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IDENTIFICATION OF POTENTIAL INHIBITOR AGAINST EXFOLIATIVE TOXIN A ASSOCIATED WITH *STAPHYLOCOCCUS AUREUS* INFECTION - A MOLECULAR DOCKING APPROACH

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ABSTRACT: *Staphylococcus aureus* is a frequent colonizer of the human body as well as a serious human pathogen. It can cope with stress factors and acquire resistance to antibiotics, thus rendering treatment difficult. Discovering new treatments for this disease is urgently required, especially in view of the emergence of multiple drug resistant organisms and to reduce the total duration of current treatments. Exfoliative toxin A (ETA), produced by *Staphylococcus aureus* causes scalded skin syndrome which is characterized by the separation of layers of skin. It affects newborns and adults primarily. Hence, therapies for Staphylococcal scalded skin syndrome (SSSS) are critically needed. Seeking a more effective compound for the treatment has been one of the great interests. In the present study, compounds from different plant extracts are permissible to interact with ETA using Schrodinger. The best effective compound gymnemic triacetate was selected from the list of different compounds based on its docking score and binding energy. The result showed that the herbal compound gymnemic triacetate possesses anti-bacterial activity by blocking exfoliative toxin A.

INTRODUCTION: *Staphylococcus aureus* (M. R. S. A) is a well know disease-causing bacterium, and disease management has become a harmful subject worldwide [1]. The pathogen city of the bacteria contains skin and soft tissue infections (SSTI), bone, joint and implant infections, pneumonia, septicemia and various toxicoses such as toxic shock syndrome, scalded skin syndrome, Bloodstream infections, osteomyelitis, septic arthritis and device related infections, necrotizing fasciitis and abscesses [2]. The human pathogen *S. aureus* exudes a number of biologically related toxins. Among them, the exfoliative toxins (ETs), [1] serotypes A (ETA) and B (ETB), causes staphylococcal scalded skin syndrome (SSSS). SSSS is differentiated by the exact division of intraepidermal layers of the skin at the desmosomes.

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The disease frequently affects newborns and can exfoliate 50% or more of the skin. Exfoliative toxin play as a serine protease, which targets Dsg-1 (desmoglein-1), formed only in the skin. The role of Dsg-1 is to continue the keratinocyte cell-cell

adhesion. Cleavage of Dsg-1 would direct to partition of skin keratinocytes, a result that would form the kind of division of layers of epidermal tissue seen in scalded skin syndrome and bullous impetigo. Natural products have traditionally and constantly been considered for hopeful new leads in pharmaceutical development [3]. The active substances present in lots of medicinal plants might be used as a beneficial substitute for staphylococcal infection [4]. A computer-aided method is an initial approach to screening new potential agents, and a discipline is a rising approach as it reduces lots of complexity of the drug discovery procedure. The selection of lead molecules with good pharmacological properties and drug-likeness is a too long process in the drug development process. *In-silico* molecular docking in one of the most potent method to find out new ligand for proteins of known structure and thus play main role in structure based drug design. Researchers frequently applied docking computer programs to discover the binding affinity for molecules that fit a binding site on the protein. In the present study, we mainly focused on identifying the potential herbal inhibitor for staphylococcal target exfoliative toxin using a molecular docking approach. The data obtained from *in silico* studies were later used for *in-vitro* studies. *Gymnemic diacetate*, *Gymnemic triacetate* was isolated from the leaf of *Gymnema sylvestre*, terpenoid, lupeol , friedelin from *Elephantopus scaber*, polysaccharide from *Tinospora cordifolia*, costunoloide, eremanthin from *Costus speciosus*, and catechin isolated from *Cassia fistula*, gallic acid and octyl gallate from *Terminalia bellirica*, were are some of the phytotherapeutic agents isolated in our lab and used for present study **Table 1**.

