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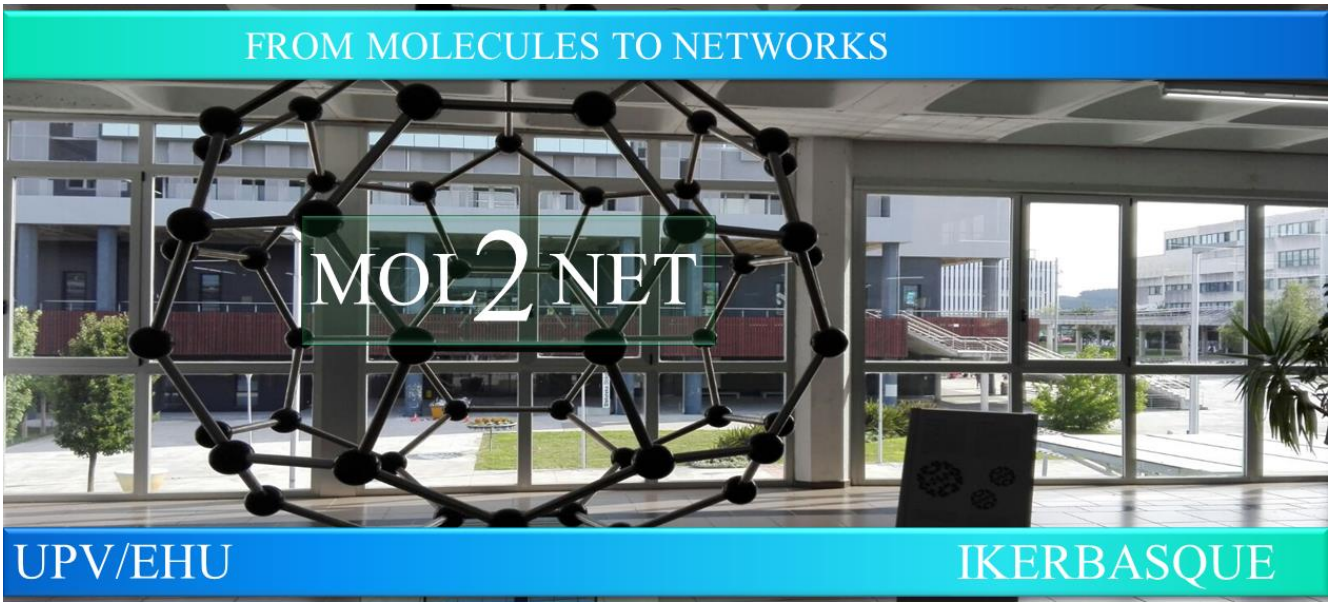

Estudo sobre utilização do Xanthohumol e seus derivados como potencial agente no tratamento do câncer de mama

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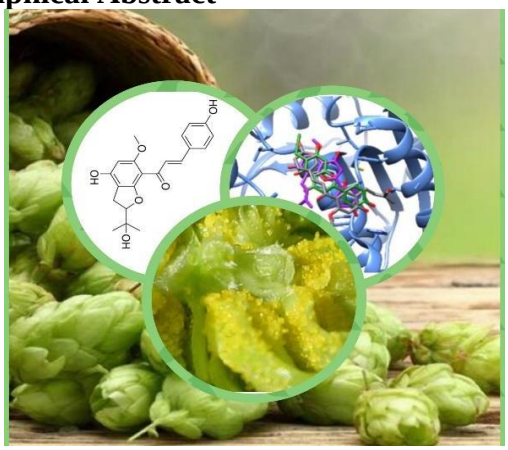
Graphical Abstract



Abstract

This article aims to devise treatments against breast cancer using molecular modeling as a basis for the discovery of new drugs. For this, a review of the article Abstract of the article: "Ligand and Structure-Based Virtual Screening in Combination, to Evaluate Small Organic Molecules as Inhibitors for the XIAP Anti-Apoptotic Protein: The Xanthohumol Hypothesis" Angeliki Mavra, Christos C. Petrou and Manos C. Vlasiou * . Since the same makes the study of a molecule of natural origin as a potential drug in the treatment of breast cancer.

