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Molecular docking of medicinal compound Lupeol with autolysin and potential drug target of UTI

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ABSTRACT

Staphylococcus aureus has gained much attention in the last few decades as it is a major cause of the Urinary Tract Infection in Diabetic patients. Autolysins are bactereolytic enzymes that lysis cell wall peptidoglycan of the bacteria, which involved in cell division, cell growth etc. Present study has been carried out to predict the anti-bacterial activity of the compound Lupeol from Elephantopus scaber by using docking studies. Molecular docking is routinely used for understanding the drug-receptor interactions in modern drug design. Autolysin and the Lupeol were docked using Discovery studio software and calculated energy value, hydrogen bond interactions and libdock score. Results indicated that this compound can inhibit the activity of autolysin by forming a strong interaction with the active site residues. Further studies are needed to illustrate its activity under in- vitro conditions.

Keywords: *Staphylococcus aureus*, peptidoglycan, Lupeol, docking and Autolysin.

INTRODUCTION

Throughout human history, natural products have been used as remedies to cure or treat illness. In some parts of the world, this tradition has been surpassed by the amazing technological and pharmaceutical developments that have emerged with the promise of easier healing. Humans continue to be affected by several diseases, mainly due to native forces such as drug-resistant microbes and insects [1] Diabetes Mellitus (DM) is the most prevalent chronic disease in the world affecting nearly 25% of the population. It is characterized by the elevation of blood sugar level that in turn leads to the excretion of glucose through urine. A higher glucose concentration

in urine serves as a culture media for the pathogenic microorganisms as well. The risk of developing infection in DM patients is higher [2,3] and Urinary Tract (UT) is the most common site for infection[4]. *Staphylococcus aureus* (*S.aureus*) is one such organism which multiplies in the UT of DM patients. Drug resistance is one of the most serious global threats to the treatment of infectious diseases [5,6].Among several drug-resistant bacteria, β-lactamase production is the most important mechanism of resistance to penicillin and cephalosporins [7]. Methicillin Resistant *Staphylococcus aureus* (MRSA) has gained much attention in the last decade, as the MRSA is a major cause of hospital acquired (nosocomial) infections. B-lactam antibiotics are the preferred drugs against *S. aureus* infections, although, *S. aureus* has developed resistance to the β-lactam antibiotics due to the production of chromosomal or plasmid mediated β-lactamases or by producing Penicillin Binding Proteins (PBPs)[8] .Treatment of infections caused by these resistant bacteria has become very difficult, since they are resistant to many antibiotics. Thereofre, concerted efforts are to be made to identify antimicrobial materials from natural products and traditional medicines. Among the several plants screened, *Elephantopus scaber (E.scaber)*, a member of the family Asteraceae known for its medicinal properties was also reported to posses antimicrobial activity [9]. *Elephantopus scaber* is a small perennial herb found in tropical conditions, almost throughout the world and Lupeol was also one of the chemical compounds that can be determined from *Elephantopus scaber* exhibiting antimicrobial activity[1,10] . But the mechanism of the anti-bacterial effect of the compound was not clearly understood. To overcome this we tried in nonconventional methods of drug designing by the use of Bioinformatics approaches. Autolysins are bacteriolytic enzymes that digest cell wall peptidoglycan of the bacteria that produce them[11] although potentially lethal; autolysins appear to be universal among bacteria that possess peptidoglycan. Peptidoglycan the substrate of autolysins is a polymer of amylo sugars cross linked by short peptides which forms a covalent matrix that surrounds the cytoplasmic membrane and constitutes the major skeletol component of the cell wall. It is a member of the Metalloprotease Gly-Gly endopeptidase family with PFAM ID PF01551.

The possibility that autolysins are involved in selective removal of peptidoglycan has led to proposals that they are involved in numerous cellular processes including cell growth, cell-wall turnover, peptidoglycan maturation, cell division, separation, motility, chemotaxis, genetic competence, protein secretion, differentiation and pathogenicity [12,13]. Lysis is caused by the presence in the microorganisms of autolytic enzymes (autolysins) which specifically hydrolyse mucopeptide polymers in the bacterial cell wall. The attack occurs, at least in some species, in a very restricted area around the point at which the bacteria will divide [14].

Present work has been carried out as an attempt to predict the mechanism of anti microbial activity of Lupeol against Autolysin enzyme.

