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Thymoquinone as a Potential Antimicrobial Agent against Resistant *Pseudomonas aeruginosa*: A Computational Chemistry Approach

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INTRODUCTION

Antimicrobial resistance is a significant public health challenge worldwide, especially in Gram-negative bacteria such as *Pseudomonas aeruginosa*. In recent years, *P. aeruginosa* has shown increasing multi- and pan-drug resistance, even to colistin, which is considered to be the last line of defence against resistant bacteria (1). Black cumin or *Nigella sativa L.*, globally used as a spice, contains the bioactive compound thymoquinone, which is promising as a natural antibacterial agent due to its chemical properties (2). The high cost and complexity of developing new antibiotics is a significant obstacle and often leads to high attrition rates. However, computational chemistry is a promising approach that optimises the selection of candidates and supports the development of targeted antibacterial agents. This can speed up the discovery process and reduce costs in the ongoing fight against antimicrobial resistance (3).

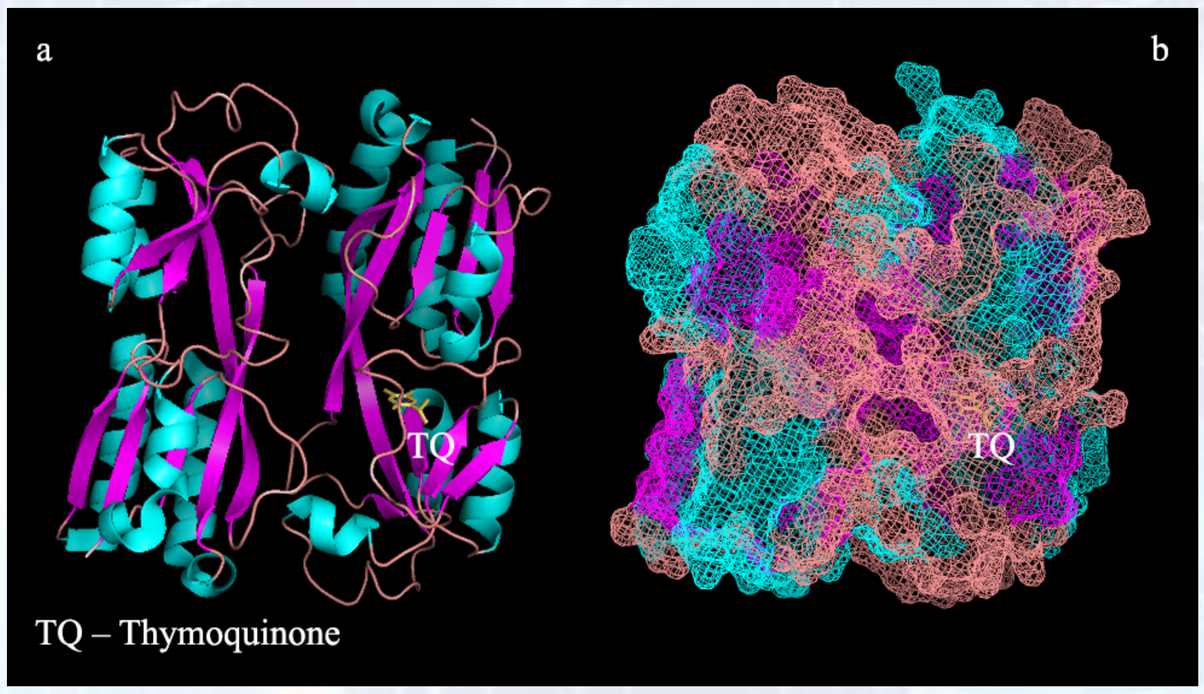

Figure 1: The Binding of Thymoquinone to the Binding Pocket of the MvfR Protein of *P. aeruginosa* in Model 1. (a) Cartoon Representation of the Binding of Thymoquinone to the MvfR Protein, (b) Mesh Representation of the Binding of Thymoquinone to the MvfR Protein. The blue colour indicates α-helices, purple β-sheets and salmon-coloured connecting loops.

AIM

The aim is to computationally evaluate thymoquinone as a potential natural antibacterial agent against resistant *P. aeruginosa* by assessing its pharmacokinetic properties and binding affinity to critical molecular targets of *P. aeruginosa*.

