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Original Article

Molecular Docking, ADMET, and Multi-Parameter Optimization (MPO) of Punicalagin-Related Compounds as ADAM17/TACE Modulators Candidate

Ariztha Delivia Putri[1], Parsaoran Siahaan[1], Mukhammad Asy'ari[1]*
[1]Department of Chemistry, Diponegoro University, Semarang, Indonesia
**Corresponding author*: asyari@live.undip.ac.id

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Abstract

ADAM17/TACE is an important target in the regulation of inflammatory responses; however, the development of selective modulators remains challenging because conventional approaches generally focus on the catalytic site. Punicalagin-related compounds have been reported to possess potential as metalloprotease modulators, yet the relationship between molecular structure, binding affinity, and pharmacokinetic properties has not been comprehensively investigated. This study aimed to evaluate punicalagin-related compounds including punicalagin (PNG), punicalin (PNL), ellagic acid (ELA), gallic acid (GAA), hexahydroxydiphenic acid (HPA), shikimic acid (SKA), 3-dehydroshikimate (DHS), 3,4-dihydroxybenzoate (DXB), and marimastat (MRM) as a reference inhibitor through an integrated in silico approach involving molecular docking, physicochemical descriptor and drug-likeness analysis, ADMET prediction, and multi-parameter optimization (MPO). This approach also supports green chemistry principles through more efficient early-stage screening of bioactive candidates by reducing the use of reagents and preliminary biological experiments. Docking results showed that PNG and PNL exhibited high binding affinities (-8.2 to -8.8 kcal/mol), but with limitations in membrane penetration, whereas HPA, ELA, and GAA demonstrated moderate affinities with more favorable pharmacokinetic profiles. Physicochemical descriptor and ADMET analyses indicated that smaller metabolites fulfilled drug-likeness criteria and exhibited better bioavailability than larger ellagitannins. MPO evaluation highlighted HPA (0.65) and ELA (0.62) as initial hit compounds with an optimal balance between target interaction and pharmacokinetic feasibility. These findings demonstrate that multi-parameter evaluation provides a more relevant strategy than single-parameter docking assessment in the early-stage identification of ADAM17/TACE modulators.

Keywords: *ADAM17/TACE; punicalagin-related; molecular docking; drug-likeness; multi-parameter optimization*

1. Introduction

ADAM17, also known as tumor necrosis factor-α converting enzyme (TACE), is a zinc-dependent metalloprotease enzyme that plays a key role in the release of membrane proteins that regulate inflammatory pathways and cell growth [1], [2], [3]. Molecules such as TNF-α and EGFR ligands released by ADAM17 have a key role in intercellular communication, making this enzyme an attractive therapeutic target for both inflammatory diseases and cancer [4], [5], [6]. Mechanistically, ADAM17 catalyzes the hydrolysis of peptide bonds through a mechanism dependent on Zn^{2+} ions in the active site, coordinated by the conserved HExxH motif. These Zn^{2+} ions play a role in activating water molecules as nucleophiles to attack the substrate peptide bonds, resulting in membrane protein shedding (ectodomain shedding). This process is a key step in the activation of inflammatory mediators such as TNF-α and modulation of EGFR signaling, so regulation of ADAM17 activity is crucial for the intensity of biological responses.

Most metalloproteinase inhibitors work by binding Zn^{2+} ions at the catalytic site, for example via a hydroxamate group [7], [8]. This strategy, while effective, is often less selective due to the risk of interactions with related enzymes. Recent findings suggest that ADAM17 activity can also be modulated through interactions outside the catalytic site, such as in the regulatory region or exosite, which affect catalytic efficiency without directly blocking

substrate access [9], [10]. This exosite approach is becoming increasingly relevant in the development of new generation inhibitors as it allows modulation of enzyme conformation without having to interact directly with Zn^{2+}, thus potentially increasing selectivity towards ADAM17 over other metalloproteases with similar catalytic sites.

Natural polyphenolic compounds are attractive candidates for ADAM17 modulation. The multi-hydroxyl aromatic skeleton of polyphenols allows for numerous hydrogen and electrostatic interactions with protein surfaces. Punicalagin, the major ellagitannin from pomegranate (*Punica granatum*), and its metabolites, such as gallic acid, have been reported to inhibit several metalloproteases[11], [12], [13]. Furthermore, biologically, punicalagin undergoes biotransformation in the body into smaller metabolites such as ellagic acid and urolithin through the activity of gut microbiota. These metabolites generally have smaller molecular size, more balanced lipophilicity, and better bioavailability, thus potentially being more relevant active forms in vivo than their parent compounds. The main challenge in developing these compounds lies in their pharmacokinetic properties; large and polar molecules generally have limited solubility, low biological penetration, and suboptimal bioavailability [14]. This reflects a balance between the strength of molecular interactions (binding affinity) and pharmacokinetic properties (drug-likeness). However, studies systematically evaluating the relationship between the structure of punicalagin-related compounds, binding affinity to ADAM17, physicochemical descriptors, ADMET profiles, and multi-parameter optimization (MPO) within a single, integrated computational framework are still limited. Most previous studies have focused on the general biological activities of punicalagin and its metabolites without simultaneously evaluating the balance between potential target interactions and pharmacokinetic feasibility. Therefore, an integrative approach is needed to support the identification of more realistic initial hit compounds for the development of ADAM17 modulators.

