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RESEARCH ARTICLE

In-silico Analysis of Endophytic Fungal Metabolites against secreted aspartic proteinase enzyme of *Candida albicans*

R. Krishna Veni, S. S. Meenambiga*
Department of Bio-Engineering, School of Engineering, Vels Institute of Science, Technology and Advanced Studies (VISTAS), Chennai-600117, Tamilnadu, India.
*Corresponding Author E-mail: **meenambiga.se@velsuniv.ac.in**

ABSTRACT:
The human microbiome includes various microorganisms where *Candida albicans* is also called as one of the member and it becomes infectious under conditions of immune dysfunctions which contribute to oral diseases such as oral candidiasis, caries and periodontal diseases. Secreted Aspartic proteinases (SAPs), a key virulence factor of *Candida albicans* have been established as a potential drug target in treating *Candida* infections. The present work focuses on the bio-active metabolites produced from endophytic fungi which were isolated from various medicinal plants with oral hygiene properties. About 6 varieties of plants were chosen which includes plants like *Mentha, Curcuma longa, Azadirachta indica, Aleo barbadensis* etc,. were found to have more oral medicinal properties. Endophytic fungi from those plants include *Ascomycetous, Trichoderma harzianum, Fusarium avenaceum*, *Talaromyces* sp., *Chaetomium* sp., *Epicoccum sorghinum,* etc,. In this study, *in silico* analysis of these 20 compounds such as koningnin, griseofulvin, viridin, piliformic acid etc., which were isolated from those endophytic fungi were performed. The compounds which passed Lipinski rule were docked against SAP 5 enzyme using Auto Dock 4.2.6 software. Most of the endophytic fungal compounds shows good Docking score among that viridin and TR-2 mycotoxin showed good docking score with highest binding energy -9.23 kCal/mol and -8.38 kCal/mol respectively against SAP 5 enzyme. Thus, these compounds could be effectively used as drugs targeting SAP 5 enzymes in treating *Candida* infections.

KEYWORDS: *Candida albicans*, Secreted aspartic proteinase 5 (SAP 5), Endophytic fungi, Docking.

INTRODUCTION:
The term endophyte means organism growing from inside tissue of the plant. Endophytic are of two groups one do not generate any external structures from host and the other one is which generate external structures like nodules. They are nothing but microorganism, which are grown from the healthy plant tissues without being harmful to the host cell. They have special ability to produce potential metabolites to enhance the power of host resistant against herbivores. From the information provided by molecular data it is proven that fungi are very much older, more than one billion years ago. This whole process is majorly depend on the bio activity of the endophytes.

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In recent most of the researchers are focused on the activity and ability of endophytic fungi which can produce various industrial, agricultural, pharmaceutical compounds. The active substance produced by them can also be used as antifungal, antibacterial, antitumor, antidiabetic agents. The working on microbial products production of drugs has started once after invention of anticancer drugs form *Penicillium*. The major relationship exist in between the endophytic fungi and the host plants are ranged from symbiotic to antagonistic or pathogenic or mutualistic *(Mishra Y et al).*

One of the member of human microbiome *Candida albicans* is a polymorphic fungus. They grow as ellipsoid cell in elongated form or as ovoid budding yeast shape. It can be also found in GI tract, the mouth, and the vagina. The species name *albicans* comes from the Latin word for white. These yeast appears as white when cultured on a plate. They are also called as opportunistic pathogens, they also remains as a harmless

group in most of the human beings for life long. At some stage of point *C. albicans* cause severe infection majorly over the sensitive tissues such as skin. And in case of certain type of infections, like thrush it can create white patches. Those infections can be life threatening and some other activities of these fungus are identified to be potentially pathogenic. Some reasons can make humans weak and make *albicans* cause infections easily such as having too much of antibiotics in regular routine, diabetes, having artificial medical devices like urinary catheter inside the body, having weak immune system. My study majorly focuses on oral hygiene properties and curing oral infections and diseases. Since oral cancer and oral infections are one of the threatening infection in recent and upcoming generations. Peoples having high possibility of having oral thrush includes patients consuming corticosteroid drugs, patients with severe diabetes, immunosuppressed individuals, and peoples who wear dentures. These can be cured by antifungal medications and drugs. Thus it also leads to side effects. To reduce that side effect the drug from medicinal plants are preferred. Thus the endophytic fungi from the medicinal host plant where chosen which has oral hygiene properties *(Jia M et al).*