METHODS

The pharmacokinetic properties of thymoquinone and its pharmacological potential and bioavailability were computationally evaluated using the SwissADME tool (4). The topologies of the receptor proteins were analysed using the CASTp web server, and triple molecular docking simulations were performed using AutoDock Vina 1.1.2. Molecular visualisation and analysis were performed with PyMol and DS Visualizer (5).

RESULTS

The results of the molecular docking showed that the binding of the thymoquinone ligand to the MvfR protein is located deep in the binding pocket of the MvfR protein of *P. aeruginosa* (Figure 1). Molecular docking simulations show a strong binding affinity to the MvfR protein in *P. aeruginosa*, which is an important regulator of virulence and quorum sensing. Seven (out of nine) models showed consistent interactions with a root mean square deviation (RMSD) of less than 5 Å, often involving the amino acid Ile236 (Figure 2). Figure 3 shows the intermolecular interactions between the thymoquinone and the amino acids within the binding pocket of the MvfR protein in Model 1.

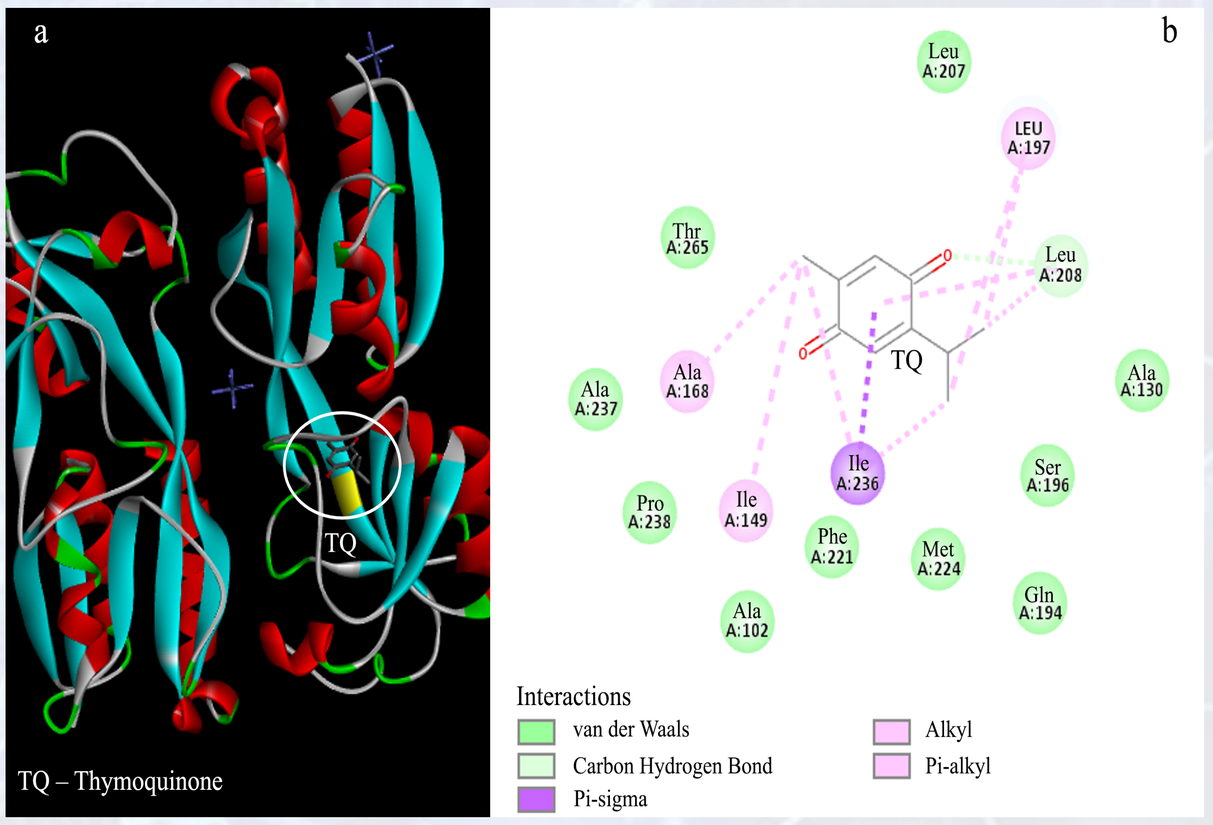

Figure 2: The Intermolecular Interactions During In Silico Binding of Thymoquinone to the MvfR protein of *P. aeruginosa* in Model 1. Binding energy = –6.3±0.00 kcal/mol, RMSD = 0 Å. (a). The Binding of Thymoquinone to the Binding Site