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In silico Evaluation of Natural chalcones as Aromatase and EGFR Tyrosine Kinase inhibitors to Combat Breast and Ovarian Cancers

M.Vijaya Jyothi[1], S.Seema Anjum[2], S.Ayisha Sultana[1], S.B.Alfeez Nas, P.Ranjitha, G.Gowthami

[1]Department of Pharmaceutical Chemistry,Raghavendra Institute of Pharmaceutical Education and Research, Anantapuramu, Andhra Pradesh, India-515721
[2]Department of Pharmaceutics, Raghavendra Institute of Pharmaceutical Education and Research, Anantapuramu, Andhra Pradesh, India-515721

ABSTRACT

Chemically α, β unsaturated carbonyl compounds are known as Chalcones and these are naturally occurring antioxidant flavonoids present in plant kingdom. Owing to their antioxidant mechanism chalcones contribute several biological activities and serve as natural molecules to treat some diseases and ailments. In this study the author had made an effort to report the available natural chalcones and their botanical sources, prediction of possibility for synthesis and anticancer activity against breast and ovarian cancer by Insilco methods using aromatase and EGFR Tyrosine Kinase enzyme models. Insilco studies had divulged that chalcones are complying the molecular properties, drug likeliness assessment studies and binding affinities with the targeted proteins and chalcones can be considered as unique leads to develop neutraceuticals and novel anticancer agents to treat breast and ovarian cancers.

KEYWORDS: Natural chalcones, Swiss ADME, Molecular docking, Aromatase, EGFR Tyrosine Kinase, Anticancer activity.

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INTRODUCTION

Chalcones are a class of polyphenolic compounds of flavonoid family. Chalcones are commonly found in plants like hops, turmeric, and liquorice especially in families like the Compositae (Asteraceae), Moraceae, and Leguminosae (Fabaceae). They can be found in spices, medicinal herbs, and culinary plants [1] adding to their wide-ranging biological significance [2] as anticancer, anti-inflammatory, antimitotic, antioxidant, and cytotoxic qualities [3]. They play a crucial role as intermediates [4] in the biosynthesis of flavonoids and isoflavonoids. Natural chalcones possess two aromatic benzene rings connected by a three-carbon α, β-unsaturated carbonyl group (C=CH–C=O), forming a conjugated reactive system that can interact with cellular targets [5]. Many chalcones also possess hydroxyl (–OH) group e.g.Butein, Cardamonin, Xanthohumol or methoxy (–OCH_3) groups on the aromatic rings e.g. Flavokawain B. Some chalcones contain methyl groups e.g. Panduratin A, Licochalcone A, coumarine moiety e.g. Isoliquiritigenin, Phloretin and contribute various therapeutic activities [6, 7]. These compounds are highly versatile and concede structural modifications that can enhance their solubility and stability. The chemical properties of chalcones also make them effective in forming complexes with proteins or DNA, further expanding their therapeutic potential [8,9] and produce promising candidates for drug development and functional food applications [10]. The present manuscript listed the names of natural chalcones present in plants and reported biological activities in Table 1.

Table 1. List of natural Chalcones, plant source and their biological activities:

Name of Chalcone	Plant source (family)	Plant part	Biological activity
Licochalcone A	*Glycyrrhiza inflata* (Fabaceae)	Root	Anti-inflammatory, antioxidant, anticancer, antimicrobial
Licochalcone B	*Glycyrrhiza uralensis* (Fabaceae)	Root	Anti-inflammatory, antioxidant, hepatoprotective
Licochalcone C	*Glycyrrhiza glabra* (Fabaceae)	Root	Antioxidant, anti-inflammatory, antimicrobial
Licochalcone D	*Glycyrrhiza* spp. (Fabaceae)	Root	Anti-inflammatory, antioxidant, antimicrobial
Licochalcone E	*Glycyrrhiza* spp. (Fabaceae)	Root	Anti-inflammatory, antimicrobial, antioxidant
Xanthohumol	*Humulus lupulus* (Cannabaceae)	Flower (hops)	Antioxidant, anti-inflammatory, anticancer, antimicrobial
Panduratin A	*Boesenbergia pandurata* (Zingiberaceae)	Rhizome	Antibacterial, anti-inflammatory, anticancer
Cardamonin	*Alpinia katsumadai* (Zingiberaceae)	Seed / rhizome	Anti-inflammatory, antioxidant, anticancer
Lonchocarpin	*Lonchocarpus* spp. (Fabaceae)	Bark / root	Anticancer, antimicrobial
Isoliquiritigenin	*Glycyrrhiza glabra* (Fabaceae)	Root	Antioxidant, anti-inflammatory, anticancer
Phloretin	*Malus domestica* (Rosaceae)	Fruit, leaf	Antioxidant, anti-inflammatory, antimicrobial
Butein	*Butea monosperma* (Fabaceae)	Flower	Antioxidant, anti-inflammatory, antidiabetic, anticancer

