Golestan University of Medical Sciences

Jorjani Biomedicine Journal

Online ISSN: 2645-3509

Molecular docking reveals curcumin and catechin as potent inhibitors of histamine N-Methyltransferase (HNMT) and its T105I and L208P variants

Mehdi Sadeghi [1*], Mehrsa Amoozadeh [2]

1. Department of Cell and Molecular Biology, Faculty of Science, Semnan University, Semnan, Iran
2. Department of Biotechnology, Faculty of Science and Modern Technologies, Semnan University, Semnan, Iran
* Correspondence: Mehdi Sadeghi. Department of Cell and Molecular Biology, Faculty of Science, Semnan University, Semnan, Iran.
Tel: +989141288121; Email: mehdisadeghi@semnan.ac.ir

Abstract

Background: Histamine plays a crucial role in regulating diverse physiological and pathophysiological functions, including gastric acid secretion, vasodilation, and bronchoconstriction. As a neurotransmitter, it is also implicated in allergic reactions, contributing to symptoms such as itching, sneezing, and inflammation. Given the potential adverse effects of histamine activity, antihistamines are frequently prescribed to mitigate its effects. However, the associated side effects of these drugs have prompted researchers to investigate natural alternatives, such as curcumin from turmeric and catechins from green tea. This study investigates the potential effect of curcumin and catechin on the histamine N-methyltransferase (HNMT) receptor and its T105I and L208P mutant variants.

Methods: Molecular docking was employed to analyze ligand-receptor interactions. The protein structure was obtained from the Protein Data Bank (PDB), and ligands were retrieved from PubChem. Ligand structures were optimized using Avogadro software, and docking studies were subsequently performed using AutoDock Tools and the Vina algorithm.

Results: Molecular docking studies have demonstrated strong binding affinities of catechin and curcumin to the target protein, with binding energies of -8.5 and -8.4 kcal/mol, respectively, which is more than twice the binding affinity of histamine (-4.0 kcal/mol). Analysis of docking results with variant proteins revealed a slight reduction in ligand binding energies compared to the normal protein. These findings suggest that both catechin and curcumin hold promise as potential therapeutic agents for patients with the studied variants of the target protein. Furthermore, docking analysis revealed key stabilizing interactions, including π-π stacking and hydrogen bonding.

Conclusion: Phe243 is a key binding site residue in HNMT, showing consistent strong interactions with all tested ligands. Its structural flexibility enables effective binding to compounds like catechin and curcumin, making it a prime target for designing new HNMT inhibitors.

Article Type: Research Article

Article History

Received: 26 May 2025
Received in revised form: 27 September 2025
Accepted: 1 October 2025
Available online: 16 February 2026
DOI: 10.29252/jorjanibiomedj.14.1.3

Keywords

Curcumin
Catechin
Histamine N-Methyltransferase
Molecular Docking

OPEN ACCESS
CC BY NC ND
© The author(s)

Highlights

What is current knowledge?

- Histamine regulates allergy, inflammation, and neurological processes via HNMT enzyme.
- Synthetic antihistamines are effective but cause significant side effects with long-term use.
- Curcumin and catechins are natural compounds with proven anti-inflammatory and antioxidant activities.

What is new here?

- Curcumin and catechin exhibit strong binding affinities (-8.5, -8.4 kcal/mol) to HNMT and its variants.
- Phe243, Gln143, Tyr146 identified as key residues for ligand interaction and inhibitor design.
- Natural compounds are proposed as safer candidates for next-generation antihistamine drug development.

Introduction

There are four different types of histamine receptors. The H1 receptor plays a role in inflammatory and allergic responses, while the H2 receptor is involved in stimulating stomach acid secretion, modulating heart function, and regulating immune responses. The H3 receptor acts as a neuronal regulator controlling neurotransmitter release, and the H4 receptor primarily participates in immune cell regulation, inflammation, and allergic responses (1). Histamine regulates various physiological and pathophysiological functions, including stomach acid secretion, blood vessel dilation, and bronchoconstriction, and also acts as a neurotransmitter (2). It plays a key role in allergic reactions, leading to symptoms like itching, sneezing, and inflammation. Since excessive histamine activity can cause health problems, antihistamines are commonly recommended to mitigate its adverse effects and may also show positive effects in treating neurological disorders (3).

Among the enzymes that regulate histamine levels, histamine N-methyltransferase (HNMT) inactivates histamine and is expressed at its highest levels in the kidneys, spleen, and intestines. To reduce side effects and treatment costs, natural alternatives such as curcumin from turmeric and catechins from green tea are being explored as potential modulators of histamine activity (4).

