Computational Investigation of Essential Oil of Fresh Jordanian *Euphorbia Herosolymitana*Boiss against Cytokine IL-1 Responsible for Inflammation

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Abstract:

The Euphorbiaceous family is a significant family that contains various medicinal plants. Euphorbiaceae is commonly used in folk medicine as an anti-inflammatory. Various plants of *Euphorbia* species were proven to have anti-inflammatory properties. Plants belonging to this family were found to contain phenolic compounds, alkaloids, steroids, flavonoids, esters, and minerals. *Euphorbia herosolymitana* Boiss belongs to the Euphorbiaceaefamily. *E. hierosolymitana Boiss* grows in different areas in Jordan. The present work aims to evaluate the anti-inflammatory activity of 39 compounds extracted from the essential oil of fresh *E. herosolymitana* against the cytokine IL-1 responsible for inflammation. The study was carried out using the molecular docking technique. A comparison was made between the latter derived from essential oil and Anakinra. Anakinra is considered a powerful anti-IL-1 to fight against inflammation and is already known for its activity against the receptor (IL-1) target.

Keywords: Cytokine IL-1; *Euphorbia Herosolymitana* Boiss; Inflammation; Molecular Modelling

Introduction:

Inflammation is a beneficial reaction for the human body; it is the first response of tissue against infection to eliminate a pathogenic agent, which can be a virus, a fungus, or a parasite. Indeed, it is an immune response, which may sometimes be harmful when uncontrolled[1].

Interleukin-1 (IL-1) is one of the cytokines responsible for the inflammatory response and plays a vital role in developing pathological conditions leading to chronic inflammation [1]. So, in the case of an uncontrolled inflammation that can cause serious problems, it is necessary to use anti-inflammatory agents, which diminish or limit the effects of this immune response[2]. Recent research has confirmed that IL-1 inhibition by anti-IL-1 agents is very effective and that IL-1 is an excellent therapeutic target for fighting inflammation [2, 3]. However, concern about herbal medicines has increased because researchers believe that herbal medicine has minimal side effects compared to synthetic drugs [4]. Several plants have long been known to treat inflammatory diseases due to the essential oils of that plant, which are used in traditional medicine [5]. Essential oils have been reported as traditional medicinal agents with antibacterial, antiviral, and antifungal activity [6].

The euphorbiaceous family is one of the most prominent families in the world, and according to Horn et al., it is the second-largest family of flowering plants [7]. Euphorbiaceous plants show different activities in humans and animals [4]. Due to phenolic compounds, alkaloids, steroids, flavonoids, esters, minerals, etc[7]. Euphorbiaceae is commonly used in folk medicine since it has several therapeutic activities, such as anti-inflammatory and anti-tumour[7]. Also, several plants of *Euphorbia* species were proven to have anti-inflammatory effects, such as *Euphorbiahirta* [8], *Euphorbia fischeriana*, *Euphorbia lactea* [9], and *Euphorbia neriifolia* [10]. Although studies about the anti-inflammatory activity of many plants in the Euphorbiaceae have been reported [11], confirmation of the anti-inflammatory activity of *Euphorbia hierosolymitana* Boiss needs further considerable research. *Euphorbia hierosolymitana* Boiss, which belongs to the Euphorbiaceous family, is a plant that grows in many areas of Jordan. Halablob is the common name of *E. hierosolymitana*. *E. hierosolymitana Boiss* grows to the height of a small round shrub, and milky latex can "bleed" from the leaves or stems when broken[12].

The present study aims to determine the anti-inflammatory activity of *Euphorbia hierosolymitana* Boiss active components as receptor (IL-1) inhibitors target using computer-aided drug discovery methods.Molecular dockingwas used to predict the interaction between active compounds of *Euphorbia Herosolymitana* Boiss and Interleukin-1 (IL-1),and the stability of these interactions was examined usingmolecular dynamics. In addition, ADMEDT and Lipinski rule to screen the interest of *Euphorbia Herosolymitana* Boissas potential inflammatory inhibitor candidates. The inflammatory activity of Euphorbia

hierosolymitana Boiss active components will compare with Anakinra (Fig .1) as a powerful anti-IL-1 drug.

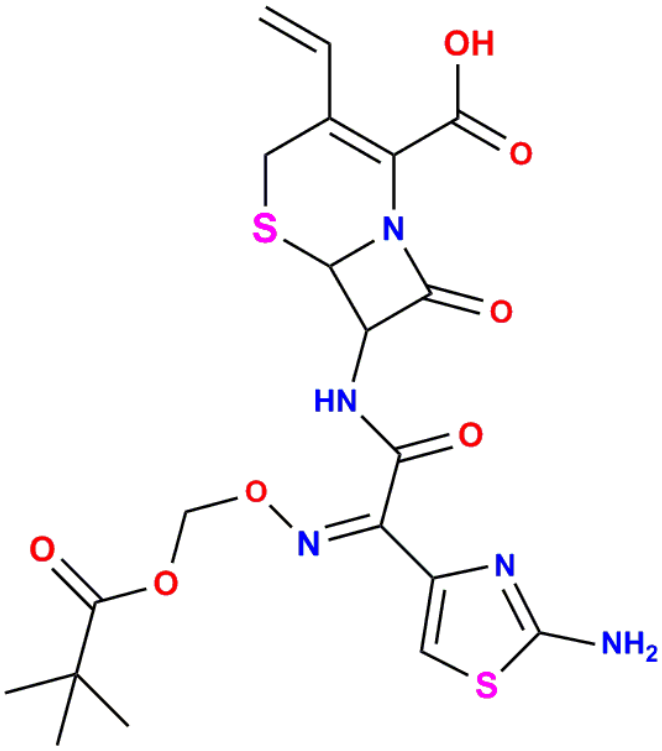

Fig 1. Anakinra

Material and methods

Molecular Docking

To evaluate the anti-inflammatory activity of the 39 compounds extracted from the essential oil of Fresh Jordanian *Euphorbia hierosolymitana* (Fig 2, Table 1), a study was carried out using the molecular docking technique [13, 14] on these compounds. First of all, the therapeutic target preparation is necessary to eliminate water and ligands already fixed on the target, and this preparation was done using Discovery Studio client 2016 (Fig 3). The 39 compounds were optimized after Sybyl-X2.0. The Sybyl-X2.0 program also allows choosing the correct position of the 39 compounds on the target. Pymol carries out the collection (ligand-receiver) to make the two entities (ligand; receiver) complex. Finally, the results were visualized with the help of the Discovery Studio client 2016 [15]. The receiver Interleukin 1 (IL-1) responsiblefor the inflammatory response was obtained after "Protein Data Bank".

