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THE STUDY OF THE PHARMACOKINETIC PREDISPOSITION AND *INSILICO* METABOLISM OF GERANIOL

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ABSTRACT

Essential oil is one of the most used plant products in drug strategies and complementary treatments. Pharmacologically, they are known for their anti-bacterial, anti-viral, anti-fungal, anti-inflammatory potential, etc. The geraniol (GE) essential oil, found in plants such as: citronella, orange, "palmarosa" and geranium, has several therapeutic purposes through its regulation of multiple signaling pathways biological processes. Biological targets and bioavailability were analyzed using Swiss ADME software, based on the interaction of the molecule with cytochrome P450 enzymes. Metabolism was analyzed by simulating possible metabolic sites with SMART Cyp software and Swiss Target Prediction. A correlation was made between the data found and the existing literature in PubMed, Scielo and Google Scholar databases. From the data obtained, it was observed that GE, with lipid-soluble characteristics, according to the stages of absorption, distribution, metabolism and excretion, has the ability to interact with specific target sites and inhibit cytochrome P450 enzymes, as well as high absorption gastrointestinal tract and overcoming the natural barriers of protection. It is understood that *in vitro* and *in vivo* studies of efficacy (disease models) and safety (acute or chronic toxicity) are necessary to attest to the therapeutic properties of GE, emphasizing that *in sílico* studies when associated with these other types of studies, we have safe and very concrete results.

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INTRODUCTION

Geraniol (GE) is an acyclic monoterpene, most commonly found as a main component of essential oils from plants such as citronella, lemon, orange, palmarosa, and geranium. In its most purified form, it is a colorless, oily liquid with a rose scent. It has a multitude of uses in industries, ranging from cosmetics to medicine ingredients, purifiers, personal hygiene, household cleaning and detergent. Having as characteristic a strong and characteristic odor (LAPCZYNSKI *et al*., 2008). Due to its common presence in plants, GE and its derivatives were evaluated as pharmacologically active, but with limited production, which makes their wider use in the market difficult. Thus, several studies have emerged looking for ways to biosynthesize geraniol (ZHOU *et al*., 2014). After several tests seeking a more pronounced production, finally a higher production of GE was obtained in *Saccharomyces cerevisiae* with an expression of geraniol synthase and arnesyl diphosphate synthase, reaching a yield of 1.68 g\L, as described by *Jiang gz* (2017). Furthermore, recently, GE has been shown to have several pharmacological properties with anti-inflammatory (DE CASSIA, *et al*., 2013), antioxidant (Shoff SM, *et al*., 1991), antimicrobial (SOLORZANO-SANTOS *et al*., 2012), and anti-tumor agents (CARNESECCHI *et al*., 2004). It has already been demonstrated that GE has several therapeutic purposes, thus suggesting that the molecule is a promising candidate for pharmacological use, through the regulation of multiple signaling pathways in various biological processes. However, the tests are still limited due to the difficulty of extracting the raw material to carry out the tests. (ZHOU *et al*., 2014). Currently, one of the most important advances in the discovery of new drugs has been the use of molecular modeling tools. Enabling the discovery of a new drug and improving the optimization of an existing prototype obtained from the study of molecules *in silico* (SANVITO *et al*., 2012). For an *in vivo*

