RESEARCH PAPER

In-silico docking of Plectranthus amboinicus against Blastomyces dermatitidis for the potential therapeutic uses

Danda Nishitha [1]*, Sathish Sankar[2]

[1]Undergraduate, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Velappanchavadi, Chennai - 600 077. Tamil Nadu, India.
[2]Department of Microbiology, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Velappanchavadi, Chennai - 600 077, Tamil Nadu, India.

***Corresponding authors:**Prof. Sathish Sankar
, Department of Microbiology, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Poonamallee High Road, Chennai – 600 077, Tamil Nadu, India. **Email:** sathish3107@gmail.com **ORCID:** 0000-0002-9389-5231 **Phone:** +91-9600690306

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Introduction:

In-silico molecular docking is a computational technique which results in the studies of bio-active peptides or chemical drug molecules that exert their action by binding with special receptors which provide the pattern, affinity and bonding confirmation. In silico studies include bio-active peptides (1). These bio-active peptides bind to specific receptors. In- silico docking helps to understand the interaction between ligand and the target protein. It helps in prediction of the most stable binding orientation by calculating the binding affinity. Molecular docking helps in activation or inhibition of biological targets. There are various docking programs such as AutoDock, AutoDock vina, pyMOL (2).

P.amboinicus (Plectranthus amboinicus) is commonly called a mint plant. It is an aromatic herb that is bio-active (3). It is considered as a therapeutic plant which helps in treating respiratory issues like asthma and cold (4). P.amboinicus consists of diuretic properties. It improves the irritable bowel syndrome and relieves indigestion. P.amboinicus decreases the pain during breastfeeding and improves the cold symptoms and tolerance subjectively. Compounds in P. amboinicus contribute to it's anti-inflammatory, antioxidant and anti microbial properties (5).

Blastomyces dermatitidis is also called Blastomycosis, is a group of thermally dimorphic fungi which is found in moist rich areas containing decomposing leaves, wood (6). It commonly causes extra pulmonary infections. Lungs are the preliminary organs affected by this virus. Early symptoms might include respiratory illness such as cough, fatigue, fever. This is usually caused by inhaling the airborne spores which are contaminated from the surrounding into the lungs in the body (7). Blastomycosis development leads to risk factors such as immunosuppression and collagen vascular disease (8). There is no particular vaccine to prevent blastomycosis. Different drugs are being introduced to prevent the Blastomyces dermatitidis.

Curcumin and quercetin are the important phytochemicals of Plectranthus amboinicus. These photochemicals are used in this study. Curcumin is a naturally occurring photochemical which acts against gastrointestinal diseases and hepatic disorders, anorexia and cough. Curcumin is mainly found in turmeric. It induces apoptosis and inhibits tumour cell proliferation, thus showing a significant role in anti-cancer therapies (9). It mainly helps in treating diseases like arthritis, rheumatoid arthritis and inflammatory bowel diseases. Curcumin acts as an antioxidant which helps in neutralisation of free radicals and boost's the body antioxidant enzymes which help in protecting cells from damage (10).Curcumin exhibits anti-inflammatory activity, which suppresses the NF-κB inflammatory signaling pathway by controlling many inflammation related genes (11).

Quercetin is a natural flavonoid which is found in fruits and vegetables like onions and apples (12). Quercetin is the most commonly used for the conditions of the heart and blood vessels. It shows a significant effect in reducing oxidative stress in blood vessels which lowers the blood pressure and improves endothelial function. It helps in the prevention of cancer (13). It helps in the increment of antioxidant enzymes such as catalase, glutathione. Quercetin shows antimicrobial and antiviral effects. It inhibits the replication of various bacteria and viruses (14). Quercetin stabilizes mast cells by inhibition of release of histamine helping in anti-allergic conditions like asthma (15).

The aim of this study is to analyze the in-silico docking of Plectranthus amboinicus against Blastomyces dermatitidis for the potential therapeutic uses. By identifying compounds with favorable binding interactions, this research contributes to the

*Author for Correspondence: : sathish3107@gmail.com

development of plant-based antifungal agents and to support various approaches in modern pharmacological research.