Helichrysetin	*Helichrysum* spp. (Asteraceae)	Flower	Antioxidant, anti-inflammatory
Bavachalcone	*Psoralea corylifolia* (Fabaceae)	Seed	Antibacterial, antifungal, anticancer
Isobavachalcone	*Psoralea corylifolia* (Fabaceae)	Seed	Antimicrobial, antioxidant, anticancer
Xanthoangelol	*Angelica keiskei* (Apiaceae)	Leaf sap	Antidiabetic, antioxidant, anticancer
Flavokawain A	*Piper methysticum* (Piperaceae)	Root	Anticancer, antioxidant
Flavokawain B	*Piper methysticum* (Piperaceae)	Root	Anticancer, anti-inflammatory
Dichamanetin	*Piper sarmentosum* (Piperaceae)	Leaf	Anticancer, antibacterial
Hydroxysafflor yellow A	*Carthamus tinctorius* (Asteraceae)	Flower	Antioxidant, anti-inflammatory, heart-protective
Echinatin	*Glycyrrhiza echinata* (Fabaceae)	Root	Antioxidant, anti-inflammatory
Kanzonol C	*Glycyrrhiza* spp. (Fabaceae)	Root	Antimicrobial, anticancer
Kanzonol Y	*Glycyrrhiza* spp. (Fabaceae)	Root	Antioxidant, antimicrobial
Aurentiacin A	*Dorstenia* spp. (Moraceae)	Root / twig	Antimicrobial, antioxidant
Pinostrobin chalcone	*Boesenbergia pandurata* (Zingiberaceae)	Rhizome	Antioxidant, antimicrobial, anticancer
Bavachinin	*Psoralea corylifolia* (Fabaceae)	Seed	Anti-inflammatory, estrogenic
Sappachalcone	*Caesalpinia sappan* (Fabaceae)	Heartwood	Antioxidant, anti-inflammatory, antimicrobial
Derricin	*Derris* spp. (Fabaceae)	Root	Anticancer
Derricidin	*Derris* spp. (Fabaceae)	Root	Anticancer
Paratocarpin A	*Paratocarpus* spp. (Moraceae)	Wood / root	Antimicrobial, anticancer
Paratocarpin E	*Euphorbia humifusa* (Euphorbiaceae)	Whole plant	Anticancer, antibacterial
Bakuchalcone	*Psoralea corylifolia* (Fabaceae)	Seed	Antimicrobial
Calythropsin	*Calythropsis* spp. (Asteraceae)	Wood	Anticancer
Pedicin	*Fissistigma* spp. (Annonaceae)	Leaf / root	Antioxidant, antimicrobial
Munchiwarin	*Crotalaria trifoliata* (Fabaceae)	Root	Anticancer
Prorepensin	*Dorstenia prorepens* (Moraceae)	Twig	Antimicrobial, anticancer
Morachalcone A	*Morus* spp. (Moraceae)	Root bark	Anticancer, anti-inflammatory
Hesperidin methyl chalcone	Citrus fruits (Rutaceae)	Peel	Antioxidant, anti-inflammatory
Chalcone (generic)	Many plants (various families)	Root, flower, bark	Antioxidant, anti-inflammatory, anticancer
Phenstatin	Synthetic analogue (Combretaceae inspired)	—	Anticancer (tubulin inhibitor)
Pashanone	Medicinal plants (various)	Root / wood	Antifungal, anticancer
Garcinol	*Garcinia indica* (Clusiaceae)	Fruit rind	Antioxidant, anti-inflammatory, anticancer
Isocordoin	*Lonchocarpus* spp. (Fabaceae)	Root	Antiprotozoal, anticancer
Lophirone A	*Lophira alata* (Ochnaceae)	Stem bark	Anticancer
Lophirone E	*Lophira lanceolata* (Ochnaceae)	Stem bark	Antimalarial, antiparasitic
Apigenin (flavone)	Parsley, chamomile (Apiaceae, Asteraceae)	Leaf, flower	Antioxidant, anti-inflammatory, anticancer
Naringenin (flavanone)	Citrus fruits (Rutaceae)	Peel, fruit	Antioxidant, anti-inflammatory, hepatoprotective

Chalcones, containing polyphenolic flavonoids exhibit anticancer activity through antioxidant mechanism by preventing oxidative damage to DNA, proteins, and lipids, which can lead to mutations and cancer initiation [11]. They also inhibit cancer cell proliferation by modulating cell cycle proteins and oncogenes involved in uncontrolled cell division. Additionally, antioxidants can trigger apoptosis, or programmed cell death in cancer cells, selectively cause cell death while sparing healthy cells [12]. They modulate important signalling pathways, such as NF-KB and MAPK, that are often overactive in cancer, reducing inflammation, preventing metastasis, and promoting tumour cell death [13]. In the present study the author has explained the impact of abnormal oestrogen levels owing to breast and ovarian cancers and predicted binding capacity of natural chalcones to aromatase enzyme and EGFR Tyrosine Kinase in regulation of hormonal balance and their anticancer potential to develop novel leads using *insilico* models [14]

1.1Role of Aromatase enzyme in Breast and Ovarian cancers

Aromatase is a key enzyme in oestrogen biosynthesis, responsible for converting androgens (such as testosterone and androstenedione) into oestrogens (oestradiol and estrone). While this process is essential for normal reproductive function, abnormal or excessive aromatase activity has been strongly linked to hormone-dependent cancers, particularly breast and ovarian cancers [15].

In breast cancer: aromatase is expressed not only in the ovaries but also in peripheral tissues such as adipose tissue, breast stromal

cells, and even within the tumour microenvironment. Postmenopausal women, who no longer produce significant ovarian oestrogen, rely heavily on aromatase in fat tissue for oestrogen synthesis. Elevated local oestrogen levels in the breast promote proliferation of oestrogen receptor–positive (ER+) tumour cells, driving tumour growth and progression. Thus, aromatase inhibitors (AIs) block the conversion of androgens to oestrogen and widely used as first-line therapy in postmenopausal women with ER+ breast cancer [16,17].

