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ORIGINAL ARTICLE

Molecular docking analysis of thymoquinone as a potential inhibitor of C-reactive protein and transforming growth factor β (TGF-β): an *in-silico* study for myocardial infarction therapeutics

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ABSTRACT

Aim Myocardial infarction (MI) is a cardiovascular disease that is the leading cause of death at all ages. Inflammation and oxidation processes constitute the basic pathophysiology of MI development. C-reactive protein (CRP) and transforming growth factor β (TGF-β) are markers that are often used to evaluate the level of inflammation, especially in MI. This study aimed to evaluate the anti-inflammatory potential of thymoquinone (TQ), the major bioactive compound of *Nigella sativa*, by assessing its binding affinity through molecular docking, in which TQ exhibited more favourable binding energies compared to the native ligand.
Methods Using the VegaZZ, PyMOL, and BIOVIA Discovery Studio tools, AutoDock Vina software was used for in silico research to test the active molecule TQ and produce visual profiles of native CRP and TGF-β ligands. Using the pkCSM method, pharmacokinetic predictions were carried out.
Results Thymoquinone (2-methyl-5-propan-2-ylcyclohexa-2,5-diene-1,4-dione) showed favourable binding affinity to both CRP and TGF-β, with docking scores of –3.60 and –4.15 kcal/mol, respectively, which are more favourable than those of the native ligands (-2.39 and –2.73 kcal/mol) and comparable to enalapril (–4.84 and –6.13 kcal/mol). The root mean square deviation (RMSD) value for CRP was 1.421 Å, while the value for TGF-β was 0.253 Å, indicating excellent structural alignment and validating the docking approach.
Conclusion These in silico findings suggest that TQ warrants further investigation in vitro and in vivo as a potential modulator of inflammatory pathways in MI.
Keywords: anti-inflammatory agents, Molecular Docking Simulation, myocardial infarction, *Nigella sativa*, thymoquinone

INTRODUCTION

Myocardial infarction (MI) is a leading cause of death worldwide, with an estimated 32% of the population experiencing death (1). Despite major advances in interventional and pharmacological therapy, the global prevalence of MI continues to rise, particularly in developing countries, due to lifestyle-related risk factors such as obesity, diabetes, and hypertension (2,3) The underlying pathophysiology of MI involves prolonged inflammation and oxidative stress, which cause endothelial dysfunction, resulting in the necrosis of cardiomyocytes and the development of MI. If left untreated, MI can cause further complications, namely, ventricular remodelling and heart failure [2]. Therefore, understanding and controlling the inflammatory process after MI remains a key focus in reducing post-infarction complications.

C-reactive protein (CRP) is an acute phase protein that is often used as a marker of inflammation in various disease conditions, one of which is MI. A study reported that high CRP levels are associated with the risk of expanding the necrotic area in MI (4). In addition to CRP, transforming growth factor β (TGF-β) is another significant factor involved in the pathophysiology of MI. TGF-β contributes to the development of myocyte hypertrophy, which is a key component in the process of ventricular remodelling after MI. In an in vivo study, the overexpression of TGF-β was associated with cardiac fibrosis and hypertrophy (5,6). Owing to their important roles, CRP and TGF-β levels may be promising therapeutic targets for patients with MI as cardioprotective agents (7).

Cardioprotective agents with both anti-inflammatory and antioxidant properties are therefore of high interest. Among current pharmacological options, angiotensin-converting enzyme inhibitors (ACEIs) such as enalapril are widely used in the

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management of MI and heart failure due to their systemic cardioprotective effects. Enalapril functions primarily by inhibiting the conversion of angiotensin I to angiotensin II, thereby reducing vascular resistance and mitigating inflammatory signalling (8). One example of an ACE-I drug that is widely used as a cardioprotective agent in patients with MI and heart failure is enalapril. Although ACEIs provide substantial clinical benefit, concerns related to long-term toxicity and side effects such as hyperkalaemia remain (9). This study mentioned enalapril as an established therapeutic relevance in MI treatment. However, it is important to note that enalapril does not directly bind to or inhibit CRP or TGF-β at their active sites (9). Therefore, it is not used as a structural positive control ligand in this docking simulation, but rather to provide a comparative context for the binding performance of thymoquinone (TQ).