TABLE 1: NAME OF THE COMPOUNDS AND PLANT SOURCES

S. no.	Plant Name	Compounds Name
1	*Gymnema sylvestre*	Gymnemicdiacetate, Gymnemic triacetate
2	*Elephantopus scaber*	Terpenoid, Lupeol, Friedelin
3	*Tinospora cordifolia*	Polysaccharide
4	*Costus speciosus*	Costunoloide, Eremanthin
5	*Cassia fistula*	Catechin
6	*Terminalia bellirica*	Gallic acid , Octyl gallate

MATERIALS AND METHODS:

Ligand Preparation: The 11 natural compounds which were isolated in our lab from different medicinal plants were selected for the present study. Checmsketch version 11.01 (http:// www.acdlabs.com) was used to draw the structure of the molecules. Ligprep module in Schrödinger was helped to assign the correct bond order of the compounds. All the structures were converted to mae format (Maestro, Schrodinger, Inc.) and optimized by way of the Optimized Potentials for Liquid Simulations (OPLS 2005) force field with a default setting [5].

Protein Preparation: 3D structure of exfoliative toxin (PDB code: 1AG) was downloaded from PDB database. Before doing the docking analysis, the target protein was prepared with help of protein preparation wizard in Maestro 9.1 [6]. The protein preparation process contains two steps. In the first step side chains were neutralized neither near the binding site nor participate in salt bridge formation. In the second step, H was added, water molecules were removed and the structure was minimized till the average root mean square deviation of the non-hydrogen atoms achieved 0.3 A °.

Glide Docking and Scoring Function: Glide calculations were performed with Impact version v18007 (Schrodinger, Inc.) [7-9]. This is a grid-based docking and its form energetically favorable interaction between the ligand and receptor molecules 2007. It suggests the performance of test calculations with diverse scaling factors like van der Waal radii of the receptor and ligand atom, as steric repulsive contact could be exaggerated, leading to refusal of the right binding form of active compounds. After confirming that the proteins and ligands were in the right form for docking studies, the Grid was formed using the grid-receptor generation option. To reduce the possibility for the non-polar part of the receptor, we scaled van der Waal radii of receptor atoms by 1.00 A ° with a partial charge cutoff of 0.25. The compounds were docked in the binding site by the Glide 'standard precision' (SP) and Glide 'extra precision' (XP) mode [9, 10.]

Glide creates confirmation within and goes by these through a sequence of filters. The first place the ligand center at a variety of grid positions of a 1 A ° grid and turns it approximately the three Euler angles. In this stage, simple score values and geometrical filters weed out doubtful binding modes.

The next filter phase engages a grid-based force field assessment and modification of docking results with torsional and rigid body actions of the ligand. The OPLS-2005 force field was used for this purpose. A little number of existing docking solutions can then be subjected to a Monte Carlo procedure to try and reduce the energy score. The final energy evaluation is done with glide score, and a single best pose is generated as the output for a particular ligand.

Gscore = a * vdW + b* Coul+ Lipo + Hbond +Metal +BuryP + RotB+ Site

Where, vdW is van der Waal energy, Coul is Coulomb energy, Lipo is lipophilic contact term, HBond is hydrogen- bonding term, Metal is a metal-binding term, BuryP is a penalty for buried polar groups, RotB is a penalty for freezing rotatable bonds, Site is polar interactions at the active site, and the coefficients of vdW and Coul are: a = 0.065, b = 0.130.

Binding Energy Calculation: The binding calculations are more perfect than the docking studies [11], Prime MM/GBSA module was used to calculate the binding energy of the complex. In the presence of partial charges, the calculation was carried out. The following equation was used to calculate the binding energy

DGbind = DE+ DGsolv + DGSA

Where, DE= Ecomplex _ Eprotein _ Eligand; (Ecomplex, Eprotein, and Eligand are the minimized energies of the protein–inhibitor complex, protein, and inhibitor, respectively. DGsolv is the generalized born electrostatic solvation energy of the complex. DGSA is a non-polar contribution to the solvation energy due to the surface area) Prime uses a surface generalized born model employing a Gaussian surface instead of a vdW surface for better representation of the solvent-accessible surface area [12, 13].