In ovarian cancer, aromatase expression has also been detected in ovarian tumour tissue. Increased aromatase activity enhances intra tumour oestrogen production, which further stimulates growth of oestrogen-sensitive ovarian cancer cells. Oestrogen generated within the ovarian tumour promotes cell proliferation, inhibits apoptosis, and supports angiogenesis, all of which contribute to cancer progression. In genetically predisposed women (e.g., BRCA mutations), this effect is even more pronounced due to compromised DNA repair mechanisms. Clinical evidence indicates that high aromatase expression in ovarian cancer is often associated with more aggressive disease and poor prognosis [18,19].

1.2 Role of EGFR Tyrosine Kinase in Breast and Ovarian Cancer

Epidermal Growth Factor Receptor (EGFR) is a trans membrane receptor tyrosine kinase that regulates vital cellular processes such as growth, survival, differentiation, and migration. When activated by binding to its ligands, EGFR undergoes dimerization and auto phosphorylation of tyrosine residues, triggering multiple downstream signalling pathways, including the MAPK/ERK and PI3K/AKT cascades. While essential for normal cell physiology, abnormal EGFR signalling is strongly associated with tumour genesis in breast and ovarian cancers [20]. chemotherapy and targeted therapies. This makes EGFR both a prognostic biomarker and a potential therapeutic target in aggressive breast cancer subtypes [21]. Targeted therapies such as tyrosine kinase inhibitors (TKIs) and monoclonal antibodies have been explored to inhibit EGFR signalling, though their effectiveness varies depending on tumour subtype and genetic background [22,23].

1.3 Effect of Chalcones on Oestrogen and other Hormones

Chalcones influence oestrogen and other hormones through multiple mechanisms. Some act as phytoestrogens, binding to oestrogen receptors (ERα and ERβ) to either mimic or block oestrogen effects, depending on the tissue and concentration [24]. Certain chalcones like xanthohumol, naringenin, and is liquiritigenin also inhibit aromatase, thereby reducing oestrogen synthesis. Others, such as **licoachalcones** and flavokawain B, may exhibit anti-androgenic effects by inhibiting enzymes like 5α-reductase, which lowers the conversion of testosterone to its more potent form, Dihydrotestosterone. Some chalcones also modulate insulin pathways, enhancing insulin sensitivity and supporting hormonal balance in metabolic disorders. Through these combined actions, chalcones can influence oestrogen, androgen, and insulin signalling pathways [25]. Some chalcones bind to oestrogen receptors (ERα, ERβ) and either mimic (agonists) or block (antagonists) the effects of oestrogen [26,27]. In this manuscript, chalcones and their remarkable effect on hormones are specified in Table:2

Table 2: List of some Chalcones and their effect on hormones

Name of the chalcone	Effect on Oestrogen / Hormones
Isoliquiritigenin	Binds ERα and ERβ (weak estrogenic). Can mimic or block estrogen depending on dose/tissue. Also modulates aromatase (estrogen synthesis).
Licochalcone A/B	Weak estrogenic activity; modulates ER signalling, anti-androgenic effect
Xanthohumol	**P**hytoestrogen - binds ERs, also **inhibits aromatase** and affects hormone-related cancers.
Bavachalcone / Isobavachalcone	Estrogen receptor modulators — may bind ER and affect transcription. Show estrogenic effects in bone, reproductive tissues.
Bavachinin	selective estrogen receptor modulator (SERM). Activates ERβ.
Flavokawain B	Anti-androgenic property; also affects apoptotic pathways in hormone-sensitive cancers.
Cardamonin	Blocks NF-κB and hormone-responsive cancer cell growth. May indirectly affect oestrogen pathways. inhibit 5α-reductase (good for prostate health, acne, etc.)
Apigenin	Weak phytoestrogen competes with oestradiol at ERs; may help balance oestrogen in oestrogen-dominant conditions.
Naringenin	Modulates oestrogen and androgen pathways, SERM-like behaviour in some tissues; also inhibits aromatase (CYP19 enzyme).

MATERIALS & METHODS

2.1 INSILICO DESIGNING Material

A) CHEM DRAW-

PerkinElmer created Chem Draw, a chemical structure drawing program that chemists use to produce realistic representations of molecules, processes, and chemical equations. It also includes capabilities for predicting NMR spectra, calculating molecular characteristics, and creating IUPAC names, making it indispensable for chemical research, publication, and education [28].

B) SWISS ADME 2.0

SwissADME is a free online tool developed by the Swiss Institute of Bioinformatics that predicts the pharmacokinetic properties,

drug-likeness, and medicinal chemistry friendliness of small molecules. It allows users to evaluate parameters such as absorption, distribution**,** metabolism, excretion (ADME), and toxicity based on molecular structure [29].

C) PUBCHEM

The National Centre for Biotechnology Information (NCBI) maintains PubChem, a free and publicly available database that contains detailed information on the chemical characteristics, structures, biological activities, and safety data of small molecules. It is often used in chemical research, drug development, and teaching, including tools for structure search, compound comparison, and bioassay data analysis [30].

D) CHIMERA SOFTWARE [1.18]

Chimera is a software for molecular modeling and visualization created by the UCSF Resource for Biocomputing, Visualization, and Informatics. It is commonly utilized for the interactive analysis and rendering of molecular structures, density maps, and associated data. The software offers various features such as structure editing, visualization of docking results, and the ability to generate high-quality images and animations suitable for publication.

E) MASTRO 12.8

Maestro serves as the graphical user interface (GUI) for Schrödinger's molecular modelling suite, which is utilized in drug discovery, computational chemistry, and molecular visualization. It offers a cohesive environment for activities such as molecular docking, dynamics simulations, protein-ligand interactions, and structure-based drug design [31,32].

