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Research Article

The Antifungal Activity Prediction and the Toxicity Of The Main Phytoconstituents of an Apiaceous Species From Algeria

Elkolli Meriem[1*], Elkolli Hayet[2] and Bouzid Djihane[1]

[1]*Department of Microbiology, Laboratory of Applied Microbiology, Faculty of Natural and Life Sciences, University of Ferhat Abbas Setif 1, Setif 19000, Algeria*

[2]*Department of Microbiology, Laboratory of Multiphasic Polymeric Materials, Département of Process Engineering, Faculty of Technology, University Ferhat Abbas of Setif 1, Setif 19000, Algeria*

**Address Correspondence to: Elkolli Meriem, elkollim@yahoo.fr*

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Abstract

The aim of this work was to determine the constituent(s) responsible for the pre-established *in vitro* antifungal activity of the whole essential oil of the Apiaceous species *Daucus crinitus*. To this end, eight fungal proteins, with different roles in the cell, were targeted (2QZX, 1BWK, 5FRB, 6K3H, 1EAG, 5UIV, 7WJM and 8JZN) by the major compounds of the essential oil. To investigate how the selected phytocompounds interact with the enzym's active sites, we employed a molecular docking study using Autodock Vina integrated into PyRx. Molinspiration Cheminformatics free web services and SwissADME free online tools were used to predict physicochemical and pharmacokinetic parameters, while OSIRIS Property Explorer online tools were used to predict toxicity risks. The β-caryophellene recorded the best energies with three enzymes; 5FRB, 8JZN and 7WJM with -8.6, -7.6 and -7.4 kcal/mol respectively, followed by Germacrene D, Isochavicol isobutyrate and β-sesquiphellandrène with binding energies sometimes close to those of the natural ligands of enzymes. The isochavicol isobutyrate, which is the major compound of the oil (39%), showed excellent pharmacokinetic properties without toxicity. This study suggests that the essential oil constituents could enhance the efficacy of antifungal drugs with the potential benefit of reducing the use of the latter in order to limit or slow down antibiotic resistance.

Keywords: *Daucus crinitus*; Antifungal; Molecular docking; Toxicity prediction

Introduction

Algeria is the largest country in Africa by land area and the tenth largest in the world, and is therefore rich in plant biodiversity with vast resource of medicinal plants. Local populations benefit from this biodiversity in herbal medicine to treat various infectious diseases because it is safe, inexpensive and widely accessible. In recent decades, even the industrialized world has seen an increase in the use of complementary and alternative medicine [1]. Among plant-derived products, Essential Oils (Eos) possess potent and broad-spectrum antimicrobial activities [2]. The family Apiaceae is characterized by releasing a relative high amount of EOs [3].

On the other hand, fungal infections cause 11.5 million serious cases and 1.5 million deaths worldwide each year [4].

Essential oils extracted from Apiaceous plants exhibit a wide range of effects, including antimicrobial and antibiotic effects [5], which corroborates the results of *in vitro* tests found subsequently on some fungi and yeasts [6]. This work aims to determine the composition/activity relationship of the essential oil of the aerial parts of the species *D. crinitus*, followed by the prediction of the pharmacotoxicity of its essential compounds.

Materials and Methods

After finding that *D. crinitus* essential oil exerts *in vitro* activity on fungi and yeasts (Table 1), we continued the molecular docking to understand the relationship between the oil composition and the antifungal effect at the molecular level.

Table 1: The antifungal activity of *D. crinitus* essential oil.

Fungal strain Origin		Concentration (Essential oil in DMSO) Inhibition zone in mm		
		1/2 v/v	1/5 v/v	1/10 v/v
Aspergillus niger	Contaminant	44	30	20
Aspergillus fumugatus	Contaminant	12	10	8
Penicillium notatum	/	20 +/-	20 +/-	20 +/-
Fusarium rosum	/	12	10	8
Trychosporum sp	Vaginal swab	33	28	21
Candida albicans	Skin	30 +/-	25 +/-	20 +/-
Note: +/-: Less dense area				

Ligand and targets choice

For the study of molecular docking as well as for pharmacotoxicity, the main compounds (>2%) were selected and their 3d structures were used (Table 2).

Protein targets were selected according to the literature (Table 3). Eight vital proteins with diverse roles in the fungal cell were the subject of the *in silico* study.

