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In silico study of the xanthine oxidase enzyme inhibition by the essential oil compounds of *Myrtus communis* plant in the treatment of gout disease

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Abstract

The present study demonstrates natural inhibition of xanthine oxidase enzyme (XO) in the treatment of gout disease where the essential oil compounds of *Myrtus communis* plant were used. To understand the interaction and effect of this compounds with xanthine oxidase enzyme; two computational chemistry theoretical methods were used; the molecular docking, and molecular dynamics simulations. The natural compounds with percentage higher than 0.1% containing *M. communis* plant were investigated such as α-pinene, isobutyl isobutyrate, myrtenol, myrtenyl acetate, eucalyptol, neryl acetate, and a-therpineole. Results reveal that the stability of natural compounds-XO complexes increased the complementarity between the ligands and the enzyme. The compounds containing plant with medium percentage demonstrated the best score and high activity and strong interaction of 2.5 Å, such as the neryl acetate and a-therpineole with energy of − 6.1085 kcal/mol and − 5.1994 kcal/mol. Also, the neryl acetate ligand can inhibit XO and interfere with Gly 231 and Lys 232. In addition, the interaction of the bulky groups generates a conformational rearrangement within the active site pocket, which is likely to increase complementarity and, consequently, the activity.

Keywords Xanthine oxidase (XO) · *Myrtus communis* · Gout disease · Molecular docking

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Introduction

Gout is a condition characterized by the accumulation of urate crystals in the joints, leading to episodes of gouty arthritis. Its prevalence appears to be increasing according to epidemiological studies. Hyperuricaemia, which corresponds to an excess of uric acid in the blood, is a major risk factor for the development of gout [1]. Xanthine oxidase (XO) plays a crucial role in urate biosynthesis by catalyzing the final stages of purine degradation [2]. It is a key enzyme which converts hypoxanthine and xanthine into uric acid, their overproduction leads to gout. The XO activity inhibition is an important therapeutic strategy for reducing uric acid production and treating gout [3]. Until now, there is a clinical need for the development of new chemical compounds for xanthine oxidase (XO) inhibition, and offering new treatments for gout [4].

However, research in this area remains active, as the exploration and discovering of new molecular skeletons. Several synthetic compounds have been used for xanthine oxidase inhibition such as chalcones [5], xanthone [6], rutin [7], triazole [8], and other heterocycle compounds [9]. Also, various inhibitors were developed such as allopurinol, and febuxostat. Unluckily, these drugs have side effects like skin rashes, hepatitis, and fever [10]. On the other hand, the use of ancient source as medicinal plant stays very efficiency where several groups research new xanthine oxidase (XO) inhibitors from natural source. Different natural compounds exhibits high activity such as flavonoids [11], flavonols [12], hydroxycinnamic acids [13], tannins [14], stilbenes [15].

To discover new drugs, in silico and computer-aided drug design methods have attracted scientific because it considered faster, cheaper and more effective solutions [16]. For example, virtual screening, is a high-through put method that allows large databases of compounds which can be identified with potential activity against XO. In addition, molecular dynamics (MD) simulations of protein–ligand complexes are used to analyse the stability and thermodynamic properties of these interactions [17, 18]. These simulations provide valuable information about the protein's response to ligand binding at the atomic level [19]. By combining these approaches with chemical synthesis techniques [20] and biological assays, it is possible to identify new drug candidates derived from natural products, thus offering new therapeutic options for patients.

Because of the various bioactive compounds containing the *Myrtus communis* plant, it has been used in traditional medicine in the treatment of bleeding, headache, conjunctivitis, pulmonary and skin diseases [21]. Several researches reported in vivo and in vitro strong activity of their extract [22]. Essential oil of *M. communis* plant containing α pinene, ocymene, cineole, 4-carene, linalool, terpineol and geranyl acetate, show a potential antioxidant, antimutagenic [23], antimicrobial [24], antifungal [25], antibiofilm, cytotoxic, and anti-acetylcholinesterase activity [26]. These compounds were used also in human neutrophils ROS inhibition [27], amylase inhibitor [28].

