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Research Article

In Silico Prediction And Molecular Docking Study on the Interaction of Bioactive Compounds of *Adenanthera Pavonina* Exploring the Potential Antifungal Activity against *Candida Glabrata* Cell Wall Proteins

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ABSTRACT

Candida glabrata infections being resistant to many azole antifungal agents, are difficult to treat. Various parts of *Adenanthera pavonina* have been used in traditional medicine. In the present study, an attempt was made to screen the bioefficacy of the identified phytoconstituents of *A. pavonina* on an *in silico* platform and identify some potential drug-like molecules that can impede important drug targets of *C. glabrata* using the molecular docking method. In a previous study related to the current research, the phytochemical profiling of the methanolic stem extract of *A. pavonina* was carried out using GC-MS to identify the phytoconstituents. The three-dimensional structure of the fungal receptors were derived by homology modeling using Modeller9v7 and the same for the ligands for which the structures were not available were drawn by ACD chemSketch. The docking of ligands and receptors were performed using PatchDock software. Druglikeliness and pharmacodynamics properties were evaluated using SWISS-ADME. GC-MS analysis of the *A. pavonina* extract revealed the presence of 17 phyto compounds, of which 2 heptyl 1,3dioxolane and methyl 4-o-methyl-d-arabinopyranoside best docked with the epithelial adhesion protein 6 receptor and cell wall transcription factor ACE2. Methyl 4-o-methyl-d-arabinopyranoside also best docked with the integral cell wall protein receptor. Although other compounds have shown good scores related to docking 2 heptyl 1, 3 dioxolane had an excellent binding affinity than the other ligands thus signifying its potent antifungal activity. 2 Heptyl 1, 3 Dioxolane was found to be BBB positive and 4-O-Methyl-D-arabinopyranoside is BBB negative. As the finding indicates, the two phyto compounds present in the methanolic stem extract of *A. pavonina* demonstrated good docking scores when docked with specific fungal cell wall receptors and thus can prove to be appropriated for the lead molecule.

Introduction

India suffers enigmatically from the encumbrance of infectious diseases given the confluence of prevailing ecological, socio-economic, and demographic factors. A disquieting upsurge in the occurrence of new and re-emerging infectious diseases has necessitated the unceasing and imperative need to discover new antimicrobial compounds with assorted chemical structures and novel mechanism of action.[1] The increasing incidence of the emergence of multidrug-resistant pathogens has drastically reduced the effectiveness of many antibiotics and the outlook for antimicrobial drugs is still uncertain, which makes it essential to search for new drugs. Various factors such as prolonged

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use of intravenous catheters, organ transplantation, immunosuppressive agents, enduring epidemics of HIV infection and undiscerning use of antimicrobial drugs has led to the intensification in antibiotic resistance among the pathogenic species.[2-5]

Over the preceding decades, the frequency of fungal infections in humans has increased, especially invasive fungal infections are of great concern for human beings as these are associated with high mortality rates, which often surpasses 50% regardless of the accessibility of a wide range of drugs for their treatment. Clinical *Candida* species responsible for candidemia remains the most imperative basis of opportunistic mycoses globally. The occurrence of mucosal and systemic infections caused by *C. glabrata*, which is time and again the second or third most prevalent source of candidiasis after *C. albicans*, has increased significantly following the extensive and augmented use of immunosuppressive therapy along with broad-spectrum antimycotic therapy.[6,7] *C. glabrata* infections being resistant to several azole antifungal agents, exclusively fluconazole are hard to treat.[8] Accordingly, *C. glabrata* infections result in elevated mortality rates in immune-compromised and hospitalized patients.

Medicinal plants are the principal source of drugs for various chemotherapeutic purposes. The growing interest in the use of traditional medicines and the increasing demand for plant-derived drugs is largely due to the existing belief that these products are quite safe and reliable compared to expensive synthetic drugs, numerous of which have adversarial side effects.[9] *A. pavonina* is a fast-growing, medium to large sized deciduous tree, 6-15 m tall and up to 45cm diameter. *A. pavonina* is extensively cultivated as a valuable multipurpose agroforestry species. Various parts of *A. pavonina* have been used in traditional medicine to treat diarrhea, gout, inflammation, asthma, boil, rheumatism, tumors and ulcers, and tonics.[10-15] *A. pavonina* has promising bioprotective activities, including anti-inflammatory activities,[16] blood pressure-lowering effect[17] antifungal, antioxidant, cytotoxic, and antiproliferative activities.[18, 19]

Bioinformatics and Computational biology plays a prominent role in designing drug molecules and enhances the probability of accelerating the drug discovery process. Molecular docking is utilized as a tool in structure-based drug design and refers to predicting the bioactive conformation of a molecule in the binding site of a target structure.[20] In the context of molecular modeling, docking is an essential means of predicting the associations between biologically relevant molecules such as nucleic acids, proteins, lipids carbohydrates and thus plays a crucial role in signal transduction. Docking of the target receptor with the drug molecules reveals the ligand receptor interactions and is frequently used to determine the binding orientation of the protein target by the drug candidates to predict the affinity and activity. Hence, docking plays an important role in the rational design of drugs.[21]

In the current scenario, novel lead molecules are designed using computational methods such as molecular docking tools, which play a significant role in predicting functional sites on protein molecular surfaces, structure-based drug designing, and exploring the interaction between the protein and the ligand molecules.[22-24]

Computational molecular docking is a research technique for foreseeing whether one molecule will bind to another, generally a protein. The technique can execute protein-ligand, protein-protein, and protein-DNA docking predictions, although the technique employed is highly variable in each area. Protein-ligand docking is done by modeling the interaction between protein and ligand. If the pair has complementary geometry and favorable biochemical interactions, the ligand will potentially bind the protein *in vitro* or *in vivo*. Docking includes the following types of interactions:

Protein-Protein Docking Interactions

This type of interaction includes two proteins of similar size and a simple technique where docking occurs without experimental measurements. Protein-protein interactions are more rigid, the two molecules tend to have flatter and smoother interface between them than that between protein-ligand interactions.[25] An essential ingredient of the scoring functions for protein-protein docking is the shape complementarity.[26] It has been possible to dock proteins that remain rigid after complex formation and the upsurge in the elucidation of the protein structure has boosted studies on protein-protein docking.

