OPEN ACCESS

Scholars International Journal of Chemistry and Material Sciences

Abbreviated Key Title: Sch Int J Chem Mater Sci
ISSN 2616-8669 (Print) |ISSN 2617-6556 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: http://saudijournals.com

Original Research Article

Targeting *STAT3* Signalling Pathway by Flavones Derivatives for Breast Cancer: Structural Based *In-Silico* Molecular Docking

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DOI: https://doi.org/10.36348/sijcms.2026.v09i01.004 | **Received:** 27.11.2025 | **Accepted:** 19.01.2026 | **Published:** 21.01.2026

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Abstract

Background: In the past decade, the median overall survival for breast cancer has improved from 11 months to a 5-year survival rate of 17.8%. This is largely feasible solely thanks to molecular oncology. The metabolic characteristics of cancer cells contrast with those of normal cells. Signal transducer and activator of transcription 3 (STAT3) is an important breast cancer-related gene, which can promote the progress of breast cancer. It has been proved in clinical and basic research that over-expressed and constitutively activated STAT3 is involved in the progress, proliferation, metastasis and chemotherapy resistance of breast cancer. Flavonoids exhibit antioxidant, antiviral, anticancer, and anti-inflammatory properties. These inexpensive pharmaceutical compounds exhibit considerable biological activities and are advantageous for various chronic conditions, including cancer. ***Purpose:*** This study aimed to assess the novel herbal STAT 3 inhibitor targeting Breast cancer through *in-silico* molecular docking. ***Method:*** STAT 3 was chosen as the target proteins in the current investigation. The bond was found using the Auto Dock software using a grid-based docking method. Compounds' 2D structures were generated, converted to 3D, and subsequently energetically lowered up to an arms gradient of 0.01 using the Merck Molecular Force Field (MMFF). ***Result:*** Structural based flavones derivatives (Chrysin, Apigenin, Luteolin & Scultellarein) found to be effective anti-lung cancer component and effectively binds to be target protein *STAT 3* with binding energy-5.89, -5.6, -5.96 &-5.96 kcal/mol for Chrysin, Apigenin, Luteolin & Scultellarein respectively and showed potent inhibitory action on STAT 3. ***Conclusion:*** The results of the current investigation demonstrated that the chosen lead molecules had significant inhibitory effects on the target *STAT 3 enzyme*, consequently disrupting mitosis and genomic integrity in cancer cells. The molecular docking analysis demonstrated significant binding energy.

Keywords: *Flavones*, Molecular docking, *STAT 3 enzyme*, Chrysin, Apigenin, Luteolin & Scultellarein.

INTRODUCTION

Breast cancer (BC) continues to be a major global health issue, imposing a considerable strain on healthcare systems globally. As the most often diagnosed cancer in women worldwide, it remains a primary cause of cancer-related mortality [1]. In the last thirty years, the terrain of British Columbia has seen significant transformation. Improvements in early diagnostic techniques, enhanced treatment options, and heightened awareness have influenced incidence, death, and survival rates [2]. Nonetheless, these enhancements have not been consistent across all areas, with considerable gaps remaining between high-income and low-to-middle-income nations [3]. The aetiology of breast cancer is multifaceted, encompassing a complex interaction of genetic, environmental, and lifestyle variables. Determining and measuring the impact of many risk variables is essential for formulating effective preventative measures and correctly allocating resources [5]. The Global Burden of Disease (GBD) research offers a thorough framework for evaluating the effects of breast cancer across various locations and temporal contexts [6]. Natural plant derivatives have demonstrated encouraging efficacy as anti-tumor and anti-cancer medicines. Their efficacy is also noted to include reduced toxicity and diminished instances of resistance to hormonal-targeting anti-cancer medicines, as opposed to the multidrug resistance observed with many anti-cancer therapies. These applications stem from their antioxidant and anti-inflammatory qualities, together with their immunomodulatory capabilities and their potential to elicit anti-proliferative and anti-apoptotic effects on cancer cells. This is conducted to demonstrate a chemopreventive property that is both prophylactic and therapeutic, and is safe for prolonged use [7-8]. Flavonoids are a category of natural compounds

characterised by phenolic structures in various forms, occurring in plants. The six subclasses of flavonoids are flavones, flavanones, flavanols, flavonols, isoflavones, and anthocyanidins. A study indicates that flavonoids possess anti-inflammatory, antiviral, anti-allergic, antioxidant, and anti-tumor activities. Research indicates that flavonoids decrease tumour development by inducing apoptosis in cancer cells. Consequently, breast cancer can be treated more safely than hazardous methods with adverse consequences by promoting the apoptosis of cancer cells and administering radiation therapy [9]. Clinical and fundamental research has demonstrated that overexpressed and constitutively active STAT3 is implicated in the progression, proliferation, metastasis, and treatment resistance of breast cancer. STAT3 is a crucial target in luminal-type breast cancer and HER2-positive tumours, significantly influencing the efficacy of associated therapies. In breast cancer, the activation of STAT3 alters the spatial localisation of the STAT3 protein, resulting in several phenotypic modifications of breast cancer cells [10]. Given the diverse pleiotropic pharmacological effects of various principal classes of flavonoids on breast cancer and their specific mechanisms of action, this investigation aims to develop a novel STAT-3 inhibitor for breast cancer.

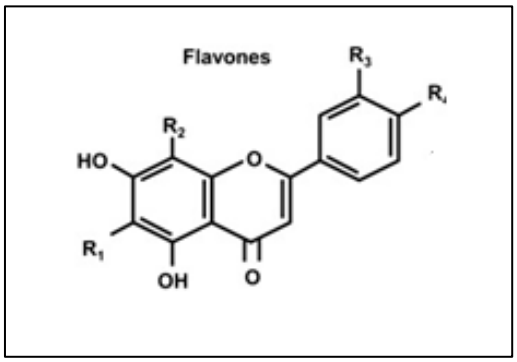
Experimental Work

Selection of Lead Molecules

Numerous contemporary and the majority of conventional pharmaceuticals have been derived from natural sources. Flavonoids, also known as bioflavonoids, are prevalent polyphenolic chemicals that serve as secondary metabolites derived from plants and fungi. In addition to their biological roles in plants, including as defence against herbivores, UV radiation, and pathogens, they also have several pharmacological effects in humans [11]. Although flavonoids are not classified as nutrients, their frequent consumption is deemed beneficial for human health. Flavonoids are synthesised via the phenylpropanoid pathway and possess a C6-C3-C6 carbon structure. In humans, these chemicals are linked to several health advantages due to their bioactive qualities, including anti-inflammatory, anticancer, anti-aging, cardioprotective, neuroprotective, immunomodulatory, antidiabetic, antibacterial, antiparasitic, and antiviral effects. The acknowledgement of natural flavonoids as a beneficial and safer source of antioxidants presents new opportunities to investigate more compounds, emphasising novel structures via innovative approaches and technologies, as well as utilising alternative natural sources [12-14].

The bioavailability, metabolism, and biological activity of flavonoids are contingent upon their configuration, the overall quantity of hydroxyl groups, and the substitution of functional groups in relation to their nuclear structure [15]. Flavanones possess a hydroxyl group at the 3-position and a C2–C3 double bond [16].

Chemical Nature Flavones Used in Current Investigation

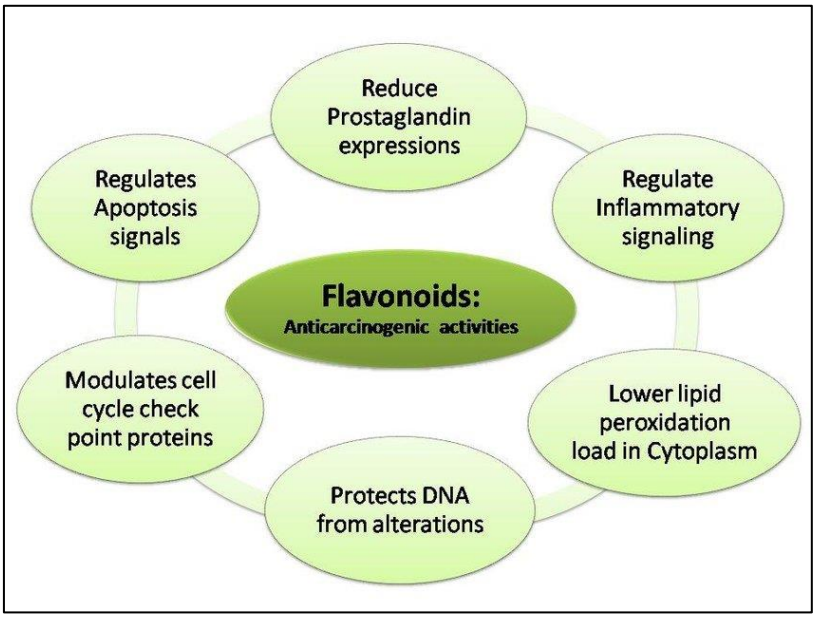


Compound	R_1	R_2	R_3	R_4
Chrysin	H	H	H	H
Apigenin	H	H	H	OH
Luteolin	H	H	OH	OH
Scultellarein	OH	H	H	OH

Anticancer Pathways of Flavonoids

The signalling pathways that elucidate the molecular mechanisms of flavonoid action are linked to the robust activity of PI3K/Akt/GSK3β/NF-κB and p38/MK2 in colitis. The decreased production of proinflammatory indicators, including IgM, IgE, iNOS, ICAM-1, HO-1, and Th1/IL-10 cytokine ratios, together with impacts on effector modulation, control, and B cell homeostasis, signifies an innovative strategy for colitis treatment [17-18]. Flavonoids regulate many cell-signaling pathways, such as PI3K/Akt, JAK/STAT, MAPK, and NF-κB, to have anticancer effects. They diminish inflammation and oxidative stress, prevent platelet aggregation, and enhance insulin sensitivity and lipid profiles, therefore benefitting illnesses such as diabetes, hyperlipidaemia, and cardiovascular disease.

