In silico analysis of Naringenin and its O-alkyl derivatives for its potential binding with Estrogen Receptor- α

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Abstract
Breast cancer remains the second-most significant cause of female mortality worldwide. The emergence of naturally occurring plant-derived compounds called phytoestrogens has aroused substantial interest in their potential to mitigate breast cancer. Phytoestrogens demonstrate structural similarities to human estrogen and can therefore interact with the estrogen receptors. Naringenin, an important flavonoid and phytoestrogen, has gathered significant attention in the field of cancer due to its potential anti-inflammatory and antioxidant properties while its O-alkyl derivatives can enhance its bioavailability and target specificity. In this study, we have screened Naringenin and four of its O-alkyl derivatives, namely Isosakuranetin, 5-O-Methylnaringenin, Sakuranetin and 4',7-Di-O-methylnaringenin for their binding affinity with estrogen receptor-α (PDB ID: 6VJD). Molecular docking studies targeting estrogen receptor-α (PDB ID: 6VJD) revealed favorable binding energies and interaction patterns for naringenin and its derivatives, suggesting potential as therapeutic agents against breast cancer.

Additionally, analysis with SwissADME highlighted the compounds' permeability across the blood-brain barrier (BBB), high absorption rates and water solubility, emphasizing their potential for therapeutic applications beyond breast cancer. Furthermore, the compounds exhibited promising pharmacokinetic profiles, synthetic accessibility and adherence to Lipinski's rule of five, supporting their candidacy for further development as therapeutic agents.

Keywords: Naringenin, Breast Cancer, Docking, Estrogen receptor- α.

Introduction

Breast cancer is a complex and diverse disease that poses a great risk to public health worldwide. Its effects are severe, leaving millions of people around the world living under a protracted and widespread shadow. This cancer, which primarily affects women, is not restricted by geography, culture, or socioeconomic status. Breast cancer has a significant impact on public health and as its prevalence rises, it poses a challenge to healthcare systems and necessitates the development of novel strategies for early identification, treatment and prevention.

Breast cancer's relevance to public health problems is further demonstrated by the fact that it is the cancer in which women are most frequently diagnosed worldwide. According to current figures, it was projected that over 2.2 million new instances of breast cancer would be reported in 2020, accounting for nearly one-fourth of the total number of cancers diagnosed globally[1]. This rising prevalence emphasizes how urgent it is to address breast cancer as a global public health priority. It has no racial or geographical boundaries. It is crucial to keep in mind that although women are predominantly affected by breast cancer, men can also be affected by this disease, although at a substantially lower rate. This gender-specific nature of breast cancer further adds a layer of complexity to the systems of healthcare.

Increased life expectancy, changes in lifestyle and dietary habits and alterations in reproductive behaviors are some of the key factors that contribute to this massive surge. Breast cancer risk has been linked to a westernized lifestyle that includes obesity, alcohol use and a lack of physical activity[2].

In the pursuit of effective preventive and therapeutic strategies, researchers have delved into the study of phytoestrogens—plant-derived polyphenols that closely resemble the mammalian estrogen hormone, 17β-estradiol. These substances have the capacity to alter a number of different molecular targets in the cancerous cells of the breast. Because phytoestrogens and estradiol have structural and functional similarities, phytoestrogens can bind to estrogen receptors with a relatively low affinity and nonetheless exhibit estrogenic and antiestrogenic effects[3–5]. They compete with 17β-estradiol for the ligand-binding area of the estrogen receptors, making them potentially relevant in breast cancer research.

The growth-promoting action of ERα is largely inhibited by the selectivity with which phytoestrogens, as well as their analogues and derivatives, bind to estrogen receptors, especially those having a preferred affinity for ERβ. In addition to their interactions with receptors, these bioactive substances limit growth by interacting with complex cell signaling networks[6-13]. This multifaceted approach underscores the potential of phytoestrogens to disrupt the molecular processes that drive breast cancer progression. Furthermore, phytoestrogens and their derivatives show a variety of modes of action including antiangiogenic and

antimetastatic properties as well as suppression of estrogen production and metabolism. Their influence goes further to the reversion of multidrug resistance which enhances their therapeutic possibilities even more.

Naringenin is a flavonoid and phytoestrogen that is often found in citrus fruits including grapefruits and oranges. Over the years, research has revealed its potential health benefits, including its inhibitory effects on breast cancer cells. Several studies have investigated the molecular mechanisms underlying the anti-cancer properties of naringenin, shedding light on its promising role as a natural compound in breast cancer prevention and treatment.

