RESEARCH PAPER

In Silico Evaluation of Ligand Interaction with Nrf2, V1a Receptor, SOD, and Angiotensin II: A Molecular Docking Study

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ABSTRACT

Background: Oxidative stress, inflammation, apoptosis, and vascular dysregulation play crucial roles in the development of chronic diseases such as cancer, cardiovascular disorders, and metabolic syndromes. Targeting regulatory proteins involved in these pathways using natural bioactive compounds has emerged as a promising therapeutic strategy. Molecular docking provides a computational approach to predict ligand–protein interactions and identify potential molecular targets.

Aim: To evaluate the binding affinity and interaction profile of the selected ligand against key regulatory proteins involved in oxidative stress and vascular signalling pathways.

Methods: Molecular docking analysis was performed to assess the interaction of Punicalligin with apoptotic and metastatic regulatory proteins, including V1a, Superoxide dismutase (SOD), NrF2, and Angiotensin II. Protein crystal structures were retrieved from the Protein Data Bank. Docking was conducted using Auto Dock 1.5.4 with the Lamarckian Genetic Algorithm (100 runs), applying a grid box of 90 Å × 90 Å × 90 Å and 0.45 Å spacing. Docked complexes were visualized using BIOVIA Discovery Studio.

Results: The Punicalligin exhibited favourable binding with all targets, reflected by negative binding energy values. Nrf2 showed the strongest binding affinity (–10.9 kcal/mol), followed by the V1a receptor (–9.6 kcal/mol), Angiotensin II (–8.5 kcal/mol), and SOD (–8.0 kcal/mol). Nrf2 and V1a formed five hydrogen bonds each, with additional π interactions enhancing complex stability.

Conclusion: Punicalligin demonstrated that the highest binding preference toward Nrf2, and V1a Receptors suggesting it as a promising molecular target for further experimental validation and molecular dynamics investigations.

Keywords: Molecular docking; Nrf2; V1a receptor; oxidative stress; hydrogen bonding; binding affinity; computational pharmacology.

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INTRODUCTION

Oxidative stress and dysregulated cellular signalling are major contributors to the pathogenesis of cancer, cardiovascular diseases, neurodegenerative disorders, and metabolic syndromes. Excessive production of reactive oxygen species (ROS) disrupts redox balance, leading to inflammation, apoptosis, and tissue injury. Regulatory proteins involved in antioxidant defence and vascular signalling have therefore emerged as important therapeutic targets.

Nuclear factor erythroid 2–related factor 2 (Nrf2) is a transcription factor that regulates antioxidant and cytoprotective gene expression through activation of the antioxidant response element pathway (1,2). Activation of

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Nrf2 enhances cellular defence against oxidative damage and inflammation.

Superoxide dismutase (SOD) is a crucial antioxidant enzyme that catalyses the dismutation of superoxide radicals into hydrogen peroxide and oxygen, thereby limiting oxidative injury and maintaining redox homeostasis (3).

The vasopressin V1a receptor plays an essential role in vascular smooth muscle contraction and blood pressure regulation, and its dysregulation contributes to cardiovascular disorders (4).

Angiotensin II, a key effector molecule of the renin–angiotensin system, is involved in vasoconstriction, oxidative stress generation, and inflammatory signalling cascades (5,6).

Molecular docking has become a valuable computational tool in drug discovery for predicting ligand–protein binding orientation, affinity, and interaction stability (7,8). By analysing hydrogen bonding and hydrophobic interactions, docking studies help identify promising molecular targets prior to experimental validation.

Therefore, the present study aimed to investigate the interaction profile of Gum Arabic with Nrf2, V1a receptor, SOD, and Angiotensin II using in silico molecular docking analysis.

MATERIALS AND METHODS

The binding interactions of punicalagin CID: 16129719 with various three-dimensional crystal structures of apoptotic and metastatic regulatory proteins, including PDBID:1YTV (vasopressin receptor protein V1a), PDBID:7X5G (SOD), PDBID:2P4K (NrF2), and PDBID:6D01 (Angiotensin II), and chemical structure of ligand was obtained from were retrieved from the Protein Data Bank (9).