ADME Calculation: Qikprop module of Schrödinger was used to calculate the ADME properties of selected compounds. Both principle and physiochemical descriptors were calculated [14]. Before performing the calculation, all the ligands were neutralized. This step is important because QikProp is not able to neutralize a structure, and so no properties will be calculated in normal mode [15]. In normal mode, it predicts the principle descriptors and physicochemical properties of all ligands with a full analysis of the Molecular weight, H bond donor, H bond acceptor, QP logpw, Qplogkp, % human oral absorption. It also estimates the suitability of the whole compounds based on Lipinski's rule of 5, which is essential for rational drug design [16, 17].

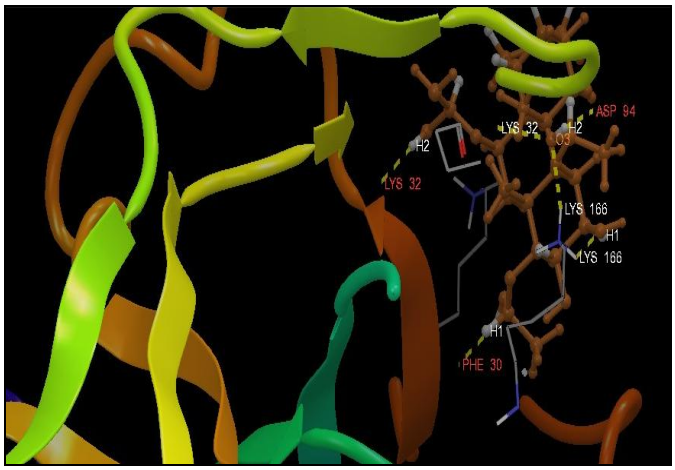
RESULTS AND DISCUSSION: In this study, we have conducted a molecular docking and binding energy calculation between the target protein and 11 plant compounds which were obtained from 6 different medicinal plants. The insilico results revealed that Gymnemic triacetate from Gymnema Sylvestre exhibited better binding affinity with the target protein than the other compounds.

Validation of the Docking Protocol: To study the molecular base of contact and binding affinity of plant compounds in the active site of exfoliative toxin molecular docking was carried out. The selected plant compounds were docked towards the exfoliative toxin A (PDB id -1AGJ). All the compounds were docked in a glide environment; the result shows the good interaction of every compound, with the exofloative toxin a protein. Based on the docking score, the ligand was ranked. The docking results revealed that all the ligands were docked into the active site of the target protein. The characteristics of the binding sites play a vital role in the ligand binding of target protein.

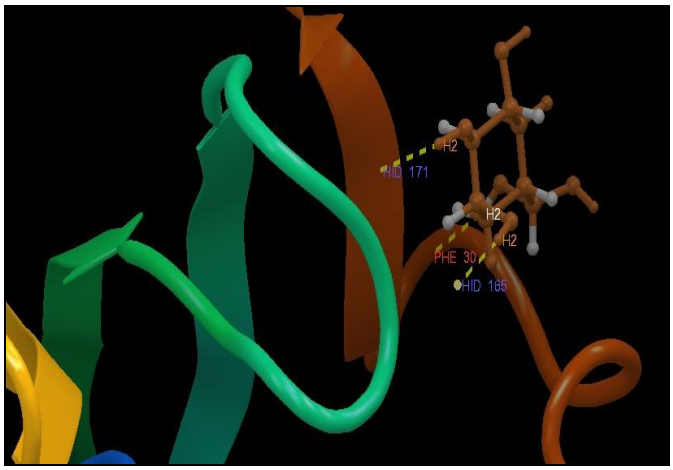
The hydrogen-bonding interactions between the compounds and target protein are mostly contributed by PHE 30, LYS 32, and HIS 165 **Fig. 1**. And the lengths of the hydrogen bonds formed by the drug molecule's target protein are listed in **Table 2**. It is seen that PHE 30 and LYS 32 alternatively form hydrogen-bonding interactions with the 11 drug molecules.

