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Identification of effective plant extracts against candidiasis: an in silico and in vitro approach

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Abstract

Background Globally, millions of people suffer from repeated fungal infections affecting the skin, keratinized tissues, and mucosal membranes. Approximately 1.7 million cases result in death with an elevated incidence rate among immunocompromised people that may later result in severe infections. Among the causative agents, *Candida albicans* are the most prevalent fungi inducing subcutaneous to invasive candidiasis. Although they are commensals in human body alteration in gut or prolonged treatments results in candidiasis. Several virulence proteins of *C. albicans* are involved in infections and secreted aspartic proteases2 (SAP2) plays an important role among them by causing damage to the reconstituted human epithelium. In the present study, phytochemicals from *Heliotropium indicum*, *Grona triflora, Ziziphus mauritiana, Atalantia racemosa, Coccinia grandis, Caryota urens, Aristolochia bracteolata, Evolvulus alsinoides, Pyrus communis* and *Commelina benghalensis* were studied against SAP2 with the help of bioinformatic tools to understand their binding efficiency.

Results The phytochemical structures were retrieved from PubChem database and the target protein structure was retrieved from PDB database with ID:3PVK. ADME profiling for phytochemicals was performed with Qikprop module, followed by docking with protein using Schrodinger software. Docking studies showed that Indicine-*N*-Oxide from *H. indicum* scored the significant glide score of − 5.54 kcal/mol. Finally, antifungal studies against *C. albicans* were conducted using several extracts of plants containing phytochemicals with considerable glide scores on docking studies. The Ethyl acetate leaf extract of *H. indicum* prominently inhibited the fungal growth when compared with the control.

Conclusion Identification of effective therapeutic candidates for the treatment of fungal infection is facilitated by the potential of *H. indicum* to hinder fungal growth and the interaction of their phytocompounds with fungal targets paves a way for developing a novel drug.

Keywords Phytochemicals, *Heliotropium indicum*, Candidiasis, SAP2, Docking

Background

Mycoses or fungal skin infections are the leading cause of human skin infections caused by dermatophytes or yeast. Although these infections are non-fatal, they are prone to superficial life threatening conditions in immunocompromised patients. According to a global survey, around 150 million people suffer from severe fungal infections and 1.5 million death cases were reported in which approximately 700,000 cases were due to invasive candidiasis [1]. The broad term Candidiasis refers to cutaneous, mucosal or organ infections through fungi of *Candida* genus that results in white patches on skin [2–4]. Candida is used to describe a class of fungi having more than 150 species. Among various species of Candida, *C. albicans* is one of the most common causes of

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Cutaneous candidiasis as they can grow on moist areas of the body and cause superficial infections characterized by the formation of lesions to wide rashes with high frequency in diabetic and HIV patients [2]. They are dimorphic commensals in healthy individual skin, mucosa and gastrointestinal tract which when imbalanced results in overgrowth and induce candidiasis [5–7]. These organisms are able to form biofilms that helps them to develop antifungal resistance by two mechanisms. In the first step, biofilms reduce the drug ability to penetrate followed by the survival of organisms under the increased oxidative stress by the development of persister cells that uses various mechanisms [8, 9]. Risk factors associated with candidiasis include long term usage of various drugs, rupture of mucosal or cutaneous barriers or via immunosuppression [10]. These yeast-type fungus are opportunistic fungi responsible for candida intertrigo in all hair bearing skin causing white patches on the skin where the epithelial cells are damaged by the cytolytic peptide toxin called candidalysin [11–14]. For the physiology and development of fungi proteolytic enzymes plays an important role by promoting morphogenesis and metabolism of fungi [15, 16]. Proteases are a family of protein comprises of ten members in which secreted aspartic proteinase1 (SAP1), secreted aspartic proteinase2 (SAP2) and secreted aspartic proteinase3 (SAP3) are responsible for the damage in the reconstituted human epithelium (RHE) followed by adhesion and are secreted by the yeast form [17–20]. The optimal pH for the SAP activity ranges from 2.0 to 7.0 thus they may be considered as a virulence factor in human infections [20]. Candidapepsin2 are also called as secreted aspartic proteinase2 (SAP2) capable of digesting C3b, C4b, and C5 complement components of host and cause inhibition of terminal complement complex formation (TCC) are one among the SAP genes required for the disease development and tissue degradation [21, 22]. Although various treatments are available with azole drugs and polyenes, prolonged usage of which can leads to resistance and as the available drugs are expensive and some are nephrotoxic it is better to choose an alternative drug [23–25]. Medicinal plants have been used traditionally for various ailments due to the presence of myriads of phytocompounds. Some of them have proved to be effective antifungal agents as crude or as a pure compound [26–29]. Plants like *Heliotropium indicum* have been widely used as a folk medicine due to its antimicrobial and anti-inflammatory effect [30, 31]. Due to its medicinal properties, survey has shown that *Grona triflora* can also be employed to treat various ailments [32]. However, scientific evidence is required in order to understand how these plant components interact with in pathogenesis of candidiasis. The current study focuses on the analysis of various phytocompounds selected from 10 different medicinal plants possessing activity against skin infections based on literature survey through their binding efficiency with the protein candidapepsin2 of *C. albicans*, followed by in vitro antifungal studies.

Methods

Protein structure retrieval

The 3D structure of Candidapepsin2 (SAP2) protein of *Candida albicans* was retrieved from Protein Data Bank (www.rcsb.org) [33]. The active site of the protein was predicted using online tool Ligsite (http://projects.biotec.tu-dresden.de/pocket/) [34].

Ligand structure retrieval

Based on the literature survey, structure of phytocompounds from 10 different medicinal plants like *H. indicum, G. triflora, Caryota urens, Evolvulus alsinoides, Ziziphus mauritiana, Atalantia racemosa, Commelina benghalensis, Aristolochia bracteolata, Pyrus communis* and *Coccinea grandis* was retrieved from PubChem database (http://www.ncbi.nlm.nih.gov/pccompound) [35].

