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Biological Activities of Chalcones

Neesha Yadav[1], Rajesh Jale[2]
Lecturer (Chemistry), Government Polytechnic College, Neemrana, Kotputli-Behror-301705, Rajasthan

Abstract: ***Chalcone natural or synthetic and chalcone derivatives have exhibited different types of biological activities. Chalcone is widely available in nature and due to its broad spectrum of biological activities, this moiety is often used in molecular design strategies. In this article I have summarised literature evidence on biological activities of chalcone derivatives.***
Keywords: Natural chalcone, Derivative, Drugs, Biological activities, Licochalcone, Inhibitory Activity.

I. INTRODUCTION

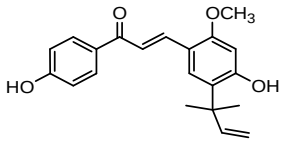
Chalcones are the precursor for synthesis of different classes of flavanoids, viz, dihydrochalcone, flavanones, flavones, flavonols, aurones and isoflavanones. Chalcones are also used in the production of pneumatic liquid crystals and photosensitive polymers.[1] Licochalcone A, an oxygenated chalcone isolated from the root of Chinese liquorice is found to inhibit fumarate reductase, a selective target present in parasite mitochondria.[2] Chalcone is a biosynthetic product of Shikimate pathway. Chalcones (1,3-diaryl propenone or 1,3-diphenyl-2-propen-1-one) constitute an important natural product which possess a wide range of biological activities, such as antiviral, antioxidant, antibacterial, antifungal, antitumor, anti-inflammatory, antimutagenic and antimicrobial. Certain prenylated chalcones isolated from *Sophara subprostrata* have shown potent inhibitory action on ulcer formation. Antimalarial activity is also shown by Licochalcone A and other oxygenated chalcones. A number of chalcone derivatives have also been found to inhibit several important enzymes in cellular systems including xanthine oxidase,[3] aldose reductase,[4] epoxide hydrolase,[5] protein tyrosine kinase[6,7] and quinone reductase.[8]

II. BIOLOGICAL ACTIVITIES OF CHALCONES

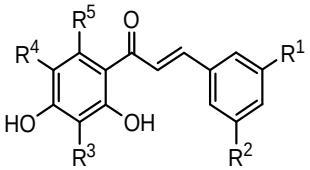
A. *Antibacterial Activity*

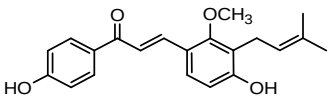
The antibacterial activity of chalcones is being increasingly documented. Many research groups either isolated and identified the structure of chalcones that possess antibacterial activity, or synthesized or modified natural chalcones. The bactericidal effects have been related to the ability of the α, β-unsaturated ketone to undergo conjugated addition to a nucleophilic group like a thiol group. Licochalcone A **(1)** and Licochalcone C **(2)** showed potent antibacterial activity especially to *Bacillus subtilis, Staphylococcus aureus* and *Micrococcus luteus.* Antibacterial study of Licochalcone A was studied by Tsukiyama et al.[9] on Gram-positive bacteria including spore-forming bacteria, such as the genera *B. coagulans, B. subtilis* and *B. stearothermophilu* (MIC = 2μgmL^{-1}) as well as *C.sporogenes* (8μgmL^{-1}) and toxin-producing bacteria such as *B. cereus* (3μgmL^{-1}) and *S. aureus* (3μgmL^{-1}). It is also effective against *Lactobacillus acidophilus, L. plantarum, Enterococcus, E. faecium* and active against *S. lactis* and *S. Mutans.*

Friis-Moller et al.[10] studied inhibitory effect of Licochalcone on various bacterial strains - *Legionella pneumophila, L.longbeacheae, L.wadsworthii, L.bozemanii, L.dumoffi* and *L.feelei.* Fukai et al.[11] have found inhibitory activity against the *Helicobacter pyroli.* Kromann et al.[12] studied Licochalcone A analogs against *S. aureus* and showed that the free hydroxyl group in 4-position of ring B was necessary for the antibacterial activity. Haraguchi et al.[13]found that strong lipophilic character of the molecule plays an essential role in the antibacterial effect.



