Natural Resources for Human Health

visaga publishing house

Original Research

View Article Online

Check for updates

Received 26 October 2022
Revised 08 December 2022
Accepted 29 December 2022
Available online 07 February 2023

Edited by Shafi Ullah Khan

KEYWORDS:
Candida albicans
resistance
natural products
molecular docking

Natr Resour Human Health 2023; 3 (2): 228-236
https://doi.org/10.53365/nrfhh/158808
eISSN: 2583-1194

An *in silico* study involving Mangiferin, 7-Epiclusianone, Fukugetin, Lapachol, Plumbagin and Guttiferone-A against *C. albicans* proteins

Artur Gomes Barros [1,*], Leonardo Pereira de Araújo [1], Nelson José Freitas da Silveira [1], Breno Régis Santos [2]

[1]Laboratory of Molecular Modeling and Computer Simulation/MolMod-CS, Institute of Chemistry, Federal University of Alfenas, Rua Gabriel Monteiro da Silva 700, 37130001, Alfenas, Brazil
[2]Institute of Natural Sciences, Federal University of Alfenas, Rua Gabriel Monteiro da Silva 700, 37130001, Alfenas, Brazil

ABSTRACT: It is notorious that since the beginnings of spacetime, the human being lives with microorganisms of countless forms, be it in a positive way as in case of Bacteroidetes present in the intestine's microbiota or negative way as in case of recent epidemic of Sars-Cov-2. So, the negative impacts caused by microorganisms are objects of study in the whole world, for instance, *Candida albicans*, which is a fungus that lives in the human body symbiotically and assists in the maintenance of body homeostasis, but the same can present an invasive features that become harmful to the human health, mainly in people who present some kind of immunodeficiency, causing its proliferation to become exacerbated, may cause the death. Said that, the use of drugs to control *C. albicans* is very important, being the nystatin and fluconazole that are the ones that are currently used. However, the updating of such medicines as time goes by becomes ineffective to some kinds of strains, since the capacity of the fungus in evolution creates resistance to medicines. So, the Discovery of new drugs is necessary and natural products are an excellent research source for the same. Therefore, this study made the methodology *in silico* of molecular docking to investigate the forms of connection of the natural compounds fukugetin, guttiferone-A, lapachol, mangiferin, plumbagin and 7-epiclusianone in potential molecular targets of fungus *Candida albicans*.

1. INTRODUCTION

The *Candida albicans* is an opportunist fungus that lives symbiotically in the human body and is present in regions such as vagina, intestine, and mouth, in which it assists in the natural process of good functioning in these certain places. However, the microorganism can develop an invasive characteristic and proliferate in an exacerbated way, becoming a problem for the society, especially in humans who have some kind of immunodeficiency, since the immune system to have some flaw cannot contain such expansion (Albarelo et al., 2021) . As an example, can mention patients with HIV, of which the most part will suffer which the proliferation of *C. albicans* (Albarelo et al., 2021). It is worth mentioning that the mechanism of proliferation of fungus is well-developed, such as its ability to go beyond the epidermis and reach the blood system, in which the liberation of spores allows the fungus to reach any internal organs of the human and allows causing multiple organ failure (Macalão et al., 2020).

Thus, there is the candidiasis, which is a disease generated mainly by *C.albicans* (M.E. De Oliveira et al., 2022) that affect mainly women in their vulvovaginal system in which the proliferation of fungus occurs in an uncontrolled way due to poor health (use of high immunodeficiency contraceptives, decompensated diabetes mellitus, use of corticosteroids), in addition there is a chance in vaginal's pH, causing vaginal itching and unusual discharge because the presence of C.albicans which as mentioned above can invade the blood system (Arwa, 2013; Macalão et al., 2020).

Furthermore, this fungus is becoming a big problem, because as treatments are used for a long time in a repeated way, the fungus will become resistant to mutations and become more resilient to the current drugs used to the treatment in such a way that it is necessary the development of new medicines as a safe and effective way to control the disease (Medina, 2022).

* Corresponding author.
E-mail address: arturgb25@gmail.com (Artur Gomes Barros)

That said, humans have been searching for new compounds since the beginning of time, mainly based on compounds from plants and other organisms called natural products. Such compounds can help humans solve problems in an effective, simple and safe way and can be found in more places (L.N. De Oliveira & Batista, 2021). Therefore, compounds known for their antifungal activities can be used in initiation survival proteins to the microorganism, in order to assist in the development of a new medicine (Hong-Zhuo et al., 2019).

As example of natural compounds, the secondary metabolites which have main objective the protection of the plant as for eventual situations which may cause some type of problem in plant development, for example, the invasion by bacteria, fugus, anthropic or natural impacts, thus as for a better adaptation of the plant and its evolution. This becomes the secondary metabolites substances with big potential to use in human health as herbal medicine, with a range of medicinal possibilities, teas and drugs (Borges & Amorim, 2020).

Among these compounds, we can be mention the guttiferone-A, which is a polyisoprenylated benzophenone found in trees of genus *Garcinia* (*Garcinia intermedia*, *Garcinia livingstonei*, *Garcinia macrophylla* and *Garcinia brasiliensis*), which has a metabolite function and in a deeper way as a monoterpenoid and a fungal inhibition through an interaction with the cell wall in addition to presenting low toxicity for humans, it has anti-enzymatic, anti-parasitic and anti-tumor potential, besides the antifungal potential evaluated here (Dias et al., 2017; Pardo-Andreu et al., 2011).

Fukugetin is a purified bioflavonoid and a compound that can be extracted from species such *Clusia columnaris* (irapuá) and *Garcinia brasiliensis* (bacupari) and has antifungal activity through the reduction of free radicals DPPH (2,2 diphenyl-1-picrylhydrazyl) in addition to inhibition by lipid peroxidation (Assis et al., 2013; Bernardi & Gardneriana, 2009) in addition to having anti-enzymatic, anti-angiogenic activities.

Another example is the lapachol, compound derived from naphthoquinones and that can be extracted from the bark of *Tabebuia avellanedae* (ipê roxo) and has antifungal activity through of oxidative stress (Lira et al., 2022; Macêdo et al., 2022) in addition to having anticancer, analgesic and antineoplastic properties.

The Plumbagin is a naphthoquinone which can be extracted from species such *Nepenthes gracilis*, *Drosophyllum lusitanicum* and *Plumbago scandens* and has antifungal effect through by delaying of germination to the inhibition of alternative oxidase that regulates the oxidative stress of fungal cells in addition to generating reactive oxygen species (Silva, 2020; Yin et al., 2020) besides this potential it also has anticancer, antimicrobial properties.

Other compounds can be tested since their ability has been proven, such as 7-epiclusianone which is a benzophenone that can be extracted of fruit, leaves, and bark of *Garcinia brasiliensis* (bacupari) and has its antifungal activity described in other studies such as the one by BARROS in 2016, and CASTRO in 2017, in addition to having antimicrobial, anti-allergic, antitumor properties.

