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A COMPUTATIONAL DOCKING APPROACH AND ANTI-FUNGAL EFFECT OF AURANTOSIDE-G AND CLOTRIMAZOLE DRUG.

Shifo Savio*[1], Abinaya Gayathri[1], Swapna Sreenivasan[1]

[1]Department of Orthodontics, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, 162, PoonamalleeHigh Road,Chennai – 600077.

*Corresponding Author: drshifobds@gmail.com

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Abstract:

Background

Candida infections often happen in the mouth. These types of germs can create thin layers that can grow inside the mouth, braces, brackets, and false teeth. In this study, Aurantoside-G, taken from the marine sponge *Theonellaswinhoei*, was compared to Clotrimazole. It was tested against important antigens from *Candida albicans*.

Methods

GLIDE 4. 0 software was used to check how well the ligands and targets fit together in this study. The shapes of the molecules Aurantoside-G and Clotrimazole were found in the PubChem database and created using the ChemDraw program. The target protein from the *Candida albicans* antigens, called Î´-14-sterol reductase (4QUV), used in this study was taken from the Protein Data Bank. The ligands and targets were studied and organized using the PymoL viewer. The GLIDE program was used to fit the ligand and target together.

Result

In this study, the weight of Aurantoside-G was found to be 344. 84 grams per mole and the weight of Clotrimazole was found to be 743. 15 grams per mole. Aurantoside-G has 1 hydrogen bond acceptor, while Clotrimazole has 15. Aurantoside-G has no H-bond donors, while Clotrimazole has 8. Aurantoside-G did not dissolve in water, but Clotrimazole dissolved very well. Aurantoside-G was more effective than Clotrimazole.

Conclusion

The final docking results show that Aurantoside-G had a much higher docking score and is similar in drug qualities to Clotrimazole. In the

future, more tests on how drugs work might help develop Aurantoside-G as a treatment for yeast infections.

Keywords: Aurantoside-G, antifungal, clotrimazole,fungal infections, molecular docking, *Theonellaswinhoei*.

1. Introduction

A common fungus called *Candida albicans* lives on the skin, in the stomach, and in the throat of healthy people. Albicans are a common part of the normal bacteria in half of the people. In most people, C. Albicans lives in our bodies as a harmless companion for life. In some cases, though, *Candida albicans* can cause infections that affect the skin or lead to serious infections throughout the body. Candida usually stays balanced in our body, but different local and environmental factors can upset this balance. This can cause it to change from being normal to becoming harmful and causing infections (Talapko et al., 2021) albicans, *C Krusei*, *C tropicalis*, and *C. glabrata* are linked to mouth infections caused by yeast (Lueyar et al., 2023). When fixing teeth problems with braces, regular brackets are often used. The design of these brackets makes it harder to keep your mouth clean, which increases the chance of more bacteria building up. Braces might hold yeast and raise the chances of getting a mouth infection called candidosis. (Grzegocka et al., 2020)

The treatments for Candida infections can be very different depending on where the infection is, the person's overall health and weak immune system, their risk factors for getting the infection, the type of Candida causing it, and sometimes how well that type responds to certain antifungal medicines (Berg & Berg, 2018). Most skin Candida infections can be treated with various creams or ointments that fight fungi, like clotrimazole or miconazole. Clotrimazole is a man-made medicine that works against many types of fungi. It is a medicine approved by the FDA to treat oral yeast infections. Clotrimazole works mainly by hurting the protective layer of the fungi's cell membrane. However, its use in medicine has been restricted due to the development of drug resistance, a high chance of causing harmful effects, limited effectiveness against infections, and unwanted side effects (Sravanthi et al., 2023) Researchers have looked at natural products that can help treat infections because they may work better against resistant germs and cause fewer side effects compared to traditional antifungal medicines. (Allert, 2019*)

The first time a natural compound called aurantoside G was made from a sea sponge called *Theonellaswinhoei*. This compound is thought to help fight fungi. To check how well Aurantoside-G can fight against fungal infections, scientists used a method called molecular docking with the proteins from *Candida albicans*.

