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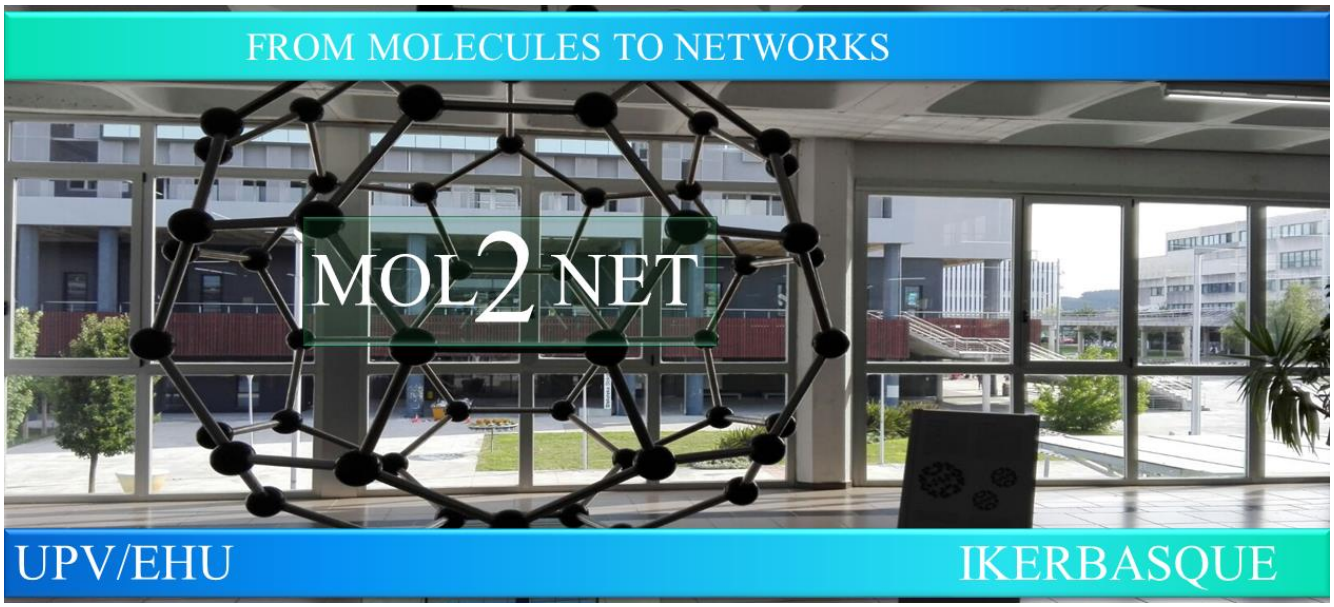

Saffron as a herbal medicine for depression – an *in silico* study

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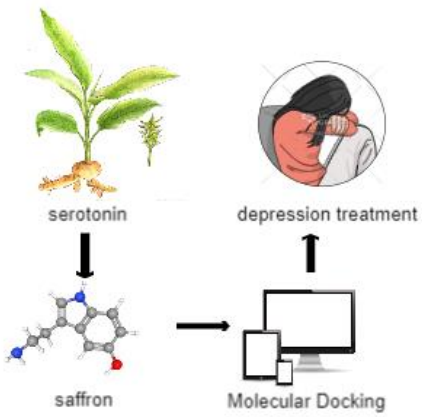
Graphical Abstract



Abstract.

A depressão é uma doença mental que assola grande parte da população mundial, com sintomas leves de tristeza à graves como o suicídio. E parte dos doentes não recebe o diagnóstico ou tratamento, que pode ser psicoterapêutica e/ou farmacológica. Desta forma, este resumo expandindo almeja propor a investigação da utilização do saffron como fitoterápico para o tratamento da depressão.

Keywords: depression, saffron, safranal and *in silico.*

Introduction

Depression, considered a mental disorder, is characterized by loss of interest/desire for everything, feelings of sadness and low self-esteem. And the most serious conditions can lead to suicide. This characteristic destroys hope and beauty in the lives of its bearers[1]. According to Del Porto (1999), the feelings of sadness and joy are of fundamental importance for human beings, as they color the affective background of psychic life. Since, sadness composes a general response to situations of loss, defeat, disappointment, stress and other adversities[2].

The World Health Organization, distinguishes depression by persistent sadness and lack of interest or pleasure in activities that were previously pleasurable. Even more so, it can negatively interfere with sleep and appetite, lack of concentration and increased fatigue. And it is the disease that most causes disability in the world. This mental disorder affects around 5% of adults worldwide. The causes of depression include complex interactions between social, psychological and biological factors. Life events such as adversity, loss, unemployment, social structure, whether in childhood or adulthood, contribute and can catalyze the development of depression[3].

The depression brings with it a cost, which is usually very high. From monetary losses (losing a job) to life itself (suicide)[1]. Depression affects all types of people – young and old, rich and poor, and women are more likely to experience depression than men[3]. According to PAHO, PAHO – Pan American Health Organization, 1 out of 4 people in the Americas suffers from a mental illness[4].

