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In silico evaluation of the impact of biomolecules on the resistance of *Calliptamus barbarus*

Avaliação in silico do impacto das biomoléculas na resistência do *Calliptamus barbarus*

Evaluación in silico del impacto de biomoléculas en la resistencia de *Calliptamus barbarous*

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ABSTRACT
In this work, we focus on *Calliptamus barbarus*, which is less known for its massive invasions compared to species like the locust *Locusta migratoria*, but is capable of forming smaller groups and causing significant damage to crops, particularly in regions already weakened by extreme climatic conditions. Cereals, vegetables, and other agricultural plants are especially vulnerable.
In this context, while pesticides play a crucial role in crop protection, their excessive and uncontrolled use poses a major threat to human health, the environment, and biodiversity. It is therefore imperative to implement more responsible management and to seek alternatives to limit these risks.
Based on a biological control approach using extracts of Ephedra major, an evolved gymnosperm found in western Algeria, we explored the inhibition of Esterase 1ESD, a key insect enzyme, by ephedra compounds. The major compounds proved to be particularly effective as inhibitors. The bio-insecticidal effect of this plant thus offers a natural and sustainable alternative to chemical pesticides.

Keywords: *in silico*, *Calliptamus barbarus*, biomolecules, *Ephedra*

RESUMO
Neste trabalho, nos concentramos no *Calliptamus barbarus*, que é menos conhecido por suas invasões maciças em comparação com espécies como o gafanhoto *Locusta migratoria*, mas é capaz de formar grupos menores e causar danos significativos às plantações, principalmente em regiões já debilitadas por condições climáticas extremas. Cereais, vegetais e outras plantas agrícolas são especialmente vulneráveis.
Nesse contexto, embora os pesticidas desempenhem um papel fundamental na proteção das culturas, seu uso excessivo e descontrolado representa uma grande ameaça à saúde humana, ao meio ambiente e à biodiversidade. Portanto, é imperativo implementar um gerenciamento mais responsável e buscar alternativas para limitar esses riscos.
Com base em uma abordagem de controle biológico que usa extratos de Ephedra major, uma gimnosperma evoluída encontrada no oeste da Argélia, exploramos a inibição da Esterase 1ESD, uma enzima importante de insetos, por compostos de efedra. Os compostos principais se mostraram particularmente eficazes como inibidores. O efeito bioinseticida dessa planta oferece, portanto, uma alternativa natural e sustentável aos pesticidas químicos.

Palavras-chave: *in silico*, *Calliptamus barbarus*, biomoléculas, Ephedra in silico, Calliptamus barbarus, biomoléculas, *Ephedra*

RESUMEN

En este trabajo nos centramos en *Calliptamus barbarus*, menos conocida por sus invasiones masivas en comparación con especies como la langosta *Locusta migratoria*, pero capaz de formar grupos más pequeños y causar daños importantes en los cultivos, sobre todo en regiones ya debilitadas por condiciones climáticas extremas. Los cereales, las hortalizas y otras plantas agrícolas son especialmente vulnerables.

En este contexto, aunque los plaguicidas desempeñan un papel crucial en la protección de los cultivos, su uso excesivo e incontrolado supone una grave amenaza para la salud humana, el medio ambiente y la biodiversidad. Por eso es imperativo aplicar una gestión más responsable y buscar alternativas para limitar estos riesgos.

Basándonos en un enfoque de control biológico mediante extractos de Ephedra major, una gimnosperma evolucionada que se encuentra en el oeste de Argelia, exploramos la inhibición de la Esterasa 1ESD, una enzima clave de los insectos, por compuestos de efedra. Los compuestos mayores demostraron ser particularmente eficaces como inhibidores. El efecto bioinsecticida de esta planta ofrece así una alternativa natural y sostenible a los pesticidas químicos.

Palabras clave: *in silico*, *Calliptamus barbarus*, biomoléculas, *Efedra*

1 INTRODUCTION

Locust invasions are a major problem for agriculture, particularly in North Africa, where they cause considerable crop losses and threaten food security. In Algeria, a particularly vulnerable country due to its geographical location, arid climate and vast territory, locust invasions represent a constant threat. These insects, whether sedentary or migratory, invade fields, orchards and pastures, devastating crops and the food resources of local communities. The most destructive species, such as *Schistocerca gregaria*, *Locusta migratoria*, *Ocneridia volxemii* and *Dociostaurus maroccanus*, cause significant damage in various parts of the country, disrupting the agricultural economy and threatening the livelihoods of rural populations (Bounechada, 2007). Managing these invasions requires a thorough understanding of the biology, ecology and migratory behavior of these insects, in order to better target the most vulnerable stages and adopt effective control strategies (Ould EL Hadj, 1991).