Thymoquinone (TQ), also known as 2-isopropyl-5-methylbenzo-1,4-quinone, is a biochemical compound that has anti-inflammatory effects. TQ is one of the main phytochemical compounds that is abundant in black cumin (*Nigella sativa*). Previous studies have reported that the TQ compound present in *Nigella sativa* has cardioprotective effects by suppressing inflammation and oxidants (10). TQ compounds also offer other beneficial properties, including anticancer, antioxidant and hepatoprotective effects (10–12). In addition, TQ has a relaxing effect on heart muscle and vasodilators by inhibiting the entry of Ca2+ ions that mediate voltage-gated Ca2+ channels. TQ has demonstrated potential in preventing myocardial reperfusion injury and ischemia-induced arrhythmias. Additionally, TQ is associated with anti-inflammatory and antioxidant properties that may positively influence the progression of various inflammation-related conditions (13,14).

Molecular docking is a widely used computational approach to simulate and predict the interaction between bioactive molecules and protein targets. It offers valuable insights into drug discovery by evaluating binding affinity and interaction profiles (14)

However, despite extensive evidence regarding thymoquinone's antioxidant and anti-inflammatory properties, there is limited understanding of its direct molecular interaction with key inflammatory mediators such as CRP and TGF-β that play crucial roles in myocardial infarction. Previous studies have mainly focused on its biochemical or in vivo effects without clarifying the molecular binding mechanisms involved (1).

The aim of this study was to assess the binding potential of TQ to CRP and TGF-β through molecular docking analysis and to compare its in silico performance with that of enalapril as a clinical benchmark. Clinically, this study hypothesizes that thymoquinone, by targeting CRP and TGF-β signalling pathways, could contribute to reducing post-infarction inflammation and myocardial remodelling, thereby offering a potential adjunct therapeutic strategy for patients with myocardial infarction.

MATERIALS AND METHODS

Materials and study design

This was an in-silico experimental study designed to evaluate the molecular interaction of thymoquinone (TQ) with C-reactive protein (CRP) and transforming growth factor-β (TGF-β) as therapeutic targets relevant to myocardial infarction. The study was conducted at the Department of Cardiovascular Medicine, Faculty of Medicine, Sultan Agung Islamic University, Semarang, Indonesia, from March to May 2024. No human or animal subjects were involved. All computational analyses were performed under identical docking conditions to ensure reproducibility, using standardized protein structures obtained from the RCSB Protein Data Bank (CRP: PDB ID 1B09; TGF-β: PDB ID 1TGJ).

Methods

Applications and Software. AutoDock Tools (v1.5.6) was used for the preparation of proteins and ligands, while docking simulations were performed using AutoDock Vina. Visualization and analysis of ligand–protein interactions were conducted with BIOVIA Discovery Studio Visualizer 2021. The 3D structure of thymoquinone (TQ) was retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov) in structure data file (SDF) format and converted to protein data bank (PDB) using Open Babel. The molecular geometry of TQ was optimized using Vega ZZ software with the MMFF94 force field, applying an energy minimization threshold of 0.01 kcal/mol to ensure a stable conformation. Protein structures of C-reactive protein (CRP, PDB ID: 1B09) and transforming growth factor beta (TGF-β, PDB ID: 1TGJ) were obtained from the RCSB Protein Data Bank (https://www.rcsb.org).

Proteins and ligand preparation. Protein preparation involved the removal of water molecules and native ligands, addition of polar hydrogen atoms, and assignment of Gasteiger charges using BIOVIA Discovery Studio. Protonation states were set to reflect physiological pH (7.4), and all histidine residues were manually checked and adjusted to the appropriate tautomeric forms using the same software. Grid box coordinates were defined separately for each protein based on their native ligand binding sites, and docking was performed via command-line execution. Pharmacokinetic properties of TQ were predicted using the SwissADME web server (https://www.swissadme.ch), which includes evaluation of absorption, distribution, metabolism, excretion (ADME), and drug-likeness according to Lipinski's Rule of Five. Toxicity profiles were assessed using the pkCSM platform (http://biosig.unimelb.edu.au/pkcsm), which estimates endpoints such as AMES mutagenicity, hepatotoxicity, hERG inhibition, and both acute and chronic oral toxicity in rodents. These computational predictions served to provide a preliminary evaluation of TQ's pharmacological and toxicological characteristics (14)

Validation of docking parameters. A measure of the mean distance that relates to the docking zone's size is the root mean square deviation (RMSD). Achieving an RMSD value of less than 2 Å is the aim. If the RMSD is less than 2 Å, the docking method is valid. In this study, three independent docking measurements were performed for each protein–ligand complex (CRP–TQ and TGF-β–TQ) to ensure reproducibility of the results. All measurements were conducted using the same protein structures and ligand samples under identical docking parameters, with the protein and ligand docking regions configured using the grid panel and grid submenu (15).