These metabolites are then made to react with the target enzyme SAP for *Candida.* A key virulence factor which are in group with 10 hydrolase are called as Secreted Aspartic Proteinase (SAPs). These enzymes in immune defence mechanism were able to disturb and degrade some selected host immune cells. The fungus been benefited by the nutrient aminoacids supplied by these enzymes. During infection they plays an important role in penetration into deeper tissues and interaction with host defence. It acts towards human haemoglobin through limited proteolysis to generate a variety of antimicrobial hemocidins. This enables them to fight against the organism of the same ecological and physiolaogical nature i.e. the organism which fits in the same environment. To complete this process they use the microbicidal peptides generated from the host protein. Preferential cleavage at the carboxyl of hydrophobic amino acid, but fails to cleave Leu 15 | Tyr 16, Tyr 16 | Leu 17, Phe 24| Phe 25 of insulin b chain. activates trypsinogen, degrades keratin. It is inhibited by pepstatin A analogs. Optimum pH is 5.0.

The durability and drug likeliness of a chemical compound or a secondary metabolite can be evaluated through Lipinski's rule of five. The pharmacokinetics of a drug which is the most important molecular property of a chemical compound that can be described using this rules. Therefore Lipinski's rule of five is essential for an endophytic fungi secondary metabolite to use as a drug compound. The secondary metabolite that obeys and satisfies the Lipinski's rule are further subjected to docking studies.

MATERIALS AND METHODS:

Bioactive compounds from endophytic fungi secondary metabolites:

The following compounds were chosen from the various PubMed Literatures:

These compounds shows efficient antimicrobial and antitumor activity and thus were selected to study the mode of interactions of these compounds with the active site of *C. albicans* SAP5 enzyme. The information about the structure of above-mentioned Metabolites were retrieved from the PubChem database.

TABLE 1: Details of plant species and the compounds isolated.

No	Plant Name	Species Name	Compound Name
1.	*Mentha*	*Ascomycetous[7]*	Chaetomugulin
			Dechlorogriseofulvin
			Griseofulvin
2.	*Curcuma longa*	*Trichoderma harzianum[19]*	Harzianopyridone, Viridin, 6-pentyl-alpha-pyrone, harzianolide
			Massoilactone
			Koningnin
3.	*Taxus brevifolia*	*Penicillium sp*	Phosmopsolides
4	*Torreya taxifolia*	*Pestdotiopsis microspora*	Torreyanic acid
5	*Sequoia sempervirens*	*Aspergillus paraiticus*	sequoiatones
6	*Taxas mairei*	*Paecilomyces sp*	Brefeldin A
7	*Aloe barbadensis*	*Talaromyces[11]*	Talathermophilins
		Xylaria	Piliformi acid
8	*Rhodomyrtus tomentosa*	*Epicoccum sorghium[10]*	Epicoccraine Epipyridone Methoxy pyridone - n- pyridone
9.	*Azadirachta indica*	*Fusarium avenaceum[8]*	Antibiotic Y

SAP5 protein structure:

Using a protein database called **CASTp server** the structure of the SAP5 protein is retrieved. The obtained 3D structure is depicted in Figure (1). The CASTp is a world wide data base with online open access which provides the user about the structure, function and properties of various macro molecules like nucleic acids. The PDB ID of the SAP5 protein is 2QZX (Figure1). For effective ligand binding the protein macro molecule is been altered first by removing the water molecules from it. SAP5 has a molecular weight of 37KDa and it is also called as one among the 10 acidic hydrolases. This enzyme is active at a pH of 3.0–7.0. There are two active chains in the protein molecule such as A chain and B chain, the number of amino acid residues present in each chain is 342. This factor is considered to be the key virulence which is meant to affect the host. The enzyme is responsible for degrading the host defense mechanism and they also serve as a supplier f nutrients to the fungus. The enzyme play major role in causing skin infection such as cutaneous candidiasis in humans. At some case