Licochalcone A (1)





Licochalcone C (2)

(3) R^1,R^3,R^4,R^5= H R^2= OH

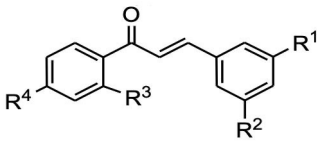
(4) R^1,R^2,R^3, R^4= H R^5= OH

(5) R^1,R^2= H R^3,R^4= CH_3 R^5= OCH_3

Fig. 1: Structure of Chalcone Derivatives (1-5)

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Very good antibacterial activity has been exhibited by isoliquiritigenine **(3)** against *S.aureus, S. epidermidis* and *S.haemolyticus*[14] and pinocembrin chalcone **(4)** against *S.Aureus.*[15] Chalcone **(5)** isolated from Dalea versicolor[16] exhibited antibacterial effect individually and in synergy with known antibiotics like Berberin, Erythromycin and Tetracycline towards the human pathogen *S. aureus* and the opportunistic pathogen *B.cereus*. Nielsen et al.[17] studied 4-carboxy chalcones **(6)** substituted in ring A and showed that many of these compounds were highly potent antibacterial compounds. The activity of these chalcones was correlated with the lipophilicity of the substituents in ring A. The lipophilicity of the substituent in ring A is essential for the activity. The lipophilic compounds are very potent and the activity gradually decreased as the substituents becomes more polar. Chalcones **(6)** and **(7)** had an inhibitory effect on bacterial growth but did not cause bacterial killing even at concentration of 16 times of the MIC, thus proving a bacteriostatic profile. The mechanism of the carboxy chalcones activity was different from that of hydroxychalcones, as the former were bacteriostatic, while the latter were bactericidal.[17] Chalcones **(8)** and **(9)** with a 2-hydroxyl group in ring B and a 3-chloro or 3-iodo group in ring A demonstrated the strongest anti-TB activity, with 90-92% inhibition, against *Mtb* H37Rv at a drug concentration of 12.5µg/mL.[18]



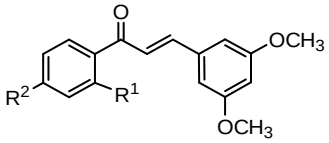
6. R^1,R^2=CF_3 R^3=H R^4=COOH
7. R^1,R^2=Br R^3=H R^4=COOH
8. R^1=Cl R^2,R^4=H R^3=OH
9. R^1=I R^2,R^4=H R^3=OH

Fig. 2: Structure of Chalcone Derivative (6-9)

B. Antileishmanial activity

Leishmaniasis is a group of prevalent diseases caused by protozoan parasites belonging to the genus *leishmania*. Synthetic and naturally occurring chalcone derivatives are reported to be potential agents against Leishmania parasites in a number of *in vitro* and *in vivo* assays. Chen et al.[2] demonstrated that Licochalcone A **(1)** inhibited the activities of both nicotinamide adenine dinucleotide reduced-fumarate reductase (NADH-FRD) and succinate dehydrogenase (SDH) in the permeabilized promastigotes in a concentration-dependent manner. Licochalcone A also inhibited the activities of SDH, NADH dehydrogenase (NDH), succinate-cytochrome C reductase (SCC) and NADH-cytochrome C reductase (NCC).

Licochalcone A probably first inhibits the FRD of the parasite, then influences the parasite respiratory chain and affects the function and ultrastructure of the parasite mitochondria and finally kills the parasite. Licochalcone C **(2)** inhibits the growth of the *L.major* parasite to the same extent as Licochalcone A does.[19] Two other chalcones **(10)** and **(11)** which showed potent activity against both extra and intracellular forms of Leishmania parasites also exhibited concentration and time dependent inhibitory effects on the activity of solubilised FRD in the parasite (IC_{50} = 153 and 118µM, respectively). Zhai et al.[20] tested chalcones **(12-14)** by inhibiting *in vitro* growth of *L. major* promastigotes (IC_{50} in the range of 4.0 -10.5µM) measured by ^{3}H-thymidine incorporation and *L.donovani* amastigotes (IC_{50} in the range of 0.65 -6.1µM) in human monocyte-derived macrophages (MDM). These compounds also inhibited the respiration of the parasites and the activity of mitochondrial dehydrogenases. The antileishmanial activity of oxygenated chalcones might be as a result of interference with the function of the parasite mitochondria.

