FEN ve MÜHENDİSLİK BİLİMLERİ DERGİSİ

Cilt/Vol: 7 Sayı/No: 1 Yıl/Year: 2025 Araştırma Makalesi/Research Article e-ISSN: 2667-7989

https://doi.org/10.47112/neufmbd.2025.70

Timokinon ve Timol'ün Histamin Reseptörleri Üzerinde Moleküler Kenetleme Analizi

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Makale Bilgisi

Geliş Tarihi: 31.01.2024
Kabul Tarihi: 30.06.2024
Yayın Tarihi: 30.04.2025

Anahtar Kelimeler:
Timokinon,
Timol,
Histamin reseptörleri,
Moleküler kenetlenme,
Nigella sativa L.

ÖZET

Çörek otu veya *N. sativa* L., dünya çapında geniş bir alana yayılmış olan değerli bitkiler arasında popüler bir şifalı ottur. Geleneksel tıpta, solunum, sindirim ve kardiyovasküler sistemlerle ilgili hastalıkları tedavi etmek için kullanılmıştır. Timokinon, özellikle *Nigella sativa* L. bitkisinde bulunan bitki kökenli bir bileşik olan timolün türevidir ve antioksidan, anti-enflamatuar ve antitümör özelliklere sahip doğal bir fenolik bileşiktir. Timol ise bir monoterpendir ve çeşitli bitkilerde doğal olarak bulunan bir uçucu yağ bileşenidir. Antioksidan, antiseptik, antimikrobiyal ve anti-enflamatuar özelliklere sahiptir. Timokinon ve timol, anti-alerjik etkilere sahiptir ve alerjik reaksiyonları hafifletmek veya önlemek için kullanılan bileşenler olarak bilinir. Bu çalışmada insan vücudunda bulunan alerji reseptörü olan H1R, H2R, H3R, and H4R histamine reseptörleri tercih edilmiştir. Yapılan moleküler yerleştirme çalışmaları sonucunda timokinon ve timolün H1R, H2R, H3R, and H4R histamine reseptörleri için önemli afiniteye sahip bir molekül olduğu gösterilmiştir.

Molecular Docking Analysis of Thymoquinone and Thymol on Histamine Receptors

Article Info

Received: 31.01.2024
Accepted: 30.06.2024
Published: 30.04.2025

Keywords:
Thymoquinone,
Thymol,
Histamine receptors,
Molecular docking,
Nigella sativa L.

ABSTRACT

Black cumin or *N. sativa* L. is a popular medicinal herb among the valuable plants, native to a wide range of areas around the world. In traditional medicine, it was used to treat diseases related to the respiratory, digestive, and cardiovascular systems. Thymoquinone is a derivative of thymol, a plant-derived compound primarily found in *Nigella sativa* L., and it is a natural phenolic compound with antioxidant, anti-inflammatory, and antitumor properties. Thymol, on the other hand, is a monoterpene and a volatile oil component naturally occurring in various plants. It possesses antioxidant, antiseptic, antimicrobial, and anti-inflammatory properties. Both thymoquinone and thymol exhibit anti-allergic effects and are known as components used to alleviate or prevent allergic reactions. In this study, the allergy receptors present in the human body, namely H1R, H2R, H3R, and H4R histamine receptors, were specifically targeted. Molecular docking studies revealed that thymoquinone and thymol exhibited significant affinity towards H1R, H2R, H3R, and H4R histamine receptors, indicating their potential as molecules of importance in the context of allergic reactions.

