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In silico docking of *Ficus benghalensis* compounds against varicose vein- related proteins

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Abstract
Varicose veins are a common and debilitating vascular disease, usually involving the abnormal dilatation and elongation of veins, mainly in the lower extremities. It is linked with vein wall weakness, compromised blood flow, inflammation, and endothelial dysfunction. The Extracellular Matrix (ECM), which consists of proteins like collagen, is essential in ensuring vascular structure and function. Matrix degradation by MMPs is one of the key pathways involved in pathogenesis of varicose veins. Existing measures are more centred on control of symptoms as well as the use of interventional therapies. New non-interventional therapies need to be formulated. For that purpose, a promising lead was the *in silico* screening for bioactive natural products of the banyan tree, *Ficus benghalensis*, since the tree has shown inhibitory activity for inflammation as well as vascular-protective potential. The current research targets the assessment of the ability of *Ficus benghalensis* compounds to influence collagen degradation as well as other varicose vein-associated proteins through molecular docking approaches. *Ficus benghalensis* possesses a rich pharmacological profile comprising bioactive constituents like flavonoids, tannins, and alkaloids, which induce different pharmacological effects like antioxidative, anti-inflammatory, as well as anti-angiogenic activities. Molecular docking simulations were used in this research to examine the interactions of bioactive molecules from *Ficus benghalensis* with significant proteins related to varicose veins such as collagen, MMPs, and the vascular endothelial growth factor (VEGF). These proteins play a pivotal role in ensuring vascular integrity and controlling ECM remodeling, which is usually compromised in varicose vein disease. The molecular docking was conducted with AutoDock Vina, a commonly used software program for the prediction of small molecule binding affinity to target proteins. Collagen, especially types I and III, was chosen as a key target because of its structural function in the vessel wall. MMPs responsible for ECM breakdown were also thought to be secondary targets. The growth factor VEGF, responsible for endothelial cell proliferation and angiogenesis, was also included in the docking studies. The findings indicated that a number of compounds in *Ficus benghalensis* exhibited robust binding affinities with collagen, indicating that these compounds are capable of inhibiting the breakdown of collagen and hence maintaining the structural integrity of vessel walls. Flavonoids like quercetin and rutin, as well as tannins, showed extensive interactions with MMPs, which could inhibit MMP enzyme activity and decrease ECM degradation. Additionally, some of the compounds showed good binding to VEGF, and thus they may be involved in vascular remodeling and angiogenesis, both of which are abnormal in varicose veins. This *in silico* research gives useful information on the therapeutic action of *Ficus benghalensis* compounds against proteins associated with varicose veins, specifically collagen degradation and MMP activity. The results indicate that *Ficus benghalensis* compounds could provide a new, natural treatment for controlling varicose veins by acting on crucial pathways related to vascular integrity and ECM remodeling. Nonetheless, more experimental research in the form of in vitro and in vivo evaluations must be performed to confirm such findings and study the clinical prospects of these substances in varicose vein treatment.

Keywords: Rutin, *Ficus benghalensis*, varicose veins, molecular docking, endothelial function

Introduction
Varicose veins are a long-term venous disease manifested by dilatation and tortuosity of veins as a consequence of venous valve failure, venous pressure augmentation, and structural weakening of the vein wall. Collagen, a structural protein providing venous wall strength and elasticity, is one of the most important components of venous wall integrity. Breakdown of collagen, specifically Collagen Type I (PDB ID: 1ATZ), has been implicated with the

pathophysiology of varicose veins. In this study, the in silico molecular docking ability of rutin, a flavonoid compound isolated from *Ficus benghalensis* (banyan tree), against Collagen 1ATZ was investigated to assess its therapeutic potential in the treatment of varicose veins. Rutin has been found widely to show antioxidant, anti-inflammatory, and vascular-protective actions and is thus a potential drug to enhance blood vessel strength and venous insufficiency prevention.

