The Antibacterial Potential of the Bioactive Cinnamon Compound *Trans*-cinnamaldehyde against *Pseudomonas aeruginosa*: A Computational Biology and Chemistry Perspective

#PP

Goran Slivšek[1,2,3], Nives Matković[4], Ivan Dolanc[1*], Sandra Mijač[5], Marin Marinović[3], Silvija Petković[2], Miran Čoklo[1]

[1]Institute for Anthropological Research, Centre for Applied Bioanthropology, Zagreb, Croatia
[2]Faculty of Medicine, University of Zagreb, Zagreb, Croatia
[3]Rijeka University Hospital Centre, Rijeka, Croatia
[4]University Hospital of Split, Split, Croatia
[5]Children's Hospital Srebrnjak, Zagreb, Croatia

[*]e-mail address: ivan.dolanc@inantro.hr

INTRODUCTION

The increase in multi-drug-resistant bacteria poses a global threat to public health and requires alternative strategies. One of these multi-drug-resistant bacteria is the opportunistic Gram-negative pathogen *Pseudomonas aeruginosa* (1). Cinnamon, a widely used spice from the *Cinnamomum verum* plant, contains bioactive compounds such as *trans*-cinnamaldehyde, which holds promise as a natural antibacterial agent due to its chemical properties. While the high attrition rate is a major obstacle in the development of new antibiotics, advances in computational biology and chemistry offer exciting possibilities (2).

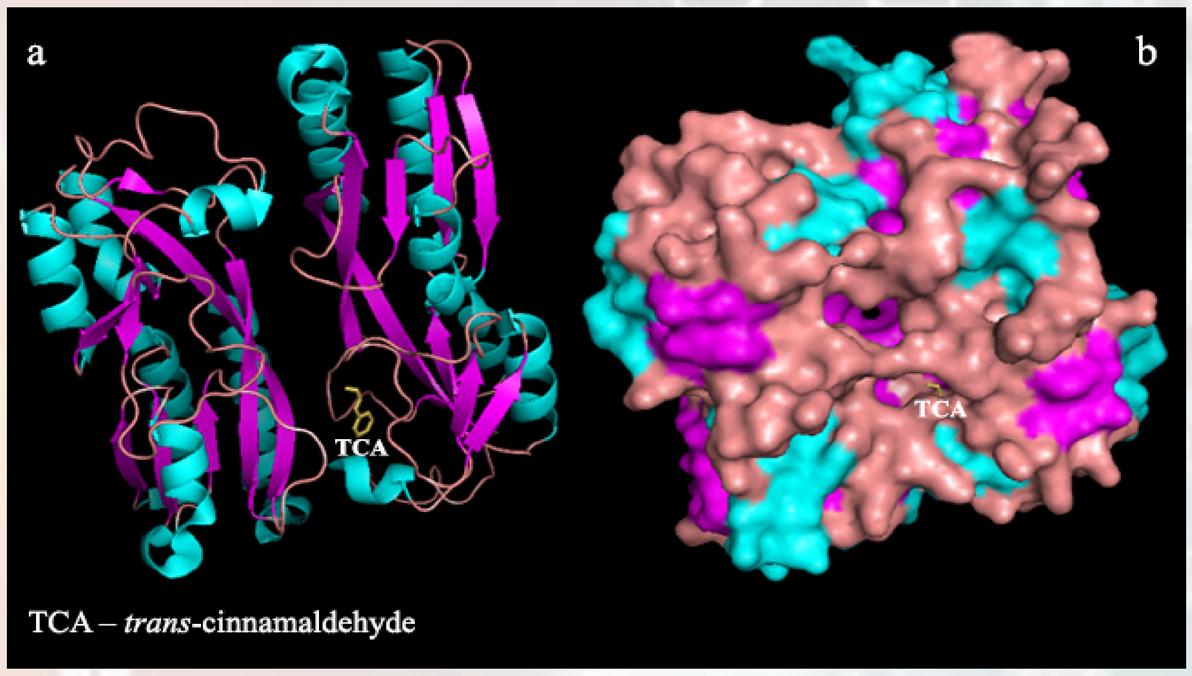

Figure 1: The Binding of *Trans*-cinnamaldehyde to the Binding Pocket of the MvfR Protein of *P. aeruginosa* in Model 1. (a) Cartoon Representation of the Binding of *Trans*-cinnamaldehyde to the MvfR Protein, (b) Surface Representation of the Binding of *Trans*-cinnamaldehyde to the MvfR Protein. The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

AIM

The aim is to evaluate the potential of *trans*-cinnamaldehyde as a natural antibacterial agent against multi-drug-resistant *P. aeruginosa* and to explore its potential therapeutic targets using computational biology and chemistry methods.