The N-methyltransferase receptor is a small, monomeric protein with a 33 kDa molecular weight. This protein is transcribed by the HNMT gene in humans. It is highly expressed in the kidneys, spleen, and intestines compared to other tissues. HNMT is the primary enzyme responsible for terminating the neurotransmitter action of histamine in the brain. It catalyzes the methylation of histamine by transferring a methyl group to the imidazole ring, using S-adenosylmethionine (SAM) as the methyl donor, resulting in the production of methylhistamine and S-adenosylhomocysteine, as shown in Equation 1 (5).

Equation.1 Catalytic activity of enzyme

Histamine + S-adenosyl-L-methionine = N(tau)-methylhistamine + S-adenosyl-L-homocysteine

The selection of the HNMT receptor is based on its critical role in histamine metabolism, The association with neurological and allergic diseases, and the potential to modulate its function through natural compounds. Understanding HNMT interactions can pave the way for alternative therapeutic strategies for inflammation, allergies, and neuropsychiatric disorders.

Competitive inhibitors are able to bind to the histamine binding site on the receptor, which consists of two chains with 292 amino acids. This protein belongs to the methyltransferase family of proteins. It can inactivate histamine by transferring a methyl group. Histamine, as a neurotransmitter, plays an important role in regulating sleep, wakefulness, and learning. Thus, this receptor contributes to central nervous system function by controlling histamine levels. Its enzymatic activity is dependent on the presence of S-adenosyl-L-methionine.

Methyltransferases are widely distributed across all domains of life, including archaea, with over 230 distinct families identified in different species. This receptor exhibits a polymorphism at position 105, where a substitution determines its functional activity - threonine (T105) is associated with higher enzymatic activity, while isoleucine (I105) corresponds to lower activity. Structural studies have identified two three-dimensional conformations of this receptor, with the T105 variant complexed with its substrate, histamine. While extensive research has been conducted, the precise physiological role of this enzyme remains incompletely understood.

This receptor does not directly participate in signalling pathways. Instead, it functions as an enzyme involved in histamine metabolism. However, it indirectly influences histamine signalling by modulating histamine levels within the nervous system and various tissues, ultimately affecting processes such as inflammation (6).

DUE histamine mediates allergic reactions, and its release can trigger allergic symptoms. These symptoms are commonly managed with antihistamine drugs, which are derived from various chemical compounds. However, these treatments can induce a range of side effects that may negatively impact patients' quality of life (7).

Given the widespread prevalence of diseases such as various cancers and cardiovascular disorders, coupled with the inevitable side effects of synthetic drugs, plants have emerged as a valuable source of natural compounds with diverse medicinal properties (8).

Examples include curcumin from turmeric and catechin from green tea (8). The well-known anti-inflammatory and antioxidant features of these compounds may also support their potential as HNMT inhibitors, creating a link between their biological effects and the focus and aim of this study.

Curcumin, the primary active polyphenol in turmeric, has been investigated as a potential therapeutic agent for a range of conditions, including various cancers, liver diseases, and cardiovascular disorders. The therapeutic effects of this compound are attributed to its anti-inflammatory and antioxidant properties, which are mediated through both direct and indirect modulation of molecules and signalling pathways implicated in disease pathogenesis. Curcumin exerts its effects by inhibiting inflammatory enzymes and proteins, including the NF-κB pathway (9).

Catechin, a pentahydroxy flavone, exists in two stereoisomeric forms and is naturally present in tea, cocoa, apples, persimmons, and various other plant sources, with tea being a particularly rich source. One notable form, epigallocatechin-3-gallate, exhibits anticancer, anti-obesity, and antimicrobial properties. Furthermore, certain catechins contribute to the reduction of chronic inflammation by inhibiting inflammatory pathways (10).

Molecular docking is a key tool in molecular biology. The goal of ligand-protein docking is to predict the most favorable binding mode(s) of a ligand to a protein with a known structure. This method is commonly used in virtual screening to evaluate numerous compounds and identify the best candidates for further research.

Molecular docking is a key technique in drug design, enabling the simulation of drug-protein interactions. It helps identify potential drug candidates that can bind to the active site of a target protein. This method not only determines the binding site of a ligand - a specific region of the protein - but also studies how the ligand interacts with the protein's amino acids. In addition, docking evaluates the binding stability of the ligand by calculating the binding energy (11). The Vina algorithm is used in this study due to its speed and accuracy in predicting ligand-protein interactions.

Given the importance of developing novel natural alternatives to antihistamines, we investigated curcumin and catechin as potential agents targeting HNMT and its key variants. Molecular docking studies were employed to examine the interactions between these ligands and the target proteins. The binding energy evaluations demonstrate a high affinity of curcumin and catechin for HNMT, in contrast to the standard ligand, histamine, suggesting the potential of these compounds as inhibitory drugs against HNMT.