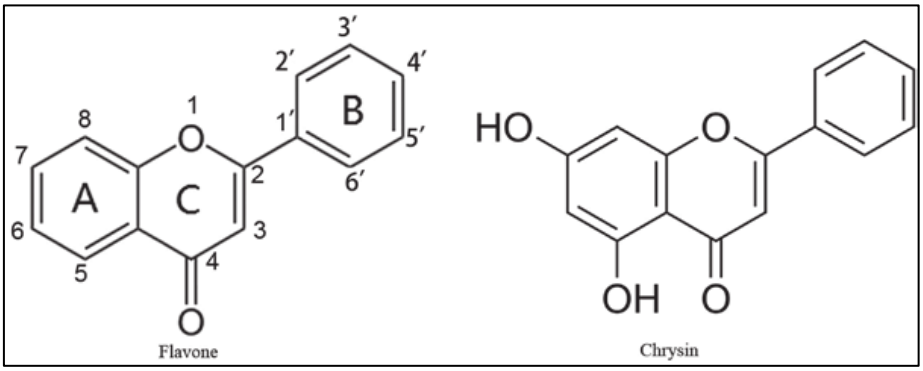
Moreover, ROS-responsive nucleotide-binding domain-like receptor 3 (NLRP3) ameliorates endothelial dysfunction by modulating nitric oxide production, which is subsequently reduced by inflammasomes, hence reducing the risk of cardiovascular disease [19-28].



Anticancer Activity of Flavonoid

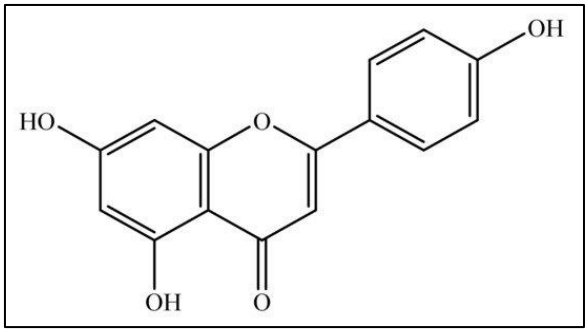
Structural based selection of lead compounds

Chrysin



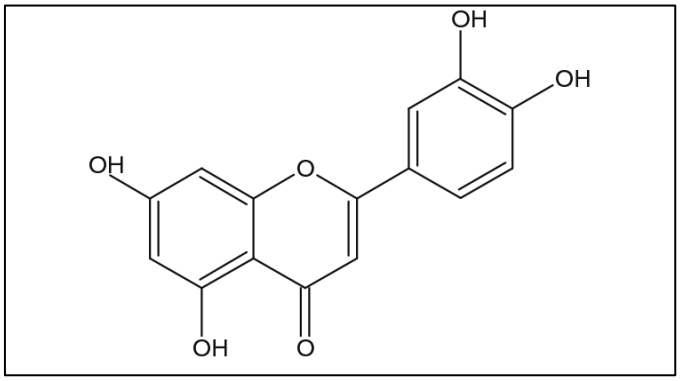
Chrysin (5,7-dihydroxyflavone), a natural polyphenolic compound, is found in several plants, honey, and propolis. It seems to possess a combination of many pharmacological effects, including anticarcinogenic, pro-apoptotic, antiangiogenic, antimetastatic, immunomodulatory, and antioxidant capabilities. The molecular mechanisms that govern the pleiotropic effects of chrysin are varied, involving interactions across cell signalling pathways across numerous levels of different illnesses [29].

Apigenin



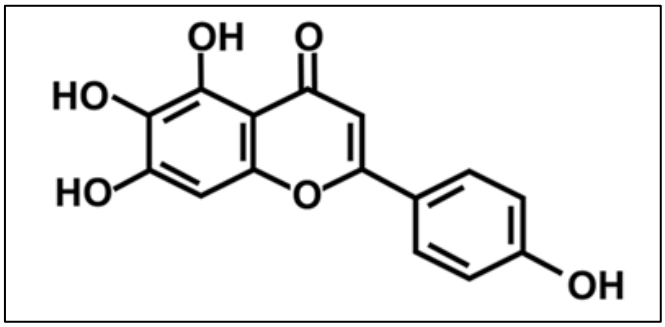
Apigenin is a naturally occurring bioactive flavonoid. It is chemically identified as 4′,5,7-trihydroxyflavone and is fundamentally associated with flavone, a subclass of flavonoids. Apigenin is biosynthesised via the phenylpropanoid pathway [30]. It is synthesised from the precursor's tyrosine and phenylalanine. Tyrosine undergoes direct deamination to become p-coumaric acid, whereas phenylalanine is transformed into cinnamic acid by non-oxidative deamination, subsequently oxidised at C-4, and ultimately converted into p-coumaric acid. Subsequent to the production of p-coumaric acid via both processes, the resultant p-coumaric acid is further activated with Coenzyme A. Three malonyl-CoA molecules are then consolidated with p-coumarate. The molecule is then aromatised to chalcone-by-chalcone synthase. Chalcone isomerase subsequently isomerises chalcone, transforming it into naringenin. In the concluding phase, naringenin undergoes oxidation to become apigenin via flavanone synthase [31-33]. Numerous biological effects of apigenin have been shown in both in vitro and in vivo research, indicating its potential anti-inflammatory, antioxidant, anti-obesity, antiproliferative, and anticancer properties [35-36].

Luteolin



Luteolin, or 3′,4′,5,7-tetrahydroxyflavone, is a flavone prevalent in celery, parsley, green pepper, and chamomile tea, with significant anti-inflammatory and antioxidant characteristics [37]. It functions as an anticancer drug against several forms of human malignancies, including lung, breast, glioblastoma, prostate, colon, and pancreatic cancers. It inhibits cancer growth both in vitro and in vivo by obstructing tumour cell proliferation, safeguarding against carcinogenic stimuli, activating cell cycle arrest, and causing apoptosis via several signalling pathways [38].

Scutellarein



Scutellarein (SCT), also known as 5,6,7,4′-tetrahydroxyflavone or 6-hydroxyapigenin, is a flavonoid classified as a flavone, characterised by the presence of four hydroxy groups at the C-5, C-6, C-7, and C-4′ positions [39]. The molecular structure of scutellarin consists of fused aromatic rings A and C, which are connected to phenyl ring B at position 2 of ring C. The molecule possesses a –OH group at C5, C6, and C4', a glucuronide (–OGlu) moiety at C7, a carbonyl group at C4, and a double bond between C2 and C3. Compounds exhibiting analogous molecular structures to scutellarin include scutellarein, which possesses a –OH group at C7; hispidulin, characterised by a –OCH3 moiety at C6; and apigenin, which contains a –H group at C6. Scientific research demonstrates that scutellarin exhibits anti-cancer properties against a diverse array of cancer cells, including those of the liver, prostate, lung, breast, colon, tongue, and kidney malignancies [40]. Scutellarin promotes apoptosis, causes cell cycle arrest, and suppresses the proliferation and development of cancer cells through many molecular targets and pathways. Scutellarin caused apoptosis in liver cancer cells by down-regulating Bcl-2, Bax, and caspase-3, indicating its potential as a viable anti-cancer therapeutic option for liver cancer. Likewise, scutellarin diminished the generation of reactive oxygen species and prompted

apoptosis in liver cancer cells by suppressing the signal transducer and activator of transcription (STAT) 3 pathway, along with its transcriptional targets Bcl-XL and Mcl-1. Subsequent research validated these findings, indicating that scutellarin inhibits the migration and invasion of liver cancer cells via suppressing the activity of STAT3, Girdin, and AKT [41-44].