Molecular docking test. Molecular docking simulations were conducted using AutoDock Vina v1.5.6 (http://autodock.scripps.edu). Docking inputs were prepared via configuration files (conf.txt) and executed using the Windows command prompt with the command vina.exe -config conf.txt -log log.txt. Each configuration file specified the receptor (.pdbqt) and ligand (.pdbqt) files, along with grid box coordinates and dimensions. The output included binding affinities, multiple li-

gand conformations, and root mean square deviation (RMSD) values for pose validation.

Docking validation was performed by redocking the native ligands of each target protein to evaluate the accuracy of the docking protocol. For C-reactive protein (CRP; PDB ID: 1B09, DOI: https://doi.org/10.2210/pdb1B09/pdb), phosphocholine was used as the reference ligand and produced an RMSD of 1.421 Å. For transforming growth factor β (TGF-β; PDB ID: 1TGJ, DOI: https://doi.org/10.2210/pdb1TGJ/pdb), the redocking of the co-crystallized ligand yielded an RMSD of 0.253 Å. Both values are within the generally accepted threshold (<2 Å), indicating reliable docking performance. RMSD was calculated using PyMOL's alignment function, comparing heavy atoms between docked and crystallographic poses. Distinct grid box centres were defined for each protein: CRP at x=139.030, y=171.723, z=34.896 and TGF-β at x=37.455, y=39.338, z=63.313, with uniform dimensions of 40×40×40 Å to ensure proper coverage of the binding site (16,17).

Data visualization for molecular docking. The goal of molecular docking data visualization is to determine the spatial configuration and three-dimensional visual depiction of protein–ligand interactions. For every ligand that is evaluated, the position and visual representation of protein binding are ascertained by analysing the visualization data to evaluate compound interactions. To determine the conformation of the TQ molecule and its binders (hydrogen and nonhydrogen bonds), the resulting molecular interactions are utilized. Biovia DS Visualizer 2021 (v21.1) software was used to visualize molecular docking data. The pdbqt file format is used to hold the visualization data (18).

Pharmacokinetic analysis and toxicity analysis. Physicochemical properties and ADME parameters of thymoquinone (TQ), such as absorption, distribution, metabolism, and excretion, were evaluated using the SwissADME platform (https://www.swissadme.ch). These analyses included gastrointestinal absorption, bioavailability score, and drug-likeness based on Lipinski's Rule of Five. In parallel, toxicity predictions were conducted using two tools: the pkCSM web server (http://biosig.unimelb.edu.au/pkcsm) and the Toxtree application. The pkCSM platform was used to assess endpoints including AMES toxicity, maximum tolerated human dose, hERG I and II inhibition, acute and chronic oral toxicity in rodents, hepatotoxicity, and skin sensitization. Meanwhile, Toxtree was used to evaluate Tetrahymena pyriformis toxicity and other relevant toxicological profiles. These computational tools provided a comprehensive preliminary evaluation of TQ's pharmacokinetic behaviour and toxicological safety(19,20).

Statistical analysis

Binding affinity (kcal/mol) and RMSD values were expressed as mean ± standard deviation from three independent docking runs per ligand–protein complex. Comparative descriptive analysis was performed between thymoquinone, native ligands, and enalapril to evaluate relative docking performance. No inferential statistics were applied because the study was computational.

RESULTS

The binding affinities of thymoquinone (TQ) toward C-reactive protein (CRP) and transforming growth factor β (TGF-β) were analysed through molecular docking simulations. Grid box dimensions were set at 40×40×40 Å³, with centre coordinates adjusted based on each protein's native ligand binding site. For CRP (PDB ID: 1B09), the grid box centre was x=139.030, y=171.723, z=34.896. For TGF-β (PDB ID: 1TGJ), the centre was x=37.455, y=39.338, z=63.313. The native ligands, phosphocholine for CRP and DIO for TGF-β, were redocked to validate the docking protocol. The root mean square deviation (RMSD) values between docked and crystallographic poses were 1.421 Å for CRP and 0.253 Å for TGF-β, both of which are within the acceptable range (<2 Å), confirming the reliability of the docking setup.