Protein-Ligand Docking Interactions

It is the most commonly used technique to predict the position, orientations and structure of a protein as it docks with ligand molecules, which can act as either promoter or inhibitor. In order to choose potential drug candidates, large libraries of ligands are efficiently scanned.[27] The interaction between protein and ligand involves high specificity along with induced-fit within the interfaces increasing the rigidity. In the last three decades several docking algorithms have been developed.[28,29] For large-scale experiments, most of these algorithms are computationally too heavy. Consequently, PatchDock a geometry-based molecular docking algorithm has been developed, which is very competent algorithm for protein-small ligand and protein-protein docking.[30] Docking transformations yielding good molecular shape complementarity could be predicted using the algorithm. Using chemical structure drawing software ACD/ChemSketch or alternatives, compounds' chemical structure can be predicted. A variety of templates are present in the ChemSketch software that simplifies the inflowing of complicated compounds, organometallic structures and polymers. It also delivers an expedient properties generator that can exhibit molecular weight,

chemical formula, percentage composition and estimated macroscopic properties such as density, molar refractivity, refractive index, molar volume and others.[31]

A study explored the anticandidal activity of the compounds isolated from *Piper nigrum* and *P. betle* by performing molecular docking wherein the phytoconstituents from the two plant species were tested against the different SAP (Secreted aspartyl proteinases) enzymes of *Candida albicans* which promotes hypha formation, adhesion and invasion of host tissues. A family of 10 *SAP* genes is expressed by *C. albicans* which is clustered into groups *SAP1* to *SAP3*, *SAP4* to *SAP6*, *SAP7*, *SAP8*, *SAP9,* and *SAP10.* Docking of the bioactive compounds and the receptor protein was carried out using Hex software. Docking of SAPs of *C. albicans* with bioactive compounds of *P. nigrum viz.* Piperine, Eugenol, Bicyclo, O-Anisic acid produced energy values of -698.77, -149.68, -143.16, and -205.91respectively. Correspondingly, the bioactive compounds of *P. betle* produced energy values such as-223.87, - 223.87- 166.50 and -159.45 for 3, 7, 11, 15-Tetramethyl-2-hexadecen-1-ol, Phytol, Phenol and 2-methoxy-3-2-propenyl2, 5- Dimethoxybenzoic acid respectively.[32]

The present study aimed to explore the biopotency of the identified phytoconstituents of *A. pavonina* on an *in silico* platform and identify some potential drug-like molecules that can impede important drug targets of the dermatophytes using molecular docking method.

Materials and Methods

In a preceding research work related to the present study, using Gas Chromatography- Masss Spectrometry (GC-MS) analysis the phytochemical profiling of the methanolic stem extract of *A. pavonina* was performed to identify the phytoconstituents. Consequently, in the present study total of 10 phyto compounds isolated from *A. pavonina* stem extract by GC-MS profiling were selected for the *in silico* analysis. Antifungal potential of these isolated phyto compounds was established by screening for the phytochemical compounds' possible targets on fungal cell wall using various Bioinformatics tools. Virtual screening of 1, 3-dioxolane, 2-benzyl-1, 3-dioxolane, 2-heptyl-1, 3-dioxolane, 3,4 hexane dione, 3-Methylmannoside, cyclopentasiloxane, isobutyl nitrate, isonitropropane, malonic acid, methyl 4-o-methyl-d-arabinopyranoside was performed against *C. glabrata* cell wall receptors Mannose-1-phosphate guanyltransferase 1 [KTB26809.1], epithelial adhesin 6 [AAT67388.1], cell wall synthesis protein KNH1[KTB25355.1], hyphally regulated cell wall protein 4 [KTB18309.1], Cell wall transcription factor ACE2 [KTB12864.1], Cell wall integrity and stress response component 4 [KTB26857.1] which were used as the target proteins for the molecular docking. Docking studies were performed by using the softwares like SWISS Model, swiss PDB viewer, ACD chemSketch, Rampage, ArgusLab 4.0.1, and PatchDock.

Selection and Preparation of Receptor

The receptor selection and preparation comprises building the receptor and identifying active sites.

Building the Receptor

Homology modeling was performed using SWISS Model freeware for depicting the three-dimensional structures of the fungal receptors. Models of the above-mentioned proteins were generated using Modeller9v7. The receptor's structural processing using a molecular docking tool was carried out carefully so that the receptors remain in stable and biologically active conformation.

Identification of the Active Site

Computationally, the active site for binding the phytoligands within the receptors was identified and analyzed. The models were further analyzed on the Rampage Ramchandran plot server and the best model was selected and was used for further docking studies.

Selection and Preparation of Ligand

Ten ligands were selected from the phytocompounds isolated by GCMS profiling with more peak value corresponding to higher concentration in methanol stem extract of *A. pavonina*. The chemical structures of these 10 phytocompounds were retrieved through the PubChem compound database at NCBI [http://pubchem.ncbi.nlm.nih.gov/] and the ligands for which the structures were not available, the 3dimension structure was drawn by using Chemsketch. Using Arguslab software, the structures downloaded in .mol files were saved as pdb files.