in the immunosuppressed patients these enzymes are more active in causing infection by penetrating into the tissues. It acts towards human haemoglobin through limited proteolysis to generate a variety of antimicrobial hemocidins. This enables them to fight against the organism of the same ecological and physiological nature. To complete this Process they use the microbicidal peptides generated from the host protein. The ligand pepstatin A is the most potent inhibitor of the aspartyl proteinases, This ligand shows a very high binding efficiency with the SAP5. SAP5 consist of many set of strong hydrogen bonds which involves aspartic residues Asp32 and Asp218 along with the residues Gly34, Gly85, Asp86, Gly220, and Thr222. These catalytic aspartic residues are highly conserved. The inhibitor binding at residues 83 and 221 are mainly taking part in the hydrogen bonding, there by forming a network of interactions. The active site region of SAP5 enzyme in complex with inhibitors isovaleric acid and statine retrieved from CASTp server. Asp218 along with the residues Gly34, Gly85, Asp86, Gly220, and Thr222. These catalytic aspartic residues are highly conserved. The inhibitor binding at residues 83 and 221 are mainly taking part in the hydrogen bonding, thereby forming a network of interactions.

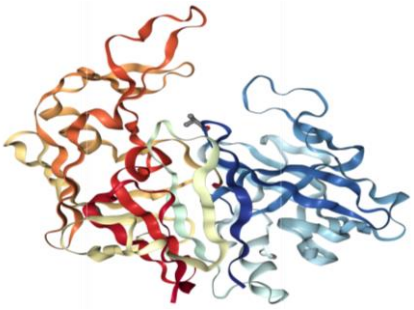

Figure 1: Secreted aspartic proteinase 5 (Sap5). PDB Id: 2QZX with chains A and B in complex with a selective inhibitor.

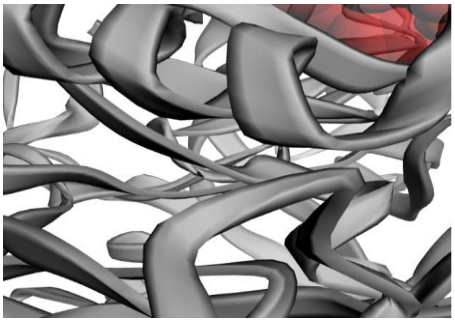

Figure 2: Active site of Secreted Aspartic Proteinase 5 (SAP 5) PDB Id: 2QZX.

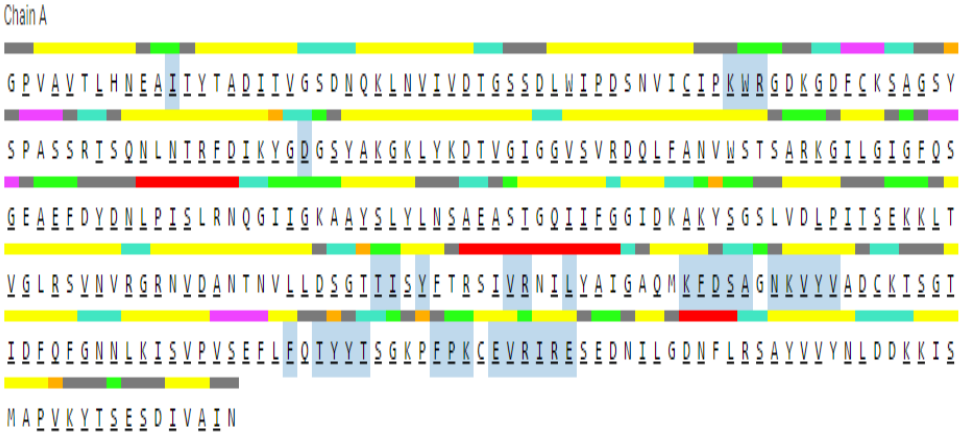

Figure 3: Results from CASTp showing the positions of active site in chain A of SAP 5 PDB Id: 2QZX