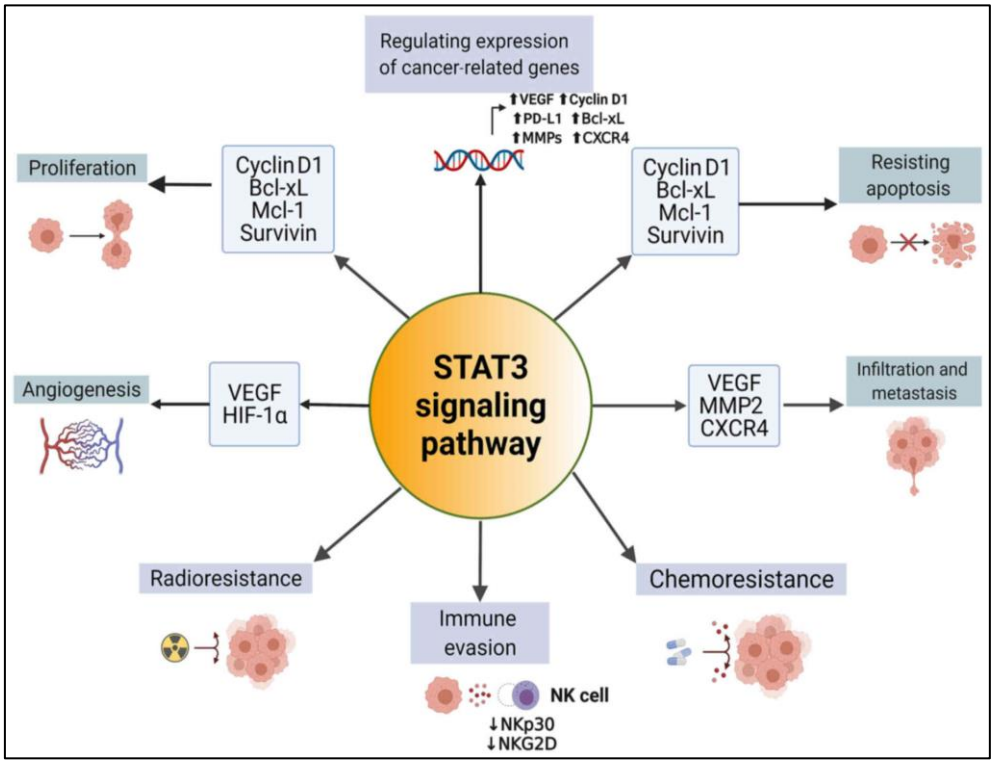
Description of Lead molecules [45-48]

Molecules	Synonym	Molecular weight	Molecule formula
Chrysin	5,7Dihydroxyflavone Chrysine	254.24 g/mol	$C_{15}H_{10}O_4$
Apigenin	5,7-Dihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one Versulin	270.24 g/mol	$C_{15}H_{10}O_5$
Luteolin	3',4',5,7Tetrahydroxyflavone Digitoflavone	286.24 g/mol	$C_{15}H_{10}O_6$
Scutellarein	Scutellarein-7-glucuronide	462.4 g/mol	$C_{21}H_{18}O_{12}$

Selection of target Ligand

Signal transducer and activator of transcription 3 (STAT3)

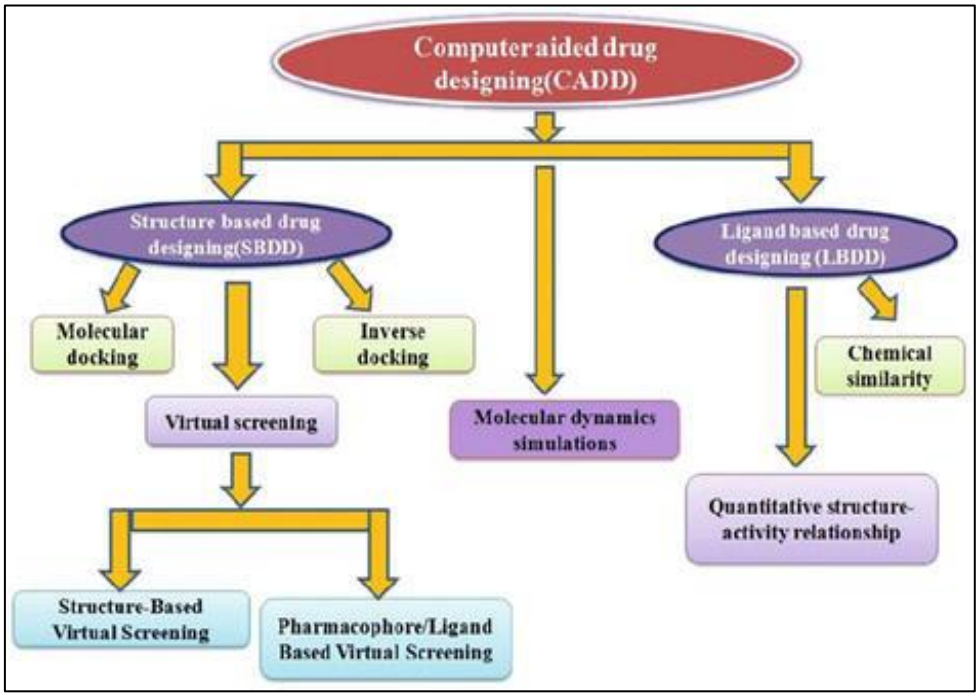
STAT3 is a significant gene associated with breast cancer that can facilitate the progression of the disease. STAT3 is a crucial protein for the growth, survival, differentiation, regeneration, immune response, respiration, metabolism, and other essential cellular processes in breast cancer. STAT3 expression and subcellular localisation are modulated by upstream signalling molecules, including Janus kinase (JAK) and epidermal growth factor receptor (EGFR). The activation of these proteins leads to the localisation of STAT3 in the nucleus or mitochondria. STAT3 in the nucleus interacts with target DNA to facilitate transcription, resulting in the synthesis of the matching protein, whereas STAT3's entry into mitochondria induces morphological or functional alterations. The translocation of STAT3 into the mitochondria induces modifications in mitochondrial protein expression and structural alterations, such as enhanced mitochondrial membrane permeability and damage to mitochondrial cristae, which are pivotal in initiating inflammation linked to tumour cells and their metabolic reprogramming. STAT3 performs a consistent regulatory role in preserving the integrity of normal tissue cells. In tumour cells, STAT3 is triggered and/or altered by several elements of the tumour microenvironment, leading to uncontrolled proliferation, invasion, and metastasis of the tumour tissue. Elevated STAT3 expression in all breast cancer patient subtypes is significantly associated with treatment resistance and reduced survival rates. Activation of STAT3 is a crucial element in the development, proliferation, metastasis, recurrence, and medication resistance of breast cancer, serving as a significant indicator of its unfavourable prognosis. Consequently, the STAT3 pathway is a prospective therapeutic target for breast cancer [49-50].



Role of STAT3 Signalling Pathway in carcinogenesis

Designing of Investigation

Molecular docking is a computer method that predicts interactions between tiny molecules (ligands) and proteins. In contrast to traditional laboratory procedures, docking significantly conserves time, expenses, and resources in drug development. HTS employs several laboratory experiments to screen for potential compounds, whereas molecular docking can virtually screen extensive chemical libraries within a few hours. Additional in-silico methodologies, including pharmacophore modelling and molecular dynamics simulations, augment molecular docking and assist in refining the docking outcomes [51]. To examine the impact of molecular docking on critical oncogenic proteins such as STAT3, protein kinase B (Akt), and vascular endothelial growth factor (VEGF). The binding affinities of chosen ligands to target proteins were evaluated to evaluate their potential use in anticancer therapies.



***In-silico* molecular Docking Approach**

Scientific Validation of Selected Flavones Derivatives targeting STAT 3 for Breast Cancer

Molecular docking studies

Ligand Preparation:

2D Structure of ligands like apigenin, chrysin, scutellarein and luteolin were drawn using ChemSketch [52], the two-dimensional structures of the prepared ligands were converted into their 3-D structures optimized with 3D geometry. The optimized structures were saved in PDB format for AutoDock compatibility. The basic structures of the prepared ligands were given below:

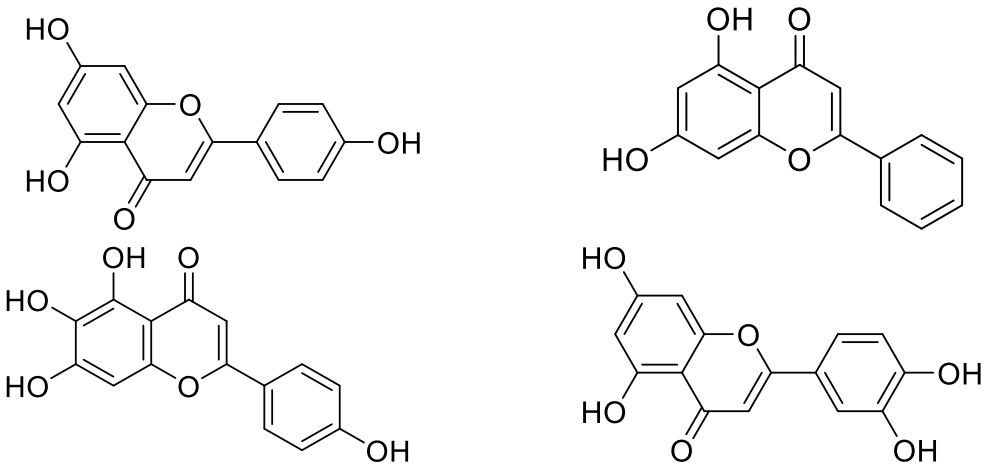


Figure 1: 2D structure of apigenin, chrysin, scutellarein and luteolin

Preparation of the grid file

The regions of interest used by Autodock were defined by considering grid area by making a grid box around the active sites. Grid box plays a central role in process of docking as it is made to cover all the amino acids present in active sites necessary for binding other than those present in receptor. Grid box has 3 thumbwheel widgets which let us change the number of points in the x, y and z dimensions. The spacing between grid points can be adjusted with another thumbwheel, the value in the study taken is 0.547 Å and No. of points considered are 48, 44 and 40 points in the x, y, and z dimensions and 13.498, 54.118 and 0.1 as x, y, z centers [53-54].