One key aspect of naringenin's anti-breast cancer activity is its ability to modulate various signaling pathways involved in cancer cell growth and proliferation. Studies have demonstrated that naringenin can induce apoptosis, or programmed cell death, in breast cancer cells. This effect is mediated through the regulation of specific genes and proteins associated with apoptotic pathways[14]. Furthermore, naringenin has been shown to exhibit anti-inflammatory and antioxidant properties. Chronic inflammation and oxidative stress are known contributors to cancer development and by mitigating these factors, naringenin may exert protective effects against breast cancer. The compound achieves this by influencing key molecular targets involved in inflammation and oxidative stress pathways[15].

Naringenin's biological capabilities can be enhanced further by modifying it with different active groups, which are typically attached to the molecule's C-7 and C-4 locations. To date, a variety of O-alkyl naringenin derivatives, both synthetic and natural, have been identified. Sakuranetin (7-O-methylnaringenin), a natural phytoalexin found in rice and kino extracts of *Corymbia torelliana* (Myrtaceae), has been studied for its anti-inflammatory and antioxidant effects. Notably, sakuranetin has been shown to have preventative effects on vascular and distal parenchymal changes which are frequently implicated in pulmonary changes seen in asthmatic patients [16]. Another ether derivative of naringenin, 7,4-di-O-methylnaringenin, has been identified in Boraginaceae plant extracts as well.

The objective of this study is to determine the binding affinity of naringenin and four of its O-alkyl derivatives, namely isosakuranetin, 5-O-Methylnaringenin, Sakuranetin and 4',7-Di-O-methylnaringenin, with the estrogen receptor-α (PDB ID: 6VJD) by screening and comparative analysis. O-alkyl derivatives of naringenin have been shown to have anti-inflammatory, anti-cancer and antioxidant properties; hence, the purpose of this study is to evaluate their potential as treatment for breast cancer.

Material and Methods

***In silico* studies - Data Mining:** Naringenin, Isosakuranetin, 5-O-Methylnaringenin, Sakuranetin and 4',7-Di-O-methylnaringenin were employed as query molecules for data mining in several public databases including PubChem, DrugBank, Protein Data Bank (PDB) and CHEMBL. SMILE notation and a 2D structures (Fig. 1) were utilized to explore the databases for further outputs.

Molecular Docking Analysis: All five compounds were subjected to molecular docking analysis to investigate their binding affinity with estrogen receptor-α (ER-α) (PDB ID: 6VJD). The docking studies were performed using AutoDockVina 4.2, a widely utilized web-based server for predicting the binding free energy of a ligand within the active site of a protein.

Protein Preparation: The Protein Data Bank database provided the crystalline structure for ER-α (PDB ID: 6VJD). The protein structure was modified by adding polar hydrogen atoms after ligands and water molecules were eliminated before docking tests. The Kollman charge was also applied to optimize the structure, converting it into the pdbqt format suitable for docking studies.

Analysis of Binding Interactions: The docking analysis focused on identifying the binding affinity of the five compounds for ER-α. Specific attention was given to the formation of hydrogen bonds between these compounds and key amino acids within the active site of ER-α. The interactions were visualized and analyzed using molecular visualization tools.

SwissADME Analysis: The goal of drug discovery is to identify molecules with the highest potential for development into medicines by screening a vast number of compounds according to various criteria. This approach is resource-intensive and time-consuming. Here, we have utilized the web tool SwissADME which is a pharmacokinetics, drug-likeness and physicochemical property prediction model.

Results and Discussion

Molecular Docking: Docking studies targeting estrogen receptor-α (PDB ID: 6VJD) were carried out using AutoDock Vina 4.2 for all five drugs (naringenin, isosakuranetin, 5-O-methylnaringenin, sakauranetin and 4',7-Di-O-methylnaringenin). For naringenin, nine binding conformations with an optimum binding energy of -8.7 kcal/mol have been observed during the docking process. The interaction was noted to include seven amino acids in particular: MET421, ILE424, HIS524, LEU387, MET343, LEU346 and LEU349 (Fig. 2b).