***In silico* antifungal study**

The combined *in vitro* and *in silico* approach allows us to better understand the link between the chemical composition of the oil and its biological activity. For this, molecular docking of the phytocompounds as well as the natural ligands was done against the selected targets proteins with PDB IDs: 2QZX, 1BWK, 5FRB, 6K3H, 1EAG, 5UIV, 7WJM and 8JZN to determine their binding affinities. The 3d structures of the phytocompounds and ligands were obtained in SDF format files from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and Molview (https://molview.org/?cid=5478883) then converted to PDB format by Open Babel tools version 2.4.1. The proteins energies optimization was realized using Chem3D v 16.0.1.4 software. The 3d structures of the target proteins were obtained in PDB format from the Protein Data Bank (https://www.rcsb.org/). Autodock Vina in PyRx 0.8 was used to generate the best predicted binding modes and corresponding binding energies. The interactions were visualized in 3d and 2d forms using BIOVIA Discovery Studio visualizer 2024 v.24.1.0.23298 software. Bonds between the ligands and interacting residues are depicted with a distance range of Å.

Pharmacokinetics and toxicity prediction

Lipinski's method was employed to assess the drug-like properties of phytocompounds, which sets limits on four specific physicochemical parameters [13]. These are the characteristics of an orally active drug: the octanol-water partition coefficient (milogP) and the number of hydrogen bond donors (n-OH and n-NH) should not exceed 5, and the number of hydrogen bond acceptors (n-ONs) should be less than 10. The molecular weight (MW) should be below 500 D, and no more than one violation should occur [14]. Molinspiration Cheminformatics free web services (https://www.molinspiration.com) and SwissADME free online tools (http://www.swissadme.ch/) were used to predict physicochemical and pharmacokinetic parameters, while OSIRIS Property Explorer online tools (https://www.organic-chemistry.org/prog/peo/) were used to predict toxicity risks.

Results and Discussion

Extraction and isolation of bioactive compounds from traditional medicine could be an interesting strategy for the discovery of new drugs [15]. Recently, computer-aided drug discovery approaches have attracted increasing attention as they can help alleviate the scale, time, and cost issues faced by conventional experimental approaches [16]. This process is typically accomplished by first predicting the molecular orientation of a ligand in a receptor and then estimating their complementarity through the use of a scoring function [17]. The results of this study show that all phytocompounds fit in the active site of the selected targets with binding energies ranging from -4.2 to -8.6 kcal/mol (Table 4). Molecular docking results reveal that the combinations of fungal protein targets 2QZX and 5UIV with Isochavicol isobutyrate, the main component of the oil, exhibit favorable binding energies (-6.1 and -7.0 kcal/mol respectively), higher than those of natural ligands, suggesting good inhibitory potential. Similarly, β-caryophyllene stood out for its ability to effectively interact with several key targets of *C. albicans*, including 1EAG, 5FRB, 8JZN, and 7WJM (-8.6, -7.6 and-7.4 kcal/mol respectively). Germacrene D also showed notable affinity with 5FRB and 8JZN. The biological implication of the targets studied, including 2QZX in biofilm formation [18] and infection [19], 5UIV in fungal growth [20], 5FRB in maintaining the integrity and function of cell membranes [21], 1EAG in the adhesion and invasion [22] and 8JZN in cell wall biosynthesis [23], reinforces the relevance of these interactions. These results suggest a promising therapeutic potential of these natural compounds, particularly as antifungal agents targeting key mechanisms of *C. albicans*.

The essential oils of different species of the Apiaceae family, proved to be a promising source of biomolecules, with antifungal potential activity [3]. The relative concentration of the principal compounds determines the biological properties of EOs [24]. Therefore, by linking these results with those *in vitro*, isochavichol isobutyrate could be involved in less density areas in *C. albicans* and Trychosporum sp. colonies, probably by interfering with fungal DNA synthesis, knowing that *C. albicans* is the most common cause of fungal infections in a growing population of immune-compromised patients [15].

On the other hand, Dahham et al. (2015) reported a significant activity of β-caryophyllene against A. niger; P. citrinum, R. oryzae and T. reesei, this activity could be attributed to its strong antioxidant activities. According to [25], In addition, Germacrene D was listed among chemical compounds with potential antimicrobial activity against *C. albicans* that were present in at least 50% of the 33 essential oils studied [25]. But it is, nevertheless, known that in a plant extract rich in phytocompounds, these compounds can act either individually, synergistically or antagonistically. At the molecular level, it was found that the majority of bonds involved in the active sites by the ligands are alkyl and VDW bonds, whereas with natural ligands there are many hydrogen bonds which gave rise to the better energies which contributes to the stabilization of the complexes protein-ligand. Isochavicol of isobutyrate interacts with GLU162, TYR161 and ARG92, LEU51, PHE67 and PRO37 like the natural ligand which explains a good binding energy but could be slightly less stable (Figure 1).