Keywords:
Chalcones; Breast cancer; Xanthohumol; Docking Molecular; Medicinal Chemistry;

Use of natural products in the treatment of cancer

Cancer consists of disordered cell growth leading to changes in the genetic code. These conditions may be related to genetic factors or inadequate lifestyle conditions. Breast cancer is the second most common cancer in the world and the most common among women. According to the National Cancer Institute (INCA), at least one third of new cases of cancer that occur in the world annually could be prevented. The treatment of breast cancer can be arduous and painful both for the patient and the family members due to the symptoms and reactions of the same, so the treatment must be administered by a multidisciplinary team aiming at a comprehensive and humanized treatment for the patient. In general, the treatment modality is between surgery, radiotherapy and chemotherapy and hormone therapy.

Faced with the occurrence and trauma left by existing conventional treatments, many studies have been carried out on the use of natural products in the treatment of diseases, including anticarcinogenic activities. These applications are often justified by the high toxicity of the drugs used. Natural chalcones can be found in vegetables, flowers and leaves, chemically, it is an α,β–unsaturated ketone. Data from 2016 from SciFinder record the existence of 92,000 chalcones from natural sources. The synthesis of chalcones has aroused interest in this area because it is considered a privileged structure due to its C6-C3-C6 skeleton, which in the chemistry of natural products arouses great pharmacological interest in the its versatility, structural variety and acceptance of substitutes, which makes the compounds obtained from its synthesis have diverse pharmacological properties, such as analgesic, anti-inflammatory, antibacterial, antituberculosis, antidiabetic, antioxidant, antiviral action, among others. Natural chalcones can be found in vegetables, flowers and leaves.

Xanthohumol is a chalcone originally found in the hard resin (lupulin) of the female flower of Humulus Lupulus, known and used industrially as an agent responsible for the aroma, bitterness and natural preservative of beer. Xanthohumol (Figure 1) has been extensively studied for its anti-inflammatory, antioxidant and anticarcinogenic properties. It undergoes thermal isomerization to isoxanthohumol, as well as 8- and 6-prenylnaringenin. The in-silico study dealt with in this summary, bring the action of Xanthohumol in the activity of combating breast cancer by means of docking molecular.

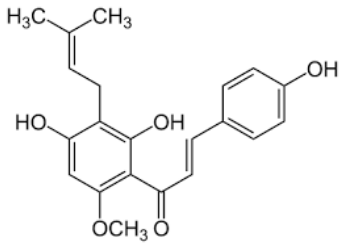


Figura 1 – Xanthohumol (XH)

Docking Molecular a computational strategy associated with medicinal chemistry

In the search for new drug candidates, the pharmaceutical industry and the research and development (R&D) sector are increasingly looking for technological and scientific innovations that contribute to the optimization of the understanding of physiological mechanisms. With this, medicinal chemistry has been gaining great space and prominence, as it has a fundamental role in the paradigm of planning and optimization of new molecules with biological activity. According to IUPAC (International Union of Pure and Applied Chemistry) medicinal chemistry involves the discovery, development, identification and interpretation of the molecular mechanism of action of biologically active compounds. In addition to the discovery of bioactive molecules, he also studies the phenomena involved in metabolism and the establishment of relationships between chemical structure and activity (SAR, structure-activity relationships).2

Associated with these factors, computational methods have been gaining visibility in medicinal chemistry associated with the planning of new drugs in the application and feasibility of tests with the intention of reducing analysis and research time, and in the cost of investment in a medication that is of

low relevance. It is estimated that the use of in silico methods can reduce the costs associated with the development of a new drug by up to 50% due to the high reliability of computational methods.

Drastically reducing the number of molecules tested and synthesized experimentally. Its application ranges from the identification, selection and optimization of candidate molecules to the proposition of new NCEs for clinical use. For this, it is fundamental to have prior knowledge about the biological process involved in the disease under study, and in the selection of the protein target, which may or may not have its (3D) structure. Among the outstanding computational methods is Molecular Docking, a technique that consists in predicting the conformity of a ligand in the active site of a macromolecule. The objective is to predict the predominant binding modes between the ligand and the protein in a known three-dimensional structure.

The docking molecular process can be divided into two stages: 1st prediction of the bioactive conformation and (ii) prediction of the affinity of the ligand for the site. Predicting the binding mode of molecules at the receptor-target interaction site is considered the simplest and most robust step in the process. It is necessary to verify the interaction between it and its target, as well as understand how a molecule fits into a given protein and calculate the affinity between them. Molecular modeling comes to contribute as a significantly useful tool in the process of planning and optimization of recognition of pharmacodynamic and kinetic properties of potentially bioactive molecules (candidates for new drugs)

Article summary: ***"Ligand and Structure-Based Virtual Screening in Combination, to Evaluate Small Organic Molecules as Inhibitors for the XIAP Anti-Apoptotic Protein: The Xanthohumol Hypothesis" Angeliki Mavra, Christos C. Petrou and Manos C. Vlasiou * [3]*** ***https://doi.org/10.3390/molecules27154825***

