Pharmacological and toxicological analysis of two enantiomers derived from citronellal monoterpene: An *in silico* approach

**Abstract:** Monoterpenes are a class of secondary plant metabolites known to exhibit a variety of effects in different biological systems. Therefore, the aim of this study was to evaluate the pharmacological and toxicological effects of the enantiomers $(R)$-$(+)$ and $(S)$-$(−)$-citronellal *in silico*. Approximately 50% of the reasons that lead to failure in development of a drug are associated with the pharmacokinetic profile and toxicology. Thus, the determinations of the pharmacokinetic profile (ADME), together with toxicity (ADMET) are important parameters in the definition of bioavailability and toxic effects of a molecule. The Pass online, Osiris and Molinspiration program were used in the study for activities *in silico*. *In silico* models are being applied for the evaluation of toxicity of compound in metabolic environment of mammals. The obtained results showed the molecule was drug-like with 29 possible activities with $Pa > 70\%$ and this monoterpenes present low toxicity theoretical risk.

**Key-words:** Oral bioavailability; Toxicity; Biological activity; Enantiomers; Secondary metabolites.

**Resumo:** Os monoterpenos são uma classe de metabolitos secundários de plantas conhecidas por apresentar uma variedade de efeitos em diferentes sistemas biológicos. Portanto, o objetivo deste estudo foi avaliar os efeitos farmacológicos e toxicológicos dos enantiômeros $(R)$-$(+)\$ e $(S)$-$(−)\$-citronelal *in silico*. Cerca de 50% das razões que levam à insuficiência no desenvolvimento de um fármaco estão associados com o perfil farmacocinético e toxicológico. Assim, a determinação do perfil farmacocinético (ADME) juntamente com a toxicidade (ADMET) são parâmetros importantes na definição de biodisponibilidade e efeitos tóxicos de uma molécula. Os softwares Pass online, Osiris e Molinspiration foram utilizados no estudo para atividades *in silico*. Modelos *in silico* são aplicados para a avaliação da toxicidade de compostos em ambientes metabólicos de mamíferos. Os resultados obtidos mostraram que as moléculas foram semelhantes a fármacos com 29 possíveis atividades com $Pa > 70\%$ e estes monoterpenos apresentaram baixo risco de toxicidade teórica.

**Palavras-chave:** Biodisponibilidade oral; Toxicidade; Atividade biológica; Enantiômeros; Metabólitos secundários.
INTRODUCTION

The terpenes are biosynthetic derivatives of condensations of C5 isoprene units from the mevalonic acid pathway, constituting one of the most important groups of secondary metabolites in the composition of essential oils from aromatic plants (OUÉDRAOGO et al., 2013; SRIVIDYA et al., 2015).

The terpenoids are known to exhibit a variety of effects in different biological systems. Many of these molecules are essential for the growth of plants, their general development and metabolism (KUMAR et al., 2012; LANGE, 2015). Citronellal is a monoterpen isolated as a non-racemic mixture of R and S enantiomers, common in the essential oils of plants of the genera *Cymbopogon* and *Eucalyptus* presenting an excellent antifungal activity. Besides the antimicrobial activity, these enantiomers revealed to have several other biological activities, among them are antioxidant, herbicide, insecticide, repellent and antitumor (SHIKATA et al., 2011; TRINDADE et al., 2015).

Among the toxicological effects of greater clinical relevance for human health, targets of researches in the bioactive natural and synthetic materials are the mutagenicity, carcinogenicity and the effects on the reproductive system. Therefore, they are the object of intensive research activity, as well as of regulated recognized testing methods (BOERSMA et al., 2000; ABDEL-RAHMAN et al., 2011). Monoterpenes are used for medical applications in creams, balms, and bath additives, as ingredients in cosmetic and cleaning products, and as food aromas (DOLDER et al., 2006). They have been proposed to be used as chemotherapeutic and chemopreventive drugs due to their inhibitory effect on the growth of cells in vitro (PATHIPATI, 2012; YILDIRIM et al., 2013).

About 50% of the reasons which lead to the insufficiency in the development of a drug are associated to the pharmacokinetic and toxicological profile. Therefore, the determination of the absorption, distribution, metabolism and excretion (ADME) pharmacokinetic profile together with the toxicity (ADMET) are important parameters in the determination of the bioavailability and toxic effects of a molecule, helping in the reduction of time and cost of research and development of new drugs (HANSCH et al., 2004; SAHU et al., 2016).