EXPERIMENTAL SECTION

The coordinates of Autolysin enzyme(1.5A° resolution, Rcryst=0.222) recently determined by the group[5] was used as a targeted basis to conduct docking studies which was downloaded from Brookheaven protein databank with PDB code 2B0P.Lupeol was selected as ligand molecule, downloaded from Pubchem database. Docking studies were performed using Libdock of Discovery studio software.

Docking analysis

The protein atoms were then typed using the CharMm force field.Ligand conformations were randomly generated and energy minimized using CharMm force field. For protein, the binding site can be found using as volume of 9A° distance for the site opening based on binding site module. Then, Libdock procedure was applied to position conformation of the ligand correctly in the active site. The procedure was performed using libdock module. The binding results could be displayed by scoring ligand poses and several scoring functions can be used for measuring the goodness of a docking study to find a top ranked pose for ligands. In this study, absolute energy, hydrogen bond interactions and Libdock score can be obtained and the latter was used as final criteria.

RESULTS

The structure of Lupeol downloaded from Pubchem and visualized in discovery studio, which was given in **Fig.1** In this representation of the compounds red color indicated the Oxygen atom, grey represented Carbon and white denoted Hydrogen atoms. The secondary structure of the receptor Autolysin showed in **Fig.2**.Structure of docked complex of Lupeol –Autolysin has been shown in **Fig.3**. Lupeol in yellow stick model. Green mesh represented the binding site. A close view of interactions has been depicted in **Fig.4**; whereas green dotted lines represented the hydrogen bonds. The details of Libdock score, energy value and hydrogen bond length were tabulated in Table.1.