There are treatments for depression, from therapies to pharmacological. However, in low- and middle-income countries, treatment and support services for depression are often absent or underdeveloped. It is estimated that over 75% of people suffering from mental disorders in these countries do not receive treatment.[3]

Therefore, this work projects the study of molecular docking for safranal, a substance present in the medicinal plant Crocus sativus popularly known as saffron. In order to identify the activity relationship with selective serotonin, noradrenaline and/or dopamine reuptake blockers. Well, it is known that in depression there is a decrease in the levels of these neurotransmitters.

Materials and Methods

The methodology used in the research will be based on *in silico* routines, therefore, it will be considered experimental, with a qualitative, quantitative and explanatory approach. Attaching to the analysis of the physical-chemical, pharmacokinetic and toxicological characteristics of the safranal substance as a Selective Serotonin Reuptake Inhibitor (SSRIs), through the use of cheminformatics tools.

ChemDraw and HyperChem

The first stage of the study will be carried out using the ChemDraw Professional software version 16.0.1.4 to carry out the molecular design – exporting them in ".mol" format. Then, using HiperChem 8.0.6 software, to optimize the structures using the semi-empirical method – AM1.

OpenBabel 3.1.1

The OpenBabel program was used to convert ".mol " files previously optimized by HiperCHem into an SDF file.

OSIRIS Property Explorer

The OSIRIS Property Explorer will be used to carry out the design of all chemical structures and perform the calculation of several relevant properties, such as mutagenicity, intestinal absorption, therapeutic employability and others.

CDK

The CDK software will be used to calculate the descriptors of the reference molecules.

Molegro Virtual Docker 5.5

Molegro Virtual Docker is an integrated software for predicting protein ligand interactions. Thus, it will be used in all aspects of binding in the process of preparing molecules to determine potential target protein binding sites and predict binding modes.

Choice of methodology

In order to contextualize the study methodology and strengthen the choice, the summary of two articles was brought, Dolabela et. al. (2018) e Sahihi (2015):

In the study by Dolabela et. al. (2018), entitled: In silico study of the activities of triterpenes and iridoids isolated from Himatanthus articulatus (Vahl) Woodson.

Was carried out in silico to predict the pharmacokinetic, toxicological and biological activities of triterpenes and iridoids isolated from Himatanthus articulatus, commonly used against malaria , skin disorders, helminthiasis, gastric ulcers, gastritis, tumors and syphilis. Comparisons were performed using the programs: ChemSketch, PreADMET and PASS online. The physical-chemical characteristics of the compounds were estimated using the Mcule property calculator and Chemicalize.org online servers. The results revealed that the non-glycosylated triterpenes and iridoids (plumericin and isoplumericin) showed intestinal absorption above 90%. Only plumericin and isoplumericin follow the Lipinsk rule, in addition to showing antineoplastic, antibacterial and antifungal activity. Lupeol cinnamate, α-amyrin cinnamate and lupeol acetate probably act on the signs and symptoms of malaria, however, lupeol acetate had a greater number of adverse reactions. All substances showed carcinogenicity, but only triterpenes showed mutagenicity. In pharmacokinetic, toxicological and biological terms, only plumericin and isoplumericin showed satisfactory results. The prediction of

biological activity, plumericin and isoplumericin demonstrated antineoplastic, antibacterial and antifungal activity confirming the popular use of this plant[5].

In the study by Sahihi (2015), entitled: In-Silico Study of the Interaction of Saffron Ligands and Beta-Lactoglobulin by Molecular Dynamics and Molecular Docking Approach.

It has been studied that Safranal, crocetin and dimethylcrocetin are secondary metabolites found in saffron and have a wide range of biological activities. An investigation of its interaction with a transport protein, such as β-lactoglobulin (β-lg), at the atomic level, can be a valuable factor in controlling its transport to biological sites. The interaction of these ligands and β-lg as a transport protein was investigated using molecular docking simulation and molecular dynamics (MD) methods. Molecular docking results showed that safranal and crocetin bind on the surface of β-lg. However, dimethylcrocetin binds in the inner cavity of β-lg. The β-lg affinity for saffron binding ligands decreases in the following order: crocetin > dimethylcrocetin > safranal. Analysis of the MD simulation trajectories showed that the β-lg and β-lg-ligand complexes became stable at approximately 3000 ps and that there was little conformational change in the β-lg-safranal and β-lg-dimethylcrocetin complexes over 10 - timescale ns. Furthermore, the atomic fluctuation profiles showed the rigidity of the ligand binding site during the simulation time. It was clearly verified that Rg and SAS increase with the binding of safranal and dimethylcrocetin suggesting a less compact structure after the binding of these two ligands to β-Ig[6].

Considerations:

Finally, the in silico molecular docking technique is extremely valuable for academia and industry, as it allows predicting trends and, consequently, reducing laboratory time.

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