In this context of agricultural pest control, the medicinal and bioactive properties of certain plants, such as *Ephedra*, are of great interest. Used in traditional medicine, *Ephedra* is recognized for its therapeutic virtues, notably in the treatment of various diseases (Hegazi & El-Lamey, 2011). In addition to its medicinal applications, *Ephedra* is a common range plant in Saudi Arabia, used as pasture for many animals due to its pleasant aroma (AL-Qarawi *et al*., 2012). These properties make this plant a subject of interest for research, particularly in the field of sustainable agriculture and pest control.

This study aims to analyze, through an in-silico approach, the inhibition of the 1ESD esterase protein by ligands derived from *Ephedra*. By establishing a structure-activity relationship between

the active compounds of this plant, the goal is to identify potential inhibitors capable of blocking the activity of the 1ESD esterase, an enzyme essential to insect metabolism. This innovative approach could lead to the development of new ecological and sustainable strategies to combat crop pests, thereby contributing to crop protection and reducing economic losses caused by locust invasions.

2 MATERIALS AND METHODS

Presentation of *Calliptamus barbarus* (Linnaeus, 1758)

Calliptamus barbarus is an insect species belonging to the family Acrididae, specifically to the subfamily Calliptaminae. It is a grasshopper species primarily found in arid and semi-arid regions, particularly in Mediterranean countries and North Africa, including Algeria, Morocco, and Tunisia. This species is of significant ecological and economic importance due to its role as an agricultural pest, capable of damaging crop production through its massive consumption of vegetation. (Lind, & Dennis, M (2004). Sengo, & Madon, (2008).Dempster, & Ploger, (2012).Tarak, & Ben Hamouda, (2017).

Morphological Characteristics

Calliptamus barbarus exhibits several distinct morphological features:

- Size: Adults typically measure between 30 and 45 mm in length, depending on environmental conditions and food availability.
- Coloration: Its body is usually brown-yellow, with darker markings that help it adapt better to its environment. Juveniles have a lighter coloration that darkens as they mature.
- Wings: The wings are well-developed, allowing the insect to move quickly, especially during migratory movements or swarming phases.

Fig.1: Photo taken by BOUKLI HACEN Ahmed Sofiane.



Ligand Selection and Protein Preparation

The ligands used in this study were selected based on their optimal yield, i.e., their maximum performance for the research objective.

Fig.2 : 2D structure of Ephedrine

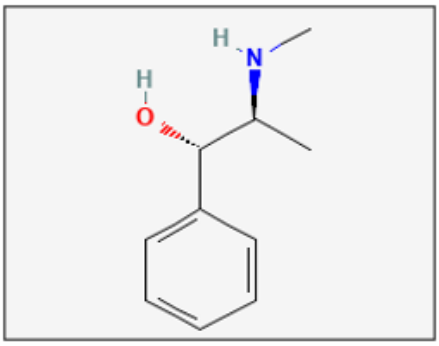


Fig. 3: 2D Structure of Pseudoephedrine

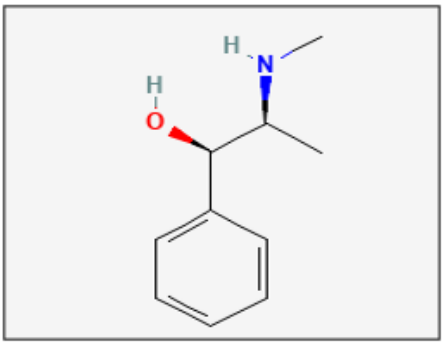


Fig.4: The Esterase enzyme 3-dimensional (3D) structure. The structure was taken from Protein Data Bank online server (https://www.rcsb.org/) and Molecular Operating Environment (MOE).