F) ADMET lab 3.0

ADMET lab 3.0 is a cutting-edge online platform for predicting chemical compounds' ADMET characteristics (Absorption, Distribution, Metabolism, Excretion, and toxicity.It offers high-throughput screening capabilities for drug discovery by integrating more than 190 machine learning-powered predictive algorithms. By offering trustworthy insights on pharmacokinetics and toxicity, the technology improves early-stage drug development decision-making by assisting researchers in identifying good candidates and effectively weeding out inappropriate ones.[33]

2.2 Insilco methods

Chemical structures of the selected compounds were initially sketched using *ChemDraw* to construct two-dimensional molecular representations with clear stereo chemical orientation. The generated structures were then cross verified for accuracy and exported. For obtaining the corresponding Simplified Molecular Input Line Entry System (*SMILES*) notations, *PubChem* was utilized. To evaluate the drug-like potential of the compounds, Swiss ADME an online tool that predicts key physicochemical and pharmacokinetic properties was used. It provided insights such as compliance with Lipinski's Rule of Five, solubility, lipophilicity, bioavailability score, and gastrointestinal absorption. To predict important key parameters like gastrointestinal (GIAB) absorption, blood–brain barrier (BBB) permeability, skin permeability coefficient (log Kp), aqueous solubility, lipophilicity (log P), molar refractivity, topological polar surface area (TPSA), hydrogen bond acceptors (HBA), hydrogen bond donors (HBD), number of rotatable bonds (RB), aqueous solubility, and synthetic accessibility scores were produced by the tool. By feeding the algorithm the molecules' SMILES representations, these characteristics were computed using ADMET lab 3.0. For interaction studies between the ligands and target proteins, molecular docking was performed using *Maestro 12.8 (Schrödinger Suite)*. The protein structures were prepared through the Protein Preparation Wizard, followed by ligand optimization. Docking simulations were then executed using the Glide module within Maestro, generating docking scores, binding affinities, and interaction profiles. This step enabled prediction of the most favourable binding conformations and molecular interactions, providing valuable insights into the compounds' potential biological activity.[34]

2.2.1 MOLECULAR DOCKING

2.2.1 A Ligand preparation:

Using the 2D Sketcher module in Maestro (Schrödinger Suite), the test compounds' chemical structures were illustrated by entering their SMILES strings. The Lig Prep tool was used to optimise the ligand by performing structural optimisations, stereochemical modifications, and neutralisation of ionisation states. After that, the energy-minimized conformers were kept for docking experiments in the working directory.

2.2.1 A Protein Target Preparation:

Protein Preparation Wizard was used to process the receptor structure, which was obtained from the Protein Data Bank (PDB ID: 3EQM & 1M17). While chains B-F were eliminated to prevent duplication, chain A and its co-crystallized ligand, Aromatase & EGFR Transferase enzymes, were kept throughout refining. To reach a stable shape, the protein structure was optimised and minimised. The Ramachandran plot, which plots the allowable torsional angles (φ and ψ) of amino acid residues,was used to evaluate the improved protein's stereochemical reliability as shown in Fig.1&2