ADMET prediction

To discover a deficient compound capable of acting as an active agent in a drug, it goes through analyses and tests that help evaluate the biological activity and specific properties.

ADMET explains the parameters and properties of Lipinski rules absorption, metabolism, and toxicity. The 39 compounds extracted from the essential oil of Fresh Jordanian Euphorbia hierosolymitana were subjected to an ADMET test by the servers "Admemesh" and "Swissadme"[16].

Molecular dynamics

Molecular docking studies the ligand's ability to fix itself on receptors after the interactions, and MD simulation method confirms the stability of interactions and molecular docking results.GROMACS simulation package (GROMACS 2020.4) performed molecular dynamic dynamics simulations. MD simulation was carried out for 100 ns in water using CHARMM36 forcefield; trajectory and energy files were written every 10 ps. The system was solvated in a truncated octahedral box containing TIP3P Water molecules. The protein was centred in the simulation box within a minimum distance to the box edge of 1 nm to satisfy the minimum image convention efficiently. Potassium/Chlorine ions were added to the complex to neutralize the overall system. Minimization was carried out for 5000 steps using Steepest Descent Method, and the convergence was achieved within the maximum force < 1000 (KJ mol-1 nm-1) to remove any steric clashes. All systems were equilibrated at NVT and NPT ensembles for 100ps (50,000 steps) and 1000ps (1,000,000 steps), using time steps 0.2 and 0.1 fs, respectively, at a temperature of 300K to ensure a fully converged system for the production run. The production runs for simulation were carried out at a constant temperature of 300 K and a pressure of 1 atm or bar (NPT) using a weak coupling velocity-rescaling (modified Berendsen thermostat) Parrinello-Rahman algorithms, respectively. Relaxation times were set to τ T = 0.1 ps and τ P = 2.0 ps. All bond lengths involving the hydrogen atom were kept rigid at ideal bond lengths using the Linear Constraint Solver (lincs) algorithm, allowing for a time step of 2 fs. The valet scheme was used for the calculation of non-bonded interactions. Periodic Boundary Conditions (PBC) were used in all x, y, and z directions. Interactions within a short-range cutoff of 1.2 Nm were calculated each time step. Particle Mesh Ewald (PME) was used to calculate the electrostatic interactions and forces for a homogeneous medium outside the long-range cutoff. The production was run for 100ns for the complex.

Binding Energy Calculations

The one-average molecular mechanics generalized Born surface area (MM/GBSA)[14, 15] approaches implemented in the MOLAICAL code [16] were used for the relative binding energy calculations, in which the ligand (L) binds to the protein receptor (R) to form the complex (RL),

$$\Delta G_{bind} = \Delta G_{RL} - \Delta G_{R} - \Delta G_{L}$$

which can be represented by contributions of different interactions,

$$\Delta G_{bind} = \Delta H - T\Delta S = \Delta E_{MM} + \Delta G_{Sol} - T\Delta S$$

where the changes in the gas phase molecular mechanics (ΔE_{MM}), solvation Gibbs energy (ΔG_{Sol}), and conformational entropy $(-T\Delta S)$ are determined as follows: ΔE_{MM} is the sum of the changes in the electrostatic energies ΔE_{ele}, the van der Waals energies ΔE_{vdW}, and the internal energies ΔE_{int} (bonded interactions); ΔG_{Sol} is the total of both the polar solvation (calculated using the generalized Born model) and the nonpolar solvation (calculated using the solvent-accessible surface area) and $-T\Delta S$ is calculated by the normal mode analysis, however, this part was neglected to reduce the computational cost since we are only interested in relative binding energies. The solvent dielectric constant of 78.5 and the surface tension constant of 0.03012 kJ mol^{-1} $Å^2$ were used for MM/GBSA calculations.

Table 1. Components of the essential oil, their percentage

Compounds	%	Compounds	%	Compounds	%
Dihydroxy-cis-Linalool oxid	0.73	Trans-Linalool oxide	0.58	Heptanal	3.41
α-Chenopodiol	3.91	Endo-Fenchol	0.54	2E.4E-Nonadienal	2.74
O-Cresol	2.08	Cis-Crysathenol	0.78	Benzaldehyde	1.86
Octadecanol	2.05	Z.Methyl isoeugenol	0.42	O-Tolualdehyde	1.61
γ-Terpineol	0.63	Caryophyllene Oxide	12.84	Cis-dihydro-α-terpinec	0.49
Trans-Myrtanol	1.57	2.2-dimethyl-3.4-octadienal	5.55	Citronellol	0.18
Thymol	1.06	Benzene-	3.80	Iso-dihydro carveol	0.34

		Acetaldehyde			
Cis-2.3-Pinanedic	0.22	6-Methyl-5-hepte 2-one	0.64	Camphor	0.41
Ethyl decanoate	0.07	2-Acetyl-5-methy furan	0.19	Endo-2-Norborneol	0.13
Decyl propanoate	1.37	Acetophenone	0.29	1.4-Cineole	0.36
Butyl-Acetate	1.00	Fenchone	0.44	Santolina alcohol	0.61
Methyl pentanoat	0.99	Linalool	0.54	α-Acorenol	0.39
5-Methyl-3-heptanone	0.06	Trans-Pine hydra	0.60	Isophytol	0.20

