ISSN: 2707-1146
e-ISSN: 2709-4189

https://doi.org/10.36719/2707-1146/54/35-45

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The Impact of Quercetin Glycosides on ACE2, AT1R, and AT2R: The Molecular Docking and in Silico Analysis

Abstract

The renin-angiotensin-aldosterone system (RAAS) plays a critical role in cardiovascular homeostasis, and its dysregulation is associated with hypertension and thrombotic disorders. In this study, we performed a comparative molecular docking analysis of four quercetin glycoside derivatives against three key RAAS-related targets: angiotensin-converting enzyme 2 (ACE2), angiotensin II type 1 receptor (AT1R), and angiotensin II type 2 receptor (AT2R). The aim is to identify ligands that inhibit AT1R to lower blood pressure, without antagonizing ACE2 and AT2R functions which are protective against thrombosis and endothelial dysfunction. The results showed quercetin 5-glucoside and 7-glucoside are promising dual-function ligands with selective AT1R inhibition and peripheral, non-blocking interaction with ACE2 and AT2R.

Keywords: *RAAS, ACE2, AT1R, AT2R, quercetin glycosides, molecular docking*

Introduction

The renin–angiotensin system (RAS) is a key regulatory pathway involved in cardiovascular homeostasis, fluid balance, and vascular tone. It has become increasingly evident in recent years that beyond its classical roles, RAS also exerts profound effects on inflammation, fibrosis, and thrombosis. The dual axis system –comprising the classical ACE1/angiotensin II/AT1R pathway and the counter-regulatory ACE2/Angiotensin-(1–7)/MasR pathway – has attracted significant attention in the pathophysiology of cardiovascular and thrombo-inflammatory disorders (Santos, Sampaio, Alzamora, Motta-Santos, Alenina, Bader, & Campagnole-Santos, 2018; Patel, Zhong, Grant, & Oudit, 2019).

Both ACE1 and ACE2 are endothelium-associated carboxypeptidases that are widely distributed in various organs, including the heart, kidneys, brain, and blood vessels. Additionally, ACE2 is present in vascular smooth muscle cells of coronary arteries and intrarenal blood vessels (Wang, Bodiga, Das, Lo, Patel, Oudit, 2012); Hikmet, Méar, Edvinsson, Micke, Uhlén, Lindskog, 2020). ACE, a highly glycosylated transmembrane protein, exists in two isoforms due to alternative splicing: somatic ACE, which consists of two domains (N- and C-domains) with distinct but overlapping substrate preferences (Turner, 2015).

Research

ACE1 converts angiotensin I into angiotensin II, a peptide that promotes vasoconstriction, oxidative stress, platelet aggregation, and pro-thrombotic responses via AT1R activation. Conversely, ACE2 plays a crucial role in the RAS by converting angiotensin II (Ang II) into angiotensin-(1-7) [Ang-(1-7)], a peptide with vasodilatory and cardioprotective effects primarily through the Mas receptor (Gheblawi, Wang, Viveiros, Nguyen, Zhong, Turner, Raizada, Grant, & Oudit, 2020).

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e-ISSN: 2709-4189

Additionally, AT2R, mentioned in some articles as another receptor for Ang II, counteracts AT1R by inducing nitric oxide production, vasodilation, and anti-fibrotic responses (Carey, Wang, Siragy, 2017). It can also hydrolyze Angiotensin I (Ang I) to generate Angiotensin-(1-9) [Ang-(1-9)], although the latter is primarily produced by carboxypeptidase A in the heart (Kuriakose, Montezano, Touyz, 2021, 2021). Beyond its role in angiotensin metabolism, ACE2 functions as a multifunctional enzyme, breaking down various bioactive peptides such as Apelin-13, Apelin-17, Apelin-36, and [des-Arg9]-bradykinin, thereby influencing multiple physiological pathways (Turner, 2015) (Fig. 1).