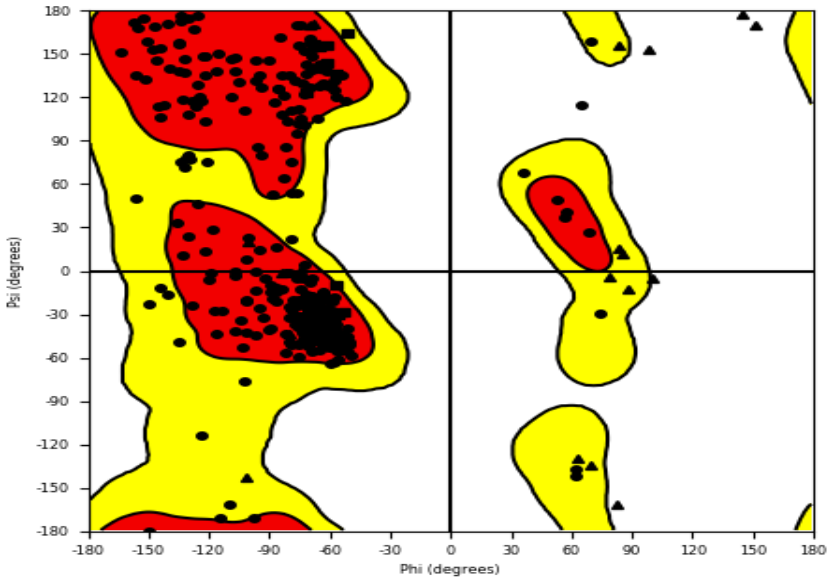


Fig.1 Ramchandran plot of enzyme 3EQM

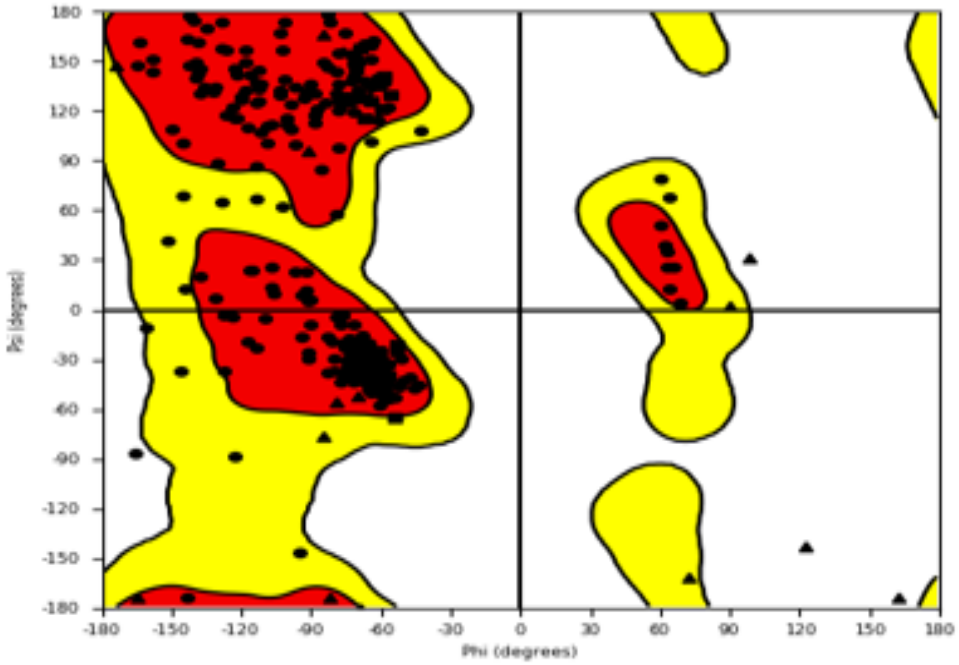


Fig.2 Ramchandran plot of enzyme 1M17

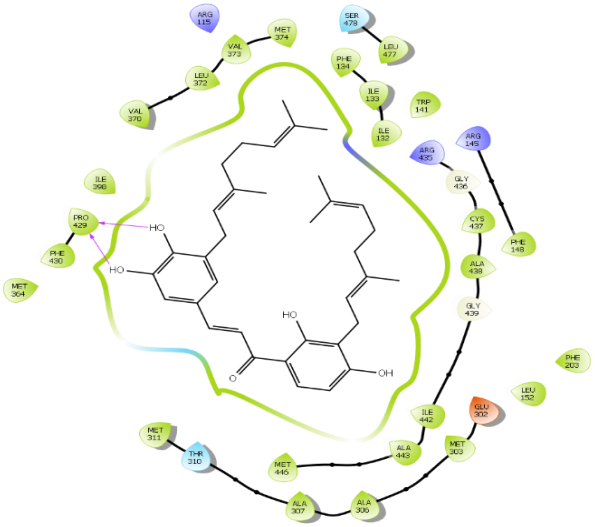
2.2.1 B Receptor Grid Generation:

To establish the docking site, a grid box was constructed around the binding pocket by selecting the atom of the co-crystal ligand. The dimensions of the docking grid were set at X = 60.07, Y = −7.07, and Z = 34.74 to ensure comprehensive coverage of the active site.

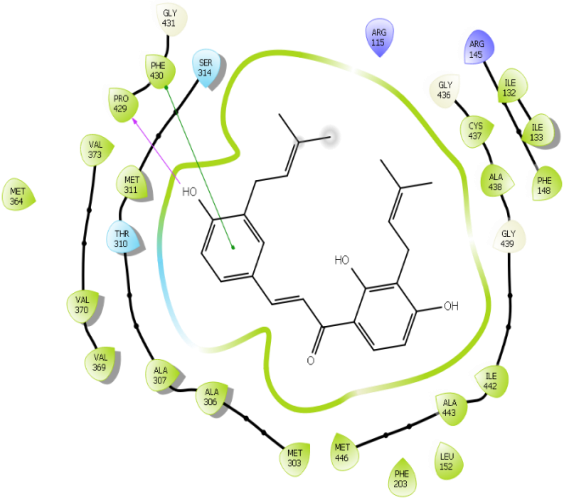
2.2.1 C Docking Process:

Molecular docking was performed using the Glide SP (standard precision) algorithm. Input files containing the receptor grid and ligand structures (saved as outmaegz files) were utilized to conduct the docking runs. The docked complexes were ranked according to their binding energy scores, with results listed from the most favourable to the least favourable interactions. The outcomes of the docking were compiled and visualized in Fig.3 & 4

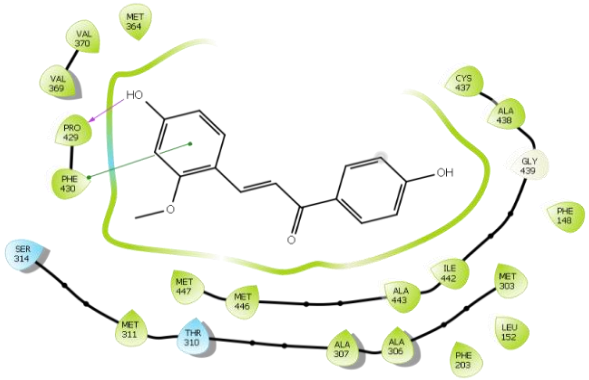
Fig.3 Ligand interactions of enzyme 3EQM with chalcones