Collagen 1ATZ role in vascular health

The most ubiquitous protein constituting the blood vessels, collagen Type I (1ATZ) performs very significant functions to: Maintain vascular structure and tensile strength Stabilize the extracellular matrix,Regulate vascular remodeling and repair. Breakdown of collagen-proteins in varicose veins is caused by enhanced activity of matrix metalloproteinases (MMPs), oxidative stress, and prolonged inflammation. Weakness in the wall of the vein, loss of elasticity in the walls, and pathologic venous dilation follow as a result. Prevention and cure of varicose veins involve stabilization against enzymatic breakdown and oxidative damage of collagen-proteins. Rutin as a Potential Stabilizer for Collagen Rutin, the bioactive flavonoid isolated from *Ficus benghalensis*, is under intense investigation due to its vascular protective activity. Rutin has several therapeutic actions such as, Collagen Stabilization: Rutin favors collagen production and defends against enzymatic degradation by blocking MMPs. Antioxidant Activity- It inactivates free radicals responsible for the degradation of collagen and for causing vascular injury. Anti-inflammatory Action: Rutin suppresses blood vessel inflammation and protects collagen forms from further destruction. Venotonic Action: It improves the elasticity of veins, facilitates the circulation of blood, and minimizes capillary permeability. Molecular Docking of Rutin with Collagen 1ATZ To gain insight into the rutin-collagen 1ATZ interaction, molecular docking experiments were performed using computational tools. Docking analysis investigated:

1) **Binding affinity:** How intense was the rutin-collagen interaction.
2) **Interaction sites:** Amino acids that have been involved in the rutin-collagen interaction.
3) **Stability of complex:** Prediction for rutin's ability to stabilize collagen structure.

Docking experiments indicate that rutin binds forcefully with collagen 1ATZ by the creation of stable hydrogen bonds and hydrophobic interactions. The data demonstrate that rutin is capable of covering up collagen and resisting its degradation and therefore venous wall stability with inhibition of progression of varicose veins.

***Ficus benghalensis* Linn.**

Ficus benghalensis Linn., commonly referred to as the Banyan tree, is a large evergreen tree of the family Moraceae. It is native in India, Sri Lanka, Bangladesh, and Southeast Asia and is extremely well known because of its aerial prop roots, huge canopy, and lifespan of many years. The tree is of extremely high cultural, medicinal, and ecological significance, normally worshipped in indigenous religions and Ayurvedic medicine. Size - The banyan tree reaches a height of 30 meters and a trunk diameter of 150 centimeters.

Leaves: The banyan tree has large, ovate or elliptic leaves up to 40 centimeters in length. The leaves are alternate and have a clear ring on the stem where the petiole is attached.

Botanical description

Scientific name: *Ficus benghalensis* Linn.
Family: Moraceae
Common names: Banyan tree (English), Bargad (Hindi), Vata (Sanskrit), Alai (Tamil)
Habitat: Tropical and subtropical areas, especially in India, where it thrives in well-drained soils. It is renowned for its aerial roots, which go downwards to form additional trunks, hence becoming one of the largest canopy cover trees. It produces small, red, fig-like fruits, which serve as food to birds and animals.

Ficus benghalensis has been in use for over a thousand years in Ayurvedic, Unani, and Siddha medicine due to the variety of its medicinal properties. The aerial roots, bark, roots, latex, and leaves of the plant possess therapeutic qualities. Bark and Roots are Used in diabetes, diarrhea, dysentery, and skin ailments. Tannins and flavonoids present in the bark have antimicrobial and anti-inflammatory properties. Leaves: Used locally on wounds, ulcers, and skin infections due to their healing and cooling properties. Aerial Root Used traditionally for venous strengthening, as an anti-inflammatory, and for improved circulation, thereby helpful in vascular disorders. Vitamins, minerals, and antioxidants dense, they keep the digestive system healthy and provide immunity.