evaluation, the work must go through several authorizations, aiming to reduce the side effects or adverse effects that do not violate ethical and moral laws when it comes to animal testing. Noting this, the first generation of *in silico* models for the prediction of pharmacokinetics is now commercially available, while other methods are being published and implemented (PAVAN *et al*., 2018). The current trend is the increasing growth of software applications, especially in research centers and universities, because *in silico* technologies, when compared to *in vitro* and *in vivo* methods, are less expensive, consume less time, and have higher yields. have greater reproducibility if the same model is used, in addition to requiring reduced synthesis of compounds with constant optimization (adding useful properties, new descriptors or new compounds) and with the potential to reduce the use of animals (DE ANDRADE *et al*., 2018).). Based on the above discussions, despite knowing the pharmacotherapeutic benefits that geraniol can exert, there is not as much pharmacokinetic and bioavailability data or information available when administered orally and the ability of this essential oil to cross the blood-brain barrier (PAVAN *et al*., 2018). Unlike *in vitro* experiments, which exist in isolation, *in silico* models allow the researcher to include a virtually unlimited set of parameters, which makes the results more applicable to the organism as a whole (CHEN *et al*., 2016). *In silico* models have been applied to pathophysiological problems to provide information that cannot be obtained practically or ethically by traditional clinical research methods, having similarities with tests in animal models (COLQUITT *et al*., 2011). Therefore, to provide new insights and support the clinical use of the GE molecule, we summarized the pharmacological activities of geraniol based on PubMed, Scielo database searches and *in silico* tests to observe its characteristics and forms of interaction and metabolism by the body. Scientific literature published in the years 2013 to 2020 was used, however, some articles published before 2013 were also included for the need to put specific information in the introduction. This work aims to predict the pharmacokinetic and pharmacodynamic characteristics of the EG from *in silico* analysis, using the Swiss ADME and SwissTargetPrediction software, in addition to simulating the possible metabolic sites with the SMARTCyp software.

METODOLOGIA

Analysis of Biological Targets: Possible binding targets with the GE molecule were evaluated using the SwissTargetPrediction software (available online at http: www.swisstargetprediction.ch Based on analyzes performed with similarity of origin and structure of the tested molecule, comparing it with a database of data from known molecules, whose pharmacological targets have already been identified and analyzed (DAINA *et al*., 2019). At first the substances were grouped into families of molecules and then the 16 most likely to be linked to the tested compound were In addition, to calculate the interaction of these molecules with geraniol, a binding score was developed, with scores between 1 and 10, with the higher the score, the greater the probability that the molecule has a binding site for geraniol.

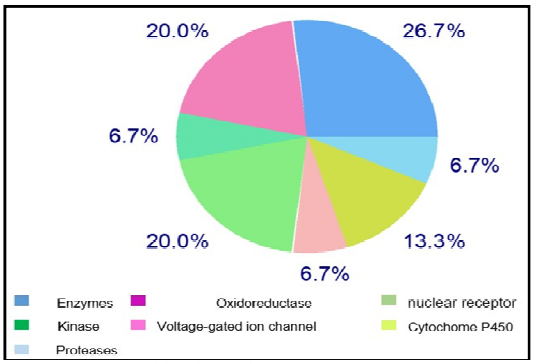
Study of the Bioavailability of the Oral Administration of Geraniol: For the study of bioavailability, the SwissADME software was used (available online at http: www.swissadme.ch) (DAINA *et al*., 2017). In this step, 5 criteria were evaluated, knowing that for a drug to have good availability, if ingested orally, it must present at least three of the following criteria: 1- Total polar surface area (ASPT) <140 A², 2- Consensus of loop<5, 3 - Molecular weight<500 daltons, 4 - Number of hydrogen bond acceptors < 10, and 5 - Number of hydrogen bond donors<5 (LIPINSKI *et al*., 2004; MONTEIRO *et al*., 2020).

Analysis of Absorption and Interaction of Geraniol with Cytochrome p450 Enzymes: In this evaluation, the SwissADME (available at http: swissadme.ch) was used. The points analyzed were permeability to the blood-brain barrier, absorption through the gastrointestinal tract, absorption in the skin, interaction with P-glycoprotein and, mainly, with important cytochrome P450 enzymes (DAINA *et al*., 2017).

***Prediction of Geraniol Metabolism Using Smartcyp Software*:** For this last analysis, another digital platform, SMARTCyp, (available at https://smartcyp.sund.ku.dk/) was used to evaluate the two-dimensional design of the GE molecule, which uses algorithms to predict metabolism. of the analyzed molecule. However, these algorithms use the cytochrome P450 activation energy required to react with a molecule, which is calculated by the density functional theory (DFT). Comparison results are guaranteed by comparison with a database of molecules that already have calculations performed, whose pharmacological targets have already been identified and analyzed. (MENDONÇA SILVA *et al*., 2014). For the interpretation of results, the lower the activation energy level, the greater the probability that a site is metabolized (RYDBERG *et al*., 2010).