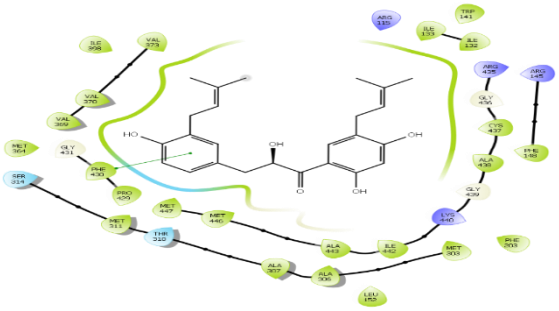
Prorepensin_CID_636780.1



Kanzonol C_CID_5316802.1

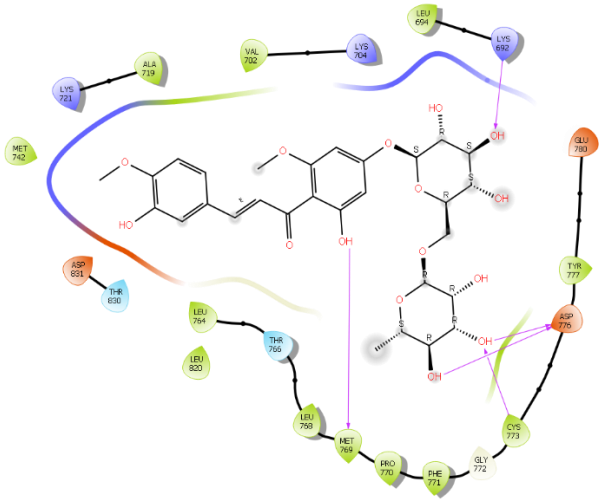


Echinatin_CID_6442675.1

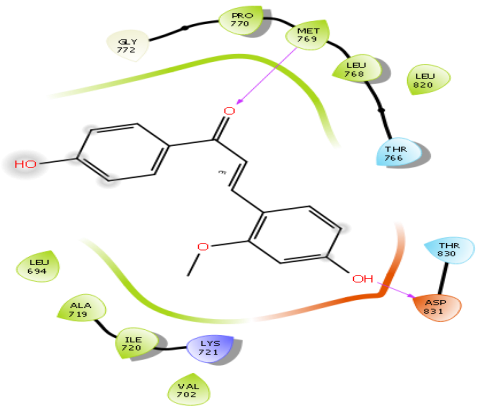


KanzonolY_CID_10001604.1

Fig.4 Ligand interactions of enzyme 1M17 with chalcones



Hesperidin methylchalcone_CID_6436550.1



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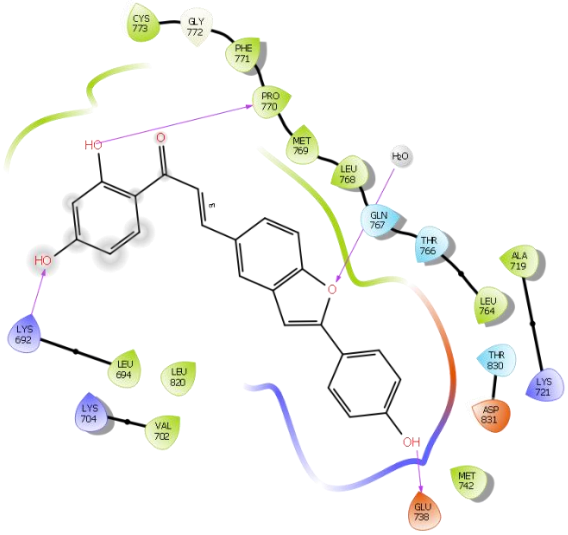
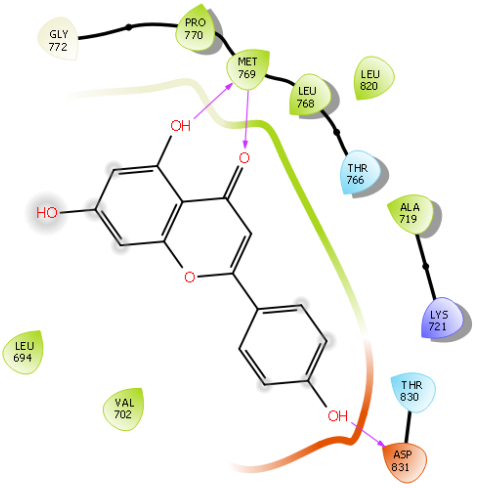


Lophirone E_CID_14376454.1



Apigenin_CID_52804

RESULT AND DISSCUSSION

Natural chalcones are α, β-unsaturated ketones (1,3-diaryl-2-propen-1-ones) that primarily exist in the (E)-configuration, which boosts their thermodynamic stability. Their conjugated C=C–C=O system contains electrophilic centres and an extensive π-electron system, contributing to their significant chemical adaptability and wide range of biological activities.

In this research, an extensive array of naturally occurring chalcones and related flavonoids was assessed. This collection included Licochalcones (A–E), Xanthohumol, Panduratin.A, Cardamonin, Lonchocarpin, Isoliquiritigenin, Butein, Helichrysetin, Bavachalcone, Isobavachalcone, Flavokawains (A and B), Dichamanetin, Xanthoangelol, Hydroxysafflor Yellow A, Aurentiacin A, Pinostrobin chalcone, Bavachinin, Sappanchalcone, Echinatin, Kanzonols (C and Y), Derricin, Derricidin, Paratocarpins (A and E), Bakuchalcone, Rubone, Calythropsin, Pedicin, Munchiwarin, Prorepensin, Morachalcone A, Hesperidin methyl chalcone, Chalcone, Phenstatin, Pashanone, Garcinol, Isocordoin, Lophirones (A and E), Apigenin, and Naringenin. Their physicochemical characteristics and molecular docking scores are compiled in Tables 3 and 4, respectively.

