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In Silico Docking Studies of Conventional and Non Conventional Antibiotics with Staphylococcus aureus

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Abstract : **In the present study a comparative insilico docking studies of Actagardine (non conventional) and Cefuroxime (conventional) with three toxins of Staphylococcus aureus (exfoliative toxins A, B and Panton-Valentine leukocidin) was carried out. These toxins are responsible for skin infections caused by this pathogen. Actagardine gave negative binding energy with all these three toxins of Staphylococcus aureus. Although the binding energies of Actagardine are less than that with Cefuroxime, due to the characteristic of antimicrobial peptides these results can be considered significant. Hence, further work can be done to develop Actagardine as a non conventional drug against Staphylococcus aureus.**

1. INTRODUCTION

In the present scenario, the emergence of drug resistant microorganisms is posing a great threat to the health of humans. We come in contact with many microorganisms here and there in our daily life. The microorganisms are developing resistance against the conventional antibiotics.

This is becoming a major problem in the treatment of diseases. This has lead to a necessity of developing alternative or non conventional drugs that can deal with this problem of drug resistance. These drugs need to be developed with the aim that the microorganisms should not be able to develop resistance against them easily. The antimicrobial peptides seem to be the most promising candidate for developing them as alternative drugs.

1.1. Antimicrobial peptide

Antimicrobial peptides are short peptides found in all classes of microorganisms from prokaryotes to eukaryotes. [1] Our body has a defence mechanism against the microorganisms that enter in the body, i.e., our immune system. Antimicrobial peptides are a part of the innate immune system of our body. [1-3] The microorganisms have less possibility of developing resistance against these antimicrobial peptides. Resistance development against antimicrobial peptides is a very energy consuming process for the microorganisms. [4] Hence, these can be treated as a potential candidate to be developed as non conventional antibiotics.

1.2. Cefuroxime

Cefuroxime is a broad spectrum antibiotic. It belongs to the class beta lactam. It belongs to the second generation cephalosporins. [5]

1.3. Staphylococcus aureus toxin

Staphylococcus aureus is a human pathogen which causes several problems in humans like superficial infections, scalded skin syndrome, endocarditis , etc. Two exfolative toxins A and B (ETA and ETB) are responsible for the scalded skin syndrome. PVL, an exotoxin, is a virulence factor for necrotizing disease. These three toxins of *Staphylococcus aureus* are used in the present study. [6]

2. METHODOLOGY

In the present study the three toxins of *Staphylococcus aureus* exfoliative toxin A (ETA), exfoliative toxin B (ETB) and Panton-Valentine leukocidin (PVL) were used for docking studies with second generation Cephalosporin, Cefuroxime, and an antimicrobial peptide Actagardine.

The PDB structures of ETA, ETB and PVL were downloaded from RCSB database [7,8]. The PDB ID of ETA, ETB and

PVL are 1DUA, 1DT2 and 1PVL respectively. The PDB structure of antimicrobial peptide Actagardine [9] (PDB ID 1AJ1 7) was downloaded from RCSB database. The structure of Cefuroxime (DrugBank Accesssion no **DB01112**) was downloaded from DrugBank [10,11].

These three toxins of *Staphylococcus aureus* i.e., ETA, ETB and PVL were docked with Cefuroxime and Actagardine respectively. Autodock 4.2 [12-17] was used for the docking studies. The PDB structures of all the toxins were checked for the presence of water molecules. The water molecules were removed from the toxin PDBs using Autodock. Polar hydrogens were added to these toxin structures. These structures were saved as the final PDB structures. These PDB structures were used for docking with Cefuroxime and Actagardine. Actagardine and Cefuroxime were fixed with two rotatable bonds. Then the grid file was generated and the docking was performed with 200 genetic algorithm runs. The results of all the six dockings were analyzed and interactions studied.

3. RESULTS

200 conformations of the docked structures were generated in the .dlg files of all these six dockings. The binding energies and the interactions of these conformations were studied. The negative binding energies with more number of hydrogen bonds were emphasized. The docked structures with no hydrogen bonds were not considered. The docked conformations were studied ranked by the energies from minimum energy to maximum energy. The binding energies and hydrogen bonds of docking interactions of the above mentioned three toxins of *Staphylococcus aureus* with Cefuroxime and Actagardine are listed in the Table 1 and Table 2 respectively.

