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Investigation and identification of some active biochemical in medical plants against CYP51 protein in candida by using molecular docking

Abubaker Abdulrahem Thanon AL GHAZAL[1], Mohammad Ibrahim KHALIL[1]*

[1] Environmental Science and Technology College, University of Mosul, Mosul, Iraq.
*E-mail: mohammadibrahim@uomosul.edu.iq

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ABSTRACT: Common and medical plants were investigated for active biochemical to bind and inhibit the CYP51 protein in candida sp., 22 important plants were chosen and 263 molecular docking reactions were done between active materials and protein, 1441 different active ligands were detected for binding in protein active site, the best 225 ligands were chosen depending the power of affinity bond. Four ligands were candidates for having the best ligand affinity bond and more safety for use according to the toxicity test program; within these ligands, the Epicatechin was found to be the best biochemical for inhibition and bonding to CYP51 protein as it subjects to Lipinski's rule of five.
Keywords: molecular docking; medical plants; *Candida* sp.

Investigação e identificação de alguns bioquímicos ativos em plantas medicinais contra a proteína CYP51 em candida usando Molecular Docking

RESUMO: Plantas comuns e medicinais foram investigadas para bioquímicos ativos para ligar e inibir a proteína CYP51 em Candida sp., 22 plantas importantes foram escolhidas e 263 reações de docking molecular foram feitas entre materiais ativos e proteínas, 1441 ligantes ativos diferentes foram detectados para ligação em proteínas sítio ativo, o melhor ligante 225 foi escolhido dependendo do poder de ligação de afinidade. Quatro ligantes foram candidatos por ter melhor ligação por afinidade e maior segurança para uso de acordo com o programa de testes de toxicidade, dentro destes ligantes a Epicatequina mostrou ser o melhor bioquímico para inibição e ligação à proteína CYP51 por estar sujeita à regra dos cinco de Lipinski.
Palavras-chave: docking molecular; plantas medicinais; *Candida* sp.

1. INTRODUCTION

Bioinformatics and in silico approach of different biochemical reactions is an essential tool for predicting the best results of important reactions, especially for drug design and antimicrobial materials, before applying any materials in lab experiments, which prevent time wasting and materials exposure (ABBAS et al., 2023). Molecular docking is one of the best tools for testing and applying active materials as ligands to bind in the active site of any protein to stop its activity and inhibit microbial virulence factors such as cell wall protein. The molecular docking depends on the affinity bond ratio between the ligand (an ion act atom donor connected by a bond to a central metal atom) and the protein as a ligand target (PIERANTONI et al., 2021).

Any drug to be considered as medicine must obey Lipiniski`s rule of five, which includes molecular weight, polar surface area, charge, lipophilicity, and hydrogen bonding, and the human body has an activity in absorption, distribution, metabolism, and excretion (ADME). All these conditions must be considered with any drug design to ensure treatment success. As there are many plants with different active materials some of them have high potential toxicity and some of them interact with many targets in the bodies, using molecular docking offers a good tool for discovering and seeking an efficient ligand to bind with a specific target to give a good and fast therapy (DAUSSIN et al, 2021).

The aim of this study is to investigate many plants for good, safe and active materials for binding and inhibiting the CYP51 protein in *Candida* sp. (Khelfaoui et al., 2021). Which is considered the most invasive pathogens in the human body using molecular docking with another bioinformatics program to simulate the binding process between many ligands and target proteins, and the results can be applied in a lab for in vivo experiments (McNUTT et al., 2021).

2. MATERIAL AND METHODS

2.1. Target protein

CYP51 (Erg11) is the most important protein in Basidiomycetes and Ascomycetes fungi and it is a target for Azol medicine and plays a role in ergosterol synthesis. The symbol of this protein is 5JLC in the protein Data Bank (PDB); the CYP51 protein has one chain (A) with 515 amino acids (Mroczyńska et al., 2021) (Figure 1).

2.2. Medical plants

Plants produce and synthesize many biochemical compounds for many reasons and function in defense and against pathogens resistance like insects, bacteria, fungi and even mammalian eating plants. So not all plants can be used or classified as medical plants (Seifzadeh et al., 2017); 22 different plants were selected for molecular docking (Table 1). From all plants, ligands were obtained by using PubChem

website and using them against CYP51 protein (SHI et al., 2020).

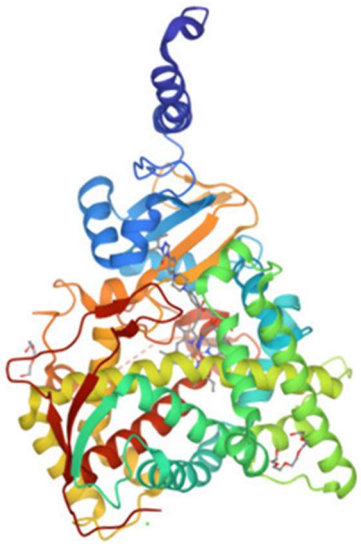

Figure 1. The 3D structure of CYP51 protein.
Figura 1. A estrutura 3D da proteína CYP51.