This study aims to evaluate the relationship between molecular structure, ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties, and interaction stability of punicalagin-related compounds against ADAM17 in silico. The approaches used include ADMET prediction and molecular docking, with a focus on how molecular characteristics affect binding ability and potential bioavailability. Specifically, this study emphasizes the analysis of the balance between binding affinity and drug-likeness using a multi-parameter optimization (MPO) approach to identify candidate compounds that have an optimal balance between biological activity and pharmacokinetic feasibility. The in silico approach in this study supports the principles of green chemistry because it allows early screening of bioactive candidates based on natural compounds by reducing the use of chemical reagents, organic solvents, and inefficient biological experiments in the early stages of drug development.

The results of this study are expected to provide insights for designing more selective polyphenols with better pharmacokinetic prospects, as well as supporting rational drug design strategies based on polyphenol metabolites.

2. Method

This research was conducted in silico using a computational approach integrating molecular docking, physicochemical and drug-likeness descriptor analysis, ADMET prediction, and multi-parameter optimization (MPO) to evaluate ligand-protein interactions and the pharmacokinetic feasibility of candidate compounds. This approach is used as an early-stage screening stage in drug discovery to efficiently identify potential candidates before experimental validation. All analyses were conducted considering the limitations of in silico methods, such as not fully representing the dynamics of biological systems and the effects of the solvent environment.

2.1 Protein Structure Preparation

The crystal structure of ADAM17 (PDB ID: 3G42) was retrieved from the RCSB Protein Data Bank. The protein was cleaned of water molecules and co-crystal ligands, then hydrogen was added, and the structure energy was minimized using UCSF Chimera with the AMBER force field. Residue protonation was performed under physiological conditions (pH ~7.4) to ensure biologically relevant ionization states. Structure validation was performed using MolProbity with evaluation of geometric parameters such as the Ramachandran plot, clash score, and rotamer outliers. Key residues in the catalytic site, including the HExxH motif and the coordination of the Zn^{2+} ion, were retained during preparation to maintain the integrity of ADAM17's catalytic function.

2.2 Ligand Dataset

Eight bioactive compounds related to the punicalagin biosynthesis pathway were obtained from PubChem, including punicalagin (PNG), punicalin (PNL), ellagic acid (ELA), gallic acid (GAA), hexahydroxydiphenic acid (HPA), shikimic acid (SKA), 3-dehydroshikimic acid (DHS), and 3,4-dihydroxybenzoic acid (DXB). Marimastat (MRM) was used as a reference inhibitor. Ligand structures were downloaded in SDF format and converted to PDB format using Open Babel. Geometry optimization was performed using a semi-empirical method to obtain the minimum energy conformation. The protonation and tautomerization states of the ligands were adjusted at physiological pH to improve the accuracy of molecular interaction prediction.

In this study, ligands were classified as punicalagin-related compounds, which include the parent compound and related structural fragments of ellagitannins. Urolithins were not included because the focus of the study was directed at compounds that are structurally closer to the direct

hydrolysis pathway of punicalagin and the main ellagitannin fragments.

2.3 Molecular Docking

Molecular docking was performed using PyRx 0.8 [15], which integrated with AutoDock Vina 1.2.0 [16], while interaction visualization was performed using Discovery Studio Visualizer 2021 [17] and UCSF Chimera 1.17 [18]. The ADAM17 protein structure (PDB ID: 3G42) uses chain A. The docking grid center was set at coordinates x = 2.32, y = 18.85, z = 128.92 with a grid size of 27.60 Å × 25.00 Å × 24.35 Å and an exhaustiveness of 8. Validation of the docking protocol was performed by redocking the co-crystal ligand N-{[4-(but-2-yn-1-yloxy)phenyl]sulfonyl}-5-methyl-D-tryptophan, onto the ADAM17/TACE structure. The native ligand was separated from the protein, then redocked using the same grid and exhaustiveness parameters as the primary docking. Redocking yielded a RMSD value of 1.689 Å indicating that the docking protocol used was able to adequately reproduce the experimental binding pose. Zn^{2+} ions were retained during protein preparation to maintain the integrity of the catalytic site. The resulting binding affinity value is an estimate of the binding free energy (ΔG), which is used as a relative indicator of interaction strength, but does not represent the absolute free energy. Ligand poses are selected based on binding affinity, consistency of interactions with conservative residues, and compatibility with the metalloprotease active site.

2.4 Physicochemical Descriptor and Drug-Likeness Analysis

Physicochemical and drug-likeness descriptors for all ligands were calculated using SwissADME, including molecular mass; hydrogen bond donor and acceptor; lipophilicity (LogP); topological polar surface area (TPSA); and number of rotatable bonds. Additional parameters such as bioavailability score and drug-likeness filters (Lipinski, Veber, Ghose, and Egan) were used to evaluate the suitability of compounds as initial candidates for ADAM17 modulation. This analysis was used to correlate physicochemical properties with membrane penetration and biological absorption potential.

2.5 ADMET Prediction

ADMET predictions were performed using SwissADME and pkCSM, with input in the form of SMILES notation for each ligand from PubChem. Parameters analyzed included gastrointestinal absorption, BBB permeability, interaction with P-glycoprotein (substrate and inhibitor), CYP450 enzyme inhibition, and toxicity parameters such as the AMES test, hepatotoxicity, and hERG inhibition. Prediction results were used as initial indicators of in silico pharmacokinetic and toxicity profiles, with interpretation based on comparisons between compounds, rather than absolute values.