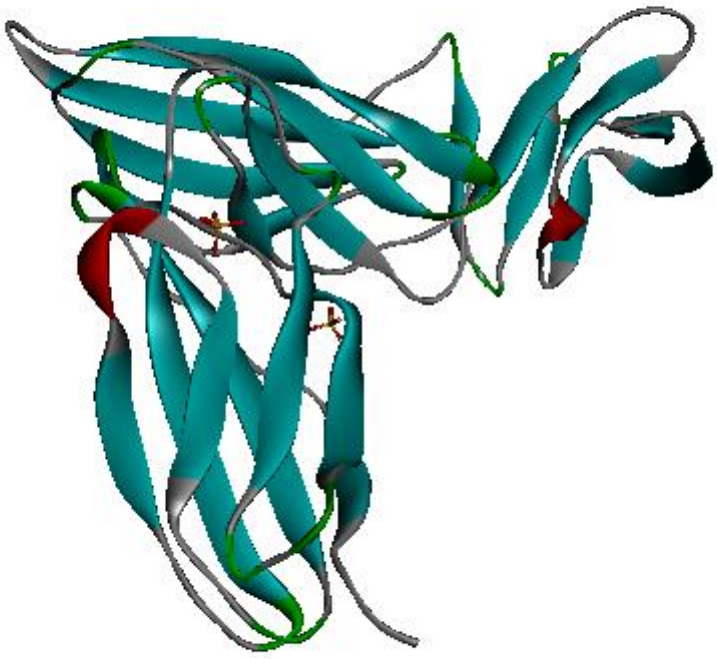

Fig 2. Therapeutic target (Pro-inflammatory cytokines IL-1; ***Pdb:1N26***)

Results and discussion

Molecular docking

Dehydroxy-cis-linalool oxid, o-Cresol, and Trans-linalool oxide have good inhibitory activity against inflammation; they bind to the target (IL-1) by two hydrogen interactions, which are the interactions the most important among the others, then there are the compounds (α-Chenopodiol; Octadecanol; Thymol; Endo-Fenchol; γ-Terpineol, Butyl-acetate, Citronellol, Iso-dihydro carveol, Acetophenone, Trans-Pine hydrate, and Santolina alcohol), each forms a single hydrogen bond with the target, also the Van-der-Waals interactions, the carbon-hydrogen bond, and the hydrophobic interactions (Alkyl, Pi-Alkyl), which expresses the good anti-inflammatory activity of the compounds (Table 2).The molecular Docking results obtained on the 39 compounds derived from the essential oil of Fresh Jordanian *Euphorbia herosolymitana* concerning the target responsible for inflammation are very interesting due to their many interactions and diversity. In order to confirm the activity of the most active compound against the receptor (IL-1) target, a comparison was made between the latter derived from essential oil and the therapeutic agent already known by their activity against the receptor (IL-1) target, according to research Anakinra is considered a powerful anti-IL-1 to fight against inflammation. This compound was subjected to a test by molecular docking in order to make a comparison with the most active compound derived from the essential oil. The presence of a single hydrogen interaction for compound Anakinra concerning IL-1 (Fig 3) expresses the importance of the inhibitory activity of this compound, but according to their comparison with the Dehydroxy-cis-linalool oxide against inflammation, Dehydroxy-cis-linalool oxide from the essential oil binds in a very interesting way to the target. Dehydroxy-cis-linalool oxide forms two hydrogen interactions between the hydrogens of the alcohol function (OH) and the residues (THR:120; THR:125), the Van-der-Waals interactions with the residues (LEU:69; SER:122; PRO:94; PRO:95; SER:177; SER:119; PHE:155; VAL:175), hydrophobic interactions (Alkyl, Pi-Alkyl) with (VAL:93; PRO:117; TRP:115) (Fig 4).These results show the capacity of Dehydroxy-cis-linalool oxide to confront the receptor (IL-1) target (Fig 4) due to the number of hydrogen interactions formed by contribution to Anakinra, which form just a single hydrogen bond with the target. The interactions obtained from molecular docking for the 39 compounds derived from the essential oil of fresh Jordanian *Euphorbia herosolymitana*against receptor (IL-1) show a strong inhibitory activity of the essential oil against inflammation.