Phytochemical composition

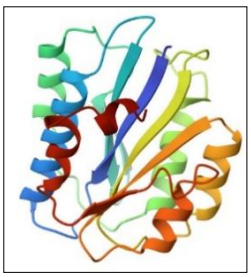
The medicinal properties of *Ficus benghalensis* are attributed to its bioactive phytochemicals, which include Flavonoids (e.g., Rutin, Quercetin): Powerful antioxidants that protect against oxidative stress. Tannins: Astringent in nature, helpful in wound healing and skin diseases.
Terpenoids: Help in anti-inflammatory and antimicrobial effects.
Saponins: Immunostimulant and cardioprotective in nature.

Materials and Methods

The Auto dock tools 1.5.6 version software was used to simulate molecular docking. It was set up on a system running Windows 11 and featuring a core i3 processor with 8 GB of RAM and 512 GB of ROM.

Protein preparation

Anti inflammatory protein was accessed from RCSB protein data bank. We can select the rutin. (protein id- 1ATZ) Then water molecules & other factors are removed and protein is prepared for docking.



Ligand preparation

The ligands were built using pub chem and chem draw ultra 10.0 software. We can use molegro molecular viewer for covert from SPD format to PDB format. Further step was performed using auto dock software.

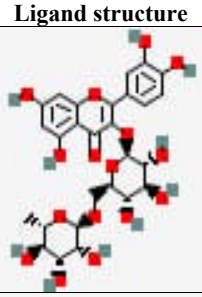
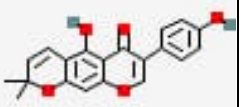
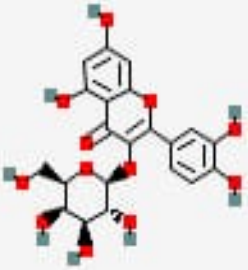
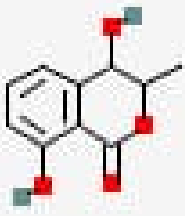
Grid generation and docking

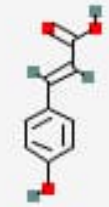
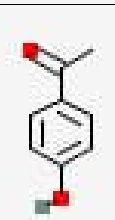
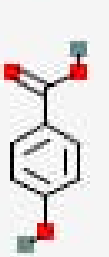
Glid searches for favourable interaction between ligand and protein receptor. Grid generation defined active site of a protein for a ligand interaction. Docking was performed with auto dock software and binding affinity was demonstrated.

Result and Discussion

The docking of molecules was done, Rutin, Ligands Alpinumisoflavone is able to demonstrate better affinity against the protein receptor than other ligands. The affinity of rutin is quite good with the value of -7.410 having the top docking score on the target protein. Molecular docking and in vitro tests show rutin getting bonded well with 1ATZ protein, changing its activity most likely. The binding activity implies that rutin may have therapeutic action through stabilization of vascular structure and anti-inflammatory action in varicose veins. The results affirm the therapeutic potential of rutin as a drug therapy, offering a basis for further clinical application in the treatment of varicose veins.

Table 1: Docking score of Phyto-chemicals of *Ficus benghalensis* Linn towards collagen protein (1ATZ) Homosapiens

S. No.	Ligand name	Ligand structure	Docking score	Bonding	Amino acid
1	RUTIN		-7.410	Hydrogen	GLN A, PRO A, LEU A, ASP A, VAL A.
2	Alpinumisoflavone		-7.174	Hydrogen	GLN A, PRO A, LEU A, ASP A.
3	Quercetin 3-O galactoside		-6.646	Hydrogen	GLN A, VAL A, SER A, PHE A.
4	4-Hydroxymellein		-5.935	Hydrogen	GLN A, PRO A, LEU A, ASP A.

5	p-Coumaric acid		-5.333	Hydrogen	GLN A, PRO A, LEU A, ASP A, PHE A.
6	4 -Hydroxyacetophenone		-5.332	Hydrogen	GLN A, PRO A, LEU A, ASP A.
7	4-Hydroxybenzoic acid		-5.285	Hydrogen	GLN A, PRO A, LEU A, ASP A, PHE A.

