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Evaluation of affinity of active components of Coriander sativum to ERG 11 in Candida glabrata by virtual molecular docking using SYBYL

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Abstract

Introduction: Resistance in microbial organisms is one of the most important therapeutic challenges faced in the last decade. Mutation in the target site, ERG11 has caused resistance in Candidal species especially, Candidal glabrata. There is an ever-increasing need for use of more natural extracts in the treatment of these infections.

Objective: To virtually assess the bond between various active components of Coriander sativum with ERG 11 gene of Candida glabrata to evaluate whether it deserves to be an alternative or an adjunct to fluconazole in the management of the drug resistant Candida glabrata induced infections.

Materials and methods: Virtual molecular docking was performed between each of the active components of Coriander sativum with that of ERG 11 gene of Candidal glabrata to assess binding affinity using SYBYL.

Results: Among the 21 molecules studied, 12 molecules showed binding with the target gene in which alpha-cedrene showed maximum bonds.

Conclusion: From the study it can be inferred that Coriander sativum has potential to act as antifungal agent but requires further validation using laboratorial studies.

Keywords: Molecular docking, ERG11, Candida glabrata, in-silico modelling, alpha-cedrene

Introduction

Candidiasis is the most common fungal infection in the oral cavity caused by Candida species. Candida albicans followed by Candida glabrata are the common species causing this infection. Though this infection is usually tackled by azole group of drugs, in the recent decade there has been emergence of resistant strains. (1)

One of the most commonly used drugs for treatment of candidal infections be it localised or systemic, is fluconazole. As there are various strains of candidal species developing resistance to this drug the management of this infection poses a challenge. (2)The infections caused by these organisms especially those belonging to glabrata species are more difficult to manage as they have an inherent resistance to most of the anti-fungal agents

used in the war against it. These resistant strains are more common with Candida glabrata.(1) There has been documentation of strains resistant to most of the commonly used antifungal agents like azole drugs, echocandins and polyenes etc. Emergence of resistant strain to fluconazole is found to be as a result of mutation of the ERG 11 gene which is the target site of the antifungal drugs which act by inhibiting conversion of ergosterol interfering with cell wall synthesis. Mutation of this gene results in alteration of the target site for the drug which eventually causes failure of the drug to bind at the site and making the organism resistant. Candida glabrata stands apart from the rest of the members in the family in its morphological as well as cultural characteristics.(3) Candida glabrata has an inherent resistance to azole drugs whereas Candida albicans are still susceptible to this drug. There might be some difference in the gene level in these organisms which makes one susceptible and another resistant to the same drug. Better understanding of this target site mutation may enable in advocating newer therapeutic agents which can overcome this emerging menace of antifungal resistance. In this study we are attempting to compare the sequence of ERG 11 gene which may hold the key to understanding this difference in drug susceptibility and may present us another dimension in drug therapy. (4)

The knowledge of medicine passed down from our ancestors may hold key to combatting this demon of resistance that is challenging the treatment of various infections. There has been a booming interest in the field of phytotherapy. Various researches have been done in the field of cancer, oral submucous fibrosis, dental caries and candidal infections. The most commonly studied herbal agents were turmeric (Curcumin), ginger, garlic etc. (5)

Before attempting to do study in fungal culture it is ideal to look for the compatibility or the affinity of the ligand or the extract molecule to the target site of interest. This can be achieved by the method of molecular docking. Molecular docking is an experimental technique which enables us to virtually assess the bonding or the affinity of two molecules to each other. This technique is helpful in the initial screening process where in we can analyse the ligands in the target site of interest and thereby find the affinity as well as the site of binding of the molecule or drug of interest. Performing drug trials following molecular docking is like a test to find out the pitfalls of the hypothesis put forward for the study. It can tell us whether the compound we are suggesting has any chances of giving desired effect or not.

The aim of this study was to virtually assess the bond between various active components of Coriander sativum with ERG 11 gene of Candida glabrata to evaluate whether it deserves to be an alternative or an adjunct to fluconazole in the management of the drug resistant Candida glabrata induced infections. Recently, pharmacophore models have been receiving recognition and have proven to be of significance in the discovery as well as invention of newer therapeutic agents in the field of medicine. Molecular docking was performed to appraise the binding sites and interaction of the target site and molecule of interest, in our case the affinity of the active components of Coriander sativum to the ERG11 gene in Candida glabrata.