RESULTS

Analysis of Biological Targets: For the analysis of biological targets and obtaining the results, the Swiss Target Prediction was used, analyzing the different types of proteins as a target for the EG. The results showed 100 possible targets from which only the first 16 were selected for analysis of possible binding of this drug in the molecule. The chosen targets were classified into 7 different protein categories, as shown in Figure 01.



Source: Prepared by the author

Figure 1. Possible biological targets for the geraniol molecule

The categories were organized as follows: 26.7% enzymatic proteins (they serve as biological catalysts in our body's chemical reactions, accelerating metabolic processes), 20.0% oxidoreductase (enzymes responsible for catalyzing oxidation-reduction reactions), 6.7% nuclear receptors (a class of proteins found inside cells that have the function of sensing and capturing the presence of hormones and other molecules) 20% kinases (a type of enzyme whose function is to transfer phosphate groups from high-energy donor molecules to specific target molecules), 6.7% voltage-gated ion channels (action potential conduction and cell signaling), 13.3% cytochrome P450 (diversified superfamily of proteins that are responsible for metabolizing a large number of substances to make them more polar and water soluble) and 6.7% Proteases (break peptide bonds between amino acids in proteins, cleavage). The 16 proteins most likely to have binding sites for the GE molecule can be seen in Table 01.

Study of Bioavailability by Oral Administration of the Geraniol Molecule: The analysis of the bioavailability of the GE molecule, when administered orally, was predicted through the following parameters: logP consensus, hydrogen acceptor number, hydrogen donor number, molecular weight and total polar surface area (ASPT). The predicted analysis data can be seen in Table 02.

Mechanisms of interaction with Cytochrome P450 Enzymes: The GE molecule was shown to be easily absorbed orally. Table 03 demonstrates some pharmacokinetic parameters related to the molecule.

Metabolism Prediction with SMARTCyp: SMARTCyp presented only the sites of metabolism by three cytochrome P450 enzymes, CYP3A4, CYP2D6 and CYP2C9, and its classification in relation to the relevance of metabolism is by color.

Table 1. List of proteins most likely to be pharmacological targets for the geraniol molecule

Biological target	Biological class	Score (01-10) *
Squalene monooxygenase	Enzyme	6
Cyclooxygenase-1	Oxidoreductase	4
Cyclooxygenase-2	Oxidoreductase	3
HMG-CoA Reductase (by homology)	Oxidoreductase	2
Progesterone Receptor	Nuclear Receptor	2
Tyrosine Protein Kinase JAK 1	Kinase	2
Tyrosine Protein Kinase JKA 2	Kinase	1
UDP-glucuronosyltransferase 2B7	Enzyme	1
HERG	Voltage controlled ion channel	1
Cytochrome P450 11B1	Cytochrome P450	1
Cytochrome P450 11B1	Cytochrome P450	1
Indoleamine 2, 3-dioxygenase	Enzyme	1
Epoxide Hydratase	Protease	1
Serine\threonine-protein kinase PIM1	Kinase	1
11-beta-hydroxysteroid dehydrogenase 1	Enzyme	1
Serina\treonina - proteína quinase PIM3	Quinase	1

Source: Prepared by the author.

Table 2. Oral bioavailability of the geraniol molecule

Parameters	Results
Formula	C10H18O
No. of hydrogen acceptors	1
No. of hydrogen donors	1
Molecular weight	154,25 g\mol
Total polar surface area (ASPT)	20,23 Å²
logP consensus	2,78

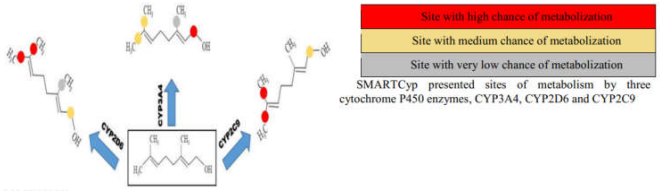
Source: Prepared by the author.

Table 3. Pharmacokinetic parameters of geraniol

Evaluated parameters	Results
Absorption from the intestinal tract	High
Permeable to blood-brain barrier	Yes
P-glycoprotein substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Skin absorption	No

Source: Prepared by the author.

The main site of metabolism in SMARTCyp for GE was Carbon 10 and carbon 01, the sites of medium and very low chance of metabolization were different according to the type of enzyme of the cytochrome P450 enzymatic complex. As seen in Figure 02.