2.3. Molecular Docking

Using the 22 plants as a source ligand obtained by using Dr. Duke's Phytochemical and Ethnobotanical databases and for finding the 3D structure, synonyms, and chemical information from authoritative sources, PubChem was used. The results used in molecular docking against the CYP51 protein using the PyRx website, each ligand was used for molecular docking and comparing among the results to choose the best one according to some properties.

2.4. Toxicity test

Each ligand is tested for toxicity in silico; each ligand is converted to Isomeric SMILES and by using eMolTox for a drug safety analysis system (SEIFZADEH et al., 2017).

Table 1. Plants used as a source of active ligand.
Tabela 1. Plantas utilizadas como fonte de ligante ativo.

no	Plant name
1	*Adiantum capillus veneris*
2	*Allium cepa*
3	*Anethum graveolens*
4	*Calendula officinalis*
5	*Cichorium intybus*
6	*Citrus aurantifolia*
7	*Citrus limonum*
8	*Commiphora myrrha*
9	*Corcus sativus*
10	*Coriandrum sativum*
11	*Cuminum cyminum*
12	*Cyperus rotundus*
13	*Dianthus caryophyllus*
14	*Eurca sativa*
15	*Glycyrrhiza glabra*
16	*Lavender angustifolia*
17	*Nigella sativa*
18	*Pimpinella anisum*
19	*Punica granatum*
20	*Thymus vulgaris*
21	*Trigonella foenum-graecum*
22	*Zingiber officinale*

3. RESULTS

226 ligands were obtained from Dr. Duke's Phytochemical and Ethnobotanical databases for all 22 plants and 1441 active sites were formed as a result of ligands docking against CYP51 protein (Shi et al., 2020); 225 ligands selected according to some specification: Affinity bond, applies to Lipinski's low, gastrointestinal (GI) absorption, blood-brain barrier (BBB), potential toxicity and toxic substructure (Table 2).

Table 2. Ligands properties of different plants used as sources.
Tabela 2. Propriedades dos ligantes de diferentes plantas utilizadas como fontes.

No	Plant	Ligand	Affinity bond	Lipiniski's role	BBB permeant	potential toxicity	toxic substructure	Gi absorption
1	*Anethum graveolens*	alpha-Amyrenone	-11.9	yes	No	Toxic	Safe	Low
2	*Thymus vulgaris*	beta carotene	-11.8	No	No	Toxic	Safe	Low
3	*Cuminum cyminum*	beta carotene	-11.8	No	No	Toxic	Safe	Low
4	*Citrus limonum*	beta carotene	-11.8	No	No	Toxic	Safe	Low
5	*Commiphora myrrha*	3-epi-alpha-Amyrin	-11.6	yes	No	Toxic	Safe	Low
6	*Corcus sativus*	Helichrysoside	-11.4	No	No	Safe	Toxic	Low
7	*Citrus limonum*	Eriocitrin	11.2	No	No	Safe	Toxic	Low
8	*Citrus limonum*	Diosmin	-11.1	No	No	Safe	Toxic	Low
9	*Corcus sativus*	Helichrysoside	-11.1	No	No	Safe	Toxic	Low
10	*Citrus limonum*	Hesperidin	-10.7	No	No	Safe	Toxic	Low
11	*Cuminum cyminum*	Apigenin 7-glucuronosyl-glucoside	-10.6	No	No	Safe	Toxic	Low
12	*Commiphora myrrha*	Campesterol	-10.5	Yes	No	Toxic	Safe	Low
13	*Citrus limonum*	Campesterol	-10.5	yes	No	Toxic	Safe	Low
14	*Nigella sativa*	Campesterol	-10.5	yes	No	Toxic	Safe	Low
15	*Thymus vulgaris*	Beta-Sitosterol	-10.5	yes	No	Toxic	Safe	Low
16	*Nigella sativa*	Beta-Sitosterol	-10.5	yes	No	Toxic	Safe	Low
17	*Commiphora myrrha*	Beta-Sitosterol	-10.5	yes	No	Toxic	Safe	Low
18	*Citrus limonum*	Beta-Sitosterol	-10.5	yes	No	Toxic	Safe	Low
19	*Citrus limonum*	Diosmin	-10.5	No	No	Safe	Toxic	Low
20	*Punica granatum*	(-)-Epicatechin	-9.5	Yes	No	Safe	Safe	High
21	*Corcus sativus*	Quercetin	-9.4	Yes	No	Toxic	Toxic	High
22	*Pimpinella anisum*	Apigenin	-9.4	Yes	No	Toxic	Safe	High
23	*Coriandrum sativum*	Apigenin	-9.4	Yes	No	Toxic	Safe	High
24	*Anethum graveolens*	Apigenin	-9.4	Yes	No	Toxic	Safe	High