Materials and methods:

Data: The 3D protein structure of plasma membrane protein RCh1P was not available in the protein data bank. Hence, the protein was modelled using the Swiss-Model online server program (https://swissmodel.expasy.org/). Template search with BLAST and HHblits has been performed against the SWISS-MODEL template library. Models are built based on the target-template alignment using ProMod3. Coordinates which are conserved between the target and the template are copied from the template to the model. Phytochemicals identified from honey namely, caffeic acid, cinnamic acid, gallic acid, syringic acid, ellagic acid were selected for the study. The two-dimensional chemical structures in structured data format (SDF) were retrieved from PubChem database and were converted into Protein data bank (PDB) format using Pymol. Antifungal drug, fluconazole was processed similarly and considered as controls.

Interaction of the drug including pharmacological effects and mechanism of action. interaction with metabolic enzymes and transporters, influence on gene expression, possible adverse effects and side effects were predicted using Passonline web server (http://www.way2drug.com/passonline). SMILES (Simplified Molecular Input Line Entry System) of each drug was fed as the input for each drug. Ten interactions with the highest Pa value is shown in Table 1 and 2. Pa (probability "to be active") is an estimate of the probability of the drug belonging to the sub-class of active compounds resembling the established set of actives in the server training set. Similarly, Pi is the probability "to be inactive" that is estimated by the server.

The physiochemical properties, lipophilicity, water solubility, pharmacokinetics and drug-likeliness were assessed using the SwissADME online server program. SMILES of each drug was used as the input.

Optimal docking areas were calculated using molsoft online server (http://www.molsoft.com). The output was viewed using a PyMOL Program.

Molecular Docking:

Molecular docking was carried out using Hex Protein Docking server. The receptor and the ligand were fed as a .pdb file and the resulting interactions with the docking score were recorded.

The program named HEX dock version 8.0.0 was used. Receptors, Curcumin and quercetin were taken and the protein, Adhesin WI-1 were adjoined. The in-silico docking was conducted. E-score which is a computational result that is specific for a particular program and energy function was obtained.

Along with the E-score, the number of hydrogen bonds were also obtained. PYMOL was carried out later. PYMOL is generally used to analyze, view and save the molecular structure that is obtained.

Results:

S. No	Phytochemicals	PubChem ID	Binding Residues	E-total
1	curcumin	969516	GLY-412 and SER-415	-285.63
2	quercetin	5280343	ARG-485(2) and ASP-447	-259.95

Molecular docking analysis was performed between selected phytochemicals from *Plectranthus amboinicus* and the target protein of *Blastomyces dermatitidis*. On molecular docking, a protein complex was obtained. The yellow bond was observed in the phytochemicals, quercetin and curcumin. The yellow band describes the interaction between the drug and their respective Proteins.When quercetin is compared to curcumin E-total, curcumin shows more binding capacity when compared to quercetin. The binding residues are considered as H-bonds. These hydrogen bonding patterns were observed.On molecular docking, curcumin and quercetin demonstrated a significant amount of binding affinity with the target protein.