Bu makaleye atıfta bulunmak için:

Ediz, E.F. & Demirel Kars, M. (2025). Molecular docking analysis of thymoquinone and thymol on histamine receptors. *Necmettin Erbakan University Journal of Science and Engineering*, *7*(1), 1-11. https://doi.org/10.47112/neufmbd.2025.70

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INTRODUCTION

The use of plants as medicine dates back to the beginning of human history. Among the promising medicinal plants, *Nigella Sativa L*. is considered a sacred seed in Islamic countries, believed to possess the cure for every ailment except death. Both Ibn Sina and Hippocrates accorded special importance to black cumin in their prescriptions [1]. Black cumin or *N. sativa L*. is a popular medicinal herb among the valuable plants, native to a wide range of areas around the world [2]. In traditional medicine, it was used to treat diseases related to the respiratory, digestive, and cardiovascular systems. Moreover, many publications have exhibited a wide range of potential beneficial effects for *N. sativa*, such as antiviral, anti-inflammatory, hypotensive, hypoglycemic, and antitumor properties. Furthermore, the beneficial effects of it have been reported by various studies for some allergic disorders such as allergic asthma, allergic diarrhea, allergic rhinitis, and allergic conjunctivitis [3]. These beneficial properties are related to certain phytochemicals found in *N. sativa*, such as thymoquinone, terpenes, saponins, flavonoids, and essential oils [4]. Thymoquinone is present in *N. sativa* oil seeds as the highest amount of volatile oil. The most beneficial features of *N. sativa* are essentially related to thymoquinone. According to research, thymoquinone exhibits several important health-friendly properties, including antioxidant activity, anti-inflammatory properties, immunomodulatory effects, antihistaminic effects, antimicrobial effects and antitumor effects. Moreover, it has been reported that thymoquinone demonstrates gastroprotective, hepatoprotective, nephroprotective, and neuroprotective effects [5]. Thymol is another important bioactive compound in *N. sativa*. It has antimicrobial, anti-inflammatory, antitumor and fungicidal effects [6,7]. Histamine was formally defined by Windaus and Vogt in 1907, with its biological roles later elucidated by Sir Henry Dale and Laidlaw in 1910 [8]. Until 1932, the role of histamine in allergic reactions was not clearly defined. However, from that point onward, researchers identified histamine as a key regulator of allergic reactions [9]. On the other hand, histamine can be considered as one of the principal mediators of the inflammatory response [10]. The H1 receptor is implicated in early-type hypersensitivity reactions, encompassing symptoms such as itching, redness, swelling, rhinitis, bronchospasm, anaphylaxis, conjunctivitis, and urticaria. Additionally, it exerts central nervous system effects, impacting sleep, attention, convulsions, and food consumption. The H2 receptor contributes to immune system activities, including mast cell degranulation, antibody synthesis, and Th1 cytokine production. The H3 receptor plays a role in the regulation of the sleep-wake cycle, cognition and learning, inflammation, and energy level maintenance. As for H4R, it is involved in functions such as immune cell chemotaxis, cytokine production, autoimmune diseases, and the modulation of colon and breast cancer, as well as nociception [11]. The advent of computer-based approaches has transformed research in life sciences, alleviating the financial burden associated with laboratory expenses and animal experimentation for medical institutions. In silico methods prove valuable for classifying proteins according to their structure and function, offering assistance in the examination of molecular interactions. Molecular docking becomes a valuable tool for assessing potential ligands and receptor complexes in natural therapeutics, contributing significantly to future studies in genetic engineering, biotechnology, and drug development [12]. Thymoquinone and thymol are known compounds that may possess anti-allergic potential. Therefore, performing molecular docking with histamine receptors aims to understand their effects on histamine receptors and elucidate potential anti-allergic mechanisms. This is the first study on the application of molecular docking of thymoquinone and thymol against Histamine 1, Histamine 2, Histamine 3, and Histamine 4 receptors. In this study, the aim is to understand and delineate how the molecular docking of histamine receptors with thymoquinone and thymol affects the allergenic reactions of cells.

MATERIALS AND METHODS

Preparation of Receptors and Ligands

The crystal structures of H1R, H2R, H3R, and H4R histamine receptors were obtained from the Protein Data Bank (PDB) [13] with the following accession numbers: 3RZE, 7UL3, 7F61, and 3P0G, respectively. The resolutions of these receptors were 3.10 Å, 3.00 Å, 2.60 Å, and 3.50 Å, respectively.