The top five ligand candidates for inhibition of the CYP51 protein depend on affinity bond and toxicity (McNutt et al., 2021; Seifzadeh et al., 2017) (Table 3), but the best ligand which has all specifications according to Lipiniski's rule of five is Epicatechin in the fruit of *Punica granatum* plant, this ligand conjugation with the target by four amino acid arginine, serine, histidine and phenylalanine (Figure 2). And the 3D ligand protein docking as in Figure 3.

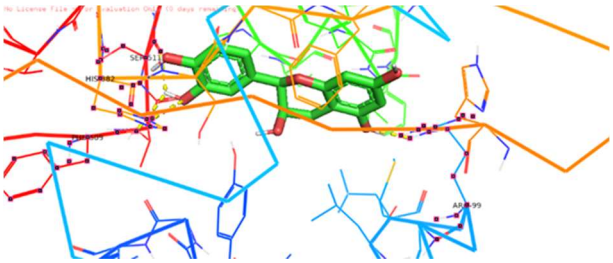

Figure 2. Amino acid conjugation with ligand.
Figura 2. Conjugação de aminoácidos com ligante.

4. DISCUSSION

The using molecular docking is the best method to find out the suitable drug and medicine to treat the infection of any microorganisms; It offers a tool to design a medicine for modified organisms that develop as a result of mutation or adaptation to environmental effects, the molecular docking results can applicable in vitro and in vivo to find out any side effect or prove the results. All active compounds were tested for their toxicity as they will be used as antimicrobial agents, the use of molecular docking reduced wasted time in seeking suitable medicine for treatment of the pathogens and to prevent infection and side effects of the using the medicine, as well as using efficient ligand to bond with target protein and inhibition its activity and block the reproduction of the organisms and prevent the body from more invasion. It's a very useful tool in molecular biology and pharmacology.

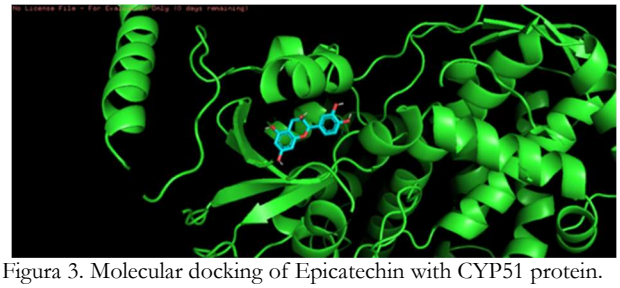

Figura 3. Molecular docking of Epicatechin with CYP51 protein.
Figura 3. Docking molecular da epicatequina com a proteína CYP51.

Table 3. Best ligand properties.
Tabela 3. Melhores propriedades do ligante.

Plant name	Part of plant	Ligand	Binding affinity	Potential toxicity	Toxic substructure	Molecular weight (g/mol)	GI absorption	BBB permeant	Lipinski
Cuminum cyminum	seed	Apiin	-9.5	safe	safe	564.49	low	no	no
Nigella sativa	seed	Astragalin	-9.5	safe	safe	448.38	low	no	no
Corcus sativus	flower	Astragalin	-9.5	safe	safe	448.38	low	no	no
Cichorium intybus	aerial part	Astragalin	-9.5	safe	safe	448.38	low	no	no
Adiantum capillus veneris	leave	Astragalin	-9.5	safe	safe	448.38	low	no	no
Punica granatum	fruit	(-)-Epicatechin	-9.5	safe	safe	290.27	high	no	yes
Dianthus caryophyllus	flower	Pelargonidin 3-glucoside	-9.2	safe	safe	468.84	low	no	yes
Anethum graveolens	leave	alpha-Amyrenone	-11.9	toxic	safe	424.70	low	no	yes
Citrus limonum	fruit	Diosmin	-11.1	safe	toxic	608.54	low	no	no
Corcus sativus	flower	Myricetin	-9.7	toxic	toxic	318.24	low	no	yes
Cuminum cyminum	seed	Apiin	-9.5	safe	safe	564.49	low	no	no

(−)-Epicatechin is an antioxidant compound that increases muscle growth, has no side effects, and can be used as anticandidal (ZHANG et al., 2021).

5. CONCLUSIONS

Molecular docking is a very promising tool to face any invasion or cataclysm by any organism or to build a vaccine to decrease the effect or kill the pathogens.

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