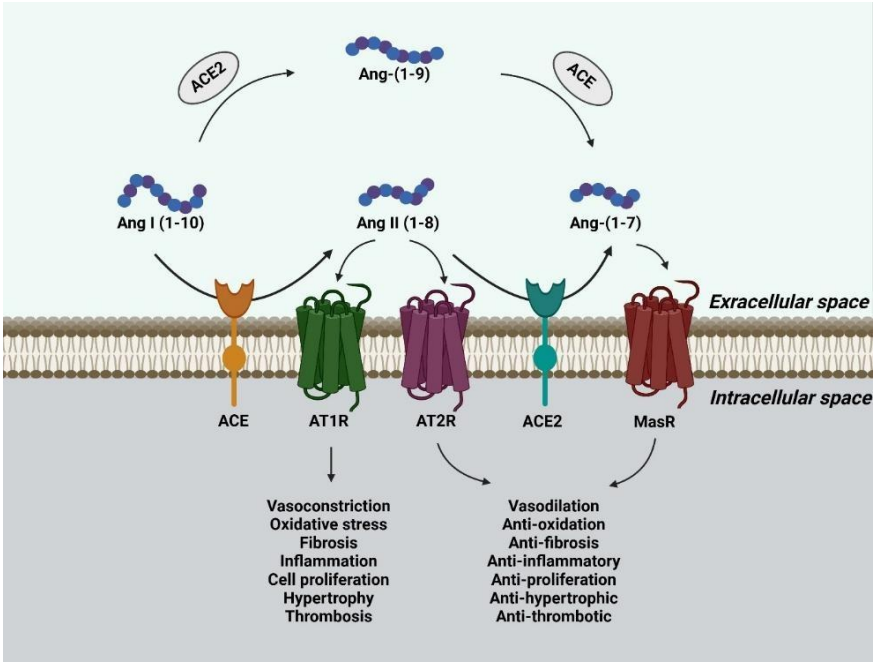


Fig. 1. Simplified illustration of RAS axis – ACE/Ang II/AT1R and ACE2/Ang-(1-7)/MasR. ACE converts Ang I (1-10) to Ang II (1-8), which activates the ACE/Ang II/AT1R signaling pathway, driving associated physiological responses. On the other hand, ACE2 catalyzes the conversion of Ang-(1-7) either directly or through the intermediate Ang-(1-9), initiating antagonist processes through the ACE2/Ang-(1-7)/MasR pathway.

The imbalance between these axes – often characterized by ACE1/AT1R overactivation and ACE-2/AT2R downregulation – has been implicated in a range of disorders including hypertension, thrombosis, acute lung injury, and cardiovascular complications (South, Brady, & Flynn, 2020). In addition, ACE2 plays a crucial role in kidney health by reducing tubulointerstitial fibrosis and protecting against diabetic renal injury (Hardenberg, Luft, 2020). Furthermore, ACE2 gained increased attention as the entry receptor for SARS-CoV-2, which also resulted in endothelial dysfunction and coagulation abnormalities, highlighting the potential of ACE2-targeted interventions (Verdecchia, Cavallini, Spanevello, & Angeli, 2020).

Several natural polyphenols, including quercetin and its analogues, have been reported to modulate RAS components by inhibiting ACE1 or influencing receptor activity. However, the direct binding affinity and molecular interaction of these compounds with ACE2, AT1R, and AT2R remain insufficiently studied. Structure-based drug design and molecular docking tools provide a powerful approach to explore these interactions in silico before proceeding to in vitro or in vivo validations (Samavati & Uhal, 2020; Galandarli, Mollayeva, Javadzade, Mammadova, & Amrahov, 2022).

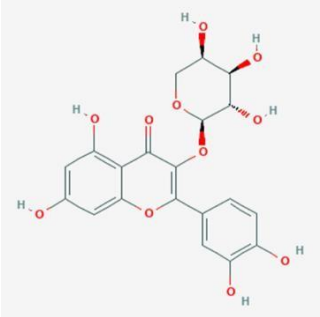
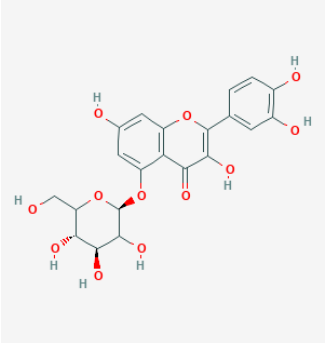
In this study, we aim to investigate the binding potential of selected quercetin-derived compounds to ACE2, AT1R, and AT2R through molecular docking and binding site analysis. The ultimate objective is to identify molecules that may enhance ACE2 and AT2R activity while

ISSN: 2707-1146
e-ISSN: 2709-4189

antagonizing AT1R, thus shifting the RAS equilibrium toward a vasoprotective and antithrombotic profile.

Material and method

Structure search and preparation of proteins and ligands. The coordinates for the ACE2, AT1R and AT2R were obtained from the PDB database (https://www.rcsb.org/). Quercetin glucosides (Fig. 2) were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). Ligands for molecular docking were prepared using Chimera (V:1.18; https://www.cgl.ucsf.edu/chimera/download.html) and AutoDock Vina (V:1.5.7; https://vina.scripps.edu/downloads/). The preparation of proteins was performed using the AutoDock software suite. Heteroatoms, including water molecules, were removed, polar hydrogens were added, non-polar hydrogens were merged, and Kollman and Gasteiger charges were assigned, as well as the conversion into.pdbqt format (Afriza, Suriyah, Ichwan, 2018). The file conversion into.pdbqt format was done to allow the file to be loaded in Autodock Vina for molecular docking simulation (Huey, Morris, Forli, 2012). Ligands downloaded from PubChem in .sdf format were converted to.pdb format using Open Babel (http://openbabel.org/wiki/Main_Page). The charges of the ligands were set to neutral, Gasteiger charges were added, and the number of torsions was kept at the default setting and conversion into.pdbqt format.

