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The potential of thymoquinone against vascular diseases: *in silico* evaluation

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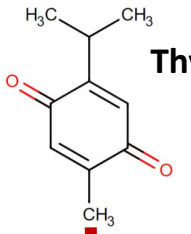
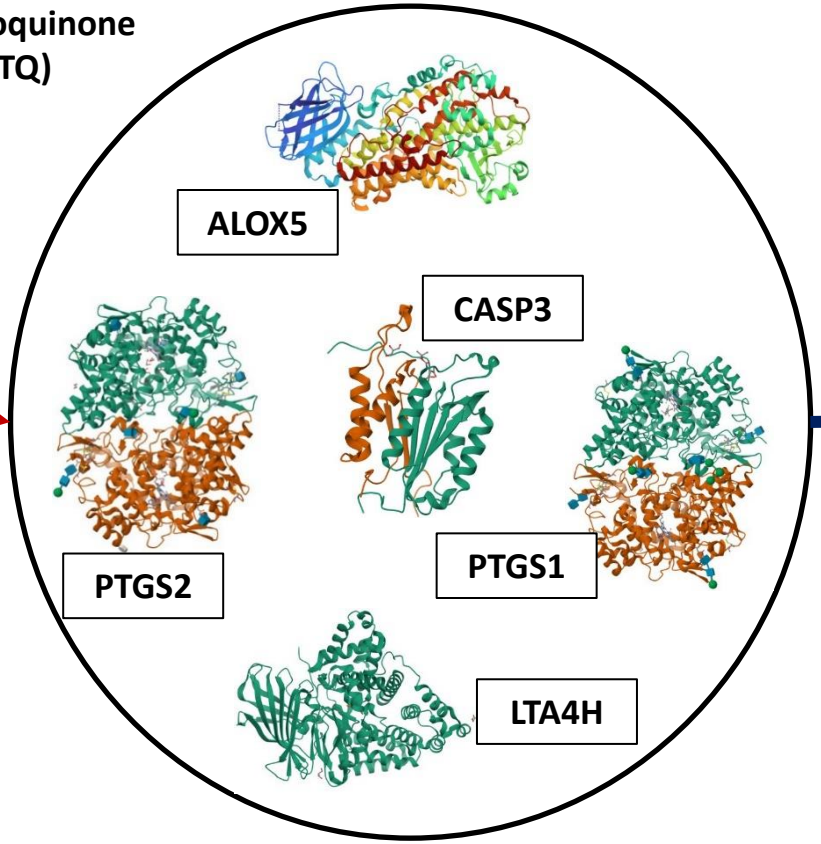
The potential of thymoquinone against vascular diseases: *in silico* evaluation



Thymoquinone (TQ)

Molecular docking



Evaluation of binding energy & scoring

Visualization of binding interaction

Abstract:

An increase in secondary complications, hypercholesterolemia, diabetes mellitus, and blood pressure leads to an increase in the risk of vascular diseases (VDs), causing more mortality and morbidity globally. VDs include the abnormal functioning of coronary, carotid, vertebral, cervical, visceral, abdominal, aortic, and peripheral vessels. Complications of microcirculation due to peripheral vascular insufficiency have received considerable attention owing to venous and arterial diseases. In such complicated situations, LTA4H, CASP3, ALOX5, PTGS1, and PTGS2 are considered significant protein targets. For example, LTA4H and ALOX5 are associated with atherosclerotic plaque formation, inflammation, and instability; CASP3 is involved in the apoptosis of vascular smooth muscle cells, while PTGS is involved in peripheral vascular resistance, platelet aggregation, vascular inflammation, and vasoconstriction. Thus, targeting expressions of these proteins could provide beneficial effects in combating the complications of vascular diseases. Thymoquinone (TQ) is one such active phytoconstituent found in the seeds of *Nigella sativa*, which possesses anti-inflammatory, antioxidant, antimicrobial, immunomodulatory, analgesic, anticancer, and antipyretic effects; however, it has not been explored for its activity in vascular complications. Accordingly, an *in-silico* investigation has been designed to evaluate the activity of TQ on the expression of proteins involved in VDs using molecular docking approaches. The findings suggested a strong molecular interaction between TQ and the set targets. The docking profile depicted the binding affinity of TQ with LTA4H, CASP3, ALOX5, PTGS1, and PTGS2 having energies of -7.4 to -5.7 kcal/mol. Therefore, it can be concluded that TQ can be a potential phytoconstituent for vascular complications; however, more *in-vitro* and *in-vivo* studies are required.