Table 2: Lipinski properties of diverse endophytic fungal metabolites

S. No	Endophytic fungal metabolites	Molecular weight (<500 Da)	Log P (<5)	H-bond donor (<5)	H-bond acceptor (<10)	Molar refractivity (<130)
1	Koningnin	270.24	2.42	3	5	70.81
2	Decholorogriseofulvin	270.24	2.42	3	5	70.81
3	Griseofulvin	290.27	1.54	5	6	72.62
4	Harzianopyridone	368.38	3.37	2	6	102.01
5	Massoilactone	270.24	1.88	3	5	69.48
6	Trichodermin	242.27	2.81	2	3	68.15
7	TR-2 mycotoxin	270.24	2.11	3	5	71.00
8	Viridin	294.39	3.23	2	4	82.75
9	Harzianolide	286.24	2.30	4	6	72.38
10	Dehydroharzianolide	318.23	1.71	6	8	75.71
11	6-pentyl-alpha-pyrone	344.32	2.70	2	7	88.20
12	Talathermophilins	302.34	2.01	5	7	74.05

13	Piliformic acid	228.24	2.97	3	3	66.80
14	Antibiotic Y	482.44	2.36	5	10	119.45
15	Epicoccraine	304.25	1.18	5	7	73.24
16.	Methoxy pyridone-N-oxide	401	3.713898	4	6	111.269058
17	Brefeldin A	125	0.328600	0	2	31.953995
18	Sequoiatones	374	3.515919	1	5	103.484764
19	Torreyanic acid	692	4.146899	2	12	173.595856
20	Phomopsolide	214	2.298400	2	4	56.660587

DOCKING STUDIES USING AUTO DOCK 4.2.4:

Docking studies were performed using the bio-active metabolites from endophytic fungi against the enzyme SAP5 using an automated bio-informatics docking based on the principle of Lamarckian genetic algorithm. The docking interactions community to study protein-ligand interactions. The principle behind Auto Dock 4.2.6 software is Lamarckian genetic algorithm. The docking interaction between the ligand and the target receptor leading to structure-based drug designing and developmental process are performed using this software. To achieve the drug development process the Auto Dock 4.2.6 uses two methodologies namely Effective search of torsional freedom and Rapid grid-based energy evaluation (Kandasamy S et al).

DISCOVERY STUDIO VISUALIZER 3.1:

Discovery Studio Visualizer 3.1, developed and distributed by Accelrys, is a free software used for visualizing the macromolecule-ligand interactions. This software is used to study the simulation of small molecules and large macromolecules. The main scope of this software includes structure-based design, simulations, ligand design, macromolecule engineering, macromolecule design and validation tools for antibody design (Dharani et al).

RESULTS AND DISCUSSION:

The endophytic fungal metabolites retrieved from PubMed literatures were checked for their Lipinski's rule. Among the 20 compounds selected, 19 compounds satisfied Lipinski's rule which is indicated in table 3. Docking analysis of the endophytic fungal metabolites was performed using Auto Dock 4.2.6 and the results give the best interaction. The receptor-ligand interactions were visualized in Discovery Studio Visualizer. The binding sites and the active site of the docked molecules is compared with the active site of the SAP protein.

Thus the compounds binding energies and the hydrogen bonds and its are given in the table 3. The compounds like, Griseofulvin, TR-2 mycotoxin, Viridin shows higher binding energies and the compounds Methoxy pyridone-N-oxide, 6-pentyl-alpha-pyrone, piliformic acid shows lower binding energies. The Lipinski values of each compound are valued and mentioned in table 3. Thus the novel compound is chosen by comparing these two tables the active sites of both the novel compound and actual protein is compared. For example the compound koningnin has binding energy of 5.86 kCal/mol and which perfectly obeys the Lipinski rule of five forms hydrogen bonds with Gly34, Gly 85, Lys 83 at the active site similar to our target protein SAP 5. The binding efficiency of each compound with the active site of SAP5 enzyme was found to be good with a strong pi bond interaction and this compound was proved to have fungicidal activity against *C. albicans.*