Mangiferin is a C-glycosyl member of xanthones and serves as a metabolite for the vegetables which can be found and extracted from the stem of the specie *Zeyheria tuberculosa* (bignoniaceae) or in leaves by mango (*Mangifera indica* L.) and has its antifungal activity through it is antioxidant and antibacterial action (Maldonado & D, 2020).

The article by R. Verma et al. (2020), carried the reach in all genome of *C.albicans* and found 94 potential drug targeted genes, among the demonstrated ones, the structs involved in this situation can be used such as target of natural compounds and theses chosen for study were according antifungal potential of each natural compound.

In this regard, the blocking or diminution of expression of certain gens will have a negative influence in development of fungus, as well as, on the proteins which they generate, as in the case of evaluated gens there is the CLN3 which synthesizes and activates a cyclin G1/S (Bar-Yosef et al., 2018), the CPH1 which generates a proteins pseudohyfal1 regulatory protein and also is involved in fungal sex life (Jha et al., 2019; Lone & Ahmad, 2020), DBF4 which originates an kinase activator protein in S-phase (Dolson et al., 2021), the gen ERG5 which synthesizes the C-22 desnaturase (Martel et al., 2010), the FAS2 which sythesizes a fatty acid synthase enzyme (Lou et al., 2019), the LTE1 which is useful as a mitosis terminator (Orellana-Muñoz et al., 2017), the SKN7 which is a regulator of SLN1-YPF1-SKN7, the SLN1 which synthesizes a histin kinase protein related to signaling of components for cell wall biosynthesis (Herrero-De-Dios et al., 2014), the TEM1 synthesizes a protein regulates of conclusion of mitosis (Orellana-Muñoz et al., 2017) and finally, there is the TUP1 which synthesizes a glycosidase (Ruben et al., 2020).

In view of the above, the methodology *in silico* of molecular docking is used to illustrate the interaction of these bioactive compounds that acting as ligands in *C. albicans* target structures that would act as receptors and in such a way, from other known substances (controls), to direct if the form of binding of substances and suggest the mode of action as antifungals (Marcelino, 2022). In short, natural compounds are being tested to combat the proliferation of fungus because they are more likely to have better answers than drugs already used, in addition to less probability of causing unscheduled results in the body of individuals (L.N. De Oliveira & Batista, 2021).

2. MATERIALS AND METHODS

All the natural compounds (guttiferone-A, 7-epiclusianone, plumbagin, lapachol, fukugetin and mangiferin) were obtained from the Pubchem (https://pubchem.ncbi.nlm.nih.gov) data base with their three-dimensional coordinates and the two-dimensional molecular structure. The amino acids residues sequences of the proteins generated by the gens: CLN3, CPH1, FAS2, SKN7, SLN1, TUP1, TEM1, DBF4, ERG5 and LTE1. They were in FASTA format from the UNIPROT database (Macdougall et al., 2020), after obtaining the sequence of amino acid residues, it was submitted to BLAST to check

whether such protein has an encrypted structure registered in the PDB (Protein Data Bank).

Table 1
Candida albicans genes and their respective control compounds.

Genes	Controls	References
CLN3	Clioquinol	Yan et al. (2018)
	Niclosamide	Garcia et al. (2018)
FAS2	MAF-1	Wang et al. (2017)
	Triclosan	Higgins et al. (2012)
CPH1	Fungichromin	An et al. (2016)
	Eugenol-tosylate	Lone and Ahmad (2020)
SLN1	RWJ-49815	Deschenes et al. (1999)
	RWJ-49968	
SKN7	Allicin	Abdelhameed and Abdullah (2021)
TUP1	Farnesol	Kebaara et al. (2008)
	Ciclopirox olamine	Niewerth et al. (2003)
	Fluconazole	
ERG5	β-sitosterol	A.K. Verma et al. (2020)
	α-sitosterol	
	Piperine	
	Fluconazole	

Then, the proteins whose crystallographed structures were not found were submitted to AlphaFold software Jumper et al. (2021) to make the process of molecular modeling by homology and in such a way determine their three-dimensional structure, only the protein generated by gene FAS2, there is the structure defined on website of Protein Data Bank (PDB) (https://www.rcsb.org) database deposited under the code 6U5V. Each target protein searched in the literature controls compounds that act on a determined protein as illustrated in Table 1 and with the control drugs found, they were prepared equally with the natural compounds for molecular docking, which was performed with the control and the specific protein which it is considered effective, in order to analyze its binding energy with the receptor and compare it with that of natural products. All the ligands and receptor were prepared using the Pymol (Schrodinger, 2017) and the MGLTools (http://mgltools.scripps.edu/) software in which the Blinding docking methodology was used to determine the Gridbox.

For the process molecular docking used the AutoDock Vina software (Trott & Olson, 2009). For the visualization the results in the form of image was used the Pymol and to visualize the connections made between the drug and the protein, the Liglpot+ (Laskowski & Swindells, 2011) softwares, but before that, the best binding of the ligand with the receptor in Pymol was converted to pdb format. Finally, the evaluation of pharmacodynamic and pharmacokinetic characteristics of the compounds was available using the software SwissADME (http://www.swissadme.ch/index.php), but prior to that the Openbabel software was used (http://www.cheminfo.org/Chemistry/Cheminformatics/FormatConverter/index.html) to convert the drug format to SMILES (smi) format and thus use it in SwissADME.

3. RESULTS AND DISCUSSION

All the compounds were obtained from the Pubchem database, in which they already had the two-dimensional molecular structure defined and shown in the Figure 1. The results of *in silico* tests show the binding energy results for the natural compounds when compared to the compounds used as controls as shown the Table 2.

From the results, it is possible to observe the two compounds stood out when compared with the others, but the other compounds shown the good results in determined proteins, the fukugetin and guttiferone-A shown the potential to act as multi-targets because have better bindings energy results than the controls compounds in 9 and 8 proteins respectively.