Keywords: vascular diseases; atherosclerosis; thymoquinone; binding energy; microcirculation; molecular docking

Introduction

Complications of vascular diseases [3]

- Vasoconstriction
- Peripheral vascular resistance
- Platelet aggregation
- Vascular inflammation
- Atherosclerotic plaque formation

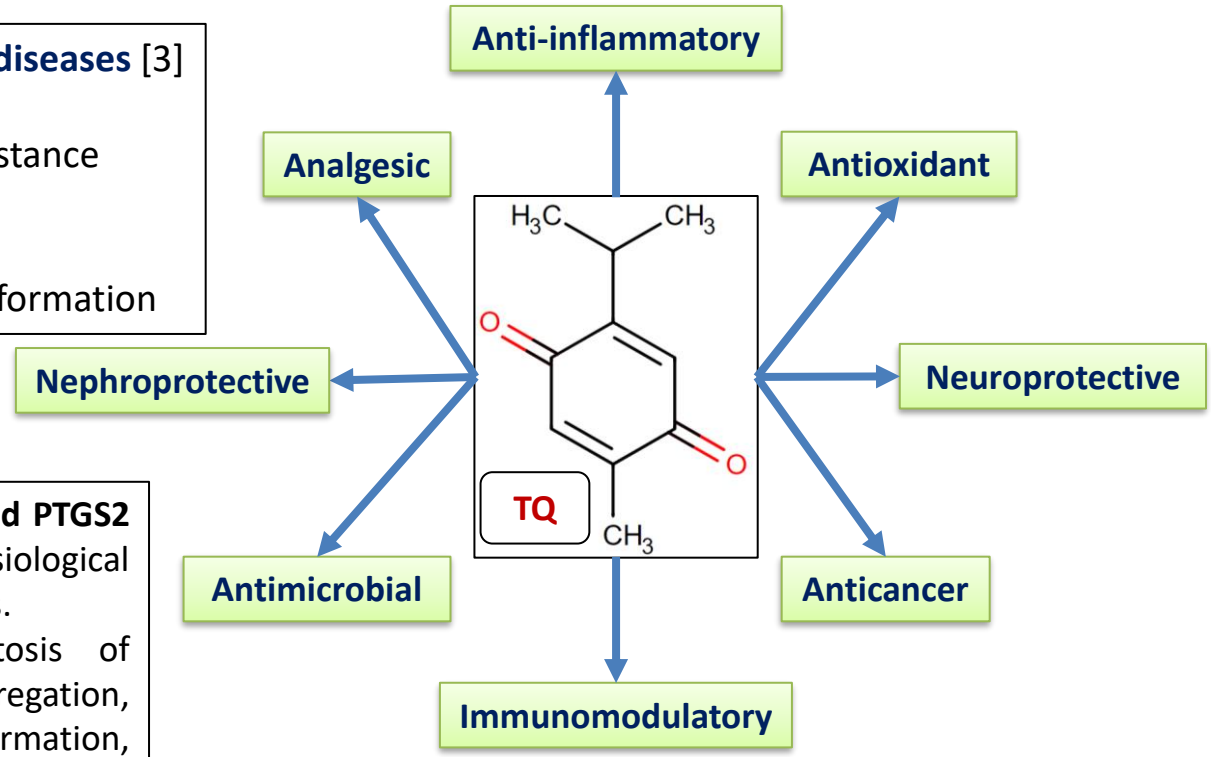


Figure 1. Biological activities of thymoquinone [1,2]

- **LTA4H, CASP3, ALOX5, PTGS1, and PTGS2** are involved in various pathophysiological complications of vascular diseases.
- These proteins control apoptosis of smooth muscles, platelet aggregation, inflammation, plaque formation, instability, and vascular resistance. [3]

Despite having a wide range of biological activities, TQ is not widely explored for vascular diseases.

Materials and methodology

1. Retrieval of target protein

The 3-dimensional structures of PTGS1 (PDB ID: 3N8W) [4], PTGS2 (PDB ID: 5F19) [5], ALOX5 (PDB ID: 3O8Y) [6], LTA4H (PDB ID: 3B7S) [7], and CASP3 (PDB ID: 3GJR) [8] were retrieved from RCSB Protein Data Bank.

2. Retrieval of ligand

The 3-dimensional chemical structure of Thymoquinone molecule was downloaded from PubChem database in PDB format.

3. Preparation of target protein

The protein structure was cleaned using AutoDock Tools [9] by,

- Deleting the water molecules
- Adding polar hydrogen
- Assigning the Kollman Charges
- Saving the protein in .pdbqt format

Materials and methodology

4. Identification of the active binding site

The active site was identified by analyzing the proteins' binding site through PyMOL software [10].