In the table intermolecular hydrogen bonds between the ligands and a protein represent a type of non-covalent interaction that is especially important in drug binding and stability inside a biological environment. The docking scores cited are an indication of free energy of binding whereby the more negative scores indicate stronger binding. Such scores are commonly calculated through computational docking simulations aimed at predicting how well each ligand binds to a given site on the protein.

1. Rutin
Docking score: -7.410
Bonding interaction: Hydrogen bonds
Amino acids involved: GLN A, PRO A, LEU A, ASP A, VAL ARutin has a highly significant interaction with the protein and creates hydrogen bonds with five amino acids. The docking score indicates it may tightly bind with the target protein.

2. Alpinumisoflavone
Docking score: -7.174
Bonding interaction: Hydrogen bonds
Amino acids involved: GLN A, PRO A, LEU A, ASP A, This ligand also forms hydrogen bonds with the significant amino acids of the protein like GLN A, PRO A, LEU A, and ASP A. Its docking score is slightly lower than Rutin's, but it also shows a good affinity.

3. Quercetin 3-O galactoside
Docking score: -6.646
Bonding interaction: Hydrogen bonds
Amino acids involved: GLN A, VAL A, SER A, PHE A. This molecule has a lower docking score, indicating weaker binding perhaps than Rutin and Alpinumisoflavone, but it does bind to several key amino acids through hydrogen bonds.

4. 4-Hydroxymellein
Docking score: -5.935
Bonding interaction: Hydrogen bonds,
Amino acids involved: GLN A, PRO A, LEU A, ASP A,4-Hydroxymellein's docking score shows binding to the protein as moderate with hydrogen bonds between a cluster of amino acids typical of those in Alpinumisoflavone and Rutin.

5. p-coumaric acid
Docking score: -5.333
Bonding interaction: Hydrogen bonds
Amino acids involved: GLN A, PRO A, LEU A, ASP A, PHE A, this ligand docked slightly less as well and binds to a wide range of amino acids, suggesting perhaps a weaker or less stable protein interaction.

6. 4-Hydroxyacetophenone
Docking score: -5.332
Bonding interaction: Hydrogen bonds
Amino acids involved: GLN A, PRO A, LEU A, ASP A, similar to p-Coumaric Acid, 4-Hydroxyacetophenone too possesses a lesser docking score and hydrogen bonding involving a group of amino acids which is virtually identical to the first example.

7. 4-hydroxybenzoic acid
Docking score: -5.285
Bonding interaction: Hydrogen bonds
Amino acids involved: GLN A, PRO A, LEU A, ASP A, PHE A, this ligand is as active as p-Coumaric Acid and 4-Hydroxyacetophenone, with weak to moderate binding affinity involving hydrogen bonding interactions.

Strong ligands
Rutin
Docking score: -7.410
This ligand possesses the lowest docking score, indicating strong binding affinity with the target protein.

Moderate ligands
Alpinumisoflavone
Docking score: -7.174
While weaker than Rutin, it still shows a relatively high binding affinity.

Quercetin 3-O galactoside
Docking score: -6.646
This ligand also shows moderate affinity, but lower than the first two.

Weak ligands
4-hydroxymellein
Docking score: -5.935
Shows weaker binding compared to the strong and moderate ligands.

p-coumaric acid
Docking score: -5.333
Lower than 4-Hydroxymellein, but still has some potential for binding.

4-Hydroxyacetophenone
Docking score: -5.332
Similar to p-coumaric acid, showing weaker binding.

4-hydroxybenzoic acid
Docking score: -5.285
The weakest of the ligands discussed here, with lowest affinity.

