Araştırma Makalesi – Original Article

Harnessing Bioactive Compounds: Hesperidin and Its Derivatives in Estrogen Receptor-Related Pathologies*

Biyoaktif Bileşiklerden Yararlanma: Östrojen Reseptörüyle İlişkili Patolojilerde Hesperidin ve Türevleri

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ABSTRACT

Aim: Hesperidin and its derivatives, including hesperetin, diosmin, diosmetin, and neohesperidin, are flavonoids predominantly found in citrus fruits. These compounds have gained significant interest due to their potential therapeutic effects, particularly in estrogen receptor-related diseases. This study aims to evaluate the binding affinities and interaction mechanisms of hesperidin and its derivatives with estrogen receptor alpha (ER-α) using molecular docking techniques.

Methods: Molecular docking simulations were performed to determine the binding energies of hesperidin derivatives with ER-α. ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) analysis was conducted to evaluate pharmacokinetic properties, including bioavailability, blood-brain barrier permeability, and intestinal absorption.

Results: Diosmin exhibited the highest binding affinity among the derivatives, with a binding energy comparable to Tamoxifen, a standard anti-cancer drug. However, its slightly lower binding energy may affect its clinical efficacy. Neohesperidin demonstrated promising affinity but had poor intestinal absorption, limiting its bioavailability. ADMET analysis revealed that while these flavonoids generally have favorable pharmacokinetic properties, factors such as poor blood-brain barrier permeability and variable absorption rates may restrict their therapeutic effectiveness.

Conclusion: Despite certain pharmacokinetic challenges, hesperidin and its derivatives exhibit promising interactions with ER-α, suggesting their potential as alternative or adjunct therapies to Tamoxifen.

Keywords: Hesperidin, Diosmin, Estrogen Receptor, Molecular Docking, Pharmacokinetics, Bioavailability

ÖZ

Amaç: Hesperidin ve türevleri olan hesperetin, diosmin, diosmetin ve neohesperidin, ağırlıklı olarak narenciye meyvelerinde bulunan biyoaktif bileşiklerdir. Bu bileşikler, özellikle östrojen reseptörüyle ilişkili hastalıklardaki potansiyel terapötik etkileri nedeniyle önemli ölçüde ilgi görmektedir. Bu çalışma, hesperidin ve türevlerinin östrojen reseptör alfa (ER-α) ile olan bağlanma afinitelerini ve etkileşim mekanizmalarını moleküler docking (bağlanma simülasyonu) teknikleri kullanarak değerlendirmeyi amaçlamaktadır.

Yöntemler: Hesperidin türevlerinin ER-α ile bağlanma enerjilerini belirlemek amacıyla moleküler docking simülasyonları gerçekleştirilmiştir. Ayrıca, biyoyararlanım, kan-beyin bariyeri geçirgenliği ve bağırsak emilimi gibi farmakokinetik özellikleri değerlendirmek için ADMET (Emilim, Dağılım, Metabolizma, Atılım ve Toksisite) analizi yapılmıştır.

Bulgular: Diosmin, türevler arasında en yüksek bağlanma afinitesini göstermiş ve bu değeriyle standart bir anti-kanser ilacı olan Tamoksifen'e yakın bir bağlanma enerjisi elde etmiştir. Ancak, biraz daha düşük bağlanma enerjisi klinik etkinliğini etkileyebilir. Neohesperidin umut verici bir bağlanma afinitesi göstermiştir, ancak zayıf bağırsak emilimi nedeniyle biyoyararlanımı sınırlıdır. ADMET analizi, bu flavonoidlerin genel olarak olumlu farmakokinetik özelliklere sahip olduğunu, ancak zayıf kan-beyin bariyeri geçirgenliği ve değişken emilim oranları gibi bazı etkenlerin terapötik etkinliklerini sınırlayabileceğini ortaya koymuştur.

Sonuç: Belirli farmakokinetik zorluklara rağmen, hesperidin ve türevleri ER-α ile umut verici etkileşimler sergilemekte olup, Tamoksifen'e alternatif veya tamamlayıcı tedavi seçenekleri olarak potansiyele sahiptir.