Table.3 List of compounds with physical properties

COMPOUNDS	LogP	M.R	TPSA	HBA	HBD	R.B	GIAB& BBB	Soluble class	Synthesis accesibility
1)Licochalcones-A	4.204	100.39	66760	4	2	6	HIGH&YES	Moderately soluble	3.23
2)Licochalcones-B	2.544	78.81	86.99	5	3	4	HIGH&YES	Soluble	2.80
3)Licochalcones-C	4.611	100.51	66.76	4	2	6	HIGH&YES	Moderately soluble	3.25
4)Licochalcones-D	4.152	102.53	86.990	5	3	6	HIGH&YES	Moderately soluble	3.33
5)Licochalcones-E	4.088		66.760	4	2	6	HIGH&YES	Moderately soluble	3.047
6)Xanthohumol	4.473	102.5	86.990	5	3	6	HIGH&YES	Moderately soluble	3.16
7)Panduratin-A	7.246	121.48	66.8	4	2	6	HIGH&YES	Poorly soluble	3.824
8)Cardamonin	3.018	76.79	66.76	4	2	4	HIGH&YES	soluble	2.62
9)lonchocorpin	4.925	92.39	46.53	3	1	3	HIGH&YES	Moderately soluble	3.51
10)Isoliquiritigen	2.918	72.32	77.76	4	3	3	HIGH&YES	soluble	2.52
12)Butin	2.582	74.34	97.99	5	4	3	HIGH&NO	soluble	2.63
13)Helichrysetin	2.685	78.81	86.99	5	3	4	HIGH&NO	soluble	2.65
14)Bavachalchme	4.614	96.04	77.76	4	3	5	HIGH&NO	Moderately soluble	3.03
15)Isobavachalcone	4.816	96.40	77.76	4	3	5	HIGH&NO	Moderately soluble	3.03

16)Xanthoangelo	5.998	119.60	77.76	4	3	8	HIGH&NO	Moderately soluble	3.57
17)Flavokawain-A	3.504	87.43	64.99	5	1	7	HIGH&YES	Moderately soluble	2.33
18)Favokawain-B	3.380	81026	55.76	4	1	5	HIGH&YES	Moderately soluble	2.73
19)Dichanetin	5.740	135.50	107.22	6	4	5	HIGH&NO	Poorly soluble	4.15
20)Hydroxy Safflor Yellow A	-1.281	138.81	295.36	16	12	6	LOW&YES	-	5.156
21)Echinatin	2.771	76.79	66.76	4	2	4	HIGH&YES	Soluble	2.68
22)Kanzonol-C	6.558	119.76	77.76	4	3	7	HIGH&NO	Moderately soluble	3.58
23)Kanzonol-Y	5.679	120.60	97.99	5	4	8	HIGH&NO	Moderately soluble	3.83
24)Aurentiacin-A	3.553	81.75	66.76	4	2	4	HIGH&YES	Moderately soluble	2.74
25)Pinostrobin chalcone	3.832	3.832	66.76	4	2	4	HIGH&YES	Soluble	2.59
26)Bavachinin	1.010.	1.010	55.87	1	0	2	HIGH&YES	Soluble	1.59
27)sappachalcone	2.409	2.409	86.99	5	3	4	HIGH&NO	Soluble	2.72
28)Derricin	5.396	5.396	46.53	3	1	6	HIGH&YES	Moderately soluble	3.06
29)Derricidin	5.168	93.52	46.53	3	1	6	HIGH&YES	Moderately soluble	3.02
30)Paratcarpin-A	6.204	116.51	55.76	4	1	3	HIGH&YES	Poorly soluble	3.95
31)Paratcarpin-E	4.272	120.92	97.99	5	4	8.0	HIGH&NO	Moderately Soluble	34.09
32)Bakuchalcone	3.194	95.52	86.99	5	3	4.0	HIGH&NO	Moderately Soluble	3.77
33)Rubone	2.806	100.73	83.45	7	1	8.0	HIGH&NO	Moderately Soluble	3.41
34)Calythropsin	2.857	78.81	86.99	5	3	4.0	HIGH&NO	Moderately Soluble	2.70
35)Pedicin	2.786	99.41	94.45	7	2	6.0	HIGH&NO	Moderately Soluble	3.45
.36)Munchiwarin	6.218	141.54	47.60	8	4	8.0	-	-	-
37)Prorepensin	8.989	168.90	97.99	5	4	13.0	-	-	-
38)Morachalcone-A	3.47	98.06	97.99	5	4	5.0	HIGH&YES	Soluble	3.23
40)Hesperidin Methyl chalcone	0.089	148.65	234.29	15	0	10.0	LOW&NO	Soluble	6.48
41)Chalcone	3.418	66.25	17.07	1	1	3.0	HIGH&YES	Moderately Soluble	2.41
42)Phenstain	2.203	84.31	74.99	6	2	6.0	HIGH&YES	Moderately Soluble	2.44
43)Pashanone	2.965	83.28	75.99	5	3	5.0	HIGH&YES	Moderately Soluble	2.88
44)Garcinol	6.95	180.60	111.90	6	3	10.0	LOW &NO	Poorly soluble	6.88
45)Isocordion	5.189	94.01	57.53	5	5	5	HIGH&YES	Moderately Soluble	2.99
46)Lophirone A	4.666	141.06	148.43	8	5	6	LOW&NO	Poorly soluble	4.49
47)Lophirone E	3.030	107.53	90.90	5	3	4	HIGH&YES	Poorly soluble	3.43
48)Apigenin	3.307	73.99	90.90	5	3	1	HIGH&YES	Moderately Soluble	2.96
49)Naringenin	-2.491	71.57	86.99	5	3	1	HIGH&YES	Soluble	3.01

