

GC-MS/FID analysis, molecular docking and ADMET prediction of the essential oil of *Myrtus communis* L.

Original Article

Abstract:

The essential oil (EO) obtained by steam distillation from the aerial parts of *Myrtus communis* L. was analyzed by GC-MS and GC-FID. The results showed the presence of 68 compounds, of which 32 were identified corresponding to 72.54% of the total oil. The major constituents were caryophyllene oxide (17.2%), spathulenol (10.3%), hexadecanoic acid (4.9%), geranyl linalool (4.9%), and salvial-4(14)-en-1-one (3.6%). Furthermore, ADMET prediction and Lipinski's rule of five showed that most major compounds of *M. communis* EO have potential drug-like properties. A molecular docking analysis was carried out with a total of three proteins including anticancer (mTOR), anti-inflammatory (COX-2) and antifungal (*Aspergillus niger*) targets. The tested compounds of the EO displayed strong interactions with the active sites of the target enzymes, showing low binding energies with mTOR (-5.5 to -8.9 kcal/mol), COX-2 (-4.8 to -7.3 kcal/mol), and antifungal (-4.5 to -8.2 kcal/mol) targets, with accepted RMSD values 1.88 Å.

Key words:

Myrtus communis, essential oil, molecular docking, RMSD, ADMET

Apstrakt:

GC-MS/FID analiza, molekulsko dokovanje i ADMET predikcija etarskog ulja vrste *Myrtus communis* L.

Etarsko ulje (EO) dobijeno destilacijom vodenom parom nadzemnih delova vrste *Myrtus communis* L. analizirano je primenom GC-MS i GC-FID metoda. Rezultati su pokazali prisustvo 68 jedinjenja, od kojih su 32 identifikovana, a koja su činila 72,54% ukupnog ulja. Glavne komponente bile su kariofilen-oksidi (17,2%), spatulenol (10,3%), heksadekanska kiselina (4,9%), geranil-linalol (4,9%) i salvial-4(14)-en-1-on (3,6%). Pored toga, ADMET predikcija i Lipinskijevo pravilo petice su pokazali da većina glavnih komponenti EO vrste *M. communis* poseduje potencijalna svojstva slična lekovima. Analiza molekulskog dokovanja sprovedena je sa ukupno tri proteina, uključujući antikancersku (mTOR), antiinflamatornu (COX-2) i antifungalnu metu (*Aspergillus niger*). Ispitivanja jedinjenja EO pokazala su snažne interakcije sa aktivnim mestima ciljnih enzima, pokazujući niske energije vezivanja za mTOR (-5,5 do -8,9 kcal/mol), COX-2 (-4,8 do -7,3 kcal/mol) i antifungalnu metu (-4,5 do -8,2 kcal/mol), uz prihvatljive RMSD vrednosti od 1,88 Å.

Ključne reči:

Myrtus communis, etarsko ulje, molekulsko dokovanje, RMSD, ADMET

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Introduction

Mammalian target of rapamycin (mTOR) is one of the most important cancer chemotherapy targets. mTOR with other key components catalyzes the phosphorylation of several critical proteins like protein kinase C (PKC), insulin growth factor receptor (IGF-1R), 4E binding protein 1 (4E-

BP1) and ribosomal protein S6 kinase (S6K). mTOR signaling plays a central role in regulating translation, nucleotide synthesis, biogenesis of lysosomes, nutrient sensing, and growth factor signaling. Thus, mTOR changes leads to tumor growth and metastasis (Guertin & Sabatini, 2007). In addition, cyclooxygenase-2 (COX-2) enzyme can be expressed in breast cancer (Chow et al., 2008),



it contributes to the tumor development, survival, hyperproliferation, transformation, and metastatic spread (Witton et al., 2004). Pharmaceutical inhibition of COX-2 can relieve inflammation and pain. Meloxicam and diclofenac are COX inhibitors that are not strictly categorized. Therefore, it is of interest to develop and design effective compounds from medicinal plants against different diseases and fungal pathogens which are linked to inflammatory disorder.

This study assesses the pharmacological effect of myrtle plant with the direct enzymes Cox-2, mTOR and *A. niger* protein and predicted the binding affinity of the phytoconstituents with target receptors and how it may be used to reduce pain.