To prepare the receptors for molecular docking, the water molecules were removed, and hydrogen atoms and Kollman charges were added to the protein structures using AutoDockTools-1.5.7 software. The structures were then optimized, and output files were obtained in PDBQT format.

The ligands used in the molecular docking, thymoquinone and thymol, were obtained from the PubChem databases (Thymoquinone: 10281 and Thymol: 6989). The molecular structures of thymoquinone and thymol were optimized using PerkinElmer Chemdraw V.22.0.0.22 at the Hartree-Fock theory level prior to the molecular docking. In summary, the crystal structures of histamine receptors H1R, H2R, H3R, and H4R were obtained from PDB. The receptors were then prepared for molecular docking by removing water molecules, adding hydrogen atoms and Kollman charges, and optimizing the protein structures. The ligands, thymoquinone and thymol, were obtained from PubChem, and their molecular structures were optimized prior to the molecular docking.

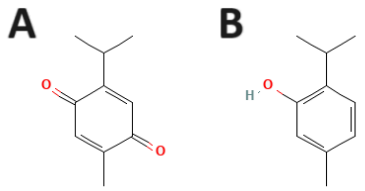

Figure 1

Molecular structures of A) thymoquinone [14] and B) thymol [15]

Molecular Docking

Molecular docking was performed using AutoDock Vina v1.1.2. The values for the dimensions of the grid box and the coordinates of its center are presented in Table 1. The dimensions of the grid box were selected to fully encompass the entire proteins for blind docking. The positions of receptor-ligand binding were visualized using Pymol Edu v.2.5.4, and the resulting binding structures were identified in 2D visual form using the BIOVIA Discovery Studio 2021 software [16,17].

Table 1

Grid box dimensions and center coordinate values for thymoquinone and thymol

RECEPTOR NAME	CODE	Center Coordinate Values (X, Y, Z)	Grid Box Values (X, Y, Z)
H1R	3RZE	27, 30, 46	70, 70, 97
H2R	7UL3	165, 165, 185	47, 40, 59
H3R	7F61	-19, 46, 0	41, 94, 42
H4R	3P0G	42, 15, 11	101, 48, 62

Determination of Pharmacokinetic/ADMET Profile

The ADMET (absorption, distribution, metabolism, excretion, and toxicity) profiles of thymoquinone and thymol were determined using the SwissADME online software from the Swiss Institute of Bioinformatics [18] to assess their pharmacokinetic properties. The SMILES strings of thymoquinone and thymol were calculated using the PubChem OEChem V2.3.0 software and shown in Table 2. The canonical SMILES strings of thymoquinone and thymol were input into the online software to calculate various parameters, including blood-brain barrier permeability, Log Kp value, binding to P-

glycoprotein, inhibition of cytochrome P450 (CYP450), clearance and volume distribution, Lipinski's rule, and bioavailability. Additionally, the *in silico* toxicity of thymoquinone and thymol was evaluated based on the OECD guidelines for oral LD50 in mice using the GUSAR-Online web-based server [19].

Table 2
SMILES strings of thymoquinone and thymol

LIGAND	SMILES STRINGS
thymoquinone	[H]C1=C(C(=O)C([H])=C(C1=O)C([H])(C([H])([H])[H])C([H])([H])[H])C([H])([H])[H]
thymol	[H]OC1=C(C([H])=C([H])C(=C1[H])C([H])([H])[H])C([H])(C([H])([H])[H])C([H])([H])[H]

RESULTS

Thymoquinone and thymol molecules were molecularly docked to four different histamine receptors (H1R, H2R, H3R, and H4R) at the molecular level, and the binding energies were calculated. The highest affinity values for each receptor were shown in Table 3 for thymoquinone and in Table 4 for thymol.