Table 1: Docking interaction of *Staphylococcus aureus* toxins and Cefuroxime

S. No.	Toxins of *Staphylococcus aureus*	Binding energy (kcal/mol)	No. of hydrogen bonds	Residues of *Staphylococcus aureus* involved in hydrogen bonding
1	ETA	-5.23	2	Lys213 Trp14
2	ETB	-6.46	2	Lys 149 Leu193
3	PVL	-5.64	3	Gln246 Asn270 Arg271

Table 2: Docking interaction of *Staphylococcus aureus* toxins and Actagardine

S. No.	Toxins of *Staphylococcus aureus*	Binding energy (kcal/mol)	No. of hydrogen bonds	Residues of *Staphylococcus aureus* involved in hydrogen bonding
1	ETA	-3.22	1	Lys213
2	ETB	-3.13	2	Arg241 Lys246
3	PVL	-3.97	5	Lys295 Asn87 Arg156 Asp92 Asn158

The interactions of Cefuroxime with ETA, ETB and PVL are shown in Figure 1, Figure 2 and Figure 3 respectively. The interactions of ETA, ETB and PVL with Actagardine are shown in Figure 4, Figure 5 and Figure 6 respectively. In the figures the green dotted line inside the wireframe ball shows the presence of a hydrogen bond. The receptor residues in the figures are shown with sticks and the ligand structure is shown as surface.

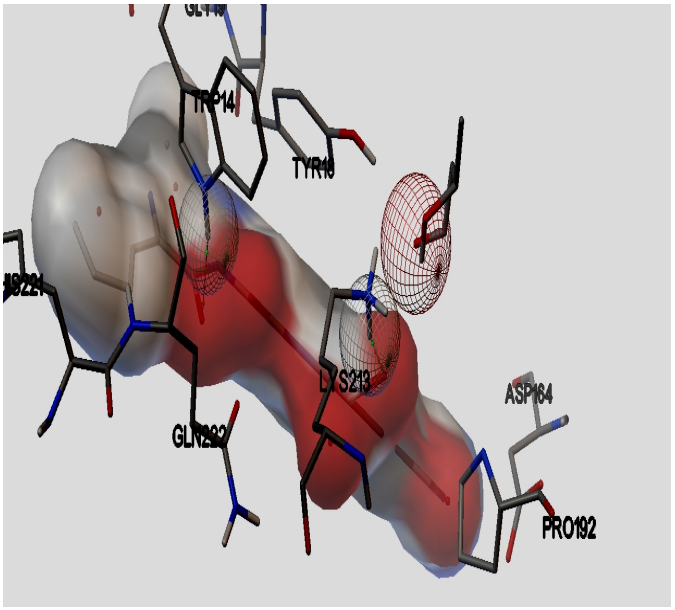

Figure 1: This figure shows the interaction between exfoliative A (ETA) of *Staphylococcus aureus* and Cefuroxime. Two hydrogen bonds formed between ETA and Cefuroxime are shown in the figure.

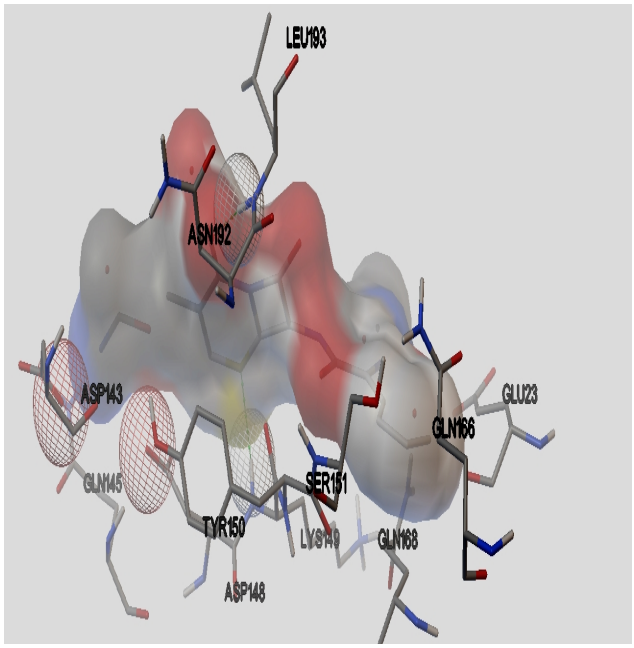

Figure 2: This figure shows the interaction between exfoliative B (ETB) of *Staphylococcus aureus* and Cefuroxime. Two hydrogen bonds formed between ETB and Cefuroxime are shown in the figure.