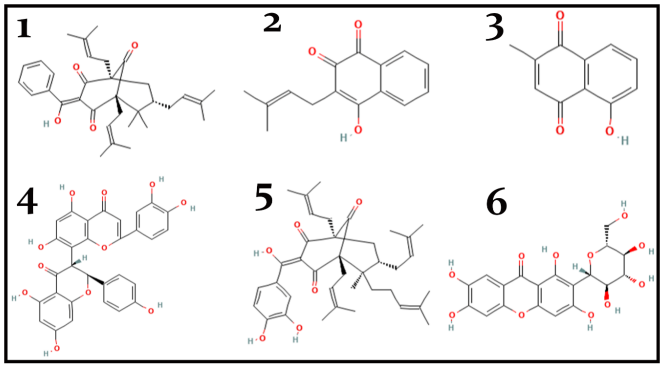

Figure 1. 2D structures by the natural compounds, being the number 1 the 7-epiclusianone, 2 the Lapachol, 3 the Pulmbagin, 4 the Fukugetin, 5 the Guttiferone-A and 6 the Mangiferin

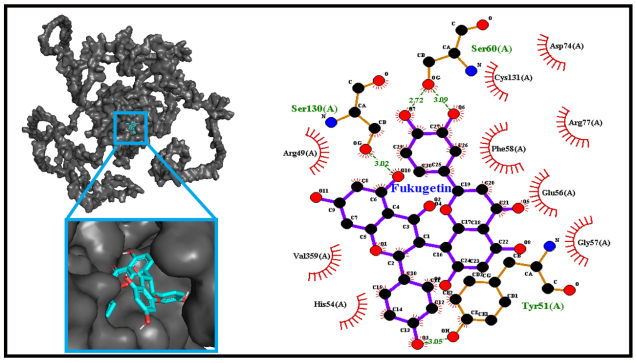

Figure 2. 3D and 2D representation of the interaction betwenn the drug Fukugetin and the protein synthesized by the CPH1 gene of *C.albicans* where in the reprentation 3D is possible to observe the drug in blue and the protein in gray in the representation 2D is possible observe the hydrogen bonds in green and the hydrophobic interactions as red arcs

In relation to the analyses obtained through the imagens above, it can be seen in the Figure 2 that it was possible to observe that the fukugetin realized the best of energy of interaction with the synthesize protein by the gene CPH1 where the energy was -9,8 kcal/mol in which realizes nine hydrophobic interactions and four hydrogen bonds of sizes 3.02 angstroms between drug's oxygen10 and the serine130 from

Table 2
Results of molecular docking obtained, classified by Kcal/mol and in the places indicated with a hyphen (-) is because they are not controlling drugs to that gene.

Compounds		GENES									
		CLN3	CPH1	DBF4	ERG5	FAS2	LTE1	SKN7	SLN1	TEM1	TUP1
	Clioquinol	-5.2	-	-	-	-	-	-	-	-	-
	Niclosamide	-7.6	-	-	-	-	-	-	-	-	-
	MAF-1	-	-	-	-	-5.6	-	-	-	-	-
	Triclosan	-	-	-	-	-6.7	-	-	-	-	-
	Fungichromin	-	-8.0	-	-	-	-	-	-	-	-
	Eugenol-tosylate	-	-6.1	-	-	-	-	-	-	-	-
CONTROL	RWJ-49815	-	-	-	-	-	-	-	-9.8	-	-
	RWJ-49968	-	-	-	-	-	-	-	-7.4	-	-
	Allicin	-	-	-	-	-	-	-3.0	-	-	-
	Farnesol	-	-	-	-	-	-	-	-	-	-5.4
	Ciclopirox olamine	-	-	-	-	-	-	-	-	-	-7.0
	Fluconazol	-	-	-	-7.6	-	-	-	-	-	-6.9
	Beta-sistosterol	-	-	-	-9.6	-	-	-	-	-	-
	Ç-sistosterol	-	-	-	-9.2	-	-	-	-	-	-
	Piperine	-	-	-	-8.3	-	-	-	-	-	-
	Guttiferone-A	-7.9	-8.1	-7.6	-9.5	-9.3	-8.3	-7.9	-9.1	-7.3	-8.1
	Fukugetin	-9.1	-9.8	-8.8	-9.8	-10.1	-9.5	-7.8	-9.2	-10.1	-10.7
RESULT	7-Epiclusianone	-8.2	-7.7	-8.3	-8.9	-9.8	-8.7	-7.0	-8.3	-6.3	-7.6
	Lapachol	-6.6	-6.7	-6.9	-7.5	-7.3	-7.7	-6.7	-7.2	-6.8	-7.0
	Plumbagin	-6.4	-6.4	-5.7	-7.2	-7.0	-7.0	-6.5	-6.4	-6.9	-6.2
	Mangiferin	-7.8	-7.4	-7.3	-8.0	-8.2	-8.9	-7.4	-7.6	-8.3	-7.5

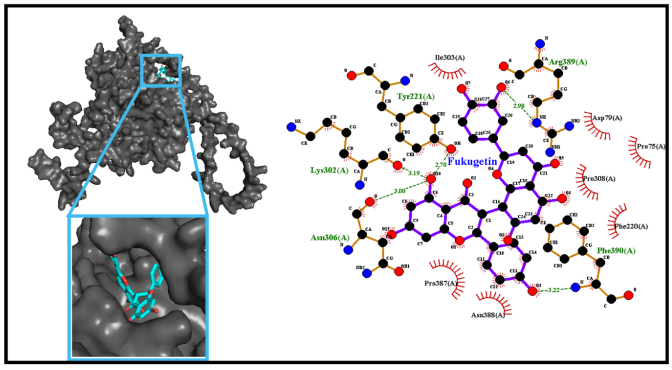

Figure 3. 3D and 2D representation of the interaction betwenn the drug Fukugetin and the protein synthesized by the CLN3 gene of *C.albicans* where in the reprentation 3D is possible to observe the drug in blue and the protein in gray in the representation 2D is possible observe the hydrogen bonds in green and the hydrophobic interactions as red arcs

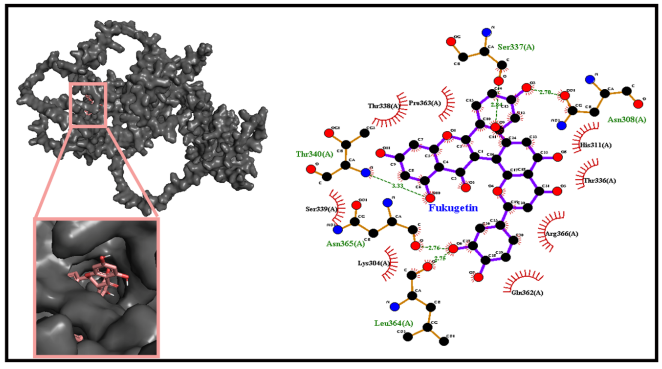

Figure 4. 3D and 2D representation of the interaction betwenn the drug Fukugetin and the protein synthesized by the DBF4 gene of *C.albicans* where in the reprentation 3D is possible to observe the drug in Pink and the protein in gray in the representation 2D is possible observe the hydrogen bonds in green and the hydrophobic interactions as red arcs

C.albicans, 2.72 and 3.09 angstroms between drug's oxygen7 and 6 respectively and the serine60 and 3.05 angstroms between the drug's oxygen3 and the tyrosine51.