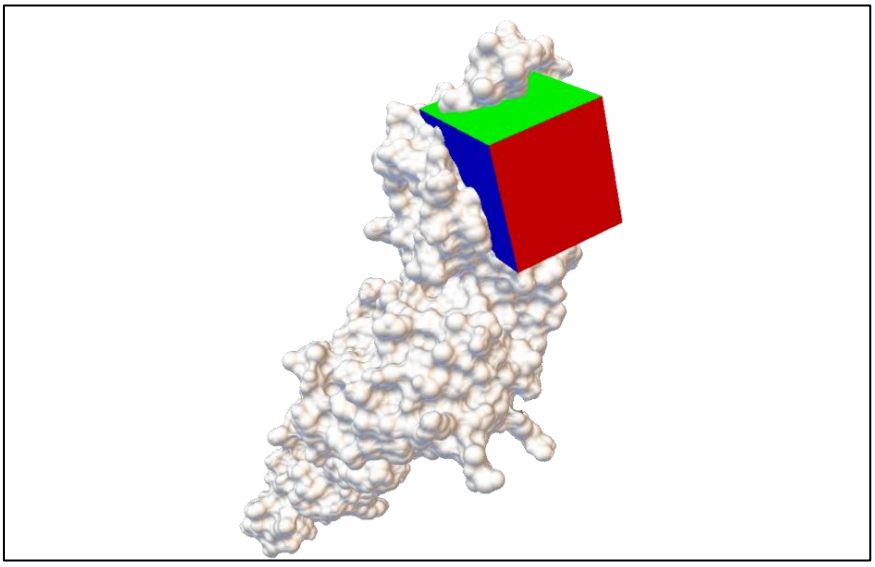


Figure 2: Grid box covering all active sites in STAT3 enzyme

Preparation of the docking file

All the calculations were carried out by using Autodock 4.2 as docking tool. The visualization and other programs necessary for docking studies were performed out by means of Pymol, Chimera, DS visualizer, MMP Plus [55-57].

Docking of beta-tubulin with Quercetin

Crystal structure

The crystal structure of the protein consisting of STAT3 enzyme is downloaded from the Protein Data Bank portal. All the primary information regarding receptor and structure (2w3l.pdb) registered in the Protein data bank was used [58-61].

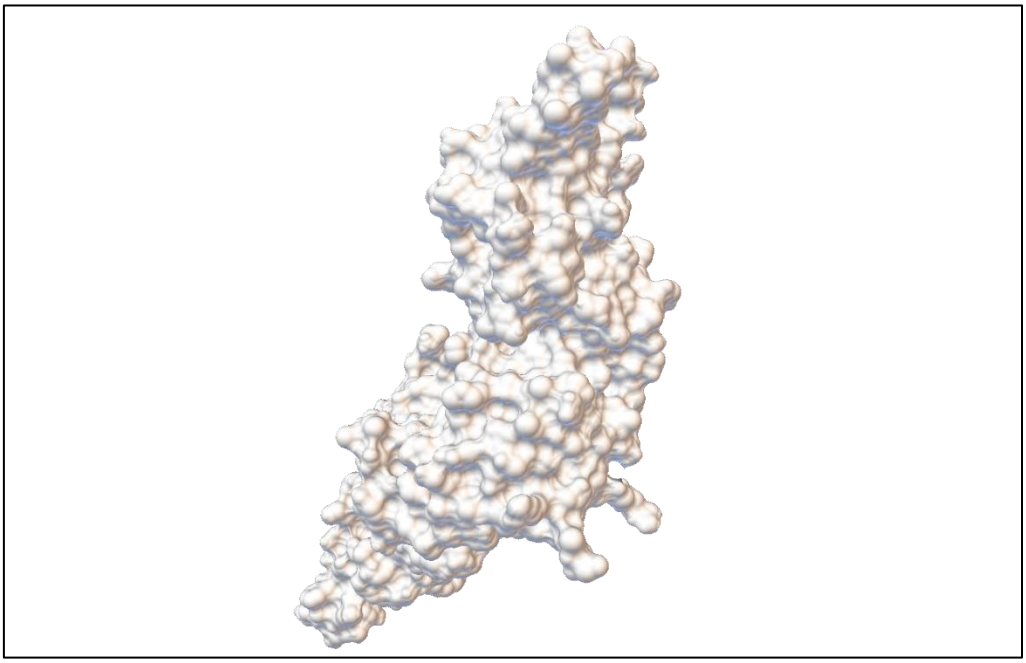


Figure 3: Crystal structure of STAT3 enzyme (PDB ID-6njs)

Processing of Protein

The downloaded receptor protein is having two chains, i.e. chain A, and B. Out of these two chains, chain B was selected for experimental purpose and other chains were removed from it. The bound ions were separated from the macromolecular complex by using software Chimera [62-65].

Molecular Docking Simulation Studies

Docking of ligands like apigenin, chrysin, scutellarein and luteolin against human STAT3 enzyme was performed by Autodock. All the bonds of each ligand were kept flexible, while no residues in receptor were made flexible [66].

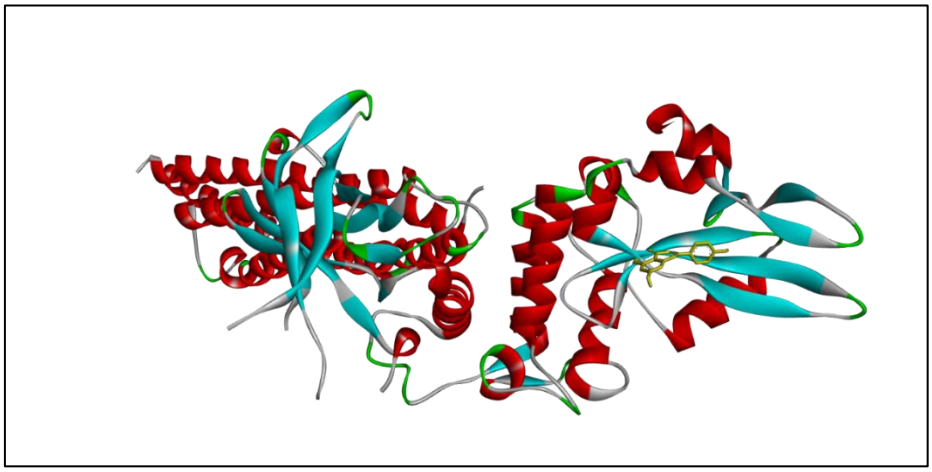


Figure 4: Binding mode of apigenin within the active site of human STAT3 enzyme

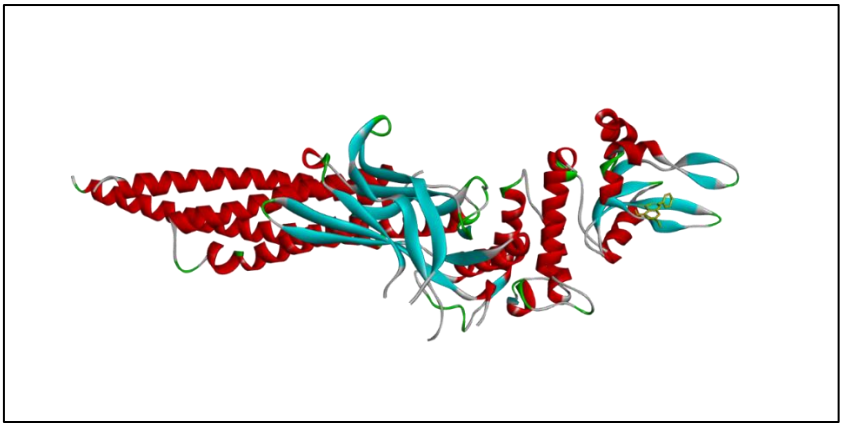


Figure 5: Binding mode of chrysin within the active site of human STAT3 enzyme

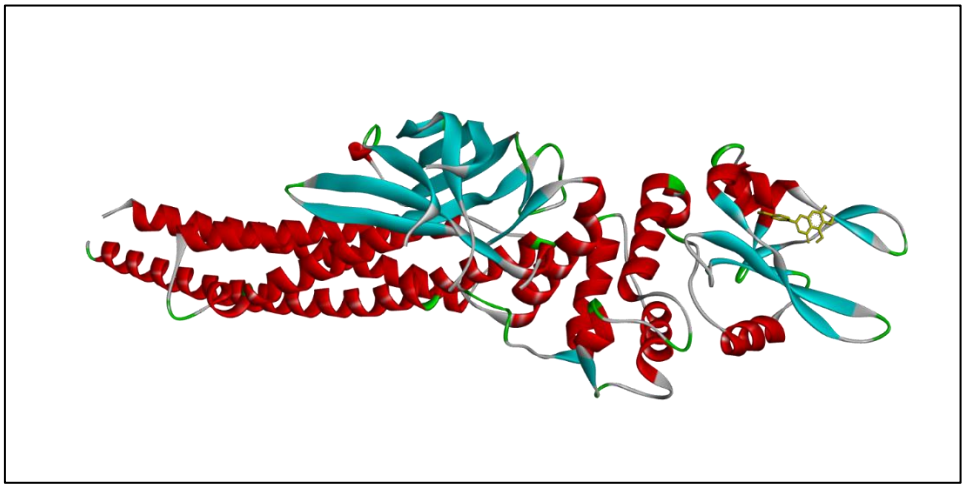


Figure 6: Binding mode of scutellarein within the active site of human STAT3 enzyme