Preparation of proteins and ligands

Maestro 9.0 version of Schrodinger suite was used for Protein preparation where protein preparation wizard was used to add hydrogen atoms and remove the water molecules within het groups [36]. Using algorithms optimization of 3D and ligand geometry were carried out with minimization of energy and LigPrep module (Schrodinger, LLC, NY, USA, 2009) was used for ligand preparation where addition of hydrogen atoms can generate the 3D structure of ligands [37, 38].

ADME studies

The properties of absorption, distribution, metabolism, excretion and toxicity of the ligand are a vital step in drug designing which was determined with Qikprop module in the Schrodinger suite [39] where the selected phytocompounds were assessed to find their drug likeliness within the parameters like rotatable bonds, molecular weight, dipole moment, hydrogen bond acceptor, hydrogen bond donor, blood brain barrier coefficient, human oral absorption, skin permeability and Lipinski's rule of three and five on QikProp module. Only those compounds that have significant ADME profile were considered for further docking studies and their pharmacological effects were validated using PASS online tool [40, 41].

Docking studies

Grid-based Ligand Docking with Energetics (GLIDE) module of Schrodinger software (http://www.schrodinger.com/) was used for to identify the ligand protein interaction and their significant binding efficiencies with

the help of glide score using XP (Xtra Precision) visualizer in which the best hits can be identified [42, 43].

Preparation of plant extract

Plant collection

Whole plants of *Heliotropium indicum* and *Grona triflora* were collected from Kanyakumari District, Tamil Nadu between November 2021 and March 2022. The collected plant materials were authenticated (BSI/SRC/5/23/2022/Tech/517 and BSI/SRC/5/23/2022/Tech/516) from the Botanical Survey of India, Southern Regional Centre, Coimbatore.

Extract preparation

Leaves, stem and root of the plants were washed, shade dried and grinded with a blender. About 50 g of each powdered samples were taken for Soxhlet extraction with 500 ml analytical grade Hexane, Ethyl acetate and Methanol solvents based on the polarity. After the extraction the crude extracts were concentrated and dried [44].

Antifungal screening

Antifungal studies of different plant extracts were carried out using Agar well diffusion method [45]. Overnight cultures of *Candida albicans* (MTCC 183) were swabbed on the Sabouraud Dextrose agar plates, 6 mm wells were punched and loaded with 100µl of different extracts (1 mg/ml) and kept for overnight incubation at 37 °C. After incubation the diameter of the zone of inhibition was measured for each well where Fluconazole was used as positive control and the respective solvents were taken as negative control [46].

Results

Structure retrieval

Structure of phytocompounds from different plants was retrieved from PubChem database with their PubChem ID. Three-dimensional structure of target protein was retrieved from PDB with ID:3PVK (Fig. 1) with about 342 amino acids in length whose active site residues were found to be THR222, THR221, ASP86, ASP32, TYR84, TYR225, ASP218, GLY220 and GLU193.

ADME studies

Three-dimensional structure of ligands generated was taken for ADME studies where seven compounds (Indicine-*N*-Oxide, 3′ Acetyl lycopsamine, *p*-Coumaric acid, Ferulic acid, Syringic acid, Vanillic acid and Caffeic acid) from *H. indicum* and four compounds (Melilotic acid, Phloretic acid, Kaempferol and Quercetin) from *G. triflora,* two compounds (Cytidine and Luteolin) from *E. alsinoides* and one compound each from *Z. mauritiana, C. grandis, A. bracteolate, P. communis and C. benghalensis*, respectively, showed drug likeliness in ADME profiling. Their PubChem structures and ADME profile was shown in Table 1 and Table 2, respectively. Pharmacological effects of these compounds were validated with PASS prediction where no antifungal activity was found for Indicine-*N*-Oxide and only the antibacterial and antiviral activities are recorded (Table 1).

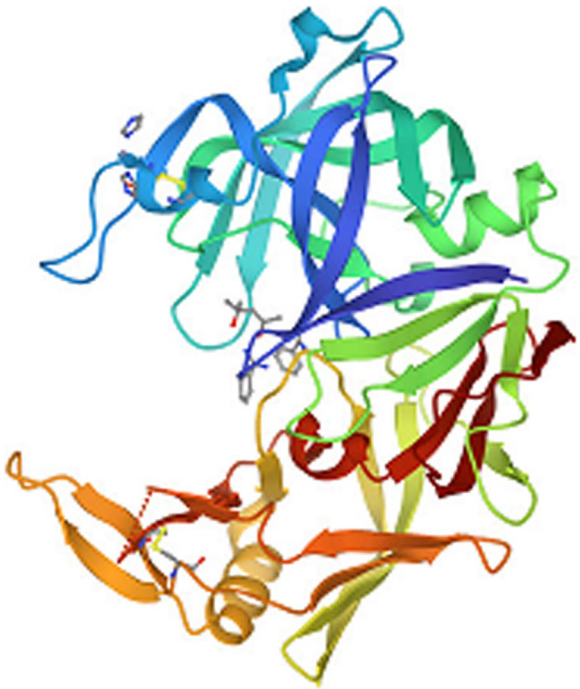


Fig. 1 Three-dimensional structure of Secreted aspartic proteinases2 from PDB

Structure based docking studies

Docking studies provides an insight of how each phytocompounds binds to the active pockets of the target protein (PDB ID: 3PVK) based on their structure. It was found that among the phytocompounds Indicine-*N*-Oxide from *Heliotropium indicum* exhibited the better binding efficiency with target with a significant glide score of − 5.54 kcal/mol when compared with the standard Fluconazole possessing a G score of − 4.66 kcal/mol followed by phytocompounds like Clindamycin, Arbutin, 3′Acetyl lycopsamine and Quercetin with glide scores of − 5.20, − 5.18, − 5.06 and − 4.98 kcal/mol, respectively, with hydrogen bond formation (Table 3). The binding mode of Indicine-*N*-Oxide with target protein was visualized using PYMOL visualizing tool where their mode of interaction was found to be with the formation of hydrogen bond. Significant interactions were observed with active site residues TYR84 and ASP86 having

bond lengths 1.9 and 2.0 Å, respectively, as shown in Fig. 2 where cyan green colour represents the ligand Indicine-*N*-Oxide and deep olive colour represents the active pocket of the target protein. The interaction of fluconazole with the active site residues of the target protein was also visualized using PYMOL software (Fig. 3). Most of the compounds from the plant *Heliotropium indicum* like Indicine-*N*-Oxide, Syringic acid, Ferulic acid and Vanillic acid bound to the active sites TYR84 of the target protein with the formation