Myrtle (*Myrtus communis* L.) is an evergreen shrub belonging to the Myrtaceae family, with 145 genera and over 5500 species (Snow et al., 2011). It grows spontaneously in the Mediterranean region (Quezel & Santa, 1963). It is also found in Asia, New Zealand, America, Southern Russia and Australia (Özek et al., 2000; Barboni et al., 2010). In Algeria, the wild plant known as „Al-Rihan”, or „el-halmouche” is used as a strong antimicrobial agent that makes it a valuable raw material in cosmetic, pharmaceutical and food industries (Bouzouita et al., 2003; Yadegarinia et al., 2006). Aerial parts of myrtle were used to treat oral wounds, urinary and digestive issues (Alipour et al., 2014; Dabbaghi et al., 2023), peptic ulcers, diarrhea, inflammations and hemorrhoids (Hosseinzadeh et al., 2011; Mahboubi, 2017; Khosropour et al., 2019).

Computational approaches represent an opportunity to identify and design pharmacologically active natural molecules that can target proteins of interest. In this context, we report the identification of volatile constituents of *M. communis* from the northern east of Algeria and use computational methods (*in silico* analysis, molecular docking, and ADMET predictions) to evaluate its potential anticancer, anti-inflammatory and antifungal properties.

Materials and Methods

Plant material and isolation of EO

Myrtus communis was collected from the region of El Milia (Jijel) located in the northeastern of Algeria. Fresh aerial parts of *M. communis* (180 g) were subjected to steam distillation in a Kaiser Lang apparatus for 3 hours. The obtained EO was collected and stored in refrigerator until analysis.

GC-FID and GC-MS analysis

The EO was analysed on an Agilent gas chromatograph (GC-FID) Model 6890, equipped

with a HP-5MS fused silica capillary column (5%-diphenyl-95%- dimethylpolysiloxane, 25 m x 0.25 mm, film thickness 0.25 µm), programmed from 50 °C (5 min) to 250 °C at 3°/min and held for 10 min. Injector and flame ionization detector temperatures were 280 and 300 °C, respectively. The EO was diluted in acetone (3.5%, v/v) and injected in split mode (1/60), helium was used as a carrier gas (1.0 mL/min). Solutions of standard alkanes (C₈-C₂₀) were analysed under the same conditions to calculate retention indices (RI) with Van del Dool and Kratz equation. Mass spectrometry was performed on an Agilent gas chromatograph - mass spectrometer (GC-MS) Model 7890/5975, equipped with HP-5MS capillary column (25 m x 0.25 mm, film thickness 0.25 µm) programmed with the same conditions as for GC-FID. The mass spectrometer (MS) ionization was set in positive electron impact mode at 70 eV and electron multiplier was set at 2200 V. Ion source and MS quadrupole temperatures were 230 °C and 180 °C, respectively. Mass spectral data were acquired in the scan mode in the m/z range 33-450. The EO constituents were identified by matching their mass spectra and retention indices (RI) with those of reference compounds from libraries such as Adams and Mc Lafferty & Stauffer.

In silico study

Ligand preparation

The structure of the ligands and the reference drug Diclofenac were drawn using ChemSkech and saved in MOL format. The ligand molecules optimization were realized by Chem 3D version 16.0 to get the stable geometries with a minimum energy and saved in PDB format. Then, they were prepared for docking by AutoDock Tools version 1.5.6.

Protein preparation

The target proteins, COX-2 (PDB ID: 3LN0) and mTOR (PDB ID: 4DRJ), as well as a protein from *A. niger* (PDB ID: 3G0I), with crystallographic resolutions of 2.20, 1.80 and 2.10 Å, respectively, were downloaded from the Protein Data Bank (<http://rcsb.org>). Then they were prepared using Discovery Studio by removing water molecules and heteroatoms, and adding polar hydrogen atoms.

Molecular docking analysis

The study of ligand protein interactions was performed using AutoDock Vina program. Ligand molecules were docked in the active site of the chosen proteins. The grid box centres for the mTOR, COX-2, and the *A. niger* protein were set at coordinates (x = 3, y = -9, z = -13); (x = 42, y = 32, z = 32) and (x = 24, y = 37, z = 60) respectively, using a grid box size

of $40 \text{ \AA} \times 40 \text{ \AA} \times 40 \text{ \AA}$. The inhibition constant (K_i) was calculated using the relation $K_i = \exp(\Delta G/RT)$, where ΔG , R and T represent the binding energy, the gas constant ($1.9872036 \times 10^{-3} \text{ kcal/mol}$) and the temperature (298.15 K) respectively (Yung-chi & Prussoff, 1973). To confirm the accuracy of the docking analysis, the root mean square deviation (RMSD) between a co-crystallized and re-docked ligand was computed (Faloye et al., 2021).