Methods

Molecular docking was performed using AutoDockTools 1.5.7 and the Vina algorithm. The 3D structures of the ligands, including histamine, catechin, and curcumin, were retrieved from the PubChem database in SDF format. Then, the ligands were converted to the Protein Data Bank (PDB) format using PyMOL, which was chosen for its robust capabilities in manipulating and visualizing molecular structures, and subsequently optimized in the Avogadro application.

To prepare the ligands for docking, their PDB structures were converted to PDBQT format. This process included adding hydrogen atoms and assigning atomic charges using the Compute Gasteiger function in PMV. To introduce rotational flexibility, torsional degrees were defined using the Torsion Tree option, and the final PDBQT files were saved.

The protein structure of HNMT was obtained from PDB (ID: 1JQD) and used as the target structure. Protein preparation for docking involved removing water molecules and any bound ligands using PMV, followed by adding hydrogen atoms and assigning atomic charges using the Coleman method. The processed protein structure was then saved in PDBQT format.

To extend the analysis, site-directed mutagenesis was performed using PyMOL, introducing T105I and L208P mutations into the HNMT protein. These mutations were selected based on their relevance to autosomal recessive intellectual disability and asthma-related polymorphisms. The mutated residues were retrieved from the UniProt database and introduced using the Protein Mutagenesis Wizard in PyMOL. The Sculpting tool was applied to refine the protein structure, ensuring stability and eliminating steric clashes. Then, the mutated protein was saved in PDB format using the “Export Molecule” option. The variants used included T105I and the L208P mutation. The structures of the generated protein variants were compared with the wild-type protein using the “Alignment” option in PyMOL.

To define the docking search space, key binding-site residues - Glu89, Gln94, Ser120, Ile142, Asn283, Glu28, and Gly60 - were retrieved from UniProt. The grid box was designed around the binding site. The grid box dimensions were X: 40 Å, Y: 40 Å, and Z: 40 Å, and the grid center coordinates were X: 43.281, Y: -33.019, and Z: -5.197. The grid center was set around the known active site of the protein to focus the search space on the key binding region.

Molecular docking simulations were performed using AutoDock Vina. Docking results, including binding energy and interaction profiles, were analyzed using BIOVIA Discovery Studio Visualizer, facilitating a comprehensive evaluation of ligand–protein interactions. Discovery Studio Visualizer was selected because of its excellent features in visualizing molecular interactions and generating high-quality images. For statistical analysis, each docking simulation was replicated ten times ($n = 10$), and the average binding energy and standard deviation values from these replicates were reported. To identify statistically significant differences in the binding energies between each ligand and various protein variants, an Analysis of Variance (ANOVA) followed by Tukey’s post hoc test was applied. Separate ANOVA was performed to assess the significance of ligand and variant effects on binding energies. All statistical analyses were conducted using the R programming language (Version 4.4.1).

Results

The variants analyzed in this study were selected based on the proximity of their mutations to the active site and the substrate-binding region of the protein (Figure 1A).

Given the functional importance of these sites, mutations occurring in their vicinity are likely to influence the structural integrity or functional behavior of the protein. In particular, alterations near the active site may interfere with enzymatic activity or ligand interaction. Table 1 provides a detailed overview of the selected variants, including their mutation positions and the predicted impacts on protein function.

To validate the molecular docking process, a redocking procedure was performed. In this step, the Vina output ligand was aligned with the

histamine (Figure 1B) ligand extracted from the HNMT protein's PDB file. By comparing the binding position of the ligand in the original PDB structure with that of the docked ligand, it was observed that the optimized native ligand and the Vina-derived ligand showed an approximate alignment (Figure 2). Structural comparison of variants with wild-type proteins reveals that the T105I variant displays more pronounced structural deviations than the native protein. Nevertheless, the low RMSD value indicates that the overall protein structures remain highly similar (Table 2).

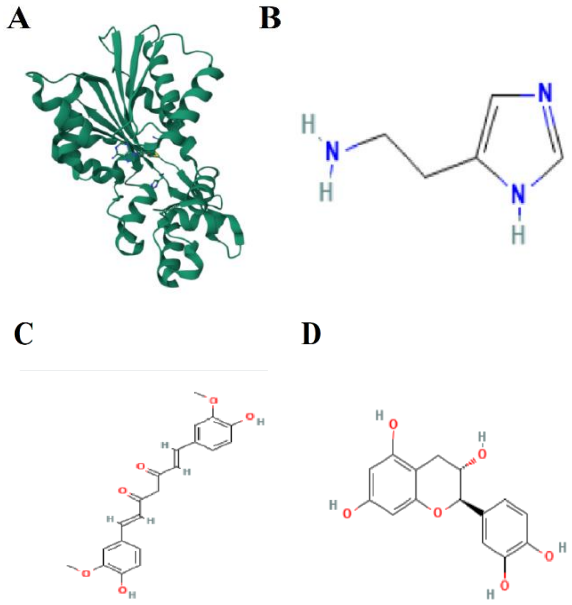

Figure 1. Structure of protein and ligands. A: HNMT, B: Histamine, C: Curcumin, D: Catechin