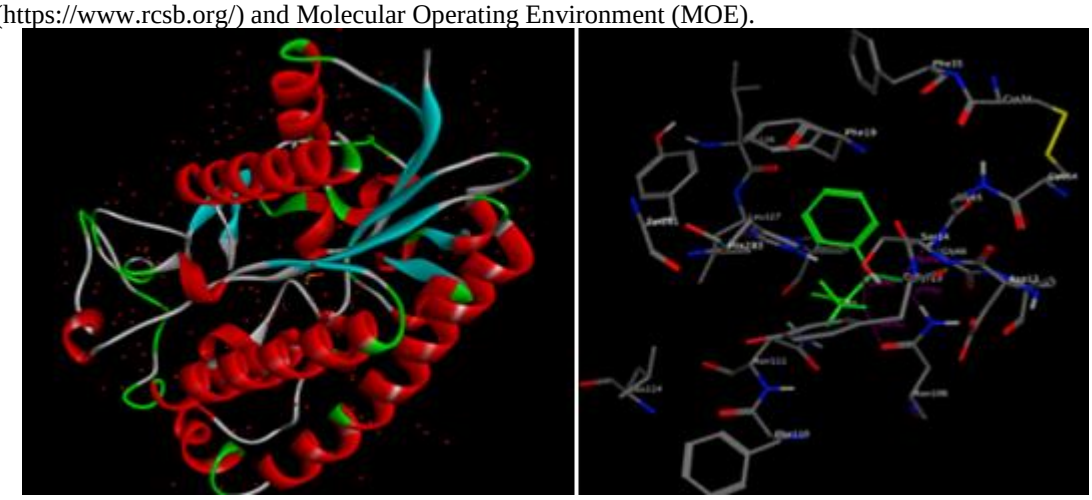


Table 1 : Some properties of molecules that have been tested.

Ligands	Molecular TPSA (Å2)	weight (g/mol)
Ephedrine	32.3 (2: don, 2: acc)	165.23 g/mol
Pseudoephedrine	32.3 (2: don, 2: acc)	165.23 g/mol

The chemical structures of these ligands were obtained using the "PubChem" database (see Fig. 1 and 2). We then drew the ligands using ChemDraw software, version 12.0.2.1076, and saved them in ".mol" format. Subsequently, the ligands were optimized with HyperChem software, version 8.0.10, and saved again in ".mol" format for molecular docking using the Molecular Operating Environment software (MOE). In this study, enzyme preparation involved downloading the enzyme with code 1ESD from the Protein Data Bank (PDB) or RCSB, with a resolution of 2,30 Å (Table 2).

Molecular docking protocol

The molecular docking protocol we adopted is based on molecular modeling and consists of two main steps. The first step, docking, involves positioning the ligand within the active site of the protein, exploring possible positions, conformations, and orientations (poses) to achieve the most stable complex . The second step, scoring, evaluates the protein-ligand complex by assessing the affinity between the ligand and the protein, assigning a score to each binding pose generated during the docking phase. This score allows us to select the best pose from among all those proposed (Nadhir *et al.,* 2010).

Table 2 : Some properties.of enzyme esterase

Protein	Classification	Method	Resolution	Chain Number	Chain lenght	Co-cristallisation ligand
1ESD	Hydrolase (serine Esterase)	X-ray Diffraction	2.30 Å	One (a)	306	Methylphosphonic acid ester group C h4 o2 p

3 RESULTS AND DISCUSSION

Molecular docking

Following the preparation of the enzyme and ligands, the next step is to position these inhibitors within the active site of the 1ESD enzyme. This is achieved using the docking module in the "MOE" software. Once the ligand-receptor complex is established, it adopts the most stable conformation, which corresponds to the lowest energy state. Upon complex formation, we analyze the resulting data. To evaluate the stability of each ligand within the 1ESD enzyme's active site, molecular docking was performed, and the results for each ligand are ranked and summarized in Table 3.

Table 3 : The docking results (binding energy) of ligands and the controls along their respective number of hydrogen bonds as well as interacting amino acids.

		Score kcal/mol	Interaction with residues
Plant Ligands	Ephedrine	-10.7822	Gly 66 (H-donor) Asn 106 (H-donor) Ser 14 (H-acceptor)
	Pseudoephedrine	-10.4140	Asn 106 (H-donor) Ser 14 (H-donor) His 283(H-donor)
Insecticides	Fipronil	-11.6799	//
	Phenylpyrazole	-8.5039	His 283 (H-donor)

Docking scores reveal significant differences in the affinity of molecules for the esterase enzyme. Among the insecticides, Fipronil exhibits the lowest score (-11.699 kcal/mol), indicating a very high affinity, while Phenylpyrazole shows a weaker affinity with a score of -8.5039 kcal/mol.

The natural ligands, ephedrine (-10.8322 kcal/mol) and pseudoephedrine (-10.4140 kcal/mol), fall between these two extremes, displaying competitive but slightly lower affinity compared to Fipronil. These results suggest that insecticides, particularly Fipronil, interact more strongly with the enzyme than plant-derived molecules, while Phenylpyrazole remains the least effective in terms of affinity.