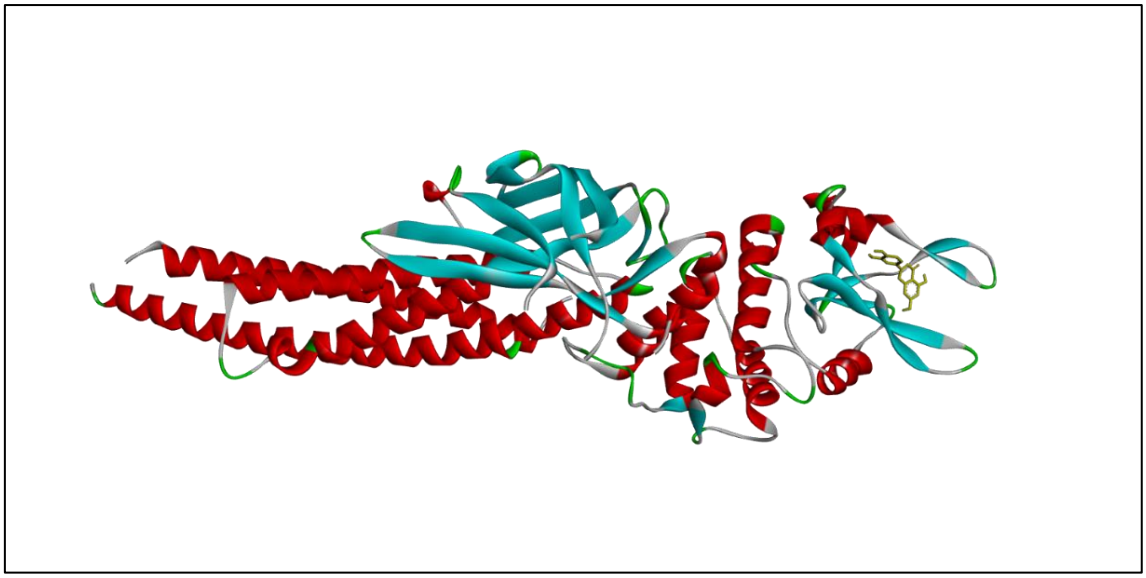


Figure 7: Binding mode of luteolin within the active site of human STAT3 enzyme

Toxicity & ADME-T Studies

The ligand molecules viz. apigenin, chrysin, scutellarein and luteolin were studied by online program OSIRIS, for prediction of presence of any toxic group as well as presence of any toxic group and ADME- T properties [67].

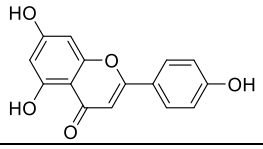
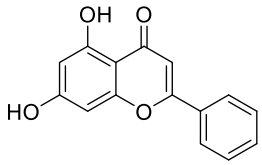
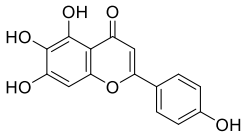
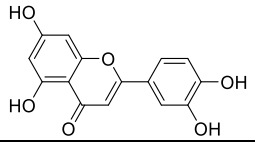
RESULT AND DISCUSSION

Breast cancer (BC) continues to be a major global health issue, imposing a considerable strain on healthcare systems globally. As the most often diagnosed cancer in women worldwide, it remains a primary cause of cancer-related mortality. Plants have been essential to human survival and growth, fulfilling fundamental requirements such as sustenance, clothing, shelter, and medicine from the beginning of time. Plants are the cornerstone of Western medicinal systems, including Ayurveda, Unani, and traditional Chinese medicine, which have addressed human health requirements for millennia. A significant segment of the populations in emerging and impoverished nations utilises herbal medicine to address their basic health issues. Traditional herbal medicines have gained appeal due to its affordability, availability, and little adverse effects. In recent years, there has been an increased focus on plant science globally to identify drug-like chemicals from widely used medicinal plants. Moreover, many naturally occurring phytochemicals, like curcumin, resveratrol, and quercetin, have demonstrated beneficial anti-cancer properties and are becoming recognised as chemotherapeutic adjuncts. Moreover, naturally occurring compounds are less detrimental to healthy cells and demonstrate preferential toxicity towards dysfunctional or sick cells in certain situations. This may elucidate why a significant proportion of items available on the market has structures that are structurally comparable to those occurring in nature. Herbal chemicals include diverse anticancer activities, including antioxidant, anti-inflammatory, antimutagenic, and apoptosis-inducing effects, which may help prevent the initial development of cancer.Flavonoids has anticancer properties since they mitigate cancer symptoms. Flavonoid uses encompass the reduction of proliferation, cell cycle arrest, induction of apoptosis, antioxidant activity, and anti-metastatic effects. Caspase-9, mitochondrial-mediated apoptosis, extrinsic pathways, caspase-8, and death receptor-mediated apoptosis signalling pathways, among others. *This work was aiming to identify novel STAT3 inhibitors for targeting breast cancer, considering the function of STAT3 in breast cancer progression and the adaptability of flavonoids against cancer.* The result of molecular docking was tabulated in table 1, showing binding energy -5.89,-5.6,-5.96 & -5.96 kcal/mol for Apigenin Chrysin, Scultellarein & Luteolin respectively. The LD50 (mol/kg) was found to be 2.352,2.367,2.312 & 2.312 for Apigenin Chrysin, Scultellarein & Luteolin respectively. The above finding suggested that each compound showed almost similar inhibitory potential against STAT3. The binding mode showed in fig.4-7 whereas 2D &3D binding interaction was shown in fig.8-15. All selected lead molecules showed good interaction with selected ligand with STAT3 enzyme. The binding interaction of lead molecules are as follows:

Lead molecule	Vanderwaal's	C-H bounding	π-Sigma	π -π T shaped	π-Alkyl	π-anion	π-σ	Unfavourable Donar
Apigenin	ILE659 Thr640 Thr641	Tyr657 Pro639 Gln644	-----	------	Val637	Glu638	--	-------
Chrysin,	Tyr657 Tyr640	Gln644 Pro639	------	------	Val637	Glu638		Thr641
Scultellarein	Thr641 Trp623 ILE659	Lys658 Gln644 Pro639	Glu637	Tyr657 Tyr640	-----	-----	--	--------
Luteolin	Thr641 ILE659 Trp623 Thr640	Gln644 Pro639 Glu638 Tyr657 Ser636	-----	-----	----	----	Val637	-----
Apigenin	ILE659 Thr640 Thr641	Tyr657 Pro639 Gln644	-----	------	Val637	Glu638	--	-------
Chrysin,	Tyr657 Tyr640	Gln644 Pro639	------	------	Val637	Glu638		Thr641
Scultellarein	Thr641 Trp623 ILE659	Lys658 Gln644 Pro639	Glu637	Tyr657 Tyr640	-----	-----	--	--------
Luteolin	Thr641 ILE659 Trp623 Thr640	Gln644 Pro639 Glu638 Tyr657 Ser636	-----	-----	----	----	Val637	-----

The pharmacokinetic profiling of the Apigenin Chrysin, Scultellarein & Luteolin ligand has revealed that it is having good pharmacokinetic profile associated without the presence of major toxic effects like reproductive effects, irritant effect, and tumorogenic properties, but shows the presence of some mutagenicity. The pharmacokinetic and toxicity profiling results of lead molecule was shown in fig.16-19& table. 2-4. Finding showed that all lead molecules followed Lipinski rule of drug likeness.

Table 1: Results of docking of ligands like apigenin, chrysin, scutellarein and luteolin against human STAT3 enzyme

Sl. No	Ligand	Structure	Binding Energy (kcal/mole)	Minimum Ligand Energy (kcal/mol)	Ki (µM)	LD50 (mol/kg)
1	***Apigenin***		-5.89	14.5355	47.76	2.352
2	***Chrysin***		-5.6	15.6501	77.9	2.367
3	***Scutellarein***		-5.96	2.1513	42.54	2.312
4	***Luteolin***		-5.96	7.7602	43.04	2.312