In silico ADMET Evaluations

The active components were studied for ADMET (absorption, distribution, metabolism, and excretion) properties and Lipinski's rule of five using the SWISSADME and Protox 3 online program for toxicity test (Daina et al., 2017). The predictions were based on physicochemical and pharmacokinetic properties such as molecular weight, number of hydrogen bond acceptors and donors, number of rotatable bonds, and the blood–brain partition coefficient.

Results and Discussion

Essential oil composition

The EO obtained from *M. communis* was pale yellow in color, with a yield of 0.25% (w/w). Thirty-two compounds were identified from the EO (Tab. 1), representing 72.54% of the total EO. The oil was dominated by oxygenated sesquiterpenes (40.2%), mainly by caryophyllene oxide (17.2%), and spathulenol (10.3%). The sesquiterpene hydrocarbons were present at 2.9%, with β -selinene (2.2%) as the major component (Fig. 1).

Oxygenated monoterpenes (1.3%) were less represented than both oxygenated sesquiterpenes and sesquiterpene hydrocarbons, with each compound below 1%. Notably, geranyl linalool (4.9%) was the only diterpene present. According to the previously reported data, this study shows a variability in chemical profiles. Our sample was characterized by high content of caryophyllene oxide and spathulenol, while previous studies reported that *M. communis* oil samples from 19 localities along the Algerian coast, were rich in α -pinene ($50.1 \pm 10.3\%$) and 1,8-cineole ($22.2 \pm 4.3\%$) (Bekhechi et al., 2019; Mohamadi et al., 2021; Belahcene et al., 2024).

Another study (Cherrat et al., 2014) reported that myrtenyl acetate (49.3%) was the major component in Moroccan oil. Similar results were described for myrtle oils from Portugal (Pereira et al., 2009), Spain (Boelens & Jiménez, 1992), Tunisia (Messaoud et al., 2011), and Iran (Shahbazian et al., 2018). In Algeria, only one population from Ain Defla showed a myrtenyl acetate content of 38.7% (Touaibia, 2016).

Limonene, which is absent in our sample, was identified as a major compound in several oils, such as *Sardania* species (44.2%) (Tuberoso et al., 2006) or in different regions of Algeria, with levels ranging from 11.1% to 23.6% (Bouzabata et al., 2010; Hennia et al., 2016).

In conclusion, we found some differences in the composition of the identified constituents in our oil compared to previously reported data. These differences may be due to factors such as geographical location or the methods of extraction and analysis of the EO.

On the other hand, phthalate derivatives (8.55%) were found at a high percentage. Due to problems regarding waste disposal in developing countries, phthalate derivatives can easily be released from waste into water and soil, resulting in possible absorption and accumulation by medicinal and dietary plants.

In silico study

Molecular docking is a computer approach used to identify ligands or organic molecules that possess both geometric and energetic compatibility with the binding site of a protein. In this study, we evaluated *in silico* different biological activities such as anticancer, anti-inflammatory, and antifungal effects. The biomolecules were docked with the proteins: mTOR (anticancer), COX-2, (anti-inflammatory), and *A. niger* protein (antifungal), with a low RMSD value of 1.88 Å.

ADMET prediction

The main components (spathulenol, caryophyllene oxide, salvial-4(14)-en-1-one, hexadecanoic acid, geranyl linalool) of the EO were tested for Lipinski's rule of five and ADMET prediction. This analysis was carried out to remove phytochemicals with poor pharmacokinetic parameters from the drug list, thus saving cost and time. All the major compounds except phthalate (which is plasticizers not tested) were predicted to have good pharmacokinetic properties and follow the Lipinski's rule of 5.

The BOILED-Egg model for gastrointestinal absorption and blood–brain barrier (BBB) permeability (Fig. 2) showed that geranyl linalool (d), located in the BOILED Egg's white, is well absorbed in the human intestine but is not predicted to penetrate the brain. In contrast, caryophyllene oxide (a), spathulenol (b), hexadecanoic acid (c), and salvial-4(14)-en-1-one (e), located in BOILED Egg's yolk, are predicted to have good BBB permeability and intestinal absorption. All tested molecules were negative for the P-glycoprotein substrate (red-dotted). The toxicity test was evaluated based on