Source: Prepared by the author.

Figure 2. GE metabolism sites predicted in SMARTCyp software for CYP3A4, CYP2D6 and CYP2C9 enzymes

DISCUSSION

Previous researches serve as a basis for proving that the geraniol molecule has therapeutic effects and can be improved if associated with *in silico* research data in order to know its potential. GE has an anti-fungal effect with inhibitory mechanisms on Trichophytonrubrum when tested at concentrations ranging from 16 to 256 µg/mL. The action took place by suppressing the development of hyphae, which changed in shape, size and width. In addition, there was leakage of intracellular content by inhibiting the synthesis of ergosterol, an essential membrane component that plays a role in the development and protection of intracellular material. (PEREIRA, *et al*., 2015). It is understood that for a drug to reach its level of desirable absorption effect, it is necessary that it has a considerable concentration and remains in the site of action for the necessary time. However, the properties of the drug need to be in agreement in the steps of absorption, distribution, metabolism and excretion, in addition to evaluating the toxicity. Because these represent approximately 40% of failures in Research for new drugs. Among these steps, metabolism stands out, which is responsible for altering not only availability but also generating toxicity. (KIRCHMAIR *et al*., 2012). In a study by Fei QI (2018). It showed that geraniol has anticancer effects, inhibiting the development of colon cancer cell line with the inhibitory concentration value (IC50) when using 20µM of the compound in the treatment, also inducing apoptosis. A decrease in bcl-2 (anti-apoptotic regulator) and an upregulation of Bax (pro-apoptosis regulator) were also observed. This resulted in DNA damage, which prevented colon cancer cells from replicating. From new *in silico* studies, potential drug candidates for the treatment of colon cancer can be obtained. (De Sá *et al*., 2021). Studying the metabolism of a drug candidate molecule through experimental techniques is a time-consuming and difficult process, which requires equipment that allows sensitivity and efficiency in the extraction of small amounts of metabolites. As a result, *in silico* methods have become increasingly attractive due to their speed, lower costs, greater ease and good results, which makes the association of the *in silico* method with the *in vivo* method valid, bringing better accuracy of results, as well as what was presented in the tests carried out with the GE molecule. (RYDBERG *et al*., 2010) In a study done in mice with

mild stress, an EG administration showed an antidepressant effect. It is observed that it may be regulating the generation of neuroleucine-1-1-1 beta by inhibiting β) which is bound to B (NF-Nf-), precursor of the induction cascade. With this the mice significant improvements in the behavior of the mice related to depression, as stated by DENG (2015). As seen in Figure 1, the seven categories of proteins described according to metabolic functionality facilitate the separation and understanding of the various binding sites. From this, more than 100 proteins that interact with the GE molecule were predicted, but only 16 were listed, as shown in Table 1, according to binding capacity, based on the fact that if GE is used as a drug, knowledge of which targets the GE has more affinity is known. From this information, the production of a drug takes place according to the reactive targets, also seeking an improvement in bioavailability, knowing that this is a property highly modulated by metabolism (SILVA *et al*., 2014). This modulation was predicted with the use of SwissADME, from the bioavailability of the drug through the oral administration of the GE molecule, in addition to the mechanisms of interaction with cytochrome p450 enzymes. For a drug to present acceptable oral bioavailability, it must meet at least three of the five items predicted in the methodology according to the reference values (LIPINSKI, 2004; MONTEIRO *et al*., 2020). As can be seen in table 2, the GE molecule was included in all five items evaluated. Noting that the ASPT data concluded that the molecule easily penetrates cells and biological barriers in the body. Such characteristics were proven in tests carried out on whole blood quantities of humans and rats, proving an ease of absorption and availability (PAVAN *et al*., 2018).