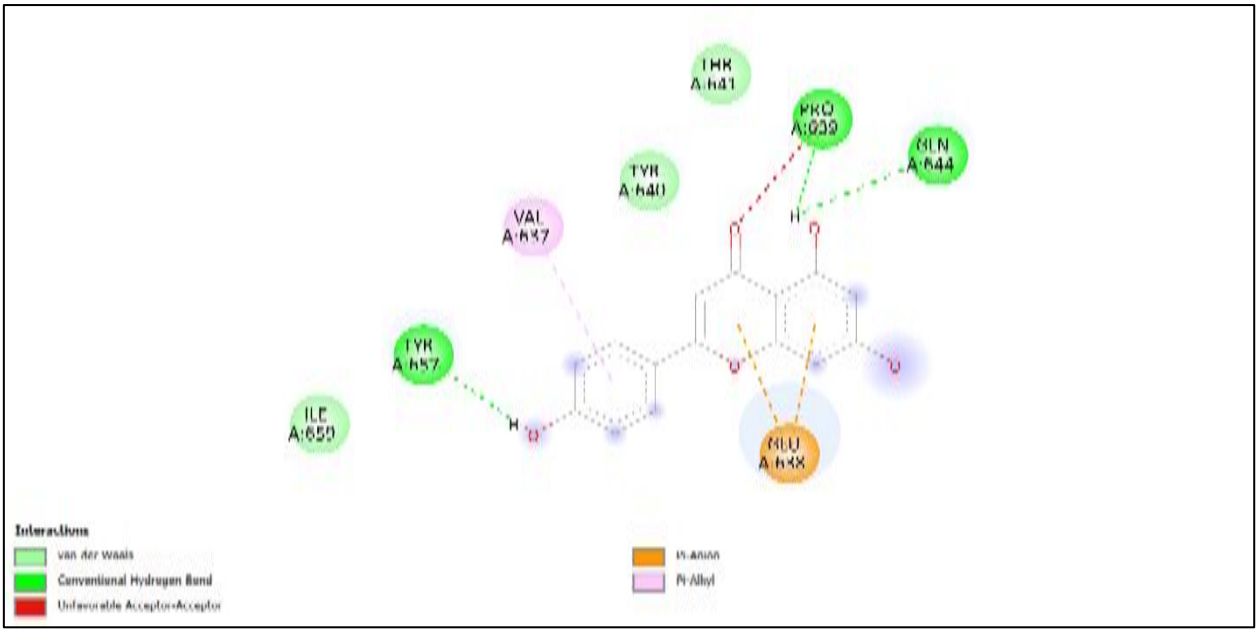


Figure 8: Two-dimensional binding mode of apigenin within the active site of human STAT3 enzyme

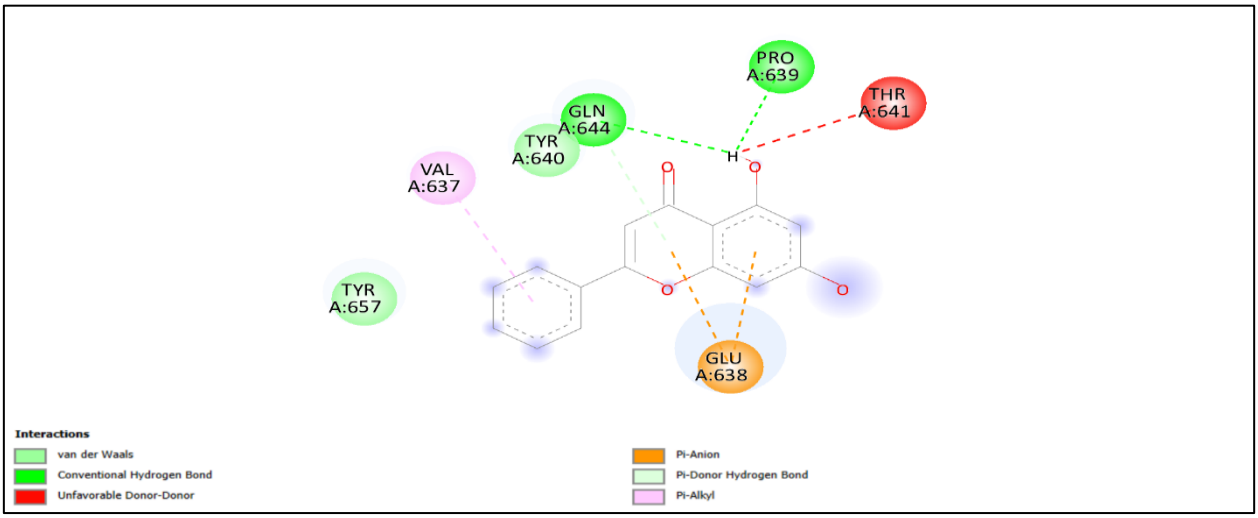


Figure 9: Two-dimensional binding mode of chrysin within the active site of human STAT3 enzyme

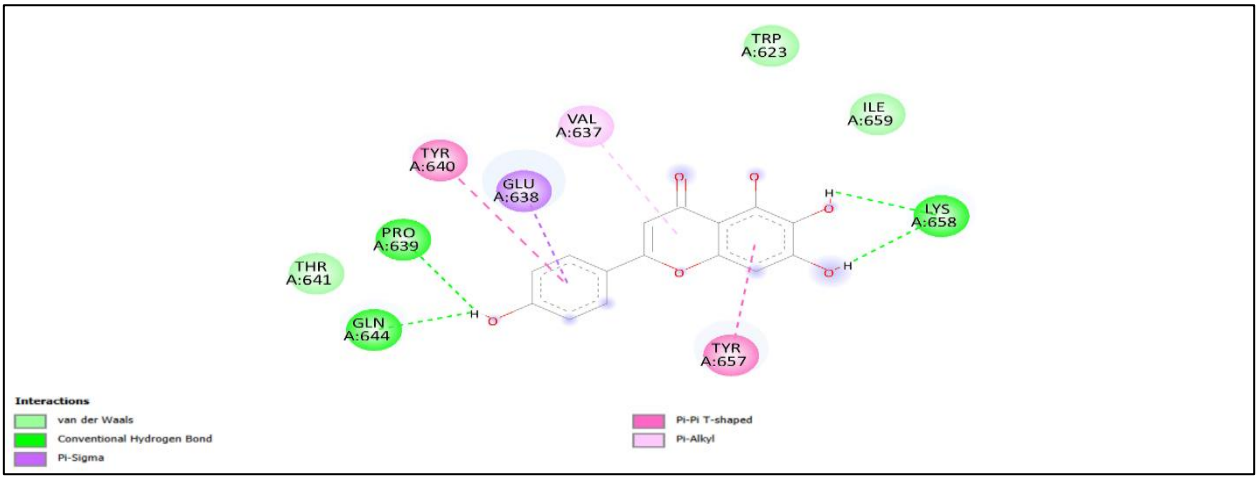


Figure 10: Two-dimensional binding mode of scutellarein within the active site of human STAT3 enzyme

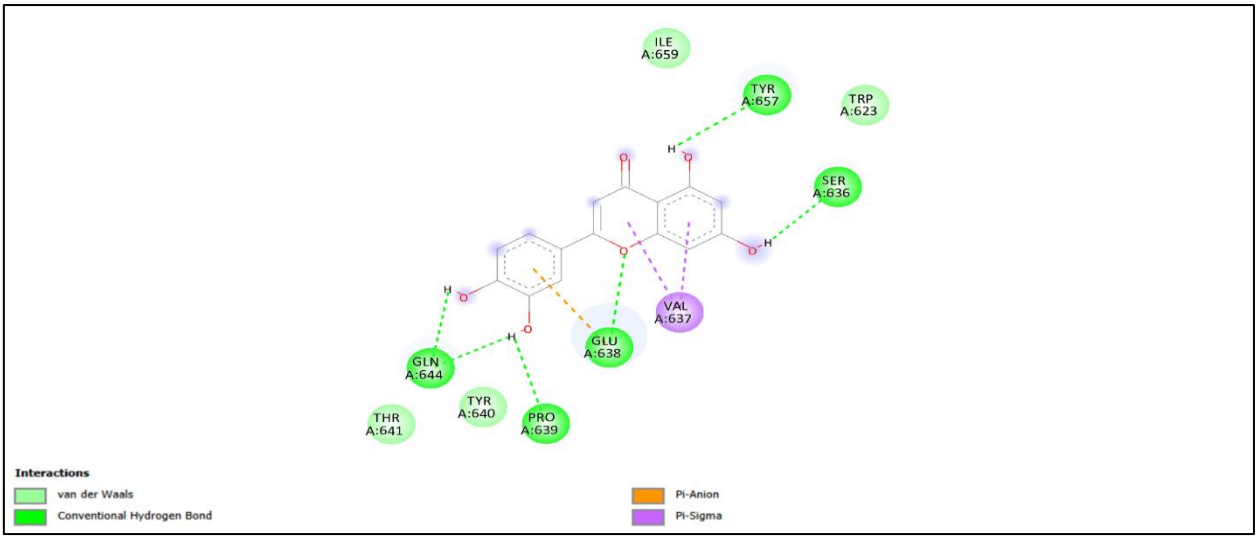


Figure 11: Two-dimensional binding mode of luteolin within the active site of human STAT3 enzyme

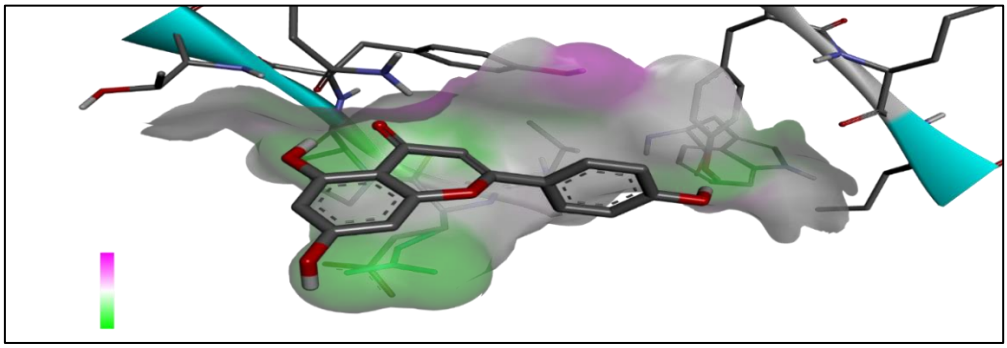


Figure 12: Three-dimensional binding conformation of apigenin within the active site of human STAT3 enzyme