For the xanthine oxidase (XO) inhibition, the *M. communis* plant was not reported. So, for the study of their activity in the XO inhibition, theatrical

approach is necessary to known the essential oil compound presented high interaction and ability. In our study, we used molecular modeling and molecular dynamics (MD) simulations to identify potential natural products targeting the xanthine oxidase enzyme (XO); and its inhibition by the major compounds of the *M. communis*'*s* essential oil for the gout disease treatment.

Materials and methods

The ligands and enzyme were constructed using Molecular Operating Environment (software MOE).

Enzyme construction and geometry optimization

The xanthine oxidase enzyme was downloaded from the Book Haven Protein Data Bank [29] (access code 3EUB) [30]. The three-dimensional structure of the enzyme was obtained by X-ray diffraction with a resolution (2.60 Å) and R-Value Free 0.268 (Fig. S1). In general, protein structures with a resolution between 1.5 and 2.9 Å are excellent quality for studying the enzyme [31, 32].

Through the use of molecular modeling, we have simplified the enzyme leaving only a single enzyme chain and a reference ligand, without extra protein chains, water molecules and co-crystallization molecules. This modification help us to give more detail in the case of interactions and the superposition between the enzyme and ligands.

In the case of enzymes, the active site is crucial because it is the place where enzyme catalyzed the chemical reactions. The enzyme is made up of several active sites composing amino acids which play an essential role by providing key residues to interact with the substrates. Once the enzyme had been prepared, we carried out a molecular mechanics calculation to find the most stable conformation (Fig. S2) [33].

Identification of the oil components

The common myrtle, is a typical Mediterranean shrub that is deeply rooted in the culture and beliefs of the people who live along the Mediterranean coast. In addition to these beliefs, it has long been credited with medicinal properties [34]. The composition of essential oil was extracted using steam distillation which dominated by a high fraction of oxygenated monoterpenes, representing 80.9% of its composition. Major components were myrtenyl acetate (38.7%), eucalyptol (12.7%), α-pinene (13.7%), and linalool (7.00%, Table 1) [35].

Construction and ligands optimization

A study of the chemical composition of *M. communis* essential oils identified 27 compounds. We reduced the number to 10 compounds which have the percentage greater than one. Oral administration is the most practical route. Lipinski's rule is a

Table 1 Profile of common myrtle essential oil extracted by steam distillation

	Compounds	Percentage
1	Isobutyl isobutyrate	3.00
2	α-Thujene	0.30
3	α-Pinene	13.70
4	B-pinene	0.10
5	δ-3-Carene	0.10
6	Myrcene	0.30
7	δ-Terpinene	0.10
8	Sabinene	0.50
9	Limonene	Trace
10	E-ocimene	0.10
11	A-terpinolene	0.20
12	Eucalyptol	12.7
13	Linalool	7.00
14	*Trans*-pinocarveol	0.20
15	Terpinen-4-ol	0.20
16	A-terpineol	1.80
17	Myrtenol	3.50
18	Linalyl acetate	2.50
19	Trans-pinocarveyl acetate	0.70
20	Myrtenyl acetate	38.7
21	P-menth-1-en-8-ol acetate	0.39
22	Neryl acetate	2.00
23	Geranyl acetate	0.40
24	*Trans*-cryophyllene	0.20
25	A-humulene	0.31
26	Caryophyllene oxide	0.50
27	Humulene epoxide	1.30

rule of thumb used by some researchers as a guide when designing a drug, as well as their toxicity studies. This study enabled us to reduce the number of compounds to nine (Table S1).

Molecular docking

The interaction between a protein and its substrate is a complex process that relies on several aspects, including the affinity between the two molecules, the distances between the amino acids of the enzyme's active site and those of the inhibitors, as well as the interaction energy, these aspects affect the enzymes function [14]. The affinity between a protein and its substrate refers to the binding strength between two molecules. This affinity is often determined by non-covalent interactions such as hydrogen bonds, electrostatic interactions, van der Waals, and hydrophobic interactions [36]. The active site of an enzyme is the region where the substrate binds and

the chemical reactions take place. The amino acids of the active site interact specifically with the substrate, forming an enzyme–substrate complex. When an inhibitor binds with active site, it can block access to the substrate or disrupt the interactions necessary for catalysis [37]. The interaction energy between a protein and its substrate or an inhibitor is a measure of the energy required to form and maintain the enzyme–substrate complex and it is determined by the intermolecular forces mentioned above. Low interaction energy may indicate low affinity between the molecules and interpreted by less efficient catalysis and less specific inhibition [38].