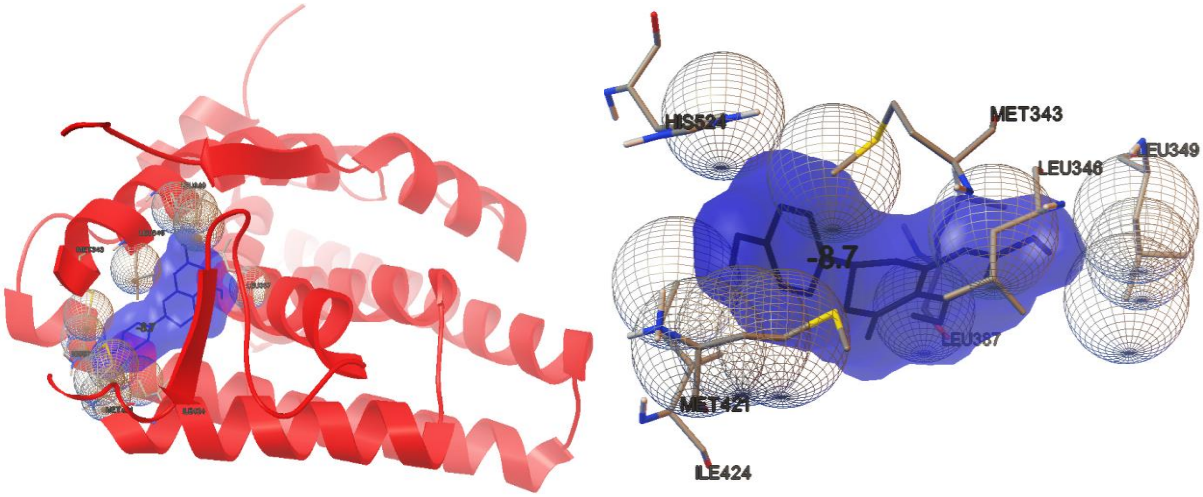
Eight binding conformations for isosakuranetin have been identified and -6.7 kcal/mol was shown to have the most favorable binding energy. Six amino acids were involved in the interaction: GLN502, GLN506, GLN499, ARG503, LEU495 and ASN439 (Fig. 3b). With an ideal binding energy of -8.2 kcal/mol, 5'-O-Methylnaringenin exhibited nine binding conformations. Nine amino acids—LEU525, HIS524, MET421, ILE424, PHE404, ARG394, LEU349

and GLU353 were implicated in the interaction (Fig. 4b). Nine binding conformations of sakuranetin (7-O-methylnaringenin) were observed with an optimum binding energy of -6.6 kcal/mol.

Six amino acids were involved in the interaction: ASN443, GLN441, ARG503, GLU444, ALA493 and GLU443 (Fig. 5b). Likewise, nine binding conformations were shown by 4',7'-Di-O-methylnaringenin, with an ideal binding energy of -6.5 kcal/mol. A total of seven amino acids were engaged in the interaction: GLN499, LEU495, ARG503, GLU444, ALA493, GLN441 and ASN439 (Fig. 6b) (Table 1 and table 2).

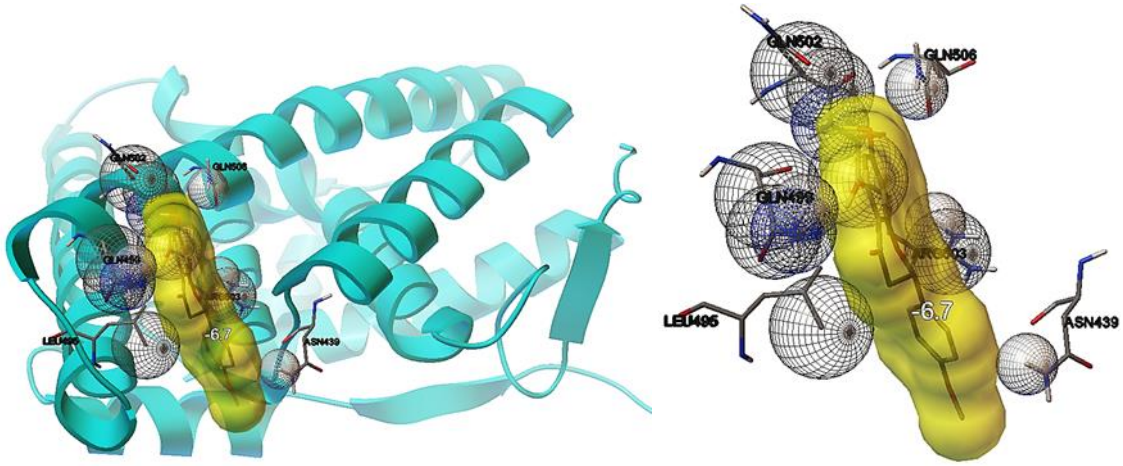
Table 1
Estimated binding free energy of naringenin and its *O* – Alkyl derivatives with estrogen receptor – α (PDB ID - 6VJD)

Compounds	Binding Free Energy (kcal/mol)
Naringenin	-8.7
Isosakuranetin (4'-O-methylnaringenin)	-6.7
5'-O-methylnaringenin	-8.2
7'-O-methylnaringenin	-6.6
4'7'-Di-O-methylnaringenin	-6.5