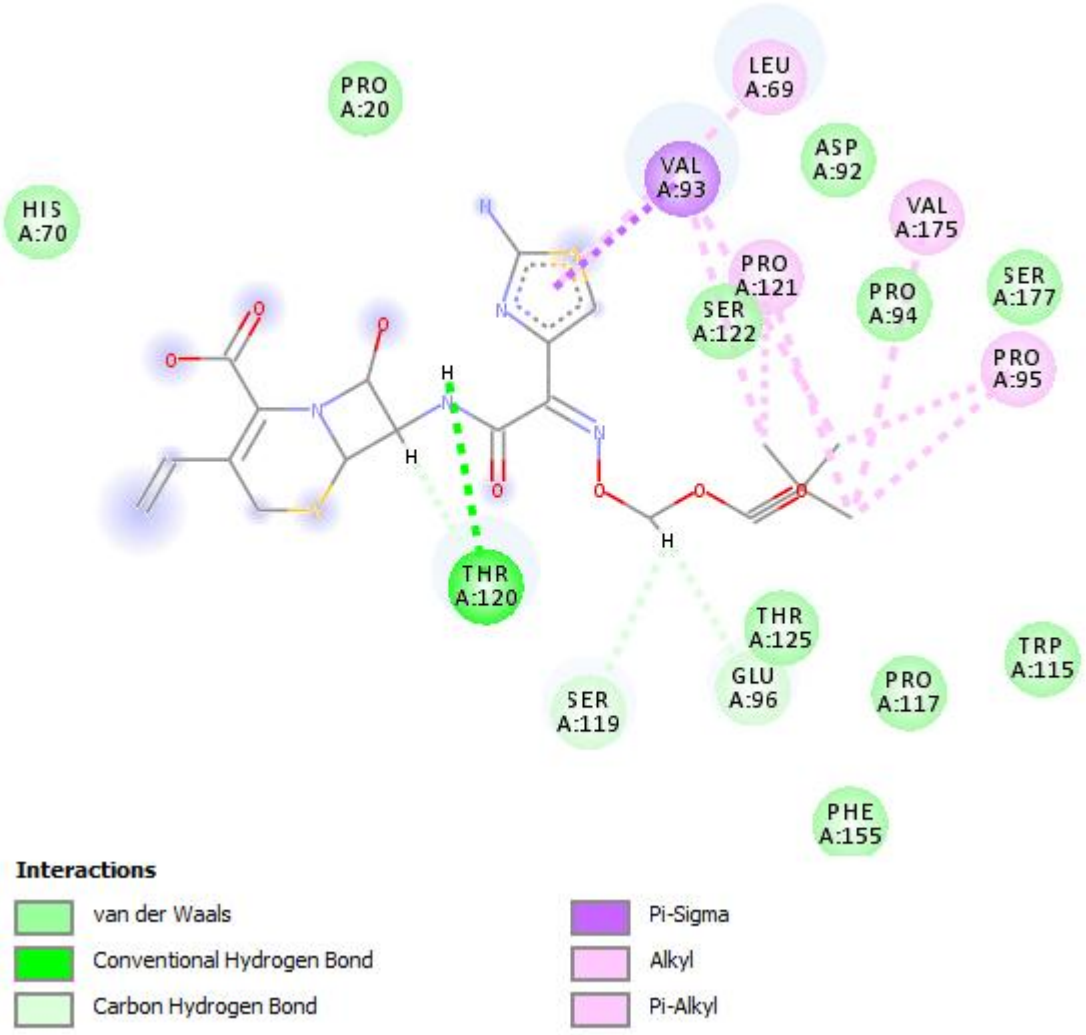

Fig 3. Anakinra against pro-inflammatory cytokines IL-1

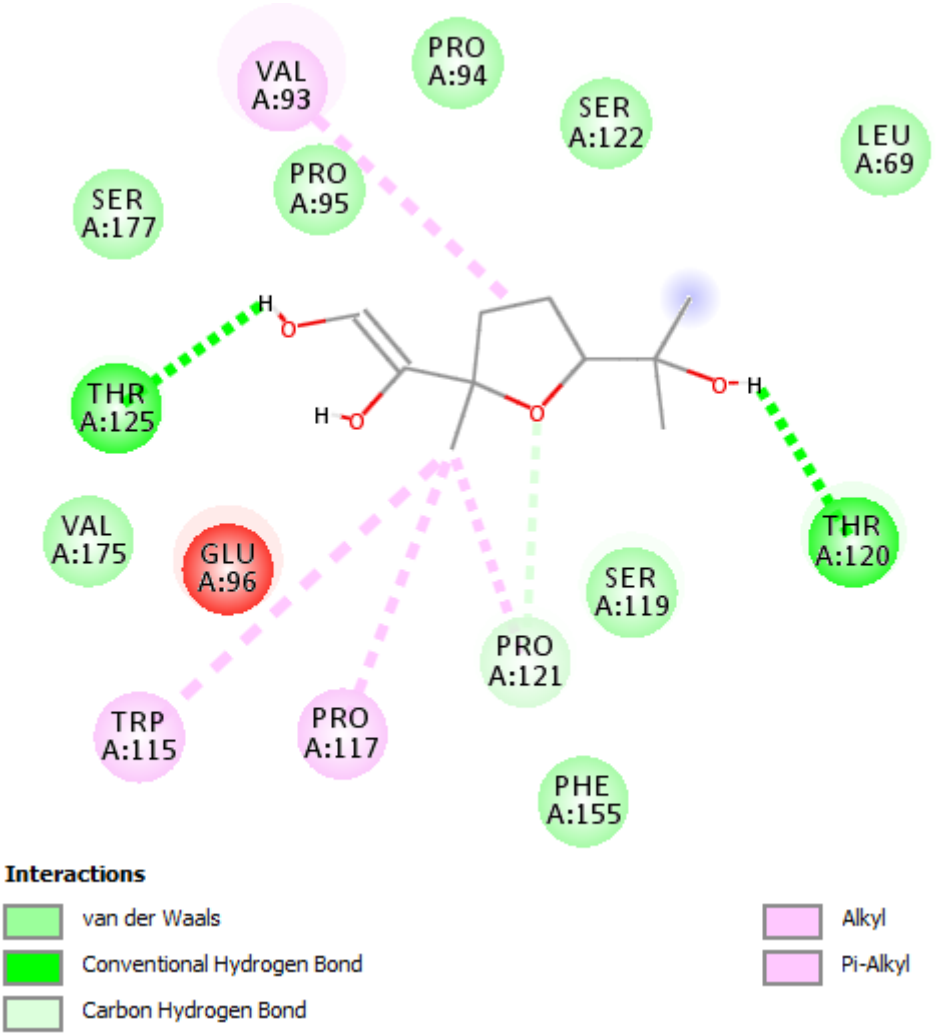

Fig 4. Dihydroxy-cis-linalool oxide against pro-inflammatory cytokines IL-1

Table 2. Score values and interactions obtained for the Pro-inflammatory cytokines IL-1 (Pdb:1N26)