Molecular dynamics

Knowledge at an atomic level of the structural and dynamic aspects of organized systems is particularly important for understanding complex molecular functions. In general, the steepest descent algorithm is used at the beginning, for 100 to 200 steps. Then the conjugate gradient algorithm can be used to complete the minimization until convergence. Convergence in the Steepest Descent algorithm is slow, but this method is extremely robust. This algorithm is mainly used when conformations are far from their energy minimum [39].

The molecular dynamics of the complexes was carried out using Hyperchem7.5 professional version software [40]. We began the dynamics by initializing the system at $t=0$, $r(t)=0$, and the initial structure, previously minimized. We then heated the system to 300 K for 1000 steps with an integration step of 1 fs. The velocities are readjusted to keep the temperature constant because the exchange between kinetic energy and potential energy [41]. The simulation time for molecular dynamics was 35 ps and 100 ps.

Results and discussion

We used molecular docking to predict how the ligand binds to the active site of the XO enzyme, by searching for the most stable binding conformations. This method enabled us to select the complex (ligand–receptor) showing the best interaction with the lowest energy, which could provide important information for drug design or understanding the underlying molecular mechanisms. The results of this study are presented in Table 2.

The docking process generally involves the following several steps such as structure preparation, search for conformations, interaction assessment between the ligand and the protein, analysis and selection of poses, and experimental validation [42, 43].

A 2D molecular screen method was assigned to MOE software, which is designed to visualize the active sites of protein–ligand complex [45]. The ligand is arranged and rendered using an improved version of the 2D representation arrangement algorithm, and protein residues are arranged around it to indicate spatial proximity links [46]. The interactions between 2.5 and 3.1 Å were considered strong, those between

Table 2 Energy balance of the best complexes formed

Ligands	Band energy (kcal/mol)	Rmsd-refine	Enerie-conf	E-place	E-refine
α-Pinene	− 4.6538	0.6020	42.6422	− 44.3352	− 3.2604
a-Therpineole	− 5.1994	0.5630	22.0125	− 47.4399	− 10.9302
Eucaliptol	− 4.7286	1.1878	46.0102	− 44.4291	− 8.4209
Isobutyl isobutyrate	− 4.2522	1.5525	− 2.9641	− 53.4330	− 13.0702
Linalool	− 4.2462	1.0354	17.0308	− 44.9977	− 4.6837
Linalyl acetate	− 4.0196	1.2930	33.7125	− 55.4214	0.9043
Myrtenol	− 3.8517	1.7441	29.3311	− 44.2351	− 0.1263
Mytenyl acetate	− 4.8746	1.1059	28.2423	− 45.4765	− 13.2145
Neryl acetate	− 6.1085	1.0237	18.4276	− 61.4137	− 12.0745

S the final score; the score of the last step, *rmsd-refine* the root mean square deviation between the pose before refinement and the pose after refinement, *Enerie_conf* the energy of the conformer, *E-place* the score of the placement phase, *E-refine* the score of the refinement step and the number of conformations generated per ligand [44]

3.1 and 3.55 Å were assumed to be medium and those above 3.55 Å were considered weak [47].

Table 2 demonstrates the energy of each compound complex. The result shows that the neryl acetate + XO complex has the best score with energy of − 6.1085 kcal/mol and it is the most active. Also, the a-therpineole + XO complex is characterized by the energy of − 5.1994 kcal/mol. The mytenyl acetate + XO, myrtenol + XO, eucaliptol + XO, α-pinene + XO, isobutyl isobutyrate + XO, linalool + XO, linalyl acetate + XO complexes present energies of − 4.8746 kcal/mol, − 4.8517 kcal/mol, − 4.7286 kcal/mol, − 4.6538 kcal/mol, − 4.2522 kcal/mol, − 4.2462 kcal/mol, − 4.0196 kcal/mol. The highest energy − 3.8517 kcal/mol was obtained with myrtenol + OX complex.