Table 1. Affinity value of the interactions between ligands and C-reactive protein (CRP) and ligands and transforming growth factor β (TGF-β)

Ligand	Affinity value	Ligand type	RMSD
Ligands and CRP			
Phosphocholine	-2.39 Kcal/mol	Native ligand	
Thymoquinone	-3.60 Kcal/mol	Test ligand	1.421 Å
Enalapril	-4.56 Kcal/mol	Clinical references	
Ligands and TGF-β			
1,4 Diethylene Dioxide (DIO)	-2.73 kcal/mol	Native ligand	
Thymoquinone	-4.15 kcal/mol	Test ligand	0.253 Å
Enalapril	-6.16 kcal/mol	Clinical references	

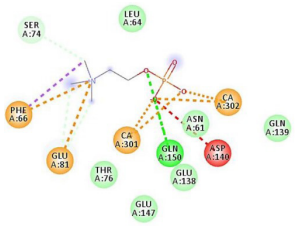
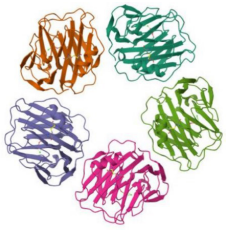
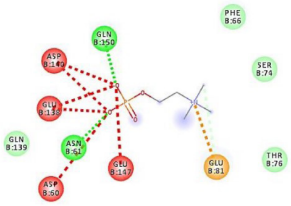
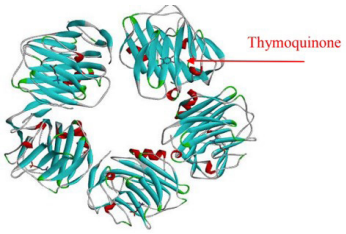
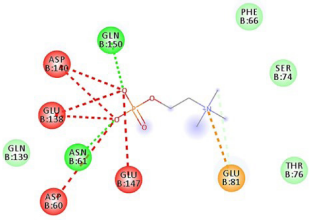
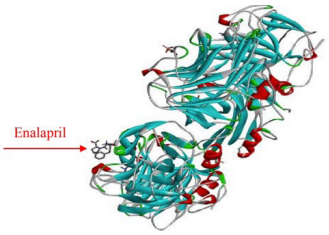
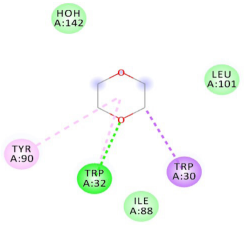
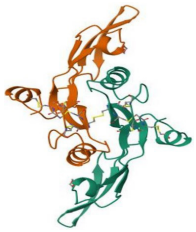
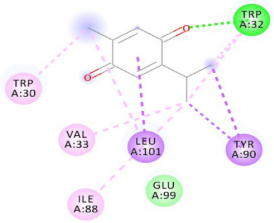
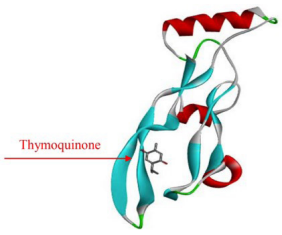
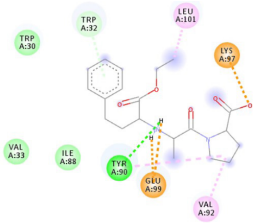
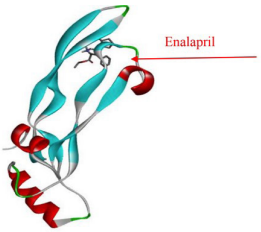
RMSD, root of mean standard deviation

For CRP, the native ligand (phosphocholine) had a binding affinity of –2.39 kcal/mol, while TQ showed a stronger affinity of –3.60 kcal/mol. For TGF-β, the native ligand (DIO) yielded a binding affinity of –2.73 kcal/mol, and TQ demonstrated a more favourable interaction with –4.15 kcal/mol. Although enalapril is not known to bind directly to the active sites of CRP or TGF-β, it was included for contextual comparison; its docking yielded binding affinities of –4.56 kcal/mol with CRP and –6.16 kcal/mol with TGF-β. These docking scores are presented solely for reference, as enalapril primarily acts through angiotensin-converting enzyme inhibition in clinical practice and does not serve as a structural positive control in this simulation.