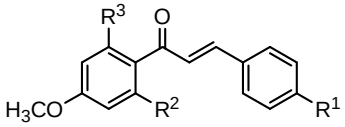


(10) R^1= H, R^2= $OCH_2CH=CH_2$
(11) R^1= H, R^2= OC_4H_9
(12) R^1= OH, R^2= H
(13) R^1, R^2 = H
(14) R^1= H, R^2= OH

Fig. 3: Structure of Chalcone Derivatives (10-14)

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Further, 2′,6′-dihydroxy-4-methoxychalcone **(15)**[21] showed a significant activity *in vitro* against promastigotes and intracellular amastigotes of *Leishmania amazonensis*, with 50% effective doses of 0.5µg/mL and 24µg/mL respectively. Its inhibitory effect on amastigotes is apparently a direct effect on the parasites and is not due to activation of the nitrogen oxidative metabolism of macrophages, since the production of nitric oxide by both unstimulated and recombinant gamma interferon-stimulated macrophages decreased rather than increasing with compound **(15).**

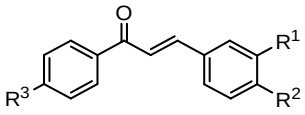


(15) R_2=R_3= OH, R=H
(16) R_2=R_3=$OCOCH_3$, R_1=H
(17) R^1=R^3=$OCOCH_3$, R_2=OH
(18) R^1=R^2=R^3=$OCOCH_3$
Fig. 4: Structure of Chalcone Derivatives (15-18)

Hermoso et al.[22] prepared dihydrochalcone derivatives **(16)** to **(18)** in order to study their effect on the activity against *L. braziliensis*, *Leishmania tropica* and *Leishmania infantum*. The substitution of the methoxy group at C-4 (ring B) by an acetate group increased both the activity and toxicity. However, a replacement of methoxy group at C-4 by an O-tetra-acetyl-β-D-glucosyl group increased the activity by almost 3-folds without increasing cytotoxicity.
Analysis of *in vitro* antileishmanial activity of chalcone derivatives by Nielsen et al.[23] indicates that ring B substitution did not play a major role for the antileishmanial activity, but substitution of hydroxyl groups by acetate groups not only increased the activity but also decreased the cytotoxicity to murine macrophages J774.

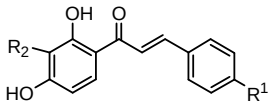
C. Antifungal activity

Chalcone derivatives also exhibit antifungal activity. It only shows activity against dermatophytes and not other types of fungi. Dermatophytes are a group of fungi which characteristically infect the keratinized areas of the body and dermatomycoses are very difficult to eradicate. Lopez et al.[24] tested chalcones **(19-22)** against a panel of human pathogenic fungi using the agar dilution method.



(19) R^1=R^3=H, R^2=NO_2
(20) R^1= OCH_3, R^2=R^3=H
(21) R^1=R^3=H, R^2= CH_3
(22) R^1=OCH_3, R^2=H, R^3=Br
Fig. 5: Structure Chalcone Derivatives (19-22)