In the Figure 3 observed that the fukugetin realized the best energy of interaction with the synthesize protein by the gene CLN3 where the energy was -9.1 kcal/mol in which realizes seven hydrophobic interaction and five hydrogens bonds of sizes 3.22 angstroms between the drug's oxygen3 and the *C.albicans*' phenylalanine390, 2.70, 3.19, 3.00 angstroms between the drug's oxygen10 and the tyrosine221, lysine302 and asparagine306 respectively and 2.98 angstroms between drug oxygen6 and arginine389.

Another interaction was observed in Figure 4 that fukugetin performed the best energy of interaction with the protein synthesized by the DBF4 gene where the energy was -8.8 kcal/mol in which it performed eight hydrophobic interactions and five hydrogen bonds of size 2.84 angstroms between drug oxygen9 and serine337 from *C.albicans*, 2.70 angstroms between drug oxygen3 and asparagine308, 3.33 angstroms between drug oxygen10 and threonine340, 2.76 and 2.75

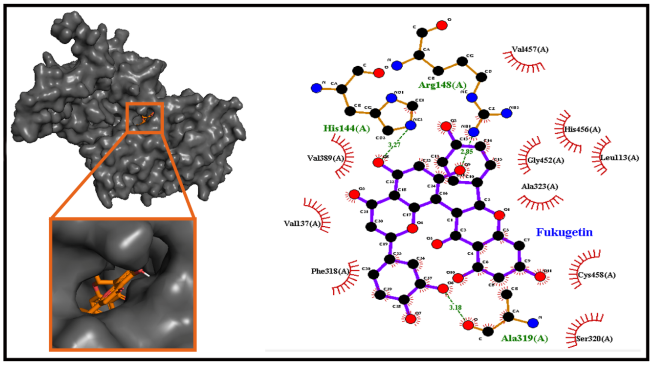

Figure 5. 3D and 2D representation of the interaction betwenn the drug Fukugetin and the protein synthesized by the ERG5 gene of *C.albicans* where in the reprentation 3D is possible to observe the drug in green and the protein in gray in the representation 2D is possible observe the hydrogen bonds in green and the hydrophobic interactions as red arcs

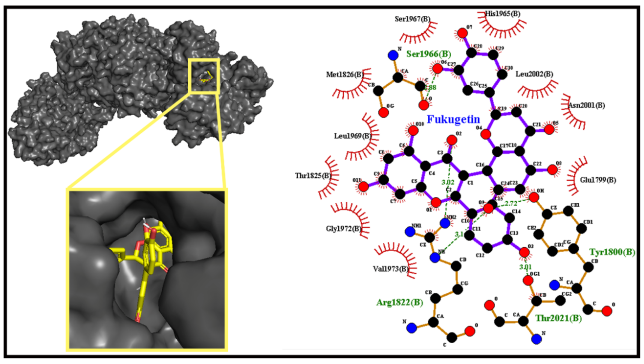

Figure 6. 3D and 2D representation of the interaction betwenn the drug Fukugetin and the protein synthesized by the FAS2 gene of *C.albicans* where in the reprentation 3D is possible to observe the drug in yellow and the protein in gray in the representation 2D is possible observe the hydrogen bonds in green and the hydrophobic interactions as red arcs

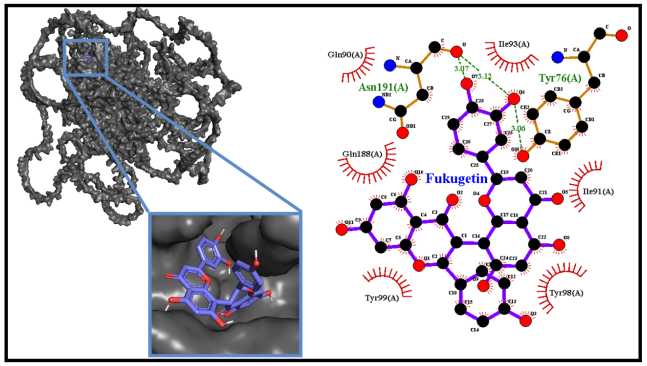

Figure 7. 3D and 2D representation of the interaction betwenn the drug Fukugetin and the protein synthesized by the LTE1 gene of *C.albicans* where in the reprentation 3D is possible to observe the drug in blue and the protein in gray in the representation 2D is possible observe the hydrogen bonds in green and the hydrophobic interactions as red arcs

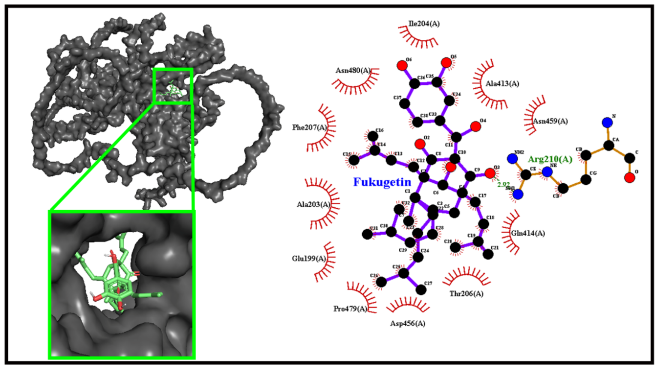

Figure 8. 3D and 2D representation of the interaction betwenn the drug guttiferone-A and the protein synthesized by the SKN7 gene of *C.albicans* where in the reprentation 3D is possible to observe the drug in green and the protein in gray in the representation 2D is possible observe the hydrogen bonds in green and the hydrophobic interactions as red arcs

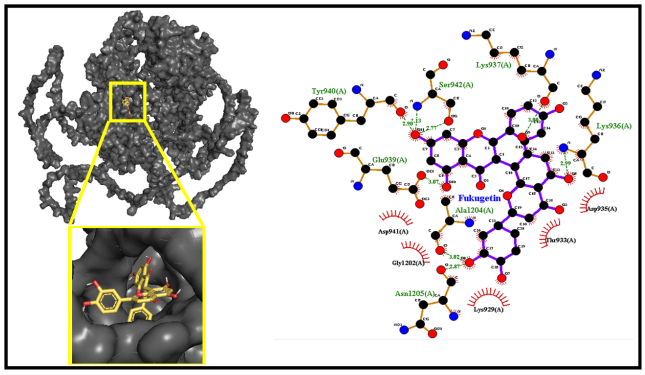

Figure 9. 3D and 2D representation of the interaction betwenn the drug fukugetin and the protein synthesized by the SLN1 gene of *C.albicans* where in the reprentation 3D is possible to observe the drug in yellow and the protein in gray in the representation 2D is possible observe the hydrogen bonds in green and the hydrophobic interactions as red arcs