Molecular docking was performed using AutoDock 1.5.4 with the Lamarckian Genetic Algorithm (LGA), employing 100 genetic algorithm runs. A grid box of 90 Å × 90 Å × 90 Å with a grid spacing of 0.45 Å was applied to define the active site region (10). The docked ligand–protein complexes were visualized and analysed using BIOVIA Discovery Studio to evaluate binding orientation and interaction stability (11).

RESULTS

Table 1: Molecular Docking Interaction Profile of punicalagin with Selected Oxidative Stress and Vascular Regulatory Proteins

Proteins	Binding energy	No. of hydrogen bonds	Hydrogen bond Residues	Amide -Pi stacked	Pi-Anion/Cation
V1a	-9.6	5	LYS A: 56 GLU A: 58 ARG A: 358 ASP A:55 GLU A:228	GLY A:27 TYR A:224	GLU A: 167 ASP A:28
SOD	-8.0	4	ARG A:204 GLU A:126 ARG A:203 GLY A:202	-	-
Nrf2	-10.9	5	THR A:560 VAL A:514 ASP A:422 VAL A:608 HIS A:516	VAL A:369 ALA A:321	-
Angiotensin II	-8.5	2	SER A:64 PHE A:1309	ILE A:130	ARG A:126

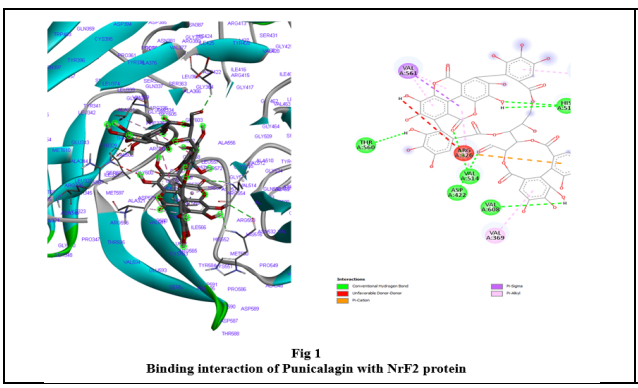

Fig 1
Binding interaction of Punicalagin with NrF2 protein

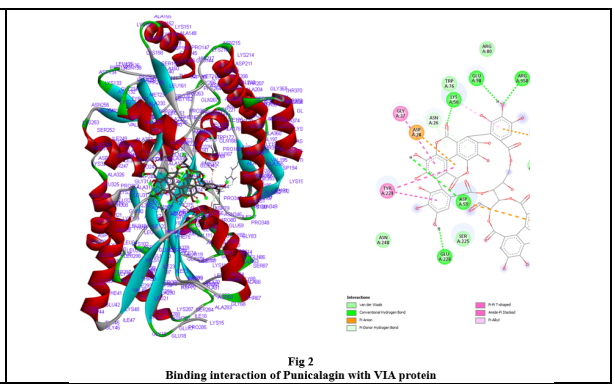

Fig 2
Binding interaction of Punicalagin with VIA protein

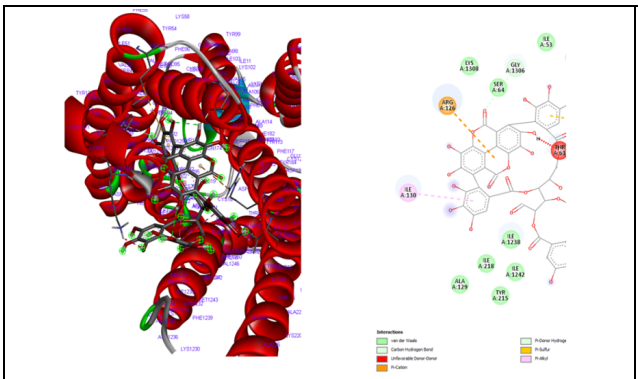

Fig 3
Binding interaction of Punicalagin with Angiotensin II

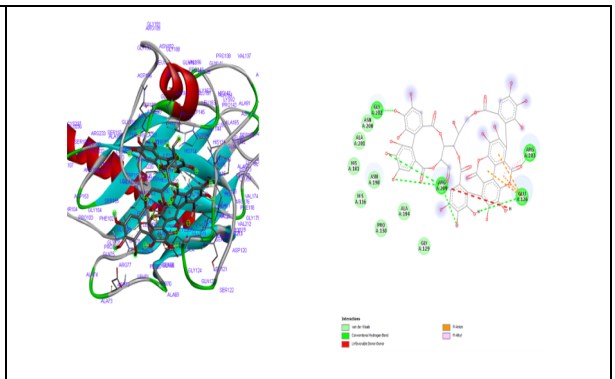

Fig 4
Binding interaction of Punicalagin with SOD protein

The docking analysis demonstrated favourable thermodynamic interactions between Punicalligin and all selected protein targets, as indicated by negative binding energy values.