Fig 5: 3D representations of the complex (ligands- receptor). A : complex Ephedrine and 1ESD, B : Pseudoephedrine and 1ESD.

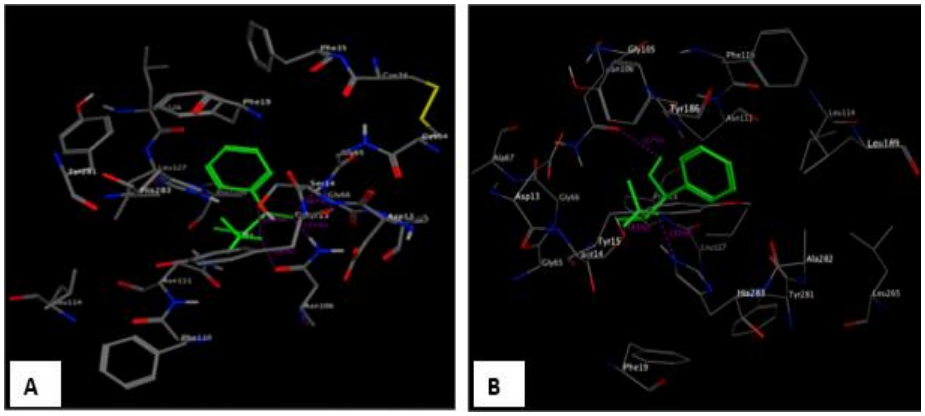


Fig 6: 3D representations of the complex (ligands- receptor). C : complex Phenylpyrazole and 1ESD, D : Fipronil and 1ESD.

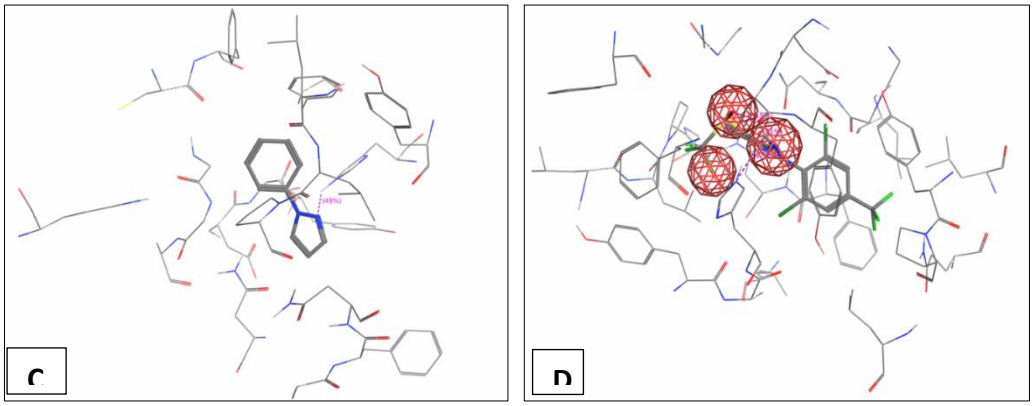


Fig 7: 3D 3D representations of the interactions between the plant ligands and their receptor.. A : complex Ephedrine and 1ESD, B : Pseudoephedrine and 1ESD.