Docking Studies

Using PatchDock the ligands were docked to the best receptor models selected from Rampage and the molecular interactions between the ligands and the receptors were generated computationally. Based on the best-fit ligand and receptor interactions scores were generated by the scoring function. The validation of predicted affinity of the ligand to the receptor and scoring was accomplished by estimating the E (free energy used for binding, Kcal/mol) value and comparing it with experimental E values. The greater the negative value of the energy by binding the superior is the affinity of the molecule to the receptor.

Study of Drug Likeness of Ligands

Lipinski filter was used for ligand prediction, according to drug-likeness criteria, namely lipophilicity, water-solubility, TPSA, GI absorption, and BBB permeation and skin permeation. SWISS-ADME was used in drug investigation[33] and ligand properties with respect to absorption, distribution, metabolism, and excretion (ADME). BOILED-EGG (Brain or intestinal estimated permeation method) is approached as an accurate model that works properly by computing the polarity of tiny molecules.[34]

Results

In silico studies in the present investigation was intended to expand the knowledge on target proteins of standard antimycotic compounds present in the stem extract of *A. pavonina*. The phytocompounds to be screened against the target protein were identified by GC-MS profiling of *A. pavonina* stem extract. Docking studies were performed to evaluate the affinity of the phytocompounds from the extract towards certain known targets in the fungal cell similar to that of the antifungal agents with a different mechanism of action. Molecular docking studies were carried out by using softwares like SWISS Model, swiss PDB viewer, ACD chemSketch, Rampage, ArgusLab 4.0.1, and PatchDock. Evaluation of *A. pavonina* methanolic stem extract for antifungal activity on *C. glabrata* using the disc diffusion method revealed the antimycotic bioactivity of the extract. Thus, the present study was designed to screen for the possible targets on the fungal cell wall for the phytocompounds isolated from the extract by GC-MS. A Survey of literature has shown the various fungal cell wall target proteins which interact with the antimetabolites.

Structure of Ligands

The chemical structure of phytocompounds viz. 1, 3-dioxolane, 2-benzyl-1, 3-dioxolane, 2-heptyl-1, 3-dioxolane, 3, 4 hexane dione, 3-methylmannoside, Cyclopentasiloxane, Isobutyl nitrate, isonitropropane, malonic acid, methyl 4-o-methyl-d-arabinopyranoside, identified from the GC-MS profile of *A. pavonina* methanolic stem extract were retrieved from the PubChem and for those for which the structures were not available were drawn using the Chemsketch to be used as ligands in the present study. The chemical structures of the ligands are depicted in Fig. 1.

Structure of Receptor

Based on this study, mannose-1-phosphate guanylyltransferase 1 [KTB26809.1], Epithelial adhesin 6 [AAT67388.1], Cell wall synthesis protein KNH1 [KTB25355.1], Hyphally regulated cell wall protein 4 [KTB18309.1], Cell wall transcription factor ACE2 [KTB12864.1], Cell wall integrity and stress response component 4 [KTB26857.1] were used for the molecular docking studies. The structure of these receptors in three dimensions was depicted (Fig. 2) by performing homology modeling using SWISS Model freeware. Models of the target proteins were generated using Modeller9v7 and further analyzed on Rampage Ramchandran plot server to select the best model for docking studies.

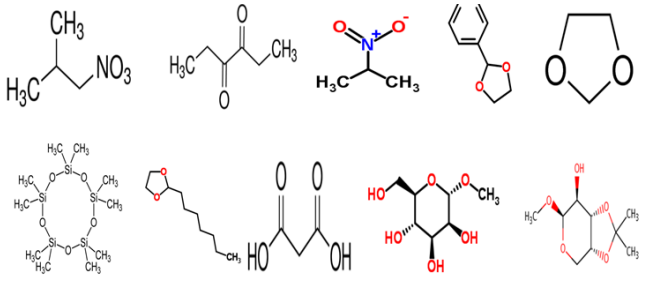

Fig. 1: Images of the ligands of *A. pavonina* retrieved from PUBCHEM database. Top: Isobutyl nitrate, 3,4 hexane dione, Isonitropropane, 2-benzyl-1,3-dioxolane and 1,3-dioxolane. Bottom: Cyclopentasiloxane, 2-heptyl-1,3-dioxolane, malonic acid, 3-methylmannoside and Methyl 4-o-methyl-d-arabinopyranoside.

Ramachandran Plot

Among the six receptors designed for the study, only three receptors, namely epithelial adhesin 6 (EA6), cell wall transcription factor ACE2 (TRANS), and cell wall integrity and stress response component 4 were found to be best-suited models for the *in silico* studies as shown in Fig. 3.

Molecular docking of the receptors and ligands were done using Patchdock to obtain the best Patchdock score as represented in Table 1. Only those solutions with more than 3300 Patchdock score were reflected as good docked models and were considered for the results.

Among all the ligands only two ligands were best docked to the receptors compared to the positive control fluconazole which was also used for *in vitro* antifungal studies. Thus, 2 heptyl 1, 3 dioxolane and methyl 4-o-methyl-d-arabinopyranoside were found to be the best molecular solutions with the three receptors epithelial adhesin 6, Cell wall transcription factor ACE2 and cell wall integrity and stress response component 4 (INT) used in the study. Fluconazole patch dock score was found

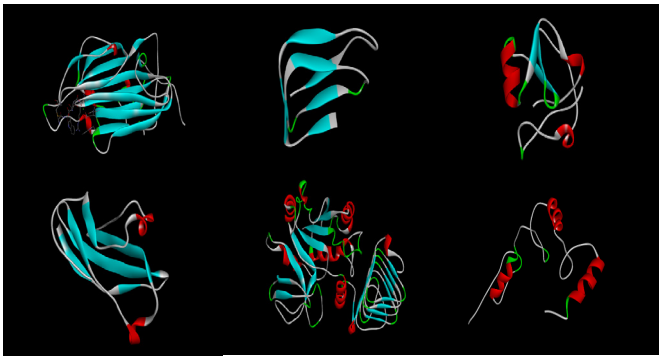

Fig. 2: Images of receptors modeled and as viewed in discover studio. Top: Epithelial Adhesin (EA6); Hyphally regulated cell wall protein 4 (HYP) and Cell wall integrity and stress response component (INT). Bottom: Cell wall synthesis protein KNH1; Mannose-1-phosphate guanylyltransferase (MPG1); Cell wall transcription factor ACE2.