№	Compounds	Molecular formula	Molecular weight g/mol	2-Dimensional structure
1	12309865	$C_{20}H_{18}O_{11}$	434.3	 Quercetin 3-O-arabinoside
2	44259222	$C_{21}H_{20}O_{12}$	464.4	 Quercetin 5-glucoside

ISSN: 2707-1146
e-ISSN: 2709-4189

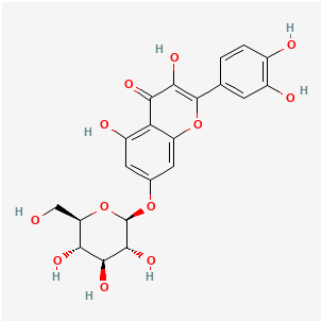
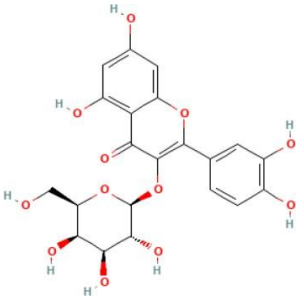
3	5282160	$C_{21}H_{20}O_{12}$	464.4	 Quercetin 7-glucoside
4	5281643	$C_{21}H_{20}O_{12}$	464.4	 Quercetin-3-O-galactoside

Fig. 2. Quercetin glucosides

Protein-ligand docking. Molecular docking was carried out using the AutoDock Vina tool (V: 1.5.7; https://vina.scripps.edu/downloads/). First, blind docking was performed, followed by precision docking. The spacing value was set to 1 angstrom, and the grid box was manually adjusted to cover the active regions of the receptor. The grid box dimensions were set to X = 20, Y = 20, Z = 20 for three proteins. The exhaustiveness value was set to 8 for the proteins. The center coordinates of the grid box were defined as shown in Table 1. All docking experiments were repeated three times to ensure reliability. Discovery Studio Visualizer (https://discover.3ds.com/discovery-studio-visualizer-download) was used to generate two-dimensional (2D) representations of protein-ligand interactions (Laskowski & Swindells, 2011). The three-dimensional (3D) images of protein-ligand complexes were created using the Chimera software (https://www.cgl.ucsf.edu/chimera/download.html) (Pettersen et al., 2004).

Table 1. Central coordinates of the Grid box

ACE2	**X**	**Y**	**Z**
1R42	39.409556	30.548984	9.472548
AT1R	X	Y	Z
6DO1	40.636558	37.312950	43.571732
AT2R	X	Y	Z
5UNG	4.839429	6.950571	-18.760843

ISSN: 2707-1146
e-ISSN: 2709-4189

Molecular docking analysis of four quercetin glycoside derivatives against ACE2 (PDB ID: 1R42), AT1R (PDB ID: 4YAY), and AT2R (PDB ID: 5UNG) was conducted to evaluate their binding affinities and interaction profiles. The results provide key insights into the potential of these ligands to modulate RAAS components relevant to hypertension and coagulation regulation.

Among the tested compounds (Fig.3), quercetin 5-glucoside exhibited the strongest binding affinity toward ACE2 (-9.0 kcal/mol), AT1R (-8.4 kcal/mol), and AT2R (-8.1 kcal/mol), followed closely by quercetin 7-glucoside (-8.8 kcal/mol, -8.6 kcal/mol, -8.6 kcal/mol, respectively). The remaining derivatives, such as quercetin 3-O-arabinoside and quercetin 3-O-galactoside, also displayed moderate-to-high affinities ranging from -8.0 to -8.7 kcal/mol.