(a) **(b)**

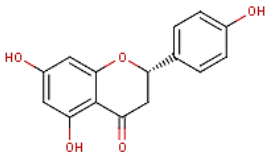
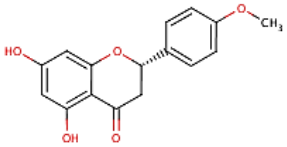
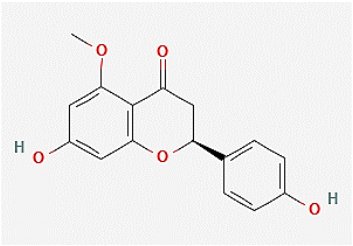
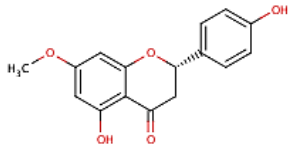
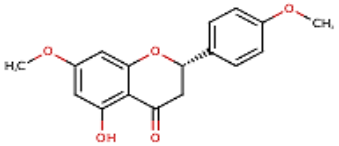
Fig. 1: Molecular docking of Naringenin onto the active region of estrogen receptor α (PDB ID: 6VJD): (a) Binding interaction between Naringenin (blue) and estrogen receptor α (red); (b) seven particular amino acids—MET421, ILE424, HIS524, LEU387, MET343, LEU346 and LEU349—were involved in the interactions between Naringenin and estrogen receptor α

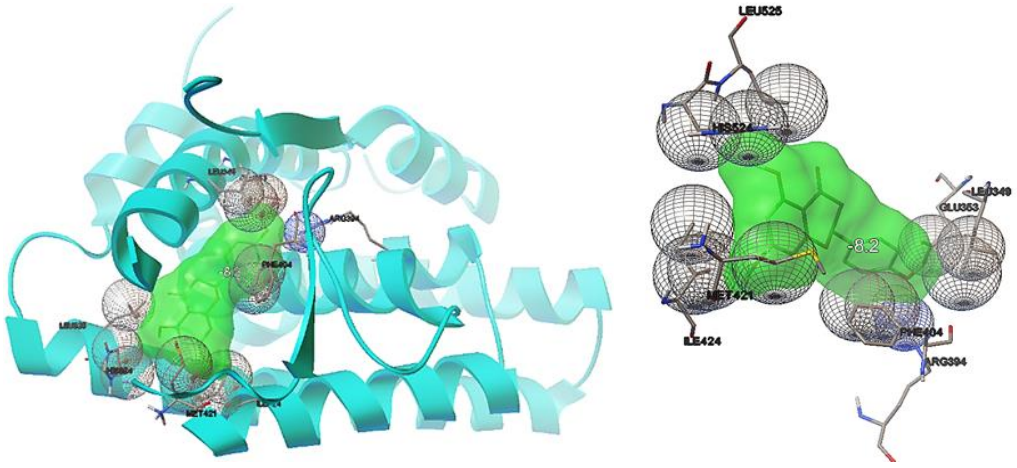


(a) **(b)**

Fig. 2: Molecular docking of 4'-O-methylnaringenin (Isosakuranetin) onto the active region of estrogen receptor α (PDB ID: 6VJD): (a) Binding interaction between 4'-O-methylnaringenin (yellow) and estrogen receptor α (blue); (b) Six particular amino acids—GLN502, GLN506, GLN499, ARG503, LEU495 and ASN439—were involved in the interactions between 4'-O-methylnaringenin and estrogen receptor α.

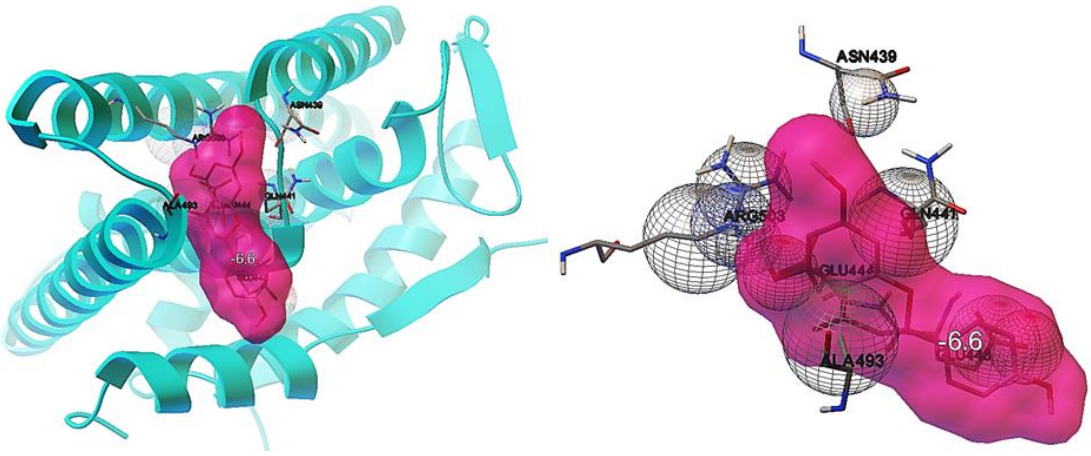
Table 2
List of interacting Aminoacids.