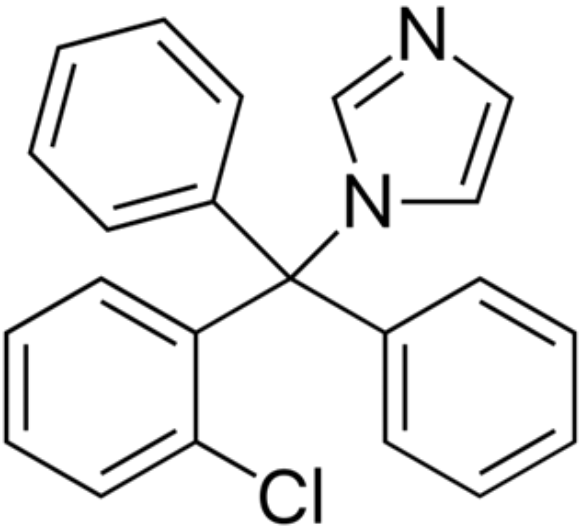


Figure 1: Chemical structure of clotrimazole.

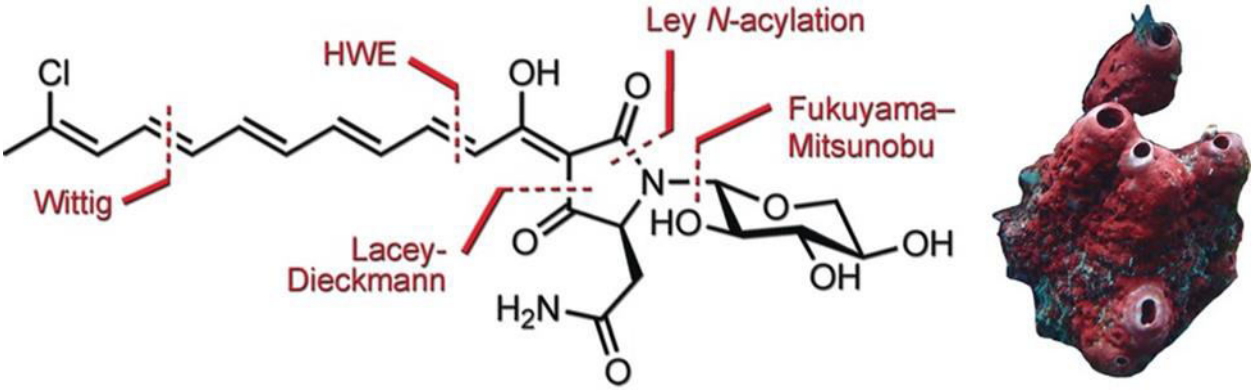


Figure 2: Chemical structure of Aurantoside-G and marine sponge*Theonellaswinhoe*.

2. Methods:

2.1 Molecular Docking:

Molecular docking is a fast and useful method that helps predict which bioactive compounds will connect with certain proteins, or which proteins a specific bioactive compound will target (Coumar, 2021). The strong antifungal effects of the compounds clotrimazole and Aurantoside-G suggest that we should do molecular docking studies to find possible targets (Luoet al., 2018) Glide 40 is a computer program used to study how small molecules fit into proteins and other biological materials. It helps check how well ligands and targets fit together in molecular docking. PubChem is the biggest collection of chemical information that is free to use. It is where ligands for clotrimazole and Aurantoside-G (Figure 1 and Figure 2) were found (Kim et al., 2016)

Now, the chemical structure of the ligand was made using ChemDraw software. Chem Draw Professional is a tool that lets users create drawings of chemical structures, reactions, and biological items and processes. The Protein Data Bank (PDB) is a collection of 3D shapes of proteins, nucleic acids, and other large biological molecules that have been experimentally studied. The target protein from *Candida albicans* called Δ-14-sterol reductase (4QUV) (Figure 3) used in this study was taken from the Protein Data Bank. The target protein and ligand were placed together using Glide software.