Fig.1. Structure of Lupeol

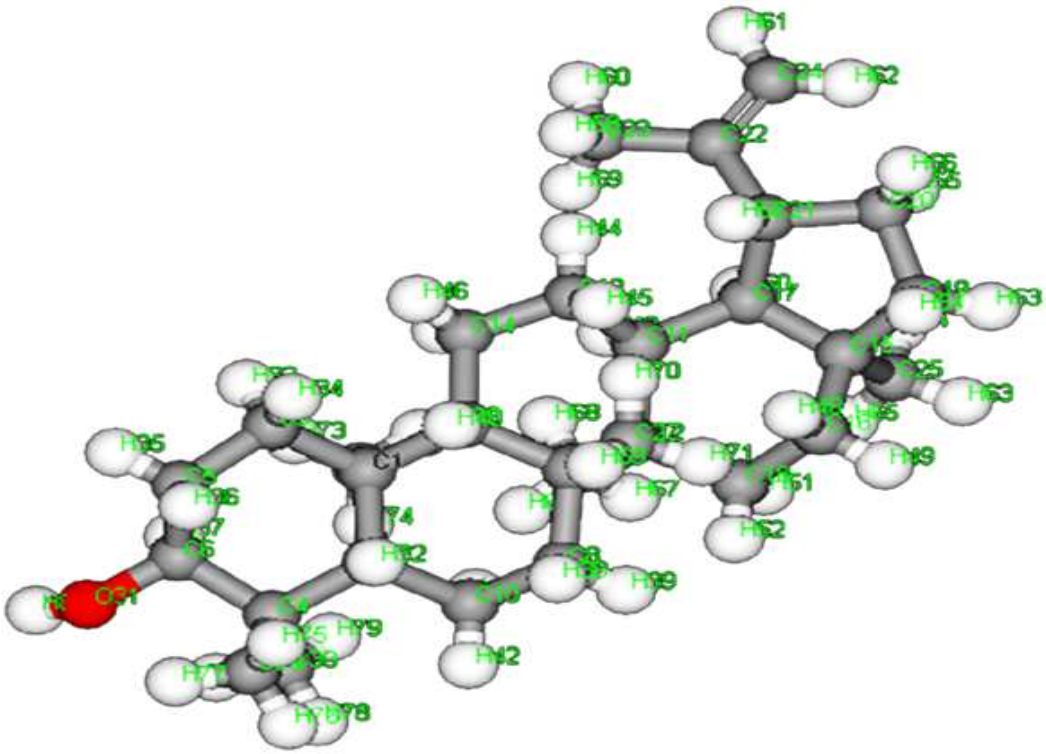

Fig.2. Secondary structure of the receptor

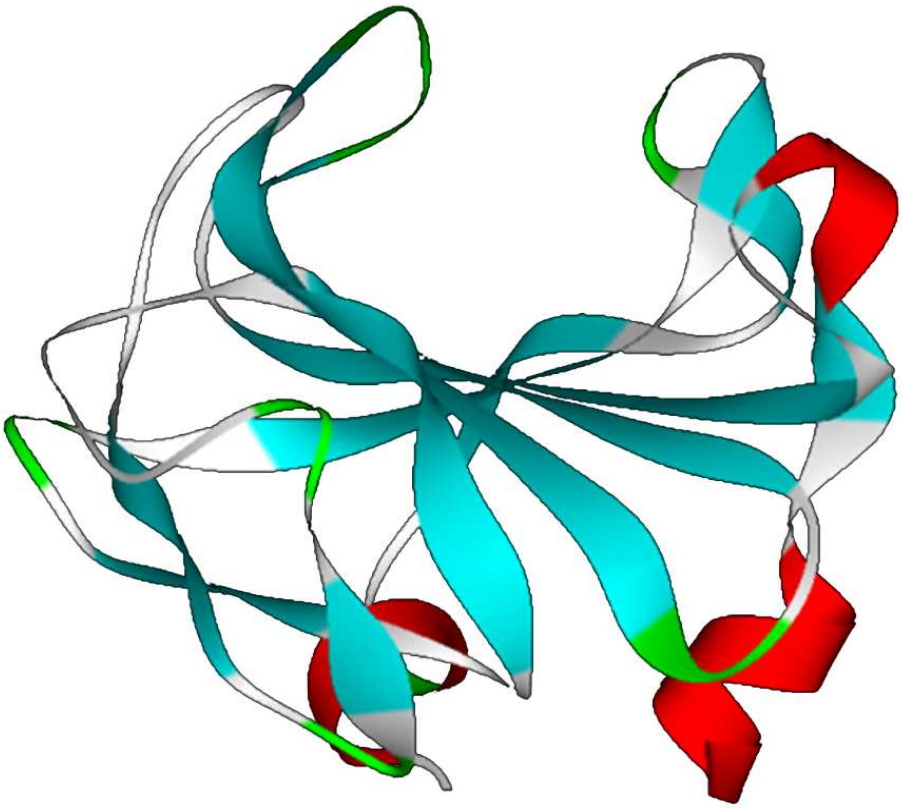

Fig.3.Lupeol exactly bound with the active site of the receptor. Active residues Gly 240,Gly241 and Gly242 (space-fill diagram),Lupeol in yellow stick model and green mesh represents the active site.