Table 3
Molecular docking results of thymoquinone to target receptors

RECEPTOR CODE	RECEPTOR NAME	BINDING ENERGY (KCAL/MOL)	RMSD Å	INTERACTIONS	INTERACTION TYPE
3RZE	H1R	-5.3	1.859	LEU A:201, LEU A:205, PHE A:119, ILE A:120, PHE A:116, ALA A:151, LEU A:154, PRO A:202	Van Der Waals, Pi-Sigma
7UL3	H2R	-5.5	1.197	LEU A:124, PRO A:123, PRO A:127, ALA A:119, TYR A:126, LEU A:229, ARG A:116, ILE A:232	Van Der Waals, Pi-Pi, Pi-Alkyl, Conventional Hydrogen Bond, Pi-Sigma
7F61	H3R	-6.4	2.333	ALA A:372, PHE A:207, PHE A:211, TRP A:371, GLY A:368, PRO A:210, PHE A:367, VAL A:214, VAL A:364, ILE A:125, THR A:215	Van Der Waals, Pi-Pi
3P0G	H4R	-6.2	1.245	LEU A:340, LEU A:53, VAL A:54, GLY A:50, PRO A:323, LEU A:324, CYS A:327, PHE A:336, ARG A:333	Van Der Waals, Pi-Pi, Conventional Hydrogen Bond

Table 4
Molecular docking results of thymol to target receptors

RECEPTOR CODE	RECEPTOR NAME	BINDING ENERGY (KCAL/MOL)	RMSD Å	INTERACTIONS	INTERACTION TYPE
3RZE	H1R	-5.8	3.427	ILE A:160, PRO A:161, PHE A:190, VAL A:187, HIS A:167, PHE A:184, TRP A:189	Van der Waals, Pi-Pi, Alkyl, Pi-Alkyl
7UL3	H2R	-5.9	2.019	FO A:9401, CYS A:102, VAL A:99, TYR A:250, ASP A:186, GLY A:187, PHE A:254, THR A:190, PHE A:251, THR A:103, TRP A:247, ASP A:98, VAL A:176	Van der Waals, Unfavorable Bump, Pi-Pi, Pi-Alkyl, Pi-Sulfur, Pi-Sigma
7F61	H3R	-6.3	1.829	SER A:365, VAL A:364, GLY A:368, VAL A:214, TRP A:371, PRO A:210, PHE A:211, PHE A:367, THR A:215, ILE A:125	Van Der Waals, Pi-Sigma, Alkyl, Pi-Alkyl
3P0G	H4R	-6.4	0.997	ARG A:333, PHE A:336, CYS A:327, ARG A:328, LEU A:324, PRO A:323, GLY A:50, LEU A:53, VAL A:54	Van der Waals, Conventional Hydrogen Bond, Pi-Pi, Alkyl

The highest affinity binding position of thymoquinone to the H1R receptor is shown and the binding interactions are illustrated in Figure 2. Thymoquinone binds to the H1R receptor with an affinity of -5.3 kcal/mol.

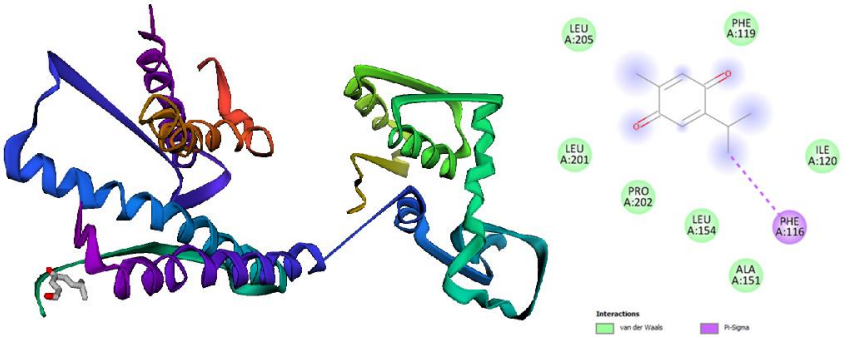

Figure 2

Interaction of the thymoquinone analog with the H1R receptor with the highest energy and two-dimensional depiction of thymoquinone binding interactions with H1R receptor

Thymoquinone's highest affinity binding position to the H2R receptor is shown and the binding interactions are illustrated in Figure 3. Thymoquinone binds to the H2R receptor with a binding energy of -5.5 kcal/mol.