Materials and Methods

Selection Of Ligand And Target

A series of 31 molecules which are recognised to be active components in Coriander sativum as determined by an elaborate literature search. Final selection of the molecules were done based on their chemical structure and properties.

Computational details

The chemical structure of the compounds was obtained from PubChem and for the compounds which did not have an existing 3D structure in PubChem, the sketch molecule function of SYBYL was used. The partial atomic charge of these molecules was obtained using Gasteiger Huckel method and Tripos force field was used for energy minimisation. All these procedures were performed with the help of SYBYL X2.1 software.

Pharmacophore based Virtual screening

Pharmacophore based virtual screening is a rapid as well as precise technique employed in identification of potent molecules which has chemical structures that have the potency for various biological functions. These molecules were further screened by the use of Lipinski's rule of five, fitness score, ADME properties. Finally, the affinity of the molecule to the substrate of interest is evaluated by molecular docking.

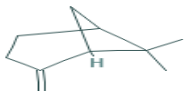
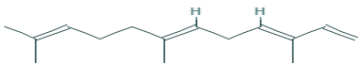
Molecular docking

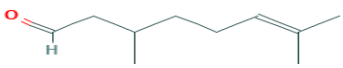
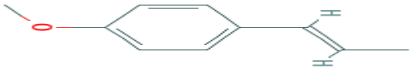
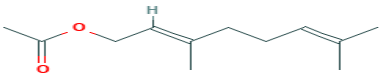
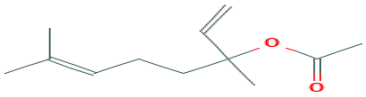
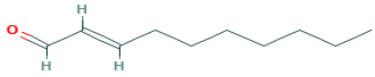
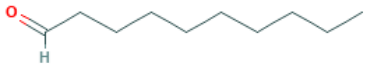
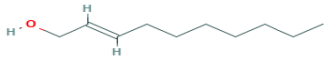
The affinity and interaction of the ligand molecule and the target site was simulated by virtual molecular docking method. The software used for molecular docking was SYBYL X2.1, which was also used for preparation of the ligand as well as the target molecule. Energy minimisation was also performed using SYBYL. Prior to molecular docking hydrogen atoms were added to the protein structure to ensure correct protonation states. The water molecules however were not included while analysing the binding affinity of the ligand and the target molecule. Grid map employed in docking analysis was 60x74x64 of 0.375Å on the active site of ERG11.

Results

Around 35 active components of Coriander sativum was obtained through literature search done in the study. The compounds with their chemical structure are given in table1.

Table1: Components of Coriander sativum selected for molecular docking with ERG11 gene.

S. No	Molecule	PubChem number	Structure
1	(S)-(+)-Linalool	6549	
2	α-pinene	6654	
3	βpinene	14896	
4	γ-terpinene	7461	
5	α-cedrene	6431015	
6	α-farnasene	5281516	
7	p-cymene	7463	

8	Limonene	22311	
9	Citronellal	7794	
10	Camphor	2537	
11	Anethole	637563	
12	Cis-dihydrocarvone	443167	
13	Geranyl acetate	1549026	
14	Neryl acetate	7780	
15	Linalyl acetate	8294	
16	α-Phellandrene	7460	
17	(E)-2-decenal	5283345	
18	Decanal	8175	
19	2-Decen-1-ol	5364942	
20	Tetradecenol	120110	
21	Dec-9-en-1-ol	25612	

After performing virtual molecular docking of all these components with ERG 11 gene, the scores were tabulated for each. The scores recorded were the suflex score, crash score, polar score and fitness scores. The scores for individual molecule are given in table 2.