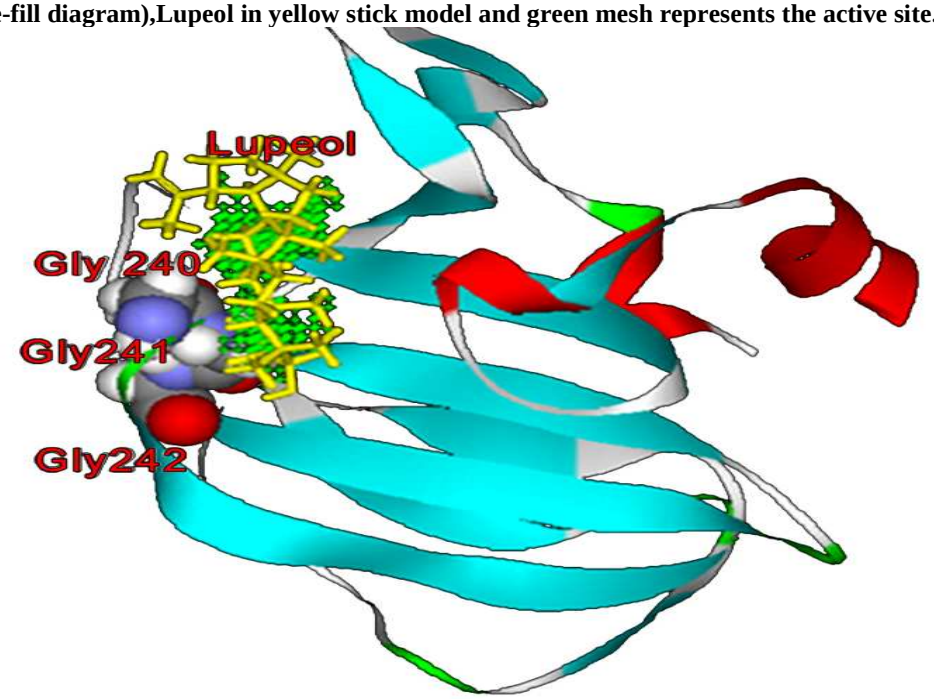

Fig.4.A close view of hydrogen bond interaction between Lupeol and the receptor

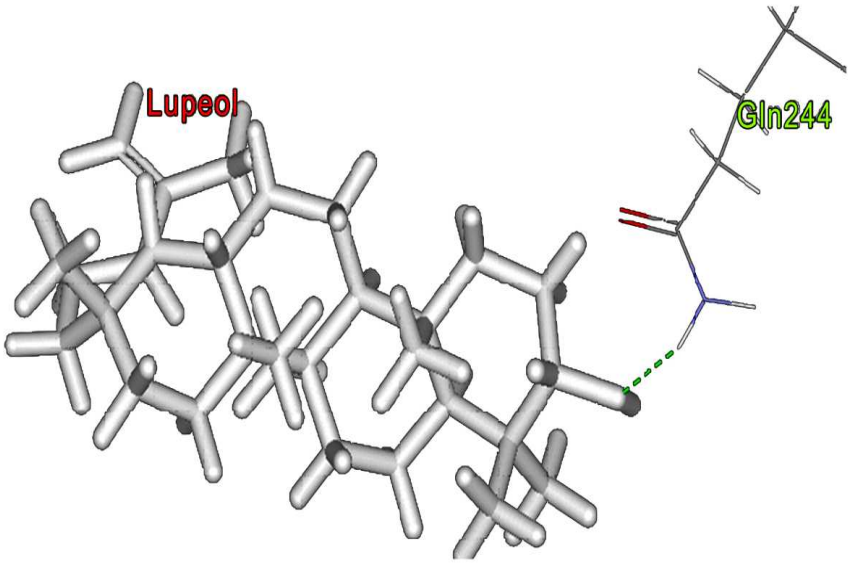

Table 1 .Docking results of Lupeol with Autolysin

Compound	No. of h bonds	Residue/Atom	Atom in compound	Bond length	Libdock score	Energy value
Lupeol	1	Gln 244/HE22	O31	1.9505	76.55	92.765

DISCUSSION

Molecular docking continues to holds great promise in the field of Computer based drug design which screens small molecules by orienting and scoring them in binding site of a protein. The overall structure obtained by docking Lupeol to Autolysin is given in Fig. 3, where the Autolysin is in ribbon drawing, Lupeol in stick drawing, and the green mesh represents the binding pocket for the receptor. From the **Fig.3**, it was clear that Lupeol was bound at the active site of the receptor. The active site loop of the target Autolysin containing the 3 consecutive Glycine residues at positions 240,241,242 [15] does not possess any other functional group other than the amino and the carbonyl group of the peptide bond and they are not involved in the formation of the secondary structures hence these groups are free to have strong atomic interactions with Lupeol with energy value 92.765. Previous studies showed that Terpenoid, isolated from same plant also possessed inhibiting activity towards Autolysin and thus act as an antibacterial agent [15].

As a result of docking studies, different conformations were generated for Lupeol. But only for the top ranked docked complex the scores were copied from the table browser view of Discovery studio for binding affinity analysis. To correlate the biological activity of receptor and the site-directed docking of Lupeol,we scored our model using Libdock score (which is PLP like score (Steric and H-bonding intermolecular functions), Higher PLP scores indicate stronger receptor-ligand binding affinity) [16,17,18].It is reported that [19] medicinal compounds like

Kaempterol,Quercetin,Luteolin and Andrographolide were inhibited Phosphoinositide 3kinase based on its Dock score, which were 65.058,71.407,69.14 and 62.735 respectively. Here through Insilico approach it was predicted that Lupeol also shown to inhibit Autolysin receptor as it had good Libdock score as 76.55 which was given in Table.1.

A close view of the binding interactions of autolysin with Lupeol was shown in Fig4. Ligand was white stick drawing and green dotted line represented the hydrogen bond. Hydrogen bond interaction also makes important contributions to the interactions between the ligand and the receptor [19]. Here a maximum of one hydrogen bond formed between autolysin and Lupeol. Thus the concept of protein-ligand interaction help in analyzing the binding properties of the receptor autolysin with its inhibitors.

CONCLUSION

The protein-ligand interaction plays a significant role in structural based drug designing. Molecular docking study was used to clarify the binding mode of the medicinal compound Lupeol. Taken together; our docking results show that there is a positive correlation between the dock scores and the inhibition of autolysin receptor. Thus, docking studies could be used as an initial screen for identifying new antagonist molecules.

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