Having already proven in some studies pharmacological actions such as anti-inflammatory, antioxidant, antibacterial and antitumor (DE CASSIA, 2013; (Shoff SM, 1991; SOLORZANO-SANTOS, 2012; CARNESECCHI S, 2004), indicating that its use as a potential GE molecule has also been shown to have a relatively short half-life of action, which is attributed to metabolic processes, rapid excretion and a wide distribution in the lipid compartments of the body (PAVAN, *et al*., 2018). With the prediction of GE metabolism sites (figure 2), SMARTCyp showed sites of metabolism for the GE molecule by three cytochrome P450 enzymes, CYP3A4, CYP2D6 and CYP2C9. CYP3D4 showed the carbon 10 site with high chance of being metabolized by this enzyme, followed by carbon 01 and carbon 08. The importance of this enzyme is given by having the lowest energy level, being able to quickly metabolize (REKHA *et al*., 2018). or that the carbon 01 site has a predisposition to be metabolized by this enzyme, followed by carbon 10 and 8 respectively, because it has affinity with this cytochrome P450 molecule of medium energy level. CYP2C9, on the other hand, showed a high chance of metabolization starting at the carbon 01 site, followed by carbon 10 and 8, which is a possibly slow sequence because it has a high level of energy, which delays the process of breaking the molecule and its metabolization, characterizing how the third option of pharmacological metabolism (SMARTCYP, 2021). GE showed high absorbance and crossing the blood-brain barrier, also because of its lipid-soluble characteristic and its low molecular weight, which is one of the properties that indicate that GE can be used in the treatment of neurodegenerative diseases. As a recent study showed that GE has inhibitory effects on proliferative proteins in Parkinson's disease, through the control of oxidative stress and lipid peroxidation with an inhibitory effect on autophagy dysfunction, which is directly linked to the accumulation of damaged proteins in the body. lumen of the endoplasmic reticulum that causes stress to the cell being associated with the death of dopaminergic cells showing that pretreatment with geraniol improves cell viability, preserving the mitochondrial membrane and decreasing the autophagy process (REKHA *et al*., 2018).

The GE showed great absorbance through the gastrointestinal tract (Table 3) reaching the circulation quickly. As it was proven in a recent research that GE, in addition to its rapid absorption, has a beneficial and protective effect against lesions caused by trinitro-benzene-sulfonic acid (TNBS)-induced colitis. Treating mice for 11 days with GE showed an improvement in the clinical signs (colon edema, ulcers and weight loss) that mice with colitis developed. GE proved to be a possible pharmacological active through its antioxidant and immunosuppressive potential, preventing the increase in nitric oxide and peroxide production in the inflammation cascade in the rat model with induced colitis (SOUBH *et al*., 2015). *In silico* research shows that enzymatic metabolism by one drug can alter plasma concentrations of another drug, generating ineffective concentrations. Being an important reason for the knowledge of drug metabolism targeting drug-drug interactions (PAVAN, *et al*., 2018). It is understood that if other drugs act as an enzyme inducer and generate metabolites, the concentration of these products will increase and cause undesirable effects. However, an enzymatic inhibition caused by a co-administered drug can cause an eventual accumulation that can reach toxic concentrations. Therefore, a competition of drugs for the same metabolizing enzyme can decrease the metabolism of any of the drugs administered together, which would decrease their excretion, reaching toxic levels in the body (WANG *et al*., 2017). Such metabolites can be subjected to *in silico* toxicity prediction methods to increase detection efficiency, helping to decide which site of the molecular structure can be modified to obtain drugs with improved properties based on the hypothesis of the problems already discussed (KIRCHMAIR *et al*., 2012). This evidence, already published on GE, demonstrates its effects and potentials related to different biological activities ranging from neurodegenerative diseases to biological actions on cancer cell lines, which have been demonstrated in clinical trials.

CONCLUSION

Knowledge about the analyzed compound, from its absorption pathways to the types of metabolizing enzymes of a given drug candidate is of paramount importance, since computational methods to predict metabolism are very important, especially for drug candidates that will promote actions against chronic diseases. Patients with these disorders make use of multiple drugs, so, from the knowledge of the main metabolic pathways, one can arrive at the improvement of a drug under study, to avoid adverse effects and guide the patient in the best way. The present work used a modern and free methodology of easy access in order to predict an important stage of the pharmacokinetics and pharmacodynamics of a drug candidate, the metabolism, despite the promising data, *in vitro* and *in vivo* studies of efficacy (in models of diseases) and safety (acute or chronic toxicity) are still needed to attest to the therapeutic properties of GE, emphasizing that *in silico* studies, when associated with these other types of studies, have very concrete results.

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