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INVESTIGATION OF HUMULEN'S BIOLOGICAL ACTIVITY VIA VIRTUAL SCREENING METHODS

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Abstract:

This article analyzes humulene, a bioactive natural compound present in essential oils, by using virtual screening. The study utilizes virtual screening to explore possible therapeutic applications of humulene in an inexpensive and time-saving manner. This research will investigate the interaction between humulene and target biomolecules, including enzymes or receptors, in its efforts to find the molecular mechanisms responsible for its pharmacological properties. These findings constitute the basis for understanding humulene's anti-inflammatory, antimicrobial, and anticancer properties and, therefore, its therapeutic potential. The data obtained in this work will provide fundamental information for the development of new therapies for various diseases or conditions.

Keywords: Humulene, A Bioactive Natural Compound

INTRODUCTION

In a world where disease prevalence is continually increasing and pathogenic resistance to pharmaceutical drugs is constantly developing, there is a continuous need for the discovery of new molecules and therapeutic agents [1]. In this respect, the molecule humulene represents a molecule of great interest, as it is part of some essential oils. Its interest for researchers has been related, so far, to its possible pharmacological properties, such as anti-inflammatory, antimicrobial, and anticancer activities [2]. However, despite numerous studies, there is still insufficient information about the pharmacokinetic and pharmacodynamic characteristics of humulene [3].

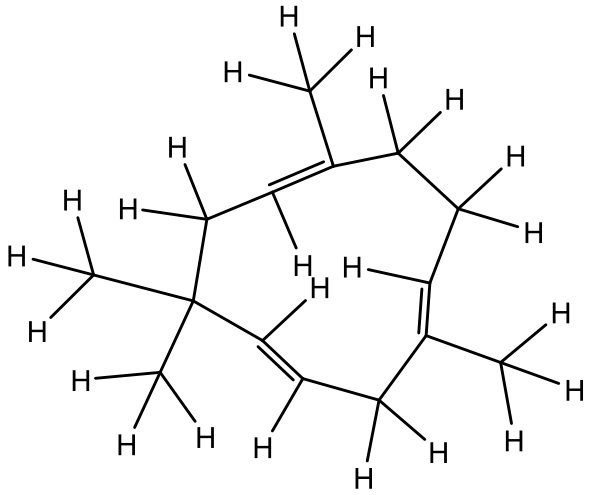

Figure-1. Humulene structure

The significance of the research is based on its attempt to close this gap in knowledge while providing, at the same time, a better understanding of the potential therapeutic applications of humulene [4]. The developed results might set the base for further development of new pharmaceuticals derived from humulene and advance our knowledge of the mechanisms that control its action inside the body [5,6].

2.2 PASS analysis

The optimized molecular structure of humulene, calculated using the DFT methodology, was used as input to the web PASS website https://way2drug.com/PassOnline, in order to predict a wide spectrum of biological activity, using the predicted activity index Pa [7]. A metabolite is considered to be an active compound when Pa > 0.7, it is considered a moderately active compound when 0.5 < Pa < 0.7, or is an inactive compound when Pa < 0.5.

2.3 Swiss ADME

In order to assess the pharmacokinetic characteristics of humulene and its derivatives (absorption, distribution, metabolism, and excretion - ADME), the SwissADME tool created by the Swiss Institute of Bioinformatics (www.swissadme.ch) was used. The SMILES strings of each compound were entered into the tool. SwissADME calculated crucial parameters related to lipophilicity, hydrophilicity, solubility, and permeability, hence providing useful information on compounds' bioavailability and their potential interaction with cellular targets [8].

2.4. Molecular Docking

Docking simulations were performed utilizing AutoDock Tools software [9] to assess the potential interactions between humulene and its derivatives with two specific target proteins: PUE (associated with intestinal inflammation) (PDB ID: 7EXZ) and Glutathione peroxidase (PDB ID: 8JZK). For each target, the regions of interaction within the active site were delineated in the AutoGrid section, with grid box dimensions and coordinates optimized to encompass the receptor's active site and enhance the precision of the docking simulations [10].