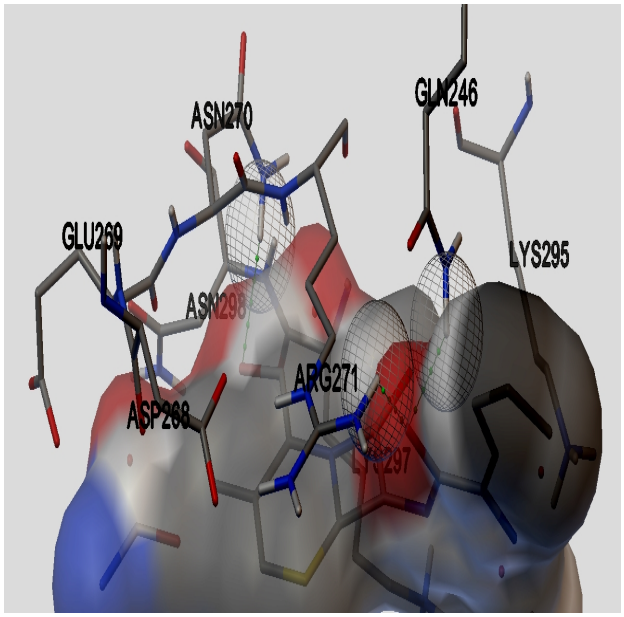

Figure 3: This figure shows the interaction between Panton-Valentine leukocidin (PVL) of *Staphylococcus aureus* and Cefuroxime. Three hydrogen bonds formed between PVL and Cefuroxime are shown in the figure.

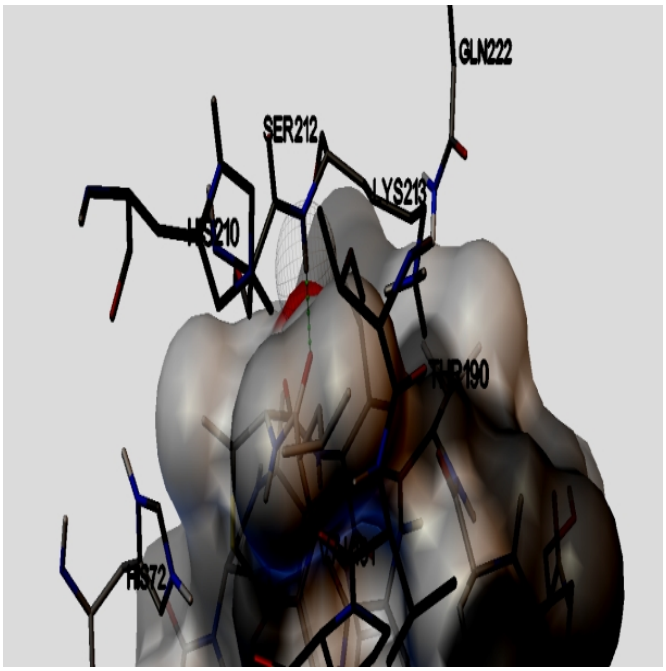

Figure 4: This figure shows the interaction between exfoliative A (ETA) of *Staphylococcus aureus* and Actagardine. One hydrogen bond formed between ETA and Actagardine is shown in the figure.

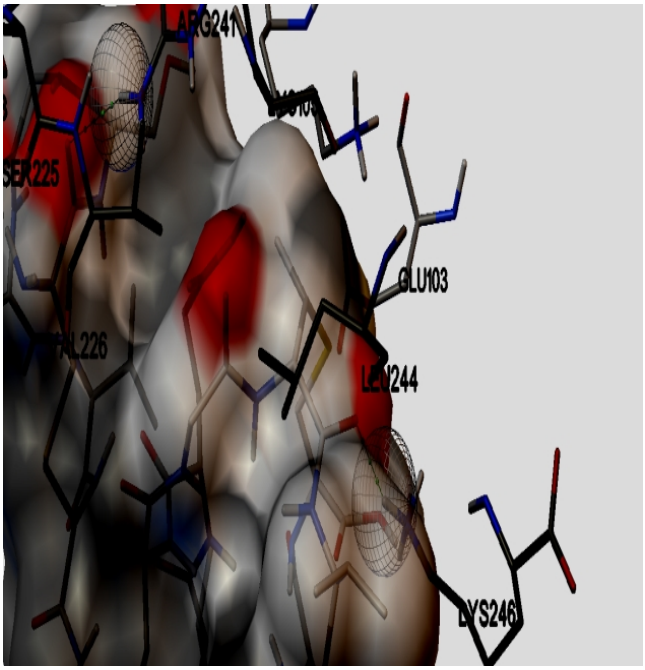

Figure 5: This figure shows the interaction between exfoliative B (ETB) of *Staphylococcus aureus* and Actagardine. Two hydrogen bonds formed between ETB and Actagardine are shown in the figure.