2.6 Multi-Parameter Optimization (MPO)

MPO was performed to assess the balance between binding affinity and pharmacokinetic profile of each ligand. MPO integrates ligand binding energies from docking; physicochemical and drug-likeness descriptors (LogP, TPSA, rotatable bonds, molecular mass); and ADMET parameters such as GI absorption and bioavailability. The parameters, normalization approaches, and weights used in MPO analysis are presented in Table 1.

Table 1. Parameters, normalization approaches, and weights in MPO analysis.

Parameters	Optimization Interpretation	Normalization Approach	Weight (wj)
Binding affinity	The lower the better	Min–max inverse normalization	0.25
GI absorption	The higher the better	Direct normalization	0.20
Bioavailability score	The higher the better	Direct normalization	0.20
LogP	Moderate values are more optimal	Range-based normalization	0.10
TPSA	Moderate values are more optimal	Range-based normalization	0.10
Molecular weight	The lower the better	Min–max inverse normalization	0.10
Rotatable bonds	The lower the better	Min–max inverse normalization	0.05

All parameters were normalized to a 0–1 scale to allow comparison between variables on different scales. Parameters with a significant contribution to the feasibility of oral candidates, such as binding affinity, GI absorption, and bioavailability score, were given higher weights than other physicochemical parameters. Weighting was performed empirically based on the parameter's general relevance to the development of oral candidates. The MPO score was calculated using the formula:

$$\mathrm{MPO}_i = \sum_{j=1}^{n} w_j \cdot P_{ij}^{\mathrm{norm}} \qquad (1)$$

The normalized parameter values (P_{ij}^{norm}) represent the partial scores of each parameter before being multiplied by their respective weights in the

final MPO calculation. The weights (w_j) are determined based on the parameter's relevance to the feasibility of the oral drug, with priority given to bioavailability and binding affinity [19]. The MPO approach is used to identify candidate compounds that have an optimal balance between biological potency and pharmacokinetic properties, making them more relevant for drug development than single-parameter-based evaluation.

3. Result and Discussion

3.1 Binding Potential and Structural Suitability of Compounds

Before ligand interaction analysis was performed, the validity of the docking protocol was first evaluated through a redocking approach on the co-crystal ligand. The redocking results of the co-crystal ligand yielded a RMSD of 1.689 Å, which is below the common threshold of 2.0 Å and indicates the validity of the docking protocol used. Analysis of the ADAM17 pocket through molecular docking identified two main pockets, P1 and P2, with distinct characteristics (Figure 1).

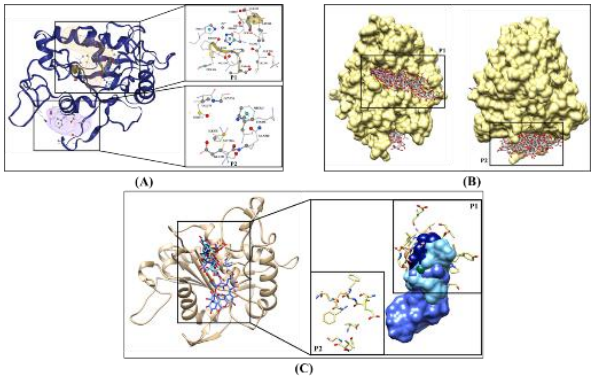

Figure 1. Identification of binding sites and docking strategies. (A) Pocket profile. (B) Random docking. (C) Directional docking.

Position P1 is a catalytic pocket containing Zn^{2+} ions and conservative residues, while P2 is located outside the catalytic core and has the potential to act as an exosite site. Ligand interactions at P1 indicate the involvement of key catalytic residues, including the HExxH motif that plays a role in the coordination of Zn^{2+} ions. Some ligands, especially punicalagin and punicalin, form an extensive hydrogen bond network with residues around the active site, potentially disrupting substrate orientation and catalytic processes. However, not all ligands show indications of direct coordination with Zn^{2+}, so it is possible that the inhibition mechanism is not entirely competitive, but may involve modulation of enzyme conformation through non-catalytic interactions.

To evaluate the potential interaction of ligands with ADAM17, molecular docking analysis was performed, yielding binding energy values as a relative indicator of the strength of the ligand–protein interaction. The results of the binding affinity calculations for all compounds are presented in Table 2.

Table 2. Ligand binding affinity based on molecular docking.

Ligand	*Binding affinity* (Random *Docking*) (kcal/mol)	*Binding affinity* (Targeted *Docking*) (kcal/mol)	Dominant binding site	Distance to Zn^{2+} (Å)
MRM	-6.9	-6.9	P1	3.122
PNG	-8.2	-8.4	P1, P2	3.788
PNL	-8.8	-8.5	P1, P2	2.476
ELA	-7.4	-7.4	P1	2.478
GAA	-6.5	-6.5	P1	4.854
SKA	-6.2	-6.2	P1	3.298
HPA	-8.2	-8.2	P1	2.414
DHS	-6.5	-6.4	P1	4.420
DXB	-6.4	-6.4	P1	6.043

Ligand binding energies were negative for all compounds, indicating favorable interactions (Table 2). Large ligands such as PNG and PNL exhibited the strongest binding affinities (−8.2 to −8.8 kcal/mol), while small/moderate ligands had intermediate affinities (−6.2 to −6.9 kcal/mol). However, the obtained binding affinity values are computational estimates and do not always correlate directly with actual biological activity, so interpretation is done comparatively between ligands.