For the PUE protein (PDB ID: 7EXZ), the size of the grid box was set at 92 × 82 × 102 Å³, and the central coordinates were located at X = 7.11, Y = -24.974, Z = -41.091. The grid parameter files (GPFs) were carefully set up to define the search volume inside the active site of the receptor, thus ensuring precise docking simulations. This structure was critical to understanding the binding properties of humulene, which provided important clues regarding its possible role in intestinal inflammation relief [48].

For Glutathione peroxidase (PDB ID: 8JZK), the grid box size was 92 × 74 × 84 Å³ with central coordinates X = 30.128, Y = 7.151, Z = -9.132. The GPFs of this target were set to allow for a precise search within the active site involving the catalytic pocket of the enzyme. The docking results of the molecules with glutathione peroxidase will provide useful information about the possible way in which humulene may interact with the enzyme, contributing to its antioxidant activity by influencing oxidative stress pathways.

3. RESULTS AND DISCUSSION

Table 1. Predicted activity profiles of humulene

№	Predicted diseases	Pa values
1.	Inflammatory Bowel disease treatment	0,983
2.	Antioxidant	0,973
3.	Platelet antagonist	0,955
4.	Antileukemic	0,948
5.	Atherosclerosis treatment	0,943
6.	Antineoplastic	0,933
7.	Platelet aggregation inhibitor	0,872
8.	Apoptosis agonist	0,873
9.	Antidiabetic	0,872
10.	Antiprotozoal	0,856
11.	Lipoprotein disorders treatment	0,843
12.	Chemoprotective	0,728

The aggregated predictions of PASS Online show that humulene displays a wide range of potential biological activities. The highest probabilities predict that it could be of possible utility in the treatment of inflammatory bowel disease, in antioxidant roles, and as a platelet antagonist. Other functions likely to be associated with humulene include the treatment of cancer, therapy for atherosclerosis, and modulation of platelet aggregation. These results underline the diversity of humulene and its utility value in treating a variety of diseases and physiological conditions.

The Log P, with P being the partition coefficient defined as a ratio of a compound's concentration in a non-polar solvent, octanol relative to that in the polar solvent water is an inherent characteristic of the molecules. It is an

expression of hydrophobicity or lipophilicity, and this property is of major importance in determining the physicochemical phenomena and biological processes [13].

Physicochemical Properties: It has a molecular mass of 204.35 g/mol with no hydrogen bond donors or acceptors, and a topological polar surface area (TPSA) of 0.00 Å². Moreover, it is very lipophilic with a Consensus LogP value of 4.26 which indicates a strong degree of hydrophobicity [14].