Table 2: Docking scores for individual molecules

S.No	Molecule	Suflex score	Crash score	Polar score	Fitness score
1	(S)-(+)-Linalool	3.7400	-1.5700	0.0000	9.1453
2	α-pinene	2.7900	-03200	0.0000	0.3813
3	βpinene	3.3100	-0.7100	0.0000	9.3091
4	γ-terpinene	2.9300	-0.9200	0.0000	1.8515
5	α-cedrene	1.4000	1.4000	1.4000	3.0024
6	α-farnasene	3.6200	-2.3100	1.3100	4.5527
7	p-cymene	2.8400	-1.4900	0.0000	3.8644
8	Limonene	2.8200	-0.4400	0.0000	5.1629
9	Citronellal	4.4800	-0.8500	1.0800	1.5515
10	Camphor	2.5900	-0.8000	1.6000	1.0620
11	Anethole	1.1300	1.1300	1.1300	4.991
12	Cis-dihydrocarvone	2.8700	-1.5800	1.1300	6.1681
13	Geranyl acetate	4.8100	1.1800	0.4500	1.4398
14	Neryl acetate	5.9700	-1.0400	1.0900	8.6622
15	Linalyl acetate	4.9500	-1.2900	0.3100	1.5633
16	α-Phellandrene	3.7400	-0.4200	0.0025	8.4173
17	(E)-2-decenal	4.2600	-0.8600	0.0000	1.5375
18	Decanal	4.4300	-0.7500	0.0000	-2.1925
19	2-Decen-1-ol	4.4300	-0.7500	0.0000	2.1925
20	Tetradecenol	5.8900	-1.1100	1.6700	-9.1273
21	Dec-9-en-1-ol	4.8300	-0.5300	0.0000	6.9033

After analysing the bonding of all the 21 molecules with the target site, it was inferred that most of the molecules with benzene rings showed better bonding with the target site in comparison to the linear chained molecules.

Molecular docking was performed suing Suflex dock to find the suitable orientation for binding of the molecule to the target site of interest i.e., the binding of various active components of Coriander sativum with the ERG 11 gene of Candida glabrata. (Figure 1) Since the crystal structure of all the molecules selected were available in PubChem database they were directly downloaded in SDF format. Since Sybl software can only work with mol2 format, formatting to mol2 was done using OPEN BABEL software. The protein and the molecules were prepared and then docking was performed. Protomol is the intended site for ligand binding. Protomol generation was performed and docking was performed. The scores obtained following Suflex docking for the active docked confirmers were tabulated. The scores taken into consideration were Suflex score, Crash score, Polar score and Fitness score. Total or suflex score is the total score which is represented as log value. It shows the binding affinities given by the hydrophobic, entropic and solvation. Crash value is the rate of inapt penetration of the molecule into the protein as well as interpenetration within the ligand molecules separated by rotatable bonds. Polar value represents the input given by the hydrogen bonding as well as salt bridge interactions to the total score obtained. The scores obtained by Suflex dock is given in table 2. The molecular weight and number of hydrogen bonds formed by the molecules are given in table 3.

Table 3: Molecular weight and number of hydrogen bonds formed by the molecules

S. N.	Molecule	Chemical formula	Molecular weight ($g\ mol^{-1}$)	Number of hydrogen bonds formed with ERG 11
1	(S)-(+)-Linalool	$C_{10}H_{18}O$	154.253	0
2	α-pinene	$C_{10}H_{16}$	136.238	0
3	βpinene	$C_{10}H_{16}$	136.238	0
4	γ-terpinene	$C_{10}H_{16}$	136.238	0
5	α-cedrene	$C_{15}H_{24}$	204.357	3
6	α-farnasene	$C_{15}H_{24}$	204.36	1
7	p-cymene	$C_{10}H_{14}$	134.21	0
8	Limonene	$C_{10}H_{16}$	136.238	0
9	Citronellal	$C_{10}H_{18}O$	154.253	1
10	Camphor	$C_{10}H_{16}O$	152.237	1
11	Anethole	$C_{10}H_{12}O$	148.205	1
12	Cis-dihydrocarvone	$C_{10}H_{16}O$	152.237	1
13	Geranyl acetate	$C_{12}H_{20}O_2$	196.29	1
14	Neryl acetate	$C_{12}H_{20}O_2$	196.29	1
15	Linalyl acetate	$C_{12}H_{20}O_2$	196.29	1
16	α-Phellandrene	$C_{10}H_{16}$	136.238	0
17	(E)-2-decenal	$C_{10}H_{18}O$	154.253	1
18	Decanal	$C_{10}H_{20}O$	156.269	0
19	2-Decen-1-ol	$C_{10}H_{20}O$	156.269	0
20	Tetradecenol	$C_{10}H_{20}O$	156.269	1
21	Dec-9-en-1-ol	$C_{10}H_{20}O$	156.269	1