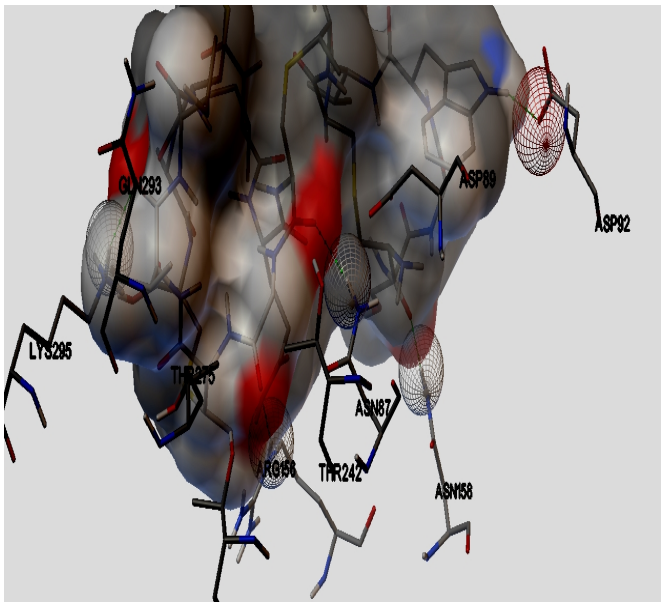

Figure 6: This figure shows the interaction between Panton-Valentine leukocidin (PVL) of *Staphylococcus aureus* and Actagardine. Five hydrogen bonds formed between PVL and Actagardine are shown in the figure.

4. DISCUSSION AND CONCLUSION

In the reported conformation of docking between Cefuroxime and ETA two hydrogen bonds are formed and the binding energy is -5.23 kcal/mol, whereas the reported conformation of docking between ETA and Actagardine forms one hydrogen bond and gives -3.22 kcal/mol binding energy. The reported conformation of docking between ETB and Cefuroxime gives a binding energy of -6.46 kcal/mol and forms two hydrogen bonds between them, and the reported conformation of docking between ETB and Actagardine results in two hydrogen bonds between them and a binding energy of -3.13 kcal/mol. The above reported conformation of docking between Cefuroxime and PVL gives a binding energy of -5.64 kcal/mol with three hydrogen bonds formed, whereas the reported conformation of docking between PVL and Actagardine gives a binding energy of -3.97 kcal/mol with five hydrogen bonds.

After analyzing the above mentioned docking results it is observed that when the three toxins of *Staphylococcus aureus*, i.e. ETA, ETB and PVL, are docked with the antimicrobial peptide Actagardine, some significant results are obtained. The hydrogen bonds are formed by the docking interaction of Actagardine with all these toxins. These dockings give the negative binding energies which show that these dockings are significant. There is a difference in the number of hydrogen bonds formed after docking the abovementioned three toxins of *Staphylococcus aureus* with Cefuroxime and Actagardine. The number of hydrogen bonds formed between ETA and Cefuroxime is more than that formed between ETA and Actagardine. The number of hydrogen bonds formed between ETB and Cefuroxime is the same as that formed between ETB and Actagardine. In case of docking interaction of PVL with Cefuroxime and Actagardine, the number of hydrogen bonds between PVL and Cefuroxime is less than that formed between PVL and Actagardine. The binding energy is more with Actagardine as compared to Cefuroxime for all these three toxins. But considering the characteristic of antimicrobial peptides, due to which the microorganisms cannot develop resistance easily against the antimicrobial peptides, these results are significant. This study is just a preliminary part for the development of Actagardine as a non conventional drug against the skin infections due to *Staphylococcus aureus.* Further work can be done to develop antimicrobial peptide as a drug against the *Staphylococcus aureus* infections.

