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Antinflammatory Potential of Thymoquinone Compounds in Nigella Sativa for Patient with Myocardial Infarction: in Silico Study

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Submitted to: JMIR Bioinformatics and Biotechnology
on: November 12, 2024

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Abstract

Background: 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 ? (TGF-?) are markers that are often used to evaluate the level of inflammation, especially in MI.

Objective: This study aimed to predict the anti-inflammatory potential of the active compound thymoquinone (TQ), which is abundant in Nigella sativa, through molecular docking.

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-? ligands. Using the pkCSM method, pharmacokinetic predictions were carried out.

Results: The TQ molecule has a high binding free energy, comparable to that of the conventional therapeutic drug enalapril, and a very favorable pharmacokinetic profile, according to a postdocking study, which included binding affinity and pharmacokinetic predictions. TQ (2-methyl-5-propan-2-ylcyclohexa-2,5-diene-1,4-dione) has good binding affinity for CRP and TGF-?, with docking scores of -3.60 and -4.15 kcal/mol, which are lower than the binding affinity values of the original ligand of -2.39 and -2.73 kcal/mol and comparable to the scores of the positive control ligand (Enalapril), which are -4.84 and -6.13 kcal/mol. The root mean square deviation (RMSD) values for CRP were 1.421 Å. On the other hand, the RMSD values for TGF-? were 0.00 Å

Conclusions: The TQ compound has the potential to be used as a natural anti-inflammatory compound in the treatment of MI.

(JMIR Preprints 12/11/2024:68738)
DOI: https://doi.org/10.2196/preprints.68738

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Conclusions: The TQ compound has the potential to be used as a natural anti-inflammatory compound in the treatment of MI.

Keywords: Antiinflammatory; Enalapril; Molecular Docking; Myocardial Infarction; Thymoquinone.

Introduction

Myocardial infarction (MI) is a leading cause of death worldwide, with an estimated 32% of the population experiencing death [1]. 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 remodeling and heart failure [2,3]. Therefore, it is very important to emphasize inflammation and oxidative stress so that patients do not develop heart failure. 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) also plays an important role in the MI process. TGF-β can trigger the onset of myocyte hypertrophy, which plays an important role in the process of ventricular remodeling 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].

Owing to their broad spectrum, cardioprotective agents that can have anti-inflammatory and antioxidant effects are increasingly in demand worldwide. Currently, the most widely used drugs as cardioprotective agents are angiotensin-converting enzyme (ACE-I) receptor inhibitors. ACEIs are able to suppress inflammatory and oxidation activities so that they can improve outcomes in patients with hypertension, congestive heart failure, left ventricular dysfunction and myocardial infarction [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. ACE-I drugs are important therapeutic tools; however, concerns regarding long-term toxicity and side effects such as hyperkalemia indicate strong limitations in their use [9].

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 (5). 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 also been shown to prevent myocardial reperfusion and ischemic arrhythmias. TQ has been reported to have anti-inflammatory and antioxidant effects that have an impact on various diseases caused by inflammation [13].

Molecular docking is an in silico method based on computational chemistry. This method can be used to find the most appropriate interaction pattern between ligand and receptor molecules. Currently, research using computational methods is very important in various aspects of research in the fields of biology and medicine. One of the benefits of using this method is that it can be used in various drug discovery and manufacturing processes. This study aimed to identify the TQ compound in Nigella sativa by docking.

Methods

Applications and Software

The Autodock tools (v1.5.6) software was utilized in this investigation. Using the Vega ZZ program, a ligand structure test (TQ compound) was carried out. The 3D files were obtained from the PubChem website (https://pubchem.ncbi.nlm.nih.gov). The target proteins included the following: from the website (www.rscb.org), the protein targets for TGF-β (PDB ID: 1TGJ; PDB DOI: https://doi.org/10.2210/pdb1TGJ/pdb) and CRP (PDB ID: 1B09; PDB DOI: https://doi.org/10.2210/pdb1B09/pdb) were downloaded. Using BIOVIA Discovery Studio, the docked ligands containing the TGF-β and CRP proteins were graphically represented. http://www.swissadme.ch. The specialist is the website where the SwissADME programs are available. To forecast toxicity, the pkCSM web server (http://structural.bioc.cam.ac.uk/pkcsm) was utilized.