The hydrogen bonds formed by these two amino acid residues have comparatively shorter lengths than those formed by other residues, which provides a signal that these hydrogen bonds are stronger than others and play significant roles in the ligand binding. Hydrogen bonds play a vital role in the structure and function of biological molecules. Compared with all the docking results, Gymnemic triacetate shows a more number of H-bond and

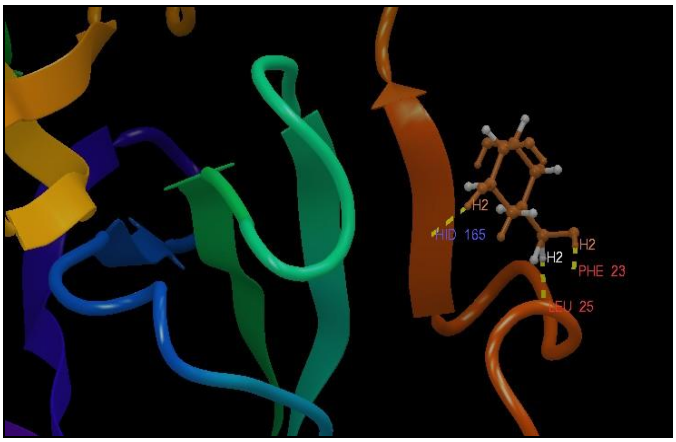
high glide scores. The docking results like atomic interaction and their docking scores glide energy, and their hydrogen bond details of the best four compounds were shown in **Table 2**. In the present study, Gymnemic triacetate, a novel compound isolated from the leaf of *Gymnema Sylvestre* shows the best docking score and docking energy with more interaction with the exfoliative toxin A.



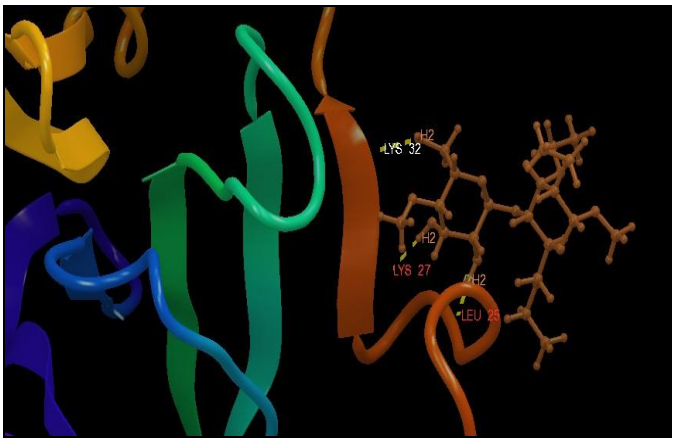
1A- The interaction between exfoliative toxins A and Compound gymnemic triacetate



1B- The interaction between exfoliative toxin A and compound Gallic acid



1C- The interaction between exfoliative toxin A and Compound polysaccharide



1D- The interaction between exfoliative toxin A and compound catechin

FIG. 1: BINDING POSES OF THE FOUR COMPOUNDS EXFOLIATIVE TOXIN A

TABLE 2: GLIDE XP DOCKING RESULTS OF BEST COMPOUNDS WITH GLIDE SCORE, ENERGY AND THEIR ATOMIC INTERACTION

S. no.	Compoud Name	No of H-bond	Atomic Interactions	H-bond Donor	H-bond Acceptor	Distance	Glide Score	Glide Energy
1	Gymnemic triacetate	6	PHE30(O)-H	Li(H)-O	PR(O)	2.128	-5.952226	-41.790596
			LYS32(O)-H	Li(H)-O	PR(O)	2.359		
			LYS32(H)-O	PR(H)-O	Li(O)	2.036		
			ASP 94(O)-H	Li(H)-O	PR(O)	1.890		
			LYS166(H)HZ1-O	PR(H)HZ1-O	Li(O)	2.127		
			LYS166(H)HZ2-O	PR(H)HZ2-O	Li(O)	2.182		
2	Gallic acid	3	HIS165(N)-H	Li(H)-O	PR(N)	2.020	-5.910564	-34.252091
			HIS171(N)-H	Li(H)-N	PR(N)	2.029		
			PHE30(O)-H	Li(H)-O	PR(O)	1.957		
3	Polysaccharide	3	LEU25(O)-H	Li(H)-O	PR(O)	1.661	-4.728687	-36.660285
			PHE30(O)-H	Li(H)-O	PR(O)	1.794		
			LYS32(H)-O	PR(H)-O	Li(O)	2.148		
4	Catechin	3	PHE23(O)-H	Li(H)-O	PR(H)	1.947	-4.545230	-35.306255
			HIS165(N)-H	Li(H)-N	PR(N)	1.991		
			LYS32(O)-H	Li(H)-O	PR(O)	1.825		