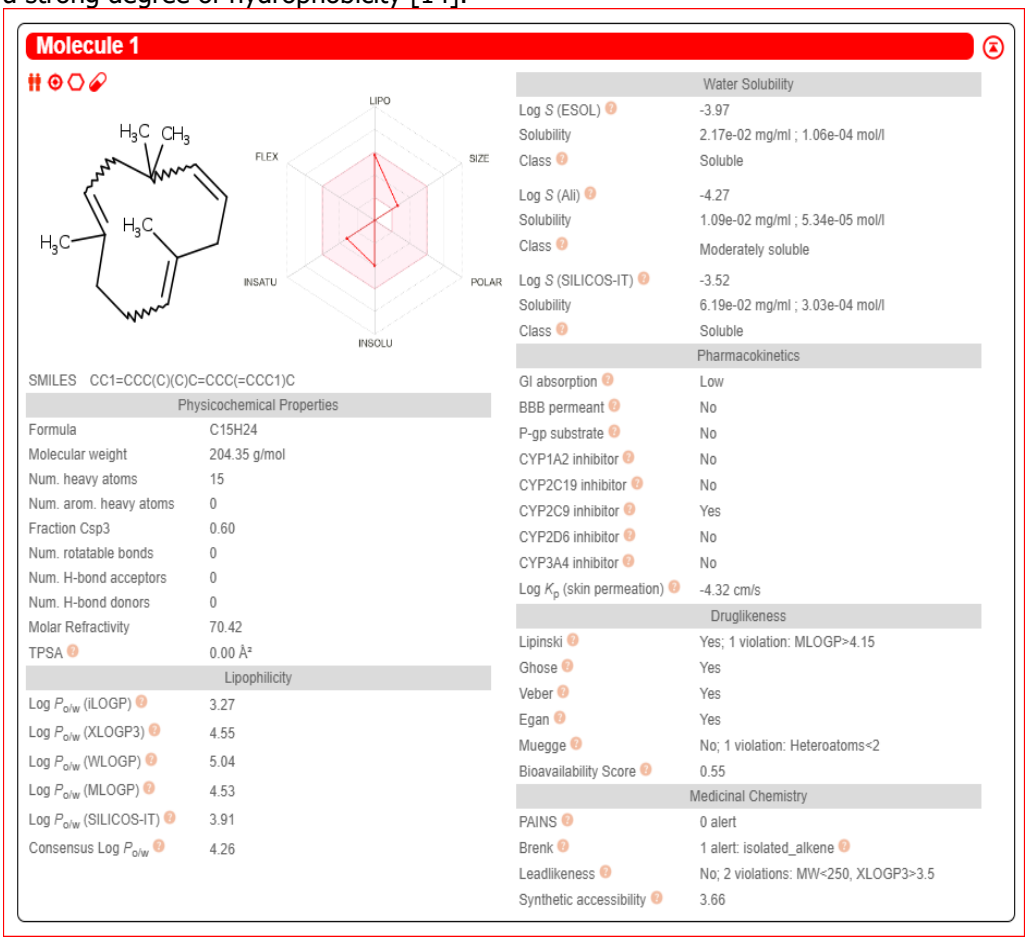

Figure-2. Swiss ADME analysis of humulene: Physicochemical, Pharmacokinetic, and Druglikeness Properties

Water Solubility: The compound is considered to be moderately soluble, with an ESOL LogS value of -3.97 (solubility ~2.17e-02 mg/mL) and an Ali LogS value of -4.27 (solubility ~1.09e-02 mg/mL).

Pharmacokinetics: The compound is poorly absorbed in the GI tract. It shows poor permeability across the blood-brain barrier. It neither acts as a substrate nor as an inhibitor with the major cytochrome P450 enzymes like CYP1A2, CYP2C19, and CYP3A4, suggesting that the compound has low chances for metabolic interaction.

Druglikeness: The compound has passed most of the druglikeness rules according to Lipinski, Ghose, Veber, and Egan but had one violation by the Lipinski rule because it had high MLOGP (>4.15). Its bioavailability score is 0.55, reflecting moderate oral bioavailability.

Medicinal Chemistry: The compound does not contain any PAINS (Pan-Assay Interference Compounds) alerts, which are indicative of low potential for nonspecific biological interactions. On the other hand, it has one Brenk alert because of the presence of an isolated alkene. The synthetic accessibility score is 3.66, suggesting moderate difficulty in synthesis.