Proteins and Ligand Preparation.

The program Biovia DS Visualizer was utilized to generate ligands, TGF-β protein, and CRP. It

involves saving all files after proteins are extracted from natural ligands and amino acid residues. The ligands employed in this investigation were TQ, which had previously been isolated from Nigella sativa's ultrasound-assisted aqueous extract. To prepare the ligand, the 3D structure of TQ was optimized via the Vega ZZ program. Following the acquisition of each chemical from the PubChem (http://pubchem.ncbi.nlm.nih.gov) database, the AutoDock tool translated each compound from the PDB format to GDPQ. The procedure involved removing superfluous components, adding hydrogen, adding a gastaiger charge, and positioning the grid box in the middle of the native ligand within the receptor's active site, which contains residues of amino acids [14,15].

Validation of Docking Parameters

The docking technique in this work was validated via AutoDock software (v1.5.6). The natural ligands of TGF-β and CRP are removed as part of the validation procedure. The grid parameters and the root mean square deviation (RMSD) are the outcomes of this method. A measure of the mean distance that is connected with 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. The protein and ligand docking regions were then configured using the grid panel and grid submenu [16].

Molecular Docking Test

We utilized AutoDock Vina software (v1.5.6) for molecular docking. The grid box specifications were set, and by using vina.exe -config conf.txt -log log.txt at the Windows command prompt, the docking and RMSD scores were retrieved from the docking operation. A new document called conf.txt contains the TQ compound pdbq and the CRP and TGF-β proteins pdbqt. Conversely, the ligand was represented by the file ligand.pdbqt, which had x, y, and z as its centers and x, y, and z as sizes. The RMSD value of the docking process was calculated using the values entered in the grid fields and the Windows command prompt. Alternatively, the command "vina.exe -config conf.txt -log log.txt" could be entered by typing "cmd" in the folder path and hitting Enter.
For every conformation, this code shows the RMSD values, docking scores, and numerous conformations. The root mean square deviation (RMSD) value is the success parameter that is used during the validation of the docking procedure. The AutoDock program (v1.5.6) (http://autodock.scripps.edu) and the redocking of native ligands of the TGF-β and CRP proteins (PDB DOI: https://doi.org/10.2210/pdb1B09/pdb and https://doi.org/10.2210/pdb1TGJ/pdb) were used to validate the docking approach. Grid parameters and RMSD were produced as a result of this procedure. The dimensions of the docking zone are related to the RMSD value. To obtain RMSD values ≤ 2 Å, which are deemed sufficient for docking, adjustments were made [17,18].

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 analyzing 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 the molecular docking data. The pdbqt file format is used to hold the visualization data [19].

Pharmacokinetic Analysis and Toxicity Analysis

Analysis of the prediction of the pharmacokinetic profile of the test ligand was performed via the pkCSM web server. The parameters tested include absorption, distribution, metabolism, and excretion (ADME) via the SwissADME program (https://www.swissadme.ch). The physicochemical properties were determined via the Lipinski rule of five, as was the oral bioavailability [20–22]. On

the other side, the Toxtree app was used to make predictions about toxicity analysis. AMES toxicity, the highest human tolerable dose, hERG-I and hERG-II inhibition, acute oral toxicity in rats, chronic oral toxicity in mice, hepatotoxicity, skin sensitization, and Tetrahymena pyriformis (T. pyriformis) toxicity were among the toxicological parameters evaluated [23,24].

Results and Discussion

The interactions between TQ compounds from Nigella sativa and TGF-β and CRP, two inflammatory indicators, were examined in this study. Reattaching the original ligand to the active cycle of TGF-β and CRP allows for the validation of the molecular docking parameters. 50 runs of the CRP and TGF-β parameters were performed using grid box points that measured 40 × 40 × 40. The CRP parameters' corresponding grid box coordinates are 139.030, 171.723, and 34.896 in x, y, and z. In addition, the TGF-β parameters' corresponding x, y, and z grid box coordinates are 139.030, 171.723, and 34.896, respectively.