Compounds	Score	Interactions	N. B	Compounds	Score	Interactions	N. B
Caryophyllene oxide	1.27	Van-der-Waals Alkyl	8 1	Trans-Myrtanol	1.21	Van der waals Alkyl	7 4
2.2-dimethyl-3.4-octadienal	1.34	Van-der-waals Alkyl	7 2	Thymol	2.46	Van der Waals **Hydrogen Bond** Alkyl; Pi-Alkyl	6 **1** 1
Dihydroxy-cis-Linalool oxid	3.32	Van der Waals **Hydrogen Bond** Carbon hydrogen Bond Alkyl; Pi-Alkyl	8 **2** 1 4	Trans-Linalool oxide	1.93	Van der waals Conventional Hydrogen Bond	7 **2**

α-Chenopodiol	2.18	Van der waals **Hydrogen Bond**	5 **1**	Endo-Fenchol	1.02	Van der waals **Hydrogen Bond** Alkyl	6 **1** 1
O-Cresol	1.91	Van der Waals **Hydrogen Bond** Pi-Alkyl	2 **2** 1	Cis-Crysathenol	1.81	Van der waals Carbon hydrogen Bond Alkyl	3 1 1
Octadecanol	3.14	Van der waals **Hydrogen Bond** Carbon hydrogen Bond	6 **1** 3	Z.Methyl isoeugenol	1.78	Van der waals Carbon hydrogen Bond Pi-Donor Hydrogen Bond Alkyl	6 1 2 1
γ-Terpineol	1.46	Van der Waals **Hydrogen Bond**	6 **1**	Benzene-Acetaldehyde	0.99	Van der Waals Carbon hydrogen Bond Pi-Donor Hydrogen Bond	5 1 1
Heptanal	1.18	Van-der-waals	9	Decyl propanoate	2.62	Van-der-waals Alkyl	10 3
2E.4E-Nonadienal	1.62	Van-der-waals	8	Butyl-Acetate	1.37	Van-der-waals **Hydrogen Bond** Alkyl; Pi-Alkyl	9 **1** 3
Benzaldehyde	0.65	Van-der-waals Pi-Alkyl	6 1	Methyl pentanoate	1.62	Van-der-waals Alkyl	9 1
O-Tolualdehyde	1.88	Van-der-Waals Carbon Hydrogen Bond Pi-Sigma Alkyl, Pi-Alkyl	7 2 1 4	5-Methyl-3-heptanone	1.73	Van-der-waals Carbon Hydrogen Bond Alkyl; Pi-Alkyl	7 1 7
Cis-dihydro-α-terpineol	2.79	Van-der-waals Alkyl	5 3	6-Methyl-5-hepten-2-one	2.19	Van-der-waals Alkyl	11 3
Citronellol	4.17	Van-der-waals **Hydrogen Bond** Alkyl	13 **1** 3	2-Acetyl-5-methylfuran	0.88	Van-der-waals Carbon Hydrogen Bond Pi-Sigma	8 1 1

						Alkyl	1
Iso-dihydro carveol	3.41	Van-der-Waals **Hydrogen Bond** Pi-Alkyl; Alkyl	7 **1** 6	Acetophenone	1.98	Van-der-waals **Hydrogen Bond** Carbon Hydrogen Bond Pi-Alkyl	12 **1** 1 2
Ethyl decanoate	3.10	Van-der-waals Alkyl	14 1	Fenchone	1.82	Van-der-waals Alkyl	8 4
Linalool	2.83	Van-der-Waals Alkyl	9 3	Nopinone	1.99	Van-der-waals Alkyl	7 4
Trans-Pine hydrate	2.44	Van-der-Waals **Hydrogen Bond** Carbon Hydrogen Bond Alkyl; Pi-Alkyl	6 **1** 1 10	Camphor	1.74	Van-der-waals Carbon Hydrogen Bond Alkyl	4 1 4
Endo-2-Norborneol	2.79	Van-der-waals Alkyl	11 1	1.4-Cineole	1.93	Van-der-waals Carbon Hydrogen Bond Alkyl	7 1 7
Santolina alcohol	2.81	Van-der-waals **Hydrogen Bond** Alkyl	13 **1** 2	α-Acorenol	2.63	Van-der-Waals Alkyl	9 3
Isophytol	5.59	Van-der-waals Alkyl	18 2				

Molecular dynamics

RMSD was calculated for the (Dehydroxy-cis-linalool oxid- pro-inflammatory cytokines IL-1) complex based on 'Backbone' atoms using GROMACS program.RMSD graph for (Dehydroxy-cis-linalool oxid- pro-inflammatory cytokines IL-1) complex shows that the structure remained stable throughout the simulation time with some fluctuation within the range of ~1 Å, a normal behaviour of globular protein (**Figure 5 A**). RMSD was calculated for the ligand (Dehydroxy-cis-linalool oxide) based on the ligand's atoms using the GROMACS program. RMSD of ligand remained reasonably stable throughout the simulation (**Figure 5 A**). RMSF was calculated for the (Dehydroxy-cis-linalool oxid- pro-inflammatory cytokines IL-1) complex based on 'C-alpha' atoms using GROMACS program. (**Figure 5B**).The radius of gyration was calculated for the (Dehydroxy-cis-linalool oxid- pro-inflammatory cytokines IL-1) complex based on 'C-alpha' atoms using the GROMACS program. The slight fluctuation within the 1 Å Rog value during the MD

simulation time indicates a slight opening and closing of the N and C terminal domains. (**Figure 5C**). The total number of hydrogen bonds formed between ligand (Dehydroxy-cis-linalool oxide) and protein (pro-inflammatory cytokines IL-1) during 100 ns of the simulation time is shown in (**Figure 6 A**). At the same time, the average Center-of-Mass Distance between (Dehydroxy-cis-linalool oxide) and protein (pro-inflammatory cytokines IL-1) during 100 ns of the simulation time is shown in (**Figure 6 B**). Finally, the system's potential energy, pressure and temperature during 100 ns of MD simulation, as obtained from the GROMACS or file, are shown in (**Figure 7**). The graph shows converged potential energy, pressure and temperature throughout the **100ns** simulations

MMPBSA Binding Energy

The Molecular Mechanics/Poisson Boltzmann Surface Area (MM/GBSA) method was selected for rescoring complexes because it is the fastest force field-based method that computes the free energy of binding, as compared to the other computational free energy methods, such as free energy perturbation (FEP) or thermodynamic integration (TI) methods. The MM/PBSA calculation was performed using g-mmpbsa software. The calculated binding free energies are shown in **Table 3**.