Table 1 Retrieved 2D structure of phytocompounds with PubChem ID and PASS online result

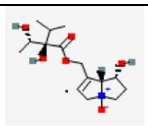
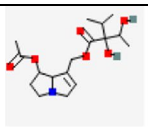
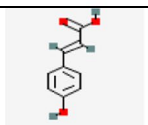
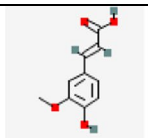
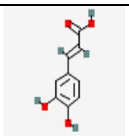
S.NO	COMPOUND NAME	PUBCHEM ID	2D STRUCTURE IMAGE	PASS ONLINE RESULTS
Heliotropium indicum				
1	Indicine-N-Oxide	280564		0,243 0,160 Cholesterol antagonist 0,157 0,076 [phosphorylase] phosphatase inhibitor 0,131 0,051 Secretase stimulant 0,131 0,051 Secretase alpha stimulant 0,197 0,120 Antibacterial 0,146 0,070 Antitussive, narcotic 0,130 0,055 Antiviral (Hepatitis) 0,244 0,169 Sphinganine kinase inhibitor 0,133 0,059 Galacturan 1,4-alpha-galacturonidase inhibitor
2	3'Acetyl lycopsamine	586647		0,580 0,005 Myc inhibitor 0,633 0,070 Membrane permeability inhibitor 0,589 0,053 Phosphatase inhibitor 0,547 0,014 DNA synthesis inhibitor 0,534 0,015 Antiviral (Rhinovirus) 0.491 0.030 APOA1 expression enhancer
3	p-Coumaric acid	637542		0,418 0,005 Tauropine dehydrogenase inhibitor 0,417 0,004 Phenylalanine decarboxylase inhibitor 0,451 0,039 Antifungal 0,444 0,033 CYP2C11 substrate 0,424 0,014 Peptide-tryptophan 2,3-dioxygenase inhibitor 0,433 0,023 Phosphatidylinositol diacylglycerol-lyase inhibitor 0,427 0,018 Linoleoyl-CoA desaturase inhibitor 0,414 0,006 Retinal dehydrogenase inhibitor
4	Ferulic acid	445858		0,447 0,060 Lipoprotein lipase inhibitor 0,429 0,041 Tpr proteinase (Porphyromonas gingivalis) inhibitor 0,430 0,044 Antifungal 0,429 0,043 Spasmolytic 0,396 0,011 Antiinflammatory, ophthalmic 0,409 0,024 CYP1A1 substrate 0,450 0,066 5 Hydroxytryptamine uptake stimulant 0,403 0,018 Angiogenesis stimulant
5	Caffeic acid	689043		0,422 0,009 Pyruvate dehydrogenase (lipoamide) inhibitor 0,453 0,041 Histidine N-acetyltransferase inhibitor 0,450 0,039 Antifungal 0,414 0,003 Leucine transaminase inhibitor 0,428 0,018 Galactose oxidase inhibitor 0,415 0,005 Laxative 0,421 0,011 Arylformamidase inhibitor 0.450 0.040 Acetylesterase inhibitor

Table 1 (continued)

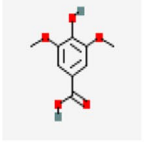
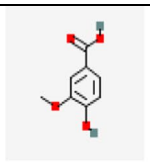
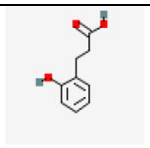
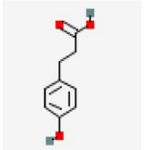
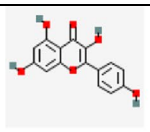
6	Syringic acid	10742		0,322 0,012 Pyruvate carboxylase inhibitor 0,337 0,027 Inotropic 0,319 0,010 UGT1A5 substrate 0,366 0,058 Antifungal 0,317 0,009 Mevalonate kinase inhibitor 0,317 0,010 Cystathionine gamma-lyase inhibitor 0,394 0,086 Fibrinogen receptor antagonist 0,335 0,028 Sclerosant
7	Vanillic acid	8468		0,311 0,010 Vanilloid agonist 0,360 0,060 Antifungal 0,306 0,006 Nitric oxide scavenger 0,333 0,034 Horrilysin inhibitor 0,313 0,014 Cysteine synthase inhibitor 0,311 0,012 Maleate isomerase inhibitor 0,302 0,004 VCAM1 expression inhibitor 0,308 0,011 UDP-glucose-hexose-1-phosphate uridylyltransferase
Grona triflora				
8	Melilotic acid	873		0,252 0,015 O-acetylhomoserine aminocarboxypropyltransferase inhibitor 0,312 0,076 Antifungal 0,246 0,010 Leishmanolysin inhibitor 0,250 0,014 2-Aminohexano-6-lactam racemase inhibitor 0,248 0,012 HDL-cholesterol increasing 0,240 0,005 Lysine decarboxylase inhibitor 0,245 0,010 Glutamine-pyruvate transaminase inhibitor
9	Phloretic acid	10394		0,308 0,087 Vanilloid 1 agonist 0,223 0,002 Free fatty acid receptor 1 agonist 0,301 0,080 Antifungal 0,243 0,022 Oligopeptidase B inhibitor 0,241 0,020 Candidapepsin inhibitor 0,228 0,007 Succinate-hydroxymethylglutarate CoA-transferase inhibitor 0,244 0,025 Gastritis treatment 0,234 0,014 Thromboxane synthase stimulant
10	Kaempferol	5280863		0,472 0,003 CTGF expression inhibitor 0,496 0,030 CYP2C19 substrate 0,548 0,082 Glycosylphosphatidylinositol phospholipase D inhibitor 0,495 0,031 Antifungal 0,487 0,026 Antiulcerative 0,465 0,003 Telomerase inhibitor 0,523 0,063 Phthalate 4,5-dioxygenase inhibitor 0,463 0,005 Antineoplastic (small cell lung cancer)

Table 1 (continued)