Table 2: The selected phytoconstituents for the *in silico* study.

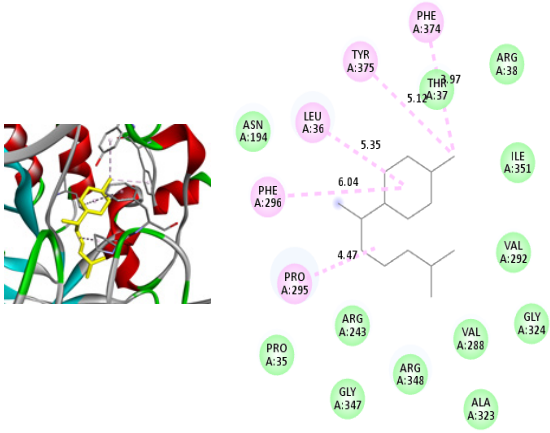
Compound	%	Pubchem CID
Isochavicol isobutyrate	39	16729190
Octyl-acetate	12,3	8164
α-pinene	9,9	6654
β-caryophellene	5,4	5281515
Myrcene	3,4	31253
β-farnesene	3,4	5281517
n-pentadecane	2,8	12391
β-sesquiphellandrene	2,6	12315492
Germacrene D	2,3	5317570

Table 3: The targeted proteins for the antifungal study.

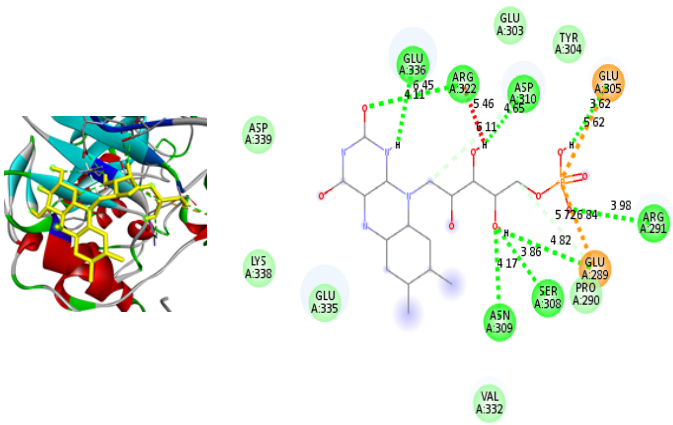
Protein	Role	Organism source	PDB code	Natural ligand/CID
Aspartyl proteases [7]	Involved in the degradation of host proteins, thus facilitating tissue invasion	*C. albicans*	2QZX	Pepstatin/5478883
Old Yellow Enzyme (OYE1) [8]	Involved in resistance to oxidative stress and adaptation to hostile conditions	*C. albicans*	1BWK	Flavin Mononucleotide/643976
14-α demethylase [9]	Essential in the biosynthesis of sterols playing a key role in the formation of ergosterol	*A. fumigatus*	5FRB	(R)-4-((4-((6-(2-(2,4-difluorophenyl)-1,1-difluoro-2-hydroxy-3-(1H-tetrazol-1-yl)propyl) pyridin-3-yl)ethynyl)phenoxy)methyl)benzonitrile 139592435
Nucleoside diphosphokinase [9]	Key enzyme in the energy metabolism of fungal cells	*A. Flavus*	6K3H	Adenosine-5'-diphosphate/6022
Aspartic proteinase (SAP2) [10]	Hydrolyzes peptide bonds of host proteins	*C. albicans*	1EAG	N-ethyl-N-[(4-methylpiperazin-1-yl)carbonyl]-D-phenylalanyl-N-[(1S,2S,4R)-4-(butylcarbamoyl)-1-(cyclohexylmethyl)-2-hyd roxy-5-methylhexyl]-L-norleucinamide/ 5496932
Thymidylate Kinase [11]	Catalyzes the phosphorylation of thymidine monophosphate (dTMP) to thymidine diphosphate (dTDP), a key step in DNA synthesis.	*C. albicans*	5UIV	dTMP/9700
Chitin synthase [12]	Chitin biosynthesis	*Phytophthora sojae*	7WJM	UDP-GlcNAc/445675
Fungal 1,3-glucan synthase [12]	Synthesis of the fungal cell wall	*S. cerevisiae*	8JZN	UDP-Glucose/8629

Table 4: Phytocompounds scoring results.