Table.4 List of compounds with docking score & toxicity

Compounds	Docking score		Hematotoxicity	Drug-induced nephrotoxicity	Eye corrosion
	Enzyme 1	Enzyme 2			
Licochalcone A	-6.4536	-5.6272	✓	✓	✓
Licochalcone B	-7.7897	-6.8639	✓	✓	
Licochalcone C	-7.0973	-6.7665	✓		✓
Licochalcone D	-8.1895	-6.6734	✓		✓
Licochalcone E	-7.0341	-7.6924	✓		✓
Xanthohumol	-8.2678	-6.5963	✓		✓
Panduratin A	-6.0968	-5.6185		●	✓
Cardamonin_	-7.7254	-7.3824	✓	✓	✓
Lonchocarpin	-6.2996	-6.7845	✓		✓
Isoliquiritigenin	-7.7243	-6.9146	✓	✓	✓
Phloretin	-6.6447	-6.6453	✓	✓	✓
Butein	-7.4115	-6.5987	✓	✓	✓
Helichrysetin	-8.1665	-6.6102	✓	✓	✓
Bakuchalcone	-7.5863				✓
Bava chalcone	_	_	✓		✓
Isobavachalcone	-7.9190	-6.9314	✓		✓
Xanthoangelol	-8.5839	-5.9688	✓		✓
Flavokawin A	-6.6790	-6.0959			✓
flavokawin b	-5.7001	-6.8369	✓		✓
Dichamanetin	-7.6647	-7.1114	✓		✓
Hydroxysafflor Yellow A	-7.0017	-6.9708		●	✓
Echinatin	-8.6683	-7.9023	✓	✓	
Kanzonol C	-8.7191	-7.0334	✓	●	✓
Kanzonol Y	-8.5948	-6.4339	✓	●	✓
Aurentiacin A	-5.9764	-7.0985	✓	✓	✓
Bavachinin	-7.3922	-7.6883	✓		✓
Sappanchalcone	-8.2881	-6.4909	✓	●	✓
Derricin	-5.5799	-6.8355	✓	✓	●
Derricidin	-5.9430	-7.3543	✓		✓
Paratocarpin A	-6.6274	-6.0824	✓		✓
Paratocarpin E	-7.6071	-6.2634	✓		✓
Bakuchalcone	-7.5863	-6.1232	✓	✓	✓
Rubone	-7.2907	-4.9652	✓		✓
Calythropsin	-8.0399	-5.9379			✓
Pedicin	-6.5745	-6.3452	_	_	_

Munchiwarin	-7.6335	-3.6055	✓✓	✓✓	✓✓
Prorepensin	-8.8625	-6.2929	_	_	_
Morachalcone A	-8.1508	-7.3064	✓✓	●	✓✓
Metrochalcone	-7.2556	-6.1015	✓✓		✓✓
Hesperidin methylchalcone	-8.5111	-7.9096			✓✓
Chalcone	-7.2213	-6.9766	✓✓	●	✓✓
Phenstatin	-6.6108	-5.9128	✓✓		✓✓
Pashanone	-6.5918	-6.5885			✓✓
Garcinol	-8.2875	-2.8827	✓✓		✓✓
Isocordoin	-7.7647	-7.1127		●	✓✓
Lophirone	-8.1550	-6.1879	✓✓		✓✓
Lophirone E	-7.2768	-7.8101	✓✓	✓✓	✓✓
Apigenin	-7.6796	-7.7849	✓✓	✓✓	✓✓
Naringenin	-7.7894	-7.1610	✓✓		✓✓

Non-toxic = ✓✓ Moderate toxic = □ Toxic = ●

Predictions from Swiss ADME indicated promising properties related to drug-likeness, solubility, and synthesis feasibility for all compounds. Molecular docking studies were performed against two cancer-related enzymes, 3EQM (linked to breast cancer) and 1M17 (associated with ovarian cancer). For the 3EQM enzyme, compounds like Prorepensin, Kanzonol C, Echinatin, Kanzonol Y, Xanthoangelol, Garcinol, and Licochalcones exhibited strong binding affinities (approximately –8 kcal/mol), while Isobavachalcone, Naringenin, Cardamonin, and Broussochalcone showed moderate affinities (around –7 kcal/mol). Conversely, for the 1M17 enzyme, Hesperidin methyl chalcone, Sappanchalcone, Xanthohumol, Licochalcones, Helichrysetin, Lophirones, Morachalcones, Rubone, Calythropsin, and Bakuchalcone displayed strong binding (approximately –8 kcal/mol), whereas Apigenin, Phloretin, Butein, and Naringenin exhibited moderate docking affinities (around –7 kcal/mol).

The Ramachandran plot analysis confirmed that both proteins were stereo chemically valid, the majority of amino acids situated in favoured or allowed zones, bolstering the reliability of the docking findings.

Insilico prediction toxicity studies indicated that most of the chalcones are free from hematotoxicity and eye corrosion. Some of the chalcones are free from nephrotoxicity.

In conclusion, chalcones are existing in nature as drug molecules hence they demonstrate all molecular properties as per the Lipinski rule and toxicity studies had revealed that most of the natural chalcones may require further invitro studies for confirmation of toxicity profile. The docking scores lie between –7 to –8 kcal/mol for Prorepensin, Kanzonols, Echinatin, Xanthoangelol, and Garcinol favouring the breast cancer enzyme binding, while Hesperidin methylchalcone, Sappanchalcone, Licochalcones, Xanthohumol, and Rubone demonstrated stronger affinities for the ovarian cancer enzyme. These results emphasize the potential of natural chalcones as promising scaffolds for the creation of anticancer drugs and this study is riveting to develop novel Nutraceuticals or herbal formulations by virtue of its respective therapeutic potential.

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