Anahtar Kelimeler: Hesperidin, Diosmin, Östrojen Reseptörü, Moleküler Docking, Farmakokinetik, Biyoyararlanım

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Introduction

Flavonoids are a diverse group of phytonutrients found in various fruits and vegetables, known for their potent antioxidant properties. Among these, the flavanones hesperidin, hesperitin, diosmin, diosmetin, and neohesperidin have garnered significant attention due to their potential health benefits. These chemicals are mostly present in the citrus fruit and have been well researched for their pharmacological activities.

Hesperidin is a flavanone glycoside predominantly found in citrus fruits such as oranges and lemons. It has a variety of biological actions, including anti-carcinogenic, anti-inflammatory, and antioxidant effects. Hesperidin has been shown to reduce blood lipid levels and enhance vascular endothelial function, thus playing a crucial role in cardiovascular health.[1] Furthermore, hesperidin has shown neuroprotective advantages, making it a good option for treating neurodegenerative illnesses.[2]

Hesperitin is the aglycone form of hesperidin and shares many of its precursor's biological activities. Hesperitin exhibits strong anti-inflammatory, antioxidant, and antimicrobial effects. It has been shown to inhibit the proliferation of various cancer cell lines and induce apoptosis, making it a significant compound in cancer research.[1] Furthermore, hesperitin's ability to cross the blood-brain barrier enhances its potential in treating central nervous system disorders.[2]

Diosmin, another flavanone glycoside, is used therapeutically in chronic venous insufficiency and hemorrhoidal disease due to its vascular protective effects. Diosmin's ability to improve venous tone, lymphatic drainage, and microcirculation is well documented.[3] Its anti-inflammatory and antioxidant properties further contribute to its therapeutic potential.[4] Recent studies have also highlighted diosmin's role in modulating glucose and lipid metabolism, suggesting benefits in managing metabolic syndrome.[3]

Diosmetin is the aglycone derivative of diosmin and possesses similar biological activities. Diosmetin is noted for its anti-inflammatory and antioxidant properties, which are attributed to its capacity to modulate key signaling pathways involved in inflammation and oxidative stress.[4] Additionally, diosmetin has shown promise in cancer therapy, where it exerts cytotoxic effects on cancer cells through the induction of apoptosis and cell cycle arrest.[4]

Neohesperidin is another important flavanone glycoside found in citrus fruits, often converted to its aglycone form, neohesperitin. Neohesperidin has demonstrated significant anti-inflammatory, antioxidant, and lipid-lowering effects.[5] Its potential in modulating glucose metabolism and enhancing insulin sensitivity underscores its utility in diabetes management. [5] Moreover, neohesperidin is studied for its neuroprotective properties, offering potential benefits in neurodegenerative diseases.[3]

Hesperidin and its derivatives have also been investigated for their interactions with estrogen receptors, particularly estrogen receptor alpha (ERα). These interactions are significant as they can influence the regulation of various biological processes. Hesperidin has been shown to regulate estrogen signaling pathways, which play a crucial role in bone health by promoting osteogenesis and reducing osteoclastic activity.[6] Furthermore, hesperidin's modulation of ERα has been implicated in its anti-cancer properties, particularly in breast cancer, where it inhibits the proliferation of cancer cells and induces apoptosis.[6] Similarly, hesperetin has been found to exhibit selective estrogen receptor modulation, contributing to its potential therapeutic effects in hormone-related conditions.[7]

This study aims to shed light on the development of novel therapeutic agents for estrogen receptor-related pathologies by investigating the detailed interactions between hesperidin and its derivatives with estrogen receptor alpha (ER-α). Given the crucial role of ER-α in diseases such as breast cancer and osteoporosis, elucidating the interaction mechanisms of these flavanones with the receptor may contribute to the

development of more targeted treatment strategies for these conditions. In this context, the findings of the study could pave the way for new approaches in cancer research and the treatment of hormone-related disorders.