Distance analysis to Zn^{2+} ions shows that HPA (2.414 Å), PNL (2.476 Å), and ELA (2.478 Å) are located relatively close to the catalytic center of ADAM17/TACE, indicating a potential stronger interaction with the metalloprotease active site. In contrast, ligands such as GAA, DHS, and DXB have a larger distance to Zn^{2+}, so they likely interact more predominantly through residues around the binding pocket. PNG still shows high affinity despite having a larger distance to Zn^{2+}, indicating that the stability of the interaction is also influenced by the contribution of other non-covalent interactions.

Figures 2 and 3 present a visualization of ligand interactions. Ligand interactions primarily involve conservative residues around the HExxH and Met-turn motifs, suggesting the potential for modulating enzyme activity through stabilization of non-productive conformations, rather than solely through direct competition with the substrate. In general, interactions are dominated by hydrogen bonds, π–π interactions, and hydrophobic interactions, with significant contributions from hydroxyl groups in forming a polar interaction network. This pattern is consistent with the characteristics of polyphenols, which are capable of forming multi-point bindings on protein surfaces.

Large ligands with a high number of hydroxyl groups form a more extensive hydrogen bonding network, thereby increasing binding affinity, particularly at the catalytic site (P1). Conversely, small ligands with more moderate polarity exhibit lower affinity but have more favorable pharmacokinetic profiles, such as better membrane permeability and bioavailability. Overall, these results indicate that binding affinity is influenced by molecular size and the number of polar groups, and needs to be considered alongside pharmacokinetic properties to assess its biological relevance.

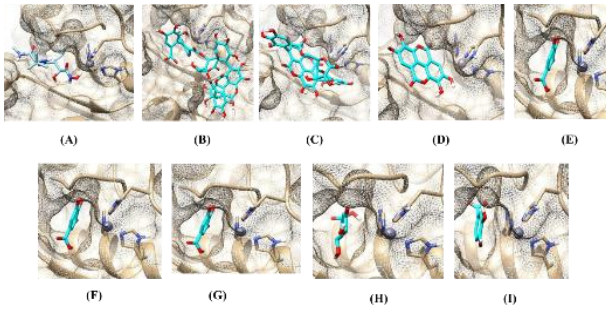

Figure 2. 3D visualization of ligands at the catalytic site. (A) MRM. (B) PNG. (C) NLP. (D) ELA. (E) GAA. (F) SKA. (G) HPA. (H) DHS. (I) DXB.

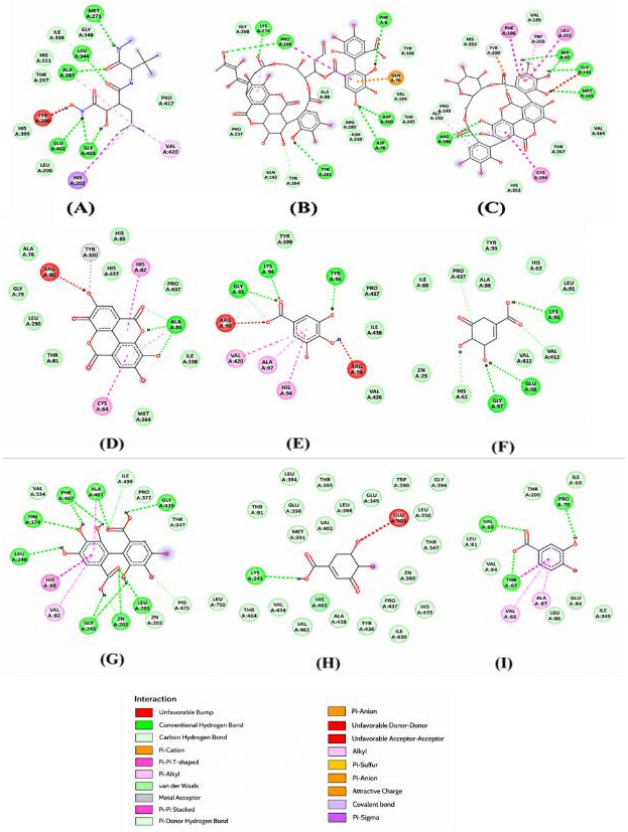

Figure 3. 2D visualization of ligand interactions with residues. (A) MRM. (B) PNG. (C) PNL. (D) ELA. (E) GAA. (F) SKA. (G) HPA. (H) DHS. (I) DXB.

3.2 Pharmacokinetic Profile Based on Physicochemical Profile and Drug-Likeness

The pharmacokinetic profiles of bioactive compounds were analyzed using SwissADME through evaluation of physicochemical parameters and drug-likeness rules, including Lipinski, Veber, Ghose, and Egan (Table 4). The drug-likeness analysis results show a contrasting difference between large ellagitannins and small/moderate metabolites (Table 4). Compounds such as punicalagin (PNG) and punicalin (PNL) have high molecular masses (>700 Da), very large TPSAs, and a high number of hydrogen bond donors and acceptors, which violate Lipinski's rule and are implicated in low membrane permeability.

In contrast, small metabolites such as GAA, HPA, SKA, DHS, and DXB fulfilled all Lipinski and Veber criteria, indicating a better balance between polarity and lipophilicity, which is important for passive absorption through biological membranes. All compounds were evaluated using Lipinski's Rule of Five, Veber's Rule (TPS, rotatable bonds), and Ghose and Egan filters [20], [21], [22]. The lower TPSA value (<140 $Å^2$) of this compound supports

better permeability potential compared to large ellagitannins.

