BioMedicalResearch 2015; 26 (4): S52-54 *ISSN 0970-938X*
www.biomedres.info

In silico approach of antibacterial compounds from mangrove - *Avicennia marina* through docking analysis

Sheela Devi A[a]*, Joseph J[a], Johanna Rajkumar[b]

[a]Assistant Professor, Department of Biotechnology, Karpaga Vinayaga College of Engineering and Technology, Chinna Kolambakkam, Tamilnadu, India
[b]Professor, Department of Biotechnology, Rajalakshmi Engineering College, Tamilnadu, India

Abstract

The term "*In - silico*" mean "any biological experiment on or in computer". This method is easy, relatively fast and used to predict pharmacology and/or toxicology hypothesis. *In - silico* software have been employed in the discovery and optimization of novel bioactive compounds with affinity to a particular target, the clarification of absorption, distribution, metabolism, excretion and toxicity properties (ADME/Tox) as well as physicochemical characterization. Urinary tract infection (UTI) is a condition in which the urinary tract is infected with a pathogen causing inflammation which is a widespread, difficult and rarely life threatening condition. *Avicennia marina* contains biologically active antibacterial, antiviral and antifungal compounds. Hence the antibacterial compounds of *A. marina* such as beta humulene, taraxasterol, alpha amyrin, venlafaxine, 3-(3-methoxy phenyl) propanoic acid and methyl 2-methylinden-3-on carboxylate were selected for this study. The docking was performed between ligands and virulent proteins of UTI pathogens, thus LIBDOCK score were analyzed, followed by Lipinski's rule of 5 were calculated. Drug like properties of these ligands were calculated by ADME calculations. Based on these results, out of 6 compounds 2 were confirmed as promising compounds against the particular pathogens. Therefore the present study play a guiding role to develop new inhibitors with better binding affinities towards the specific virulent protein of pathogens, followed by invention of novel drug to treat UTI.

Keywords: *Avicennia marina*, drug discovery, mangrove plant, molecular docking, urinary tract infection

Accepted July 07 2015

Introduction

Antimicrobial properties of medicinal plants are being increasingly reported from different parts of the world [1]. Plants are very significant to human, because they have several dynamic constituents which are precursor to synthesize many drug [2]. India has a rich flora that is widely distributed throughout the country. Herbal medicines are basis of treatment and cure variety of diseases. Plant based drugs were commonly used in India and China [3]. Mangrove plants and their products have been widely used in traditional medicine. These plants have various natural products with enormous pharmaceutical significance and also exhibiting antimicrobial, anti viral, anti larval and anti insecticidal activity [4]. Urinary tract is among the most common sites of bacterial infection in humans [5]. Urinary tract infections (UTIs) are among the most prevalent infectious diseases, with a extensive economic burden on society [6]. *Escherichia coli* is the commonest cause of all type of UTIs [7]. UTI was more widespread among females compared to males. *E. coli* was the most prevalent isolates (43.9%), followed by *Staphylococcus aureus* (21.6%), *Candida albicans* (16.4%), *Klebsiella pneumonia* (14.7%) and *Pseudomonase aeruginosa* (3.4%) [8]. Cytotoxic necrotizing factor 1 (CNF1) are toxins produced by uropathogenic *E.coli* (UPEC). CNF1 exerted a strong positive influence on expression of genes involved in innate immunity and signal transduction and a negative impact on metabolism and transport associated genes [9]. It is 115-kDa and expressed by 40% of UPEC isolates and up to 30% of diarrheal *E. coli* isolates [10]. Lipopolysaccharides are necessary for the activity of the protease (OmpT) [11]. OmpT is one of the virulent genes thought to be important in *E. coli* mediated UTI [12]. Alpha-toxin known as alpha-hemolysin (Hla), is the major cytotoxic agent released by *S. aureus* [13]. This toxin consists chiefly of beta-sheets (68%) with only about 10% alpha-helices, and it perform major function in host cell, that is development of pores in the cellular membrane, eventually causing cell death [14]. Staphylococcal protein A (SPA) is an im-

portant virulence factor which enables *S. aureus* to evade host immune responses [15].