Materials and Methods

Protein and Ligand Preparation:

ER-a (PDB ID:3ERT) 3D crystal structure was downloaded from the protein data bank.[8] The 3ERT structure found in the Protein Databank represents estrogen receptor alpha in complex with 4-hydroxytamoxifen. 3ERT is classified as a nuclear receptor [9]. Tamoxifen is the most widely used selective estrogen receptor modulator in breast cancer. Therefore, the 3ERT structure complexed with 4-hydroxytamoxifen was used. Protein structure was prepared with the help of Discovery Studio program.[10] Since 3ERT has a homodimer structure, one of the chains was removed and monomerized. The ligand and water molecules in the 3D crystal structure were removed. The smiles structures of the ligands were taken from PubChem (https://pubchem.ncbi.nlm.nih.gov/) database and converted to pdb file format via Novoprolabs converter (https://www.novoprolabs.com/tools/smiles2pdb). Hesperidin, hesperetin, diosmin, diosmetin, neohesperdin molecules were used as ligands. The natural 4-hydroxy-tamoxifen hesperidin and its derivatives in 3ERT crystal structure were used for control.

Molecular docking:

Autodock Vina was used in molecular docking studies. Receptor and ligand molecules were made ready for docking with the help of Autodock 4.2.6 program.[11] By determining the binding site of the original ligands in the crystal structure of the receptor molecules; grid box settings were created. Grid box settings were set to x = 27.432, y =-2.033, z = 26.269 coordinates and 30x30x30 dimensions. For each ligand, the structure with the lowest binding energy was determined as the best structure. After docking, the interactions between receptor and ligand molecules were examined using Discovery Studio Visualizer program.

Determination of Pharmacokinetic and Toxicological Properties:

Pharmacokinetic, toxicity properties of the ligands were determined using pKCSM (https://biosig.lab.uq.edu.au/pkcsm/) web tools. SMILES structures of hesperidin and its derivatives were loaded into pKCSM to obtain ADMET properties.

Results

Molecular docking studies

The molecular docking data for the binding of hesperidin and its derivatives to the estrogen receptor protein (3ERT) are presented in ***Table 1***. 4-Hydroxytamoxifen is the natural ligand in the crystal structure of 3ERT and was again docked and validated.

Table 1. Summary of the estimated binding affinity (measured in kcal/mol) of the docked ligands against the ER-a receptor and the specific residues with which they interact at the binding sites.

Ligands	Binding energy (kcal/mol)	Interacted residues with ligand		
		Hydrogen bond	Pi-Sulfur	Alkyl and Pi- Alkyl
4OHT (Reference)	-9,8	GLU353	MET343	ALA350, MET388, LEU428, LEU525
Tamoxifen (Anticancer drug)	-9,0			LEU346, ALA350, TRP383, LEU525
Diosmin	-8,8	LEU525, VAL534, LEU536	MET343, ASP351	ALA350, LEU384, LEU387, MET388, LEU391, LEU525
Neohesperidin	-8,6	CYS530	MET343	LEU346, ALA350, LEU525
Hesperidin	-8,5	GLU380, TRP383, CYS530, VAL535	MET343	LEU346, ALA350, LEU525
Diosmetin	-7,8	GLU353	MET343	ALA350, LEU387, LEU525
Hesperitin	-7,1	THR347, GLY420, HIS524	MET343	ALA350, TRP383, LEU525

The docking analyses were validated against ligand 4-hydroxy-tamoxifen. The best docking findings were shown by the natural ligand 4-hydroxytamoxifen, which had the most advantageous free bond kinetic energy of-9.8 kcal/mol. Diosmin has a free bond kinetic energy of-8.8 kcal/mol, while tamoxifen, an anticancer medication, falls closely behind with a value of-9.0 kcal/mol. The highest compound was the positive control compound 4-hydroxytamoxifen (OHT). It is seen that diosmine, one of the hesperidin derivatives, has a binding energy close to tamoxifen. It binds to a binding site similar to the reference ligand, as indicated by the amino acids marked in red in ***Table 1***. Hesperidin and its derivatives have the potential to be 3ERT inhibitors by interacting with amino acids in the 3ERT active site. The interactions between the 3ERT receptor molecule and the binding ligands are given in the ***Figure 1.***