5. REFERENCES

[1] Giuliani A., Pirri G., Nicoletto S. F. "Antimicrobial peptides: an overview of a promising class of therapeutics.", *Central European Journal of Biology*, 2007, 2(1) , pp. 1-33.

[2] Ahmad, A., Ahmad, E., Rabbani, G., Haque, S., Arshad, M., and Khan, R.H., "Identification and Design of Antimicrobial Peptides for Therapeutic Applications," *Current Protein and Peptide Science*, 2012, 13, pp. 211-223.

[3] Lai, Y. and Gallo, R. L., "AMPed Up immunity: how antimicrobial peptides have multiple roles in immune defense**,"** *Trends in Immunology*, 2009, Vol. 30, Issue 3, pp131–141.

[4] Baltzer, S. A. And Brown M.H., "Antimicrobial Peptides – Promising Alternatives to Conventional Antibiotics", *Journal of Molecular Microbiology and Biotechnology*, 2011, 20, pp. 228–235.

[5] Gaurav, K., Karmakar, S., Kundu, K., Kundu, S., "Design, Development and Synthesis of Novel Cephalosporin Group of Antibiotics", *Antibiotic Resistant Bacteria - A Continuous Challenge in the New Millennium*, InTech, 2012, pp. 487-503.

[6] Bien, J. ,Sokolova, O., and Bozko, P., "Characterization of Virulence Factors of Staphylococcus aureus: Novel Function of Known Virulence Factors That Are Implicated in Activation of Airway Epithelial Proinflammatory Response", *Journal of Pathogens*, 2011, Article ID 601905, 13 pages.

[7] Berman, H. M., Westbrook, J., Feng, Z., Gilliland, G., Bhat, T. N., Weissig, H., Shindyalov, I. N., and Bourne, P. E., "The Protein Data Bank", *Nucleic Acids Research*, 2000, Vol. 28, 1, pp.235-242.

[8] Rose, P. W., Bi, C., Bluhm, W. F., Christie, C. H., Dimitropoulos, D., Dutta, S., Green, R. K., Goodsell, D. S., Prlic, A., Quesada, M., Quinn, G. B., Ramos, A. B., Westbrook, J. D., Young, J., Zardecki, C., Berman, H. M., and Bourne, P. E., "The RCSB Protein Dta Bank: new resources for research and education", *Nucleic Acids Research*, 2013, Vol. 41, Database issue, pp. D475-D482.

[9] Zimmermann, N., and Jung, G., "The three-dimensional solution structure of the lantibiotic murein-biosynthesis-inhibitor actagardine determined by NMR", *Em. J. Biochem*, 1997, *246, pp*. 809-819 .

[10] Wishart, D. S., Knox, C., Guo, A. C., Shrivastava, S., Hassanali, M., Stothard, P., Chang, Z., and Woolsey, J., "DrugBank: a comprehensive resource for in silico drug discovery and exploration", *Nucleic Acids Research*, 2006, Vol. 34, Database issue, pp. D668–D672.

[11] Wishart, D. S., Knox, C., Guo, A. C., Cheng, D., Shrivastava, S., Tzur, D., Gautam, B., and Hassanali, M., "DrugBank: a knowledgebase for drugs, drug actions and drug targets", *Nucleic Acids Research*, 2008, Vol. 36, Database issue, pp. D901–D906.

[12] Sanner, M. F., "Python: A Programming Language for Software Integration and Development", *J. Mol. Graphics Mod*., 1999, Vol 17, February, pp. 57-61.

[13] Sanner, M.F., Spehner, J.-C., and Olson, A.J., "Reduced surface: an efficient way to compute molecular surfaces", *Biopolymers*, 1996, Vol. 38, (3), pp. 305-320.

[14] Bajaj, C, Park, S., Thane, A., "A Parallel Multi-PC Volume Rendering System, ICES and CS Technical Report", *University of Texas*, 2002.

[15] Sanner, M. F., "Python: A Programming Language for Software Integration and Development", *J. Mol. Graphics Mod.*, 1999, Vol 17, February, pp. 57-61.

[16] Bajaj, C, Pascucci, V., Schikore, D., "Fast IsoContouring for Improved Interactivity", *Proceedings of ACM Siggraph/IEEE Symposium on Volume Visualization, ACM Press*, San Francisco, CA, 1996, pp. 39 – 46.

[17] Sanner, M. F., Stoffler, D., and Olson, A. J., "ViPEr a Visual Programming Environment for Python", 10th International Python Conference, February 2002.