It should be noted that all the inhibitors from both parties interact with the xanthine oxidase (XO) enzyme. These results show that the orientation of the ligands plays a very important role in the positioning of the ligands in the active site of the enzyme, and it can be concluded that the introduction of bulky groups causes a conformational rearrangement within the active site pocket, which is likely affect complementarities and therefore activity [48, 49].

Figs. 1 and 2 illustrate the interaction energy of α-pinene + XO complex and a-therpineole + XO complex. The α-pinene + XO complex (Fig. 1), with interaction energy of − 4.6538 kcal/mol, does not exhibit any type of binding. In the case of a-therpineole + XO complex, the hydrogen bond-type interaction presented with residue Tyr 381, a distance of 3.18 Å, and an energy of − 0.6 kcal/mol, suggesting that the a-therpineole ligand can inhibit XO and interfere with residue Tyr 381 (Fig. 2). In addition, the eucaliptol + XO complex (Fig. S3) has a hydrogen bond-type interaction; H-acceptor with residue Arg 147, with a distance of 2.98 Å and energy of − 1.8 kcal/mol. This confirms that the ligand eucalyptol can inhibit XO and interfere with residue Arg 147. The isobutyl isobutyrate + XO complex (Fig. S4) has a hydrogen bond-type interaction with Arg 167, with a distance of