Table 1. The Chemical composition (%) of the EO of *M. communis*

Peak	*Compounds	%	RI	Rt(mn)
1	Menthone	0.23	1148	19.13
2	Decanal	0.40		20.27
3	Pulegone	0.33	1233	21.38
4	<i>p</i> -anisaldehyde	0.27	1247	21.99
5	Nonanoic acid	0.57	1267	22.37
6	α -cubebene	0.61	1345	25.13
7	(Z)- β -damascenone	0.34	1361	25.26
8	Nerylacetone	0.33	1434	26.95
9	<i>E</i> -beta-ionone	0.37		27.85
10	β - selinene	2.26	1489	28.18
11	Norcopaanone	0.39		29.84
12	1,5-Epoxy salvial-4(14)-ene	2.53		30.18
13	Spathulenol	10.34	1577	30.47
14	Caryophyllene oxide	17.23	1581	30.57
15	Salvial-4(14)-en-1-one	3.66	1594	30.80
16	Humulene epoxide II	1.93	1608	31.20
17	Benzophenone	0.84	1626	31.71
18	Mustakone	2.20	1676	32.69
19	Murol-5-en-4-one(cis-14-nor-)	0.55	1688	33.00
20	(E)-2-Hexyl-cinnamaldehyde	1.11	1748	34.12
21	Hexahydrofarnesyl acetone (6,10,14-Trimethyl-2-pentadecanone)	2.28		35.95
22	Phthalate	5.11		36.51
23	Methyl hexadecanoate	0.87	1921	37.65
24	Phthalate	3.00		38.42
25	hexadecanoic acide	4.97		38.41
26	Ethyl hexadecanoate	1.34		38.98
27	Geranyl linalool	4.91		39.78
28	9,12-Octadecadienoic acid (Z,Z)-, methyl ester	0.79		40.91
29	7,10,13-Hexadecatrienoic acid, methyl ester	0.47		41.03
30	Linoleate methylester	1.14		42.13
31	9,12-Octadecadien-1-ol	0.73		42.24
32	Phthalate	0.44		48.37
	Oxygenated Monoterpenes	1.26		
	Hydrocarbons Sesquiterpenes	2.87		
	Oxygenated Sesquiterpenes	40.17		
	Diterpenes	4.91		
	Others	23.33		
	Total	98.94		

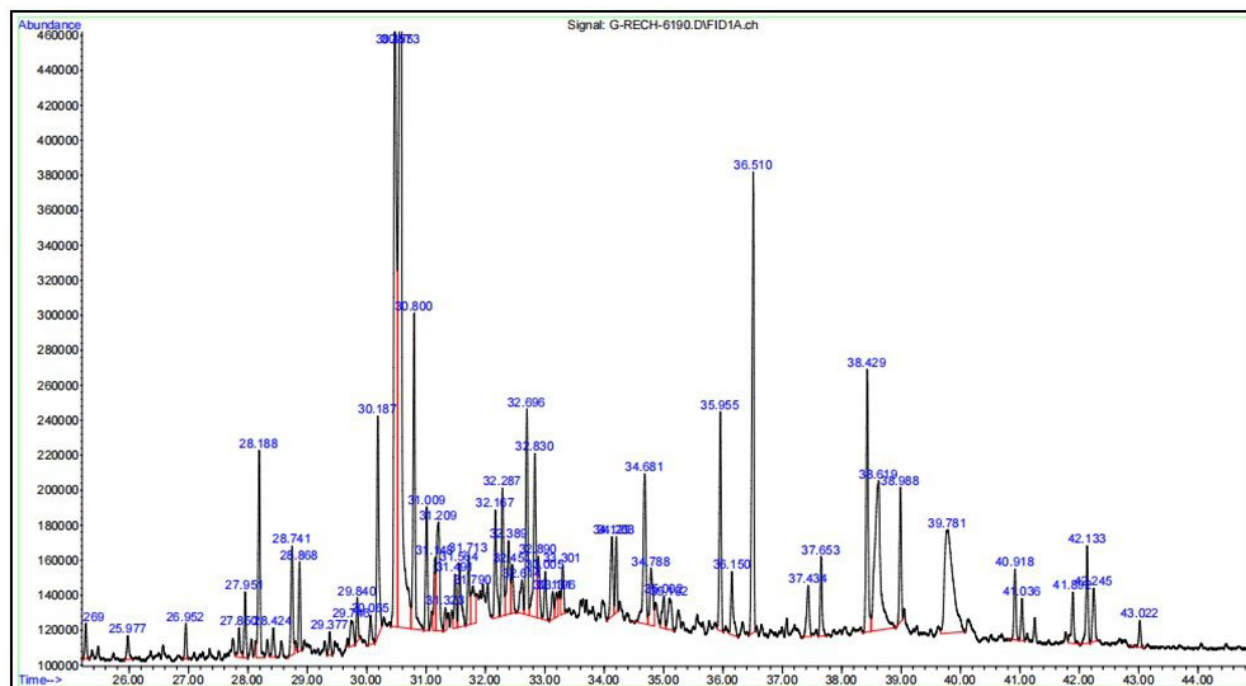


Fig. 1. GC-MS chromatogram of the EO of *M. communis* L.