Table 1. HNMT variants in this study

Type	Description
T105I	Resulting from the C314T polymorphism in the HNMT gene, leads to reduced enzymatic activity
L208P	Reduces protein stability, resulting in impaired inactivation of histamine and consequently decreased histamine stability and enzymatic activity in the central nervous system

The binding energies of curcumin (Figure 1C) and catechin (Figure 1D) with various HNMT protein variants are more than twice as strong as that of histamine. This enhanced binding can be attributed to the larger molecular size of curcumin and catechin, their greater number of reactive functional groups capable of interacting with the protein, and their optimal fit within the protein's binding site.

A key factor in their stronger binding is the presence of two aromatic rings in curcumin and catechin, which form robust π–π stacking interactions with aromatic amino acids - abundantly present among the interacting residues (Table 3) - along with additional hydrogen bonds. Docking results indicate that catechin has the highest binding affinity for wild-type HNMT (-8.5 kcal/mol). Furthermore, the analysis shows that two amino acids, Phe243 and Phe22, play a critical role in catechin's interaction with all HNMT variants (Figure 3).

While the protein variants show slightly reduced binding affinities for catechin and curcumin, their binding energies remain more than double that of histamine. These findings suggest that curcumin and catechin could act as potent histamine inhibitors across all studied protein variants, making them promising natural antihistamine candidates worthy of further investigation.

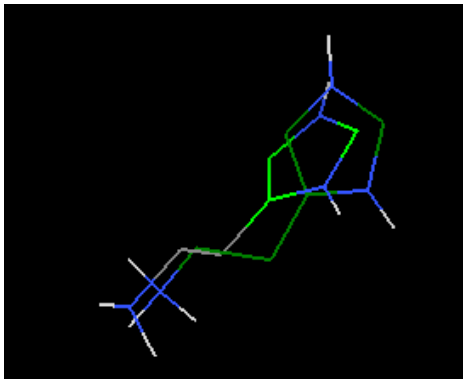

Figure 2. The results of re-docking indicating the similarity between the two ligands

Table 2. Protein structural alignment and comparison with HNMT native.

Protein	RMSD
Native	0.00 Å
T105I	0.13 Å
L208P	0.118 Å

Statistical analysis of the binding energies revealed that curcumin and catechin demonstrated a significantly stronger binding affinity for the protein variants compared to histamine (Adjusted P-Value), with a mean binding energy difference exceeding 4 kcal/mol (Table 4). A significant difference in binding energy was also observed between curcumin and catechin for both the native HNMT and the L208P variant (Adjusted P-Value). Furthermore, significant differences were found in histamine binding to the native HNMT versus the L208P variant, as well as in catechin binding when comparing the T105I and L208P variants (Adjusted P-Value) (Table 4).

Table 3. The obtained results for binding energy, dissociation constant, and interacting amino acids

Protein	Drugs	Average binding affinity (kcal/mol) (Standard deviation)	Binding constant (mol/L)	Interacting amino acids
HNMT Native	Histamine	-4.05 (0.05)	1.16×10^{-3}M	• **Asp67, Gln143, Ile142, Gly60**
T105I	Histamine	-4.01 (0.07)	9.80×10^{-4}M	• **Glu118, Tyr147, Val88, Glu89, Gly60, Ser120**
L208P	Histamine	-3.96 (0.069)	1.16×10^{-3}M	• **Phe243, Leu244, Tyr146, Trp179**
HNMT Native	Curcumin	-8.07 0.029	6.85×10^{-7}M	• **Phe19, Gln143, Phe243, Tyr15, Cys196, Tyr147**
T105I	Curcumin	-8.17 (0.14)	9.61×10^{-7}M	• **Phe19, Gln143, Tyr146, Tyr15, Glu246, Asp242, Leu8, Phe243**
L208P	Curcumin	-8.07 (0.17)	8.12×10^{-7}M	• **Cys196, Leu244, Phe243, Trp183, Trp179, Met32, Leu23, Gln143, Tyr146**
HNMT Native	Catechin	-8.5 (0)	5.79×10^{-7}M	• **Tyr198, Leu244, Phe243, Cys196, Phe22, Asn283, Glu28, Tyr15**
T105I	Catechin	-8.2 (0)	9.61×10^{-7}M	• **Leu244, Tyr147, Tyr15, Phe243, Phe22, Glu28**
L208P	Catechin	-8.2 (0)	9.61×10^{-7}M	• **Glu28, Asn283, Phe22, Phe243**

