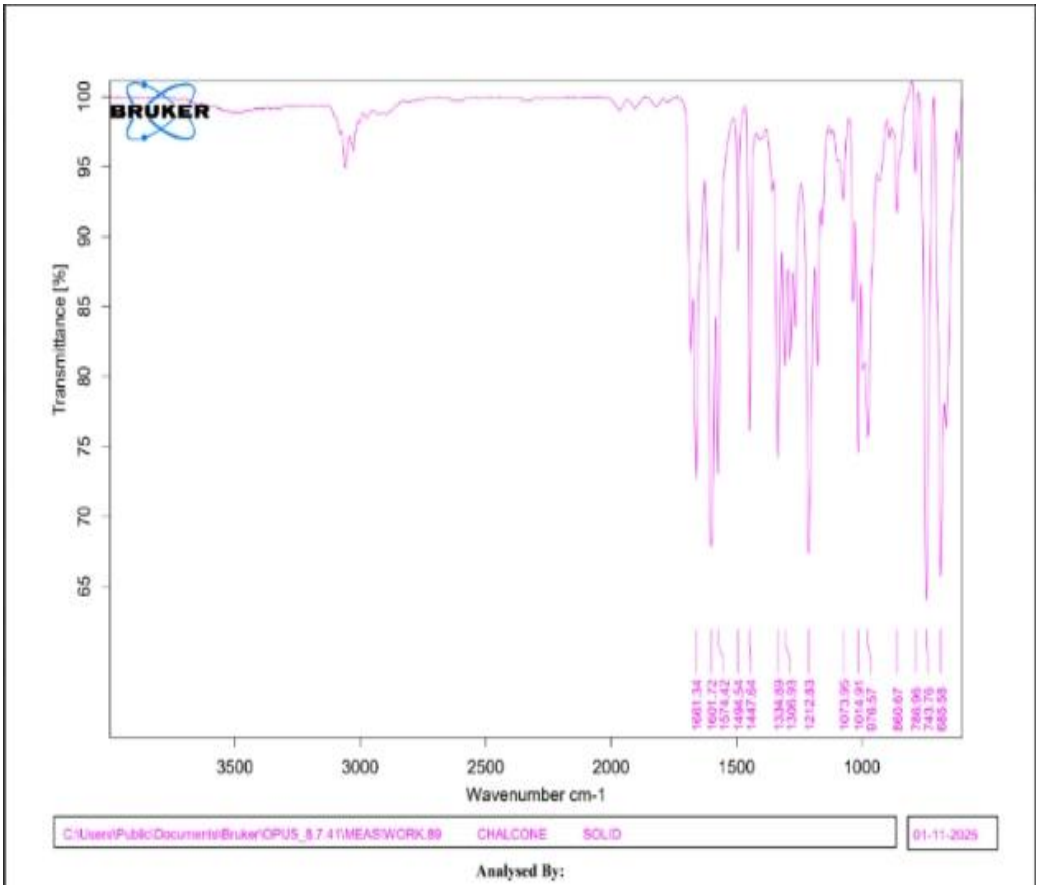

Fig No:19 FTIR Studies of chalcone (1,3-Diphenylprop-2-en-1-one)

The absorption spectrum of chalcone shows a peak around 3000cm^{-1}. As we observed the peak it indicates 3020cm^{-1} the presence of two aromatic rings and also observed the carbonyl group at 1660cm $^{-1}$ and it will be confirmed as chalcone .

4-CHLORO CHALCONE:

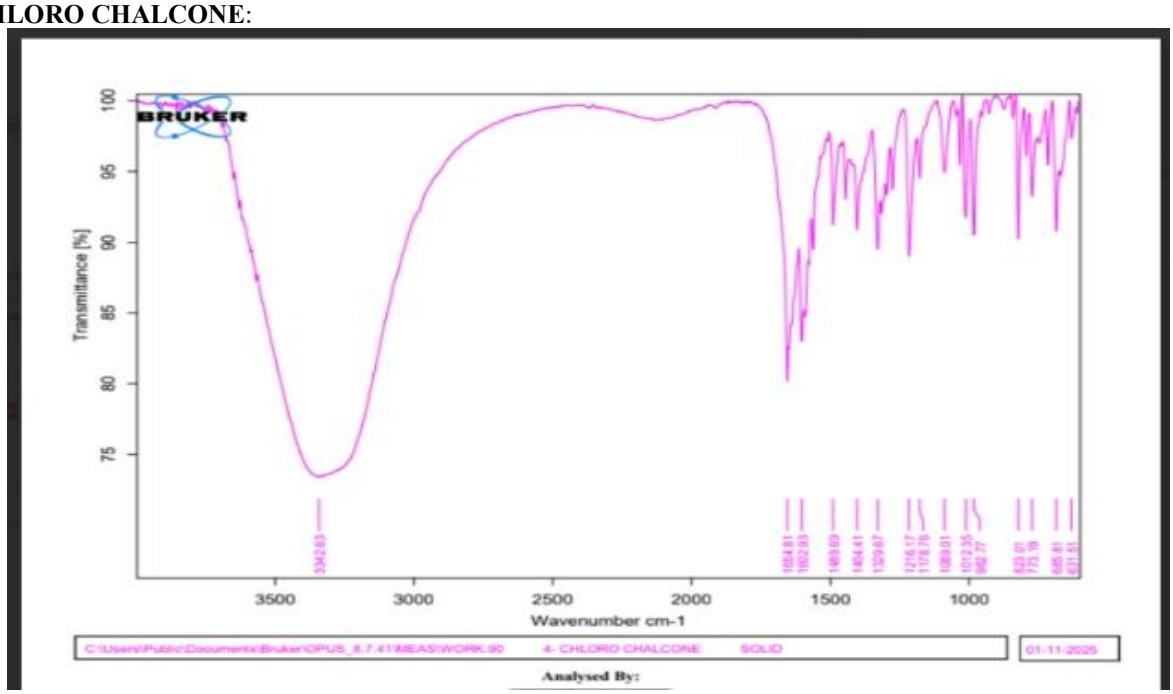

Fig No: 20

FTIR studies of 4-chloro chalcone (1-(4-chlorophenyl)-3-phenylprop-2-en-1-one)
The chlorine group exhibits absorption in range of 700-800cm^{-1} .As we observed the peak at 762cm^{-1} it indicates presence of cl functional group and it will be confirmed as 4-chlorochalcone.

ANTIMICROBIAL ACTIVITY OF CHALCONE:

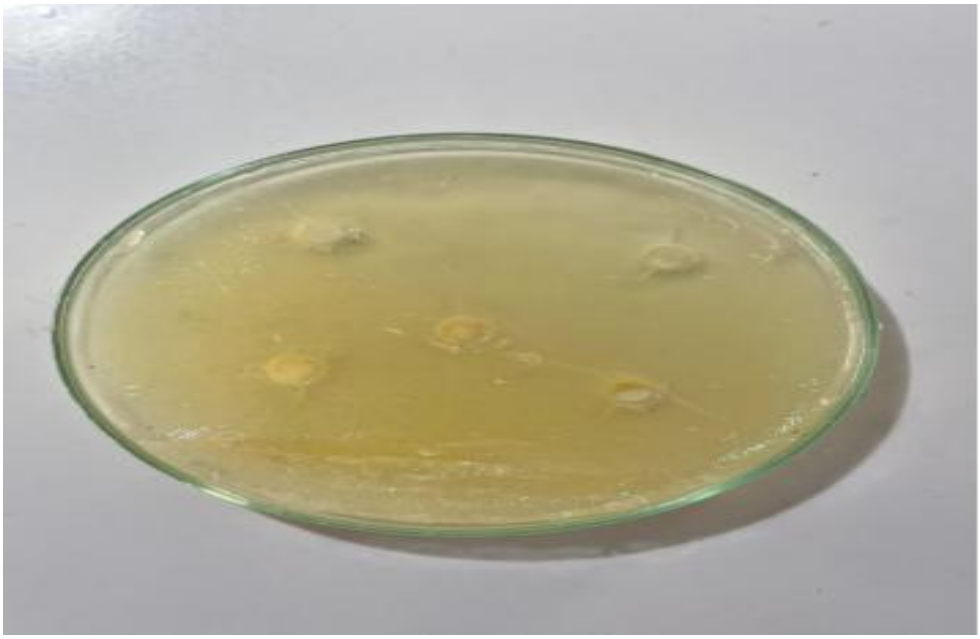

Fig No:21-Zone of inhibition for antibacterial activity of chalcone and amikacin

Chalcone shows moderate anti-bacterial activity. A zone of inhibition of chalcone is 30mm in the bacteria culture it has moderate- stronger than low-activity natural compounds but weaker than high potency like amikacin.