Nrf2 exhibited the strongest binding affinity (–10.9 kcal/mol), forming five hydrogen bonds with THR A:560, VAL A:514, ASP A:422, VAL A:608, and HIS A:516. Additional amide–π stacking interactions were observed with VAL A:369 and ALA A:321, contributing to enhanced structural stability. The V1a receptor showed a binding energy of –9.6 kcal/mol with five hydrogen bonds involving LYS A:56, GLU A:58, ARG A:358, ASP A:55, and GLU A:228. π–anion/cation interactions with GLU A:167 and ASP A:28 further strengthened the complex. Angiotensin II demonstrated moderate binding (–8.5 kcal/mol) with two hydrogen bonds (SER A:64 and PHE A:1309) and limited π interactions. Superoxide dismutase showed a binding energy of –8.0 kcal/mol with four hydrogen bonds but lacked additional π interactions. The overall binding affinity ranking was: Nrf2 > V1a receptor > Angiotensin II > SOD.

DISCUSSION

The present in-silico investigation demonstrated punicalligin strongest binding affinity toward Nrf2 and the V1a receptor, implying key role in hypertension. The highly negative docking scores and multiple stabilising hydrogen and π-interactions indicate strong structural compatibility within their active binding domains. Since oxidative stress is a fundamental contributor to hypertension and cardiovascular dysfunction (1), identifying antioxidant-regulating targets is of major therapeutic importance.

Hypertension is closely linked with excessive generation of reactive oxygen species (ROS), which promotes endothelial dysfunction, vascular inflammation, and increased peripheral resistance (1,3). Nrf2 functions as a master regulator of antioxidant defence by inducing transcription of cytoprotective enzymes including superoxide dismutase, catalase, and glutathione peroxidase (2). Impairment of Nrf2 signalling has been associated with increased oxidative injury and progression of cardiovascular diseases (2). Enhancement or stabilisation of Nrf2 activity has therefore been proposed as a protective strategy against oxidative stress–mediated vascular damage (2,3).

In addition to redox regulation, vascular tone control plays a central role in blood pressure maintenance. The V1a receptor, a subtype of vasopressin receptor, mediates vasoconstriction and contributes to systemic vascular resistance (4). Overactivation of V1a receptor signalling has been implicated in cardiovascular dysregulation and elevated blood pressure (4). Modulation of this receptor may therefore influence haemodynamic balance and vascular responsiveness.

Angiotensin II is a central effector molecule of the renin–angiotensin system and a major inducer of oxidative stress and vascular remodelling in hypertension (5,6). Persistent angiotensin II signalling enhances NADPH oxidase activation and promotes endothelial dysfunction (6). Conversely, superoxide dismutase plays a critical antioxidant role by scavenging superoxide radicals and maintaining vascular redox balance (7). Even moderate ligand interactions with these targets may contribute synergistically to attenuation of oxidative damage and cardiovascular protection.

At the molecular level, hydrogen bonding significantly contributes to ligand specificity and binding stability, while π-interactions enhance hydrophobic stabilisation within protein binding pockets (8).

However, molecular docking provides a static computational representation of ligand–protein interaction and does not fully account for dynamic conformational flexibility in physiological systems. Therefore, molecular dynamics simulations and experimental validation are necessary to confirm the functional relevance of these findings (12).

CONCLUSION

Overall, the molecular interaction findings suggest that punicalligin may exert a protective role in hypertension through coordinated modulation of Nrf2-mediated antioxidant defence and V1a receptor–mediated vascular regulation. This dual-target interaction may highlights its potential as a promising candidate for the management of oxidative stress–associated cardiovascular disorders.

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