Structurally, the high number of hydroxyl groups in ellagitannins contributes to their ability to form strong hydrogen bonds with proteins, while simultaneously increasing polarity and decreasing membrane diffusion. This confirms the relationship between physicochemical properties and biological distribution capacity. Although physicochemical and drug-likeness parameters provide an initial indication of a compound's profile as a drug, these results do not directly reflect in vivo biological activity, but rather serve as an initial filter in the selection of candidate compounds.

Table 4. Physicochemical profile and drug-likeness of bioactive compounds

Parameter	Ligand								
	MRM	**PNG**	**PNL**	**ELA**	**GAA**	**HPA**	**SKA**	**DHS**	**DXB**
Molecular Mass (g/mol)	331,4	1084,72	782,53	302,19	170,12	248,27	174,14	174,15	153,11
H Donor	5	17	13	4	4	2	4	4	2
H Acceptor	5	30	22	8	5	4	5	5	4
LogP	0,51	1,46	-0,29	1,10	0,70	2,79	-1,72	-1,39	-0,54
Molar Refractivity	84,86	252,09	180,45	75,31	39,47	66,87	38,43	38,84	35,51
Ro5 *Violation*	0	3	3	0	0	0	0	0	0
Water Solubility (log S)	-1,49	-7,73	-4,88	-2,94	-1,64	-3,19	0,23	0,02	-1,85
Lipophilicity (XLogP3)	0,51	1,46	-0,29	1,10	0,70	2,79	-1,72	-1,39	-0,54
Insaturation (Fraction Csp3)	0,80	0,10	0,18	0	0	0,43	0,57	0,57	0
Flexibility (*Rotatable Bonds*)	5	2	0	0	1	3	1	1	1
Permeability (TPSA)	127,76	526,60	385,24	141,34	97,99	74,60	97,99	97,99	80,59
Bioavailability	0,55	0,17	0,17	0,55	0,56	0,85	0,56	0,56	0,56

Note: marimastat (MRM), punicalagin (PNG), punicalin (PNL), ellagic acid (ELA), gallic acid (GAA), hexahydroxydiphenic acid (HPA), shikimic acid (SKA), 3-dehydroshikimate (DHS), and 3,4-dihydroxybenzoate (DXB).

3.3 ADMET Predictions of Bioactive Compounds

The ADMET profiles of bioactive compounds were predicted using SwissADME and pkCSM to evaluate absorption, distribution, metabolism, excretion, and toxicity (Table 5). ADMET predictions showed clear pharmacokinetic differences between the compounds (Table 5). Based on the data, although PNG and PNL showed high predicted intestinal absorption, both compounds have very large TPSA and molecular masses, and are substrates/inhibitors of P-glycoprotein. This condition indicates that absorption predictions based on computational models may not fully represent actual in vivo bioavailability, especially for complex polyphenolic compounds with dynamic transport and metabolism mechanisms [23]. In contrast, some small metabolites such as HPA and GAA show moderate to low absorption, indicating limitations in initial penetration, even though they structurally better meet drug-likeness criteria.

In terms of distribution, most compounds exhibit low blood-brain barrier (BBB) permeability, potentially minimizing side effects on the central nervous system. However, DXB has the highest logBB value (0.06), indicating potential distribution to the CNS and warranting further development. In contrast, PNG and PNL exhibit very low BBB permeability (logBB <−3), likely limiting them to the peripheral system. High plasma protein-free fractions (Fu) in SKA and DHS (>0.8) indicate greater availability of compounds to interact with their targets, while ELA, with a low Fu (0.08), indicates a high degree of protein binding that may limit free distribution [24], [25].

Metabolic profiles showed that most compounds did not show significant inhibitory potential against CYP450 enzymes, except ELA which has the potential to inhibit CYP1A2 [24] [26], so the risk of metabolic interactions is relatively low, although it still requires experimental verification. In terms of excretion, MRM showed high clearance (log 1.69 ml/min/kg), while PNG and PNL had lower clearance indicating a potential longer duration of action [24]. Toxicity evaluation showed that all compounds were predicted to be non-mutagenic (negative AMES) and had relatively low oral toxicity (LD50 > 1.1 mol/kg). However, the indication of hERG inhibition in PNG indicates a potential cardiotoxicity risk that requires attention. Predictions for hepatotoxicity and skin sensitization were negative for all compounds [25], [27].

Overall, these in silico ADMET results provide a preliminary overview of the pharmacokinetic and toxicity profiles of the compounds, with PNG and PNL demonstrating favorable peripheral absorption and distribution profiles, although interactions with P-gp need to be considered. Compounds such as DXB require attention regarding CNS distribution, while HPA and GAA may require formulation optimization to improve bioavailability. Toxicity predictions such as AMES, hERG, and LD50 in this study are not interpreted as definitive evidence of safety, but rather as preliminary indicators based on an in silico approach. Therefore, all these results should be interpreted with caution considering the limitations of computational methods that do not fully represent complex biological systems and still require further experimental validation.

Table 5. ADMET profile of bioactive compounds.