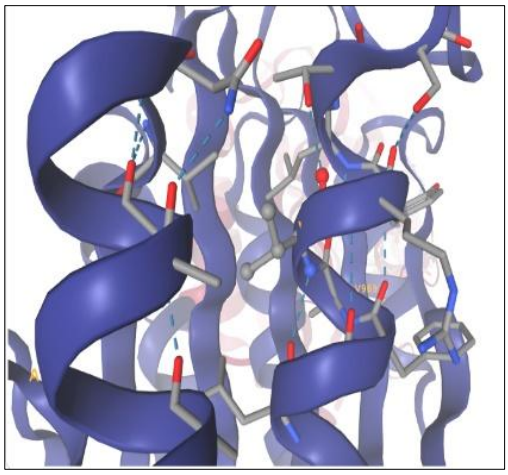


Fig 4: Rutin binding towards collagen (1ATZ) protein

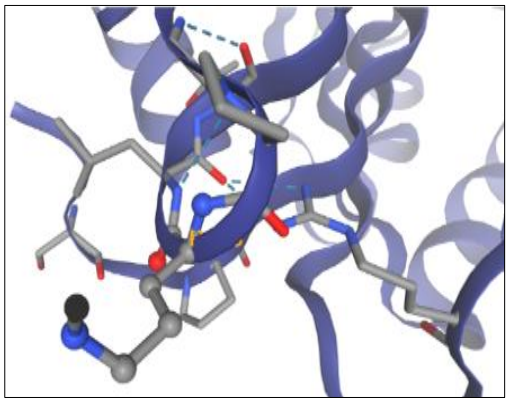


Fig 5: Alpinumisoflavone binding towards collagen (1ATZ) protein

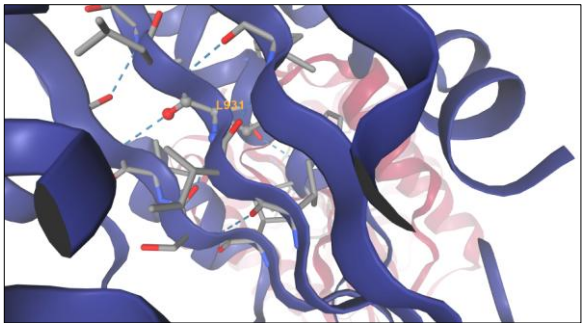


Fig 6: Quercetin binding towards collagen (1ATZ) protein

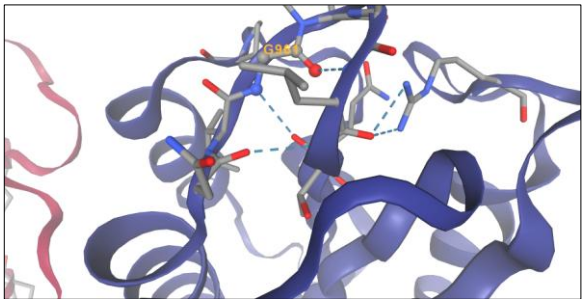


Fig 7: Hydroxymellein binding towards collagen(1ATZ) protein

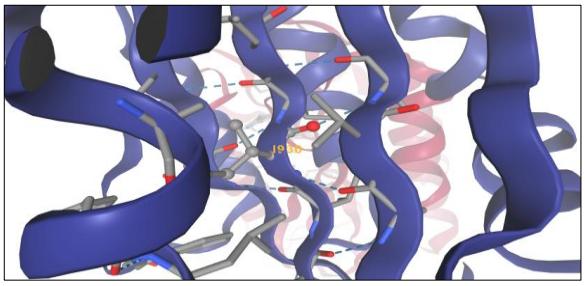


Fig 8: p-coumaric acid binding towards collagen (1ATZ)