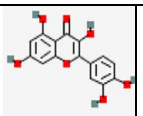
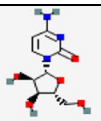
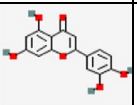
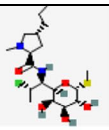
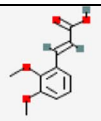
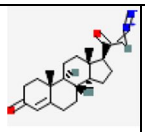
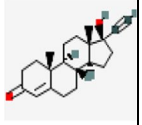
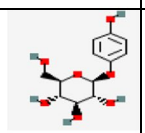
11	Quercetin	5280343		0,483 0,023 CYP2E1 inducer 0,465 0,006 CTGF expression inhibitor 0,490 0,032 Antifungal 0,486 0,028 Vasodilator, coronary 0,509 0,052 Ovulation inhibitor 0,468 0,013 UGT2B4 substrate 0,498 0,044 Aminobutyraldehyde dehydrogenase inhibitor 0,456 0,004 CYP1B1 substrate
Evolvulus alsinoides				
12	Cytidine	6175		0,345 0,065 Phosphoinositide 5-phosphatase inhibitor 0,360 0,080 Dementia treatment 0,345 0,065 Antifungal 0,365 0,085 Diabetic neuropathy treatment 0,288 0,011 5-Formyltetrahydrofolate cyclo-ligase inhibitor 0,295 0,018 Ketol-acid reductoisomerase inhibitor 0,280 0,003 Glyceraldehyde-3-phosphate dehydrogenase (NADP+) inhibitor 0,290 0,013 4-Alpha-glucanotransferase inhibitor
13	Luteolin	5280445		0,526 0,032 Linoleate diol synthase inhibitor 0,503 0,009 UGT2B4 substrate 0,520 0,027 Antifungal 0,540 0,048 Platelet aggregation stimulant 0,519 0,029 Nucleotide metabolism regulator 0,503 0,012 Hydroxylamine reductase (NADH) inhibitor 0,530 0,041 Oxygen scavenger 0,501 0,013 Magnesium-protoporphyrin IX monomethyl ester
Ziziphus mauritiana				
14	Clindamycin	446598		0,481 0,003 Antimycoplasmal 0,553 0,100 CDP-glycerol glycerophosphotransferase inhibitor 0,433 0,007 Antibiotic 0,460 0,041 Dermatologic 0,383 0,002 Protein 50S ribosomal subunit inhibitor 0,467 0,148 CYP2H substrate 0,362 0,069 Antithrombotic 0,308 0,017 Antiacne 0,291 0,002 Protein 30S ribosomal subunit inhibitor
Commelina benghalensis				
15	2,3-Dimethoxycinnamica cid	735842		0,388 0,049 Sigma receptor agonist 0,367 0,028 2-Oxoaldehyde dehydrogenase (NADP+) inhibitor 0,391 0,052 Antifungal 0,390 0,053 Spasmolytic 0,361 0,025 Tyrosine 3 hydroxylase inhibitor 0,406 0,070 CYP2D16 substrate 0,389 0,054 Phosphatidylserine decarboxylase inhibitor 0,345 0,010 Keratolytic 0,347 0,013 N-methyl-2-oxoglutaramate hydrolase inhibitor
Aristolochia bracteolata				

Table 1 (continued)

16	21-Diazoprogesterone	104633		0,277 0,149 Ecdysone 20-monooxygenase inhibitor 0,139 0,016 Premenstrual syndrome treatment 0,237 0,114 Antifungal 0,131 0,012 Estrogen alpha receptor agonist 0,193 0,076 Vitamin-K-epoxide reductase (warfarin-insensitive) inhibitor 0,289 0,171 Antiinflammatory 0,237 0,119 Antimetastatic 0,120 0,004 Lipocortins synthesis agonist
Coccinea grandis				
17	Ethisterone	5284557		0,153 0,005 5-Alpha-reductase 2 inhibitor 0,256 0,109 CYP1A2 inhibitor 0,273 0,127 Antiinfective 0,269 0,123 Opioid kappa 3 receptor antagonist 0,314 0,170 Cytoprotectant 0,144 0,001 Progesterone receptor A antagonist 0,245 0,103 Hydroxylamine reductase (NADH) inhibitor 0,142 0,002 Lipocortins synthesis agonist 0,221 0,082 Peroxidase substrate
Pyrus communis				
18	Arbutin	440936		0,635 0,001 Isomaltulose synthase inhibitor 0,639 0,006 Bilirubin oxidase inhibitor 0,646 0,014 Antifungal 0,666 0,037 Fibrinolytic 0,629 0,003 Glycerol-3-phosphate oxidase inhibitor 0,625 0,002 Triose-phosphate isomerase inhibitor 0,647 0,027 Phosphatase inhibitor 0,625 0,005 CYP1A inducer

of H–O bond. Similarly, Quercetin, Kaempferol and Melilotic acid from the plant *Grona triflora* also bound to the active site residues ASP32, TYR84 and THR222 of the protein. Compounds like Cytidine, Luteolin from *Evolvulus alsinoides* and Clindamycin from *Ziziphus mauritiana* formed five bonds on interacting with the protein. These compounds had successfully bound to the active site residues ASP32, GLU193 and THR222 of the target. However, compounds like 21-Diazoprogesterone, Ethisterone and Phloretic acid showed no interactions with the target protein.

Antifungal screening

Based on the docking results two plants were selected as most of their phytocompounds exhibited better ADME profile and binding efficiencies compared to other plants. Among the different extracts of plant samples, Ethyl acetate leaf extract of *Heliotropium indicum* shows a maximum diameter of zone of inhibition of 18 mm when compared to all other extracts (Fig. 4). Both positive and negative controls exhibited no efficacy against the organism as depicted in Table 4.