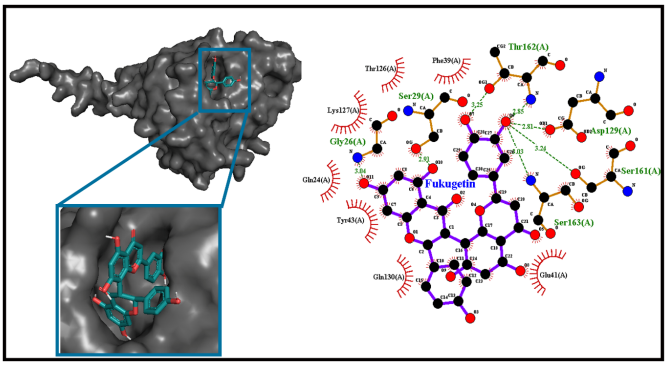

Figure 10. 3D and 2D representation of the interaction betwenn the drug fukugetin and the protein synthesized by the TEM1 gene of *C.albicans* where in the reprentation 3D is possible to observe the drug in blue and the protein in gray in the representation 2D is possible observe the hydrogen bonds in green and the hydrophobic interactions as red arcs

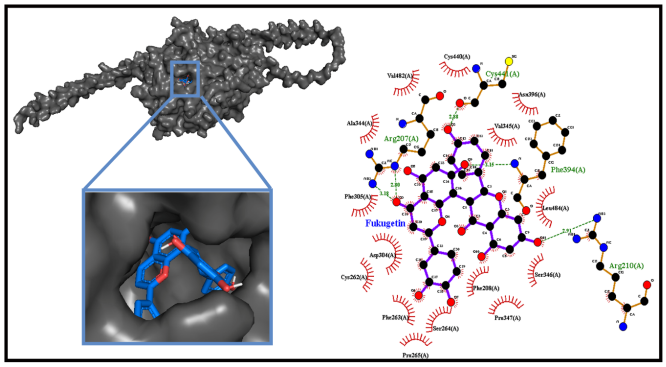

Figure 11. 3D and 2D representation of the interaction betwenn the drug fukugetin and the protein synthesized by the TUP1 gene of *C.albicans* where in the reprentation 3D is possible to observe the drug in green and the protein in gray in the representation 2D is possible observe the hydrogen bonds in green and the hydrophobic interactions as red arcs

angstroms between oxygen6 and asparagine365 and leucine364.

In Figure 5, it is observed that fukugetin performed the best energy of interaction with the protein synthesized by the ERG5 gene, where the energy was -9.8 kcal/mol in which it performed ten hydrophobic interactions and three hydrogen bonds of sizes 2.85 angstroms between the drug oxygen9 and *C.albicans* arginine148, 3.27 angstroms between drug oxygen8 and histidine144 and 3.18 angstroms between drug oxygen6 and alanine319.

Figure 6 shows that fukugetin had the best interaction energy with the protein synthesized by the FAS2 gene, where the energy was -10.1 kcal/mol in which it performed ten hydrophobic interactions and five hydrogen bonds of sizes 2.88 angstroms between drug oxygen6 and *C. albicans* serine1966, 3.02 and 3.16 angstroms between drug oxygen3 and 9 and arginine1822, 2.72 angstroms between drug oxygen9 and tyrosine1800, 3.01 angstroms between oxygen3 and threonine2021.

In Figure 7, it is observed that fukugetin had the best interaction energy with the protein synthesized by the LTE1 gene, where the energy was -9.5 kcal/mol in which it performed six hydrophobic interactions and three hydrogen bonds of sizes 3.06 angstroms between drug oxygen6 and *C.albicans* tyrosine76 and 3.07 and 3.12 angstroms between drug oxygen7 and 6 and asparagine191.

Another observation in Figure 8 was that guttiferone performed the best energy of interaction with the protein synthesized by the SKN7 gene where the energy was -7.9 kcal/mol in which it performed eleven hydrophobic interactions and a hydrogen bond of size 2.92 angstroms between drug oxygen9 and *C. albicans* arginine210.

In Figure 9, it is observed that fukugetin performed the best energy of interaction of natural drugs with the protein synthesized by the SLN1 gene, where the energy was -9.2 kcal/mol in which it performed five hydrophobic interactions and eight hydrogen bonds of sizes 3.07 angstroms between drug oxygen10 and *C. albicans* glutamate939, 2.77, 3.13 and 2.90 angstroms between drug oxygen11 and serine942 with two bridges and tyrosine940 with only one bridge respectively, 3.02 and 2.87 angstroms between drug oxygen6 and alanine1204 and asparagine1205 respectively, 2.99 angstroms between oxygen8 and lysine936 and 3.00 between oxygen9 and lysine937.

Figure 10 shows that fukugetin performed the best energy of interaction with the protein synthesized by the TEM1 gene, where the energy was -10.1 kcal/mol in which it performed seven hydrophobic interactions and seven hydrogen bonds of sizes 3.04 angstroms between drug oxygen11 and *C. albicans* glycine26, 2.91 angstroms between drug oxygen10 and serine29, 3.25 and 2.85 angstroms between drug oxygen7 and 6, respectively, and threonine162, 2.81, 3.24 and 30.03 angstroms between oxygen6 and aspartate129, serine161 and serine163 respectively.

Finally, it is observed that fukugetin performed the best energy of interaction with the protein synthesized by the TUP1 gene in Figure 11, where the energy was -10.7 kcal/mol in which it performed fifteen hydrophobic interactions and five hydrogen bonds of sizes 2.80 and 3 .18 angstroms between drug oxygen5 and arginine207 from *C.albicans*, 2.88 angstroms between drug oxygen3 and cysteine441, 3.15 angstroms between drug oxygen9 and phenylalanine394 and 2.91 angstroms between drug oxygen11 drug and arginine 210.

Finally, make an evaluation of Lipinski's rules and solubility by SwissADME software, in which was found that guttiferone and the 7-epiclusianone violated only one Lipinski' rule, while the fukugetin violat three, the mangiferin two and the lapachol and the plumbagin both no violate any rule, even though these results the Lipinski's rules is a parameter which must be evaluated, but treatment of diseases there are many drugs which not follow these rules and are still used (Viana et al., 2021), in addition about the water solubility, the mangiferin, the lapachol and the plumbagin are soluble in water, while the guttiferone, the fukugetin and the 7-epiclusianone are not soluble probably this parameter can interfere a little with the bioavailability of the drug, since compounds that are insoluble in water are also not soluble in the blood and need a transporter to reach more specific places in the human body, however it is already something that has been trying to be solved as discussed by Lee (2020).

Therefore, with the results above, it is analyzed that the natural compounds had a good interaction with the fungal protein, which may cause a decrease in the expression of certain genes which impair the proliferation of *C. albicans* or a worsening in the protein activity of certain proteins which the genes explored above synthesize. Thus, we have fukugetin, which obtained better binding energy with protein compounds, and may be a great inhibitor of *C. albicans*, as well as being able to inhibit *Leishmania* exposed by (Pereira et al., 2011), through this we have that fukugetin has a high antimicrobial activity.