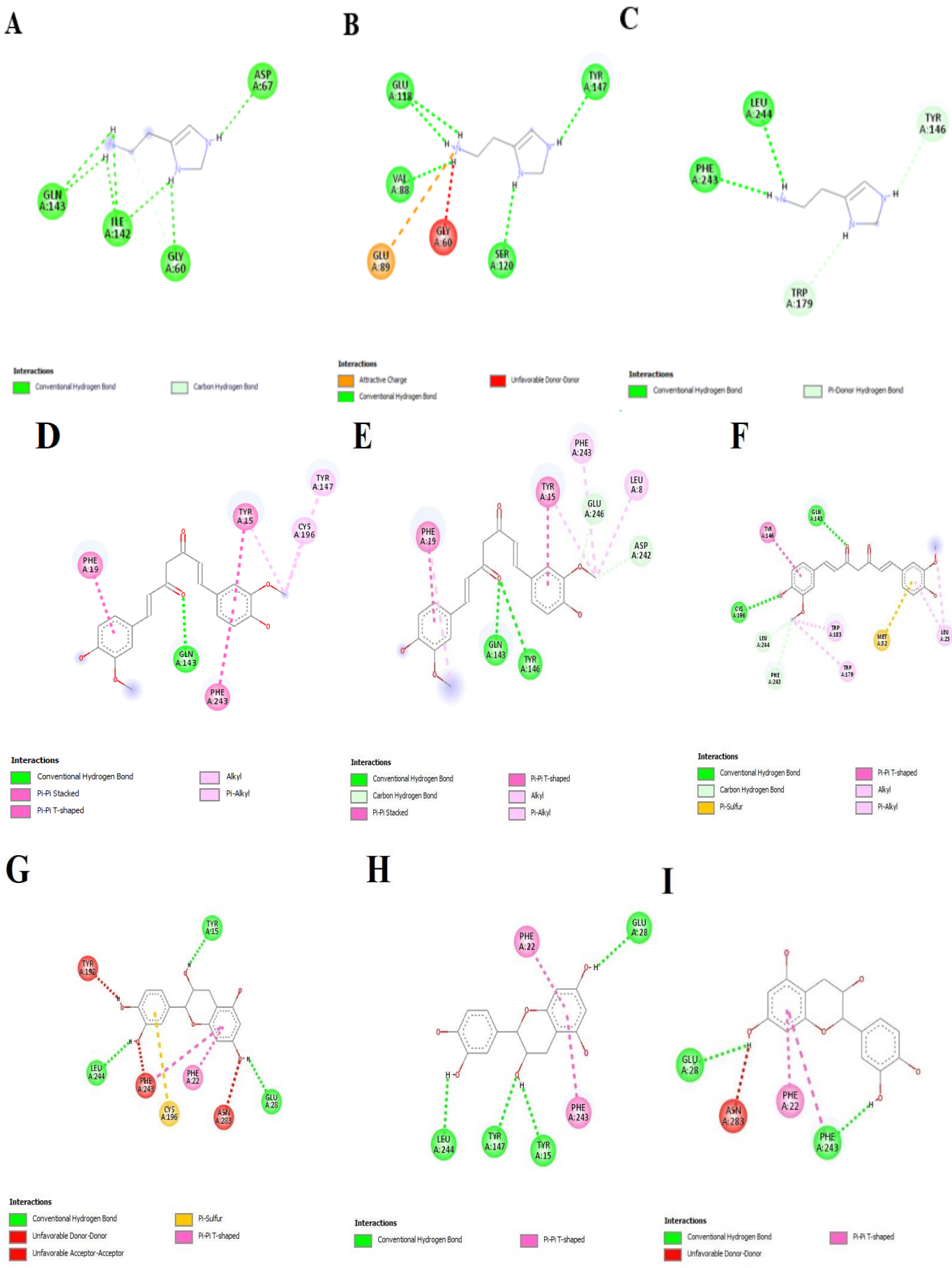

Figure 3. The interactions between wild-type and variant HNMT proteins with histamine, curcumin, and catechin. A: Interaction between wild-type HNMT and histamine. B: Interaction between the HNMT T105I variant and histamine. C: Interaction between the HNMT L208P variant and histamine. D: Interaction between wild-type HNMT and curcumin. E: Interaction between the HNMT T105I variant and curcumin. F: Interaction between the HNMT L208P variant and curcumin. G: Interaction between wild-type HNMT and catechin. H: Interaction between the HNMT T105I variant and catechin. I: Interaction between the HNMT L208P variant and catechin.