Phytochemical	Structure	PubChem CID	Interacting Aminoacids
Naringenin		439246	MET421 ILE424 HIS524 LEU387 MET343 LEU346 LEU349
Isosakuranetin (4'-O-methylnaringenin)		160481	GLN502 GLN506 GLN499 ARG503 LEU495 ASN439
5'-O-methylnaringenin		182315	LEU525 HIS524 MET421 ILE424 PHE404 ARG394 LEU349 GLU353
Sakuranetin (7'-O-methylnaringenin)		73571	ASN439 GLN441 ARG503 GLU444 ALA493 GLU443
4'7'-Di-O-methylnaringenin		14057196	GLN499 LEU495 ARG503 GLU444 ALA493 GLN441 ASN439



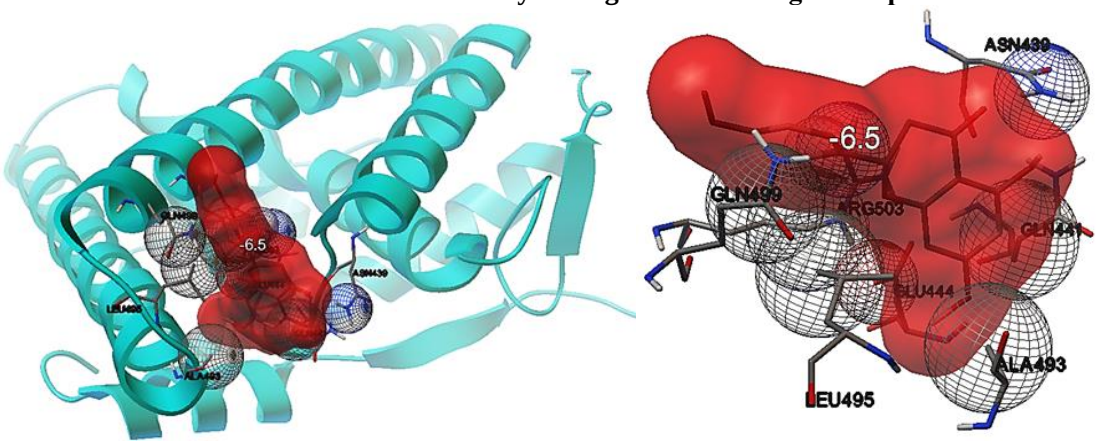
(a) **(b)**

Fig. 3: Molecular docking of 5'-O-methylnaringenin onto the active region of estrogen receptor α (PDB ID: 6VJD): (a) Binding interaction between 5'-O-methylnaringenin (green) and estrogen receptor α (blue); (b) Eight particular amino acids—LEU525, HIS524, MET421, ILE424, PHE404, ARG394, LEU349 and GLU353—were involved in the interactions between 5'-O-methylnaringenin and estrogen receptor α.



(a) **(b)**

Fig. 4: Molecular docking of 7'-O-methylnaringenin (Sakuranetin) onto the active region of estrogen receptor α (PDB ID: 6VJD): (a) Binding interaction between 7'-O-methylnaringenin (pink) and estrogen receptor α (blue); (b) Six particular amino acids—ASN439, GLN441, ARG503, GLU444, ALA493 and GLU443—were involved in the interactions between 7'-O-methylnaringenin and estrogen receptor α.



(a) **(b)**

Fig. 5: Molecular docking of 4'7'-Di-O-methylnaringenin onto the active region of estrogen receptor α (PDB ID: 6VJD): (a) Binding interaction between 4'7'-Di-O-methylnaringenin (red) and estrogen receptor α (blue); (b) Seven particular amino acids—GLN499, LEU495, ARG503, GLU444, ALA493, GLN441 and ASN439—were involved in the interactions between 4'7'-Di-O-methylnaringenin and estrogen receptor α.

SwissADME Analysis: The analysis of naringenin and its O-alkyl derivatives has been performed with SwissADME. The compound's canonical SMILES representations were obtained from PubChem and analyzed on the SwissADME website. Isosakuranetin, 5'-O-methylnaringenin, Sakuranetin and 4'7'-Di-O-methylnaringenin, in contrast to Naringenin, demonstrate permeability across the blood-brain barrier (BBB). All five compounds show high absorption rates and water solubility. The substances that do not function as P-glycoprotein (P-gp) substrates include naringenin and 5'-O-methylnaringenin.