Binding Energy Calculation: Docking methods begin with a known protein structure and a known ligand structure and plan to quickly make an optimal protein ligand-bound conformation. The docked complexes were minimized with the help of local optimization features in prime in Prime MM-GBSA method. This method was helped to find out the binding free energy of set of compounds to receptor. The OPLS-AA force field and GBSA continuum solvent mode was helped to calculated the binding energies of the docked complex. The interaction energy was calculated after a minimization was carried out on a docked ligand in which atoms within 7.5 Å from the ligand were free to move (other atoms were fixed). The interaction energy comprises an implicit solvation (H_2O) term. Van der Waals, solvation and electrostatic energy as well as solvent accessible surface area (SASA) were calculated for each minimized complex. Finally, based on the composite scoring, the complexes were ranked and listed in **Table 3**.

TABLE 3: CALCULATED ENERGIES OF SELECTED FOUR COMPOUNDS WITH EXFOLIATIVE TOXIN A

S. no.	Compound Name	G_{vdw}	G_{solv}	G_{bind}	Prime MM-GBSA Complex Energy
1	Gymnemic triacetate	-23.504527	-1224.966497	-31.068592	-10819.820650
2	Gallic acid	-17.832152	-1233.194439	-36.886060	-27.742075
3	Polysaccharide	-25.729197	-1236.545855	-55.964184	61.554173
4	Catechin	-24.245792	-1237.148119	-44.665691	7.396180

ADME Calculation: These four compounds selected from docking studies were additionally estimated for their drug-like actions through analysis of pharmacokinetic parameters necessary for absorption, distribution, metabolism, excretion, and toxicity (ADMET) by use of QikProp. Predicted properties of the entire four compounds were listed in **Table 4**. The molecular weight of the selected compounds existed in the range between 150 to 470. H bond donors were in the range between 3 and 5, whereas H bond acceptor of the chosen compounds found to be in the range between 8-15. The predicted water/gas partition coefficient was in the range 15 22 for most of the compounds. Predicted skin permeability & log Kp (QPlogKp) negatively ranged between 4-1, and predicted human oral absorption on 0–100% scale was found to be in the intermediate levels of 50 and 65. **Table 4** explains the drug-likeness property of the compounds. The jointed approach of docking, binding energy calculation, and ADME prediction was used to identify the binding affinity of these compounds with the receptor and also validate them as potential candidates for second-generation drug discovery.

TABLE 4: DRUG LIKENESS PROPERTY CALCULATED BY QIKPROP SIMULATION

S. no.	Compound Name	Mole. weg	HB Donor	HB Acceptor	QPlog PW	QPlogKp	% of Human Oral Absorption
1	Gymnemic triacetate	474.59	5	15.3	22.601	-4.018	65.075
2	Gallic acid	178.185	5	8.5	16.439	-4.927	51.753
3	Polysaccharide	454.514	3	18.7	21.674	-1.792	68.032
4	Catechin	302.367	5	10.2	18.67	-4.846	60.426

CONCLUSION: With the current torrent of data, computational modes have become crucial to biological examination. In the present study computational approach was helped to recognize the mechanism of interactions and binding capacity between exfoliative toxins A with selected natural compounds. Anti-diabetic activities of these 11 compounds were proved experimentally. In the present effort, we have tried to identify the antibacterial activity of these compounds through molecular docking analysis. The examination of the best-docked ligands allowed us to know the binding manner of compounds used in this study and verify the role as anti-bacterial agent. Binding energies of the drug enzyme (receptor) connections are significant to explain how to fit the drug binds to the target macromolecule. Compared to all compounds, Gymnemic triacetate isolated from the leaf of *Gymnema Sylvestre* shows very good interaction with exfoliative toxin A.

So, these phytocompounds should be subjected to extra experimental analysis to validate these results.

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