5. Assessment of binding energy and interactions

- Grid box was assigned on the proteins' active site.
- Molecular docking was performed using AutoDock Vina based on scoring functions.
- Scoring and ranking were based on binding energies of the docked ligand-protein poses.
- The binding site was visualized and binding interactions with the residues were studied using BIOVIA Discovery Studio Visualizer [11].

Result and discussion

Table 1. Binding energies and hydrogen-bonding interaction of TQ with the target receptors. The binding energies are in the range of -7.4 to -5.7, which suggests strong binding interaction between the compound and the protein targets.

Compound	Target	PDB ID	Binding energy (kcal/mol)	H-bonding
TQ	PTGS1	3N8W	-7.4	Leu352, Ile523, Gly526, Ala527, Ser530
TQ	PTGS2	5F19	-7.2	Ala199, Ala202, Gln203, Thr206, His207, Phe210, Tyr385, His386, Trp387, His388
TQ	ALOX5	3O8Y	-6.6	Arg370, Ala453
TQ	LTA4H	3B7S	-6.3	Gly268, Gly269, His295, Gln296, Tyr383, Arg563
TQ	CASP3	3GJR	-5.7	Lys137, Tyr195, Tyr197

Result and discussion

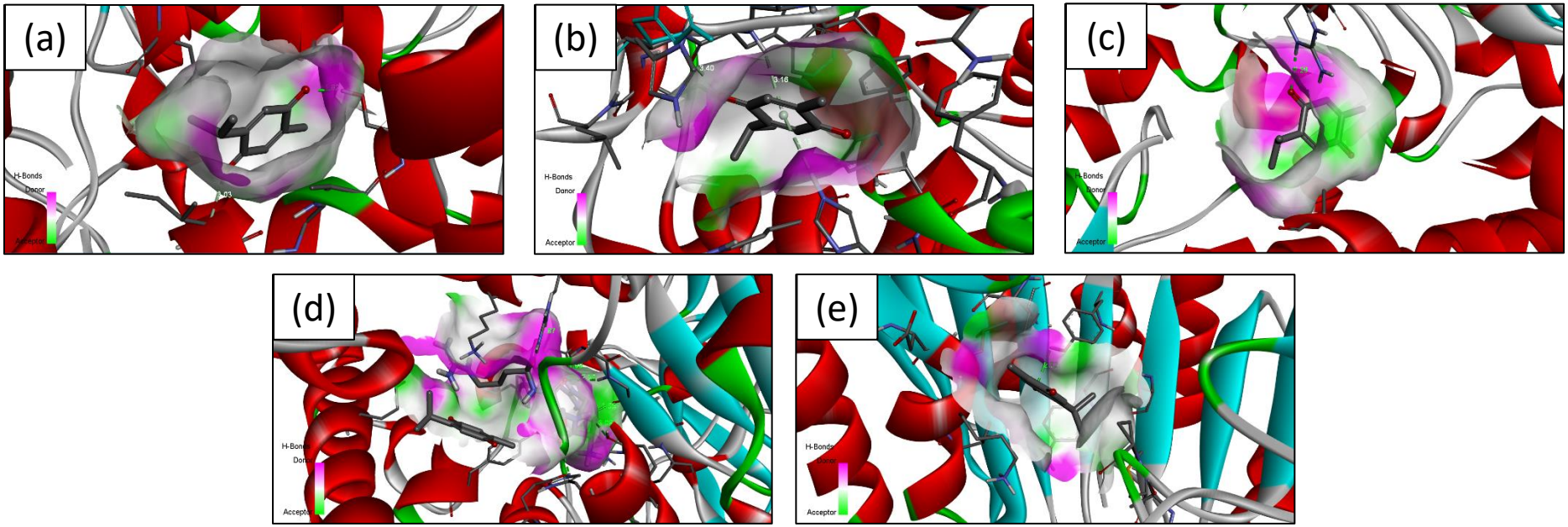


Figure 2. Binding interaction between TQ and (a) PTGS1 (b) PTGS2 (c) ALOX5 (d) LTA4H (e) CASP3, showing the binding pockets of the protein targets and the H-bond interactions.

Conclusion

- The molecular interaction between TQ and the identified target proteins of vascular diseases shows good binding energy.
- However, TQ suffers from low bioavailability and permeability, which is required to be optimized for formulation development toward improvement of bioavailability.
- Formulating nanocarriers of the hydrophobic TQ might solve the drug delivery issues.
- Molecular docking study revealed a strong interaction of the drug to the set targets for the treatment of VD.
- To establish the efficacy of TQ on VDs, further *in-silico* evaluation of the pharmacodynamic potential of the agent would be useful.
- Furthermore, *in-vitro* and *in-vivo* research findings are required to validate the results.

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