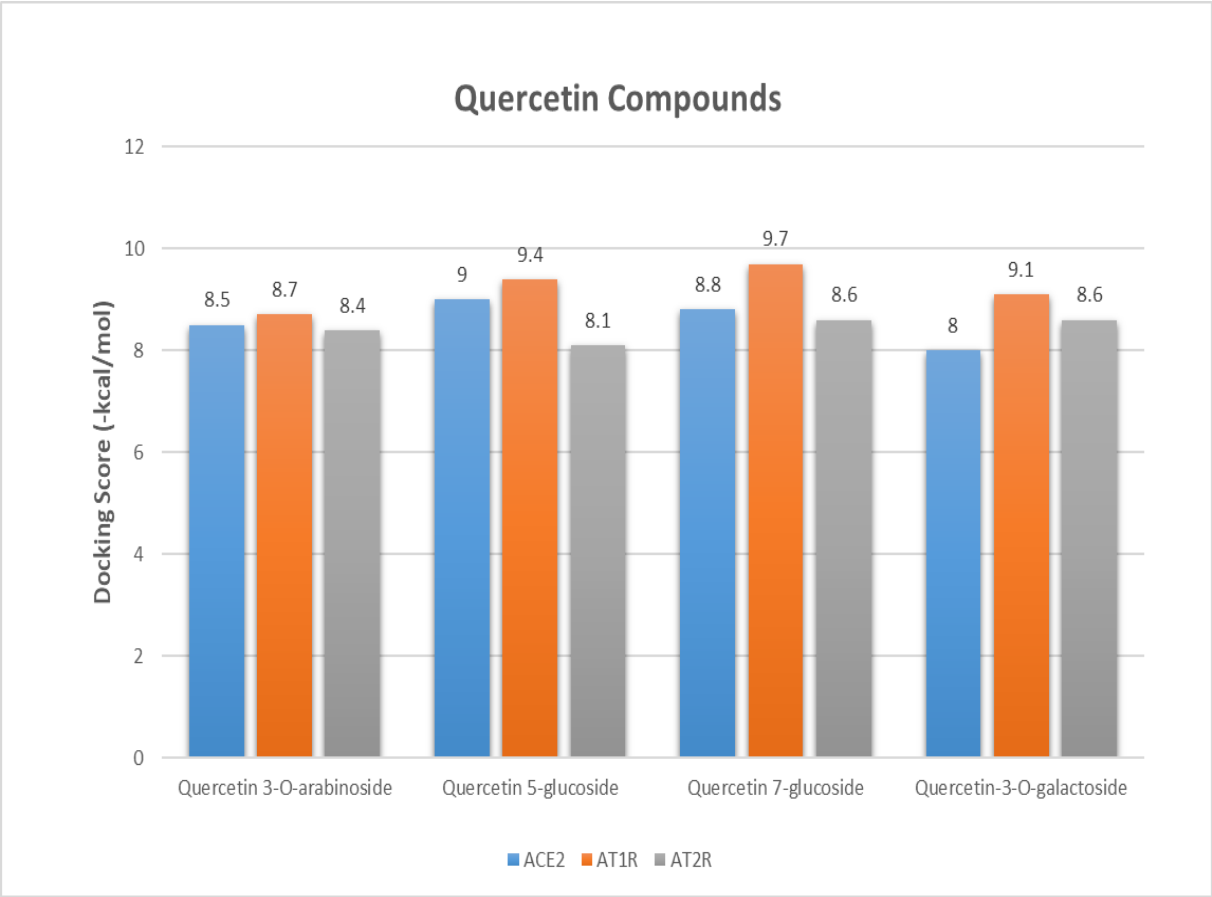


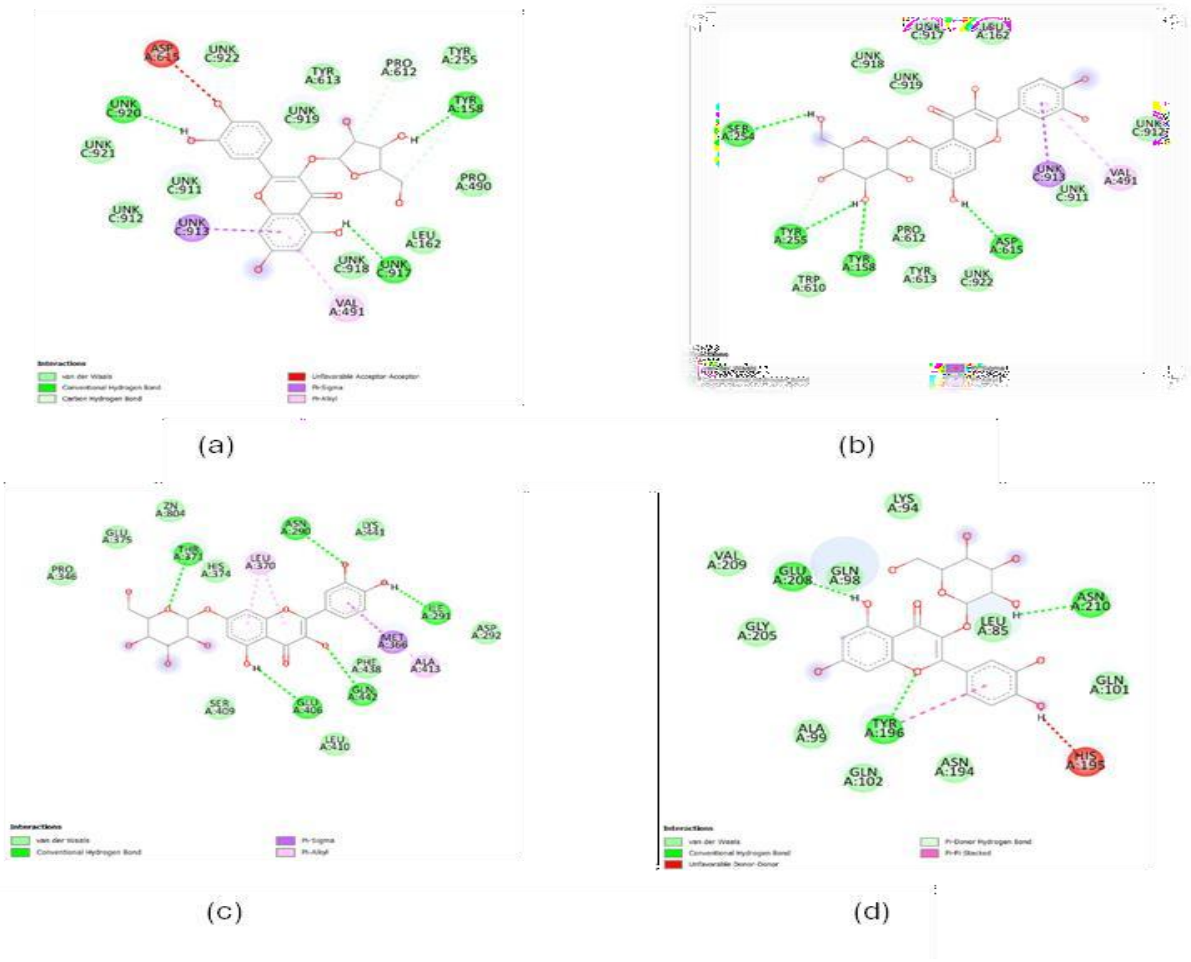
Fig. 3. Docking score between the test ligands and ACE2, AT1R, AT2R