Table 3. Calculated binding free energies of tested compounds [kJ/mol]

Complex	ΔG	Van der Waal energy	Electrostatic energy	Polar solvation energy	SASA energy
Ligand (Dehydroxy-cis-linalool oxide) and protein (pro-inflammatory cytokines IL-1)	-64.839 +/- 13.931	-100.395 +/- 10.839	-40.602 +/- 17.180	88.288 +/- 12.530	-12.130 +/- 0.795

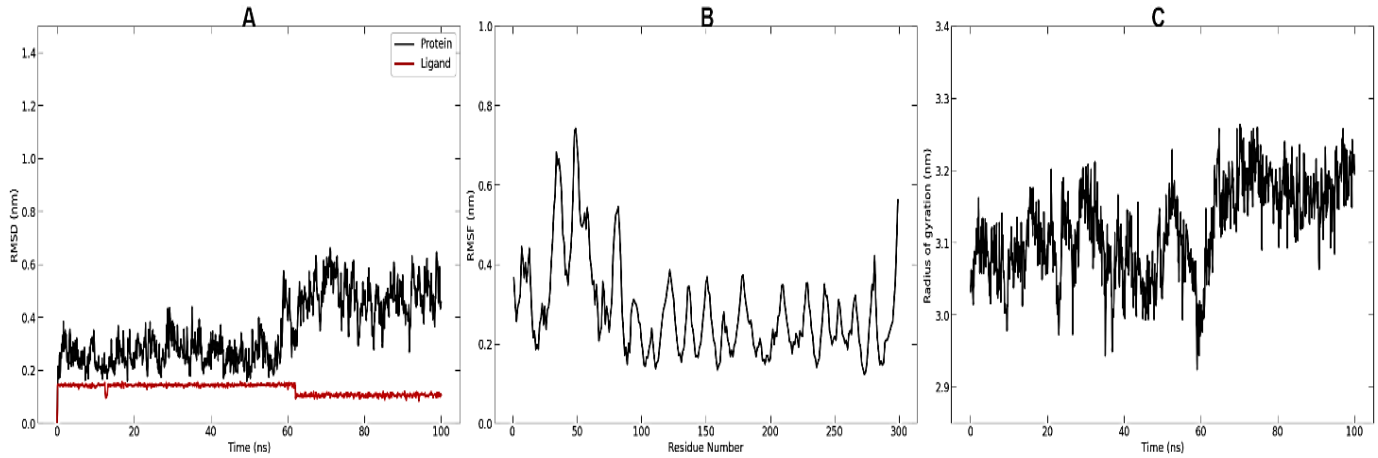

Figure 5.(A) RMSD, **(B)** RMSF and **(C)** Radius of gyration of the complex during 100ns.

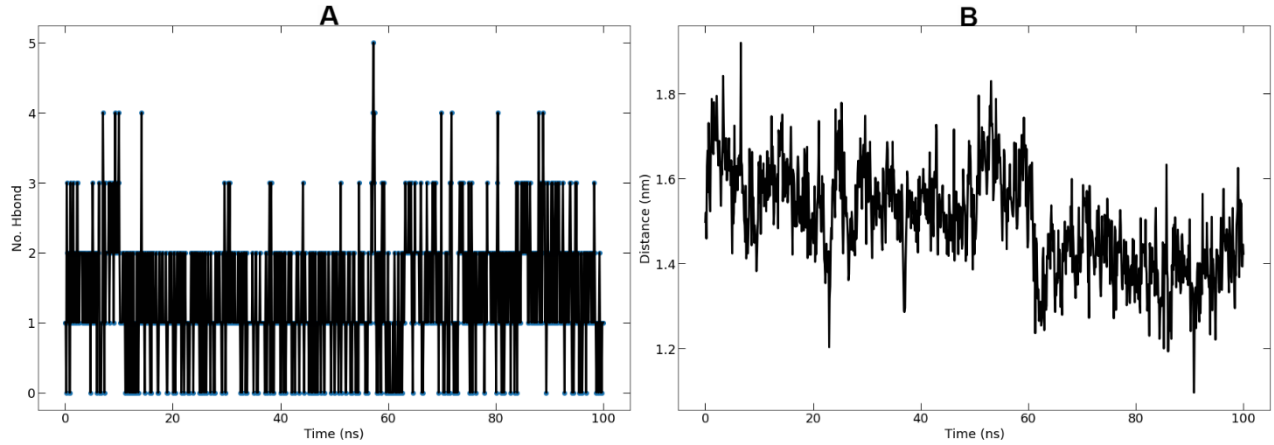

Figure 6.(A) Hydrogen Bonds (Protein-ligand) and **(B)** Average distance between Ligand and the Protein for the complex during 100ns.