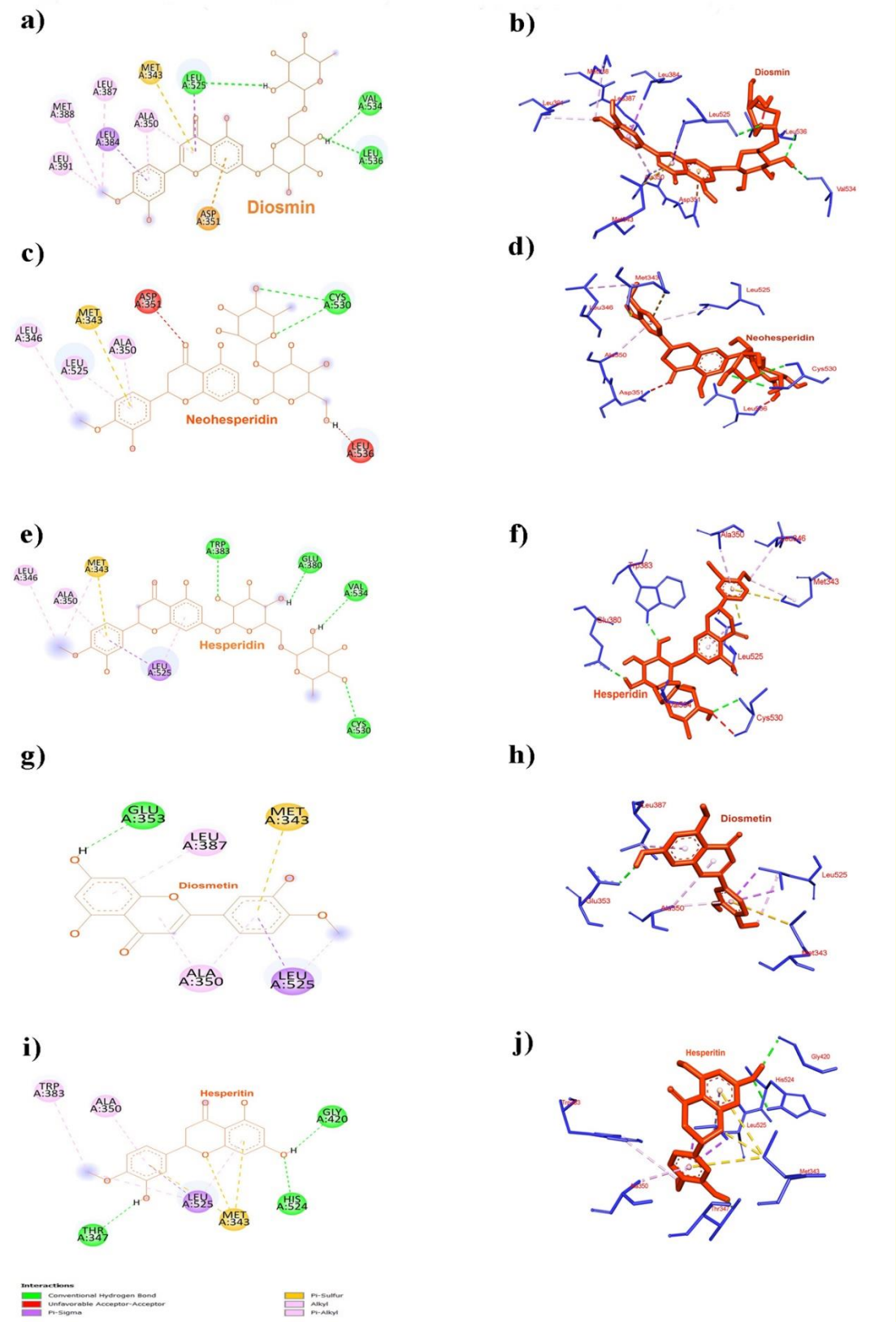

Figure 1. Binding pose profile of Ligands in the ER-a binding domain two-dimension (2D) and three-dimension (3D) interactions analysis. Diosmin and ER-a binding domain 2D and 3D interactions (a-b). Neohesperidin and ER-a binding domain 2D and 3D interactions (c-d). Hesperidin and ER-a binding domain 2D and 3D interactions (e-f). Diosmetin and ER-a binding domain 2D and 3D interactions (g-h). Hesperitin and ER-a binding domain 2D and 3D interactions (i-j).