List the amino acid residues involved in the molecular interactions between thymoquinone (TQ) and the target proteins CRP and TGF-β, as detailed in the following interaction analysis. These interactions were further visualized using BIOVIA Discovery Studio to generate 2D and 3D interaction diagrams, shown in Figures 1 to 4. TQ exhibited hydrogen bonding with Gln150 (2.8 Å) and Thr76 (3.1 Å) on CRP, alongside hydrophobic contacts with Phe66, Ser74, and Glu81. For TGF-β, TQ formed hydrogen bonds with Trp32 (3.0 Å) and interacted hydrophobically with Leu101 and Tyr90. These interactions contribute to the stable binding conformation of TQ within the active pockets of CRP and TGF-β, supporting its predicted anti-inflammatory potential. The visual evidence and specific residue contacts reinforce the molecular docking results and highlight TQ's capability to engage with key residues relevant to inflammatory regulation (Table 2).

The pharmacokinetic parameters of TQ absorption, distribution, metabolism, and excretion were predicted via the SwissADME tool. In addition, physicochemical tests using the pkCSM strategy were performed to predict drug similarity to the test ligand. The Lipinski 5 rules refer to the physicochemical properties. This is because every parameter's value is a multiple of five, meaning that the molecular weight, octa-

Table 2. Ligand - C-reactive protein (CRP) and Ligand - transforming growth factor β (TGF-β) interaction of molecular docking visualized in three dimensions (3D)

No	Ligand	Docking Interaction Ligand and Protein	3D Visualization
Ligands and CRP			
1	Phosphocholine (PC)		
2	Thymoquinone		
3	Enalapril		
Ligands and TGF-β			
1	1,4 Diethylene Dioxide		
2	Thymoquinone		
3	Enalapril		

nol–water partition coefficient (LogP), H-bond acceptor, and H-bond donors must all be less than 500 daltons, 10, and 5, respectively (5). Compounds that fulfil Lipinski's rule can be used as active oral drugs (10,13). The physicochemical analysis showed that thymoquinone (TQ) fulfilled all parameters of Lipinski's Rule of Five, with a molecular weight of 164.2 g/mol, two hydrogen bond acceptors, no hydrogen bond donors, and a logP value of 1.6. These properties indicate good lipophilicity and potential oral bioavailability, supporting its suitability as a drug-like molecule (Table 3).

The results of the ADME prediction test on the TQ compound showed the compound had a high absorption capacity in the digestive tract, which strengthens the use of the TQ compound as an oral drug (Table 4).

Table 3. The TQ's physicochemical properties

Formula	Molecular weight	H-Bond Acceptor	H-Bond Donors	Log P
$C_{10}H_{12}O_2$	164.2 g/mol	2	0	1.6

Table 4. ADME (Absorption, Distribution, Metabolism, and Excretion) predictions of TQ (Thymoquinone) predictions of Thymoquinone (TQ)

ADME	Parameter	Outcome/remark
A (Absorption)	GI Absorption	High
	TPSA	34,14
	Bioavailability Score	0,55
D (Distribution)	BBB	YES
	P-GP Substrate	NO
M (Metabolism)	CYP1A2 Inhibitor	NO
	CYP2C19 Inhibitor	NO
	CYPC9 Inhibitor	NO
	CYP2D6 Inhibitor	NO
	CYP3A4 Inhibitor	NO
E (Excretion)	LogKp	-5.74 cm/s

GI, gastrointestinal absorption; TPSA, topological polar surface area; BBB, blood–brain barrier; CYP, cytochrome P450 enzyme.

Toxicity predictions were performed using the pkCSM platform (http://biosig.unimelb.edu.au/pkcsm). TQ was not predicted to be mutagenic in the AMES test and did not exhibit hERG I or II inhibition, suggesting a low risk of cardiotoxicity. The predicted maximum tolerated dose in humans was 0.89 log mg/kg/day, and the highest tolerated dose in rats was estimated at 1.743 mol/kg. However, TQ was predicted to be hepatotoxic and a potential skin sensitizer. Chronic oral toxicity analysis estimated a dose of 2.378 log mg/kg that could result in liver damage. Additionally, the *Tetrahymena pyriformis* toxicity value was predicted to be 1.758 log mM. While these results suggest that TQ does not pose significant cardiac toxicity, the predicted hepatotoxicity represents a substantial limitation for its potential clinical use. Further experimental validation, particularly through in vitro and in vivo studies, is necessary to clarify its safety profile, especially regarding hepatic effects (Table 5).