Molecular interaction analysis revealed that (Fig. 4) quercetin 5-glucoside and quercetin 7-glucoside consistently interacted with key residues in the catalytic site of ACE2, including HIS374, GLU375, GLU402, and ASN290, which are known to play vital roles in substrate recognition and enzymatic function (Towler et al., 2004) (Table 2). However, based on the binding mode and absence of deep catalytic blockage, these interactions may result in modulatory effects rather than full inhibition (Pettersen, Goddard, Huang, Couch, Greenblatt, Meng, & Ferrin, 2004).

Fig. 4. Visualization of the molecular interactions of ACE2 with various ligands. (a) quercetin 3-O-arabinoside, (b) quercetin 5-glucoside, (c) quercetin 7-glucoside, (d) quercetin 3-O-galactoside

ISSN: 2707-1146
e-ISSN: 2709-4189

Table 2. Interaction profiles between ACE-2 and test ligands.



	Compounds	Hydrogen bonds	Hydrophobic interactions	Number of interactions
	Quercetin 3-O-arabinoside	Trp^{158}, Unk^{920}, Unk^{917}	Unk^{918}, Val^{491}, Tyr^{613}, Leu^{162}, Pro^{490}, Tyr^{255}, Pro^{612}, Unk^{919}, Unk^{922}, Unk^{921}, Unk^{911}, Unk^{912}, Unk^{913}	16
	Quercetin 5-glucoside	Ser^{254}, Tyr^{255}, Tyr^{158}, Asp^{615}	Trp^{610}, Pro^{612}, Tyr^{613}, Unk^{922}, Unk^{911}, Unk^{912}, Unk913, Val491, Leu162, Unk^{917}, Unk^{918}, Unk^{919}	16
	Quercetin 7-glucoside	Thr^{371}, Asn^{290}, Ile^{291}, Gln^{442}, Gln^{406}	Pro^{346}, Glu^{375}, Zn^{804}, His^{374}, Leu^{370}, Lys^{441}, Asp^{292}, Ala^{413}, Met^{366}, Phe^{438}, Leu^{410}, Ser^{409}	17
	Quercetin 3-O-galactoside	Glu^{208}, Asn^{210}, Tyr^{196}	Lys^{94}, Leu^{85}, Gln^{101}, Asn^{194}, Gln^{102}, Ala^{99}, Gyl^{205}, Val^{209}, Gln^{98}	12

ISSN: 2707-1146
e-ISSN: 2709-4189

Conversely, both ligands showed robust interactions with AT1R active site residues, particularly ARG167, VAL108, TYR35, and TRP84, which are central to the orthosteric binding pocket of angiotensin II (Table 3 and Fig.5). These interactions suggest competitive inhibition potential of AT1R, potentially contributing to vasodilation and blood pressure reduction mechanisms, consistent with prior reports on flavonoid-AT1R interactions. Regarding AT2R (Table 4), binding profiles of the ligands showed lower binding depths compared to AT1R, further confirming the preservation of AT2R activity rather than antagonism. Ligands such as quercetin 3-O-arabinoside and quercetin 3-O-galactoside, while showing comparable scores (-8.4 and -8.6 kcal/mol, respectively), demonstrated fewer key residue interactions, reducing their therapeutic priority (Fig.6).

Taken together, quercetin 5-glucoside emerges as the most promising dual-acting ligand due to strong AT1R inhibition and ACE2/AT2R modulation without antagonism. Quercetin 7-glucoside follows closely with a similar favorable binding pattern (Towler, Staker, Prasad, Menon, Tang, Parsons, Ryan, Fisher, Williams, Dales, Patane, & Pantoliano, 2004).