Parameters	Ligand								
	MRM	**PNG**	**PNL**	**ELA**	**GAA**	**HPA**	**SKA**	**DHS**	**DXB**
Water Solubility (log mol/L)	-1.85	-2.89	-2.89	-3.18	-2.56	-2.89	-0.52	-0.32	-1.79
Intestinal Absorption (%)	40.3	100	100	86.7	43.4	29.7	46.7	40.9	79.3
P-gp Substrate	Yes	Yes	Yes	Yes	No	Yes	No	No	No
P-gp Inhibitor	No	Yes	Yes	No	No	No	No	No	No
BBB Permeability (log BB)	-0.92	-4.11	-3.39	-1.27	-1.1	-1.98	-0.68	-0.57	0.06
Fraction Unbound (Fu)	0.46	0.38	0.36	0.08	0.62	0.27	0.8	0.81	0.63
CYP Inhibition	–	–	–	CYP1A2	–	–	–	–	–
Total Clearance (log ml/min/kg)	1.69	-0.28	0.1	0.54	0.52	0.41	0.69	0.67	0.63
AMES Toxicity	No	No	No	No	No	No	No	No	No
hERG II Inhibitor	No	Yes	No	No	No	No	No	No	No
Oral LD50 (mol/kg)	1.89	2.48	2.48	2.4	2.22	2.48	1.16	1.21	2.2

Note: marimastat (MRM), punicalagin (PNG), punicalin (PNL), asam elagat (ELA), asam galat (GAA), asam heksahidroksidifenat (HPA), asam shikimat (SKA), 3-dehidroshikimat (DHS), and 3,4-dihidroksibenzoat (DXB).

3.4 Multi-Parameter Optimization (MPO)

A multi-parameter optimization (MPO) evaluation was performed to assess the balance between binding affinity and pharmacokinetic properties of the compounds, with the comparative results visualized in a bar chart (Figure 4). This approach integrates molecular docking data, physicochemical and drug-likeness profiles, and ADMET parameters into a single composite score to provide a more comprehensive assessment of the initial feasibility of candidate compounds [28], [29].

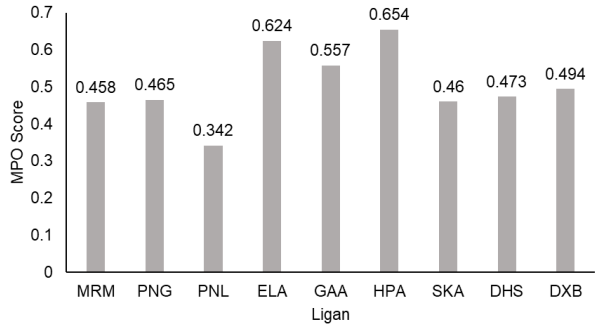

Figure 4. Comparison of ligand multi-parameter optimization (MPO) analysis results.

MPO results showed that small/moderate metabolites such as HPA (0.65) and ELA (0.62) had the highest scores, reflecting an optimal combination of interaction with ADAM17 and pharmacokinetic feasibility. In contrast, large ligands such as PNG (0.46) and PNL (0.34) showed lower scores due to their high molecular mass and polarity, which limited bioavailability despite their strong binding affinity. Other metabolites such as GAA (0.56) and DXB (0.49) showed moderate scores, reflecting a balance between interaction stability and biological penetration ability.

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The MPO score is obtained by integrating parameters normalized to a range of 0–1 and multiplying each parameter's weight based on its relevance to the candidate's oral viability. Parameters such as binding affinity, GI absorption, and bioavailability score contribute significantly to the final score, while physicochemical parameters such as TPSA, molecular weight, and rotatable bonds play a role in balancing the permeability and flexibility of the molecule.

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These findings emphasize that high binding affinity does not always equate to potential as an early candidate, making multi-parameter evaluation crucial in the early stages of drug discovery. Specifically, small metabolic derivatives of punicalagin demonstrate more realistic potential as early candidates due to their ability to balance target interactions and pharmacokinetic profiles. Previous MPO studies similarly highlighted that balancing potency with ADMET feasibility can reduce late-stage attrition in drug development [28].

However, the MPO approach has limitations, particularly related to the sensitivity of parameter weightings, which can influence the final ranking of candidates. Furthermore, MPO does not consider dynamic factors such as protein flexibility and the effects of the biological environment, requiring confirmation through molecular dynamics simulations and experimental testing. Recent reviews also note that MPO should ideally be complemented by dynamic and systems-level approaches to improve predictive accuracy during lead optimization [29].

Overall, MPO provides a more comprehensive evaluation framework than single-parameter-based approaches, emphasizing the importance of balancing biological potency and pharmacokinetic feasibility in the selection of candidate compounds.

4. Advanced Strategy and Development

Based on the integrative results of molecular docking, physicochemical and drug-likeness profiles, ADMET, and MPO, further studies are needed to validate the therapeutic potential of candidate compounds. Considering the limitations of the *in silico* approach, molecular dynamics (MD) simulations for 100–200 ns are recommended to evaluate the stability of the ligand–ADAM17 complex and the interaction dynamics at key residues around the HExxH motif [31], [32].

Experimental validation through enzymatic inhibition assays is necessary to determine the

inhibitory potential and the inhibition mechanism (competitive or non-competitive). Additional approaches such as quantum mechanics or spectroscopy-based studies can be used to examine molecular interactions, including possible coordination with Zn^{2+} [33], [34].

These results can be further utilized for structural optimization by balancing binding affinity and pharmacokinetic properties. Overall, this stepwise approach suggests that small metabolites of punicalagin-related compounds have more realistic prospects as early candidates for ADAM17 modulation, but further experimental validation is still needed [31], [35].