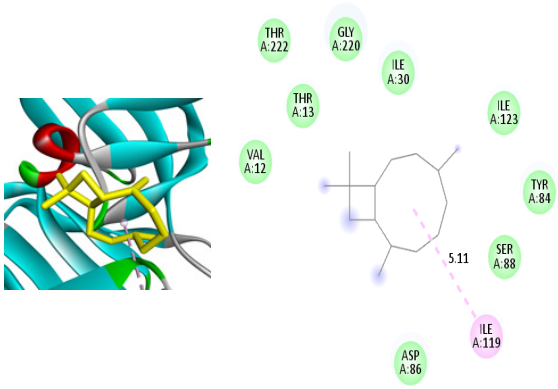
Ligand/ Protein	β-caryophellene	n-pentadecane	β-farnesene	Germacrene D	Isochavicol isobutyrate	Myrcene	Octyl-acetate	α-pinene	β-sesquiphellandrene	Natural ligand
Binding energies (kcal/mol)	7WJM	7WJM	7WJM	7WJM	7WJM	7WJM	7WJM	7WJM	7WJM	7WJM
1BWK	-5.9	-5.1	-4.6	-6.5	-5.3	-4.6	-5	-5.5	-6.6	-6.8
1EAG	-6.5	-4.6	-4.7	-6.2	-5.9	-4.6	-4.4	-5.1	-5.6	-7.8
2QZX	-5.7	-4.6	-5.3	-5.5	-6.1	-4.9	4.2	-5.1	-5.8	-5.8
5FRB	-8.6	-5.9	-6.3	-7.8	-6.6	-5.1	-5.1	-6.4	-6.8	-11.4
5UIV	-6.6	-5.8	-6.4	-5.6	-7	-6.2	-5.8	-5.8	-6	-5.9
6K3H	-6	-4.4	-4.9	-6.1	-5.9	-4.3	-4.5	-4.7	-5.8	-8.1
7WJM	-7.4	-4.6	-5	-6.8	-6.2	-5.4	-4.2	-6	-5.5	-8.7
8JZN	-7.6	-5.2	-5.6	-7.8	-6.2	-5.3	-5.2	-6.4	-7	-8.3