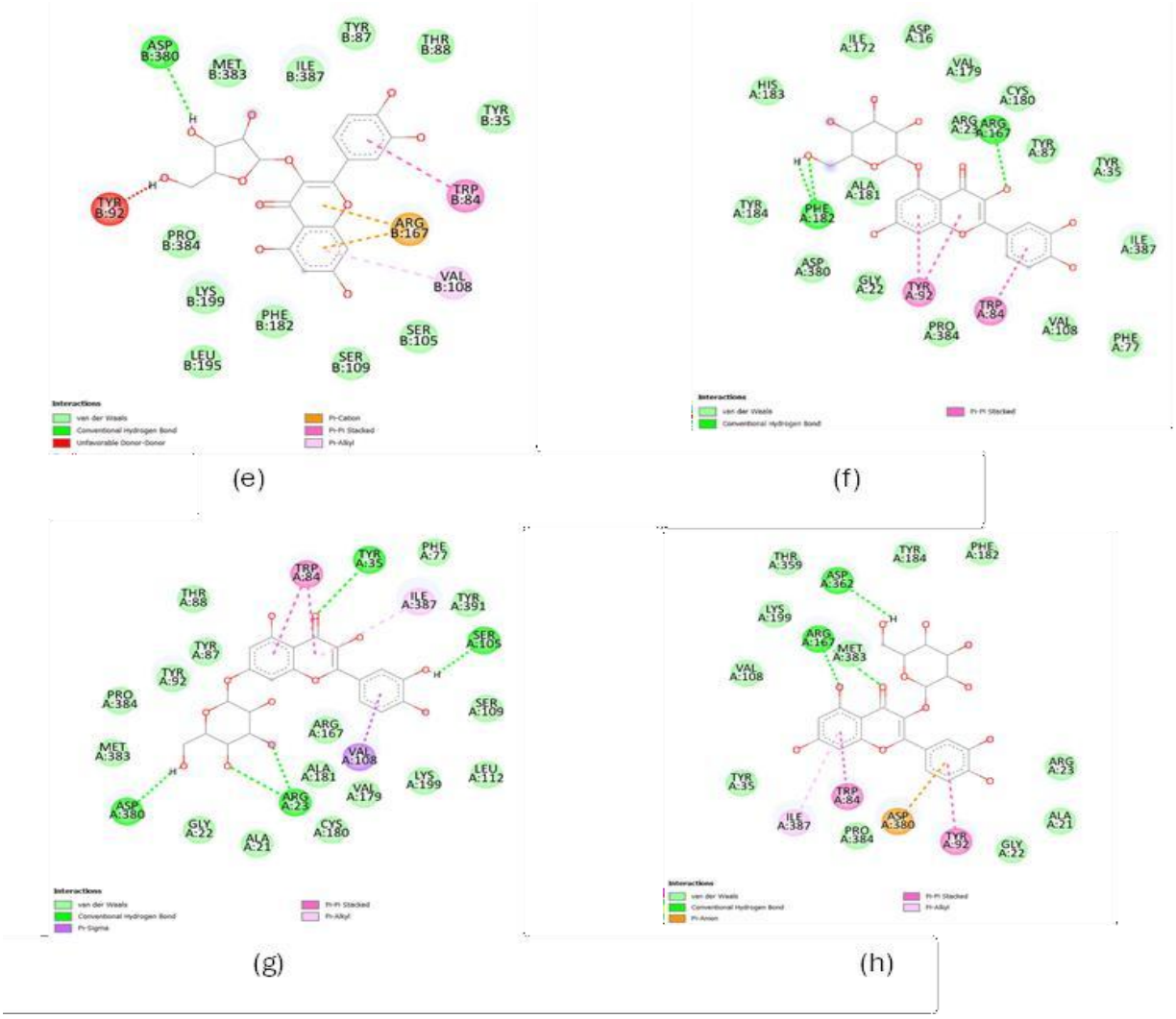


Fig. 5. Visualization of the molecular interactions of AT1R with various ligands. (e) quercetin 3-O-arabinoside, (f) quercetin 5-glucoside, (g) quercetin 7-glucoside, (h) quercetin 3-O-galactoside

ISSN: 2707-1146
e-ISSN: 2709-4189

Table 3. Interaction profiles between AT1R and test ligands.