5. Conclusion

This study demonstrates that the potency of punicalagin-related compounds in modulating ADAM17 is determined not only by the strength of binding affinity, but also by the balance with pharmacokinetic properties. Large ellagitannins such as punicalagin and punicalin have high binding affinity, but show limitations in terms of drug-likeness and bioavailability. In contrast, small/moderate metabolites such as HPA, ELA, and GAA exhibit a better balance between target interaction and pharmacokinetic profile, reflected in higher MPO scores.

These findings confirm that multi-parameter-based evaluation is more relevant than a single-parameter approach in the early stages of drug discovery. Therefore, these small polyphenol metabolites may serve as initial hit compounds for ADAM17/TACE modulation rather than definitive oral drug candidates. However, given the limitations of the in-silico approach, further studies using molecular dynamics simulations and experimental validation are needed to confirm their biological relevance and therapeutic potential.

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References

[1] de Queiroz T.M., Lakkappa N., dan Lazartigues E., 2020, ADAM17-Mediated Shedding of Inflammatory Cytokines in Hypertension, Frontiers in Pharmacology, https://doi.org/10.3389/fphar.2020.01154

[2] Duan Y.W., Chen S.X., Li Q.Y., dan Zang Y., 2022, Neuroimmune Mechanisms Underlying Neuropathic Pain: The Potential Role of TNF-α-Necroptosis Pathway, International Journal of Molecular Sciences, https://doi.org/10.3390/ijms23137191

[3] Kim H.J. et al., 2020, ADAM17 Genetic Variants and the Response of TNF-α Inhibitor in Rheumatoid Arthritis Patients, Pharmacogenomics and Personalized Medicine, 13, https://doi.org/10.2147/PGPM.S235035

[4] van Loo G., dan Bertrand M.J.M., 2023, Death by TNF: A Road to Inflammation, Nature Reviews Immunology, https://doi.org/10.1038/s41577-022-00792-3

[5] Tatsumi M. et al., 2023, Ectodomain Shedding of EGFR Ligands Serves as an Activation Readout for TRP Channels, PLoS One, 18,1, https://doi.org/10.1371/journal.pone.0280448

[6] Schumacher N., dan Rose-John S., 2022, ADAM17 Orchestrates Interleukin-6, TNFα and EGF-R Signaling in Inflammation and Cancer, Biochimica et Biophysica Acta Molecular Cell Research, 1869,1, https://doi.org/10.1016/j.bbamcr.2021.119141

[7] Gao L., Li L., Zhang D., Qiu J., Qian J., dan Liu H., 2024, TAPI-1 Exhibits Anti-tumor Efficacy in Human Esophageal Squamous Cell Carcinoma Cells via Suppression of NF-κB Signaling Pathway, Digestive Diseases and Sciences, 69,1,81-94, https://doi.org/10.1007/s10620-023-08181-z

[8] Calligaris M. et al., 2021, Strategies to Target ADAM17 in Disease: From Its Discovery to the iRhom Revolution, Molecules, 26,4,944, https://doi.org/10.3390/molecules26040944

[9] Bienstein M., Minond D., Schwaneberg U., Davari M.D., dan Yildiz D., 2022, In Silico and Experimental ADAM17 Kinetic Modeling as Basis for Future Screening System for Modulators, International Journal of Molecular Sciences, 23,3, https://doi.org/10.3390/ijms23031368

[10] Minond D., 2020, Novel Approaches and Challenges of Discovery of Exosite Modulators of a Disintegrin and Metalloprotease 10, Frontiers in Molecular Biosciences, https://doi.org/10.3389/fmolb.2020.00075

[11] Yang L., Fan C., Shu T., dan Wang S., 2021, Punicalin Alleviates TNF-α- and IL-1β-Induced Chondrocyte Dysfunction and Cartilage Metabolism via Mediating FOXO3 Signaling Axis, Journal of Food Biochemistry, 45,8, https://doi.org/10.1111/jfbc.13755

[12] Cao Y., Chen J., Ren G., Zhang Y., Tan X., dan Yang L., 2019, Punicalagin Prevents Inflammation in LPS-Induced RAW264.7 Macrophages by Inhibiting FoxO3a/Autophagy Signaling Pathway, Nutrients, 11,11,2794, https://doi.org/10.3390/nu11112794

[13] Čolić M. et al., 2022, Immunomodulatory Activity of Punicalagin, Punicalin, and Ellagic Acid Differs from the Effect of Pomegranate Peel

Extract, Molecules, 27,22,7871, https://doi.org/10.3390/molecules27227871

[14] Caballero V., Estévez M., Tomás-Barberán F.A., Morcuende D., Martín I., dan Delgado J., 2022, Biodegradation of Punicalagin into Ellagic Acid by Selected Probiotic Bacteria: A Study of the Underlying Mechanisms by MS-Based Proteomics, Journal of Agricultural and Food Chemistry, 70,51, https://doi.org/10.1021/acs.jafc.2c06585

[15] Home S.D., dan Dallakyan S., 2015, Small-Molecule Library Screening by Docking with PyRx, Methods in Molecular Biology, 1263.

[16] Trott O., dan Olson A.J., 2010, AutoDock Vina: Improving the Speed and Accuracy of Docking with a New Scoring Function, Efficient Optimization, and Multithreading, Journal of Computational Chemistry, 31,2, https://doi.org/10.1002/jcc.21334 .

[17] BIOVIA D.S., 2005, Discovery Studio Visualizer v21.1.0.20298, Dassault Systèmes.