CYP inhibition is present in isosakuranetin, sakuranetin and 4'7'-Di-O-methylnaringenin, but not in naringenin or 5'-O-methylnaringenin. All five compounds have good synthetic accessibility and follow Lipinski's rule of five (Table 3). With the exception of naringenin, all compounds exhibit strong GI tract absorption potential and a high probability of crossing the blood-brain barrier (BBB) in the BOILED egg model (Fig. 7). A visual depiction of each compound's pharmacokinetic characteristics is also provided by the spider web chart which offers thorough insights into the compounds' potential as therapeutic agents.

The molecular docking of naringenin and its O-alkyl derivatives with the estrogen receptor (ER) targeted against breast cancer presents a promising avenue for its therapeutic intervention. Naringenin, a flavonoid found abundantly in citrus fruits, has been recognized for its potential anticancer properties, which include its ability to modulate estrogen signaling pathways implicated in breast cancer development and progression[16]. The estrogen receptor, particularly ERα, plays a pivotal role in the regulation of breast cancer cell proliferation and survival [17]. Naringenin's ability to interact with ERα suggests its potential as a selective estrogen receptor modulator (SERM), exerting either agonistic or antagonistic effects depending on the cellular context[18].

Molecular docking studies enable the prediction of the binding affinity and mode of interaction between naringenin and ERα, providing valuable insights into the structural basis of their interaction. O-alkyl derivatives of naringenin are sought after to enhance the bioavailability and target specificity, offering improved pharmacokinetic properties and potentially greater efficacy in treating diseases such as breast cancer[19].

The results of molecular docking studies targeting estrogen receptor-α (ER-α) provide valuable insights into the interaction between the receptor and five compounds namely naringenin, isosakuranetin, 5-O-methylnaringenin, sakuranetin and 4',7-Di-O-methylnaringenin. The docking simulations conducted using AutoDock Vina 4.2 revealed distinct binding conformations and binding energies for each compound, elucidating the molecular basis of their interaction with ER-α.

Table 3
SwissADME analysis

Phytochemical	Physicochemical property	Water solubility		Pharmacokinetics					Drug likeness	Medicinal Chemistry
	Mol. Weight (g/mol)	Log S (ESOL)	Solubility (mg/ml)	GI Absorptio	BBB Permeant	P-gp Substrate	CYP2C19 Inhibitor	Log Kp Skin Permeatio	Lipinski	Lead likeness
Naringenin	272.25	-3.49	8.74e-02	High	No	Yes	No	-6.17	Yes	Yes
Isosakuranetin	286.28	-3.70	5.70e-02	High	Yes	No	Yes	-6.02	Yes	Yes
5'-O-methylnaringenin	286.28	-3.35	1.26e-01	High	Yes	Yes	No	-6.41	Yes	Yes
Sakuranetin	286.28	-3.70	5.70e-02	High	Yes	No	Yes	-6.02	Yes	Yes
4’7'-Di-O-methylnaringenin	300.31	-3.90	3.74e-02	High	Yes	No	Yes	-5.88	Yes	Yes