Table 4. ANOVA test analysis results. Gray rows correspond to the assessment of drug effect in different variants, and white rows correspond to the assessment of variant effect in different drugs

Biological Markers and Compounds	Comparison	Energy difference (kcal/mol)	Adjusted P-Value
Native HNMT	Histamine-Curcumin	- 4.020	0.001
	Histamine-Catechin	- 4.450	0.001
	Curcumin-Catechin	- 0.430	0.001
T105I	Histamine-Curcumin	- 4.160	0.001
	Histamine-Catechin	- 4.190	0.001
	Curcumin-Catechin	- 0.030	0.749
L208P	Histamine-Curcumin	- 4.110	0.001
	Histamine-Catechin	- 4.240	0.001
	Curcumin-Catechin	- 0.130	0.034
Histamine	Native HNMT-T105I	0.040	0.379
	Native HNMT-L208P	0.090	0.013
	T105I-L208P	0.050	0.226
Curcumin	Native HNMT-T105I	- 0.100	0.552
	Native HNMT-L208P	0.000	0.999
	T105I-L208P	0.100	0.552
Catechin	Native HNMT-T105I	0.300	0.001
	Native HNMT-L208P	0.300	0.001
	T105I-L208P	0.000	0.999

Studies have demonstrated that Phe243 plays a critical role in substrate translocation by the transporter. This residue acts as a "gatekeeper" (Figure 4), facilitating substrate transfer through conformational reorientation. Moreover, Phe243 is recognized for its importance in rational drug design, particularly for developing selective inhibitors. These inhibitors can block substrate entry without obstructing its exit - a key therapeutic strategy for addressing amino acid transport disorders (12).

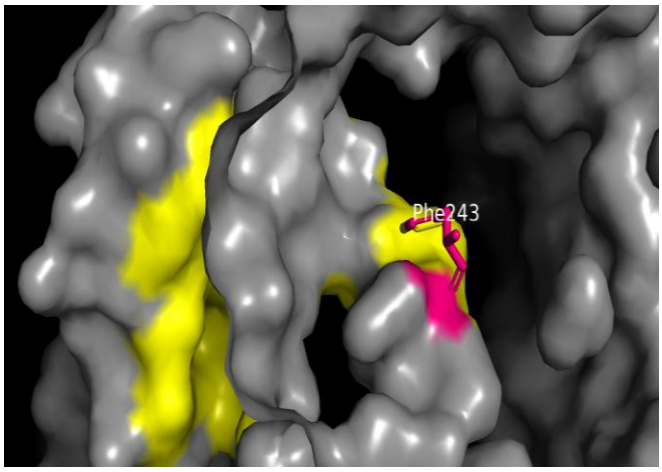

Figure 4. Phenylalanine 243 functions as the gatekeeper of the enzyme's active site. The binding pocket (Shown in yellow) and Phe243 (Displayed in stick mode and highlighted in hot pink) are illustrated using PyMOL.

Discussion

According to the docking results analysis Phe243, Gln143, Tyr146, Tyr147, Leu244, and Tyr15 are among the most frequently observed interacting amino acids. The consistent involvement of these residues across multiple ligands suggests they form a conserved, pharmacologically important binding pocket on the HNMT protein. Phe243 shows the highest recurrence rate in ligand-protein interactions, indicating its critical role in binding both wild-type and variant HNMT proteins. This residue forms hydrophobic interactions with the benzofuran ring of vilazodone, contributing to enhanced stability of the enzyme-drug complex. Additionally, the ergoline ring of dihydroergotamine binds to Phe243. This amino acid plays a particularly significant role in mediating interactions between histamine, curcumin, and catechin due to the presence of hydrophobic regions in both the ligands and the enzyme. Its conserved function is observed across both wild-type and mutated HNMT variants, highlighting its importance in molecular recognition and binding stability (13).

The molecular docking analysis of metoprine with the HNMT enzyme revealed critical interacting residues, most notably Tyr15. In the binding of dihydroergotamine to HNMT, this drug is surrounded by several key amino acids, including Tyr15, which plays a central role in stabilizing the ligand–enzyme complex (13).

When benzo-pyrene inhibitors bind to HNMT's active site, the tyrosine residue at position 15 (Tyr15) plays two crucial roles. First, its aromatic side chain forms π–π stacking interactions with the aromatic rings of the inhibitors. Second, upon inhibitor binding, Tyr15 undergoes significant conformational changes in its side chain to achieve optimal binding geometry. Tyr15 contributes to complex stabilization by forming a network of hydrophobic interactions and aromatic–aromatic contacts that help position inhibitors in the binding pocket while maintaining enzyme inhibition. This functionally important residue participates similarly in the binding of both curcumin and catechin to both wild-type HNMT and its T105I variant (14).

Phe22 plays a role in forming histamine's binding site in the HNMT protein. In docking studies, compounds like dihydroergotamine and ergotamine (Potential HNMT inhibitors) form important hydrophobic interactions with this amino acid, contributing to ligand-enzyme binding stability. Phe22 is also crucial for catechin binding to both wild-type and variant HNMT proteins. The aromatic structures of catechin and dihydroergotamine engage in π–π and hydrophobic interactions with this amino acid's ring.