Table 5. Predicted toxicity of TQ (Thymoquinone) compounds from *Nigella sativa*

No	Model name	Predicted value
1	AMES toxicity	NO
2	Hepatotoxicity	YES
3	Minnow oxicity	1.758 log mM
4	Acute oral toxicity in rats	1.743 mol/kg
5	Chronic oral toxicity in rats	2.378 mol/kg
6	hERG I inhibitor	NO
7	hERG II inhibitor	NO
8	Max. tolerable dose in humans	0.89 log mg/kg/day
9	Skin sensitization	YES
10	*T. pyriformis* toxicity	0.138 log ug/L

AMES, Ame's mutagenicity test; hERG, human ether-à-go-go-related gene potassium channel;
T. pyriformis, *Tetrahymena pyriformis* toxicity.

DISCUSSION

The present study provides computational evidence supporting the potential of thymoquinone (TQ) as a cardioprotective compound through molecular interaction with inflammatory and fibrotic mediators such as C-reactive protein (CRP) and transforming growth factor-β (TGF-β). These findings strengthen the growing body of literature suggesting that TQ plays a significant role in modulating post-infarction inflammation and myocardial remodelling.

Several recent investigations have demonstrated that TQ effectively downregulates pro-inflammatory cytokines and oxidative stress markers associated with myocardial injury. It was reported that TQ improved cardiac histology and reduced TNF-α and IL-6 expression in isoproterenol-induced myocardial infarction in rats (14). Likewise, a previous study showed that TQ attenuated fibrosis and reduced TGF-β expression in cardiac tissue was confirmed, supporting its role in inhibiting remodelling-related pathways (5). These *in vivo* data are consistent with our computational prediction that TQ interacts with residues critical for TGF-β signalling, potentially explaining its observed antifibrotic activity.

The anti-inflammatory potential of TQ through CRP modulation also aligns with previous studies demonstrating that TQ suppresses oxidative and inflammatory responses by inhibiting NF-κB and reducing CRP levels in cardiovascular and hepatic models (10,13). Such activity underscores the hypothesis that TQ may contribute to cardioprotection by interfering with CRP-mediated inflammatory cascades. Furthermore, accumulating evidence suggests that elevated CRP level serves not only as a marker but also as an active participant in the amplification of oxidative stress and tissue inflammation during myocardial injury (21). Previous investigations have revealed a significant association between CRP and uric acid concentrations in acute coronary syndrome, indicating that increased oxidative burden parallels heightened inflammatory signalling within cardiomyocytes (22). These insights reinforce the present findings and support the concept that targeting CRP-regulated pathways may represent a promising molecular mechanism underlying the cardioprotective potential of thymoquinone.

In addition to its molecular interactions, TQ exhibits favourable pharmacokinetic characteristics that support its therapeutic viability. Recent studies indicated that TQ has good oral bioavailability, high gastrointestinal absorption, and adherence to Lipinski's Rule of Five (23,24). Consistent with these findings, the present computational evaluation indicated good absorption potential and absence of mutagenicity or cardiotoxicity, further supporting TQ's suitability as a drug-like molecule. Nonetheless, possible hepatotoxicity predicted in silico should be interpreted cautiously, as mild hepatic enzyme elevation has been observed with chronic TQ exposure (24)

Overall, these results reinforce that TQ possesses dual anti-inflammatory and antifibrotic properties that could be beneficial in limiting post-infarction remodelling. The combined literature evidence from recent in vivo studies supports the molecular docking predictions, suggesting that TQ could serve as a complementary therapeutic candidate targeting CRP- and TGF-β–mediated pathways (25–27). However, because this study is purely computational, further experimental validation through *in vitro* binding assays and *in vivo* myocardial infarction models is essential to confirm the pharmacological relevance of these interactions.

This *in-silico* study suggests that thymoquinone (TQ), the major bioactive compound of *Nigella sativa*, has potential modulatory effects on key inflammatory mediators involved in myocardial infarction, namely C-reactive protein (CRP) and transforming growth factor β (TGF-β). The findings indicate that TQ may contribute to cardioprotection by targeting inflammation-related pathways. Although these computational

results are promising, experimental validation through *in vitro* and *in vivo* studies is essential to confirm its biological activity, therapeutic potential, and safety profile.

It must be emphasized that molecular docking assesses binding potential but does not provide evidence of biological activity or functional outcomes such as suppression of CRP or TGF-β levels. Moreover, this study lacked comprehensive visual representations of ligand–protein interactions, limiting the interpretive strength of the docking findings. Therefore, while the data suggest that TQ could serve as a candidate for further exploration, extensive *in vitro* and *in vivo* validation is essential to confirm its therapeutic efficacy and safety.

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TRANSPARENCY DECLARATION

Conflicts of interest: None to declare.

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