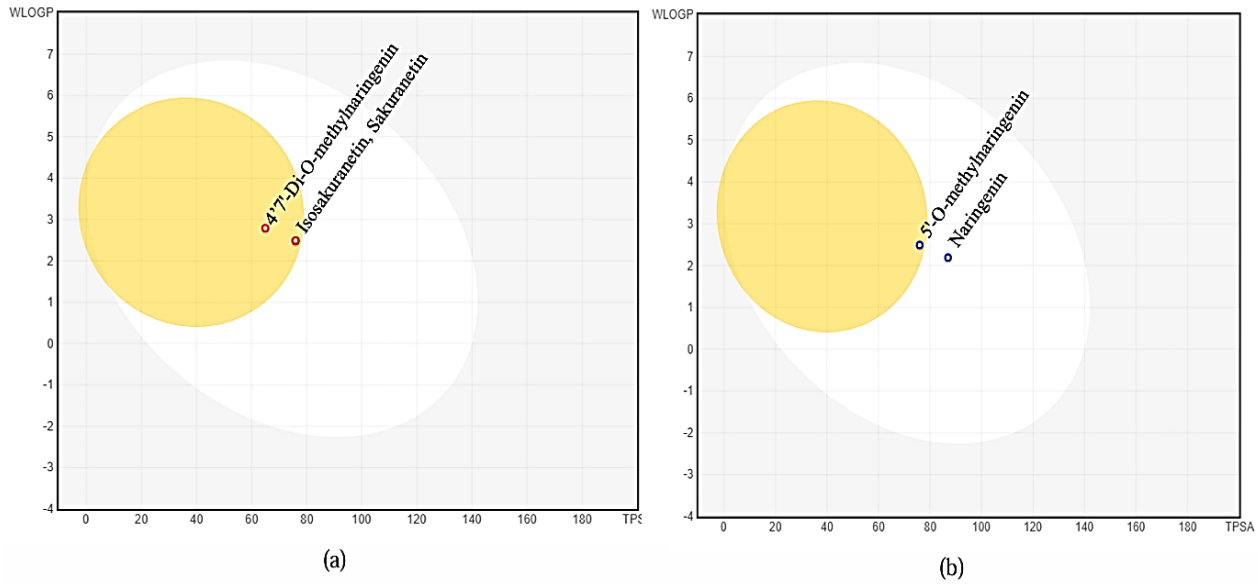


Fig. 6: BOILED-Egg graph of Naringenin and its O-Alkyl derivatives: Points within BOILED-Egg's yolk are compounds that are expected to pass across the blood-brain barrier passively. Points in the BOILED-Egg's white are compounds that are expected to be passively absorbed via the gastrointestinal tract. Blue dots represent compounds projected to be eliminated through the central nervous system by the P-glycoprotein. Red dots indicate compounds that the P-glycoprotein is unlikely to remove from the central nervous system. (a) BOILED-Egg graph of isosakuranetin, sakuranetin and 4’7'-Di-O-methylnaringenin. (b) BOILED-Egg graph of naringenin and 5'-O-methylnaringenin.