In addition to this compound, guttiferone-A also receives an interaction highlight with the fungus proteins, proving to be a good antifungal, in addition to acting with antiplasmodial as described by Wairata et al. (2021) and is also a compound which can act against *Staphylococcus aureus* and *Bacillus cereus*

as illustrated by Khameneh et al. (2021) thus revealing a very efficient antimicrobial activity of this metabolite.

Another compound analyzed was 7-epiclusianone, which had promising binding energies, thus being able to be an antifungal potential as well as having an antibacterial potential elucidated by Zhang et al. (2021) which has a great activity against Streptococcus mutants having an inhibition with a low concentration of the compound, so again it can be analyzed that one more of the plant metabolites would have a great antimicrobial action in living beings.

Also, as another potential, there is lapachol, which also obtained an antifungal potential analyzed in the results above, in addition to those presented by De Sá et al. (2019), which inhibits the mycosis *Paracoccidioides brasiliensis*, in addition, it has an antibacterial potential against Staphylococcus aureus as observed by Figueredo (2022), with this lapachol has deep foundations that it is a great antimicrobial plant secondary metabolite with potential activity in mammals.

Furthermore, there is plumbagin, which obtained reasonable binding energies, but even so it can still be classified as a good antifungal, as presented by Jaradat et al. (2021) where the metabolite inhibits more than four types of fungi, namely: *Microsporum canis*, *Trichophyton mentagrophytes*, *Trichophyton rubrum* and *Ascosphaera apis*. Thus, revealing that plumbagin is a great antifungal agent.

Finally, there is mangiferin, which obtained certain binding energies classified as good with the proteins of *C.albicans*, thus being a good antifungal potential to be evaluated and, in addition to the previously demonstrated results, there is also research such as that of Loan, Nguyen Thi Truc, et al.2021 who analyzed the ability of mangiferin to inhibit the growth of *Escherichia coli*, *Samonella ssp* and *Aspergillus flavus*, while the study by Singh et al. (2012) evaluated the inhibition of some species bacterial (*Bacillus pumilus*, *B. cereus* and *Salmonella virchow*) and some species of fungi (*Thermoascus aurantiacus* and *Aspergillus flavus*), with that through several aspects, and a generalized analysis, it is concluded that mangiferin would also be a great antimicrobial compound to be applied.

4. CONCLUSION

In the present study, it was possible to use plant-derived drugs to analyze their binding energy to proteins synthesized by selected genes from the fungus *C. albicans* based on the main action of the metabolite in the plant.

Fukugetin and guttiferone-A showed more relevant potentials in relation to the alteration in the expression of almost all genes, and consequently in the synthesis of the respective proteins originated by such nucleotide sequences, only the protein generated by the SLN1 gene that revealed to have better controls than natural products tested here, so other compounds from plants will need to be researched to replace the control drug.

Thereby, the drugs showed excellent antifungal performance in the *in silico* research, making them possible candidates to be used to control the proliferation of *C.albicans in vivo* and *in vitro* tests for better confirmation of the results.

5. ACKNOWLEDGMENT

We would like to thank CNPq for the support.

CONFLICTS OF INTEREST

There were not any conflicts discussed by actors of the study.

ORCID

Artur Gomes Barros	0000-0002-0456-6867
Leonardo Pereira de Araújo	0000-0003-0212-3365
Nelson José Freitas da Silveira	0000-0001-9257-7322
Breno Régis Santos	0000-0002-3980-9013

AUTHOR CONTRIBUTIONS

AGB, LPA - Research concept and design, AGB, LPA - Collection and/or assembly of data, AGB, LPA - Data analysis and interpretation, AGB - Writing the article, NJFS, BRS - Critical revision of the article, NJFS, BRS - Final approval of the article.

REFERENCES

Abdelhameed, B., Abdullah, E., 2021. Clinical and Microbiological Evaluation of the Effect of Heat Killed *Lactobacillus acidophilus* and Garlic Extract on *Candida albicans* in a Group of Elderly Denture Wearers. Egyptian Dental Journal. 67(2), 1475–1486. https://dx.doi.org/10.21608/edj.2021.52408.1414

Albarelo, E.V., Scotti, F.M., De Literatura, .M.O.Q.O.P.C.H.P.A.U.R., 2021. Revista Ibero-Americana de Humanidades. 7(12), 506–521.

An, D., Wang, X., Li, J., Jiang, S., Ma, X., Zhang, H., Li, .., J., 2016. The activity of fungichromin against the formation of *Candida albicans* biofilm. Biological and Pharmaceutical Bulletin, 1948–1954. https://doi.org/10.1248/bpb.b16-00380

Arwa, P.S., 2013. Estudo químico e busca de substâncias bioativas de *Garcinia brasiliensis*. http://hdl.handle.net/11449/105819

Assis, D.M., Gontijo, V.S., Pereira, I.D.O., Santos, J.A.N., Camps, I., Nagem, T.J., De Barros, .., T, N.M., 2013. Inhibition of cysteine proteases by a natural biflavone: behavioral evaluation of fukugetin as papain and cruzain inhibitor. Journal of Enzyme Inhibition and Medicinal Chemistry. 28(4), 661–670. https://doi.org/10.3109/14756366.2012.668539

Bar-Yosef, H., Gildor, T., Ramírez-Zavala, B., Schmauch, C., Weissman, Z., Pinsky, M., Kornitzer, .., D., 2018. A global analysis of kinase function in *Candida albicans* hyphal morphogenesis reveals a role for the endocytosis regulator Akl1. Frontiers in Cellular and Infection Microbiology. 8, 17. https://doi.org/10.3389/fcimb.2018.00017

Bernardi, C.A., Gardneriana, G., 2009. *Garcinia Gardneriana* (Planchon e Triana) Zappi. como alternativa de anti-inflamatório tópico para o tratamento de doenças da pele : um estudo pré-clínico. https://hdl.handle.net/1884/26695

Borges, L.P., Amorim, V.A., 2020. Metabólitos secundários de plantas secondary plant metabolites. Revista Agrotecnologia, Ipameri. 11, 54–67.