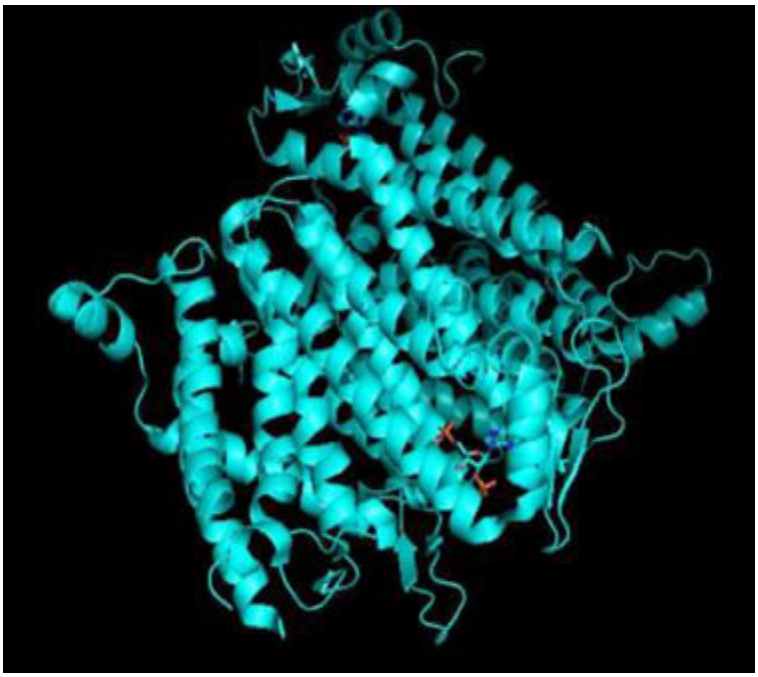


Figure 3: Structure of *Candida albicans* target protein delta(14)-sterol reductase (4QUV).

3. Results

Molecular docking is a powerful computational technique used to predict the interaction between a small molecule (like a drug) and a target protein. In the context of Candida albicans, molecular docking can help identify potential antifungal compounds by targeting specific proteins involved in the fungus's pathogenicity and survival mechanisms. In the present study the molecular docking approach of Aurantoside-G a natural drug with the perspective antigens of *C.albicans* fungi which is a sterol reductase enzyme was enumerated. The results reveal that Aurantoside-G binds with sterol reeducates enzyme at different binding cavities position and exerts maximum binding affinity of -9.4kcal M^{-1} energy value. (Table.1). The energy affinity and binding pockets of Aurantoside-G with target is exerted through adjacent amino terminal links (Figure 4) and the binding energy value of -9.9 is considerable a good energy value when compared to that of standard antifungal Clotrimazole drug of -9.1kcal M^{-1}. The bioavailability score value of Aurantoside-G is also significant with 0.55 which is higher than Clotrimazole drug 0.11.