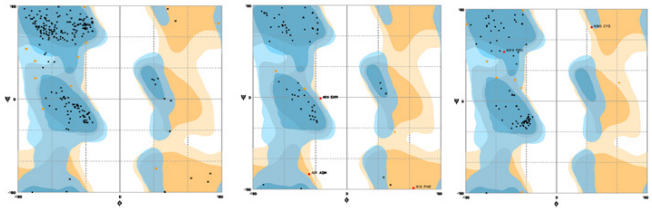

Fig. 3: Image showing the Rampage (Ramachandran Plot) results of Epithelial adhesion protein, Cell wall integrity, and stress response component 4, and Cell wall transcription factor ACE2.

to 4048, 4690, and 3534 for EA6, INT and TRANS models, respectively. Similarly the score for 2 heptyl 1, 3 dioxolane was 3456, 3745 and 3576 for EA6, INT, and TRANS. And for methyl 4 O methyl d-arabino pyranoside the score was 3356, 3421 and 3444 for EA6, INT and TRANS respectively (Fig. 4).

From the autodock results obtained using the PyRx software, it was found that fluconazole was found to have the least binding energy. The lesser the value of binding energy the greater is the affinity towards the receptor.

The binding affinity was found to be -5.4Kcal/Mol for the 2 heptyl 1, 3 dioxolane and INT complex which was found to be more than the other solutions and almost similar compared to the positive control as illustrated in Table 2.

Docking Solutions

The *in silico* studies hence reported that the 2 heptyl 1, 3 dioxolane was the best solution towards the cell wall integrity and stress response component 4 receptor in accordance with the positive control as shown in Figs 5-11. The Patchdock score was 3745 with the integrase protein receptor compared to 4690 for the fluconazole.

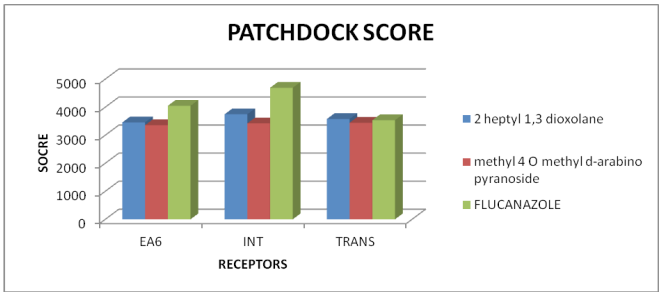

Fig. 4: Graph showing the patch dock scores of the three ligands and receptors.EA6: epithelial adhesion protein (Model 6); INT: integral cell wall protein receptor; TRANS: Cell wall transcription factor ACE2.

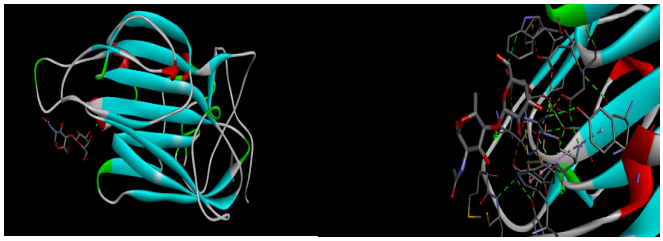

Fig. 5: Docking solution between 2 Heptyl 1, 3 dioxolane and EA6. Image retrieved from Discovery studio.

Drug Likeliness

From the results, it was predicted that out of the two screened ligands, 2 Heptyl 1, 3 Dioxolane was found to be a stronger candidate drug than the 4-O-methyl-D-arabinopyranoside. Two molecules 2 Heptyl 1,3-dioxolane and methyl 4-O-methyl-D-arabinopyranoside (Table 3)

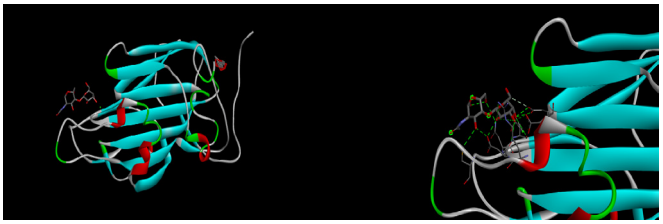

Fig. 6: Docking solution between Methyl 4 O methyl d-arabino pyranoside and EA6. Image retrieved from Discovery studio.

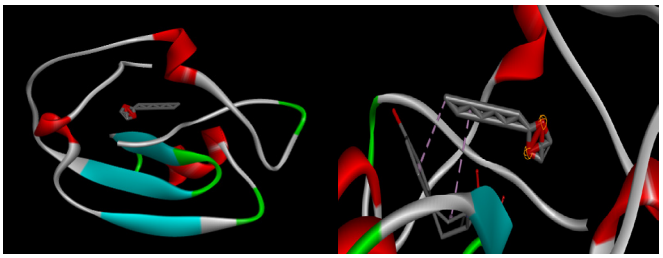

Fig. 7: Docking solution between 2 heptyl 1, 3 dioxolane and INT. Image retrieved from Discovery studio.