acute oral toxicity. The main compounds belong to the category 5, indicating that they are practically non-toxic and may be suitable for oral use.

Effect on the anticancer target mTOR

The major compounds of the EO were screened with the active site of anticancer protein mTOR (PDB ID: 4DRJ) (Marz et al., 2013), and were observed to have good binding affinity. The docking score is summarized in **Tab. 2**. Based on the results, caryophyllene oxide elicited the best binding energy at (-8.9 kcal/mol), followed by spathulenol (-8.1 kcal/mol), salvial-4(14)-en-1-one (-8.1 Kcal/mol), geranyl linalool (-7.9 kcal/mol), and hexadecanoic acid (-5.5 kcal/mol). The molecular interaction analysis of molecules is presented in **Fig. 3**.

The visualization of the interaction results was performed using the Discovery Studio program. Caryophyllene oxide with the highest inhibition potential participated in two hydrophobic interactions with PHE2039 and TYR2105 amino acids. Spathulenol interacts with the GLU85 amino acid via a hydrogen bond, which increases the stability of the ligand-protein complex. This compound also exhibits a π - σ interaction with TYR2105 and a π -alkyl interaction with PHE2108. Salvial-4(14)-en-1-one exhibits four hydrophobic interactions, of which three are π -alkyl interactions (with PHE2108, TRP2101, and TYR2105) and one is a π - σ interaction (with PHE2108). Geranyl linalool interacts with TRP2101, PHE2108, PHE2039, TYR2105, PHE77, TYR57, and TRP90 through

hydrophobic interactions. Hexadecanoic acid also shows hydrophobic interactions with ILE87, VAL86, TRP90, PHE77, PHE130, and TYR57.

Effect on anti-inflammatory target COX-2

The major compounds of EO were evaluated as a potential inhibitors of inflammation against COX-2 protein (PDB ID:3LN0) (Wang et al., 2010). **Tab. 3** shows the binding affinities, inhibition constants (K_i), and amino acid residues involved in the interactions. The binding affinity range of the phytochemicals was from -7.3 to -4.8 kcal/mol. These affinities were compared with diclofenac