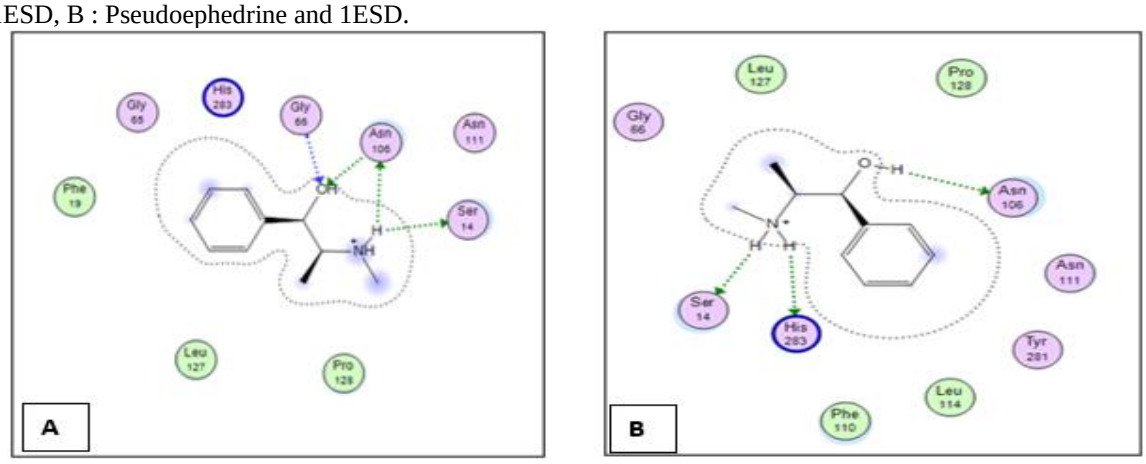
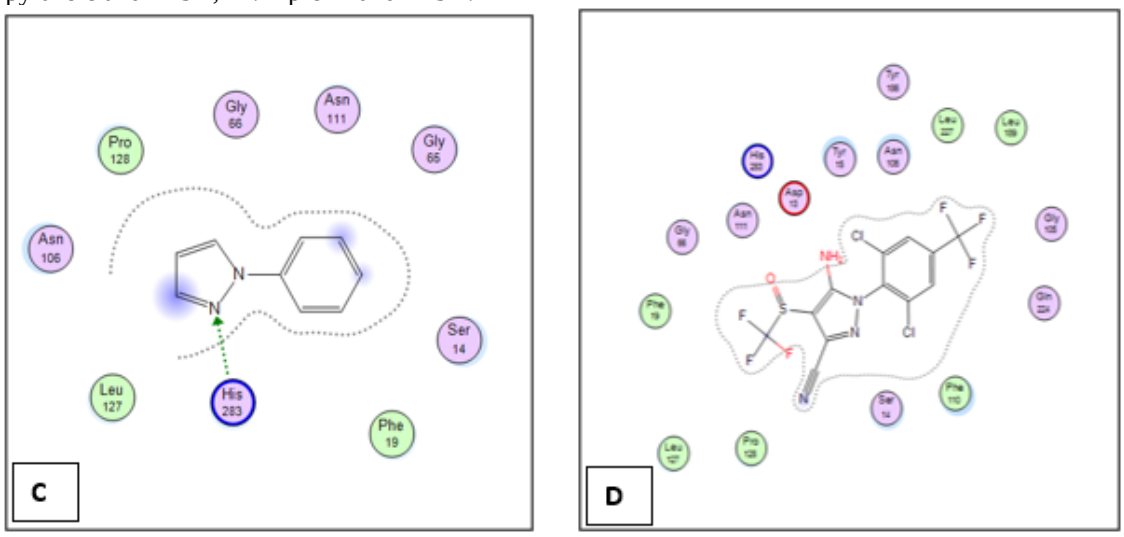


Fig 8: 3D 3D representations of the interactions between the insecticides ligands and their receptor.. C : complex Phenylpyrazole and 1ESD, D : Fipronil and 1ESD.



The results show that natural ligands (ephedrine and pseudoephedrine) primarily interact with the esterase enzyme through hydrogen bonds involving residues such as Ser 14, Asn 106, and Gly 66, which stabilize their binding and confer moderate affinity (scores around -10 kcal/mol). In contrast, insecticides exhibit varied behaviors: Fipronil, with the lowest score (-11.699 kcal/mol), displays strong affinity likely due to hydrogen interactions, while Phenylpyrazole, with a single hydrogen bond (His 283), shows weaker affinity (score of -8.5039 kcal/mol). Overall, natural ligands provide specific and moderate interactions, whereas insecticides demonstrate stronger but less selective binding.

Plant-derived ligands establish multiple hydrogen interactions with the enzyme, resulting in moderate and specific affinity. Insecticides, particularly Fipronil, achieve higher overall affinity due to hydrophobic interactions or other types of bonds, though with less specificity for particular residues.

4 CONCLUSION

This study highlights the comparison between the effectiveness of natural compounds derived from *Ephedra major* and that of chemical insecticides in inhibiting the esterase enzyme (1ESD). On one hand, natural compounds, such as ephedrine, stand out for their specificity and stabilizing interactions with the enzyme, offering a promising alternative due to their competitive efficiency and reduced environmental impact. On the other hand, chemical insecticides, like Fipronil, show higher but less selective affinity, often at the cost of increased toxicity to ecosystems. The study thus emphasizes the potential of natural bioinsecticides as a sustainable solution to the

challenges posed by conventional insecticides, combining effectiveness with environmental preservation.

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