In order to estimate the test ligand's binding affinity value with the functioning target protein, the molecular docking test is a helpful tool in drug design. Using the pkCSM model, the in silico method was also used to pharmacokinetic prediction. Table 1 displays the binding affinities of the native ligand (PC), test ligand (TQ), and positive control ligand (Enalapril) for CRP. The native ligand on CRP has an affinity value of -2.39 kcal/mol (100%), while the affinity value of the test ligand (TQ) is -3.60 kcal/mol (150.62%). The TQ compound shows better CRP binding affinity than the native ligand does. However, the affinity value of the test ligand (TQ compound) is not better than that of the control ligand (Enalapril), with an affinity value of -4.56 kcal/mol (190.79%). TQ has valid RMSD values (<2 Å), namely, 1.423 Å, 1.491 Å, and 1.349 Å (average of 1.421 Å). Valid RMSD values indicate slightly different structural conformations during docking.

Table 1. Affinity value of the interactions between ligands and CRP.

Ligand	Affinity Value	Percentage	Ligand Type	RMSD
Phosphocholine	-2,39 Kcal/mol	100%	Native Ligand	1,421 Å
Thymoquinone	-3,60 Kcal/mol	150,62%	Test Ligand	
Enalapril	-4,56 Kcal/mol	190,79%	Control Ligand	

The binding affinity values of the test ligand (TQ), native ligand (DIO) for TGF-β and positive control ligand (Enalapril) are presented in Table 1. The native ligand on TGF-β has an affinity value of -2.73 kcal/mol (100%), while the affinity value of the test ligand (TQ compound) is -4.15 kcal/mol (152.01%). The TQ compound shows better CRP binding affinity than the native ligand does. However, the affinity value of the test ligand (TQ) is not better than that of enalapril, which has an affinity value of -6.16 kcal/mol (225.64%). TQ has a valid RMSD value (<2 Å), which was 0.00 Å in 3 tests. A lower RMSD value suggests a somewhat altered structural conformation upon docking.

Table 2. Affinity value of the interactions between ligands and TGF-β.

Ligand	Affinity Value	Percentage	Ligand Type	RMSD (Å)
1,4 Diethylene Dioxide (DIO)	-2,73 kcal/mol	100%	Native Ligand	0,00 Å
Thymoquinone	-4,15 kcal/mol	152,01%	Test Ligand	
Enalapril	-6,16 kcal/mol	225,64%	Control Ligand	

Tables 3 and 4 show the visualization of 3-dimensional (3D) interactions between the test ligands (TQ and enalapril compounds) and the receptors (native ligands of CRP and TGF-β). The ligands

interact with amino acid residues of CRP and TGF-β through hydrogen bonds and other nonhydrogen bond interactions. In the TQ compound, good TQ–CRP interactions were obtained between hydrogen and nonhydrogen bonds with the amino acids Gln150, Gln139, Glu81, Thr76, Ser74, and Phe66. Moreover, in the TQ-TGF-β interaction, good results were also obtained between hydrogen and nonhydrogen bonds with the amino acids Trp 32, Trp30, Ile88, Leu101, and Tyr90. The TQ compound has the potential to have good anti-inflammatory effects based on the binding affinity and RMSD values measured; nevertheless, it is not superior to current therapy (enalapril).

Table 3. Ligand-CRP interaction of molecular docking visualized in three dimensions (3D).