Discussion

Skin is a protective barrier of the body that carries numerous microbes as commensals for a healthy body which includes bacteria and fungi species within that the fungi *C. albicans* plays an important role in human microbial biota [47]. Although these are beneficial, at times they may progress into infectious agent affecting the skin and mucosal membranes which is also a major concern. Studies have considered fungal proteases as virulent factors as they can interfere with many biological assays and thereby results in inflammation in the host at lower pH and interfere the immune system [15, 21, 48]. Reports have been revealing the importance of SAP2 virulence protein in the pathogenesis of candidiasis in diseased models [49, 50]. Thus, the current study focussed on SAP2 protein to identify novel safe drug against candidiasis. The target protein of this study obtained from PDB possess chain A with 342 amino acids sequence length and 36.92 k Da in weight. Generally, drug designing was carried out with clinical trials as an important step to understand the pharmacokinetic profile of the drug compound their side effects and

Table 2 ADME profile of phytocompounds using QikProp Module

Molecule name	No. of rotatable bonds	Molecular weight	Dipole moment	SASA	Donor hydrogen bonds	Acceptor hydrogen bonds	QPlogP for octanol/gas
Normal range	**0.0–15.0**	**130.0–725.0**	**1.0–12.5**	**300.0–1000.0**	**0.0–6.0**	**2.0–20.0**	**8.0–35.0**
Commelina benghalensis							
2,3-Dimethoxycinnamic acid	5	208.213	4.739	414.151	1	3.5	9.744
Heliotropium indicum							
Indicine-*N*-Oxide	8	315.366	8.382	553.78	2	8.15	17.388
Ferulic acid	5	194.187	6.295	420.153	2	3.5	11.367
3′-Acetyllycopsamine	8	341.403	4.667	622.994	1	7.45	16.35
Caffeic acid	5	180.16	7.175	392.531	3	3.5	12.706
p-Coumaric acid	4	164.16	6.69	381.465	2	2.75	10.645
Syringic acid	4	198.175	3.44	400.033	2	4.25	10.721
Vanillic acid	3	168.149	4.027	360.214	2	3.5	9.897
Ziziphus mauritiana							
Clindamycin	10	424.982	4.393	664.829	4	11.8	24.779
Evolvulus alsinoides							
Luteolin	4	286.24	4.716	503.697	3	4.5	16.593
Cytidine	5	243.219	3.514	437.255	5	10.8	20.154
Aristolochia bracteolata							
21-Diazoprogesterone	3	340.464	7.087	595.173	0	7	16.395
Coccinea grandis							
Ethisterone	2	312.451	5.802	554.641	1.5	2.75	15.057
Desmodium triflorum							
Kaempferol	4	286.24	5.622	501.402	3	4.5	16.695
Melilotic acid	4	166.176	7.038	381.362	2	2.75	10.725
Phloretic acid	4	166.176	5.872	385.788	2	2.75	10.427
Quercetin	5	302.24	3.533	512.235	4	5.25	18.32
Pyrus communis							
Arbutin	8	272.254	4.239	478.271	5	10	20.369

Molecule name	QPlogP water/gas	QPlogP octanol/water	QPlog BB for brain/blood	QPlogKp for skin permeability	No. of metabolic reactions	Human oral absorption	Rule of five	Rule of three
Normal range	**4.0–45.0**	**− 2.0–6.5**	**− 3.0–1.2**	**− 8.0 to − 1.0**	**1.0–8.0**	**1,2 (or)3 L, M, H**	**Max 4**	**Max 3**
2,3-Dimethoxy-cinnamic acid	6.237	2.135	− 0.625	− 2.601	2	3	0	0
3′-Acetyl lycops-amine	9.182	1.917	− 0.66	− 4.995	5	3	0	0
Caffeic acid	9.871	0.558	− 1.569	− 4.524	2	2	0	1
Clindamycin	19.536	2.121	− 0.671	− 5.019	6	2	0	0
Syringic acid	8.374	0.971	1.072	− 3.848	3	3	0	0
Vanillic acid	8.12	1.046	0.989	− 3.776	2	2	0	0
Cytidine	19.957	− 1.965	− 1.886	− 5.489	4	2	0	0
21-Diazoproges-terone	8.821	1.94	− 1.14	− 4.263	4	3	0	0
Ethisterone	6.598	3.117	− 0.312	− 2.724	3	3	0	0
Ferulic acid	8.031	1.378	− 1.189	− 3.697	2	3	0	0
Indicine-*N*-Oxide	11.471	1.258	− 1.149	− 3.214	6	3	0	0
Kaempferol	12.28	1.06	− 1.803	− 4.533	4	3	0	0
Luteolin	12.30	0.96	− 1.947	− 4.851	4	3	0	0
Melilotic acid	7.56	1.416	− 0.891	− 3.27	3	2	0	0
p-Coumaric acid	7.787	1.443	− 1.096	− 3.621	1	3	0	0

Table 2 (continued)

Molecule name	QPlogP water/gas	QPlogP octanol/water	QPlog BB for brain/blood	QPlogKp for skin permeability	No. of metabolic reactions	Human oral absorption	Rule of five	Rule of three
Normal range	**4.0–45.0**	**− 2.0–6.5**	**− 3.0–1.2**	**− 8.0 to − 1.0**	**1.0–8.0**	**1,2 (or)3 L, M, H**	**Max 4**	**Max 3**
Phloretic acid	7.564	1.329	− 1.021	− 3.576	3	2	0	0
Quercetin	14.36	0.387	− 2.309	− 5.422	5	2	0	1
Arbutin	18.704	− 0.995	0.873	− 4.251	5	2	0	0