METHODS

The topological surface of the multiple virulence factor regulator (MvfR) receptor protein of *P. aeruginosa* was analysed using the Computer Atlas of Surface Topography of Proteins (CASTp) web server, while molecular modelling simulations were performed using AutoDock Vina v1.2.5 based on the crystal structure of the ligand binding site of the MvfR protein (3). The modelling grid box was constructed based on the binding site for the native ligand of the Pseudomonas quinolone signal (PQS) including the MvfR inhibitor M64, which is co-crystallised in the crystal structure from the RCSB Protein Data Bank (4). These modelling simulations were performed in triplicate and the resulting models were analysed to determine binding affinity and key interaction patterns. The tools used for this purpose were UCSF Chimaera, PyMol and DS Visualiser.

RESULTS

The results of the molecular docking showed that the binding of the *trans*-cinnamaldehyde ligand to the MvfR protein is located deep in the binding pocket of the MvfR protein of *P. aeruginosa* (Figure 1). Four of the nine models showed a hydrophobic interaction with the amino acid Ile236 of the MvfR protein. Model 1, which also met the root mean square deviation (RMSD) < 5 Å criterion, had the most favourable binding energy and thus the highest binding affinity, suggesting that the amino acid Ile236 may play an important role in binding a small, hydrophobic ligand to the binding pocket of the MvfR protein (Figure 2). Figure 3 shows the intermolecular interactions between the *trans*-cinnamaldehyde and the amino acids within the binding pocket of the MvfR protein in model 1.

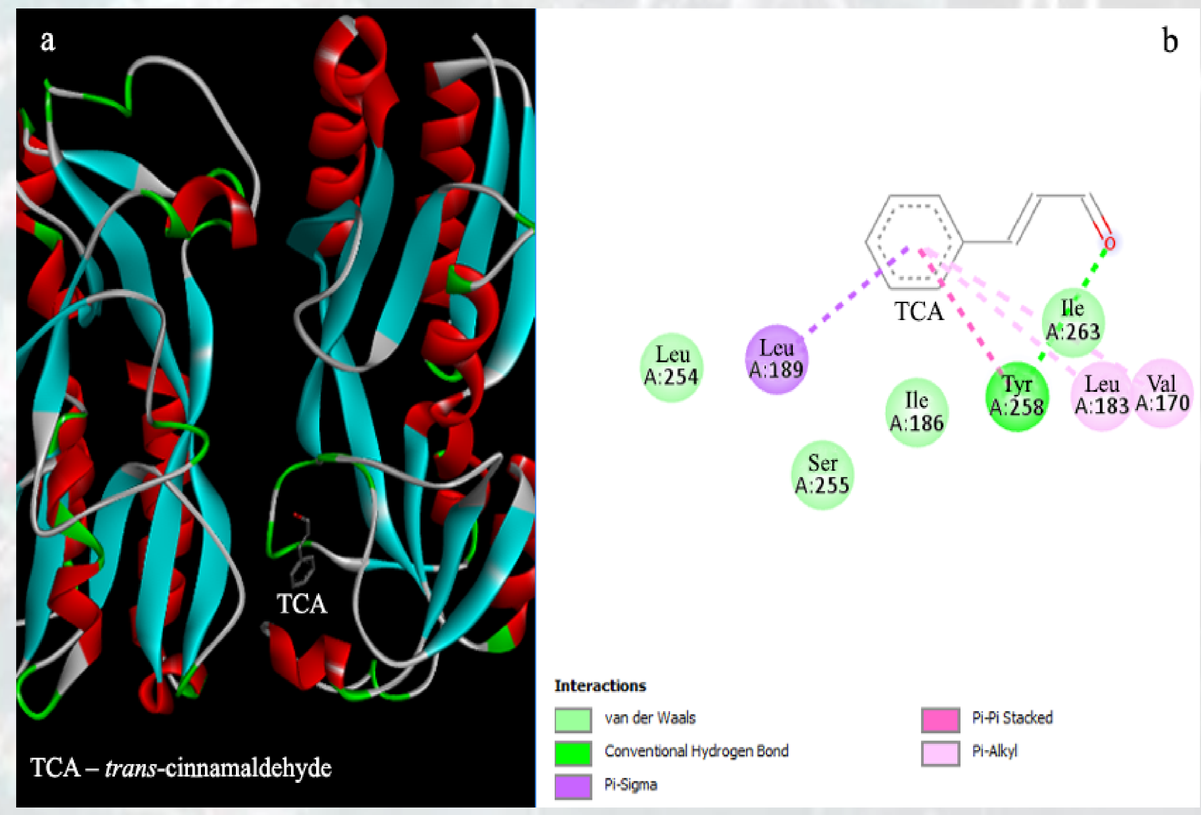

Figure 2: The Intermolecular Interactions During In Silico Binding of *Trans*-cinnamaldehyde to the MvfR Protein of *P. aeruginosa* in Model 1. Binding energy = –6.5±0.00 kcal/mol, RMSD = 0 Å. (a) The Binding of *Trans*-cinnamaldehyde to the Binding Site of the MvfR Protein. α-helices are marked in red, 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 *Trans*-cinnamaldehyde. A – amino acid, Å – ångström, Ile – isoleucine, kcal/mol – kilocalorie per mole, Leu – leucine, RMSD – root mean square deviation, Ser – serine, TCA – *trans*-cinnamaldehyde, Tyr – tyrosine, Val – valine.