of the MvfR Protein. α-helices are marked in red, β-sheets in blue, loops in grey and green connections between different structures. (b) The Interaction Network of the Amino Acids of the MvfR Protein and the Thymoquinone. A – amino acid, Å – ångström, Ala – alanine, Gln – glutamine, Ile – isoleucine, kcal/mol – kilocalorie per mole, Leu – leucine, Met – methionine, Phe – phenylalanine, Pro – proline, RMSD – root mean square deviation, Ser – serine, Thr – threonine, TQ – thymoquinone.

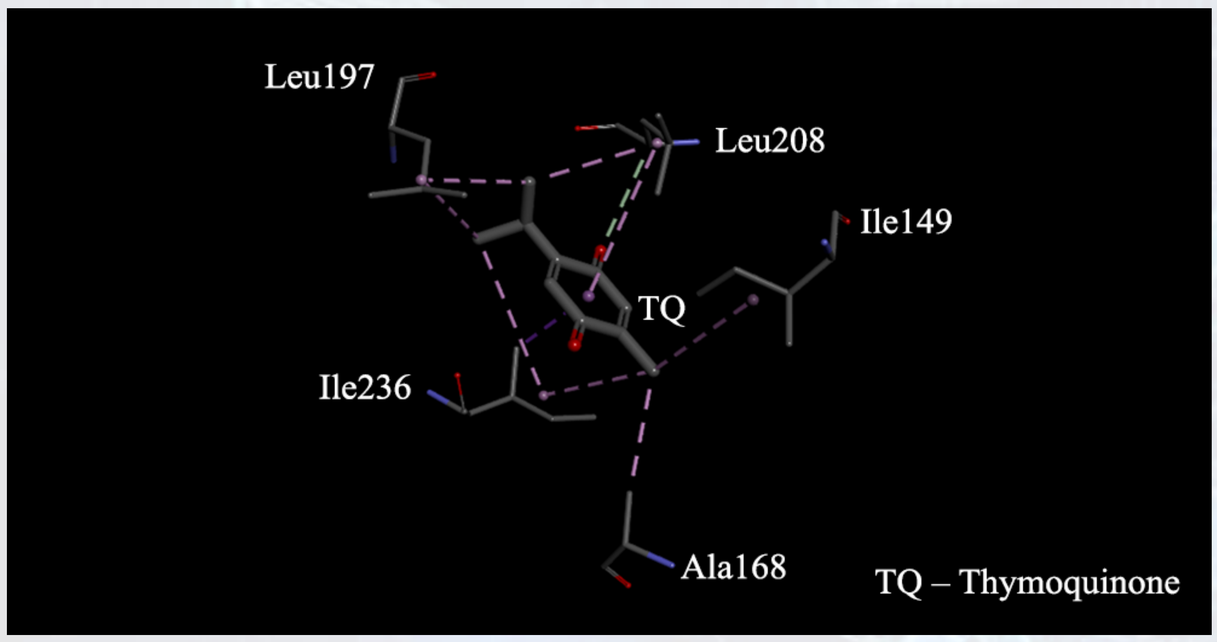

Figure 3: The Intermolecular Interactions between the thymoquinone and the Amino Acids within the Binding Pocket of the MvfR Protein of *P. aeruginosa* in Model 1. The intermolecular interactions are shown by dashed lines and the colours differ depending on the type of interaction, conventional hydrogen bonds are marked in green, violet π-alkyl interactions, violet π-sigma interactions and pink π-π stacks.

CONCLUSION

Computational chemistry can enhance the development of new antibiotics. Thymoquinone shows favourable pharmacokinetics and a strong binding affinity to the MvfR protein in *P. aeruginosa*. Thymoquinone shows potential as an antimicrobial agent against *P. aeruginosa*, but further in vitro and in vivo tests, including toxicological studies, are needed to evaluate its cytotoxicity.

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