SAR (Structure Activity Relationship) was done to observe the influence of the substituents on ring A. Firstly, electron donating groups tended to weaken the antifungal activity and secondly, the electron-withdrawing groups in the *p*-position increased the potency. Nevertheless, when the NO_2 or Cl group is in 2-position, a decrease in the activity is observed suggesting that the presence of these group in the ortho-position of ring could introduce important steric effects that results from the size of substituents and the repulsion between them.
The prenylated chalcones **(23)** and **(24)**[25] isolated from the leaves of *Maclura tinctoria* were found active against fungal pathogens *Candida albicans* with IC_{50} 3µg/mL and 15µg/mL respectively. The methanolic extract of *Zuccagnia punctata*[26] consisting of 2′,4′-dihydroxy-3′-methoxychalcone **(25)** and 2′,4′-dihydroxychalcone **(26)** displayed very good activities against *Phomopsis longicolla* Hobbs CE117 with MIC 6.25µg/mL and 3.12µg/mL respectively. *P.longicolla* is a primary agent of seed decay, a highly severe pathogen that affects soybean seed's quality and yield, and is present in almost every region of soybean production in the world. *C.truncatum* is among the most common soyabean pathogens. It is the causative agent of soyabean anthracnose, a disease acquired mainly in the last growing step that affects stems and pods diminishing the number of seeds and their weight.

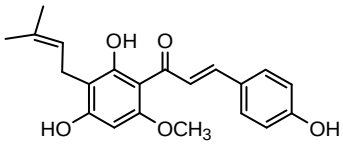


(23) R^1=OH, R^2=CH_2-CH=$C(CH_3)_2$
(24) R^1=OH, R^2=$CH_2CH(OH)C(CH_3)$=CH_2
(25) R^1=H, R^2=OCH_3
(26) R^1=R^2=H

Fig. 6 : Structure Chalcone Derivatives(23-26)

D. Antiviral activity

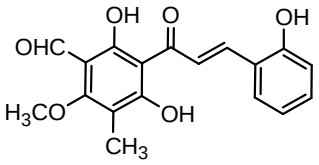
Chalcones exhibits potent inhibitory activity against plant viruses and human rhinoviruses. The variable antiviral activity of chalcone suggests that the activity of each chalcone depends on specific substitution patterns. Hydroxy and methoxy substituted chalcone derivatives were investigated by Onyilagha et al.[27] and Malhotra et al.[28] for activity against tomato ring spot nepovirus (ToRSV) infectivity.



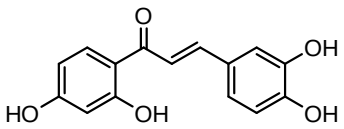
(27) Xanthohumol

Fig. 7: Structure of Chalcone Derivatives (27)

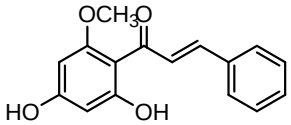
Wang et al.[29] reported that Xanthohumol **(27)** was a selective inhibitor of HIV-1 and may represent a novel therapeutic agent for HIV-1 infection. The target of Xanthohumol on HIV-1 may lie on the steps of post reverse transcription. Interestingly, Wu et al.[30] demonstrated that chalcone **(28)** from the genus *Desmos* showed potent anti-HIV activity (EC_{50} 0.022µg/mL) with a good therapeutic index (TI) with value 489. A C-4 methoxy group in the chalcone skeleton may be critical for anti-HIV activity. On the other hand, Ru(II)/Ru(III) polypyridyl complexes containing 2,6-(2′-benzimidazolyl)-pyridine/chalcone as co-ligand[31] inhibited HIV replication by 50% with a concentration of 0.1µg/mL.



(28)



(29)



(30)

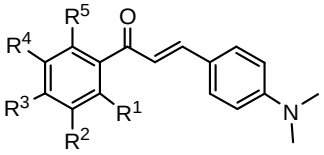
Fig. 8: Structure of Chalcone Derivatives (28-30)

It has been showed that Butein **(29)** at the concentration of 50µg/mL caused more than 50% inhibition of HIV-1 protease.[32] Cardamonin **(30)** showed anti-HIV activity with IC_{50} = 31µg/mL.[32]

E. Anti-inflammatory activity

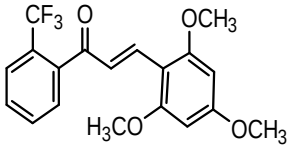
The inhibition of prostaglandin E2 (PGE2) and nitric oxide (NO) production has been proposed as a potential therapy for different inflammatory disorders. Release of large amounts of NO may lead to tissue damage. In the inflammatory diseases such as rheumatoid arthritis, excessive NO production by activated macrophages has been observed. Therefore, it would be interesting to develop potent and selective inhibitors of NO for potential therapeutic use.