De Oliveira, L.N., Batista, A.M., 2021. Potenciais Interações Medicamento-Alimento e Medicamento-Planta Medicinal em

Farmácias Distritais de um Município do Seridó Potiguar. Infarma-Ciências Farmacêuticas. 33, 257–268. http://dx.doi.org/10.14450/2318-9312.v33.e3.a2021.pp257-268

De Oliveira, M.E., De Lima, W.G., Alves, C.F.B., Herrera, K.M.S., Santos, P.C., De Souza, D.D.G., Santos, .., B, H., 2022. Synergetic action of atorvastatin and fluconazole against fluconazole-resistant *Candida albicans* in vitro and in a murine model for intra-abdominal Candidiasis. Brazilian Journal of Development. 8(5), 41115–41137. https://doi.org/10.34117/bjdv8n5-543

De Sá, N.P., Cisalpino, P.S., Bertollo, C.M., Santos, P.C., Rosa, C.A., De Souza, D.D.G., Johann, .., S., 2019. Thiosemicarbazone of lapachol acts on cell membrane in *Paracoccidioides brasiliensis*. Medical Mycology. 57(3), 332–339. https://doi.org/10.1093/mmy/myy045

Deschenes, R.J., Lin, H., Ault, A.D., Fassler, J.S., 1999. Antifungal properties and target evaluation of three putative bacterial histidine kinase inhibitors. Antimicrobial Agents and Chemotherapy. 43(7), 1700–1703. https://doi.org/10.1128/aac.43.7.1700

Dias, A.L.T., Loyola, A.B.A.T., Coelho, L.F.L., 2017. https://bdtd.unifal-mg.edu.br:8443/handle/tede/1187

Dolson, A., Sauty, S.M., Shaban, K., Yankulov, K., 2021. Dbf4-dependent kinase: DDK-ated to post-initiation events in DNA replication. Cell Cycle. 20(22), 2348–2360. https://doi.org/10.1080/15384101.2021.1986999

Figueredo, F.G., 2022. Atividade antibacteriana de derivados do lapachol e norlapachol e avalição da inibição de bombas de efluxos em linhagens de *Staphylococcus aureus*. http://www.repositorio.ufc.br/handle/riufc/66913

Garcia, C., Burgain, A., Chaillot, J., Pic, E., Khemiri, I., Sellam, A., 2018. A phenotypic small-molecule screen identifies halogenated salicylanilides as inhibitors of fungal morphogenesis, biofilm formation and host cell invasion. Scientific Reports. 8(1), 11559. https://doi.org/10.1038/s41598-018-29973-8

Herrero-De-Dios, C., Alonso-Monge, R., Pla, J., 2014. The lack of upstream elements of the Cek1 and Hog1 mediated pathways leads to a synthetic lethal phenotype upon osmotic stress in *Candida albicans*. Fungal Genetics and Biology. 69, 31–42. https://doi.org/10.1016/j.fgb.2014.05.010

Higgins, J., Pinjon, E., Oltean, H.N., White, T.C., Kelly, S.L., Martel, C.M., Moran, .., P, G., 2012. Triclosan antagonizes fluconazole activity against *Candida albicans*. Journal of Dental Research. 91(1), 65–70. https://doi.org/10.1177/0022034511425046

Hong-Zhuo, S.H.I., Chang, W.Q., Zhang, M., Hong-Xiang, L.O.U., 2019. Two natural molecules preferentially inhibit azole-resistant *Candida albicans* with MDR1 hyperactivation. Chinese Journal of Natural Medicines. 17(3), 209–217. https://doi.org/10.1016/S1875-5364(19)30023-8

Jaradat, N., Khasati, A.I., Al-Maharik, N., Eid, A.M., Jundi, W., Zatar, N.A.A., Jamous, .., R., 2021. Isolation, identification, and antimycotic activity of plumbagin from *Plumbago europaea* L. roots, leaves and stems. Pakistan Journal of Pharmaceutical Sciences. 34(4), 1421–1428.

Jha, A., Vimal, A., Bakht, A., Kumar, A., 2019. Inhibitors of CPH1-MAP kinase pathway: ascertaining potential ligands as multi-target drug candidate in *Candida albicans*. International Journal of Peptide Research and Therapeutics. 25(3), 997–1010. https://doi.org/10.1007/s10989-018-9747-0

Jumper, J., Evans, R., Pritzel, A., Green, T., Figurnov, M., Ronneberger, O., Potapenko, .., A., 2021. Highly accurate protein structure prediction with AlphaFold. Nature. 596(7873), 583–589. https://doi.org/10.1038/s41586-021-03819-2

Kebaara, B.W., Langford, M.L., Navarathna, D.H., Dumitru, R., Nickerson, K.W., Atkin, A.L., 2008. *Candida albicans* Tup1 is involved in farnesol-mediated inhibition of filamentous-growth induction. Eukaryotic cell. 7(6), 980–987. https://doi.org/10.1128/ec.00357-07

Khameneh, B., Eskin, N.A.M., Iranshahy, M., Bazzaz, B.S., 2021. Phytochemicals: a promising weapon in the arsenal against antibiotic-resistant bacteria. Antibiotics. 10(9), 1044. https://doi.org/10.3390/antibiotics10091044

Laskowski, R.A., Swindells, M.B., 2011. LigPlot+: multiple ligand-protein interaction diagrams for drug discovery. Journal of Chemical Information and Modeling. 51, 2778–2786. https://doi.org/10.1021/ci200227u

Lee, M.K., 2020. Liposomes for enhanced bioavailability of water-insoluble drugs: in vivo evidence and recent approaches. Pharmaceutics. 12(3), 264. https://doi.org/10.3390/pharmaceutics12030264

Lira, L., Macedo, R.G., Batista, B., Santos, L., Siqueira, I.., Atividade, A.D., Do, Avellanedae, E.D.T., 2022. https://periodicos.set.edu.br/cadernobiologicas/article/view/10806

Lone, S.A., Ahmad, A., 2020. Inhibitory effect of novel Eugenol Tosylate Congeners on pathogenicity of *Candida albicans*. BMC Complementary Medicine and Therapies. 20, 131. https://doi.org/10.1186/s12906-020-02929-0

Lou, J.W., Iyer, K.R., Hasan, S.M., Cowen, L.E., Mazhab-Jafari, M.T., 2019. Electron cryomicroscopy observation of acyl carrier protein translocation in type I fungal fatty acid synthase. Scientific Reports. 9(1), 12987. https://doi.org/10.1038/s41598-019-49261-3

Macalão, A.L.S., Junior, E.J.P., Gomes, J.M.P.F., Ribeiro, M.A.M., Manzi, P.S., Cunha, T.L., 2020. Análise do tipo de dano causado por Croton urucurana em *Candida albicans*. RESUMOS - Educação em Saúde. 8, 315.