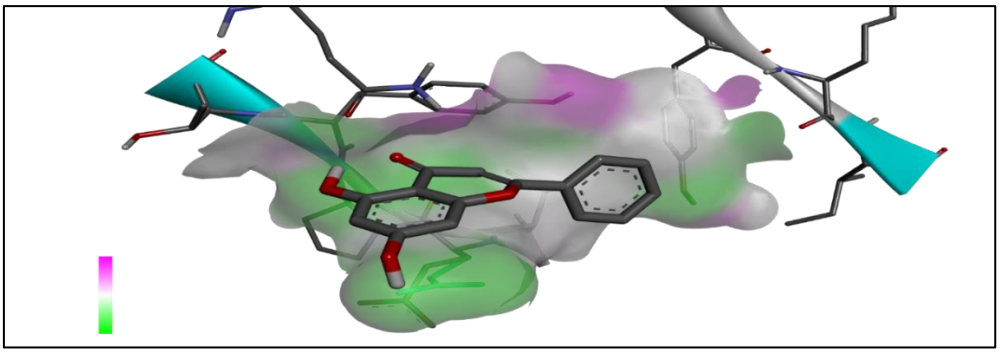


Figure 13: Three-dimensional binding conformation of chrysin within the active site of human STAT3 enzyme

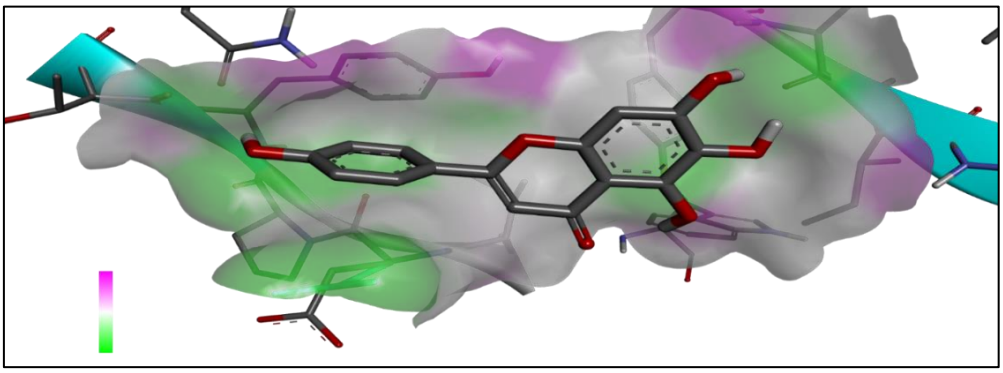


Figure 14: Three-dimensional binding conformation of scutellarein within the active site of human STAT3 enzyme

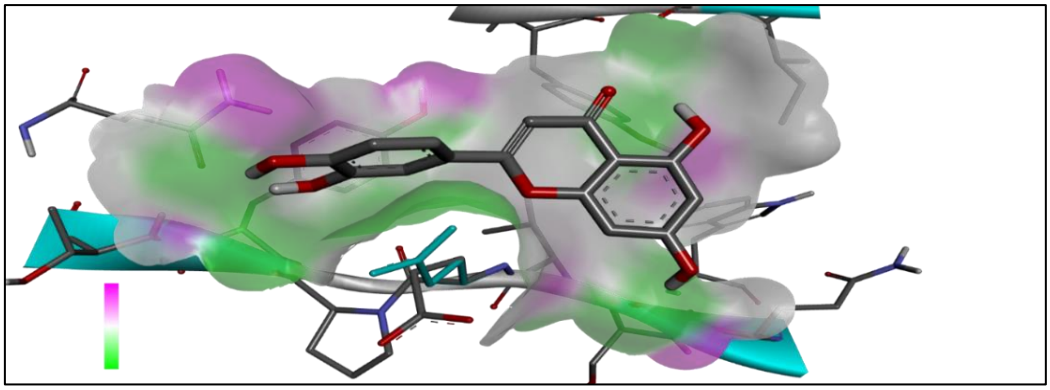


Figure 15: Three-dimensional binding conformation of luteolin within the active site of human STAT3 enzyme