Figure 2 shows the SAS, H-Bond and hydrophilicity properties of the ligands dockigged with 3ERT. SAS surface is shown with blue color scale 25.0, 22.5, 20, 17.5 and green color scale 15.0, 12.5, 10.0. The hydrogen bond surface is shown with the donor color in purple and acceptor in green. Figure 2 illustrate the measurement of solvent-accessible surface area, highlighting how much a molecule can interact with the solvent. Additionally, it addresses the hydrophobic nature of the compound, which is influenced by the presence of nonpolar groups or molecules in water, due to water's tendency to exclude nonpolar substances.

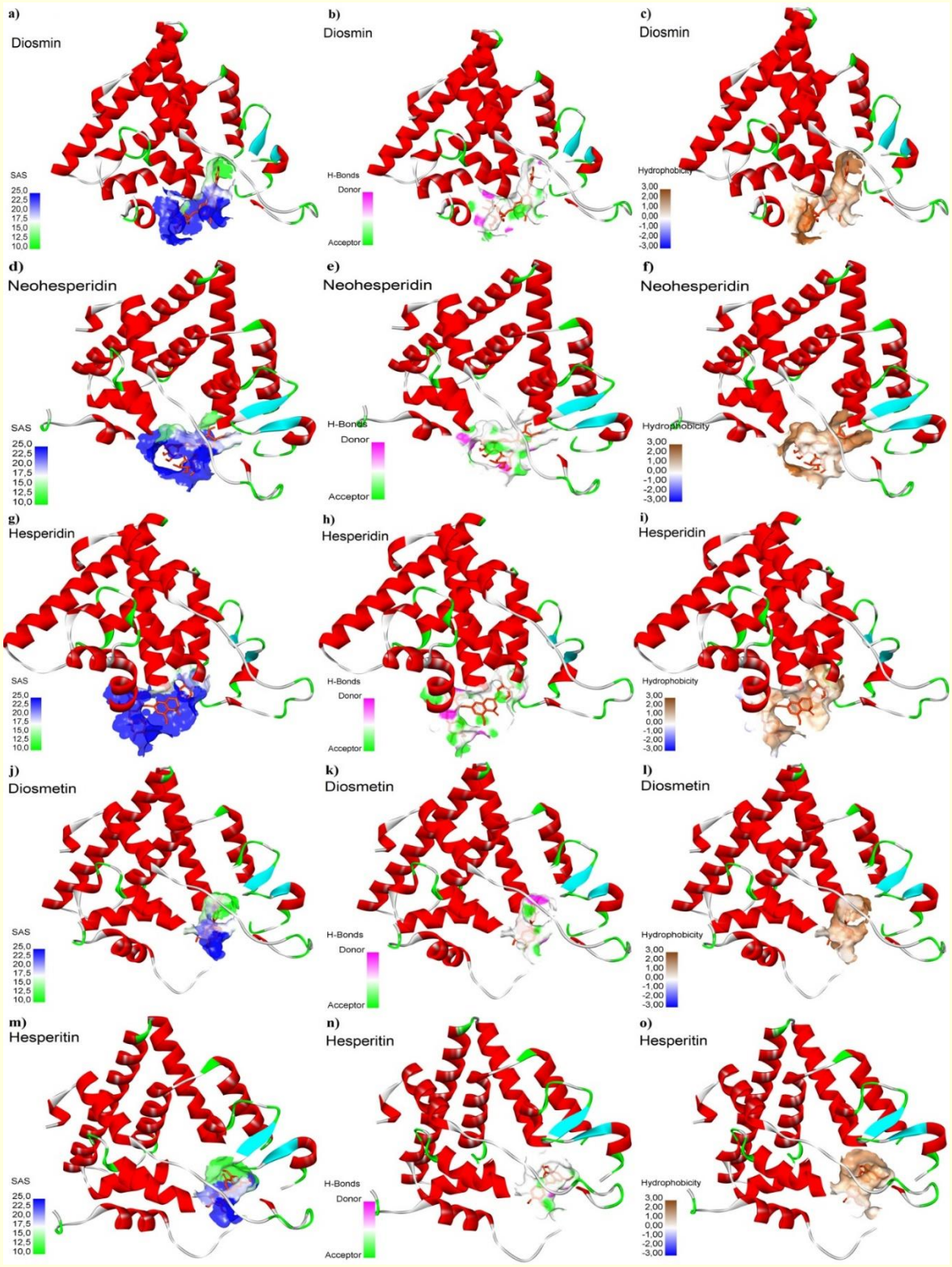

Figure 2. SAS, H-bond (Donor –Acceptor), and Hydrophobicity of 3ERT with Ligands.

Investigation of ADMET Properties

The ADMET prediction of hesperidin and its derivatives using pKCSM can be seen in ***Table 2***.

Table 2. ADMET features

ADMET	Parameters	Hesperidin	Hesperitin	Diosmin	Diosmetin	Neohesperidin
Absorption	**Permeability of Caco2** (log Papp in 10-6 cm/s)	0,505	0,294	0,305	0,326	0,570
	Absorbency in the gastrointestinal system (human) (%)	31,481	70,277	29,319	79,898	20,652
	Permeability of Skin (log Kp)	-2,735	-2,737	-2,735	-2,735	-2,735
Distribution	**VDss (human)** (log L/kg)	0,996	0,746	1,428	0,709	0,348
	Permeability of BBB (log BB)	-1,715	-0,719	-1,795	-0,954	-1,72
	Permeability of CNS (log PS)	-4,807	-2,976	-4,836	-2,316	-4,872
Metabolism	**Substrate for CYP2D6** (Yes/No)	No	No	No	No	No
	Inhibitior of CYP2D6 (Yes/No)	No	No	No	No	No
	Substrate for CYP3A4 (Yes/No**)**	No	No	No	No	No
	Inhibitor of CYP3A4 (Yes/No)	No	No	No	No	No
Excretion	**Clearance Total** (log ml/min/kg)	0,211	0,044	-0,113	0,598	0,222
	Substrate for renal OCT2	No	No	No	No	No
Toxicity	**AMES toxicity** (Yes/No)	No	No	No	No	No
	Max. tolerated dose (human) (log mg/kg/day**)**	0,525	0,25	0,565	0,42	0,389