metabolism. However, this stage often leads to adverse findings which results in the failure of the drug development as the compound studied may not be suitable for a particular disease [51]. Thus, employing computational approach of ADME profiling for compounds prior to in vitro and in vivo studies helps to reduce these issues [52]. In the present work, Computational approaches have been extensively used to identify potent phytocompounds containing medicinal plants to target *C. albicans* causing Candidiasis. All phytocompounds were selected from different plants based on their literature survey and subjected to ADME profile and found that only a few showed the drug likeliness within the given parameters of Lipinski's rule of five suggesting that they possess excellent pharmacological properties to be utilized in drug development. Poor drug likeliness of the compounds in the ADME toxicity studies implies that those compounds have poor absorption and permeability in the human body which in turn affects the bioavailability of drugs and results in drug failure [53]. From Table 2 it is evident that most of the compounds that showed drug likeliness in ADME toxicity profile are phenols, flavonoids and alkaloids that possess properties like good absorption contributing to the drug bioavailability. According to studies, Molecular docking plays a vital role in drug discovery process with most promising candidates from ADME profile were considered [54, 55]. Docking helps us to understand the binding affinity and interactions of compounds with the active pockets of target [56]. Thus, we performed docking studies for compounds showing drug likeliness in ADME profiling and only those compounds with their structures have been discussed throughout the study. In silico docking studies of the compounds in the present study revealed that for each compound the interaction differs due to their differences in interacting moieties. However, most compounds that were subjected to docking successfully binds to at least one active site residues of the protein with the formation of hydrogen bond. The removal of water molecules and other residues from the protein structure improves the ability of drug target interactions. Based on the findings, it's obvious that the phytocompounds from *H. indicum* and *G. triflora* seems to be more drug-like and actively interacted with Candidapepsin2, suggesting that these plants could be exploited to establish effective Candidiasis therapies. Studies have showed that Indicine-*N*-Oxide is the active component responsible for the antitumour activity of *H. indicum* [57]. Present study revealed that Indicine-*N*-Oxide also possess better antifungal activity against Candidapepsin2 when compared with all other phytocompounds and standard drug taken for study. Therefore, presence of this active component may be responsible for the effectiveness of *H. indicum* as traditional folk medicine against infections followed for several years. Figure 3 represents how the standard drug fluconazole bound to the active site THR222 and TYR84 of the target protein where salmon colour represents the drug and deep olive green colour represents the active sites of the target protein. With the formation of O–H and H–O bonds having bond lengths 2.0 and 1.9 Å respectively the standard molecule also effectively binds to the target. From these docking results it is evident that the phytocompound present in *Heliotropium indicum* and *Grona triflora* exerts much efficiency than the standard drug against *Candida albicans*. However, further studies are also required to validate the effect of these compound against infections. Apart from Indicine-*N*-Oxide, the compound Quercetin also exhibited significant interactions (Additional file 1: Fig. S5) whose antifungal activity has been proved in previous studies [58]. Current study elucidates its efficiency in binding to the drug target SAP2 as shown in Table 3 with the formation of 3 bonds. As we have implicated in silico studies as a prior step in identification of effective medicinal plants to develop phytomedicine against fungal infection, it was observed that more phytocompounds from the plants *H. indicum* and *G. triflora* exhibited drug likeliness and successfully docked with the target protein in its active sites. Thus, those two plants were chosen for screening antifungal activity and from the results it is evident that ethyl acetate leaf extracts of both the plants showed antifungal activity whereas ethyl acetate leaf extracts of *H. indicum* possess potential anticandidal activity when compared to *G. triflora*. However, fluconazole does not exhibit antifungal potential on in vitro studies which may be due to the drug resistance developed by the strain used in the current study. The plant *H. indicum*

Table 3 Interaction of Phytocompounds with Candidiapepsin2 (SAP2)

S.No	Name of the ligand (Pubchem Id)	Residues interaction	Bond length (Å)	No. of hydrogen bonds	G-score (Kcal/Mol)
Heliotropium indicum					
1	Indicine-*N*-Oxide (280564)	TYR84(H–O)	1.9		
		ASP86(H–O)	2.0	3	− 5.54
		THR221(H–O)	2.0		
2	3′ Acetyllycopsamine (586647)	ASP218(H–O)	2.2		
		GLY220(H–O)	2.0	3	− 5.06
		GLY220(H–O)	2.1		
3	Syringic acid (10742)	TYR84(H–O)	1.8	2	− 3.72
		THR222(O–H)	1.9		
4	Caffeic acid (689043)	ASP32(H–O)	1.7	3	− 3.27
		ASP32(H–O)	2.2		
		ASP32(H–O)	1.9		
5	Ferulic acid (445858)	TYR84(H–O)	1.8	1	− 2.83
6	*p*-Coumaric acid (637542)	GLY85(H–O)	1.9	2	− 2.53
		THR222(O–H)	2.4		
7	Vanillic acid (8468)	TYR84(H–O)	1.9	1	− 2.17
Desmodium triflorum					
8	Quercetin (5280343)	ASP218(H–O)	1.8		
		ASP86(H–O)	1.8	3	− 4.98
		ASP32(H–O)	2.3		
9	Kaempferol (5280863)	TYR84(H–O)	2.0		
		ASP32(H–O	2.1	4	− 4.40
		ASP32(H–O)	2.0		
		THR222(H–O)	2.0		
10	Melilotic acid (873)	THR222(O–H)	1.7	2	− 3.16
		THR221(H–O)	1.8		
Evolvulus alsinoides					
11	Cytidine (6175)	ASP32(H–O)	1.7		
		ASP32(N–O)	3.3		
		ASP218(H–O)	1.9	5	− 4.95
		ASP86(H–O)	1.8		
		ASP86(H–O)	1.8		
12	Luteolin (5280445)	ASP86(H–O)	2.3		
		ASP86(O–O)	3.5		
		ASP32(H–O)	1.9	5	− 4.62
		GLU193(H–O)	1.8		
		GLU193(H–O)	1.8		
Ziziphus mauritiana					
13		THR222 (H–O)	2.6		
	Clindamycin (446598)	THR222(H–O)	2.3		
		THR222(O–H)	2.4	5	− 5.20
		THR221(H–O)	2.1		
		TYR225(H–O)	2.0		
Pyrus communis					
14		SER88(H–O)	2.0		
	Arbutin (440936)	GLY220(H–O)	1.6	3	− 5.18
		ASP218(H–O)	1.8		
Commelina benghalensis					
15		THR222(O–H)	2.3		

Table 3 (continued)

S.No	Name of the ligand (Pubchem Id)	Residues interaction	Bond length (Å)	No. of hydrogen bonds	G-score (Kcal/Mol)
	23 Dimethoxycinnamic acid (735842)	ILE223(O–H)	1.8	2	− 3.59
Standard					
16	Fluconazole (3365)	TYR84(H–O)	1.9	2	− 4.66
		THR222(O–H)	2.0		