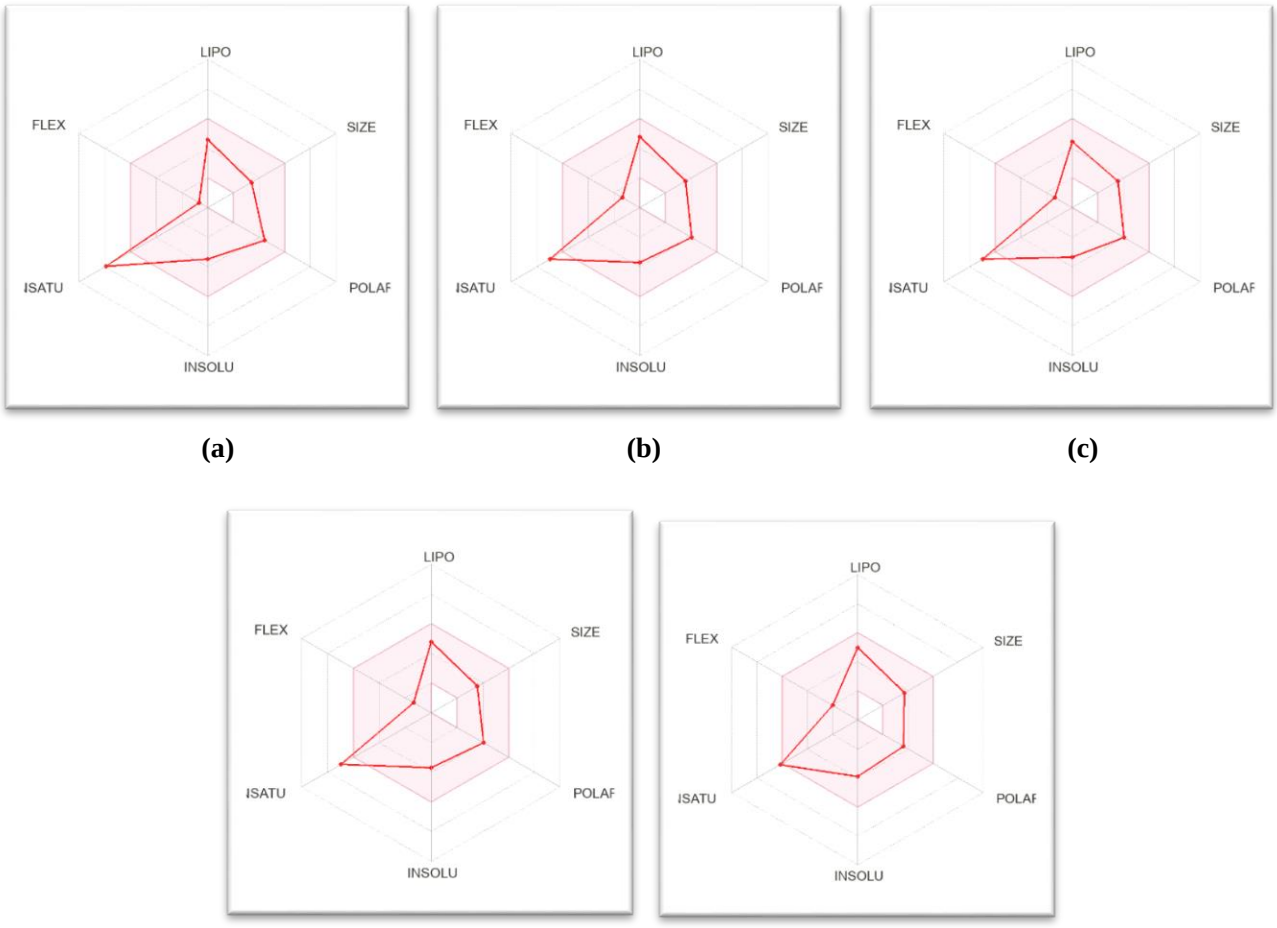


Fig. 7: Radar chart for (a) Naringenin, (b) Isosakuranetin, (c) 5-O-Methylnaringenin, (d) Sakuranetin and (e) 4',7-Di-O-methylnaringenin. The bioavailability radar considers six physicochemical variables to offer a succinct picture of medication similarities. The molecules under investigation have the following properties: lipophilicity (LIPO), size, polarity, insolubility and irreducibility (insaturation) and FLEX. The particular requirements for these characteristics are listed below: Size, defined by Molecular Weight (MW); Lipophilicity, indicated by XLOGP3 within the range of -0.7 to +5.0; Polarity determined by Topological Polar Surface Area (TPSA) between 20 and 150 g/mol; Insolubility and Irreducibility, expressed through a threshold of 130 0A2 and Log S not exceeding 6; Solubility Saturation, requiring at least 0.25 percent of carbons in the sp3 hybridization; and Flexibility, restricted to a maximum of 9 rotatable links.

For naringenin, the most favorable binding energy of -8.7 kcal/mol was observed, followed by 5'-O-methylnaringenin, with a binding energy of -8.2.

The results provide detailed information on the binding modes and interaction interfaces of naringenin and its O-alkyl derivatives with ER-α, offering insights into their potential as modulators of estrogen signaling pathways. These findings strengthen our understanding of the structure-activity relationship of these compounds and may guide the rational design of novel therapeutics targeting ER-α in breast cancer and other estrogen-related diseases.

The analysis of naringenin and its derivatives using SwissADME revealed several important pharmacokinetic characteristics, shedding light on their potential as therapeutic agents. Notably, isosakuranetin, 5'-O-methylnaringenin, sakuranetin and 4'7'-Di-O-methylnaringenin demonstrated permeability across the blood-brain barrier (BBB), suggesting possible central nervous system effects. Anti-breast cancer drugs require blood-brain barrier (BBB) permeability to address potential metastasis to the brain, ensuring comprehensive treatment coverage and reducing the risk of neurological complications, thereby enhancing patient outcomes[20].

Interestingly, naringenin and 5'-O-methylnaringenin were identified as substances that do not function as P-glycoprotein (P-gp) substrates. This characteristic may confer advantages in terms of reduced susceptibility to drug efflux mechanisms, potentially enhancing their efficacy in clinical settings[21].

Moreover, the presence of CYP inhibition in isosakuranetin, sakuranetin and 4'7'-Di-O-methylnaringenin suggests possible interactions with cytochrome P450 enzymes which

could influence drug metabolism and efficacy[22]. However, it is important to consider the potential for drug-drug interactions when utilizing these compounds in combination with other medications.

Additionally, all five compounds demonstrated good synthetic accessibility and adherence to Lipinski's rule of five, indicating favorable drug-like properties[23]. This suggests that these compounds have the potential for efficient synthesis and development as pharmaceutical agents. The spider web chart provided a visual depiction of each compound's pharmacokinetic characteristics, offering comprehensive insights into their potential as therapeutic agents[24].

This visualization tool aids in the comparison and prioritization of compounds based on their pharmacokinetic profiles, facilitating decision-making in drug discovery and development.

Conclusion

The molecular docking of naringenin and its O-alkyl derivatives with the estrogen receptor against breast cancer represents a valuable strategy for exploring the therapeutic potential of this natural compound. By providing insights into the molecular mechanisms of action, molecular docking studies can guide the development of naringenin-based therapeutics and can facilitate the discovery of novel treatment strategies for breast cancer. The analysis of naringenin and its O-alkyl derivatives using SwissADME revealed promising pharmacokinetic characteristics including BBB permeability, high absorption rates and favorable drug-like properties. These findings underscore the potential of these compounds as therapeutic agents against breast cancer.

Despite the promise of molecular docking studies in elucidating the interactions between naringenin and the estrogen receptor, it is important to acknowledge certain limitations. Computational predictions from docking simulations should be validated through experimental assays such as binding studies or functional assays to confirm the biological relevance of the predicted interactions. Additionally, the complexities of *in vivo* pharmacokinetics and pharmacodynamics must be considered when translating computational findings into clinical applications. Additional preclinical and clinical investigations are needed to validate these findings and to determine the therapeutic potential of these substances in relevant disease circumstances.

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