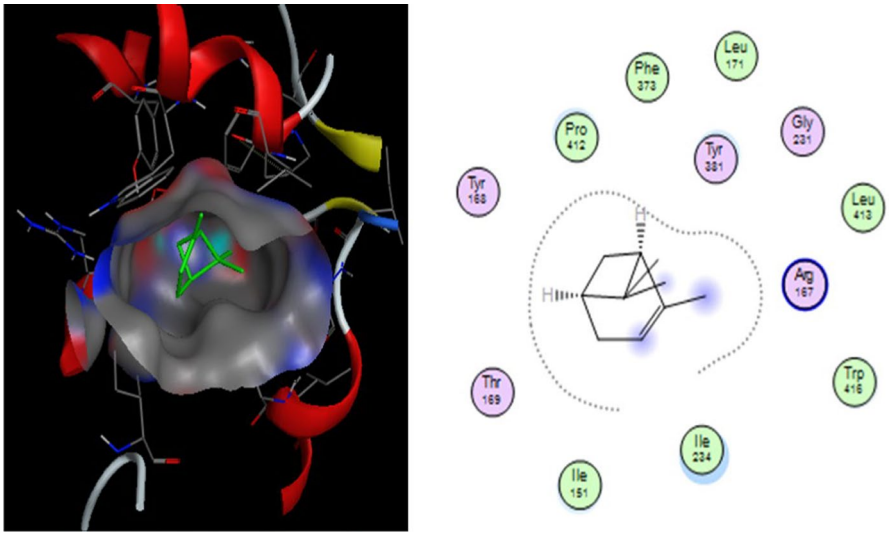

Fig. 1 Interaction diagram of α-pinene + XO complex

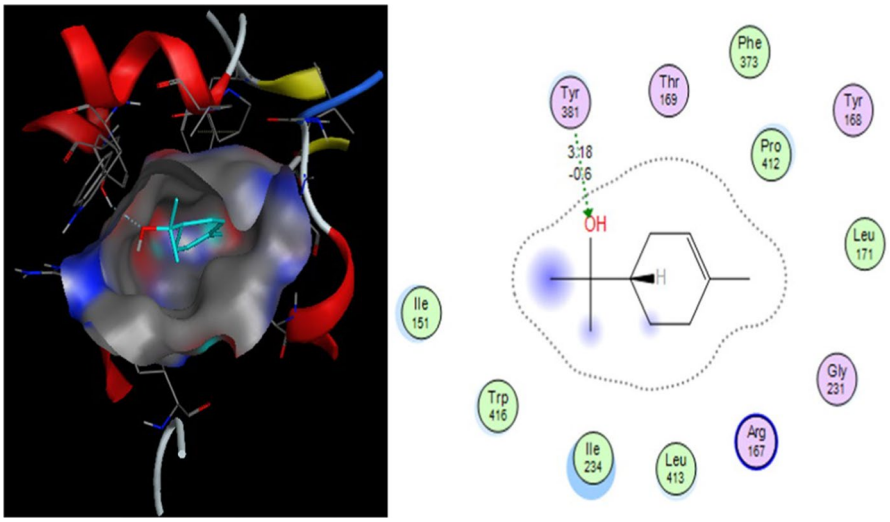

Fig. 2 Interaction diagram of a-therpineole + XO complex

3.32 Å and an energy of − 1.1 kcal/mol. It presents also two other interactions with the carbon of the isobutyl isobutyrate ligand and the Trp 416 residue (H–Pi bond type) with distances of 3.94 and 4.58, and energy of − 0.7 kcal/mol. This result shows that the isobutyl isobutyrate ligand can inhibit XO and interfere with residues Arg 167 and Trp 416.

Fig. S5 presents the interaction of linalool which has a hydrogen bond (H-donor) strong interaction with Tyr 258, a distance of 3.07 Å, and energy of − 1.1 kcal/mol. Also, linalyl acetate has hydrogen bond interactions with Arg 167 and Tyr 381 (Fig. S6), with distances of 3.15–2.81 Å and energies of − 2.7 and − 1.9 kcal/mol, and another interaction bond with the ligand carbon Trp 416 residue with a distance of 4.49 Å and energy of − 0.7 kcal/mol. This demonstrates that the linalyl acetate ligand can inhibit XO and interfere with the Arg 167, Tyr 381 and Trp 416 residues.

Myrtenol (Fig. S7) exhibits two hydrogen bond-type interactions; the H-acceptor, and H-donor with residues Glu 511 and His 260. The distances were 3.05 and 2.94 Å with energies of − 1.1 and − 2.7 kcal/mol, suggesting that the myrtenol ligand can inhibit XO and interfere with residues Glu 511 and His 260.

The mytenyl acetate (Fig. S8) exhibits a strong hydrogen bond interaction with Arg 270, a distance of 2.97 Å, and energy of − 2.9 kcal/mol. However, neryl acetate (Fig. S9) displays hydrogen bond interactions with Gly 231 and Lys 232, with distances of 3.48 Å and 2.98 Å, and energies of − 0.9 and − 9.4 kcal/mol. This indicates that the neryl acetate ligand can inhibit XO and interfere with Gly 231 and Lys 232 [50].

Once all the complexes were formed, we performed a geometry optimization and a time-dependent molecular dynamics calculation to search for the most stable conformation [51]. The variation of energy for the first 35 ps of higher compounds content such as myrtenyl acetate, eucaliptol, and α-pinene was illustrated in Fig. 3. The compounds presented a stable energy in the range of 900–1400 kcal/mol, and