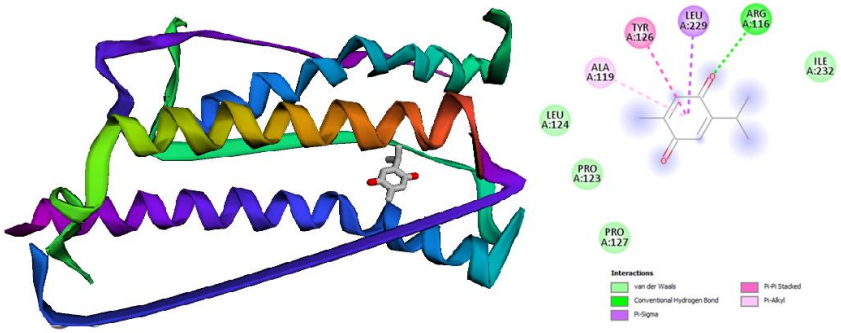

Figure 3

Interaction of the thymoquinone analog with the H2R receptor showing the highest energy conformation and two-dimensional representation of the binding interactions of thymoquinone with the H2R receptor

The highest affinity binding position of thymoquinone to the H3R receptor is depicted and the binding interactions are illustrated in Figure 4. Thymoquinone binds to the H3R receptor with a binding energy of -6.4 kcal/mol.

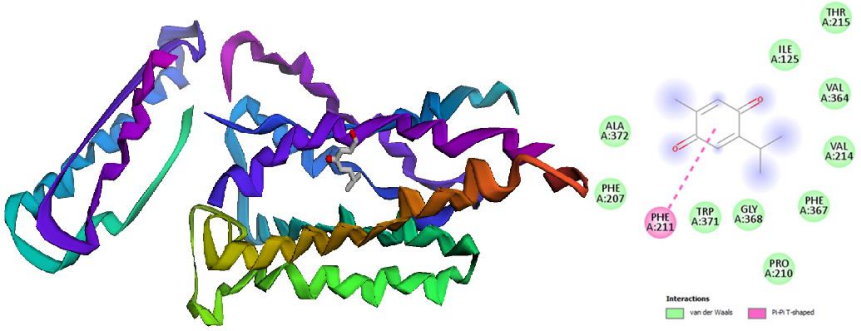

Figure 4

Interaction of the highest energy thymoquinone analog with the H3R receptor and two-dimensional representation of the interaction of thymoquinone with the H3R receptor

The binding position of thymoquinone with the highest affinity to the H4R receptor is shown and along with the binding interactions displayed in Figure 5. Thymoquinone has a binding affinity of -6.2

kcal/mol to the H4R receptor.

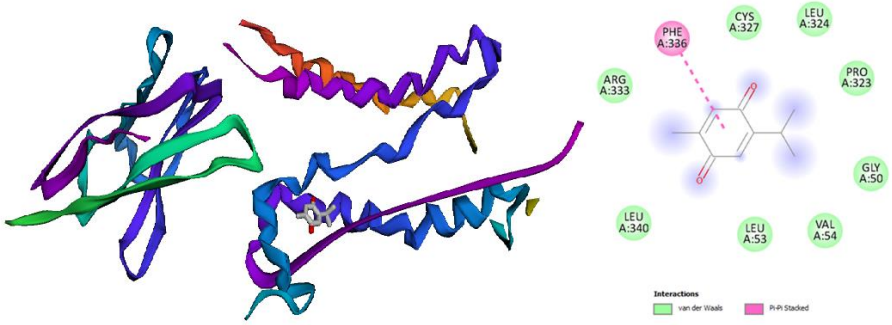

Figure 5

Interaction of the highest energy thymoquinone analogue with the H4R receptor and two-dimensional depiction of the binding interactions of thymoquinone with the H4R receptor

The binding position of thymol with the highest affinity to the H1R receptor is shown and along with the binding interactions displayed in Figure 6. Thymol has a binding affinity of -5.8 kcal/mol for the H1R receptor.