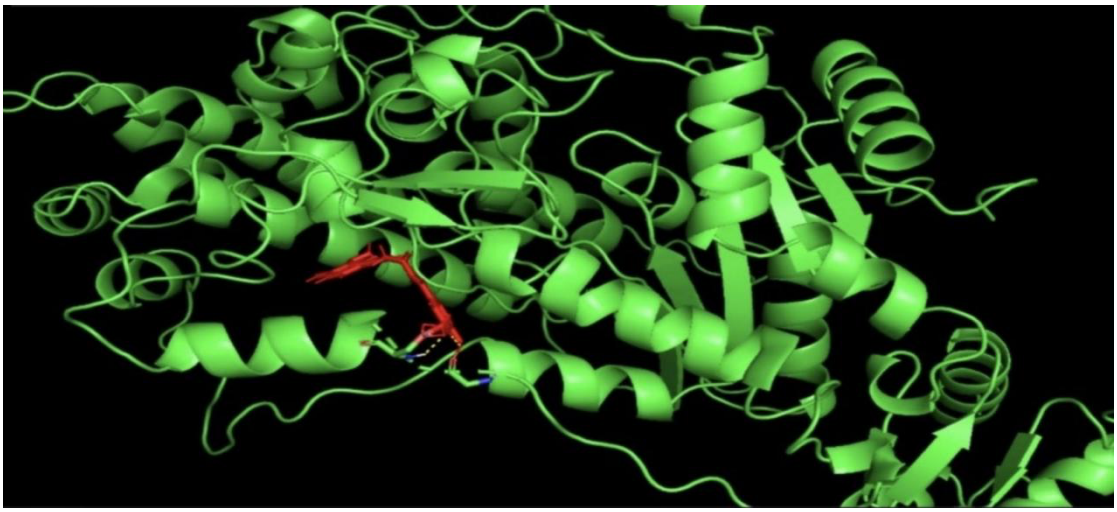

Figure 1: On in-silico docking, results revealed that curcumin exhibited strong interactions with the protein active site. Curcumin binds to the residues GLY-412 and SER-415, suggesting that these residues play a major role in stabilising ligand-protein interactions. The E-total obtained was -285.63.

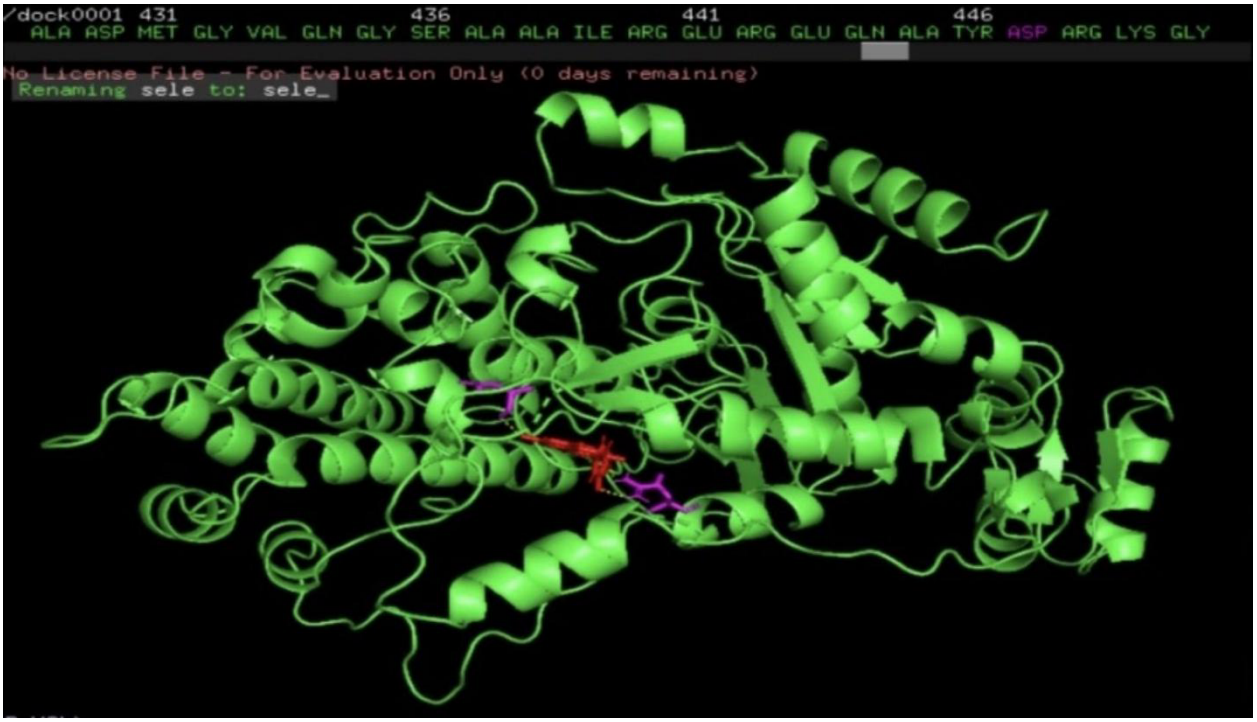

Figure 2: On in-silico docking, results revealed that quercetin also showed a significant binding with the protein, producing an E-total of -259.95. On in-silico docking, the photochemical quercetin binds to the residues ARG-485(2) and ASP-447. These interactions mostly stabilize through hydrogen bonds.