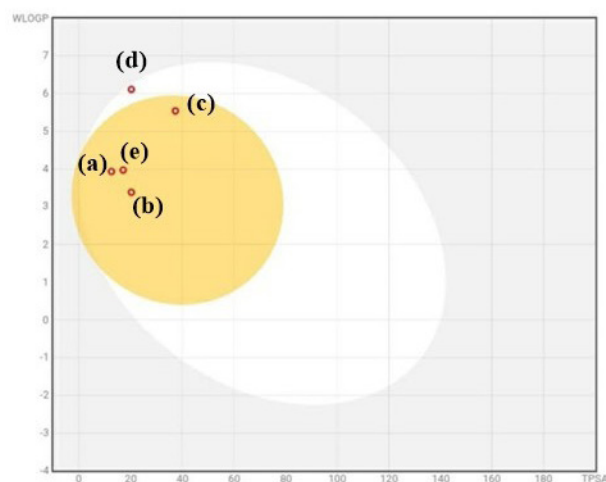
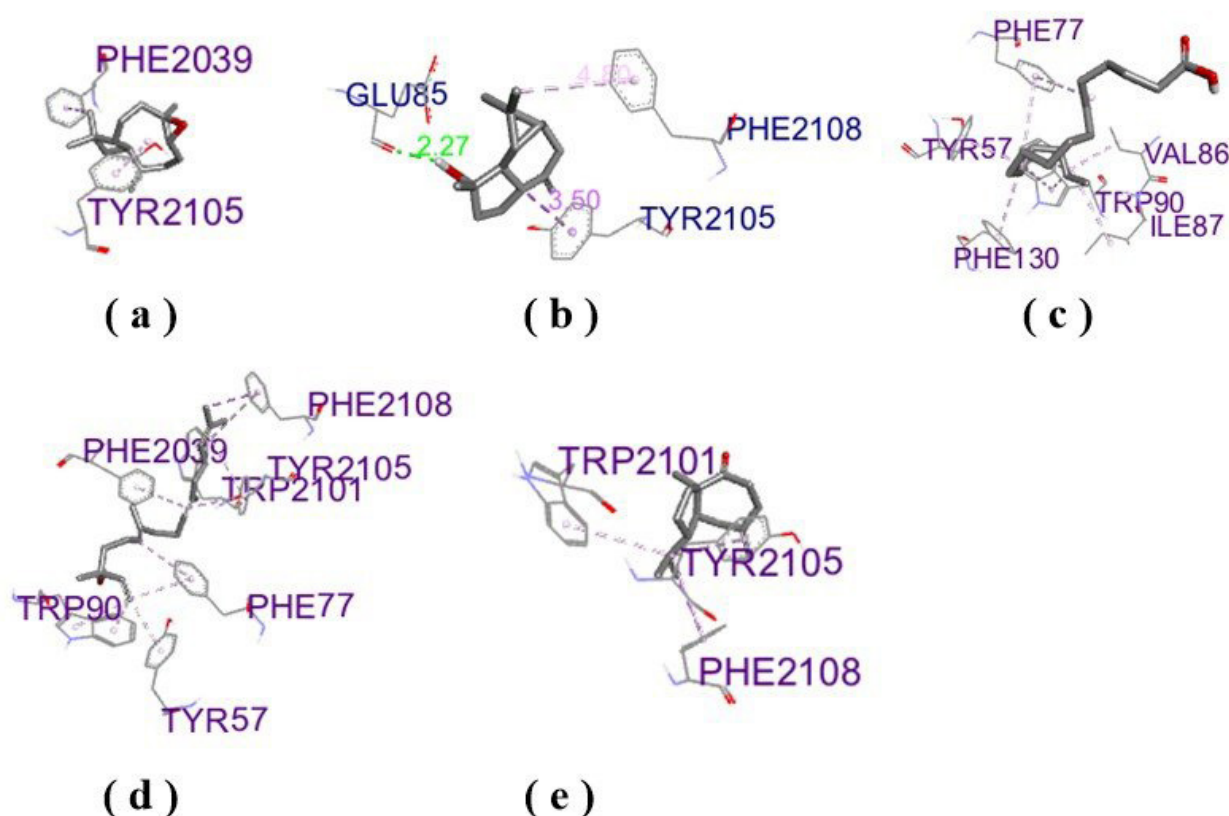


Fig. 2. BOILED-Egg model of caryophyllene oxide (a), spathulenol (b), hexadecanoic acid (c), geranyl linalool (d), salvial-4(14)-en-1-one (e).

Table 2. Docking analysis of the EO with anticancer target protein mTOR

Ligand name	ΔG (kcal/mol)	K_i (μM)	Residues
Caryophyllene oxide	-8.9	0.29	PHE2039, TYR2105
Spathulenol	-8.1	1.15	GLU85, TYR2105, PHE2108
Hexadecanoic acid	-5.5	92.87	ILE87, VAL86, TRP90, PHE77, PHE130, TYR57.
Geranyl linalool	-7.9	1.61	TRP2101, PHE2108, PHE2039, TYR2105, PHE77, TYR57, TRP90
Salvial-4(14)-en-1-one	-8.1	1.15	PHE2108, TRP2101, TYR2105

**Fig. 3.** Interactions of mTOR with caryophyllene oxide (a), spathulenol (b), hexadecanoic acid (c), geranyl linalool (d), salvial-4(14)-en-1-one (e)