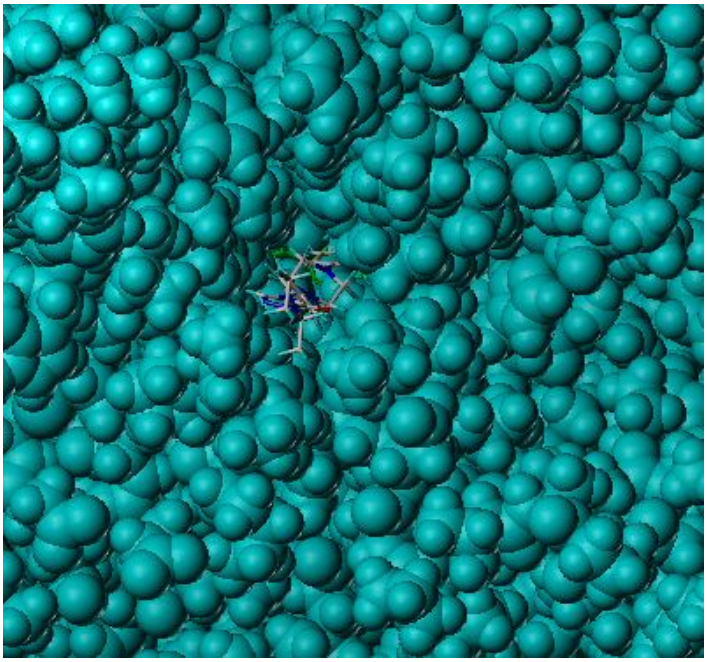


Figure 1: Bonding between alpha cedrene and ERG 11 gene using SYBYL.

Discussion

Molecular docking is an in-silico modelling technique which helps in assessing the ability of a drug molecule to the bind to the target site and show pharmacological effect. This technique has achieved lot of recognition in the past decade as it helps in getting a rapid insight of the exact binding site of the target and the ligand molecules of interest.(6)

In this study, we assessed the binding affinity between various active components of Coriander sativum and ERG11. ERG11 is the site for binding of anti-fungal drugs in Candida glabrata. In the past few decades there has been an emerging menace of anti fungal resistance in Candida species especially Candida glabrata.(7) Candida glabrata has an inherent resistance to the azole group of drugs which is a challenge as fluconazole is the drug of choice for infections caused by C.glabrata.(2)

From the current study we were able to infer that among the 21 active components trialled around 12 showed one or more bonds with the target site, whereas 9 showed no bonds with the target site. This actually suggest that Coriander sativum can be an alternative to fluconazole in the treatment of infections by C.glabrata.

In a study conducted by Roger Kist et al in the year 2018, they proposed 8 novel mTOR inhibitors that act by the similar mechanism like that of Rapamycin using pharmacophore searching and analysis followed by molecular docking.(8) Wang et al, 2017 conducted a study for analysing the effect of components of Himalayan cedar oil as PTP1B inhibitor using molecular docking. (9) Antypenko et al (2018) performed a molecular docking study where they evaluated the anti-fungal activity of 9 novel acyl thiourea molecules in 14α-demethylase (CYP51) and N-myristoyltransferase (NMT) of fungal strains to see if they can be useful in their growth inhibition.(10) Koparde et al (2018) found that coumarin-maltol hybrids are useful as anticancer agents by evaluating their effects on HeLa cell lines and then looks for their anti-bacterial activity on 4TZK enzyme of E. coli using molecular docking and found that it has both anti-cancer and anti-bacterial properties.(11) Rajaraaman et al (2018) evaluated anti-fungal properties of 1-Acetyl-4-(4-hydroxyphenyl) piperazine using molecular docking and inferred that their properties enable their use as an anti-fungal drug.(12) Sathya et al (2015) conducted an in-silico modelling where the effect of benzylthio-1H-benzo[d]imidazol-1-yl acetic acid derivatives as a potent CRTh2 antagonist was analysed and they found that around 28 of the molecules had shown to have potential to be a drug in inhibiting the target site.(13)

The need of the hour is the discovery of newer drugs in treating infections especially anti-fungal targets in the treatment of Candidal infections as they are the ones with most resistance to all the anti-fungal drugs used in their management.(14) (15)From our study, it can be suggested that coriander may be a promising natural alternative to Fluconazole in the treatment of Candidal infections.

Conclusion

The use of in-silico models in drug discovery has gained attention in the past decade. With the increasing challenge of newer and newer strains of resistant organisms the need of the hour is the development of newer naturally occurring herbal agents which can replace these synthetic pharmaceutical agents. In our study we performed molecular docking using active components of Coriander sativum on ERG 11 gene of Candida glabrata and found that around 12 out 21 compounds showed bond with the target site suggesting a possible potential as an anti-fungal agent. Further microbial studies are required to assess if they can be used as an alternative treatment modality in fungal infections.

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