The capacity of a substance to permeate Caco-2 cells while exhibiting excellent absorption in the gut of humans is indicated by its high permeability. If absorption from the intestine is less than 30%, the substance is considered poorly absorbed. In addition, Caco2 permeability logPapp> 0.9 Caco2 permeability is considered high.[12] Hesperidin, hesperetin diosmin and diosmetin have acceptable intestinal absorption. Neohesperidin has low intestinal absorption. Hesperidin and its derivatives have low Caco2 permeability. logVDss> 0.45 means that the compounds are well distributed in tissues, logVDss <-0.15 means poor distribution.[12] Hesperidin derivatives have good distribution properties in tissues. LogBB values less than -1 indicate poor blood-brain barrier permeability.[12] As a result, the fact that hesperetin and diosmetin can pass across the blood brain barrier, also known as the BBB, suggests that they have a high level of BBB penetration. The BBB is not well penetrated by substances such as hesperidin, diosmin, and neohesperidin. P450 inhibitors have the ability to dramatically change these medications' pharmacokinetics. CYP2D6 and CYP3A4 are enzymes found in the human liver and play an important role in the metabolism of many drugs and substances. Hesperidin and its derivatives are not substrates and inhibitors of the CYP2D6 and CYP3A4 enzymes. When combined with renal OCT2 inhibitors, hesperidin and its derivatives do not exhibit renal OCT2 substrates, suggesting that none of the compounds are hazardous. Hesperidin and its derivatives have no AMES toxicity.

Discussion

In this study, the interactions of Hesperidin and its derivatives with the estrogen receptor (ER-α) were investigated by molecular docking and ADMET analysis. Diosmin stood out as the most potent Hesperidin

derivative, showing binding affinity close to Tamoxifen. However, the binding energy of Diosmin is not as high as Tamoxifen, suggesting that its clinical efficacy may be lower compared to Tamoxifen.