	Compounds	Hydrogen bonds	Hydrophobic interactions	Number of interactions
	Quercetin 3-O-arabinoside	Asp^{380}	Met^{383}, Ile^{387}, Tyr^{87}, Thr^{88}, Tyr^{35}, Trp^{84}, Arg^{167}, Val^{108}, Ser^{105}, Ser^{109}, Phe^{182}, Ley^{195}, Lys^{199}, Pro^{384},	15
	Quercetin 5-glucoside	Arg^{167}, Phe^{182}	His^{183}, Ile^{172}, Asp^{16}, Val^{179}, Arg^{23}, Cys^{180}, Tyr^{87}, Tyr^{35}, Ile^{387}, Phe^{77}, Val^{108}, Trp^{84}, Pro^{384}, Tyr^{92}, Gly^{22}, Asp^{380}, Tyr184, Ala^{181},	20
	Quercetin 7-glucoside	Tyr^{35},Ser^{105} Arg23, Asp^{380}	Trp^{84}, Phe^{77}, Ile^{387}, Tyr^{391}, Ser^{109}, Leu^{112}, Lys^{199}, Val^{179}, Cys^{180}, Ala^{181}, Arg^{167}, Ala^{21}, Gly^{22}, Met^{383}, Pro^{384}, Tyr^{92}, Tyr^{87}, Thr^{88}	22
	Quercetin 3-O-galactoside	Arg^{167}, Asp^{362}	Arg^{23}, Ala^{21}, Gly^{22}, Tyr^{92}, Asp^{380}, Pro^{384}, Trp^{84}, Ile^{387}, Tyr^{35}, Val^{108}, Lys^{199}, Met^{383}, Thr^{359}, Tyr^{184}, Phe^{182}	17

Table 4. Interaction profiles between AT2R and test ligands.

	Compounds	Hydrogen bonds	Hydrophobic interactions	Number of interactions
	Quercetin 3-O-arabinoside	Tyr^{189}, Ser^{1108},	Tyr^{108}, Gln^{37}, Lys^{38}, Ser^{36}, Leu^{190}, Gly^{1109}	8
	Quercetin 5-glucoside	Tyr^{108}	Asp^{297}, Leu^{190}	3
	Quercetin 7-glucoside	Arg^{182}	Tyr^{108}, Tyr^{103}, Ile^{196}	4
	Quercetin 3-O-galactoside	Tyr^{189}	Tyr^{108}, Gln^{37}, Lys^{38}, Leu^{190}, Ser^{36}, Asp^{297}, Gly^{1109}	8