The drugs dihydroergotamine, ergotamine, and vilazodone interact with Tyr147. In studies of metoprine-HNMT binding, this amino acid forms hydrogen bonds with metoprine's chlorophenyl ring, stabilizing the complex and contributing to enzyme inhibition. Beyond hydrogen bonding, Tyr147 also mediates hydrophobic interactions with vilazodone - the drug's aromatic rings bind to the active site through these interactions. This amino acid's role is evident in binding histamine (T105I variant), catechin, and curcumin (Wild-type HNMT), with shared features being π–π interactions between ligand aromatic rings and Tyr147's phenyl ring, plus hydrogen bonds with functional groups like hydroxyls.

Glu28, Gln143, and Asn283 in HNMT's binding site interact with vilazodone. Negatively charged glutamate can form hydrogen bonds and electrostatic interactions with vilazodone's functional groups. The polar amino acids glutamine and asparagine also form hydrogen bonds with this drug. Gln143 participates in histamine and curcumin binding, while Asn283 and Glu28 are involved in catechin-receptor interactions. These residues enable diverse ligand binding through hydrogen bonds and electrostatic interactions that stabilize ligand binding (13).

Gly60 is recognized as a key amino acid in the HNMT structure. For proper HNMT function, a molecule called SAM is required. This cofactor transfers its methyl group to histamine, thereby inactivating it. The Gly60Asp variant introduces an additional carboxyl group in the SAM binding site, altering the spatial conformation of the binding site and disrupting enzyme function. This amino acid is observed in both wild-type HNMT and the T105I variant in relation to histamine binding.

In studies examining the effect of SAM and histamine binding on the HNMT receptor, Phe22 emerges as a crucial amino acid in the HNMT active site that plays an important role in histamine binding. In the absence of SAM, this amino acid does not form stable interactions with histamine. When SAM is present, π–π interactions form between the aromatic ring of this amino acid and histamine, strengthening substrate binding. This amino acid is also involved in catechin interactions with wild-type HNMT and the T105I and L208P variants.

Additionally, Glu28, due to its carboxylate group in the side chain, forms electrostatic interactions and hydrogen bonds with histamine, playing a significant role in ligand binding. This amino acid is observed in catechin interactions with wild-type HNMT and the T105I and L208P variants (15).

Conclusion

In this study, we used molecular docking techniques and related software to examine the binding ability of various ligands, including histamine, curcumin, and catechin, to the HNMT receptor and two mutant forms of this protein. Catechin and curcumin bind to the protein with free binding energies of -8.5 kcal/mol and -8.4 kcal/mol, respectively, showing significantly stronger binding compared to histamine (-4.0 kcal/mol). This indicates that these compounds are more effective than histamine and suggests their potential use in developing natural compound–based drugs to counteract acute histamine effects in inflammatory processes, allergic reactions, central nervous system regulation, metabolism regulation, and immune system function. Analysis of the variants shows they exhibit lower binding energies and reduced affinity for the studied compounds compared to the original protein version. Given the target protein's role and related ligands in neurological, allergic, and metabolic disorders, studying different mutations of this protein helps gain more information about contributing disorders. The docking results reveal key amino acids involved in drug binding mechanisms to this protein. Amino acids Phe243, Gln143, Tyr146, Tyr147, Leu244, Tyr15, and Tyr146 are among the most frequently observed residues in the docking results, which have also been confirmed in studies of other ligands binding to this protein. Phe243 is the most recurrent amino acid in ligand–protein interactions, highlighting its key importance in the binding mechanism of ligands to both the protein and its studied variants. Studies show this amino acid has flexibility in the ligand binding site and changes its orientation to facilitate ligand transfer within the protein's binding site. The current study also demonstrates the crucial role of this amino acid in binding catechin and curcumin. The findings of this study can contribute to a detailed investigation of the interaction mechanism between drugs and the HNMT protein, the role and function of key amino acids, as well as the development of novel antihistamine agents derived from natural sources based on a rational design strategy.

To strengthen and validate these findings, future research must include experimental studies. In vitro assays can confirm the binding affinities of catechin and curcumin to HNMT and its variants, while in vivo studies would provide insight into their actual biological effects and therapeutic potential.

Acknowledgement

The authors of this article would like to express their gratitude to Semnan University.

Funding Sources

The current research work has no source of funding.

Ethical Statement

Not applicable. This article was conducted using software and data analysis.

Conflicts of Interest

The authors declare no competing interests.

Author Contributions

Conceptualization, M.S. and M.A.; Methodology, M.S. and M.A. Software, M.A.; Formal analysis, M.A.; Investigation, M.S. and M.A.; Data curation, M.S. and M.A.; Writing-Original draft preparation, M.S. and M.A.; Writing-Review and Editing, M.S. and M.A.; Visualization, M.A.; Supervision, M.S.