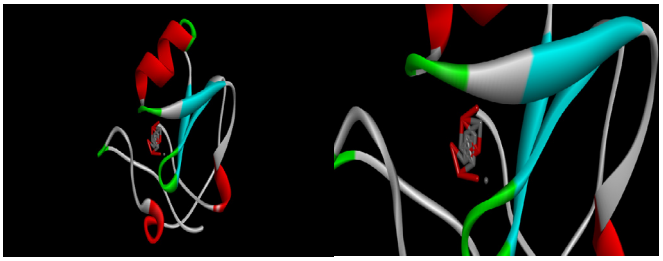

Fig. 8: Docking solution between Methyl 4 O methyl d-arabino pyranoside and INT Image retrieved from Discovery studio.

Table 1: The Patchdock scores of three receptors and ligands. EA6: epithelial adhesion protein (model 6); INT: integral cell wall protein receptor; TRANS: Cell wall transcription factor ACE2

Compounds	*EA6*	*INT*	*TRANS*
2 heptyl 1,3 dioxolane	3456	3745	3576
methyl 4 O methyl d-arabino pyranoside	3356	3421	3444
Fluconazole	4048	4690	3534

Table 2: Table showing the binding affinity values of three receptors and ligands. EA6: epithelial adhesion protein (model 6); INT: integral cell wall protein receptor; TRANS: Cell wall transcription factor ACE2.

Compounds	*EA6*	*INT*	*TRANS*
Fluconazole	-7.3	-8.32	-5.2
2 heptyl 1,3 dioxolane	-5.1	-5.4	-5.23
Methyl 4 O methyl d-arabino pyranoside	-4.12	-4.9	-5.14

Table 3: Table showing the ADME properties and pharmacokinetics values of the proposed drugs.

	2 Heptyl 1, 3 dioxolane	*Methyl 4-o-methyl-d-arabinopyranoside*
Lipophilicity Log Po/w (iLOGP)	3.1	0.84
Lipinski	Yes; 0 violation	Yes; 0 violation
Bioavailability Score	0.55	0.55
Synthetic accessibility	2.57	4.3
Water Solubility	Soluble	Highly soluble
TPSA	18.46 Å^2	99.38Å^2
Pharmacokinetics		
GI absorption	High	Low
BBB permeant	Yes	No
P-gp substrate	No	
CYP1A2 inhibitor	No	No
CYP2C19 inhibitor	No	No
CYP2C9 inhibitor	No	No
CYP2D6 inhibitor	No	No
CYP3A4 inhibitor	No	No
Log Kp (skin permeation)	-5.01 cm/s	-0.37

Fig. 9: Docking solution between 2 heptyl 1,3 dioxolane and TRANS Image retrieved from Discovery studio.

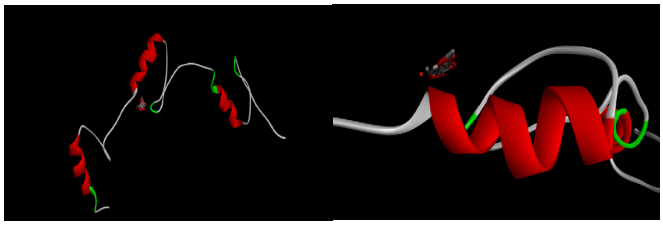

Fig. 10: Docking solution between Methyl 4 O methyl d-arabinopyranoside and TRANS. Image retrieved from Discovery studio.

screened, were studied for ADME properties, TPSA values < 140 Å^2 proves that the compounds are highly absorptive in nature. A boiled egg model is also proposed for computing the lipophilicity and polarity of these two ligands. The Boiled egg analysis of these 2 molecules (Figs 12-14) has shown that they are highly absorbable in the gastrointestinal tract. 2 Heptyl 1,3 Dioxolane was found to be BBB positive and 4-O-Methyl-D-arabinopyranoside is BBB negative.

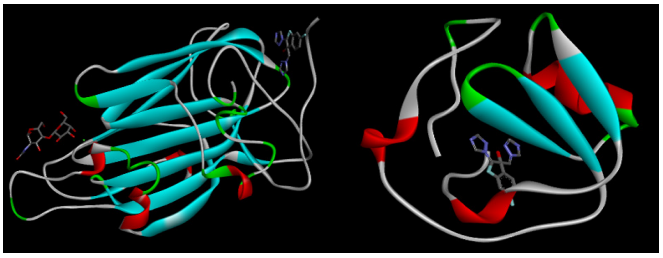

Fig. 11: Docking solution between Flucanozole and epithelial adhesin 6(EA6), cell wall transcription factor ACE2 (TRANS), and cell wall integrity and stress response component 4 (INT). Image retrieved from Discovery studio.

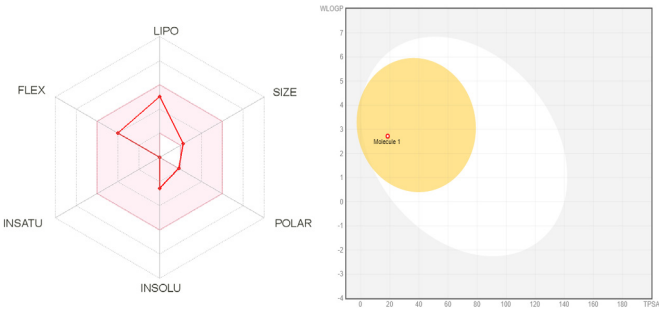

Fig. 12: Left: Oral availability prediction chart. A Coloured zone is a suitable physicochemical space for oral bioavailability. Right: Boiled egg plot to show the highest probability of being absorbed by the gastrointestinal tract. [For 2 Heptyl 1, 3 Dioxolane]