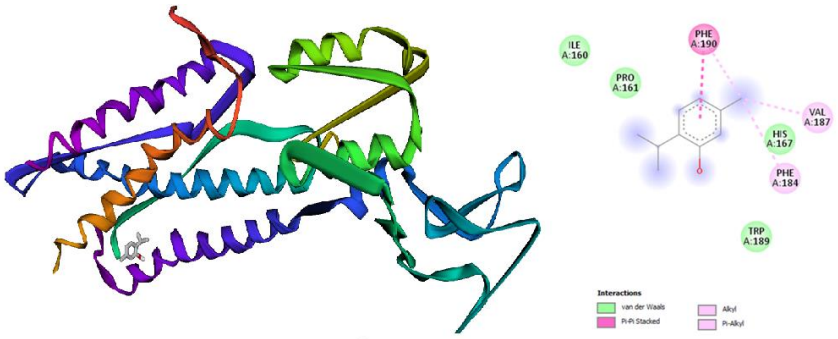

Figure 6

Interaction of the highest energy thymol analogue with the H1R receptor and two-dimensional depiction of the binding interactions of thymol with the H1R receptor.

The binding position of thymol with the highest affinity to the H2R receptor is shown and along with the binding interactions displayed in Figure 7. Thymol has a binding affinity of -5.9 kcal/mol for the H2R receptor.

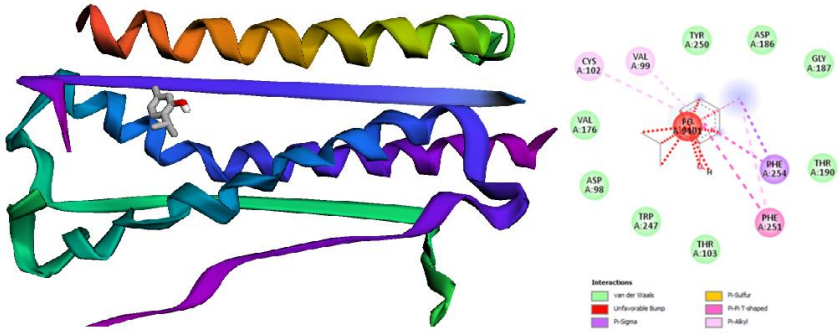

Figure 7

Interaction of the highest energy thymol analogue with the H2R receptor and two-dimensional depiction of the binding interactions of thymol with the H2R receptor.

The binding position of thymol with the highest affinity to the H3R receptor is shown and along with the binding interactions displayed in Figure 8. Thymol has a binding affinity of -6.3 kcal/mol for the H3R receptor.

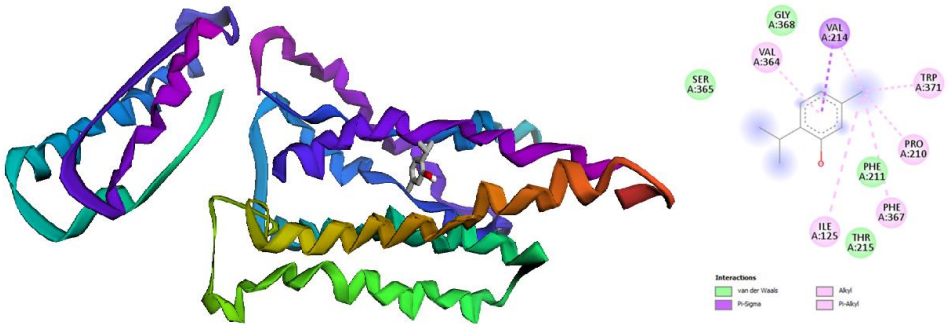

Figure 8

Interaction of the highest energy thymol analogue with the H3R receptor and two-dimensional depiction of the binding interactions of thymol with the H3R receptor.

The binding position of thymol with the highest affinity to the H4R receptor is shown and along with the binding interactions displayed in Figure 9. Thymol has a binding affinity of -6.4 kcal/mol for the H4R receptor.