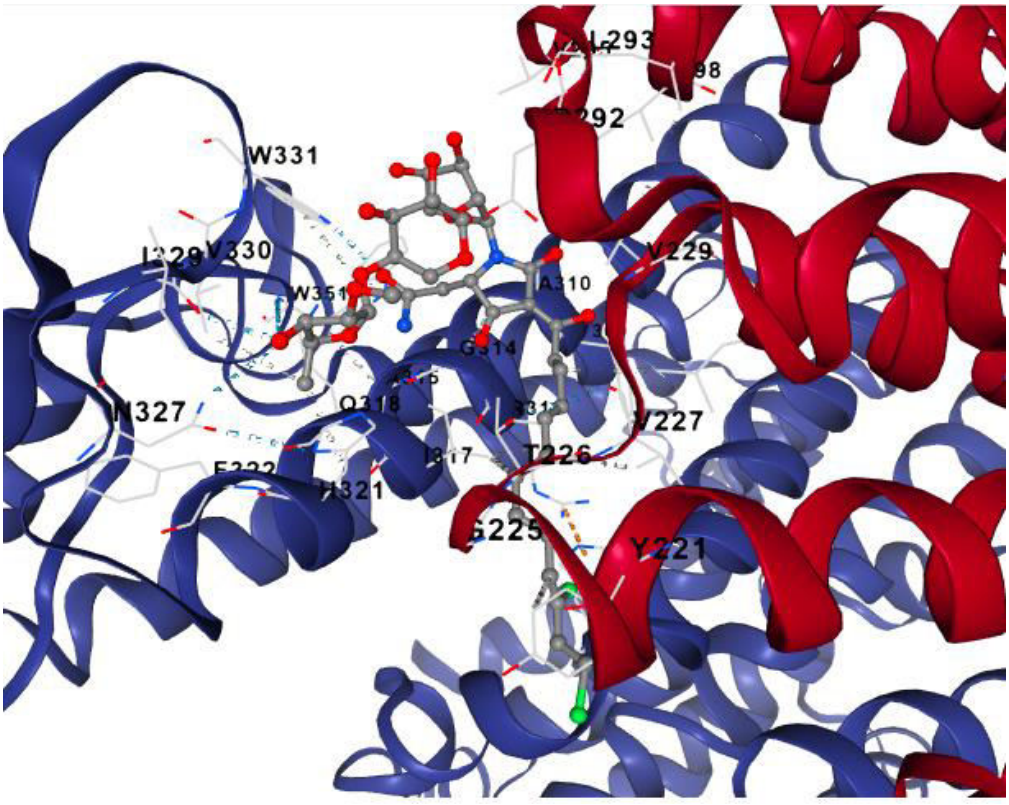
Lipinski's Rule of Five, also known as Pfizer's Rule of Five, is a set of guidelines used to evaluate the drug likeness of a chemical compound. It helps determine if a compound has the properties that would make it likely to be an orally active drug in humans.The rule states that, in general, an orally active drug has no more than one violation of the following criteria as No more than 5 hydrogen bond donors (the total number of nitrogen-hydrogen and oxygen-hydrogen bonds).No more than 10 hydrogen bond acceptors (all nitrogen or oxygen atoms).A molecular mass less than 500 daltons.A calculated octanol-water partition coefficient (Log P) that does not exceed 5.These criteria are important for a drug's pharmacokinetics, including absorption, distribution, metabolism, and excretion (ADME) in the human body. The present results reveals that the Aurantoside-G has adhere to all Lipinski rule with 1 hydrogen bond acceptor and nil hydrogen bond donor. Since it is not water soluble Aurantoside-G can be used as topical applications as cream for candidiasis. Clotrimazole has water soluble and it

also adheres all the necessary Lipinski rule and oral bioavailablity. The PYMOL view of drug target interaction of aurantoside G with sterol reductase was depicted in 3D approach for better ligand target binding (Figure 5).

Table 1: Molecular docking scores of selective ligands

Parameters	**Aurantoside-G**	**Clotrimazole**
Formula	C33H43ClN2O15	C22H17ClN2
Molecular weight	344.84 g/mol	743.15 g/mol
Binding energy (Affinity)	-9.9 kcal M^{-1}	-9.1 kcal M^{-1}
No.of.H. bonds acceptors	1	15
No. of. H-bond donors	0	8
Water solubility	Not soluble	Highly soluble
Lipinski	2 violations	3 violations
Bioavailability score	0.55	0.11