Methodology

Selection of protein and preparation of its structure

Rho activating domain of *E. coli* CNF1 (PDB ID**:** 1HQ0), crystal structure of ompT from *E. coli* (PDB ID**:** 1I78), SPA (PDB ID: 2JWD) and alpha-hemolysin from *S. aureus* (PDB ID: 7AHL) were selected in our study. The protein structures were downloaded from protein data bank (http://www.rcsb.org/pdb/) establish ed by Brookhaven National Laboratories (BNL) in 1971. The proteins were prepared for docking by the removal of water molecules and heteroatom from the downloaded protein structures. Crystallographic disorders and unfilled valence atoms were corrected using alternate conformations and valence monitor options and were subjected to energy minimization by applying CHARMM (Chemistry at HARvard Macromolecular Mechanics) force fields. CHARMM is program for macromolecular dynamics; it can be used for energy minimization, normal modes and crystal optimizations and also X-Ray incorporates free energy methods for chemical and conformational free calculations.

Selection of ligand and preparation of its structure

Beta humulene (L1), taraxasterol (L2), alpha amyrin (L3), venlafaxine (L4), 3-(3-methoxy phenyl) propanoic acid (L5) and methyl 2-methylinden-3-on carboxylate (L6) present in *A.marina* were selected in our study. The structures of the ligands were downloaded from PubChem database. Hydrogen bonds were added and the energy was minimized using CHARMm force field.

Interaction studies of binding and calculation of ADME / TOX

The exact fit of the ligand to a receptor was studied using LibDock module in the Discovery Studio Accelrys® software corporation, San Diego, USA. The interactions of the drugs with the target were analyzed using the receptor-ligand interaction protocol of the software. The receptor cavities were explored and the active site residues selected were used for the interaction with the drugs. With the intention of find out the drug like properties for the ligands ADME calculation was performed by using Accord for Excel 6.1, an accelry's product.

Results and Discussion

According to the result of docking, out of 6 compounds, only 4 had docking with Rho activating domain of *E. coli* CNF1 and SPA; and 3 had docking with alpha-hemolysin and ompT. It was given in table 1. The compound venlafaxine had high Libdock score with Rho activating domain of *E. coli* CNF1, alpha hemolysin and ompT. Compound taraxasterol had high score with SPA. The docked pose of these 4 were shown in Fig 1 (A, B, C and D respectively). In Fig 1, the green lines denoted the hydrogen bonds. All the amino acid residues which involved in molecular interactions were shown in Blue color and the Ligands were shown in grey color. ADME prediction is the most crucial step in drug discovery. Drugs which satisfy these properties only will survive in the Phase 1 clinical trial [16]. Out of 6, most of the compounds satisfy ADME properties and Lipinski's rule of 5.

Protein - Pubchem ID	**Ligand**	**Libdock Score**	**Absolute energy**
IHQ0	L2	91.353	90.429
	L4	103.427	45.38
	L5	91.616	22.311
	L6	82.678	69.109
2JWD	L2	102.539	55.68
	L4	95.152	46.978
	L5	87.466	22.055
	L6	60.728	61.377
7AHL	L4	95.99	53.449
	L5	87.329	22.794
	L6	84.82	69.109
1I78	L4	91.473	36.826
	L5	80.729	22.314
	L6	67.441	69.109

Table 1. *Docking results of proteins with ligands*

Based on the *in silico* drug designing analysis through molecular docking results and ADME values, the two active principles such as venlafaxine and taraxasterol from *A.marina* were confirmed as a promising antibacterial compound against *E. coli* and *S. aureus*. Hence further analysis through *invitro* and *invivo* studies will prove the action of these compounds.

Conclusion

Thus we concluded that the compounds render antimicrobial action against UTI pathogens, hence it may be used as drug to treat UTI. The results of our study not only give a base for further research but also useful for drug development. Hence our study should therefore play a guiding role in the experimental design and development of antibacterial drug in the present and future to treat UTI and many ailments. Also our study provides us hope to overcome failures of drug resistance profiles. This study also means a natural alternative to antibiotics, which is an exhilarating and potentially extreme area of research.