The antitumor activity of the prenylated chalcone Xanthohumol (XN) has received great attention due to its capacity to inhibit DNA synthesis, intracellular ROS induction, and interruption of the BIG3-PHB2 interaction, which occurs between the guanine nucleotide exchange protein inhibited by A 3 (BIG3) and prohibitin 2 (PHB2) in the cytoplasm of breast cancer cells. Among the most used therapies in the treatment of cancer is programmed cell death. XIAP is an antipoptopic protein, in addition to this, cellular IAP-1 (cIAP-1) and cIAP-2 play a critical role in the regulation of tumor necrosis factor (TNF) receptor-mediated apoptosis.

Due to these characteristics, these proteins are considered therapeutic targets for the treatment of cancer. A . Based on this, the work proposed by the authors performs computational screenings based on the structure of the XIAP protein, using the SMILE chemical format to describe the initial molecular structure of XN. The authors used the SwissSimilarity Webserver, a free online tool that evaluates the pharmacokinetics and drug-likeness and chemical activity of new molecules. To verify the available screening libraries, the chosen one was "ZINC drug", finding a total of 10,639,400 similar structures. Of these, only 400 were candidate molecules (on the same server).

In order to refine and minimize the number of candidate molecules, pharmacokinetic scores were predicted using pkCSM, reducing to 62 candidate molecules with characteristics to be considered drugs based on the first structure (Xanthohumol). To further reduce the number of candidate molecules, structure-based screening was performed using AutoDock, concluding that (E)-1-(4-methoxyphenyl)-3-(p-tolyl)prop-2-en-1-one and (E)-3-(4-hydroxyphenyl)-1-(2,4,6-trihydroxyphenyl)prop-2-en-1-one) were the best candidates.

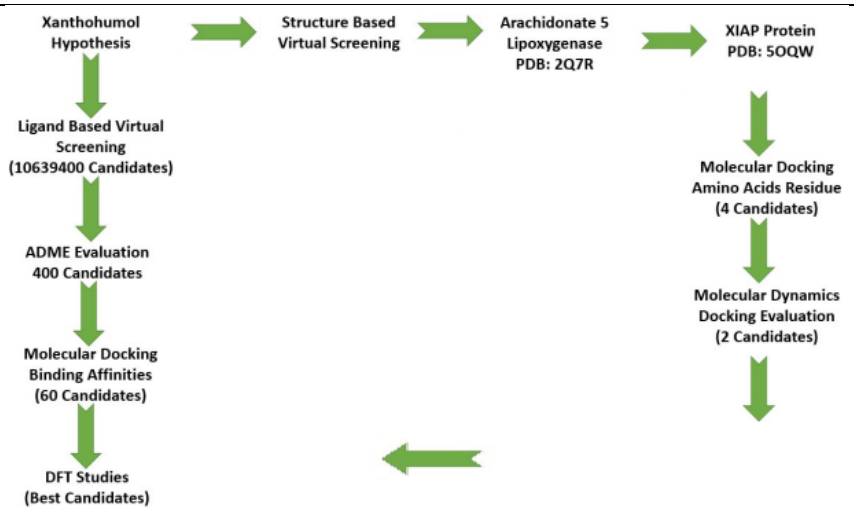


Figure 2: Study flowchart [3]

The authors evaluated the results after a series of ligand-receptor couplings, calculating ligand binding affinities and observing the best position of conformational overlaps.
After setting the best overlays. Evaluating the binding affinities, the fit results of the major ligands were validated by re-fitting them to the same defined regions of the receptor using AutoDock Vina. The authors used iGEMDOCK to carry out structure-based pharmacophoric modeling, while Protein Data Bank was used to encode the crystalline structure of the XIAP protein (5OQW). And the ligand molecules (the best candidates including Xanthohumol) were collected by the Drug Bank.