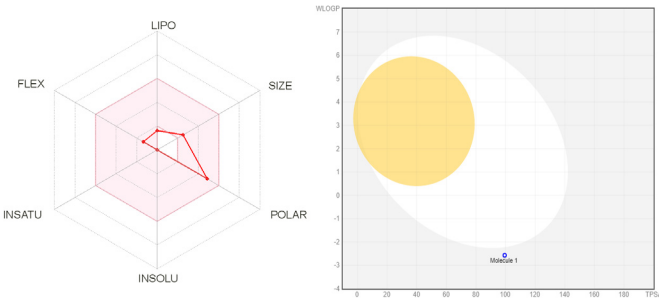

Fig. 13: Left: Oral availability prediction chart. A Coloured zone is a suitable physicochemical space for oral bioavailability. Right: Boiled egg plot to show the highest probability of being absorbed by the gastrointestinal tract. [For 4-O-Methyl-D-arabinopyranoside]

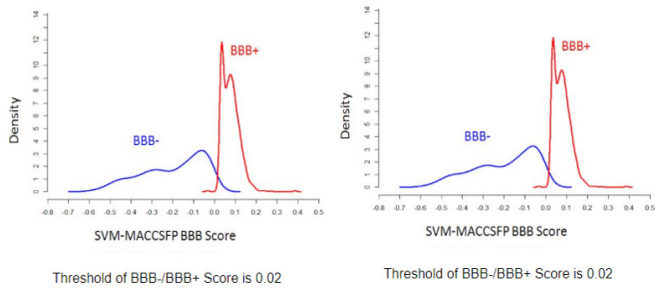

Fig. 14: Images showing the BBB prediction graphs. Left: 2 Heptyl 1, 3 Dioxolane Right: 4-O-Methyl-D-arabinopyranoside].

Discussion

In molecular modeling, docking is a method that envisages one molecule's preferred orientation to the other when bound to each other to form a stable complex.[35] Molecular

docking attempts to predict the binding approach by assessing different bound conformations' energy scores with a scoring function. Currently, the docking technique is exploited to predict a ligand-receptor complex's tentative binding parameters in advance.[36] Drug candidates find the ligand-binding sites as the most promising targets, which depend upon the inhibition or regulation of the target protein functions. Ligand-based methods depends on the shape similarity concept, although the structure-based methods bank on scoring functions against a panel of targets.[37]

The contemporaneous investigation was employed to compare the mechanism of antifungal activity exerted by the standard antimycotic drug and the antimycotic compounds present in *A. pavonina* by screening for the possible target proteins on the cell wall of *C. glabrata*. Docking study was performed for evaluating the affinity of the 10 major phytocompounds isolated from *A. pavonina* by GC-MS analysis for their affinity towards fungal proteins that are known targets for some antifungal agents with a different mechanisms of action. The results of the present *in silico* analysis demonstrated that among the six receptors selected for the docking studies with the 10 phytoconstituents only three proteins viz. epithelial adhesin 6, Cell wall transcription factor ACE2 and cell wall integrity and stress response component 4 were displayed as the best-suited models for docking as per analysis of Ramachandran plot. Among the phytocompounds only two ligands 2 heptyl 1,3-dioxolane and methyl 4-O methyl d-arabinopyranoside were best docked and thus the best molecular solution with the three receptors compared to the positive control, fluconazole. Fluconazole demonstrated the least binding energy in the autodock results and hence has a greater affinity towards the receptor. The protein-ligand interaction was best exerted by 2 heptyl 1, 3-dioxolane, cell wall integrity, and stress response component 4 with more binding affinity and significant docking score than that between the fluconazole and the protein and hence was found to be the best solution in the present docking study.

Corresponding to the results of the present study, Pasko *et al.*[38] investigated the mode of action of fluconazole a fluorine-substituted, bis-triazole antifungal agent, which encompasses disruption of lanosterol conversion to ergosterol means of binding to fungal cytochrome P-450 resulting in subsequent disruption of fungal membranes. The study also emphasized on the activity of fluconazole against *Aspergillus* spp., *Blastomyces dermatitidis*, *Candida* spp., *Coccidioides immitis*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, and *Paracoccidioides brasiliensis* in several animal models. Also, various clinical trials and reports revealed fluconazole usage in treatment of candidiasis, predominantly oropharyngeal and esophageal infections in immunocompromised hosts.

In accordance with the present investigation, Latha *et al.*[39] investigated the biologically active compounds with therapeutic efficacy of *Acacia torta Craib* by GC-MS profiling of the ethanolic plant extract. A totsl of 20 compounds were identified from the plan among which five of the lead compounds were scrutinized for docking against the human penicillin binding protein using iGEMDOCK to analyze their efficiency in impeding the receptor among which highest fitness energy of -79.4206 (kcal/mol) was demonstrated by 1-Pentene, 1,3-diphenyl-1-(trimethylsilyloxy) followed by Benzoic acid, 4-methyl-2-trimethylsilyloxy ester with –66.7366 (kcal/mol), 1,3-dioxolane, 2 with -64.1737(kcal/mol), 2-dioxolane with 61.9449 (kcal/mol) and the last being Tetramethylsilane. It was also reported that the average connection pair was best for 2-heptyl 1,3-dioxolane with 29.25 (kcal/mol), which is in line with the results of the present investigation. Similar results for 2-heptyl 1,3-dioxolane were also demonstrated with efficient binding with the penicillin-binding protein present in the *Streptococcus pneumoniae* in another docking study.[40,41]