Many studies have been done using endophytic fungi which also includes the compound Diketopiperazine isolated from *Penicillium sp*, which are potent inhibitors against Hsp90 thus its invitro and in vivo analysis further provided a crud compound which can be used against Hsp90 (Sharma R et al). Other applications includes their role in skin cancer, the two compounds namely Heptadecanoic acid and 16 methyl isolated from the fungal strains of *Hypocrea* species GC-MS result shows their efficient activity against skin cancer protein. The *Trichoderma* species are known to produce fatty acids and some novel cytotoxic compounds such as Trichodenone which shows significant cytotoxicity against p288 cell line they also has antibacterial, antifungal, antiptotozal, antiviral activity (Kandasamy S et al). Ketoconazole is a commercially available antifungal agent is used as a reference compound. These are high dosage antifungal agents which is supplemented for long period of time. This drug is used for the infections such as candidiasis, oral thrush, chronic mucocutaneous candidiasis, blastomycosis etc., Its major role is inhibiting the synthesis of ergosterol by interacting with the enzyme P-450 which is responsible for conversion of Lanosterol to Ergostero (Gomez-Gracia O et al).

The activities of *C. albicans* is already checked through in silico method with the compounds from plants. Thus the plant phytochemicals such as equal and emodin were found to have good docking score and are suggested as drug compound against Candida infections (Meenambiga SS et al). Various endophytic fungal secondary metabolites have shown anti Candidal activity. Qiu et al., (2010) reported that the tree Gingko biloba produce the endophytes *A. nidulans* and *A. oryzae* shows the presence of flavonoids in them. 1- Eicosanol, an arachidyl alcohol and the sesquiterpene compound eudesma-5, 11(13)-dien-8, 12-olide were also present in the extract of A. nidulans (Qiu M et al). Eudesmanes were found to be present in many endophytic fungi such

as Xylaria sp. and Nodulisporium sp (Park MS et al) (Santoss Filho FC et al). Guerrero-Perilla et al., (2015) performed docking studies on 32 natural compounds against NMT enzyme of C. albicans which showed that flavonoids, xanthones, quinones, alkaloids have better interaction with NMT than terpenoids, phenolics and coumarins when compared to previously reported synthetic inhibitor (Guerrero-Perila C). Benzofuran-triazole derivatives with antifungal property were subjected to docking studies against NMT to study their interaction efficiency and they showed good binding affinity (Liang Z et al).

Table 3: Molecular docking analysis of secondary metabolite of endophyic fungi.

S, No	COMPOUND NAME	BINDING ENERGIES (kCal/mol)	NO. OF H BONDS	H BOND INTRACTING RESIDUE
1	Koningnin	-7.09	3	Gly A 34,Gly A 85, Lys A 83
2	Decholorogriseofulvin	-7.54	1	Gln A 282
3	Griseofulvin	-8.02	1	Gln A 282
4	Harzianopyridone	-7.96	2	Gly A 85,Asp A 32, Asp A 86
5	Massoilactone	-6.18	1	
6	Trichodermin	-7.07	1	Gln A 282
7	TR-2 mycotoxin	-8.38	2	Ser A 277
8	Viridin	-9.23	1	Gln A 282
9	Harzianolide	-7.10	3	Arg A 312, Arg A 297, Glu A 278
10	Dehydr- harzianolide	-6.49	1	Tyr B 284
11	6-pentyl-alpha-pyrone	-5.94	1	Arg A 297
12	Talathermophilins	-7.71	1	Gln A 282
13	Piliformic acid	-5.52	2	Arg A 228
14	Antibiotic Y	-7.37	3	Leu A 280, Ser A 277, Lys A 257, Gln A 282
15	Epicoccraine	-6.80	4	Lys A 257,Cys A 256, Gln A 282,
16	Methoxy pyridone-N-oxide	-4.37	2	Val A 296, Tyr B 252
17	Brefeldin A	-7.50	3	Glu A 278, Arg A 312, Arg A 297
18	Sequoiatones	-7.75	2	Leu A 280, Gln A 282
19	Phomopsolide	-7.21	2	Arg A 292, Gln A 282.