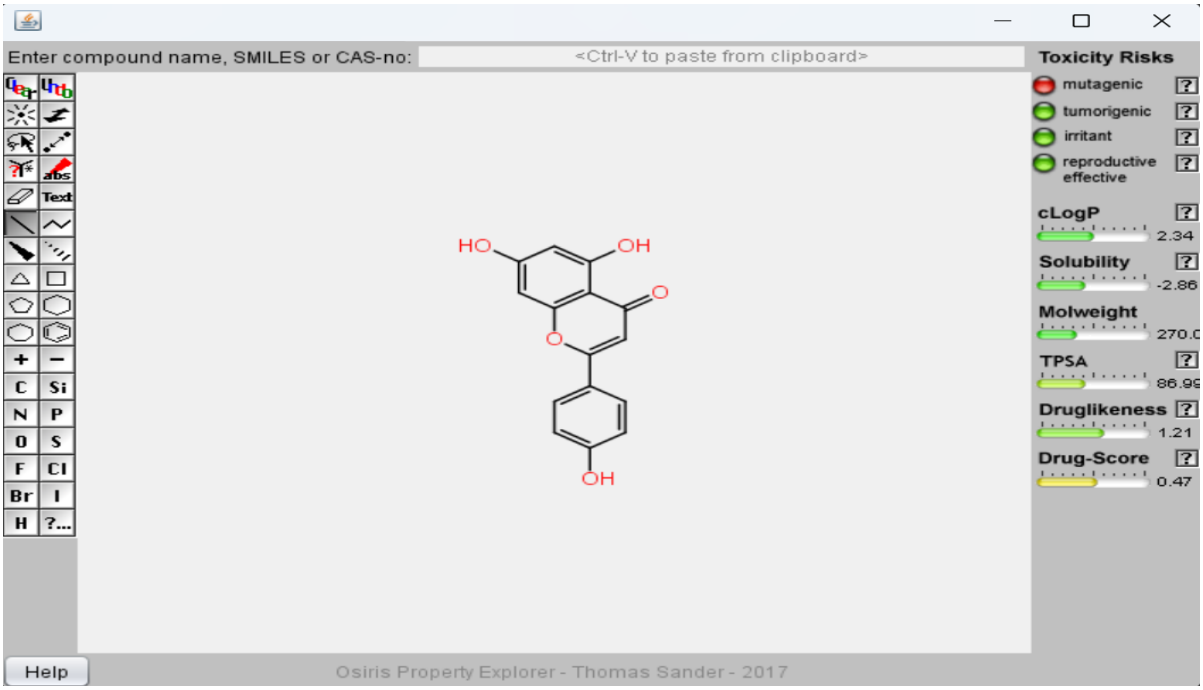


Figure 16: Pharmacokinetic and toxicity profiling of apigenin

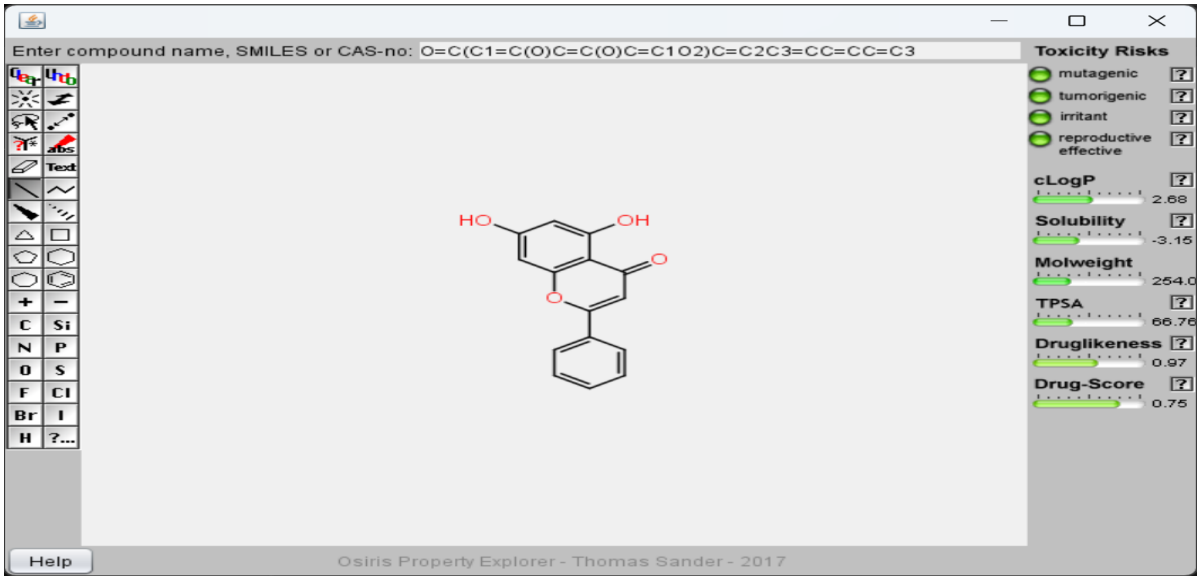


Figure 17: Pharmacokinetic and toxicity profiling of chrysin

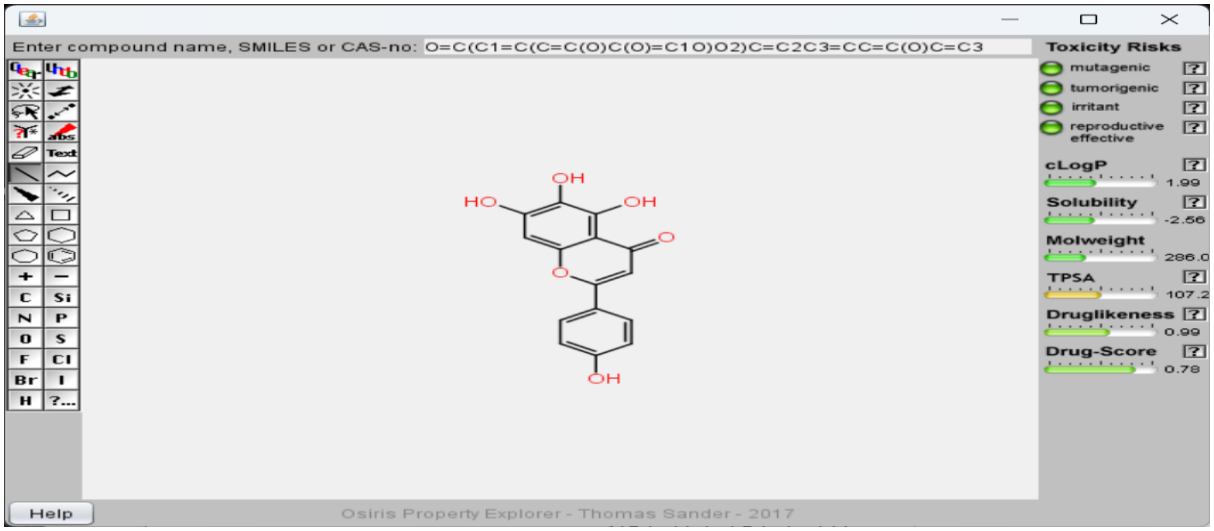


Figure 18: Pharmacokinetic and toxicity profiling of scutellarein

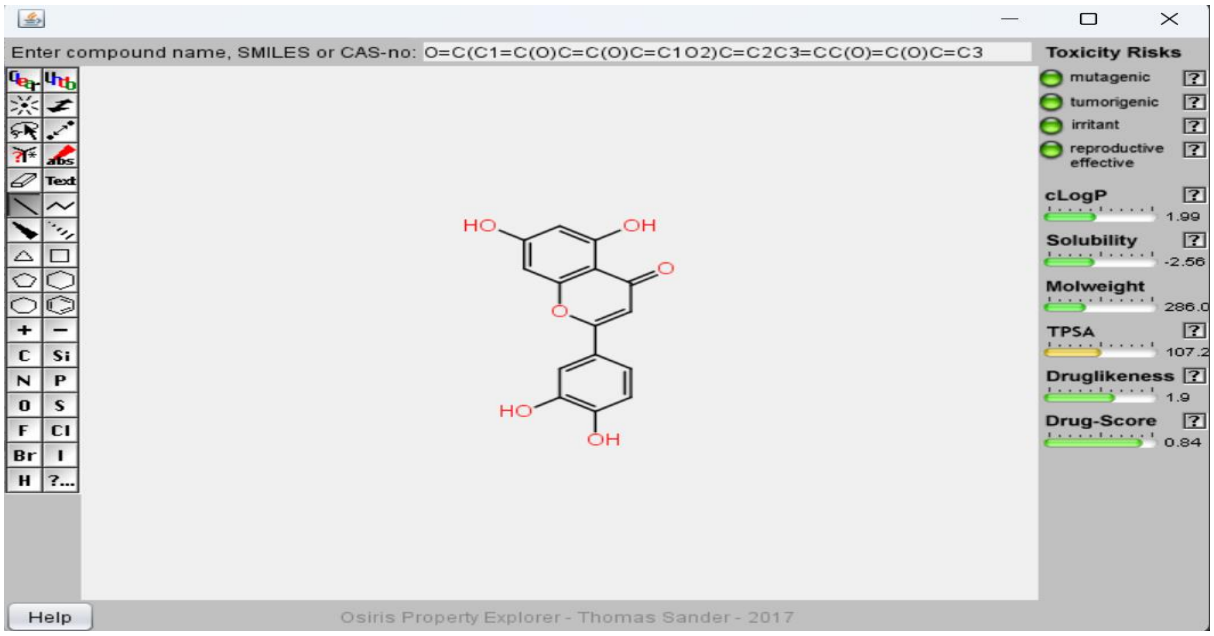


Figure 19: Pharmacokinetic and toxicity profiling of luteolin

Table 2: Pharmacokinetic Profiling of lead molecules

Compound	ADMET			
	Mutagenic	Tumorigenic	Irritant	Reproductive effectivity
Apigenin	NO	NO	NO	NO
Chrysin	NO	NO	NO	NO
Scultellarein.	NO	NO	NO	NO
Luteolin	NO	NO	NO	NO

Table 3: Lipinski Properties of lead molecules

Compound	*cLogP*	Solubility	Mol.wt.	TPSA	Drug likeness	Drug score
Apigenin	2.34	-2.86	270	86.90	1.21	0.47
Chrysin	2.68	-3.15	254	66.76	0.97	0.75
Scultellarein.	1.99	-2.56	286	107.2	0.99	0.78
Luteolin	1.99	-2.56	462	107.2	1.9	0.84

Table 4: Drug likeness of lead molecules

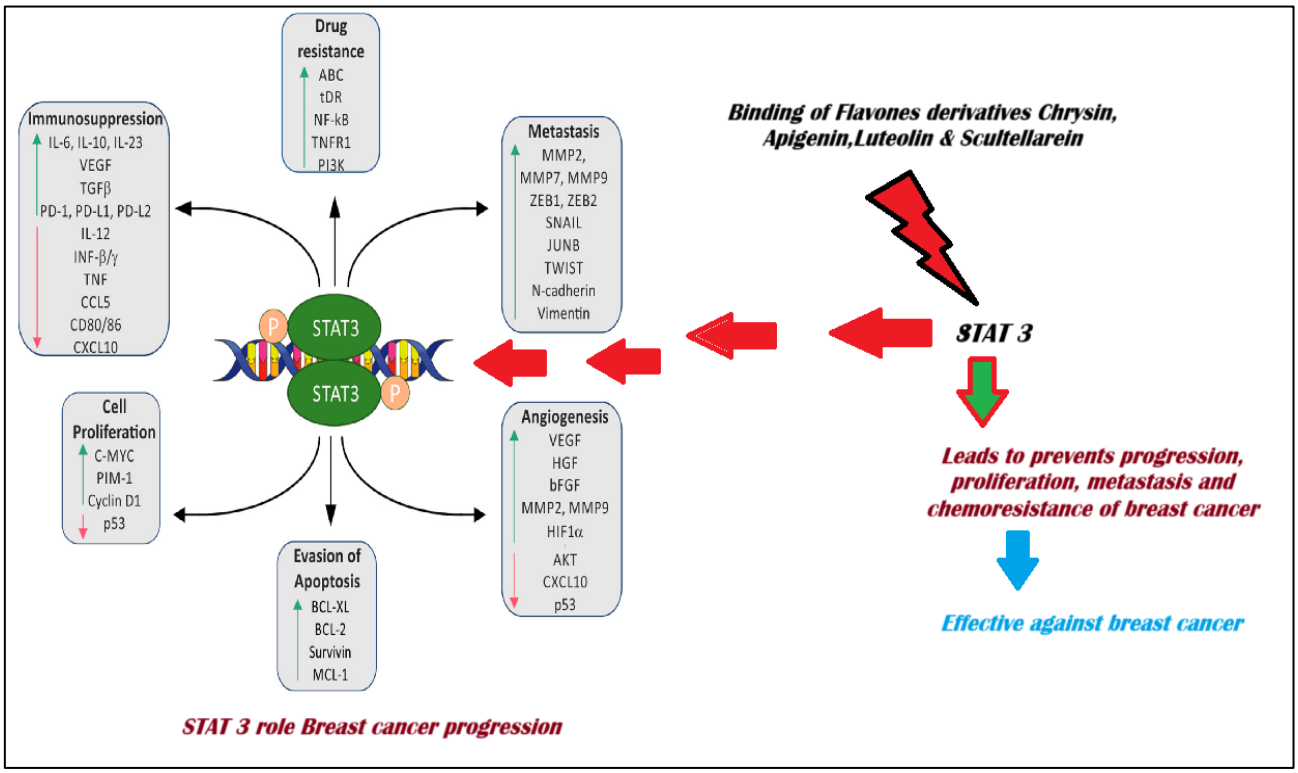
Compound	Lipinski rule of five	H bond donar (<5)	H bond acceptor (<10)
Apigenin	Yes	3	5
Chrysin	Yes	2	4
Scultellarein.	Yes	7	10
Luteolin	Yes	4	6

CONCLUSION

The structural based flavones derivatives molecular docking studies against STAT 3 demonstrated that the selected lead compounds (Chrysin, Apigenin, Luteolin & Scultellarein) exhibited potent inhibitor of STAT 3 having almost similar LD50 and showed effective against breast cancer using as adjuvant therapy.

Divulgence of Investigation

The proposed mechanism of action of selected flavonoids was showed as:



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