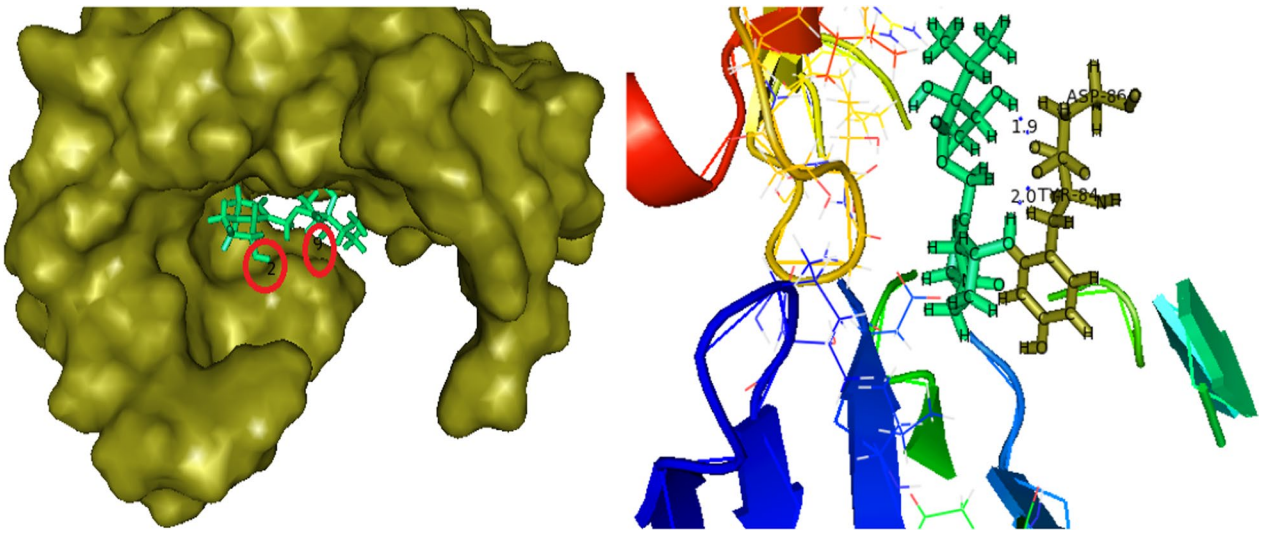


Fig. 2 Interaction of Indicine-*N*-Oxide with Candidapepsin2 with least Glide Score − 5.54 kcal/mol

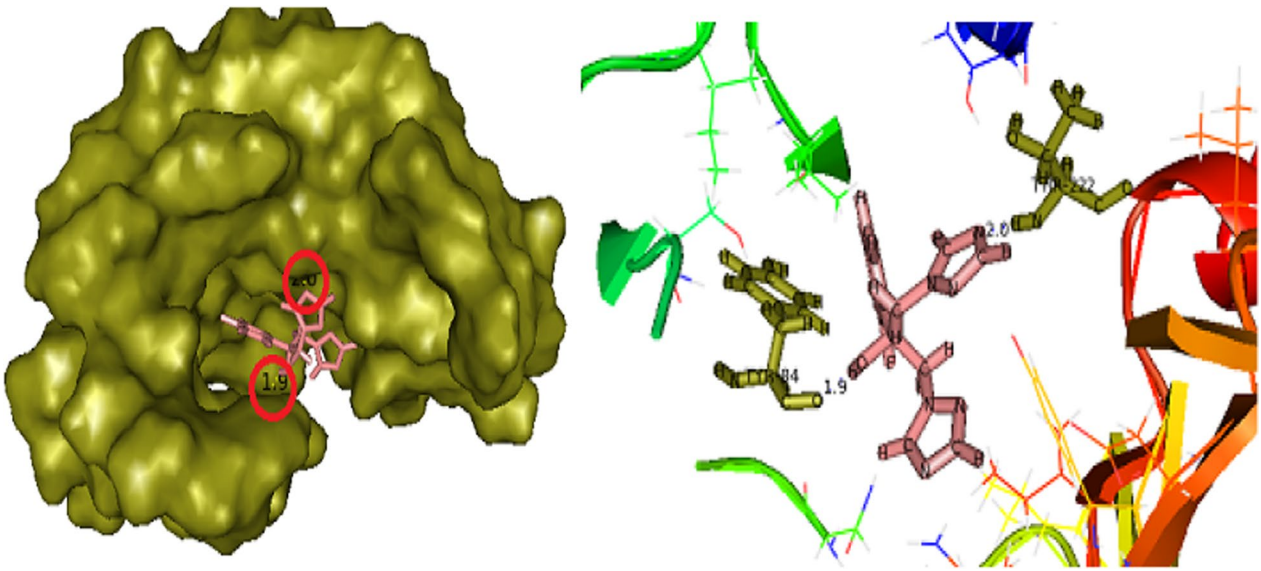


Fig. 3 Interaction of Fluconazole with Candidapepsin2 with least Glide Score − 4.66 kcal/mol