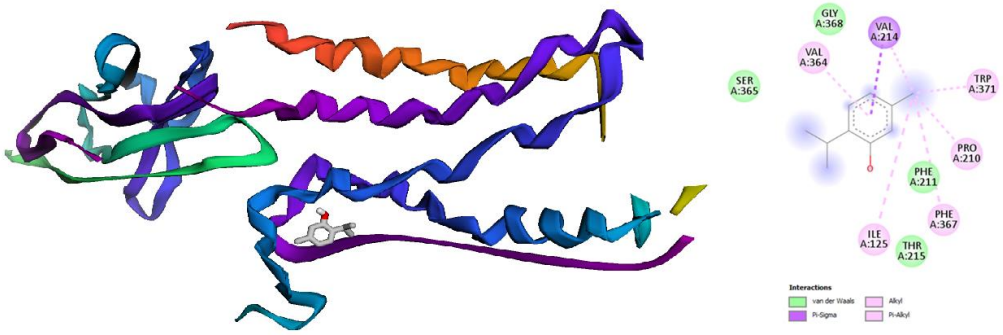

Figure 8

Interaction of the highest energy thymol analogue with the H4R receptor and two-dimensional depiction of the binding interactions of thymol with the H4R receptor.

Thymoquinone and thymol's pharmacokinetic/ADMET profile results, which were conducted to determine whether they can be considered as potential drug-like compounds, are listed in Table 5.

Table 5

ADMET parameters and acute oral toxicity of Thymoquinone and Thymol predicted by SwissADME and GUSAR online estimations

PARAMETER	THYMOQUINONE	THYMOL
Blood-brain barrier (BBB) permeability	BBB+	BBB+
Gastrointestinal drug absorption (GI-DA)	High	High
P-glycoprotein (P-gp) substrate	Non-substrate	Non-substrate
CYP1A2 inhibitor	No	Yes
CYP2C19 inhibitor	No	No
CYP2C9 inhibitor	No	No
CYP2D6 inhibitor	No	No
CYP3A4 inhibitor	No	No
Daily Kp (skin permeability)	−5.74 cm/sn	-4.87 cm/sn
Lipinski's Rule	Acceptable	Acceptable
(MW ≤ 500, logP ≤5, HBD ≤5, HBA ≤10)	MLOGP>4.15	MLOGP>4.15
Bioavailability score	0.55	0.55
Rat LD_{50} lethal dose (mg/kg) / OECD Class	1979 / (IV)	1303 / (IV)

DISCUSSION AND CONCLUSIONS

In this study, the specific allergy receptors present in the human body, namely H1R, H2R, H3R, and H4R histamine receptors, were targeted. Molecular docking studies revealed that thymoquinone and thymol exhibited significant affinity towards H1R, H2R, H3R, and H4R histamine receptors, indicating their potential importance as molecules in the context of allergic reactions.