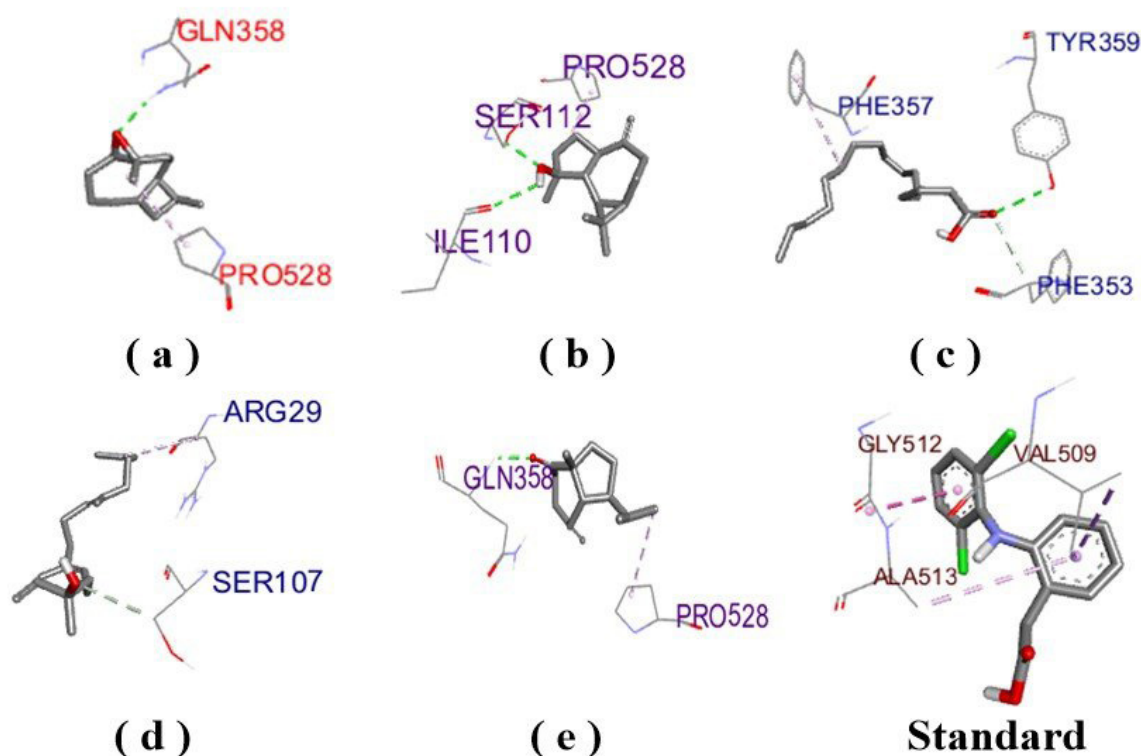
(-8.1 kcal/mol). The 2D interaction diagrams of the biomolecules are presented in Fig. 4. Diclofenac formed four hydrophobic interactions, including two π - σ interactions (with VAL509), one π -alkyl interaction (with ALA513), and one amide- π stacked interaction (with ALA513 and GLY512) (Fig. 4). Among the tested molecules, spathulenol (-7.3 kcal/mol) showed the best anti-inflammatory potential against COX-2, with a low inhibition constant ($K_i = 4.44 \mu M$). It formed one hydrophobic interaction with PRO528 and two hydrogen bonds with SER112 and ILE110.

Effect on *A. niger* target protein

For the antifungal activity, we evaluated the major compounds of EO with the *A. niger* target protein (PDB ID: 3G0I (Reetz et al., 2009)). We note that, a drug is more effective if its inhibition constant is lower and the value of the binding energy is negative. Molecular docking results are illustrated in **Tab. 4**. Caryophyllene oxide revealed the most effective effect with a low inhibition concentration $0.97 \mu M$ and good binding energy (-8.2 kcal/mol), followed by salvial-4(14)-en-1-one (-7.7 kcal/mol) and spathulenol (-7.5 kcal/mol). Hexadecanoic acid was revealed less effective against these fungal strains. 2D diagram of the biomolecules with *A. niger* target

Table 3. Docking analysis of the EO with anti-inflammatory target protein COX-2

Ligand name	ΔG (Kcal/mol)	Ki (μM)	Residues
Caryophyllene oxide	-6.8	10.34	GLN358, PRO528.
Spathulenol	-7.3	4.44	SER112, ILE110, PRO528
Salvial-4(14)-en-1-one	-6.8	10.34	PRO528, GLN358.
Hexadecanoic acid	-4.8	302.74	TYR359, PHE353, PHE357
Geranyl linalool	-5.7	47.27	ARG29, SER107.
Diclofenac (standard)	-8.1	1.15	VAL509, ALA513, GLY512

**Fig. 4.** Interactions of COX-2 with caryophyllene oxide (a), spathulenol (b), hexadecanoic acid (c), geranyl linalool (d), salvial-4(14)-en-1-one (e) and diclofenac (standard).

protein is represented in Fig. 5.