Figure 4: Binding affinity of Aurantoside-G with Sterol reductase protein



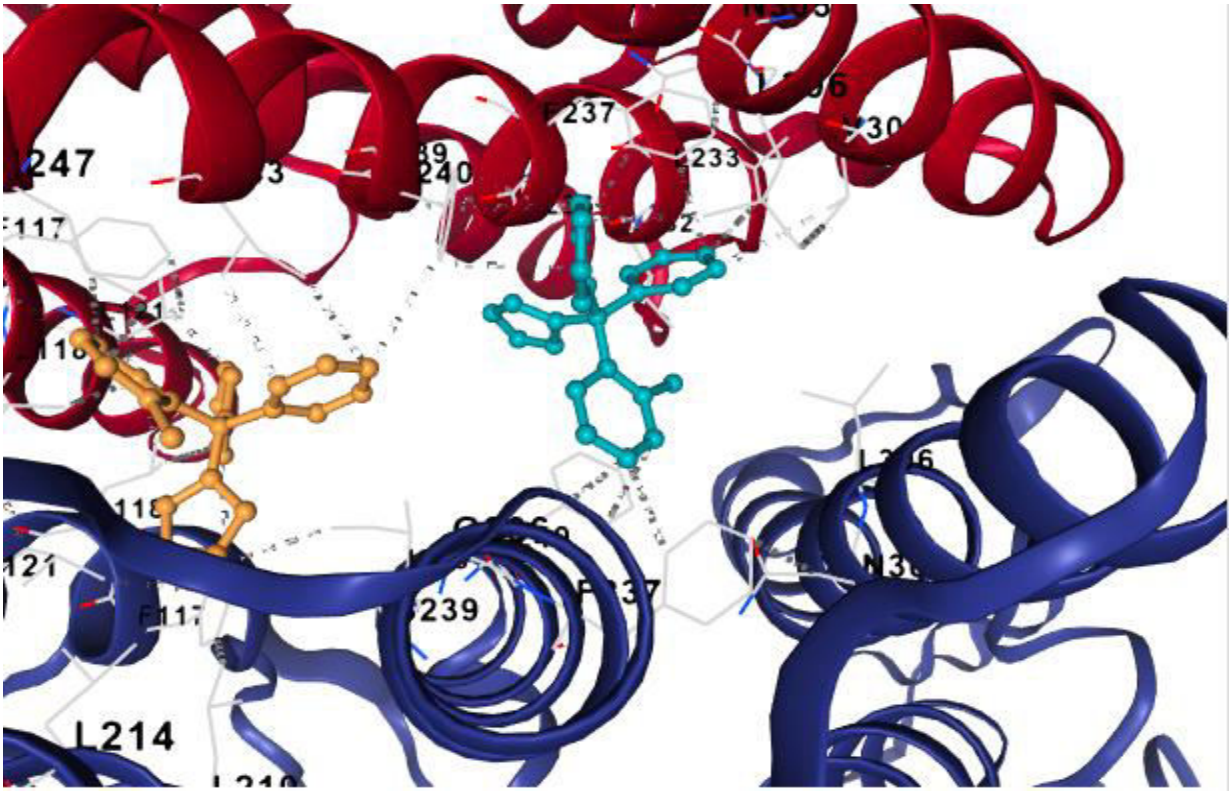


Figure.5 PYMOL view of Aurantoside-G and Sterol reductase interactions

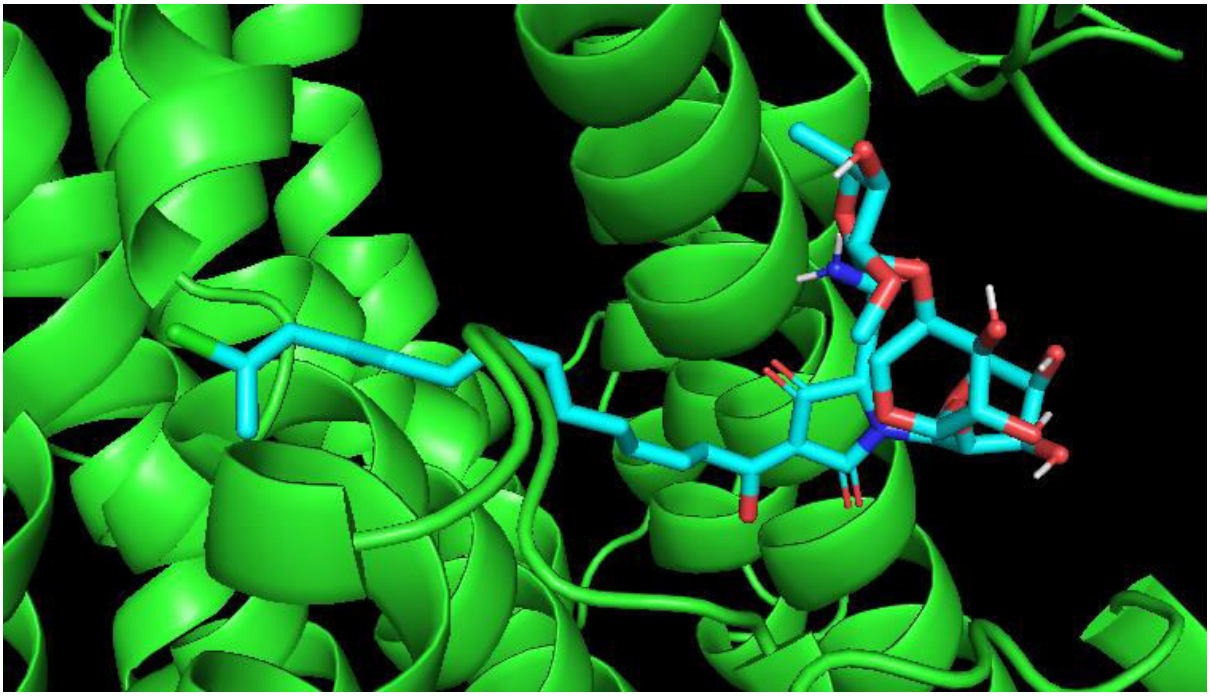


Figure.6 Binding affinity of Clotrimazole with Sterol reductase protein

4. Discussion

Molecular docking studies on Candida albicans are crucial for identifying potential antifungal agents by predicting how small molecules, such as drugs or phytochemicals, interact with fungal proteins. These studies help in understanding the binding affinity and stability of these interactions, which is essential for drug development.Recent research has focused on targeting specific proteins in Candida albicans that are involved in its pathogenicity and resistance mechanisms. For example, a study identified key proteins like HOG1, TSA1, TRX1, GPX3, SOD1, and YHB1 as potential targets for antifungal drugs1. Another study explored the binding efficiency of phytochemicals from various plants against the SAP2 protein of Candida albicans, showing promising results for compounds like Indicine-N-Oxide (Hassan et al., 2024).

Candida albicans is a type of yeast that naturally lives on your body, typically found in small amounts in areas like your mouth, skin, and intestines. It's usually harmless, but when the balance of healthy bacteria in your body is disrupted, it can overgrow and cause infections known as candidiasis (Martins et al., 2014).Accumulation and adhesion of *C.albicans* in the oral cavity is an initial step in candidosis. Moreover, the presence of orthodontic appliances over time favors the candidal presence. Clotrimazole, a broad-spectrum antifungal drug used to treat candidiasis has microbial resistance and cellular toxicity(Stringer, 2011).To overcome this, naturally occurring Aurantoside-G was compared with Clotrimazole and was molecular docked against *Candida albicans* antigens in this study.