[18] Pettersen E.F. et al., 2004, UCSF Chimera: A Visualization System for Exploratory Research and Analysis, Journal of Computational Chemistry, 25,13, https://doi.org/10.1002/jcc.20084

[19] Nchinda A.T., dan Menzel K., 2026, Optimizing Drug Discovery in Resource-Limited Settings: Multi-Parameter Optimization and Data-Driven Workflows, ACS Medicinal Chemistry Letters, https://doi.org/10.1021/acsmedchemlett.5c00501

[20] Ivanović V., Rančić M., Arsić B., dan Pavlović A., 2020, Lipinski's Rule of Five, Famous Extensions and Famous Exceptions, Chemia Naissensis, 3,1, https://doi.org/10.46793/chemn3.1.171i

[21] Ani R., Anand P.S., Sreenath B., dan Deepa O.S., 2020, In Silico Prediction Tool for Drug-Likeness of Compounds Based on Ligand-Based Screening, International Journal of Research in Pharmaceutical Sciences, 11,4, https://doi.org/10.26452/ijrps.v11i4.3310

[22] Caminero Gomes Soares A., Marques Sousa G.H., Calil R.L., dan Goulart Trossini G.H., 2023, Absorption Matters: A Closer Look at Popular Oral Bioavailability Rules for Drug Approvals, Molecular Informatics, 42,11, https://doi.org/10.1002/minf.202300115

[23] Seelig A., 2020, P-Glycoprotein: One Mechanism, Many Tasks and the Consequences for Pharmacotherapy of Cancers, Frontiers in Oncology, https://doi.org/10.3389/fonc.2020.576559

[24] Pires D.E.V., Blundell T.L., dan Ascher D.B., 2015, pkCSM: Predicting Small-Molecule Pharmacokinetic and Toxicity Properties Using Graph-Based Signatures, Journal of Medicinal Chemistry, 58,9,4066-4072, https://doi.org/10.1021/ACS.JMEDCHEM.5B00104

[25] Daina A., Michielin O., dan Zoete V., 2017, SwissADME: A Free Web Tool to Evaluate Pharmacokinetics, Drug-Likeness and Medicinal Chemistry Friendliness of Small Molecules, Scientific Reports, 7,1, https://doi.org/10.1038/srep42717

[26] Testa B., Pedretti A., dan Vistoli G., 2012, Reactions and Enzymes in the Metabolism of Drugs and Other Xenobiotics, Drug Discovery Today, 17,11-12,549-560, https://doi.org/10.1016/J.DRUDIS.2012.01.017

[27] Yang H. et al., 2019, admetSAR 2.0: Web-Service for Prediction and Optimization of Chemical ADMET Properties, Bioinformatics, 35,6,1067-1069, https://doi.org/10.1093/BIOINFORMATICS/BTY707

[28] Segall M.D., 2012, Multi-Parameter Optimization: Identifying High Quality Compounds with a Balance of Properties, Current Pharmaceutical Design, 18,9,1292-1310, https://doi.org/10.2174/138161212799436430

[29] Pennington L.D., dan Muegge I., 2021, Holistic Drug Design for Multiparameter Optimization in Modern Small Molecule Drug Discovery, Bioorganic and Medicinal Chemistry Letters, 41,128003, https://doi.org/10.1016/J.BMCL.2021.128003

[30] Nicolotti O., Giangreco I., Introcaso A., Leonetti F., Stefanachi A., dan Carotti A., 2011, Strategies of Multi-Objective Optimization in Drug Discovery and Development, Expert Opinion on Drug Discovery, 6,9,871-884, https://doi.org/10.1517/17460441.2011.588696

[31] Aghahosseini F., Bayat M., Sadeghian Z., Gheidari D., dan Safari F., 2024, Synthesis, Molecular Docking Study, MD Simulation, ADMET, and Drug Likeness of New Thiazolo[3,2-a]Pyridine-6,8-Dicarbonitrile Derivatives as Potential Anti-Diabetic Agents, PLoS One, 19,9,e0306973, https://doi.org/10.1371/journal.pone.0306973

[32] El Khatabi K., Aanouz I., Alaqarbeh M., Ajana M.A., Lakhlifi T., dan Bouachrine M., 2021, Molecular Docking, Molecular Dynamics Simulation, and ADMET Analysis of Levamisole Derivatives Against the SARS-CoV-2 Main Protease (MPro), Bioimpacts, 12,2,107, https://doi.org/10.34172/BI.2021.22143

[33] dos Santos Correia P.R., de Souza A.H.D., Chaparro A.R., Tenorio Barajas A.Y., dan Porto R.S., 2023, Molecular Docking, ADMET Analysis and Molecular Dynamics (MD) Simulation to Identify Synthetic Isoquinolines as Potential Inhibitors of SARS-CoV-2 MPRO, Current Computer-Aided Drug Design, 19,5,391-404,

https://doi.org/10.2174/1573409919666230123150013

[34] Bakheit A.H., Attwa M.W., Kadi A.A., Ghabbour H.A., dan Alkahtani H.M., 2023, Exploring the Chemical Reactivity, Molecular Docking, Molecular Dynamic Simulation and ADMET Properties of a Tetrahydrothienopyridine Derivative Using Computational Methods, Crystals, 13,7,1020, https://doi.org/10.3390/CRYST13071020

[35] Moussaoui M. et al., 2024, QSAR, ADMET, Molecular Docking, and Dynamics Studies of 1,2,4-Triazine-3(2H)-One Derivatives as Tubulin Inhibitors for Breast Cancer Therapy, Scientific Reports, 14,1,16418, https://doi.org/10.1038/S41598-024-66877-2