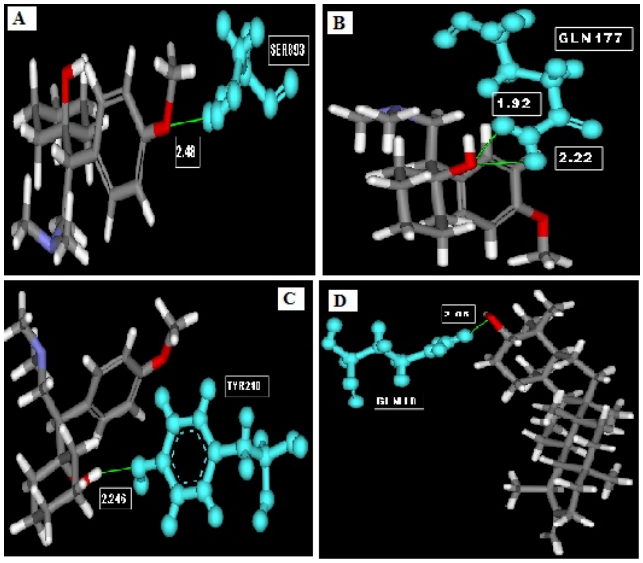

Figure 1. *The docked pose of ligands with proteins (A) Docked pose of L4 with 1HQ0, (B) Docked pose of L4 with 7AHL, (C) Docked pose of L4 with 1I78 and (D) Docked pose of L2 with 2JWD)*

Acknowledgment

We would like to thank Prof. Dr. Niranjali Devaraj, Department of Biochemistry, Chennai University and Prof. Dr. Ramalingam, Department of Biotechnology, Anna University for their valuable suggestions.

References

1. Rai PK, Mehta S, Gupta RK, Watal G. "A Novel Antimicrobial Agents Trichosanthes Diocia" *International Journal of Pharma and Bioscience 2010;* 1(3): 1-9.
2. Dhankhar Sandeep, Ruhil S. "Aegle marmelos Correa: A Potential Source of Phytomedicine" *Journal of Medicinal plant Research 2011;* 5(9): 1497–1507.
3. Duraipandiyan V, Ignacimuthu S. "Antibacterial and antifungal activity of *Cassia fistula* L. : an ethno medicinal plant" *J. Ethnopharmacol 2007;* 112(3): 590-594.
4. Premnathan M, Chandra K, Bajpai S.K, Kathiresan K. "A survey of some Indian marine plants for antiviral activity" *Botanica marina 1992;* 35(4): 321-324.
5. Kunin CM. "Urinary tract infections in females" *Clin Infect Dis1994;* 18(1):1-12.
6. Grabe M et al "Guidelines on Urological Infections." *European Association of Urology,* 2011.
7. Leslie C, Albert B, Sussman M. "Urinary Tract Infections" *Microbiology and microbial infections 1998;* 9(3): 1005-1009.
8. Al-Jiffri O *et al* "Urinary Tract Infection with *Esherichia coli* and Antibacterial activity of some plants extracts" *International Journal of Microbiological Research 2011;* 2(1): 01-07.
9. Tamako, Garcia and Christy A, "Ventura L. Cytotoxic Necrotizing Factor 1 and Hemolysin from Uropathogenic *Escherichia coli* Elicit Different Host Responses in the Murine Bladder" *Infection and Immunity 2013;* 81 (1): 99–109.
10. Hofman P *et al* "Rossi B. *Escherichia coli* cytotoxic necrotizing factor-1 (CNF-1) increases the adherence to epithelia and the oxidative burst of human polymorphonuclear leukocytes but decreases bacteria phagocytosis" *J. Leukoc. Biol 2000;* 68(4): 522–528.
11. Kramer RA *et al* "Lipopolysaccharide regions involved in the activation of *Escherichia coli* outer membrane protease OmpT" *Eur. J. Biochem 2002;* 269(6): 1746– 1752.
12. Carl F. Marrs *et al* "Variations in 10 putative uropathogen virulence genes among urinary, faecal and per-urethral *E. coli* " *J. Med. Microbiology 2002;* 51(2):138-142.
13. Bhakdi S, Tranum-Jensen. "□-toxin of *Staphylococcus* aureus" *Microbiol Rev 1991;* 55(4): 733–51.
14. Bubeck Wardenburg J, Schneewind O. "Vaccine protection against *Staphylococcus aureus* pneumonia" *J. Exp Med 2008;* 205(2): 287–94.
15. Antonina A et al, "Prevalence of *Staphylococcus aureus* protein A (spa) mutants in the community and hospitals in Oxfordshire" *BMC Microbiology 2014;* 14(63): 1-11.
16. Lipinski CA, Lombardo F, Dominy Bw, Feeney PJ. "Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings" *Adv Drug Deliv Rev2001;* 46: 3-25.

Correspondence to:

A. Sheela Devi
Department of Biotechnology
Karpaga vinayaga college of engineering and technology,
Chinna Kolambakkam, Tamilnadu
India