ANTIMICROBIAL ACTIVITY OF 4-CHLORO CHALCONE:

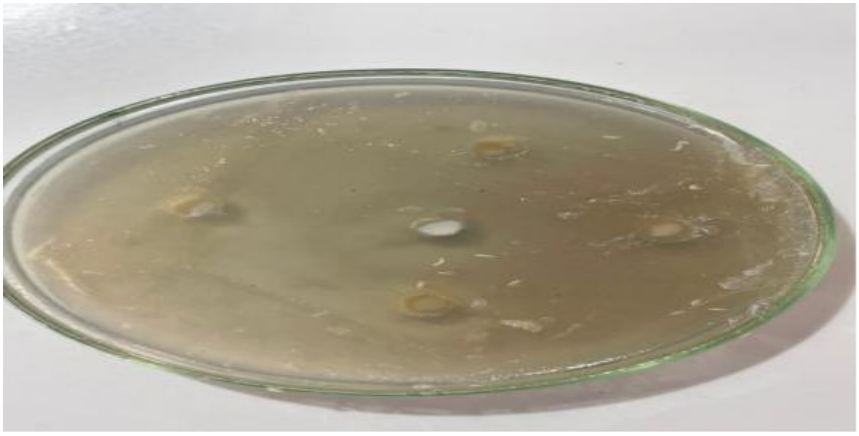

Fig No:22- Zone of inhibition for antibacterial activity of 4-chloro chalcone and amikacin

The 4-chloro chalcone shows stronger inhibition zone than chalcone. A zone of inhibition of 4-chloro chalcone is 29mm in the bacteria culture media.
Halogen substitution (Cl) enhances antibacterial activity by improving cell penetration and possibly interfering with bacterial enzymes. This makes 4-chloro chalcone a promising lead compound for further drug development.

Table no.2: - Diameters of zone of inhibition

S.NO	NAME OF THE TABLE	DIAMETER
1	CHALCONE (1,3-Diphenylprop-2-en-1-one)	30mm
2	4-CHLORO CHALCONE (1-(4-chlorophenyl)-3-phenylprop-2-en-1-one)	29mm

CONCLUSION

Chalcone and its derivatives represent a structurally versatile and biologically potent class of compounds with significant promise in antimicrobial drug development. Their core α, β-unsaturated carbonyl scaffold facilitates interactions with microbial enzymes, membranes, and nucleic acids, contributing to broad-spectrum activity against bacteria, fungi, and even resistant strains. The ease of synthetic modification particularly at the aromatic rings allows for fine-tuning of physicochemical properties such as lipophilicity, electronic distribution, and hydrogen bonding potential, which directly influence antimicrobial efficacy.

Numerous studies have demonstrated that the introduction of electron-donating groups (e.g., –OH, –OCH_3) or electron-withdrawing groups (e.g., –NO_2, –Cl) can significantly enhance antimicrobial potency. Derivatives bearing halogens, heterocycles, or nitrogen-containing moieties often show improved activity against Gram-positive and Gram-negative bacteria, as well as pathogenic fungi. These effects are attributed to increased membrane permeability, inhibition of microbial enzymes such as DNA gyrase and β-lactamase, and disruption of biofilm formation.

Importantly, chalcone derivatives have shown activity against multidrug-resistant organisms, including MRSA (*Methicillin-resistant Staphylococcus aureus*), *Candida albicans*, and *Pseudomonas aeruginosa*, underscoring their relevance in addressing the global challenge of antimicrobial resistance. Their relatively simple synthesis, favourable pharmacokinetic profiles, and low cytotoxicity further enhance their appeal as lead scaffolds in medicinal chemistry.

In conclusion, chalcone and its derivatives offer a compelling platform for the design of next-generation antimicrobial agents. Continued exploration of structure-activity relationships (SAR), mechanism of action studies, and formulation strategies will be essential to translate these compounds from bench to bedside. Their integration into modern drug discovery pipelines could contribute meaningfully to the development of safe, effective, and resistance-breaking therapies for infectious diseases.

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