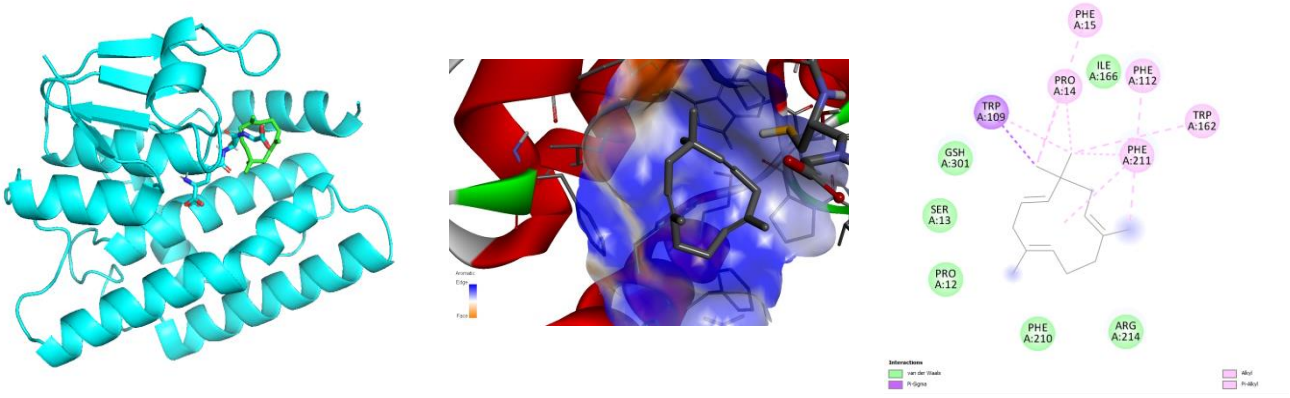

Figure-3. Docked orientations of humulene with Glutathione peroxidase (PDB ID: 8JZK)

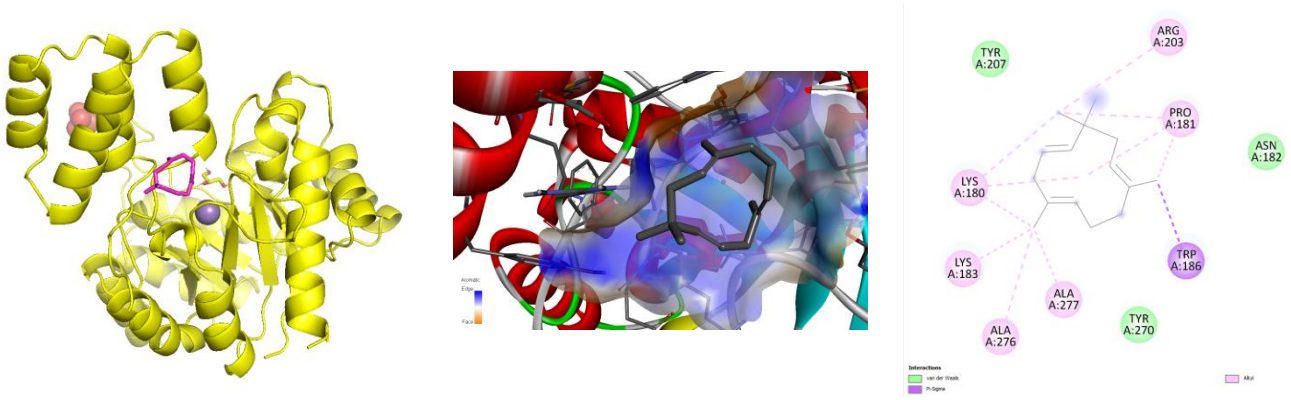

Figure-4. Docked orientations of humulene with PUE (intestinal inflammation) (PDB ID: 7EXZ)

The docking simulations showed that the binding energies of humulene with the two target proteins were as follows: for PUE, intestinal inflammation, PDB ID 7EXZ [Fig.4], the calculated binding energy was -5.94 kcal/mol; this showed moderate affinity between humulene and the receptor and may play a role in the modulation of intestinal inflammation. On the other hand, the binding energy of Glutathione peroxidase (PDB ID: 8JZK) [Fig.5] was −6.43 kcal/mol, which indicates a better interaction with the enzyme. This lower binding energy reveals that humulene could also be able to efficiently modulate the antioxidant activity of the enzyme—suggesting a probable improvement in its protective role against oxidative stress [15]. The results provide crucial insights into the molecular interactions between humulene and key proteins involved in inflammation and antioxidant defense mechanisms [16].

CONCLUSION

Computational evaluation of humulene points toward a potential role as a therapeutic agent. Docking results reveal moderate to strong binding affinities that are indicative of possible roles in inflammation regulation and augmentation of antioxidant mechanisms, with PUE (PDB ID: 7EXZ, -5.94 kcal/mol) and Glutathione Peroxidase (PDB ID: 8JZK, -6.43 kcal/mol). SwissADME assessment indicated moderate solubility, low gastrointestinal absorption, and limited metabolic interactions, while scoring profiles suggested favorable druglikeness and synthetic accessibility. PASS Online predictions further emphasize its versatility, with promising activities in inflammation, oxidative stress regulation, and platelet aggregation modulation. These results corroborate the potential of humulene for therapeutic purposes and require experimental confirmation.

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