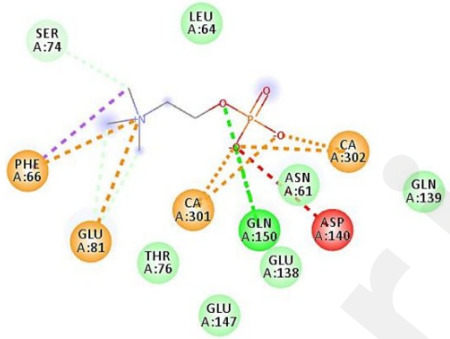
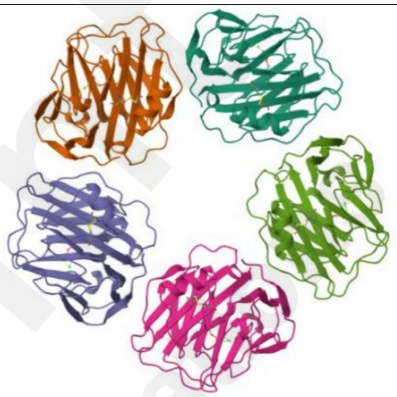
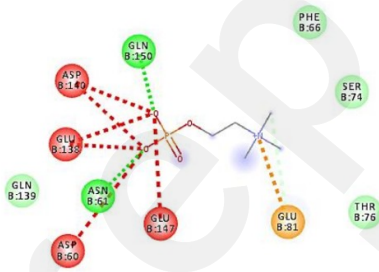
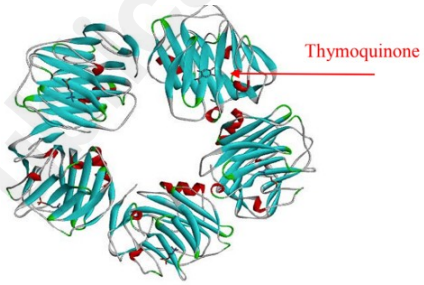
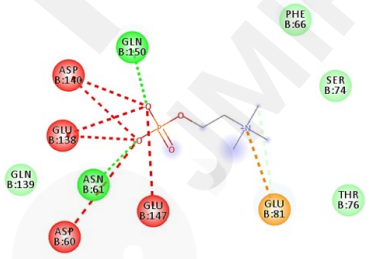
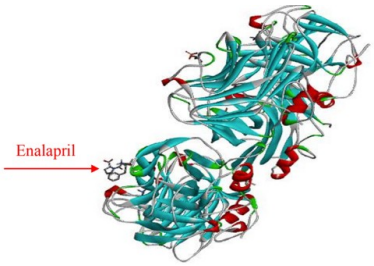
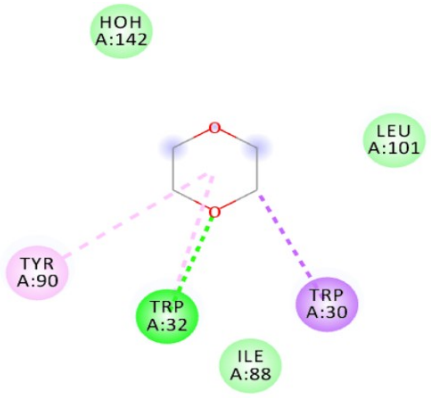
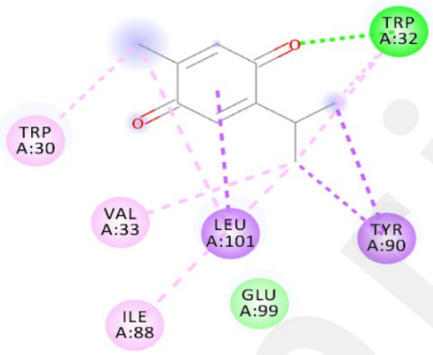
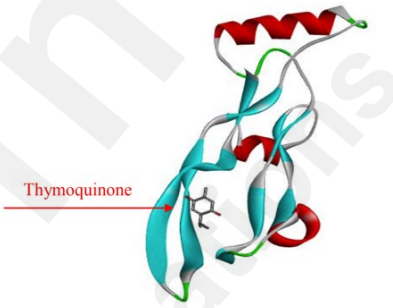
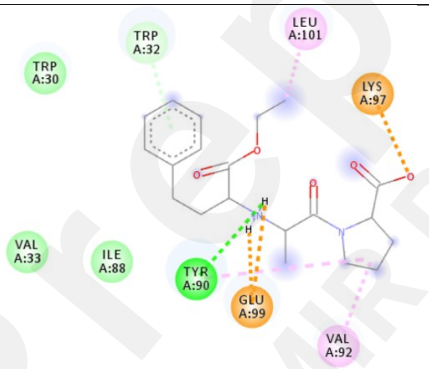
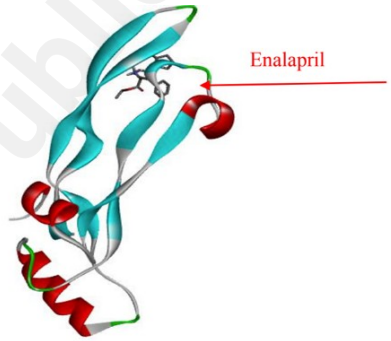
No	Ligand	Docking Interaction Ligand and Protein	3D Visualization
1	Phosphocholine (PC)		
2	Thymoquinone		
3	Enalapril		