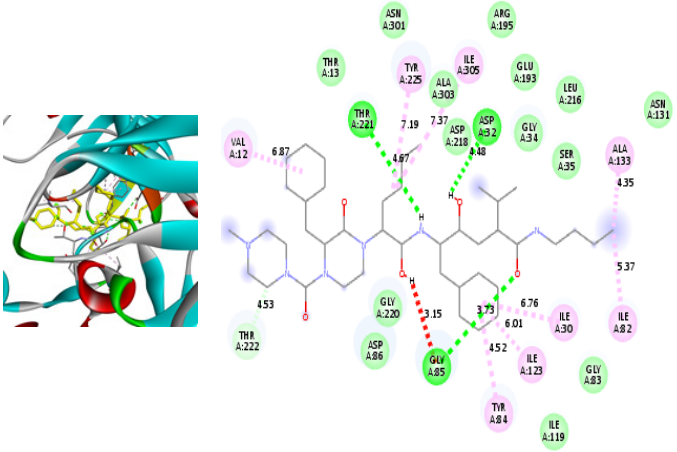
1BWK/ β-sesquiphellandrene



1BWK/NL



1EAG/ β-caryophellene



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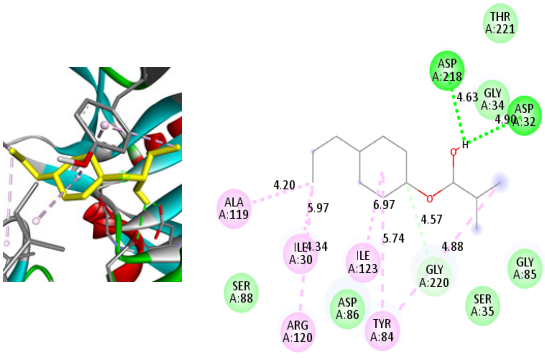
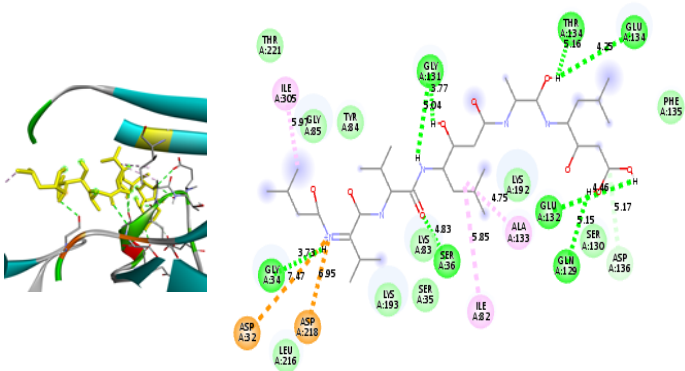
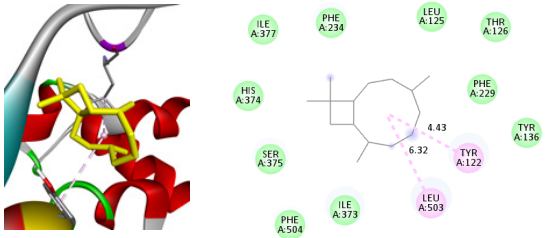