Macdougall, A., Volynkin, V., Saidi, R., Poggioli, D., Zellner, H., Hatton-Ellis, E., Auchincloss, .., H, A., 2020. UniRule: a unified rule resource for automatic annotation in the UniProt Knowledgebase. Bioinformatics. 36(17), 4643–4648. https://doi.org/10.1093/bioinformatics/btaa485

Macêdo, F.A.D.A., Coélho, M.L., Ribeiro, M.C., Barros, E.D.S., Gomes, J.P.D.S., Batista, C.L., De Sousa, .., P, R., 2022. Análise das atividades farmacológicas da Handroanthus serratifolius. Research, Society and Development. 11, 5611222891–5611222891. https://doi.org/10.33448/rsd-v11i2.22891

Maldonado, G., D., 2020. Actividad antioxidante y antifúngica de extracto de semilla de mango (*Mangifera indica* L.) en Colletotrichum sp. https://hdl.handle.net/20.500.12098/1034

Marcelino, R.C., 2022. Molecular docking study involving bioactive natural compounds against SARS-CoV-2 proteins. Natural Resources for Human Health. 2(4), 366–377. https://doi.org/10.1128/mBio.00206-20

Martel, C.M., Parker, J.E., Bader, O., Weig, M., Gross, U., Warrilow, A.G.S., Kelly, .., L, S., 2010. A clinical isolate of *Candida albicans* with mutations in ERG11 (encoding sterol 14α-demethylase) and ERG5 (encoding C22 desaturase) is cross resistant to azoles and amphotericin B. Antimicrobial Agents and Chemotherapy. 54(9), 3578–3583. https://doi.org/10.1128/aac.00303-10

Medina, A.J.P., 2022. Prevalencia de genes de resistencia al fluconazol y voriconazol de cepas de *Candida albicans* aisladas de pacientes del Complejo Hospitalario Policial Luis Nicasio Sáenz- 2018. http://cybertesis.unmsm.edu.pe/handle/20.500.12672/17706.

Niewerth, M., Kunze, D., Seibold, M., Schaller, M., Korting, H.C., Hube, B., 2003. Ciclopirox olamine treatment affects the expression pattern of *Candida albicans* genes encoding virulence factors, iron metabolism proteins, and drug resistance factors. Antimicrobial Agents and Chemotherapy. 47(6), 1805–1817. https://doi.org/10.1128/aac.47.6.1805-1817.2003

Orellana-Muñoz, S., Dueñas-Santero, E., Arnáiz-Pita, Y., Iglesias, F.D.R., Correa-Bordes, J., De Aldana, C.R.V., 2017. The Int1 anillin and the Sep7 septin collaborate to maintain cellular ploidy in *Candida albicans*. Scientific Reports. 8, 2257. https://doi.org/10.1038/s41598-018-20249-9

Pardo-Andreu, G.L., Nuñez-Figueredo, Y., Tudella, V.G., Cuesta-Rubio, O., Rodrigues, F.P., Pestana, C.R., Curti, .., C., 2011. The anti-cancer agent guttiferone-A permeabilizes mitochondrial membrane: ensuing energetic and oxidative stress implications. Toxicology and Applied Pharmacology. 253(3), 282–289. https://doi.org/10.1016/j.taap.2011.04.011

Pereira, I.O., Assis, D.M., Juliano, M.A., Cunha, R.L.O.R., Barbieri, C.L., Sacramento, L.V.S., Santos, .., H, M., 2011. Natural products from *Garcinia brasiliensis* as Leishmania protease inhibitors. Journal of Medicinal Food. 14(6), 557–562. https://doi.org/10.1089/jmf.2010.0018

Ruben, S., Garbe, E., Mogavero, S., Albrecht-Eckardt, D., Hellwig, D., Häder, A., Elshafee, .., O., 2020. Ahr1 and Tup1 contribute to the transcriptional control of virulence-associated genes in *Candida albicans*. MBio. 11(2), 206–220. https://doi.org/10.1128/mBio.00206-20

Schrodinger, L.L.C., 2017. The PyMol molecular graphics system, version 2.0. Schrödinger, LLC,. .

Silva, L.N., 2020. Mecanismos de resistência a múltiplas drogas no complexo *Candida haemulon*. Brazilian Journal of Clinical Analyses. 10.21877/2448-3877.201600407

Singh, S.K., Tiwari, R.M., Sinha, S.K., Danta, C.C., Prasad, S.K., 2012. Antimicrobial evaluation of mangiferin and its synthesized analogues. Asian Pacific Journal of Tropical Biomedicine. 2(2), 884–887. https://doi.org/10.1016/S2221-1691(12)60329-3

Trott, O., Olson, A.J., 2009. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function. Efficient Optimization, and Multithreading. Journal of Computational Chemistry. 30, 455–461. https://doi.org/10.1002/jcc.21334

Verma, A.K., Maurya, S.K., Kumar, A., Barik, M., Yadav, V., Umar, B., Balarabe, .., A, B., 2020. Inhibition of multidrug resistance property of *Candida albicans* by natural compounds of parthenium hysterophorus L. An In-Silico approach. Journal of Pharmacognosy and Phytochemistry. 9(3), 55–64. https://doi.org/10.22271/phyto.2020.v9.i3a.11480

Verma, R., Pradhan, D., Maseet, M., Singh, H., Jain, A.K., Khan, L.A., 2020. Genome-wide screening and in silico gene knockout to predict potential candidates for drug designing against *Candida albicans*. Infection, Genetics and Evolution. 80, 104196. https://doi.org/10.1016/j.meegid.2020.104196

Viana, D.C.F., Moura, J.A.D.S., Branco-Júnior, J.F., Ramalho, E.A.V.D.F., Pitta, I.D.R., Pitta, M.G.D.R., 2021. Análise do Mercado de Oncológicos e Novas Substância Ativas para o Tratamento do Câncer Oncology Market Analysis and New Active Substances for Cancer Treatment. Brazilian Journal of Development. 7(12), 110107. https://doi.org/10.34117/bjdv7n12-006

Wairata, J., Sukandar, E.R., Fadlan, A., Purnomo, A.S., Taher, M., Ersam, T., 2021. Evaluation of the Antioxidant, Antidiabetic, and Antiplasmodial Activities of Xanthones Isolated from *Garcinia forbesii* and their in silico Studies. Biomedicines. 9(10), 1380. https://doi.org/10.3390/biomedicines9101380

Wang, T., Xiu, J., Zhang, Y., Wu, J., Ma, X., Wang, Y., Shang, .., X., 2017. Transcriptional responses of *Candida albicans* to antimicrobial peptide MAF-1A. Frontiers in Microbiology. 8, 894. https://doi.org/10.3389/fmicb.2017.00894

Yan, C., Wang, S., Wang, J., Li, H., Huang, Z., Sun, J., Shi, .., P., 2018. Clioquinol induces G2/M cell cycle arrest through the up-regulation of TDH3 in *Saccharomyces cerevisiae*. Microbiological Research. 214, 1–7. https://doi.org/10.1016/j.micres.2018.05.006

Yin, Z., Zhang, J., Chen, L., Guo, Q., Yang, B., Zhang, W., Kang, W., 2020. Anticancer effects and mechanisms of action of plumbagin: Review of research advances. BioMed Research International. 2020, 6940953. https://doi.org/10.1155/2020/6940953

Zhang, Q., Ma, Q., Wang, Y., Wu, H., Zou, J., 2021. Molecular mechanisms of inhibiting glucosyltransferases for biofilm formation in *Streptococcus mutans*. International Journal of Oral Science. 13(1), 30. https://doi.org/10.1038/s41368-021-00137-1