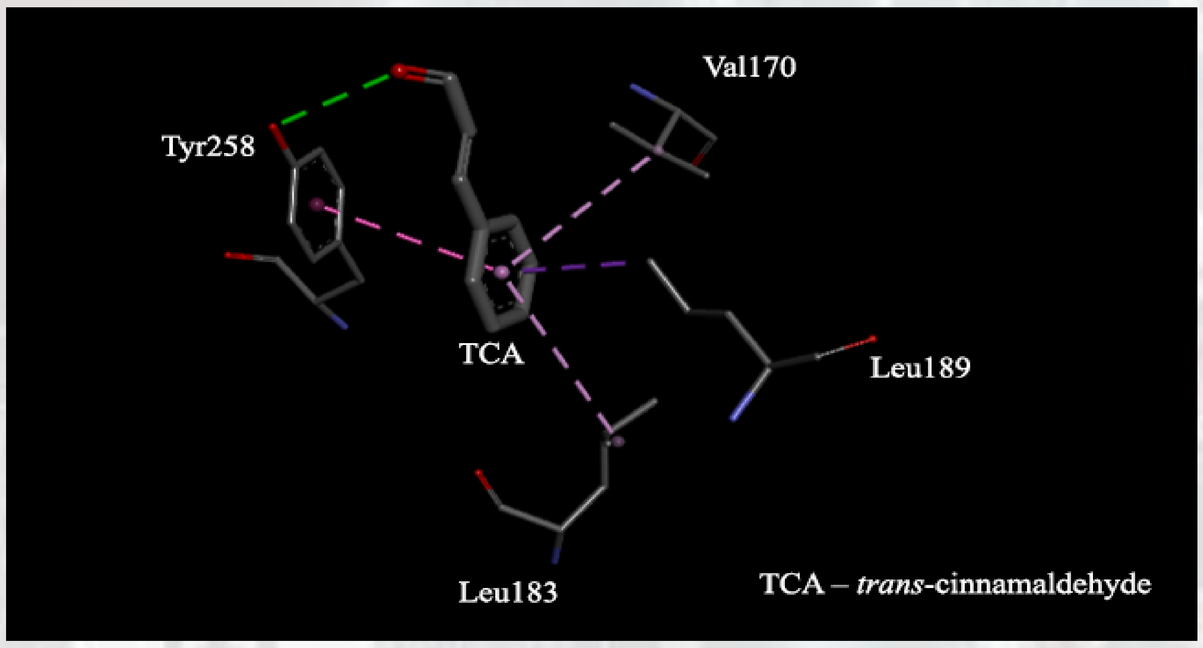

Figure 3: The Intermolecular Interactions between the *Trans*-cinnamaldehyde and the Amino Acids within the Binding Pocket of the MvfR Protein of *P. aeruginosa* in Model 1. The intermolecular interactions are shown by dashed lines and the colours differ depending on the type of interaction, conventional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

CONCLUSION

Trans-cinnamaldehyde could be a potential inhibitor of the MvfR protein, which is a key factor for virulence and quorum sensing of *P. aeruginosa*. The results suggest that the amino acid Ile236 of the MvfR protein may play an important role in the binding of small hydrophobic ligands to the binding pocket of the MvfR protein, which could influence the function and conformation of the MvfR protein. In vitro and in vivo tests need to be performed to confirm these findings.

REFERENCES

1 Francesca Prestinaci et al. Antimicrobial Resistance: A Global Multifaceted Phenomenon. Pathog Glob Health. 2015; 109 (7): 309–318. DOI: 10.1179/2047773215Y.0000000030.

2 Munawar Abbas et al. Antimicrobial Properties and Therapeutic Potential of Bioactive Compounds in Nigella sativa: A Review. Molecules. 2024; 29 (20): 1–34. DOI: 10.3390/molecules29204914.

3 Oleg Trott et al. AutoDock Vina: Improving the Speed and Accuracy of Docking with a New Scoring Function, Efficient Optimization and Multithreading. J Comput Chem. 2010 Jan; 31(2): 455–461. DOI: 10.1002/jcc.21334.

4 Tomoe Kitao et al. Molecular Insights into Function and Competitive Inhibition of Pseudomonas aeruginosa Multiple Virulence Factor Regulator. mBio. 2018 Jan; 16;9 (1): 1–13. DOI: 10.1128/mBio.02158-17.