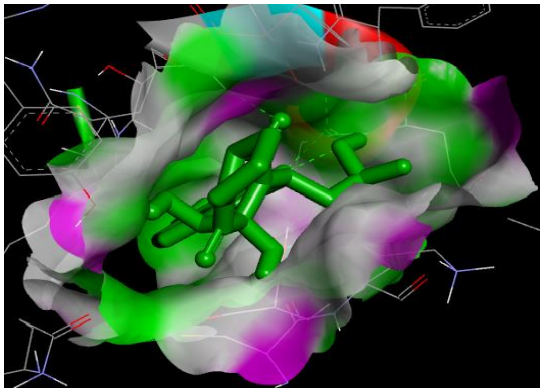

Figure 4: Docked confirmation of the compound viridin with SAP5 active site.

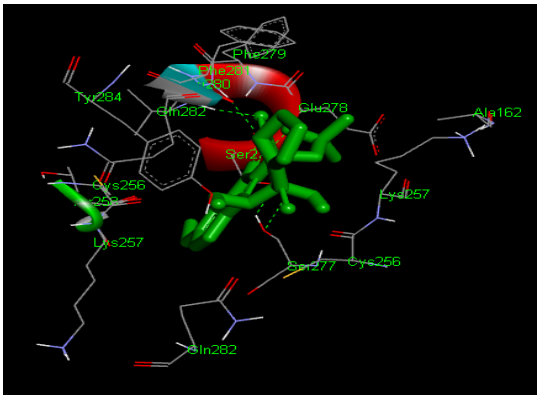

Figure 6: 3D interaction of TR-2 Mycotoxin with SAP enzyme.

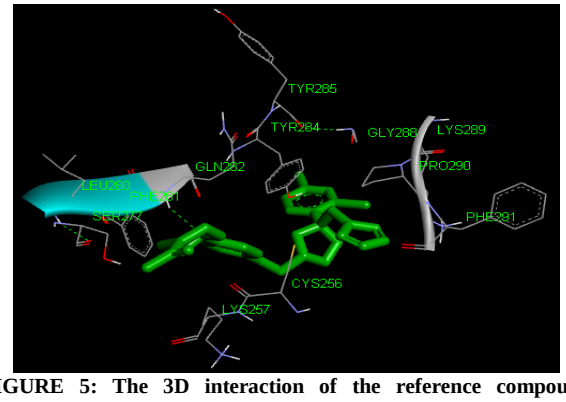

FIGURE 5: The 3D interaction of the reference compound ketoconazole with sap enzyme

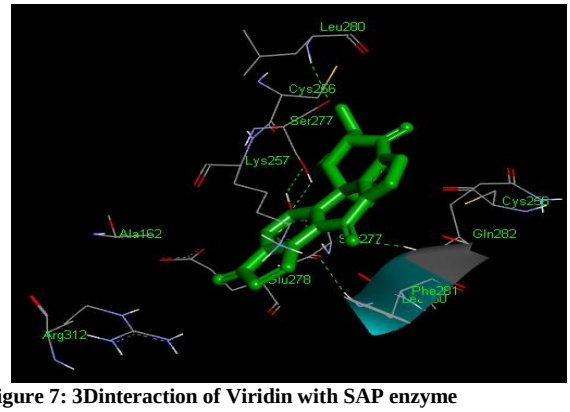

Figure 7: 3Dinteraction of Viridin with SAP enzyme

CONCLUSION:

The improvement of natural compounds with more biological activity is needed for treating selective infections. The analysis was already done with plant phenolic compounds against SAP enzyme provides same resulting compounds which can be used as drug. They also compared with in-vivo literature to confirm the possible reactions of the plant using solvent extraction method. The current study made it possible to identify new compounds which can be used as drug compound. Secondary metabolites from endophytic fungi possess antifungal properties against *C. albicans* but the study about their mechanism of action is still lacking the need of demand. The SAPs are used to evade the host defense mechanism and degrade foreign tissue. The experiment with the in-vitro model and the Strains of *C. albicans* shows less virulent and also caused little damage because the strains of *C.albicans* is altered by deleting the SAP1, SAP2, and SAP3. In our study the endophytic fungal metabolites viridin with -9.23 kCal/mol and TR-2 mycotoxin with -8.38 kCal/mol show good docking score were suggested as a good drug compounds against oral infections caused by *Candida albicans*. Thus, this will be a lead to develop a drug based on the molecular interactions analyzed, that specifically inhibits the SAP enzyme pathway of *C. albicans.*

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