Chalcone **(31)** was significantly active as a scavenger of superoxide anion generated by stimulated human neutrophils or by the hypoxanthine/xanthine oxidase system (HX/XO), with IC_{50} values of 0.1µM and 0.3µM, respectively. It inhibited the inducible NO synthase (iNOS) expression through a superoxide-dependent mechanism in stimulated mouse peritoneal macrophages and protected cells against oxidant stress. Herencia et al.[33-36] tested a series of chalcone derivatives for possible anti-inflammatory effect.



(31) $R^1=R^4=R^5=H$, $R^2=R^3=OH$
(32) $R^1=R^5=OCH_3$, $R^2=R^3=R^4=H$
(33) $R^1=R^4=OCH_3$, $R^2=R^3=R^5=H$
Fig. 9 : Structure of Chalcone Derivatives(31-33)

Chalcones **(32)** and **(33)** caused a concentration dependent inhibition of the production of NO with IC_{50} values of 0.6μM and 0.7μM respectively, whereas 2′,4′-dimethoxylation, trimethoxylation due the lack of methoxylation, as well as dichlorination led to less active or inactive compounds. The active compounds could display their inhibitory profile against NO and PGE2production by acting as inhibitors of inducible NO synthase and cyclooxygenase-2 expression.

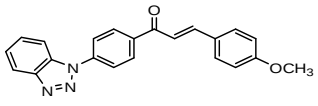


(34)
Fig. 10: Structure of Chalcone Derrivative (34)

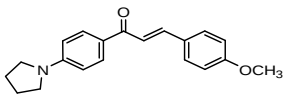
Trimethoxychalcone derivatives containing various patterns of fluorine, were evaluated by Rojas et al.[37] for their influence on nitric oxide production. 2,4,6-Trimethoxy-2′-trifluoromethylchalcone **(34)** inhibited the production of NO and prostaglandin E2 in lipopolysaccharide-stimulated RAW 264.7 macrophage cells. The inhibition (76.3% inhibition at the concentration of 10mM) was dose-dependent without any evidence of a cytotoxic effect.
Dimethylamino-chalcones[38] were also studied *in vitro* for their inhibitory activity on the production of NO and PGE2 mediators produced by lipopolysaccharide (LPS)-stimulated RAW 264.7 macrophage cells.

F. Antifilarial activity

Antifilarial activity of chalcone derivatives were evaluated by Awasthi *et al.*[39]on *Setaria cervi* using glutathione-*S*-transferase (GST) enzyme as a drug target. The compounds 1-(4-benzotriazol-1-yl-phenyl)-3-(4-methoxyphenyl) prop-2-en-1-one (**35**) and 3-(4-methoxyphenyl)-1-(4-pyrrolidin-1-yl-phenyl)prop-2-en-1-one **(36)** showed a significant suppression ($P < 0.01$) in GST activity of adult female parasite extract at 3μM concentration *in vitro*. However, GST activity was detected along with depletion in GSH level. More or less, all compounds showed a paralyzing effect on the motility and viability of parasites, ranging from 25% to 97% inhibition. The compounds **(35)** and **(36)** exhibited major irreversible effects on viability and resulted in parasite death and also inhibited the GST activity by 84-100% *in vitro.* Anti-filarial activity of chalcones on GST of adult parasites was reported for the first time.



