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Research Article

MOLECULAR DOCKING STUDIES OF PLANT DERIVED COMPOUNDS

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ABSTRACT

Molecular docking was carried out against two target proteins which are helpful for MRSA infection with the help of accelrys discovery studio to understand the applicability of the method to differentiate between the active and inactive compounds. Molecular docking of thirty two structurally diverse inhibitors were carried out and it was observed that though some false positives were also obtained; considering the limitations of the available docking programs, the results were promising. The high molecular weight compounds with heterocyclic rings showed very low binding energy, but did not comply with Lipinski's rule. The active constituents that were docked with the protein are Baicalein, Biochanin, Carnosol, Genistein, Orobol, Resveratrol, Rhein, Gallic acid, Pyrithione, Resveratrol and Linozolid .The compound Orobol was found to interact more towards the target protein like showing highest Dock score.

Keyword: MRSA Infection, Staphylococcus aureus, Accelrys Discovery, Orobol.

INTRODUCTION

MRSA

MRSA stands for methicillin-resistant *Staphylococcus aureus* (*S. aureus*) bacteria. This organism is known for causing skin infections in addition to many other types of infections. There are other designations in the scientific literature for these bacteria according to where the bacteria are acquired by patients, such as community-acquired MRSA (CA-MRSA or CMRSA), hospital-acquired or health-care-acquired MRSA (HA-MRSA or HMRSA), or epidemic MRSA (EMRSA).

Types of MRSA infections

Furuncles, Carbuncles, Impetigo, Cellulitis, Meningitis, Osteomyelitis, Endocarditis Toxic Shock Syndrome, Mastitis.

Staphylococcus Aureus

Staphylococcus aureus is a gram-positive cocci, catalase and coagulase positive bacterium. *Staphylococcus aureus* cause disease through the production of toxin or through direct invasion and destruction of tissue. Infections caused by S. aureus remain a significant cause of mortality and morbidity in tropical countries. The principal site of staphylococcal colonization is the anterior nares. 20 to 40% of adults remain colonized for months or even years. Increased nasal colonization rates have been noted in insulin dependent diabetes, individuals on haemodialysis, those on ambulatory peritoneal dialysis, intravenous drug users and patients receiving routine allergy injections. It has also been suggested that patients with symptomatic human immunodeficiency virus infection have an increased colonization risks.

Clinical Presentation

The range of disease caused by CA-MRSA is similar to that caused by CA-methicillin sensitive *Staphylococcus aureus* (MSSA). The most common lesions are abscesses and cellulitis. Frequently, abscesses are accompanied with an area of central necrosis. Furuncles (boils) are also common, particularly in the context of a MRSA outbreak. Frequently MRSA infections are reported by patients to be ―spider bites. This is not because a spider bite has actually occurred, but because CA-MRSA lesions often have a similar appearance to a spider bite—a raised red tender lesion that may progress to develop a necrotic center. Fever, leukocytosis, and systemic signs of inflammation are often absent. Less commonly—but not infrequently—CA-MRSA presents as: impetigo, folliculitis, deep-seated abscesses, pyomyositis, osteomyelitis, necrotizing fasciitis, staphylococcal toxic-shock syndrome, pneumonia, and sepsis. Serious systemic infections are more common among persons with a history of injection drug use, diabetes, or other immuno compromising conditions.

CURRENT DRUG

Penicillin Binding Protein 2A

The multiple antibiotic resistances of methicillin-resistant strains of Staphylococcus aureus (MRSA) has become a major clinical problem worldwide. The key determinant of the broad-spectrum beta-lactam resistance in MRSA strains is the penicillin-binding protein 2a (PBP2a). Because of its low affinity for beta-lactams, PBP2a provides transpeptidase activity to allow cell wall synthesis at beta-lactam concentrations that inhibit the beta-lactam-sensitive PBPs normally produced by S. aureus. The crystal structure of a soluble derivative of PBP2a has been determined to 1.8 A resolution and provides the highest resolution structure for a high molecular mass PBP.

Dehydrosqualene Synthase Y129A

Dehydrosqualene synthase of Staphylococcus aureus is involved in the synthesis of golden carotenoid pigment staphyloxanthin. This pigment of S. aureus provides the antioxidant property to this bacterium to survive inside the host cell.