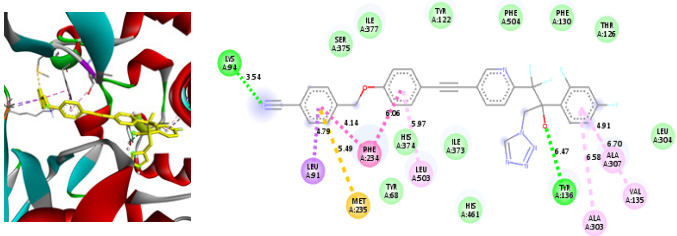
2QZX/ Isochavicol of isobutyrate



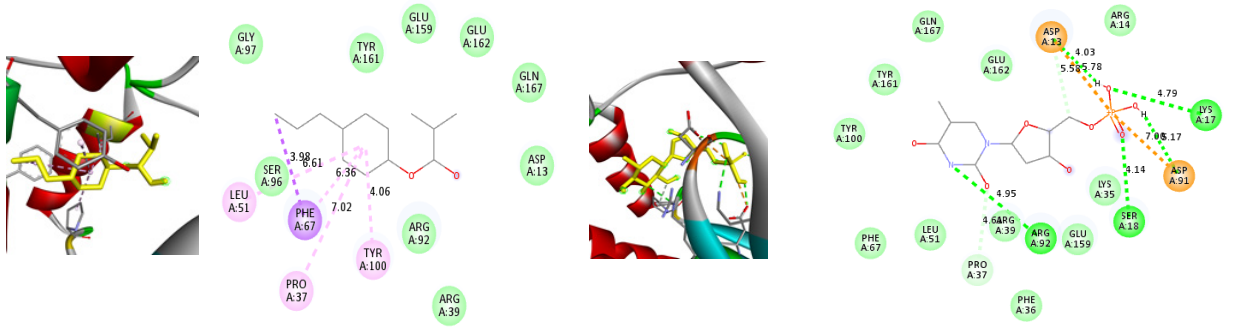
2QZX/NL

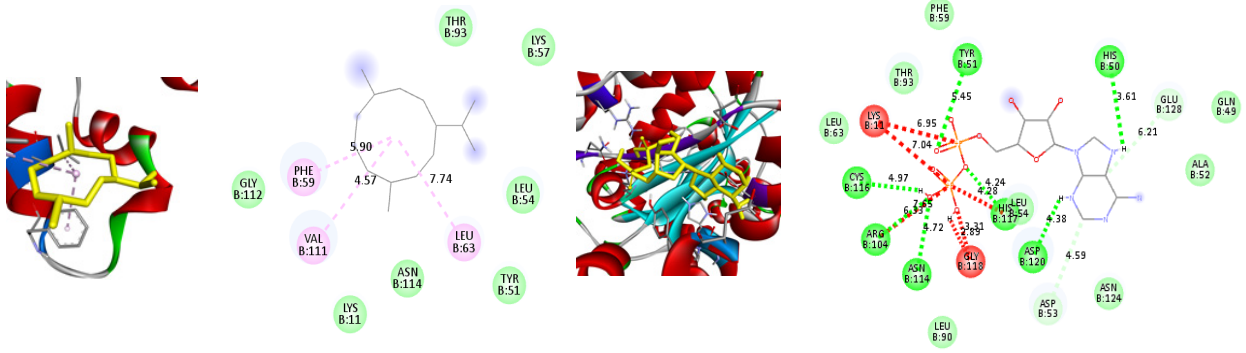


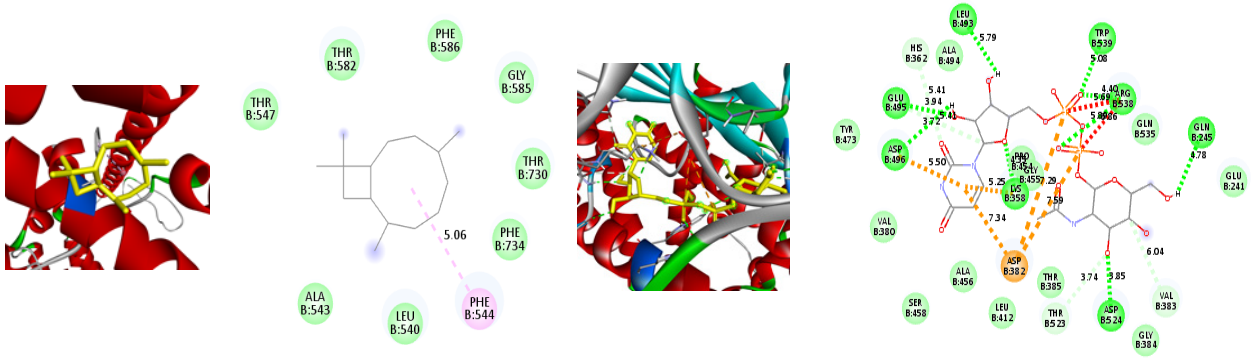
5FRB/ β-caryophellene



5FRB/NL







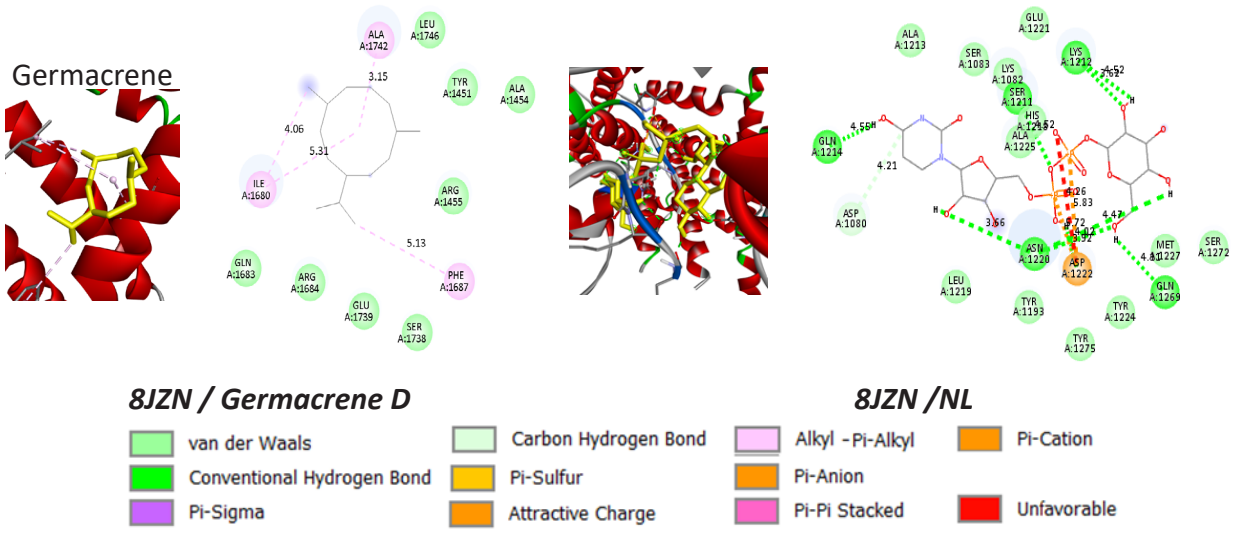


Figure 1: Interaction and bond distances of ligands inside the active site pocket as shown by molecular surface maps; NL: natural ligand.