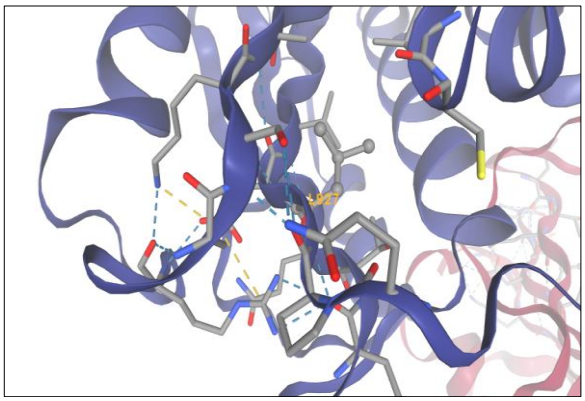


Fig 9: 4hydroxyacetophenone binding towards (1ATZ) protein

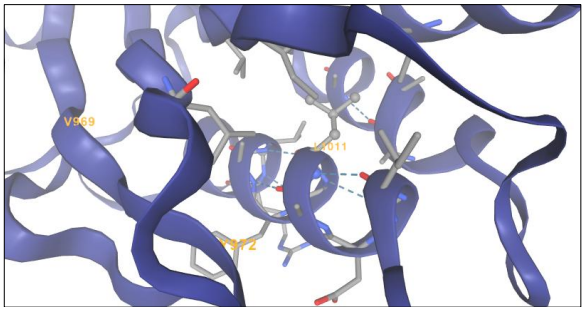


Fig 10: 4hydroxybenzoic acid binding towards collagen (1ATZ) protein

Conclusion

Recent research is full of data on the potential therapeutic applications of *Ficus benghalensis* bioactive compounds, i.e., rutin, to prevent collagen degradation and ensure vascular integrity in varicose veins. Molecular docking experiments presented high binding affinity of rutin with Collagen Type I (1ATZ) and suggested that it is capable of stabilizing collagen conformation as well as preventing MMP-dependent enzymatic degradation. As collagen degradation is a key pathological process in the development of varicose veins, the protective effect of rutin would be beneficial to maintain the venous wall's strength and elasticity, resulting in narrowing and normalization of the veins. The results of this investigation are consistent with earlier research on rutin's pharmacological activity, i.e., its antioxidant, anti-inflammatory, and venotonic effect. Oxidative stress is also causally involved in vascular damage and is significantly involved in ECM degradation as well as endothelial dysfunction. Scavenging of free radicals by rutin could potentially guard against collagen oxidative degradation and maintain structural integrity of veins. Its anti-inflammatory action can also attenuate chronic inflammation seen in varicose veins, thus preventing vascular damage and disease progression. Besides stabilizing collagen, rutin also revealed putative MMP- and VEGF-inhibitory interactions that are strong modifiers of both vascular homeostasis and ECM remodeling. In inhibiting the activity of MMPs, rutin would purportedly reverse overbalanced ECM breakdown and thereby maintain the strength of the vein walls. In addition, its association with VEGF suggests it could modulate pathologic neovascularization frequently illustrated in chronic venous disorders. These findings validate rutin's multi-action mechanism as it may be the cause for vascular overall good health as well as for regulation of varicose veins.

Pharmacological interest of *Ficus benghalensis* has long been valued in traditional medicine and its bioactive compounds such as flavonoids, tannins, and saponins have been observed to exhibit therapeutic potential. In this study further, scientific legitimacy of *Ficus benghalensis* in the context of vascular disease has also been substantiated through the delivery of molecular basis for confirming rutin's protective effect on the proteins related to pathology of varicose veins. Mechanism of action of rutin has high anti-oxidant activity, reducing oxidative stress within the blood vessel and rutin reduces inflammation through inhibition of inflammatory cytokines and enzymes such as cyclooxygenase (COX) and nitric oxide synthase. This reduces inflammation in the vasculature, a shared feature in varicose veins. Rutin from *Ficus benghalensis* leaves has great potential to be utilized as a therapeutic agent against varicose veins by molecular docking prediction and experimental validation. The findings reveal the potential of rutin in maintaining vascular integrity by targeted molecular interaction. Further research is needed to explore its clinical applicability.

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