(35)



(36)
Fig. 11: Structure of Chalcone Derivatives (35-36)

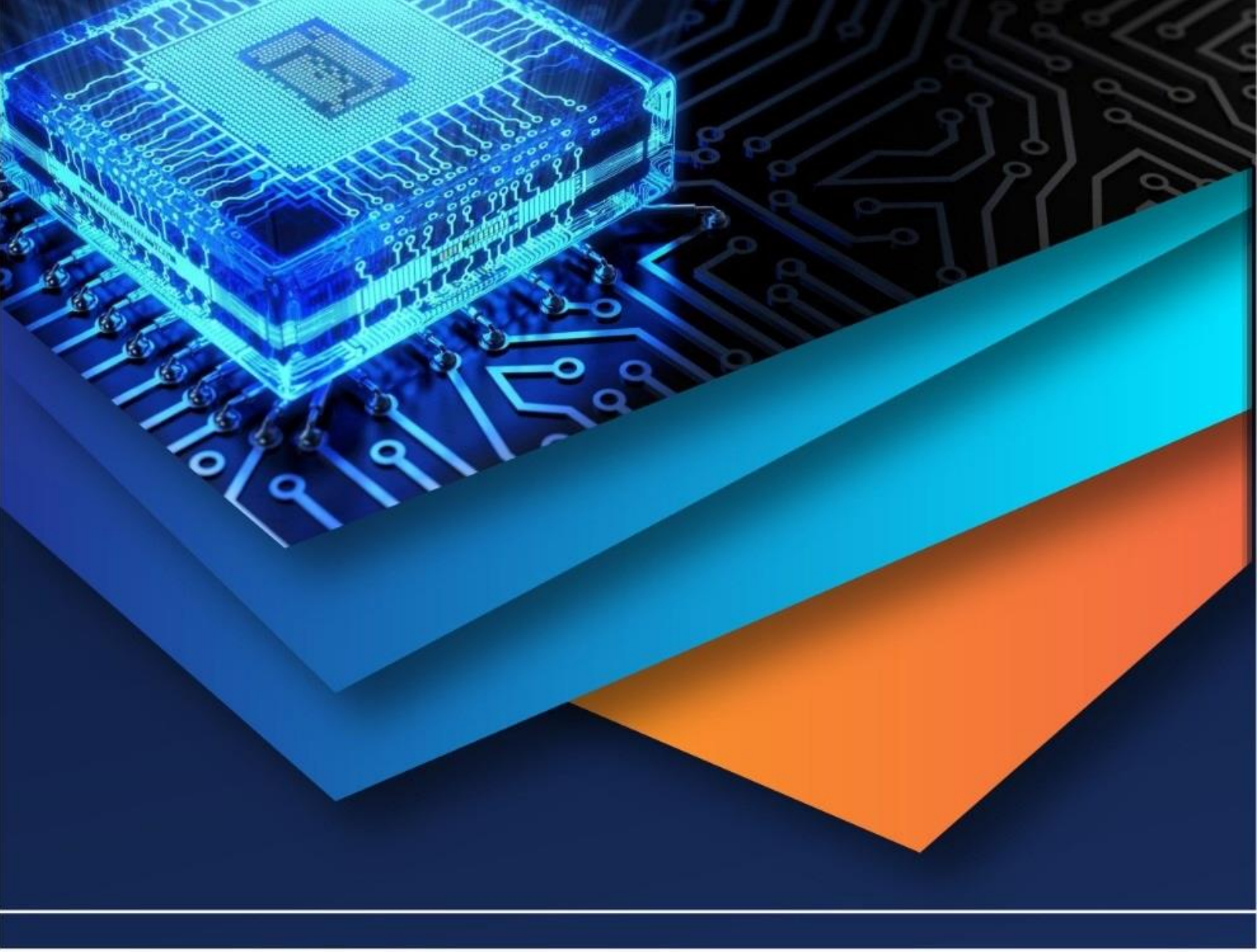
III.CONCLUSIONS

This article has summarized different biological activities of natural and synthetic chalcone like anti-filarial, anti-inflammatory, antiviral, antileishmanial, antifungal and antibacterial activity. Their importance stems from this broad bioactivity and ease of synthesis are a driving force for researchers to synthesize new derivatives of chalcone for therapeutic applications. Researchers can modify the chalcone scaffold to develop potent drug candidate specially by incorporating heterocyclic ring (N,O,S) to enhance activity against specific disease targets.

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