In line with the present study, Rehman *et al.* [42] accomplished virtual screening of nepetolide, a tricyclic clerodane-type diterpene, isolated from *Nepeta suavis* through Patchdock online docking server, which resulted in identification of primarily hydrophobic interactions between ligand nepetolide and receptors proteins. The results indicate that nepetolide exhibits various pharmacological actions including antibacterial, antioxidant, cytotoxic, anticancer, anti-inflammatory and analgesic activities and could be considered as a lead compound for developing drugs. *In silico* investigation of nepetolide against cyclooxygenase-2 (Cox-2), epidermal growth factor receptor(EGFR) and lipoxygenase-2 (Lox-2) targets revealed that the interaction of the EGFR, Cox-2 and Lox-2 with nepetolide have the atomic contact energy of -10.69, -11.83, -13.44 kcal/mol with in Patchdock. The docking of the three receptors with nepetolide also displayed the hydrogen bonding range between 1.8 and 3.75 Å.

In a similar study, Singh *et al*. [43] accentuated the antifungal potency of a cell-permeable metabolite from *Penicillium radicum* called wortmannin (Wtmn), which is a phosphoinositide 3-kinase (PI3K) inhibitor by executing molecular docking studies against potential antifungal targets. The study reported that the action of the target site viz. mevalonate-5-diphosphate decarboxylase (1FI4), responsible for sterol/isoprenoid biosynthesis; exocyst complex component SEC3 (3A58) where Rho- and phosphoinositide-dependent localization is present and Kre2p/ Mnt1p a Golgi alpha1, 2-mannosyltransferase (1S4N) involved in the biosynthesis of yeast cell wall glycoproteins were impeded by Wtmn more efficiently than that by the standard antifungal agents like voriconazole and nikkomycin. Wtmn than the two antifungal agents demonstrated effective binding and greater specificity for the target by maintaining a tightly closed conformation through the simulation due to their ability to anchor

both catalytic dyad residues and flap residues, which in turn specified greater specificity towards the structure of the enzyme. The study provided valuable insight into designing highly specific inhibitors against the antifungal enzyme by exploring the structural specificity of all the three inhibitors towards the available protein structures congruent with the inference of the present investigation.

Conclusion

Results of molecular docking study using the isolated phytoconstituents of *A. pavonina* stem extract with specific targets on *C. glabrata* surface revealed that in relation to the docking 2 heptyl 1,3 dioxolane seems to be a better fit than the other ligands with specific cell surface receptors displaying the potent antifungal activity of the ligand 2 heptyl 1,3-dioxolane against the fungal species.