ISSN: 2707-1146
e-ISSN: 2709-4189

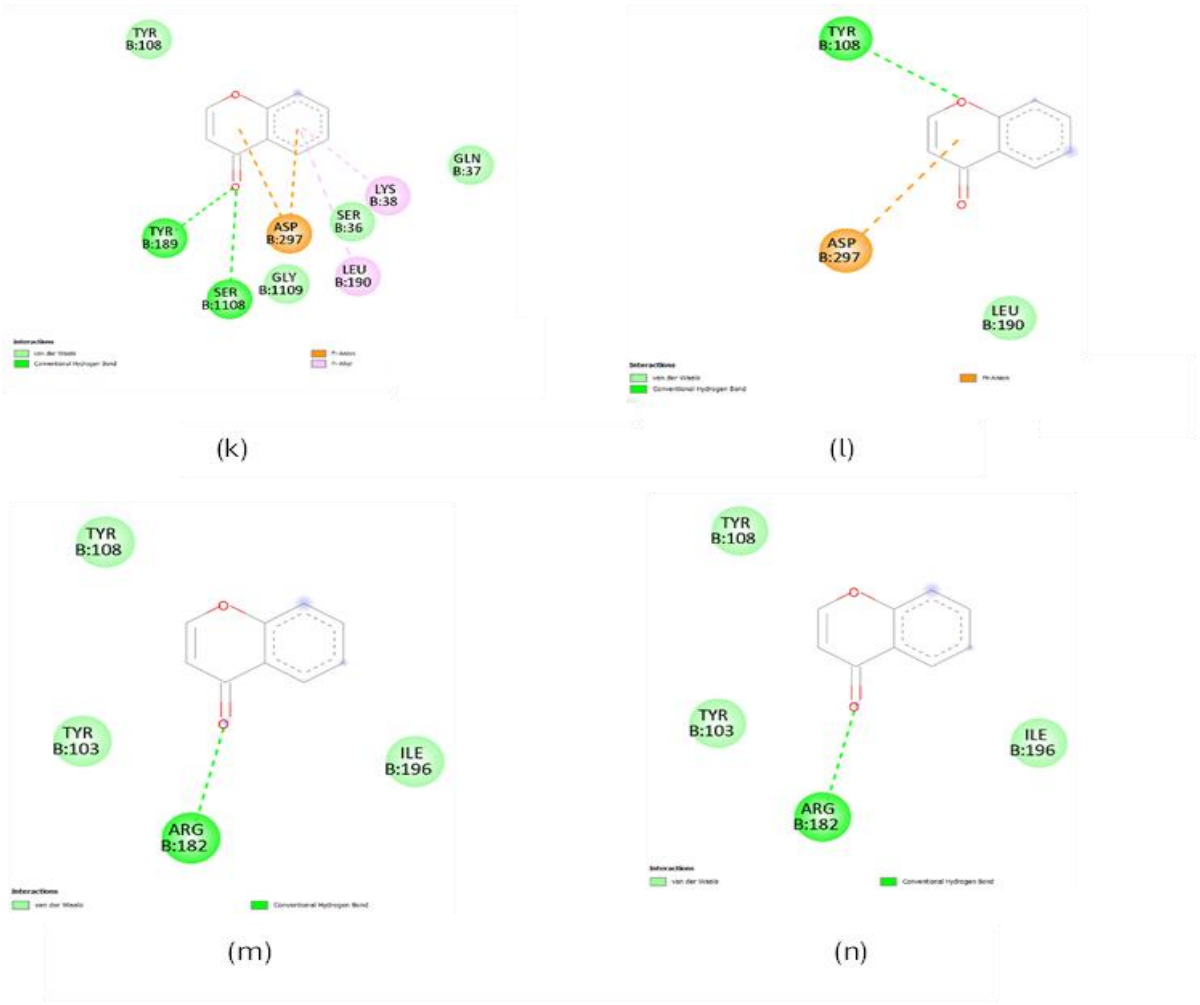


Fig. 6. Visualization of the molecular interactions of AT2R with various ligands. (k) quercetin 3-O-arabinoside, (l) quercetin 5-glucoside, (m) quercetin 7-glucoside, (n) quercetin 3-O-galactoside.

Discussion

The results of this docking investigation offer important new information about the therapeutic potential of quercetin glycoside derivatives in modifying thrombosis and hypertension by targeting RAAS components. For RAAS regulation, blocking AT1R while maintaining ACE2 and AT2R activity is the optimal pharmacological strategy. According to Santos et al. (2018), AT1R inhibition is a proven method of lowering hypertension and averting harmful cardiovascular effects associated with excessive angiotensin II signaling. According to the docking data, quercetin 5-glucoside and quercetin 7-glucoside interact with important active site residues like ARG167, VAL108, TYR35, and TRP84, making them the most potent AT1R inhibitors (Verdecchia, Cavallini, Spanevello, & Angeli, 2020).

In contrast, ACE2 and AT2R are critical for vasodilation and anti-thrombotic mechanisms (Gheblawi, Wang, Viveiros, Nguyen, Zhong, Turner, Raizada, Grant, & Oudit, 2020). While some quercetin glycosides exhibited high docking scores against ACE2, interaction mapping revealed that binding was largely to peripheral or semi-catalytic regions rather than to the enzymatic active site. This is an important finding, as the full inhibition of ACE2 could disrupt its protective functions, particularly in counteracting angiotensin II-driven vasoconstriction and thrombosis (Wang, Bodiga, Das, Lo, Patel, Oudit, 2012).

AT2R plays a protective role in vascular homeostasis, counterbalancing AT1R-induced effects (Carey, Wang, Siragy, 2017). The docking analysis confirms that quercetin derivatives, particularly quercetin 5-glucoside and 7-glucoside, interact favorably with AT2R without deep binding into the

ISSN: 2707-1146
e-ISSN: 2709-4189

core active site. This suggests a modulatory role rather than antagonism, which aligns with the therapeutic goal of preserving AT2R function.

It's interesting to note that quercetin 3-O-arabinoside and quercetin 3-O-galactoside had similar binding scores but weaker interactions at important AT1R residues, suggesting a lesser inhibitory potential. As a result, these substances might not be as effective AT1R antagonists. These results provide compelling evidence for the choice of quercetin 5-glucoside as the most promising dual-function ligand, with quercetin 7-glucoside coming in second. By potently inhibiting AT1R while maintaining ACE2 and AT2R function, these drugs have a desired pharmacological profile that is in line with treatment approaches for hypertension and thrombotic risk reduction.

Conclusion

This molecular docking study provides a structural basis for the potential therapeutic effects of quercetin glycosides in RAAS modulation. Among the tested compounds:

1. Quercetin 5-glucoside demonstrated the strongest binding affinity to AT1R (-8.4 kcal/mol), while maintaining non-inhibitory interactions with ACE2 (-9.0 kcal/mol) and AT2R (-8.1 kcal/mol).
2. Quercetin 7-glucoside followed closely with high docking scores (-8.6 kcal/mol for AT1R, -8.8 kcal/mol for ACE2, and -8.6 kcal/mol for AT2R).
3. These two ligands emerged as the most promising candidates for selective AT1R inhibition while preserving ACE2 and AT2R functionality, contributing to antihypertensive and potential antithrombotic effects.
4. Quercetin 3-O-arabinoside and quercetin 3-O-galactoside showed moderate binding scores but had fewer interactions with AT1R, making them less ideal for targeted inhibition.
5. The study confirms that quercetin glycosides may serve as potential dual-targeting ligands that shift RAAS balance toward a vasodilatory and anti-thrombotic profile.

Future research should include in vitro and in vivo validation to confirm these molecular interactions and functional effects in biological systems.

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Received: 02.09.2024
Accepted: 17.02.2025