The protein structure was prepared using CHIMERA software, before completing molecular coupling of the ligand and receptor, the ligands were optimized by adding hydrogen using CHIMERA software which also captured ligand-amino acid residue interactions. It was verified that the chemical structure of the molecules could interact with the 5-lipoxygenase protein (code 2Q7R for crystal structure in the Protein Data Bank). After evaluating the docking protocol, the two selected molecules were evaluated according to the energies and amino acid residues of the two best candidates in the XIAP protein and the best fits can be seen in the table below:

Table 1: Energies and amino acid residue of the best two candidates on the XIAP protein [3]

Complex	Total Energy (KJ/mole)	Energy H_{Bond} (KJ/mole)	Energy VDW (KJ/mole)	Amino Acid Residue H_{Bond}	Amino Acid Residue VDW Interactions
A-5OQW	−69.10	0	−69.10	None	Leu 307, Thr 308, Trp 310, Glu 314, Gln 319, Trp 323, Tyr 324
B-5OQW	−74.13	−12.08	−62.05	Ser 278, Val 279, Trp 310	Val 279, Gly 293, Glu 294, Asp 296, Trp 310

HOMO/LUMO orbital differences were determined, showing that B ((E)-3-(4-hydroxyphenyl)-1-(2,4,6-trihydroxyphenyl) prop-2-en-1-one) has greater reactivity and better binding affinity between the two best candidates. In the docking image below, it is possible to verify the binding pocket of the XIAP protein, managing to verify the best conformations for the candidates to interact.

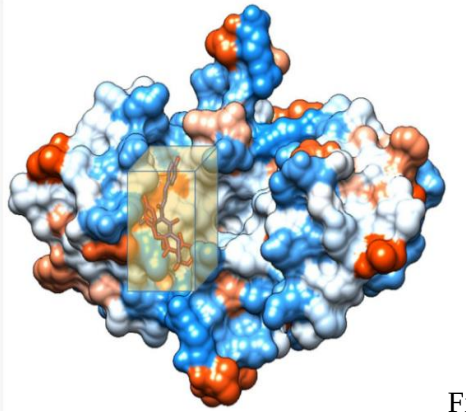


Figure 3. Binding pocket of XIAP protein. [3]

In the image below, the interaction of amino acid residues of the XIAP protein with the candidates can be seen.

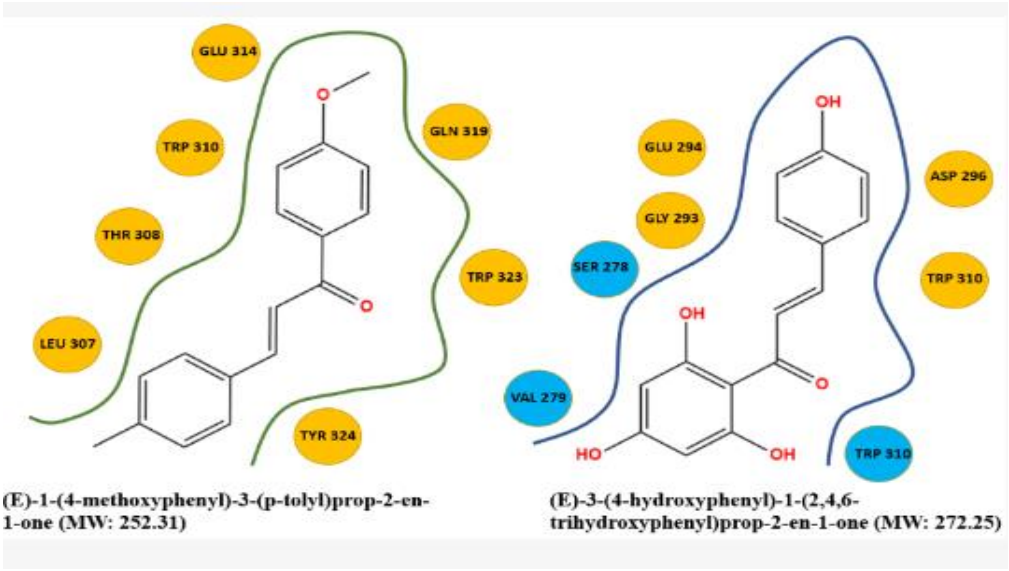


Figure 4. Amino acid residue of XIAP protein interacting with the two molecules (blue color: Hbonds). [3]

The best candidate was B ((E)-3-(4-hydroxyphenyl)-1-(2,4,6-trihydroxyphenyl) prop-2-en-1-one) and the aspect considered most important was the ability that the molecule must have 5 acceptors and 4 donors of hydrogen bonds. The interaction with the XIAP protein created three hydrogen bonds with the amino acids Ser 278, Val 279 and Trp 310. It passes all of Lipinski's rules to be considered a drug and does not penetrate the blood-brain barrier, an important aspect in its future use as a anticancer agent. The candidate showed no hepatotoxicity or cardiotoxicity, in addition to not causing skin sensitization. the maximum tolerated dose is 0.373 (log mg/Kg/day).

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