Within the scope of this study, thymol and thymoquinone molecules were modelled in a computer environment, and their binding to histamine receptors and possible interactions are discussed in the conclusion section. Table 3 demonstrates that thymoquinone has the lowest binding energy among the target receptors and Table 4 illustrates the lowest binding energies among the target receptors for thymol. As a result of docking, the H3 receptor exhibits the highest affinity. When the RMSD is high, as shown in Figure 2, thymoquinone exhibits a strong affinity for binding to the active site. However, due to the presence of methyl groups in its structure on the receptors ALA A:372, PHE A:207, PHE A:211, TRP A:371, GLY A:368, PRO A:210, PHE A:367, VAL A:214, VAL A:364, ILE A:125, and THR A:215, there is a steric hindrance that results in a high value of 2,333 A in the same plane as the amino acid groups. This is the structure of thymoquinone, with an RMSD value of 1.245 and a bond energy of -6.2 kcal/mol to its active site, LEU A:340, LEU A:53, VAL A:54, GLY A:50, PRO A:323, and LEU in its active region. Van der Waals, Pi-Pi, and conventional hydrogen bonds involving structures A:324, CYS A:327, PHE A:336, and ARG A:333 suggest a preference for the H4R receptor, indicating selective blocking. In Table 4, ARG A:333, PHE A:336, CYS A:327, ARG A:328, LEU A:324, and PRO are located in the active site with a binding energy of -6.4 kcal/mol to H4R and 0.997 RMSD of the thymol target receptor. A:323, GLY A:50, LEU A:53, VAL A:54, and Van der Waals, Conventional Hydrogen Bond, Pi-Pi, and Alkyl interactions with amino acids in the region closer to the active center, compared to the thymoquinone structure, showed no steric effect as much as thymoquinone. In Figure 7, FO9401 exhibits an interaction classified as an Unfavorable Bump. Such interactions typically involve physical clashes or steric hindrances between molecules. This scenario can prevent the molecules from aligning or binding properly, thereby negatively impacting the overall binding affinity. The binding position of FO9401 may involve one or more of these unfavorable interactions. Consequently, the interaction between FO9401 and the H2R receptor is characterized as unfavorable. It is shown in Figure 9 that it adapts more to the active center conformation. Both thymoquinone and thymol exhibit similar properties in terms of ADMET parameters and oral toxicity trials (Table 5). Both thymokinon and thymol possess the ability to cross the blood-brain barrier (BBB+), indicating their potential effects on the central nervous system [20]. Both compounds are highly absorbed from the gastrointestinal system, suggesting that they could possess high bioavailability when administered orally [21]. Thymoquinone and thymol are not substrates of P-glycoprotein, meaning they are not actively pumped out of cells, which may suggest that their effects could be more prolonged. Specifically, thymoquinone has been shown not to inhibit any CYP isozymes, indicating a low potential for interactions with other drugs [22]. However, thymol has slower skin permeability compared to thymoquinone. Herein, we suggest that inhibiting CYP1A2, one of the most crucial enzymes in the microsomal P450 system, may extend the bioavailability of thymol-based drugs. In particular, we suggest that the thymol-based formulations may serve as an alternative to chemically synthesized drugs, for the symptomatic treatment of allergic asthma, pruritus, and dermatitis symptoms, as Histamine H4R receptor antagonists. In the existing literature, Badary et al. (1998) reported in their study that the LD50 value of thymoquinone was determined to 2400 mg/kg (1520-3770 mg/kg) following oral administration [15]. This value surpasses the prediction obtained through the GUSAR online tool. In a study conducted by Tisserand and Young in 2013, an acute toxicity investigation associated with oral administration of thymol revealed an LD50 dose of 1220 mg/kg [16]. The GUSAR online prediction estimated LD50 values lower than the in vivo experimental results, with a dose value of 1979 mg/kg for thymoquinone and 1303 mg/kg for thymol.

The results obtained from GUSAR online prediction align with the findings of in vitro studies. Considering the results, predictions emerged from in silico analyses are noteworthy as such they ease to estimate the interactions of thymol and thymoquinone based drugs to a considerable extent and reduce the number of animal experiments during drug development.

Acknowledgements
We gratefully acknowledge Necmettin Erbakan University R.A.C. of Science and Technology (BITAM) for their support.

Ethical Statement
The present study is an original research article designed and produced by the authors.

Author Contributions
Research Design (CRediT 1) E.E. (%50) - M.D.K. (%50)
Data Collection (CRediT 2) E.E. (%50) - M.D.K. (%50)
Research - Data Analysis - Validation (CRediT 3-4-6-11) E.E. (%50) - M.D.K. (%50)
Writing the Article (CRediT 12-13) Author 1 E.E. (%50) - M.D.K. (%50)
Revision and Improvement of the Text (CRediT 14) E.E. (%50) - M.D.K. (%50)

Financing
This research was not supported by any public, commercial, or non-profit organization.

Conflict of interest
The authors declare no conflict of interest for the present study.

Sustainable Development Goals (SDG)
Sustainable Development Goals: Not supported.

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