On visualisation and structural analysis of the docked complexes performed using pyMOL, the more negative is the value of E-total, the more is the binding capacity.The binding affinity of curcumin is comparatively higher when compared to quercetin binding affinity. Lower (more negative) binding energy corresponds to higher bonding interactions, higher bonding strength and greater stability of ligand-protein complex. Therefore, curcumin may possess a higher potential to inhibit the target protein function compared to quercetin.Overall, the interaction pattern suggests that the phytochemicals from *Plectranthus amboinicus* are capable of forming stable complexes with the fungal protein target through hydrogen bonding supporting their possible antifungal activity against *Blastomyces dermatitidis*.

Discussion:

From the results obtained, several photo chemicals exhibit significant interactions with selected fungal target proteins of Blastomyces dermatitidis using molecular docking approaches. From the previous results, it's observed that curcumin interacts with CRP at GLN 150 and ASP140 through the hydrogen bonds. Both the docking and simulation studies show that hothead curcumin consists of the potential as an antiviral

against the COVID-19 (16). Curcumin analogous as a promising ALK-5 inhibitor with the significant binding energy and H-bonding interaction (17). From the other studies, it can be stated that quercetin acts as an anti-Parkinson's agent and it plays an important role in inhibiting the conversion of angiotensin 1 to angiotensin 2 to enhance the blood pressure in the body (18).From the previous study, ten analogues of quercetin were found to be docked at the active site cavity with a favorable ligand-protein molecular interaction and interestingly from the ADME toxicity analysis. These analogues improved the pharmacological properties of quercetin (19). The secondary metabolites, quercetin, catechin and apigenin have inhibited the formation of beta-hematin through molecular interactions and is considered as an antimalarial agent (20). This study also shows the interactions between the drug and protein used in this study. On molecular docking of photochemicals in *Syzygium Aromaticam* demonstrated that compounds such as masilinic acid and oleanolic acid strongly bind to fungal metabolic enzymes such as 6C85 and 6C8W indicating their inflammatory potential against the pathogen (21). The present study investigated the binding affinity of phytoconstituents from *Plectranthus amboinicus* against target proteins of *Blastomyces dermatitidis* using molecular docking approaches. The results demonstrated that several phytochemicals exhibited significant interactions with the selected fungal target, suggesting their potential role as inhibitors of fungal growth and virulence. These findings are consistent with earlier studies reporting antimicrobial and antifungal activities associated with *P. amboinicus* extracts and essential oils. Phytochemical analyses of this plant have revealed the presence of diverse bioactive compounds such as flavonoids, phenolics, terpenoids, and essential oil constituents including thymol, carvacrol, and limonene, which are known to possess strong antimicrobial properties (22).The docking results obtained in this study indicate that selected compounds from *P. amboinicus* interact effectively with the active site residues of the target protein, forming hydrogen bonds and hydrophobic interactions that stabilize the ligand–protein complex. Such interactions are critical determinants of inhibitory potential in molecular docking studies. Similar observations have been reported in computational screening studies of other medicinal plants, where plant-derived metabolites displayed strong binding affinities toward microbial targets, highlighting their potential as lead compounds for antifungal drug development. Based on the previous molecular docking studies, *Plectranthus amboinicus mainly focused on targets related to cancer and metabolic disorders. LC-MS profiling* combined with docking analysis revealed that several phytoconstituents of the plant exhibit strong interactions with α-amylase and α-glucosidase enzymes (23).Previous experimental studies have proved that extracts of this plant exhibit broad-spectrum antimicrobial activity, including inhibition of different pathogenic microorganisms. Furthermore, the molecular docking analysis revealed that selected ligands comply favourable binding energy thresholds exhibiting stable ligand-protein complexes. Despite these promising results, molecular docking provides only a predictive model of ligand–protein interactions.

Conclusion:

From the results obtained, it can be concluded that in-silico docking of Plectranthus amboinicus shows potential therapeutic uses against Blastomyces dermatitidis. It highlights the potential of photochemicals derived from *Plectranthus amboinicus* as possible anti fungal agents against *Blastomyces dermatitidis.* Overall, the interaction pattern suggests that the phytochemicals from *Plectranthus amboinicus* are capable of forming stable complexes with the fungal protein target through hydrogen bonding supporting their possible antifungal activity against *Blastomyces dermatitidis*.Further studies are to be conducted to know about the study in detail about the therapeutic uses of Plectranthus amboinicus against Blastomyces dermatitidis.

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