Data Availability Statement

Public data has been used in this research.

Use of Artificial Intelligence

The English text was edited using artificial intelligence.

References

1. Akdis CA, Simons FER. Histamine receptors are hot in immunopharmacology. Eur J Pharmacol. 2006;533(1-3):69-76. [View at Publisher] [DOI] [PMID] [Google Scholar]
2. Thangam EB, Jemima EA, Singh H, Baig MS, Khan M, Mathias CB, et al. The Role of Histamine and Histamine Receptors in Mast Cell-Mediated Allergy and Inflammation: The Hunt for New Therapeutic Targets. Front Immunol. 2018;9:1873. [View at Publisher] [DOI] [PMID] [Google Scholar]
3. Hrubisko M, Danis R, Huorka M, Wawruch M. Histamine Intolerance-The More We Know the Less We Know. A Review. Nutrients. 2021;13(7):2228. [View at Publisher] [DOI] [PMID] [Google Scholar]
4. Joskova M, Mokry J, Franova S. Respiratory Cilia as a Therapeutic Target of Phosphodiesterase Inhibitors. Front Pharmacol. 2020;11:609. [View at Publisher] [DOI] [PMID] [Google Scholar]
5. Li J, Sun C, Cai W, Li J, Rosen BP, Chen J. Insights into S-adenosyl-l-methionine (SAM)-dependent methyltransferase related diseases and genetic polymorphisms. Mutat Res Rev Mutat Res. 2021;788:108396. [View at Publisher] [DOI] [PMID] [Google Scholar]
6. Horton JR, Sawada K, Nishibori M, Zhang X, Cheng X. Two Polymorphic Forms of Human Histamine Methyltransferase. Structure. 2001;9(9):837- 49. [View at Publisher] [DOI] [PMID] [Google Scholar]
7. Lee HS, Kim S-H, Kim KW, Baek JY, Park H-S, Lee KE, et al. Involvement of human histamine N-methyltransferase gene polymorphisms in susceptibility to atopic dermatitis in Korean children. Allergy Asthma Immunol Res. 2012;4(1):31-6. [View at Publisher] [DOI] [PMID] [Google Scholar]
8. Gielecińska A, Kciuk M, Mujwar S, Celik I, Kołat D, Kałuzińska-Kołat Ż, et al. Substances of Natural Origin in Medicine: Plants vs. Cancer. Cells. 2023;12(7):986. [View at Publisher] [DOI] [PMID] [Google Scholar]
9. Hewlings SJ, Kalman DS. Curcumin: A Review of Its Effects on Human Health. Foods. 2017;6(10):92. [View at Publisher] [DOI] [PMID] [Google Scholar]
10. Isemura M. Catechin in Human Health and Disease. Molecules. 2019;24(3):528. [View at Publisher] [DOI] [PMID] [Google Scholar]
11. Morris GM, Lim-Wilby M. Molecular Docking. Methods Mol Biol. 2008:443:365-82. [View at Publisher] [DOI] [PMID] [Google Scholar]
12. Mikou A, Cabayé A, Goupil A, Bertrand H-O, Mothet J-P, Acher FC. Asc-1 Transporter (SLC7A10): Homology Models And Molecular Dynamics Insights Into The First Steps Of The Transport Mechanism. Sci Rep. 2020;10(1):3731. [View at Publisher] [DOI] [PMID] [Google Scholar]
13. Jiménez EM, Żołek T, Hernández Perez PG, Miranda Ruvalcaba R, Nicolás-Vázquez MI, Hernández-Rodríguez M. Drug Repurposing to Inhibit Histamine N-Methyl Transferase. Molecules. 2023;28(2):576. [View at Publisher] [DOI] [PMID] [Google Scholar]
14. Farag NA, Mohamed SR, Soliman GAH. Design, synthesis, and docking studies of novel benzopyrone derivatives as H1-antihistaminic agents. Bioorg Med Chem. 2008;16(19):9009-17. [View at Publisher] [DOI] [PMID] [Google Scholar]

15. Chu Q, Sun S, Li C, Qu G, Sun Z. Elucidating the impact of S-adenosylmethionine and histamine binding on N-methyltransferase conformational dynamics: Insights from an in silico study. J Mol Graph Model. 2025;136:108961. [View at Publisher] [DOI] [PMID] [Google Scholar]

Cite this article as:

Amoozadeh M, Sadeghi M. Molecular docking reveals curcumin and catechin as potent inhibitors of histamine N-Methyltransferase (HNMT) and its T105I and L208P Variants. *Jorjani Biomedicine Journal.* 2026;14(1):3-9. http://dx.doi.org/10.29252/jorjanibiomedj.14.1.3