Neohesperidin was found to have a binding affinity close to Diosmin, but low intestinal absorption. This low absorption may limit the bioavailability of Neohesperidin. However, a study in the literature reported that the absorption was increased by converting Neohesperidin to propionyl ester form and the effects of modified Neohesperidin on breast cancer cell line showed positive results. This study shows that the bioavailability problems of Neohesperidin can be solved by such chemical modifications.[13]

Other docking studies in the literature support that Hesperidin and its derivatives may have similar effects to Tamoxifen but may differ in efficacy. For example, one study showed that Hesperidin in combination with Tamoxifen enhanced the antiproliferative effects of Hesperidin in breast cancer cell lines and that this combination produced a more potent cytotoxic effect compared to Hesperidin or Tamoxifen alone. These findings suggest that Hesperidin may produce synergistic effects when used in combination with Tamoxifen.[14]

Other studies in the literature also support these findings. For example, a study by Zhang et al. showed that the effects of Hesperidin on ER-α may be beneficial by increasing bone mineral density in diseases associated with estrogen deficiency such as osteoporosis.[15] Furthermore, it has been reported that the anti-inflammatory effects of Hesperidin may be modulated through estrogen receptors.[16] This is consistent with the finding in our study that Hesperidin showed strong binding propensity with ER-α.

However, the pharmacokinetic properties of Hesperidin and its derivatives may also significantly affect the bioavailability and therapeutic potential of these flavonoids. ADMET analyses have shown that Hesperetin and Diosmetin have high intestinal absorption and therefore are well translocated into the systemic circulation.[17] However, Neohesperidin was found to have low intestinal absorption and therefore bioavailability may be limited. These findings point to potential challenges in the clinical use of Neohesperidine.[18]

The pharmacokinetic profile of Hesperidin is in line with other findings in the literature. In particular, a study by Pires et al. suggests that Hesperidin has low blood-brain barrier permeability, so it may exert limited effects on the central nervous system.[12] However, the higher blood-brain barrier permeability of Hesperetin suggests that this derivative could be used as a potential therapeutic agent in neurological diseases.[19]

Conclusion

This study examined the interactions of hesperidin and its derivatives with estrogen receptor alpha (ERα) through molecular docking techniques. The results indicate that flavanones possess strong binding potential to estrogen receptors, which may allow the development of novel therapeutic agents for estrogen-related pathologies, especially diseases like breast cancer and osteoporosis. The findings highlight the potential for hesperidin and its derivatives to act as selective estrogen receptor modulators, offering new avenues for the treatment of hormone-related disorders. Further validation of these results in clinical studies is essential to fully assess the therapeutic efficacy of these compounds. Additionally, the study's findings suggest that hesperidin derivatives may be beneficial in treating a wide range of conditions, including neurodegenerative diseases, diabetes, and cardiovascular disorders.

In conclusion, this study provides an essential scientific foundation for better understanding and developing the pharmaceutical and clinical applications of hesperidin and its derivatives. The continued exploration of these compounds may significantly contribute to the advancement of therapeutic options for various estrogen-related and chronic diseases.

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The authors declared no potential conflicts of interest.