A key tool in computer-assisted drug design and structural molecular biology is molecular docking. Predicting the predominant binding mode(s) of a ligand with a protein that has a known three-dimensional structure is the aim of ligand-protein docking. Docking can be used to rank the results of virtual screening on large compound libraries and suggest structural hypotheses explaining how the ligands inhibit the target (Morris & Lim-Wilby, 2008).In an article by Pradhan et al., 2021, Molecular docking of opportunistic fungi with a bioactive compound from *C. sinensis* n-heptadecanoic-1.Using the CB-dock tool, molecular docking was performed, and various opportunistic fungal proteins were docked with the ligand compound n-heptadecanol-1. The most noteworthy results were observed about *C. albicans*, *R. oryzae*, and*A. niger*. The problem of drug insufficiency that could potentially function as an anti-fungal agent is resolved by n-heptadecanoic-1, which demonstrates therapeutic potential and supports our study. According to an article by Gracia etal,Synthesis, Molecular Docking, and Anti-mycotic Evaluation of Some 3-Acyl Imidazo[1,2-*a*] pyrimidines.

5. Conclusion

The overall docking result shows that compound Aurantoside-G exhibited a significantly high docking score and drug-likeness similar to Clotrimazole drug. Further pharmacology screening in the future may lead to the compound Aurantoside-G for anticandidal drug therapy.

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