Conclusion

In conclusion, the *M. communis* EO analyzed in the present study was characterized by high levels of caryophyllene oxide and spathulenol, while other Algerian *M. communis* samples mainly contained α -pinene and 1,8-cineole. Molecular docking study of the active compounds revealed that *M. communis* may exert good anticancer activity by modulating the mTOR signaling pathway. Furthermore, spathulenol showed the strongest inhibitory activity against the inflammatory target COX-2 in comparison with the reference drug diclofenac. Most of the major

compounds of the EO exhibited potential antifungal activity against *A. niger*. ADMET prediction showed that the main compounds of the EO are likely to be safe and orally active, with favorable pharmacokinetic properties.

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Table 4 . Docking analysis of the EO with *A. niger* target protein

Ligand name	ΔG (Kcal/mol)	Ki (μM)	Residues
Caryophyllene oxide	-8.2	0.97	ALA217, ILE193, CYS350, LEU215, LEU349, PHE196, PHE244, TYR314
Spathulenol	-7.5	3.17	PHE344
Salvia-4(14)-en-1-one	-7.7	2.26	TYR314, ALA217, CYS350.
Hexadecanoic acid	-4.5	502.34	TRP284, GLN283, ARG240, LYS347, LEU349.
Geranyl linalool	-5.4	109.95	ARG258, LYS243, LYS347, PHE244, ARG240, LEU349.

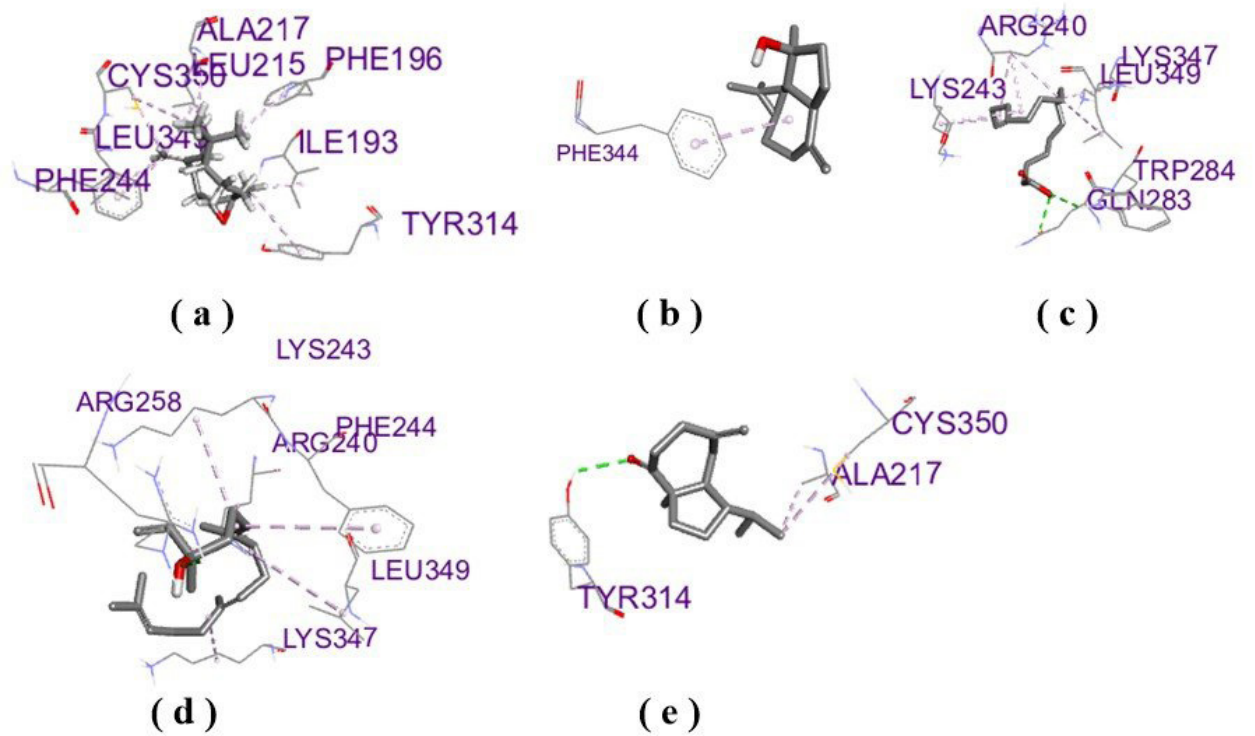


Fig. 5. Interactions of *A. niger* target protein with caryophyllene oxide (a), spathulenol (b), hexadecanoic acid (c), geranyl linalool (d), salvia-4(14)-en-1-one (e)

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