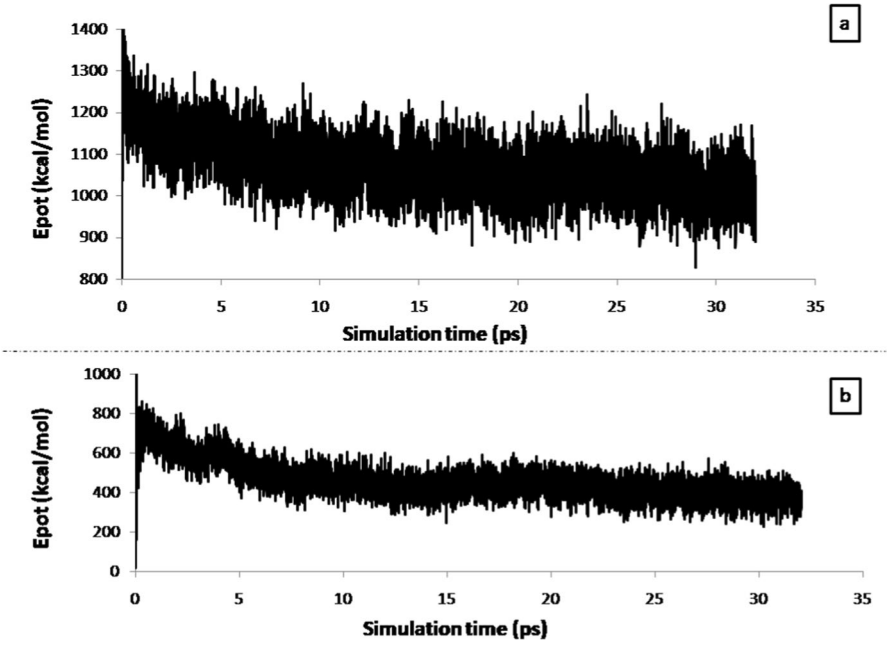

Fig. 3 Variation in the potential energy of the myrtenyl acetate + XO complex (**a**), and eucaliptol + XO complex (**b**)

200–800 kcal/mol. Also, the total energy was well-conserved even though uses of the same time step.

Also, the same variation of energy was presented for other compounds for the first 100 ps (Fig. S10). The results reveal that compounds have the same stability and maintain the same types of interactions with the residues of the active site of the target (Fig. 4).

Conclusion

We studied the approach of xanthine oxidase (XO) with the majority compounds of the essential oil of the plant *M. communis*; in a theoretical way by two methods of computational chemistry: molecular docking, molecular dynamics simulations. The study is based on the calculation of interaction energies and bond distances to explain the binding of the inhibitor to the enzyme's active site. The results show that the interaction of the bulky groups generates a conformational rearrangement within the active site pocket, which is likely to increase complementarities and consequently activity. In addition, the score functions revealed that all the ligands studied have an affinity for the enzyme with lower interaction energies and therefore complementarity. We measured the distances between the R groups of each inhibitor and those of the side chains of the amino acids making up the active site, and these distances showed strong, medium and weak bonds.

In summary, the integration of in silico methods such as virtual screening and molecular dynamics simulations represents a powerful and efficient approach to new drug discovery, particularly for the development of therapies targeting xanthine

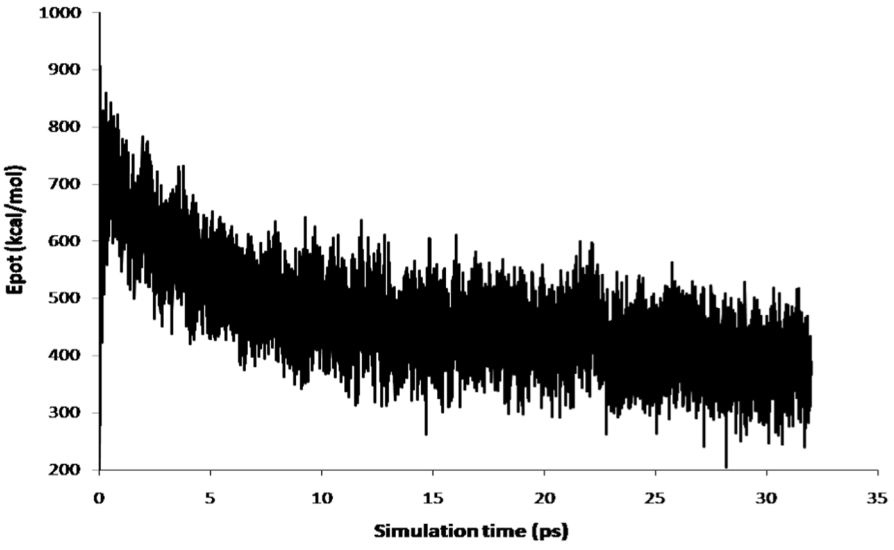

Fig. 4 Variation in the potential energy of the a-therpineole + XO complex

oxidase in the treatment of gout. The present theoretical and experimental studies indicate that the *M. communis* plant has great potential as a remedy for gout disease.

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Data availability The data is available for this publication.

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