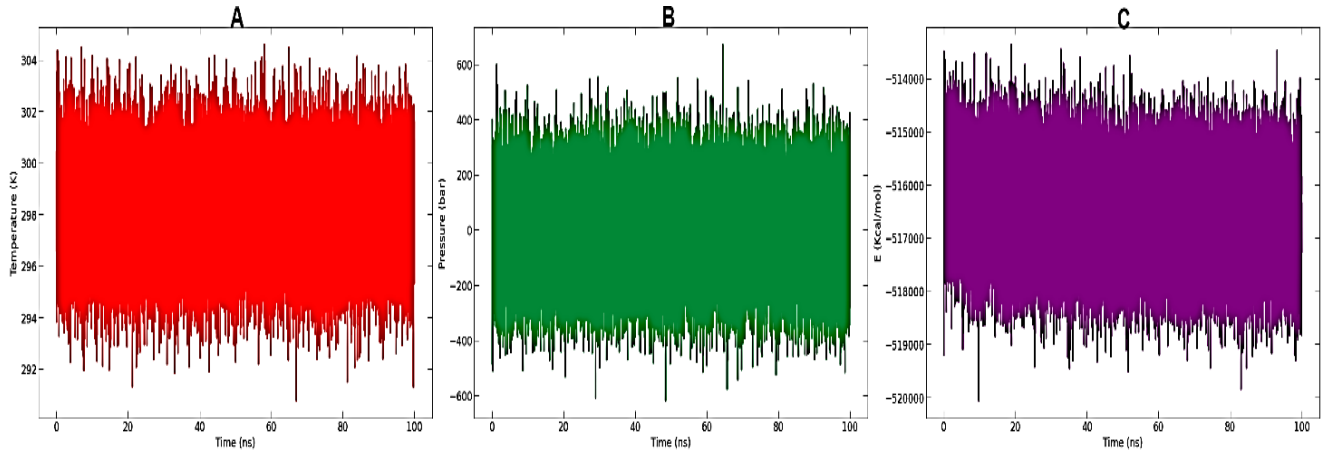

Figure 7. From left to right: **(A)** Temperature, **(B)** pressure and **(C)** potential energy during the 100ns MD simulations

ADMET prediction

The Admet test results show that the compounds satisfy Lipinski's rules, so the 39 compounds from the essential oil can be inhibitory agents against inflammation (Table 5). The absorption, metabolism, and toxicity properties show a good profile accepted for the 39 compounds. At the level of absorption, the 39 compounds have good intestinal absorption, optimal permeability for Caco2- and high passive permeability for MDCK (Madin-Darby Canine Kidney) [17, 18],The compounds (Z-methyl isogonal, Thymol, Octadecanol, Benzaldehyde, O-cresol, Benzene Acetaldehyde, Acetophenone, 2-Acetyl-5 methyl furan, Decyl propanoate, and O-tolu aldehyde) have been predicted as Cyp1A2 inhibitors, the compounds (Camyophyllene oxid) as an inhibitor of CyP2C19, the compounds (Isophytol, Alpha-Acorenol, Caryophyllene oxide) predicted as inhibitors of CyP2C9, the compound (Isophytol) is predicted as a substrate for P-gp. According to the metabolism profile, the toxicity properties show that the compounds (2E, 4E-Nonadienal, and Dehydroxy-cis-linalool oxide) are mutagenic, and the compounds (Gamma-Terpineol, O-cresol, 2E, 4E Nonadienal, 2.2-demethyl-3.4-octadienal, cis-dihydro-alpha-terpineol) are carcinogenic (Table 6). Generally, these results express a good profile for the 39 compounds derived from the essential oil.

Table 4. Admet's results for the 39 compounds obtained concerning "Lipinski's rule."

Compounds	**Log P** ≤ 4.15	**H-bond Acceptor** ≤ 10	**H-bond Donor** ≤ 5	**Rotatable bonds** ≤ 10	**Molecular Weight** ≤ 500
O-tolu aldehyde	1.63	1	0	1	120.15
Cis-dihydro-alpha-terpineol	2.51	1	1	1	154.25
Citronellol	2.72	1	1	5	156.27
Iso-dihydro-Carveol	2.48	1	1	1	154.25
Ethyl-decanoate	3.29	2	0	10	200.32
Linalool	2.70	1	1	4	154.25
Trans pine hydrate	2.45	1	1	0	154.25
Endo-2-Norborneol	1.84	1	1	0	112.17
Santolina-Alcohol	2.69	1	1	3	154.25

Isophytol	4.88	1	1	13	296.53
Decyl propanoate	3.82	2	0	11	214.34
Butyl-acetate	2.17	2	0	4	116.16
Methyl-pentanoate	2.17	2	0	4	116.16
5-Methyl-3-heptanone	2.28	1	0	4	128.21
6-Methyl-5-hepten-2-one	2.23	1	0	3	126.60
2-Acetyl-5-methyl furan	1.93	2	0	1	124.14
Acetophenone	1.64	1	0	1	120.15
Fenchone	2.21	1	0	0	152.23
Nopinone	1.98	1	0	0	138.21
Camphor	2.12	1	0	0	152.23
1.4-Cineole	2.68	1	0	1	154.25
Alpha-Acorenol	3.04	1	1	1	222.37
Caryophyllene-oxide	3.15	1	0	0	220.35
2.2-dimethyl-3.4-octadienal	2.55	1	0	4	152.23
Alpha-chenopodiol	2.83	2	2	1	238.37
Benzene Acetal-dehyde	1.33	1	0	2	120.15
Heptanal	2.01	1	0	5	138.21
2E, 4E-Nonadienal	2.32	1	0	5	138.21
O-Cresol	1.55	1	1	0	108.14
Benzaldehyde	1.36	1	0	1	106.12
Otadecanal	4.86	1	1	16	270.49
Trans-Mytranol	2.31	1	1	1	154.25
Thymol	2.32	1	1	1	150.22
Trans-Linalool-oxide	2.45	2	1	2	170.25
Endo-Fenchone	2.42	1	1	0	154.25
Cis-Chrysanthenol	2.33	1	1	0	152.23
Gama-Terpineol	2.40	1	1	0	154.25
Dihydroxy-Cis-Linalool oxide	1.59	4	3	2	202.25
Z-methyl isoeigonol	2.75	2	0	3	178.23

Table 5. The properties of absorption, metabolism, and toxicity obtained for the 39 compounds of the essential oil