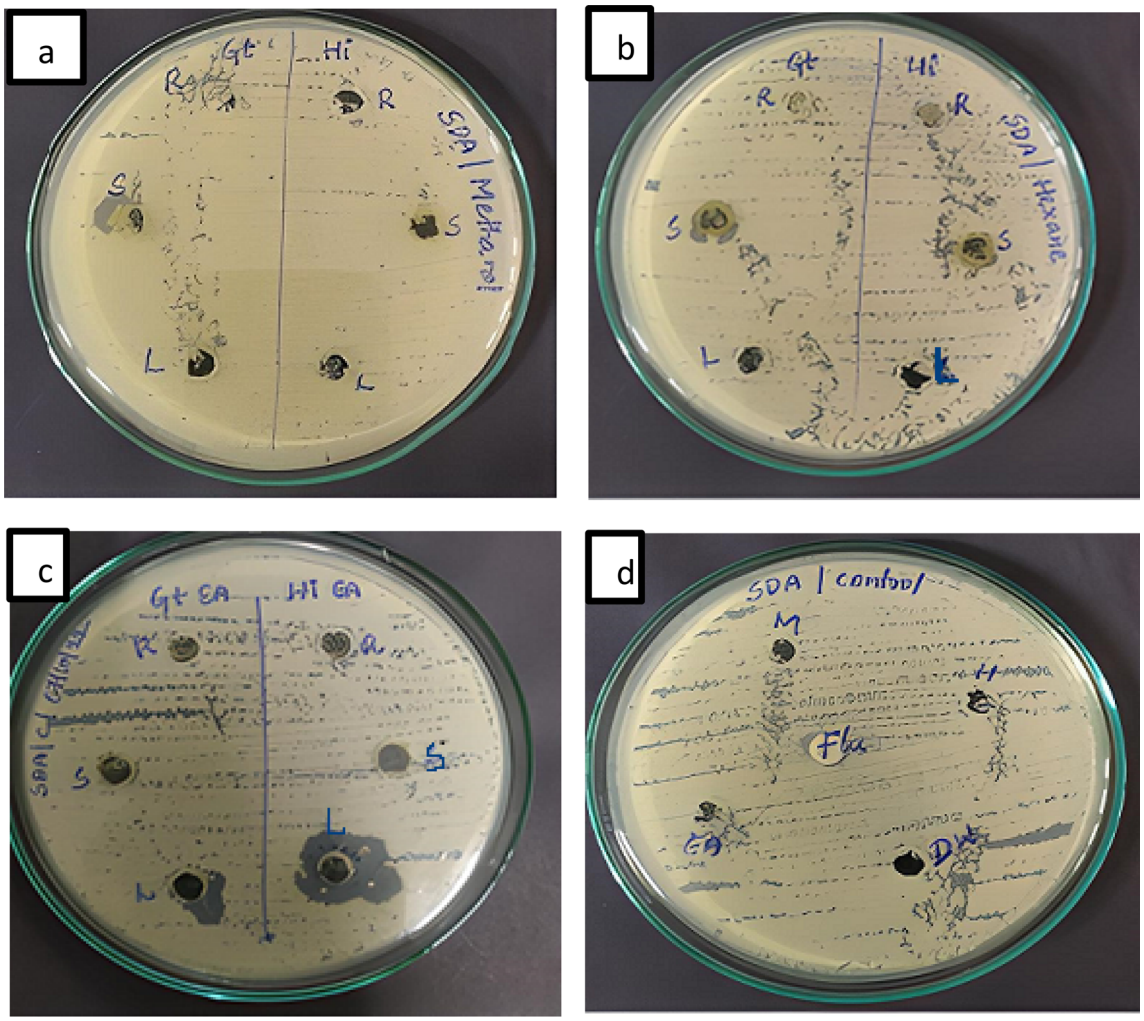


Fig. 4 Antifungal activity of plant extracts against *Candida albicans* by Agar well diffusion method. **a** Represents the antifungal activity of methanolic extracts of root (R), stem (S) and leaf (L), **b** represents the antifungal activity of hexane extracts of root (R), stem (S) and leaf (L), **c** represents the antifungal activity of ethyl acetate extracts of root (R), stem (S) and leaf (L), **d** represents the control plate with methanol (M), ethyl acetate (EA), hexane (H)and distilled water (DW) as negative controls and a positive control Fluconazole (Flu)

Table 4 Antifungal activity of Plant Extracts against *Candida albicans*

S. No	Sample (100 µl)	Zone of inhibition (mm)				
		Hexane	Ethyl acetate	Methanol	Distilled water	Positive control (Fluconazole-50 µg)
1	*Heliotropium indicum*				–	–
	Leaf	–	18	–		
	Stem	–	–	–		
	Root	–	–	–		
2	*Grona triflora*					
	Leaf	–	10	–		
	Stem	–	–	–		
	Root	–	–	–		
3	*Negative control*	-	-	-		

was reported to possess various medicinal properties like anti-inflammatory and antitumour activity wherein its leaf paste was used for skin related ailments traditionally [59]. Current study also reveals that leaves of the plant possess potent antifungal activity when compared to other parts of the plant. Recently, studies have shown that the ethyl acetate leaf extracts of *O. americanum* exhibited antimicrobial activity against varied microbial species [46]. Similarly, in vitro antifungal screening unveils that ethyl acetate extract among other extracts possess better antifungal activity and the plant *H. indicum* rich in alkaloids and phenolic compounds are excellent drug candidates against fungi.

Conclusion

Candidiasis is a fungal infection caused *Candida* limited to skin and mucous membranes often leads to systemic infections. Although it is not life threatening, it may be one of the causes for other chronic lethal diseases. Prolonged usage of drugs available in the market results in resistance and side effects which paves a way for efficient drug discovery. In the present study, suitable drug candidates were screened from ADME results and subjected to docking against target unveiled that Indicine-*N*-Oxide from *H. indicum* have significant binding affinity towards TYR84 and ASP86 residues of target with glide score − 5.54 kcal/mol. In addition to that, antifungal screening showed the ability of inhibiting the growth of *C. albicans* by *H. indicum* leaf extracts. Further studies will be conducted to evaluate the stability of compounds and to understand the efficiency of *H. indicum* and *G. triflora* plant extracts against candidiasis.

Abbreviations

HIV	Human immunodeficiency virus
RHE	Reconstituted human epithelium
SAP	Secreted aspartic proteases
SAP2	Secreted aspartic proteases2
C3b, C4b, and C5	Complement components of immune system
TCC	Terminal complement complex formation
ADME	Absorption, distribution, metabolism, excretion and toxicity
3D	Three dimensional
PDB	Protein data bank
G score	Glide score

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s43094-023-00489-x.

Additional file1. Figure S5: Interaction of Quercetin with Candidapepsin2 with least Glide Score -4.98 Kcal/mol.

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Author contributions

VAB had done the ADME, Docking, antifungal studies and drafted the manuscript. SLV had done the PASS online predictions and PYMOL visualization for the docked standard complex. RS had designed the study, edited the manuscript and guided to carry out this work**.** The final manuscript was read and approved by all authors.

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Availability of data and materials

All data generated or analysed during this study are included in this article.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publications

Not applicable.

Plant authentication

The plants used in this study were authenticated at Botanical Survey of India, Southern Regional Centre, Coimbatore under the number BSI/SRC/5/23/2022/Tech/516 for ***Grona triflora*** and BSI/SRC/5/23/2022/Tech/517 for ***Heliotropium indicum***.

Competing interests

We declared that there is no conflict of interest in the studies.

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