Current first-line antifungal agents such as Amphotericin B, Fluconazole and Itraconazole, may decrease the severity of fungal infection to some extent, but the poor drug bioavailability, drug toxicity and poor water solubility seriously restrict their clinical utility [26]. Some questions concerning the safety of synthetic compounds have encouraged more detailed studies of plant resources [27]. For this essential oil, the major compound isochavicol isobutyrate is the safest according to the *in silico* prediction, it exhibits good solubility and absorption, making it suitable for oral or cutaneous administration (Table 5). Most compounds have a value of miLogP (hydrophobicity) below 5, except for β-caryophellene (5.17), β-farnesene (5.84), n-pentadecane (8.19), and Germacrone (5.43), indicating that they may have low aqueous solubility. Substances with increased lipophilicity may be more susceptible to metabolism in the liver and lipophilicity can influence their excretion, they can be stored in fatty tissues and exhibit a prolonged presence in the body having consequences for pharmacological activity and toxicity [28]. The low values of TPSA suggest good membrane permeability. On the other hand, most compounds are moderately soluble except for n-pentadecane, which may affect their oral bioavailability. It is worth noting that a TPSA score below 140 is considered ideal for drug-like molecules [29]. The intestinal permeability is mostly low except for isochavicol isobutyrate and octyl-acetate. All the compounds show good skin permeability coefficient (log Kp) to be within -4.93 to -2.10 cm/s, lying between the acceptance range -8.0 to -1.0 cm/s [30]. Cytochromes (CYP). are a superfamily of isoenzymes that constitute key player in drug elimination through metabolic biotransformation [31] but most reactions are undertaken by CYP2C9, CYP2C19, CYP2D6 and CYP3A4 [32]. β-farnesene and n-pentadecane inhibit CYP1A2 which may slow down the degradation of some drugs, thus increasing their plasma concentration and potentially their side effects thus influencing their toxicity. It is one of the most important enzymes in the liver which metabolises many clinical drugs [33].

CYP2C19 is inhibited by β-caryophellene and β-sesquiphellandrene, it is also CYP2C19 is responsible for the metabolism of approximately 10 % of commonly used therapeutic agents [34] and CYP2C9 which constitutes approximately 20% of the cytochrome P450 protein content of human liver microsomes [35] is inhibited by α-pinene, β-caryophellene, β-farnesene, β-sesquiphellandrene and Germacrene D. Octyl-acetate inhibits the CYP3A4 implicated in the metabolism of drugs. Such unwanted inhibitions may have clinical consequences ranging from lack of therapeutic efficacy to severe toxicity. Only CYP2D6 is not inhibited by any molecule. Importantly, although CYP2D6 constitutes just 2%-4% of total hepatic CYP content, it is a cardinal drug-metabolising enzyme involved in the metabolism of approximately 20% of commonly used drugs [36]. Finally, some compounds present moderate irritant risks (Octyl-acetate and α-pinene), and myrcène with tumorigenic, irritant and reproductive risks which may exclude them from use as potential drugs. Indeed, despite the therapeutic benefits observed, β-myrcene has come under scientific scrutiny due to an alleged risk as a potential human carcinogen [37].

Table 5: Calculated physicochemical and pharmacokinetic parameters of the docked phyto compounds.

Compound	Isochavicol isobutyrate	Octyl-acetate	α-pinene	β-caryophellene	Myrcene	β-farnesène	n-pentadecane	β-sesquiphellandrene	GermacreneD
Physicochemical and pharmacokinetic parameters (Molinspiration Cheminformatics)									
<	3.5	3.84	3.54	5.17	3.99	5.84	8.19	4.9	5.43
TPSA (oA)<500	26.3	26.3	0	0	0	0	0	0	0
MW<500 (g/mol)	204.27	172.27	136.24	204.36	136.24	204.36	212.42	204.36	204.36
MV	205.94	191.34	151.81	229.95	162.24	239.82	264.18	234.9	234.9
nON<10	2	2	0	0	0	0	0	0	0

nOHNH<5		0	0	0	0	0	0	0	0	0
Lipinski's violation		0	0	0	1	0	1	1	0	1
Solubility and pharmacokinetics properties (SwissADME)										
Water solubility		S	S	MS	MS	S	MS	PM	MS	MS
BBB permeant		Yes	Yes	Yes	No	Yes	No	No	No	No
Gastrointestinal absorption		High	High	Low	Low	Low	Low	Low	Low	Low
Log Kp : Skin permeation: cm/s		-4.9	-4.93	-3.95	-4.44	-4.17	-3.27	-2.1	-3.71	-4.18
Cytochromes inhibitors	CYP1A2	No	No	No	No	No	Yes	Yes	No	No
	CYP2C19	No	No	No	Yes	No	No	No	Yes	No
	CYP2C9	No	No	Yes	Yes	No	Yes	No	Yes	Yes
	CYP2D6	No	No	No	No	No	No	No	No	No
	CYP3A4	No	Yes	No	No	No	No	No	No	No
Toxicity risks (OSIRIS Property Explorer)		-7.8	-7.8	-7.8	-7.8	-7.8	-7.8	-7.8	-7.8	-7.8
Mutagenic		No	No	No	No	No	No	No	No	No
Tumorigenic		No	No	No	No	Yes	MR	No	No	No
Irritant		No	Yes	Yes	No	Yes	MR	No	Yes	No
Reproductive effective		No	No	No	No	Yes	MR	No	No	No