References

1. Parivuguna V, Gnanaprabhal R, Dhanabalan R, Doss A. Antimicrobial properties and phytochemical constituents of *Rheo discolor* Hance. Ethnobot Leaflets. 2008; 12: 841-45.
2. Davis J. Inactivation of the antibiotics and the dissemination of resistance genes. Science. 1994; 264: 375-382.
3. Ng PC. Systemic fungal infections in neonates. Arch Dis of Childhood. 1994; 71: F130–F135.
4. Service RF. Antibiotics that resist resistance. Science. 1995 ; 270: 724-727.
5. Gonzalez CE, Venzon D, Lee S, Mueller BU, Pizzo PA, Walsh TJ. Risk factors for fungemia in children infected with human immunodeficiency virus: a case-control study. Clin Infect Dis. 1996; 23: 515–521.
6. Sinnott, J. T. (1987). *Candida (Torulopsis) glabrata*. Infect. Control. 8:334–336.
7. Sobel, JD. Pathogenesis and epidemiology of vulvovaginal candidiasis. Ann. N.Y. Acad. Sci. 1988. 544: 547–557.
8. Hitchcock CA, Pye GW, Troke PF, Johnson EM, Warnock DW. Fluconazole resistance in *Candida glabrata*. Antimicro. Agents Chemo. 1993; 37: 1962–1965.
9. Parekh J, Chanda S. *In vitro* antimicrobial activities of extracts of *Launaea procumbens* Roxb. (Labiateae), *Vitis vinifera* L. (Vitaceae) and *Cyperes rotundus* L. (Cyperaceae). Afri J Biomed Res. 2006; 9: 89-93.
10. Watt JM, Breyer-Brandwijk MG. The medicinal and poisonous plants of southern and eastern Africa. 2nd Edn. E and S Livingstone Ltd. Edinburgh, 1962.
11. Holdsworth DK. Medicinal Plants of Papua New Guinea, South Pacific Commission Technical paper No.175, Noumea, New Caledonia. 1977.
12. Kirtikar KR, Basu BD. Indian Medicinal Plants. Bishen Singh, Mahandra Pal Singh Publishers, Dehradun, India. 1980; 1: 802-803.
13. Burkill HM. The useful plants of West Tropical Africa. Royal Botanical Gardens, Kew, Richmond, United Kingdom. 1994; Vol. 2.
14. Jayasinghe PKIDE, Bandara BMR., Ekanayaka EWMA, Thevanesam V. Screening for antimicrobial activity of *Acronychia pedunculata* (Ankenda) and *Adenanthera pavonina* (Madatiya) against bacteria causing skin and wound infections in humans. Proceedings of the Peradeniya University Research Sessions, Sri Lanka. 2006; 11: 105.
15. Duke JA. Dr. Duke's Phytochemical and Ethnobotanical Databases. Green Pharmacy Garden, Fulton. 2009.
16. Olajide OA, Echianu CA, Adedapo AD, Makinde JM. Anti-inflammatory studies on *Adenanthera pavonina* seed extract. Inflammopharmacology. 2004; 12(2): 196-202.
17. Adedapo ADA, Osude YO, Adedapo AA, Moody JO, Adeagbo AS, Olumayokun A, Olajide OA, Makinde JM. Blood pressure lowering effect of *Adenanthera pavonina* seed extract on normotensive rats. Rec Nat Prod. 2009; 32: 82-89.
18. Rodrigo SK, Jayasinghe ULB, Bandara BMR. Antifungal, antioxidant and cytotoxic activity of *Acronychia pedunculata* and *Adenanthera pavonina.* Proceedings of the Peradeniya University Research Sessions, Sri Lanka. 2007; 12(1): 94-95.
19. Bhadran S, George SA, Malla, S and Harini BP. Screening of bioprotective properties of various plant extracts and gas chromatography-mass spectrometry profiling of *Adenanthera pavonina* stem extract. Asian J Pharm Clin Res. 2017; 10: 188-94.
20. Blaney J, Dixon J. A good ligand is hard to find: Automated docking methods, Perspect. Drug Disc. Des. 1993; 1: 301-319.
21. Kitchen DB, Decornez H, Furr JR, Bajorath, J. Docking and scoring in virtual screening for drug discovery: methods and applications, Nat Rev Drug Discov. 2004; 3(11): 935-949.
22. Huang SY, Zou X. An iterative knowledge-based scoring function to predict protein-ligand interactions: I. Derivation of interaction potentials. J. Comput. Chem., 2006; 27: 1866–1875.
23. Srivastava V, Gupta SP, Siddiqi MI, Mishra BN. Molecular docking studies on quinazoline antifolate derivatives as human thymidylate synthase inhibitors, Bioinform. 2010; 4: 357-365.
24. Fukunishi Y, Nakamura H. Prediction of ligand-binding sites of proteins by molecular docking calculation for a random ligand library. Protein Sci. 2011; 20: 95–106.
25. Ehrlich LP, Wadey RC. Protein-protein docking. Reviews in Computational Chemistry. 2003; 17: 61.
26. Chen R, Mintseris J, Janin J, Weng Z. A protein–protein docking benchmark. Proteins. 2003; 52: 88–91.
27. Smith RD, Engdahl AL, Dunbar JB Jr, Carlson HA. 2012. Biophysical limits of protein-ligand binding. J Chem Inf Model., 52(8): 2098-2106.
28. Gardiner EJ, Willett P, Artymiuk PJ. Protein docking using a genetic algorithm. Proteins. 2001; 44: 44–56.
29. Gray JJ, Moughon S, Wang C, Schueler-Furman O, Kuhlman B, Rohl CA, Baker D. Protein–protein docking with simultaneous optimization of rigid-body displacement and side-chain conformations. J Mol Biol. 2003; 331: 281–299.
30. Duhovny D, Nussinov R, Wolfson HJ. Efficient unbound docking of rigid molecules. In: Guigo R., Gusfield D., editors. Proceedings of the Fourth International Workshop on Algorithms in Bioinformatics. Springer-Verlag GmbH Rome, Italy. 2002; 185–200.
31. Pagenkopf B. ACD/HNMR Predictor and ACD/CNMR Predictor advanced chemistry development. J Am Chem Soc. 2005; 127 (9): 3232–3232.
32. Mani P, Menakha M, Al- Aboody MS, Alturaiki W, Vijayakumar R. Molecular docking of bioactive compounds from Piper plants against secreted aspartyl proteinase of Candida albicans causing oral candidiasis. International Journal of Pharmaceutical and Clinical Research, 2016; 8(10): 1380-1389.
33. Daina A, Michielin O, Zoete V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci Rep 2017; 7: 42717.
34. Daina A, Zoete V. A BOILED-Egg To Predict Gastrointestinal Absorption and Brain Penetration of Small Molecules. ChemMedChem 2016; 11(11):1117-1121.
35. Lengauer T, Rarey M. Computational methods for biomolecular docking. Curr Opin Struc Bio. 1996; 6 (3): 402–406.
36. Dar AM, Mir S. Molecular Docking: Approaches, types, applications and basic challenges. J Anal Bioanal Tech. 2017; 8: 356.
37. McPhillie MJ, Cain RM, Narramore S, Fishwick CW, Simmons KJ. Computational methods to identify new antibacterial targets. Chem Biol Drug Des. 2015; 85: 22–29.
38. Pasko MT, Piscitelli SC, Van Slooten AD. Fluconazole: A New Triazole Antifungal Agent. DICP. 1990; 24(9): 860–867.
39. Latha R, Fathima M, Ganesan S. GC-MS analysis and *in silico* docking analysis of extracts of *Acacia torta* Craib. Asi J Sci Techn. 2017; 8(7): 5119-5123.
40. Kumar ASG, Javvadi RK, Kumar VK, Reddy ME, Reddy VY, Harshavardhan G, Akbar M D. Effect of methanolic extract of *Adenanthera pavonina* linn on Dalton's Ascitic Lymphoma. Ind J Res Pharma Biotech. 2014; 1(1): 138-141.

41. Sasikala RP, Meena KS. *In Silico* Molecular Docking Studies of Multi-Potential Compounds Isolated from *Premna Serratifolia* L., Inn J Life Sci. 2016; 4(3): 1-7.
42. Rehman TU, Khan AU, Abbas A, Hussain J, Khan FU, Stieglitz K, Ali S. Investigation of nepetolide as a novel lead compound: Antioxidant, antimicrobial, cytotoxic, anticancer, anti-inflammatory, analgesic activities and molecular docking evaluation. Saud Pharm J. 2018; 26: 422–429.
43. Singh V, Praveen V, Tripathi D, Haque S, Somvanshi P, Katti SB, Tripathi CKM. Isolation, characterization and antifungal docking studies of wortmannin isolated from *Penicillium radicum.* Nat Sci Rep. 2015; 5: 11948.

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