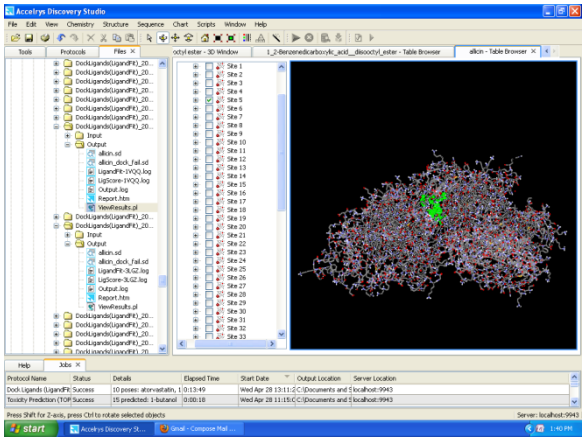
MATERIALS AND METHODS

1. Weight 10-50 mg plant samples in eppendorf tubes. Keep cold!! Ice bath or cold room. Sample weight should not differ between samples (9-11 mg is fine). If large differences, the extraction volume should vary: e.g. sample weight 20mg, 1ml extraction medium, sample weight 10mg, 0,5ml extraction medium.
2. Add 1 ml of chloroform: methanol:H2O (20:60:20) mixture including internal standards + mixer beads. Shake 3 min in mixer (30 Hz).
3. Centrifuge in eppendorf centrifuge, 10 min, 14 000 rpm. Take out mixer beads before centrifugation.
4. Take out 200 µl of supernatant (volume depends on amount and type of plant material) and add to GC/MS vial (or LC/MS vial if samples will be analysed by LC/MS). Dry in speed-vac concentrator.
5. Run the sample in GC equipment.
6. Derivatization and GC/MS analysis
7. PDB : *The Protein Data Bank (PDB) 3-D structural data of large biological molecules, such as proteins and nucleic acids*
8. *Pub Chem:* PubChem was a database of chemical molecules. To identify the web user.
9. Accelrys Discovery Studio: Accelrys software for chemical research, especially in the areas of drug discovery and material. To docking the proteins and various ligands

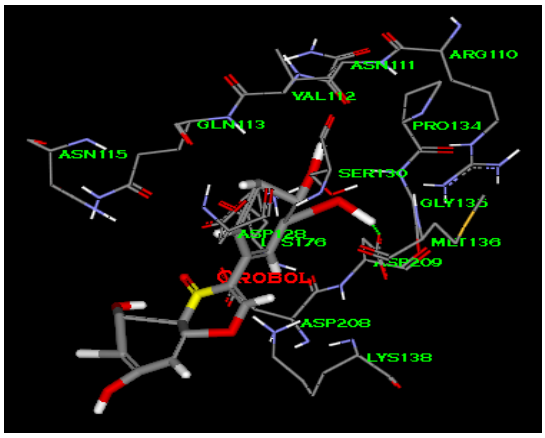
10. ADMET: The ADMET Descriptors Protocol was selected and to identified result.

11. TOPKAT: The TOPKAT protocol was selected and to identified result

RESULTS AND DISCUSSION

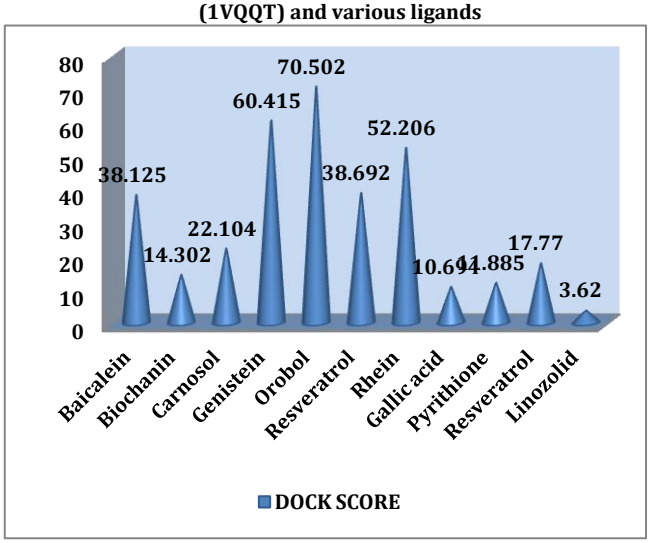


Rigid docking- Docked pose 5 of protein



Orobol

(1VQQT) and various ligands



Graphical representations of compounds with respect to their dock score

The molecular docking investigation of the selected plant compounds were performed against two target proteins which are helpful for MRSA infection. The selected molecular drug targets like PBP2a and structure of dehydrosqualene synthase Y129A from *S. aureus* with compounds. This study was highly monitored to screen the compounds based on Dock score (Based on Binding affinities) and Drug likeness scores which includes ADMET and Topkat.The ADMET analysis and the toxicity prediction helped in the identification of the more suitable inhibitor.

The dock score of the compounds were observed out of which Orobol had the best score (70.502) and satisfactory physiochemical parameters. The compound Carnosol did not have a very satisfactory dock score (22.104) but it qualified all the important criterions for being a good drug. A good drug score & drug likeness score are the two properties that are important for becoming a successful drug.

The docking scores of Biochanin (14.302) with PBP2A and Pyrithione (11.885) and reserveratrol (17.77) with dehydrosqualene synthase Y129A from *S. aureus* possess quite satisfactory docking scores but they show slight toxicity and hence cannot be used as a drug.

CONCLUSION

The ADMET properties show that only Gallic Acid and Carnosol of all the compounds are non-toxic. All the others show slight toxicity and thus cannot be considered for use as a drug. Though Carnosol shows a non-toxic nature, it's docking score is not up to the level of satisfaction.

Thus Gallic Acid can be treated as a potential inhibitor of PBP2a, and can be considered as a good drug for MRSA infections and suggested for further clinical testing. It is clear that Gallic acid satisfied almost all properties like drug likeness value, drug score, lower logP values and Lipinski's rule of five. The active constituents that were docked with the protein are in that Orobol was found to have a very satisfactory dock score.

Baicalein, Biochanin, Carnosol, Genistein, Orobol, Resveratrol, Rhein, Gallic acid, Pyrithione, Resveratrol and Linozolid .The compound Orobol was found to interact more towards the target protein like showing highest Dock score.

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