Author Contributions

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References

1. Pyrzynska K. Hesperidin: A Review on Extraction Methods, Stability and Biological Activities. Nutrients 2022;14(12):2387. Available from: https://doi.org/10.3390/nu14122387
2. Choi S-S, Lee S-H, Lee K-A. A Comparative Study of Hesperetin, Hesperidin and Hesperidin Glucoside: Antioxidant, Anti-Inflammatory, and Antibacterial Activities In Vitro. Antioxidants 2022;11(8):1618. Available from: https://doi.org/10.3390/antiox11081618
3. Borghi SM, Pavanelli WR. Antioxidant Compounds and Health Benefits of Citrus Fruits. Antioxidants 2023;12(8):1526. Available from: https://doi.org/10.3390/antiox12081526
4. Ortiz AdC, et al. Therapeutic Effects of Citrus Flavonoids Neohesperidin, Hesperidin and Its Aglycone, Hesperetin on Bone Health. Biomolecules 2022;12(5):626. Available from: https://doi.org/10.3390/biom12050626
5. Khorasanian AS, et al. The effects of hesperidin supplementation on cardiovascular risk factors in adults: A systematic review and dose–response meta analysis. Frontiersin Nutrition 2023;10:1177708. Available from: https://doi.org/10.3389/fnut.2023.1177708
6. Hu H-Y, et al. Hesperidin Anti-Osteoporosis by Regulating Estrogen Signaling Pathways. Molecules 2023;28(19):6987. Available from: https://doi.org/10.3390/molecules28196987
7. Safe S, et al. Flavonoids: structure–function and mechanisms of action and opportunities for drug development. Toxicol Res 2021; 37:147–162. Available from: https://doi.org/10.1007/s43188-020-00080-z
8. Berman HM, et al. The Protein Data Bank. Nucleic Acids Res 2000;28(1):235-42. Available from: https://doi.org/10.1093/nar/28.1.235
9. Shiau AK, et al. The structural basis of estrogen receptor/coactivator recognition and the antagonism of this interaction by tamoxifen. Cell. 1998; 95(7):927-37. Available from: https://doi.org/10.1016/s0092-8674(00)81717-1.
10. BIOVIA DS, Dassault Systèmes, Discovery Studio. San Diego, CA, USA: Accelrys Inc; 2017
11. Morris GM, et al. AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. J Comput Chem. 2009; 30(16):2785-91. Available from: https://doi.org/10.1002/jcc.21256
12. Pires DE, Blundell TL, Ascher DB. pkCSM: Predicting Small-Molecule Pharmacokinetic and Toxicity Properties Using Graph-Based Signatures. J Med Chem 2015; 58(9):4066-72. Available from: https://doi.org/10.1021/acs.jmedchem.5b00104
13. Madureira MB, et al. Naringenin and Hesperidin as Promising Alternatives for Prevention and Co-Adjuvant Therapy for Breast Cancer. Antioxidants 2023;12(3):586. Available from: https://doi.org/10.3390/antiox12030586
14. Khamis AA, Ali EMM, Salim EI. Synergistic effects of bee venom, hesperidin, and piperine with tamoxifen on apoptotic and angiogenesis biomarker molecules against xerographic MCF-7 injected rats. Sci Rep 2024;14:1510. Available from: https://doi.org/10.1038/s41598-023-50729-6
15. Zhang, Q., et al. Antiosteoporotic effect of hesperidin against ovariectomy-induced osteoporosis in rats via reduction of oxidative stress and inflammation. Journal of Biochemical and Molecular Toxicology, 2021; 35(8):e22832. Available from: https://doi.org/10.1002/jbt.22832
16. Liu XM, et al. Dietary total flavonoids intake and risk of mortality from all causes and cardiovascular disease in the general population: a systematic review and meta-analysis of cohort studies. Mol Nutr Food Res 2017;61(6); 1601003 Available from: https://doi.org/10.1002/mnfr.201601003
17. Xia N, et al. Synthesis of Hydrophobic Propionyl Neohesperidin Ester Using an Immobilied Enzyme and Description of Its Anti-proliferative and Pro-apoptotic Effects on MCF-7 Human Breast Cancer Cells. Frontiers in Bioengineering and Biotechnology 2020 8:544714. Available from: https://doi.org/10.3389/fbioe.2020.01025
18. Abdullahi SH, Uzairu A, Shallangwa GA. In-silico activity prediction, structure-based drug design, molecular docking and pharmacokinetic studies of selected quinazoline derivatives for their antiproliferative activity against triple negative breast cancer (MDA-MB231) cell line. Bull Natl Res Cent 2022; 46:2. Available from: https://doi.org/10.1186/s42269-021-00690-z
19. Evans JA, Mendonca P, Soliman KFA. Neuroprotective Effects and Therapeutic Potential of the Citrus Flavonoid Hesperetin in Neurodegenerative Diseases. Nutrients 2022;14(11):2228. Available from: https://doi.org/10.3390/nu14112228