Note: miLogP: Logarithm of partition coefficient between n-octanol and water. TPSA: Topological polar surface area. MW: Molecular weight. MV: Molecular volume. nON: Number of hydrogen bond acceptors. nOHNH: Number of hydrogen bond donors. No: no indication found. S: Soluble. MS: Moderate to soluble. PM: poor to moderate. VS: very soluble, MR medium risk

BOILED-Egg is an intuitive method to predict simultaneously two key ADME parameters, i.e. the passive gastrointestinal absorption and Brain access (BBB). Although conceptually very simple as it relies on two physicochemical descriptors only (WLOGP and TPSA, for lipophilicity and apparent polarity [31]. The Figure 2 represents the localisation of our phytoconstituents; points located in the yellow region are molecules predicted to passively permeate through the BBB, while points located in the white region are molecules predicted to be passively absorbed by the gastrointestinal tract. Red dots are for molecules predicted to not to be effluated from the central nervous system by the P-glycoprotein [38]. Molecules 1, 2, 3 and 5 are located in the yellow zone, meaning they can potentially cross the Blood-Brain Barrier (BBB) and exert an effect on the central nervous system. Molecules 4,6 and 8 are located outside the yellow zone, in the white zone, meaning they have good gastrointestinal absorption but are unlikely to cross the BBB. Molecule 7, has a very high WLOGP (8.19), indicating excessive lipophilicity, which may be a problem for solubility and bioavailability.

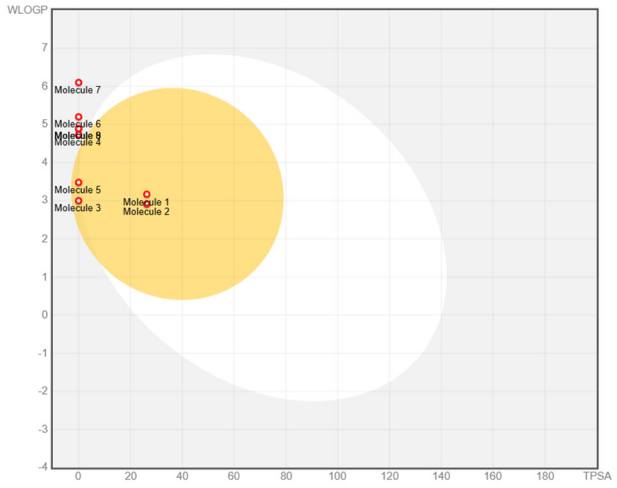


Figure 2: BOILED-Egg model of the phytocompounds calculated by SwissADME. **Note:** Yellow: Molecules can cross the Blood-Brain Barrier (BBB) (potential CNS effects). White: Molecules have good intestinal absorption (high gastrointestinal permeability). Red: the molecule is not actively expelled and may remain in cells longer. 1. Isochavicol isobutyrate, 2:Octyl-acetate, 3:α-pinene, 4: β-caryophellene, 5:Myrcene, 6: β-farnesène, 7:n-pentadecane, 8:β-sesquiphellandrene, 9: GermacreneD.

Conclusion

In this study, we presented the antifungal and pharmacokinetic profile, drug similarity, and toxicity profile of nine main compounds from *D. crinitus* essential oil, which demonstrated high binding affinity to fungal target proteins and favorable pharmacokinetic properties. Molecular docking results suggest that β-caryophellene, germacrene D, and β-sesquiphellandrene also contribute to the antifungal effect suggesting a promising therapeutic potential of these natural compounds, particularly as antifungal agents targeting key mechanisms of *C. albicans*. Moreover, *in silico* toxicity predictions indicate that isochavicol isobutyrate is a promising candidate for further development due to its low toxicity and good bioavailability. These results suggest that *D. crinitus* essential oil constituents could serve as potential antifungal agents or enhancers of existing antifungal treatments, potentially reducing the need for synthetic antifungal drugs and mitigating resistance. Further experimental validation is needed to confirm these *in silico* predictions and explore their clinical applicability.

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