Table 4. Ligand-TGF-β interaction of molecular docking visualized in three dimensions (3D).

No	Ligand	Docking Interaction Ligand and Protein	3D Visualization
1	1,4 Diethylene Dioxide		
2	Thymoquinone		
3	Enalapril		

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, octanol–water partition coefficient (LogP), H-bond acceptor, and H-bond donors must all be less than 500 daltons, 10, and 5, respectively [25]. Compounds that fulfill Lipinski's rule can be used as active oral drugs [26,27]. The results of the physicochemical test (Table 5) revealed that the TQ compound meets the Lipinski rule, indicating that TQ can be used actively as an oral drug. Table 6 shows the results of the ADME prediction test on the TQ compound. The compound has a high absorption capacity in the digestive tract, which strengthens the use of the TQ compound as an oral drug.

Table 5. 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 6. ADME predictions of 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

The results of the toxicity prediction test for the TQ compound are shown in Table 7. The AMES toxicity test is a method that is widely used for initial screening of a compound that is mutagenic. The results of the AMES toxicity test revealed that the TQ compound is not mutagenic. The hepatotoxicity prediction of the TQ compound was positive, indicating that this TQ compound has hepatotoxic properties. In addition, TQ can increase skin sensitivity in the form of contact dermatitis. A chronic oral toxicity test revealed that the estimated dose of TQ, 2.378 log/mg/kg, can cause liver damage. The estimated TQ dose of 1.743 mol/kg is the highest dose that can technically still be given to test animals (rats). The results of the Minnow toxicity test revealed that TQ at an estimated dose of 1.758 log mM did not cause toxicity. The estimated high dose of TQ that is safe for humans (in phase I clinical trials) is 0.89 log mg/kg/day. The TQ compound does not inhibit hEGR I or II, so it does not cause toxicity to the heart. Therefore, TQ compounds have the potential to be anti-inflammatory and play a role in cardioprotection, especially in patients with MI.

Table 7. Predicted toxicity of TQ compounds from *Nigella sativa*.

No	Model Name	Predicted Value
1	AMES Toxicity	No
2	Hepatotoxicity	Yes
3	Minnow Toxicity	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

Conclusions

In silico studies of TQ compounds from Nigella sativa plant extracts revealed that these compounds have potential anti-inflammatory and antioxidant effects. Although TQ compounds do not have better affinity values for CRP and TGF-β than standard therapy does, TQ compounds have better affinity

scores than native ligands do; thus, TQ compounds also have the potential to reduce CRP and TGF-β levels. The physicochemical properties of TQ indicate that the compound can be used as an oral drug and has a good pharmacokinetic profile. Toxicity predictions indicate that TQ has no toxic effects on the heart, so it can be used as a cardioprotective agent. Although flavonoid compounds have shown potential anti-inflammatory properties as cardioprotective agents, further in vitro and in vivo studies are needed to support this claim.

Acknowledgements

Researchers would like to thank the teaching staff at the Faculty of Medicine, Islamic Sultan Agung University.

Conflicts of Interest

none declared.

Abbreviations

ACEi: angiotensin converting enzym inhibitor
ADME: absorption, distribution, metabolism, and excretion
CRP: C-reactive protein
MI: myocardial infarction
TGF-β: transforming growth factor-β
TQ: Thymoquinone
RMSD: root mean square deviation
RCT: randomized controlled trial

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