Compounds	**Absorption**		**Metabolism**						**Toxicity**	
			Substrate	**Inhibitor**						
	$CaCo^{2-}$	**MDCK**	**P-gp**	**1A2**	**2C19**	**2C9**	**2D6**	**3A4**	**AMES**	**Carcinogens**

	Permeability	**Permeability**								
O-tolu aldehyde	-4.3	$2.7.10^{-5}$	No	Yes	No	No	No	No	No	No
Cis-dihydro-alpha-terpineol	-4.193	2.10^{-5}	No	No	No	No	No	No	No	Yes
Citronellol	-4.25	2.10^{-5}	No	No	No	No	No	No	No	No
Iso-dihydro-Carveol	-4.34	$1.8.\ 10^{-5}$	No	No	No	No	No	No	No	No
Ethyl-decanoate	-4.48	$2.5.\ 10^{-5}$	No	No	No	No	No	No	No	No
Linalool	-4.375	$2.3.\ 10^{-5}$	No	No	No	No	No	No	No	No
Trans pine hydrate	-4.43	$2.\ 10^{-5}$	No	No	No	No	No	No	No	No
Endo-2-Norborneol	-4.43	$4.6.\ 10^{-5}$	No	No	No	No	No	No	No	No
Santolina-Alcohol	-4.328	$2.\ 10^{-5}$	No	No	No	No	No	No	No	No
Isophytol	-4.486	$9.2.\ 10^{-6}$	Yes	No	No	Yes	No	No	No	No
Decyl propanoate	-4.538	$2.2.\ 10^{-5}$	No	Yes	No	No	No	No	No	No
Butyl-Acetate	-4.215	$3.\ 10^{-5}$	No	No	No	No	No	No	No	No
Methyl-pentanoate	-4.264	$3.2.\ 10^{-5}$	No	No	No	No	No	No	No	No
5-Methyl-3-heptanone	-4.326	$2.6.\ 10^{-5}$	No	No	No	No	No	No	No	No
6-Methyl-5-hepten-2-one	-4.439	$2.1.\ 10^{-5}$	No	No	No	No	No	No	No	No
2-Acetyl-5-methyl furan	-4.557	$1.7.\ 10^{-5}$	No	Yes	No	No	No	No	No	No
Acetophenone	-4.246	$2.7.\ 10^{-5}$	No	Yes	No	No	No	No	No	No
Fenchone	-4.618	$2.2.\ 10^{-5}$	No	No	No	No	No	No	No	No
Nopinone	-4.483	$2.5.\ 10^{-5}$	No	No	No	No	No	No	No	No
Camphor	-4.582	$2.2.\ 10^{-5}$	No	No	No	No	No	No	No	No
1.4-Cineole	-4.355	$1.6.\ 10^{-5}$	No	No	No	No	No	No	No	No
Alpha-Acorenol	-4.344	$1.6.\ 10^{-5}$	No	No	No	Yes	No	No	No	No
Caryophyllene oxide	-4.679	$1.8.\ 10^{-5}$	No	No	Yes	Yes	No	No	No	No
2.2-dimethyl-3.4-octadienal	-4.518	$1.6.\ 10^{-5}$	No	No	No	No	No	No	No	Yes
Alpha-Chenopodiol	-4.356	$1.7.\ 10^{-5}$	No	No	No	No	No	No	No	No

Benzene Acetaldehyde	-4.291	$3.3.\ 10^{-5}$	No	Yes	No	No	No	No	No	No
Heptanal	-4.390	$2.3.\ 10^{-5}$	No	No	No	No	No	No	No	No
2E, 4E-Nonadienal	-4.533	$3.\ 10^{-5}$	No	No	No	No	No	No	Yes	Yes
O-Cresol	-4.284	$3.1.\ 10^{-5}$	No	Yes	No	No	No	No	No	Yes
Benzaldehyde	-4.306	$2.2.\ 10^{-5}$	No	Yes	No	No	No	No	No	No
Octadecanal	-4.828	$1.3.\ 10^{-5}$	No	Yes	No	No	No	No	No	No
Trans-Mytranal	-4.404	$2.6.\ 10^{-5}$	No	No	No	No	No	No	No	No
Thymol	-4.387	$2.4.\ 10^{-5}$	No	Yes	No	No	No	No	No	No
Trans-Linalool-oxide	-4.253	$2.7.\ 10^{-5}$	No	No	No	No	No	No	No	No
Endo-Fenchol	-4.538	$2.7.\ 10^{-5}$	No	No	No	No	No	No	No	No
Cis-chrysanthenol	-4.284	$2.3.\ 10^{-5}$	No	No	No	No	No	No	No	No
Gama-Terpineol	-4.431	$1.6.\ 10^{-5}$	No	No	No	No	No	No	No	Yes
Dihydroxy-cis-linalool oxide	-4.501	$9.6.\ 10^{-5}$	No	No	No	No	No	No	Yes	No
Z-methyl isoeugenol	-4.524	$1.7.\ 10^{-5}$	No	Yes	No	No	No	No	No	No

Caco-2 Permeability (Optimal: higher than -5.15 Log unit). MDCKMadin-Darby Canine Kidney Permeability (Low permeability: $<2.10^{-6}$cm/s; medium permeability: 2-20. 10^{-6}cm/s; high passive permeability: > 20. 10^{-6}cm/s).

Conclusion:

The interactions obtained from molecular docking for the 39 compounds derived from the essential oil of fresh Jordanian *Euphorbia herosolymitana*against receptor (IL-1) show a strong inhibitory activity of the essential oil against inflammation. The most important inflammations inhibitor compounds are Dehydroxy-cis-linalool oxid, o-Cresol, and Trans-linalool oxide. Due to molecular docking binding score with the target (IL-1), by two hydrogen interactions. In contrast, Anakinra has single hydrogen interaction concerning IL-1.

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