As a result is observed the need for analysis which enables to predict and characterize the pharmacological and toxicological profiles in silico and in vivo of biologically active molecules such as the monoterpenes citronellal.

Therefore, the aim of this study was to evaluate the pharmacological and toxicological effects of the enantiomers (R)-(+) and (S)-(−)-citronellal in silico.

MATERIAL AND METHODS

Pass online

The spectrum of biological activities of a chemical compound is the set of different types of biological activities which reflect the results of the interaction of the compound with several biological entities (AL-REHAILLY et al., 2011). The biological activity is defined qualitatively ("Yes" / "No") suggesting that the spectrum of biological activity represents the "intrinsic" property of a substance depending only on theirs structural and physical-chemical characteristics (KOUTSOUKAS et al., 2011; SRINIVAS et al., 2014).

Pass (Prediction of Activity Spectra for Substances) is a (http://www.pharmaexpert.ru/passonline/index.php) projected as a tool to assess the general biological potential of an organic molecule applicant to become a drug (NIGSCH et al., 2011). Pass provides simultaneous predictions of many types of biological activities based on the structure of the organic compounds. Therefore, Pass may be used to estimate the profiles of the biological activities relatively to the virtual molecules, before their chemical synthesis and biological tests. Pa (probability "of being active") and Pi (probability "of being inactive") estimates the categorization of the potential compounds to belong to the subclass of active or inactive compounds respectively (CHAND, 2011; KHURANA et al., 2011).

Osiris

The prediction process of biological effects executed by the software Osiris (http://www.organic-chemistry.org/prog/peo/) is based on a set of pre-computerized molecular fragments which originate the toxicity alerts, in the case of being found in the currently projected molecular structure. The Osiris toxicity predictions result from the mutagenicity, tumorigenicity, irritability, effects on the reproductive system, cLogP value, druglikeness and drug-score of the molecules (URSU et al., 2010; URSU et al., 2011).

Lipinski’s rule of five, also known as the Pfizer’s rule of five is a rule to evaluate drug likeness. It determines whether a chemical compound with assured pharmacological or biological activity, has properties that would make it a likely orally active drug in humans. This rule describes the molecular properties, which are important for a drug's pharmacokinetics in the human body including their absorption, distribution, metabolism and excretion ("ADME").

The rule states that most "drug-like" molecules have cLogP ≤ 5, molecular weight ≤ 500, number of hydrogen bond acceptors ≤ 10 (nALH ≤ 10) and the number of hydrogen bond donor’s ≤ 5 (nDLH ≤ 5). Molecules violating more than one of these rules may have problems with bioavailability. The rule is called "Rule of 5" because the border values are 5, 500, 2*5, and 5 (LIPINSKI et al., 2001; LIPINSKI, 2004).

Molinspiration

Molinspiration, a web based software used to obtain parameters such as mi Log P, total polar surface area (TPSA), drug likeness. Mi Log P, is calculated as a sum of fragment based contributions and correction factors which is used to check good permeability across the cell membrane (VERMA, 2012). The total polar surface area (TPSA) relates to hydrogen bonding potential of particular molecule and is a very good predictor of drug transport properties such as bioavailability, intestinal absorption, and blood brain barrier penetration etc. The calculation of volume is based on group contributors. The number of rotatable bonds measures molecular flexibility, which is a
very good descriptor of absorption and bioavailability of drugs (ERTL et al., 2000). The drug likeness score of enantiomers [(R)-(+) and (S)-(−)-citronellal] compound was calculated by considering mi Log P (partition coefficient), molecular weight, number of heavy atoms, number of hydrogen acceptor, number of hydrogen donor and number of violation, number of rotatable bonds and volume. The bioactivity of the compound was checked by calculating the activity score of GPCR ligand, ion channel modulator, nuclear receptor ligand, kinase inhibitor, protease inhibitor, enzyme inhibitor with the help of software.

RESULTS AND DISCUSSION

Pass online calculation

The analysis of the possibility of activities of the two enantiomers (R)-(+) and (S)-(−)-citronellal revealed that the molecules were drug-like with 29 possible activities in the $\text{Pa} > 70\%$ (Table 1) and numerous druglike properties in the $\text{Pa} > 30\%$, for example: antifungal activity (Pa: 0.580 and Pi: 0.020), anhiphilic activity (Pa: 0.421 and Pi: 0.014), anti-infective activity (Pa: 0.389 and Pi: 0.050), insecticide (Pa: 0.487 and Pi: 0.004), hepatoprotective activity (Pa: 0.355 and Pi: 0.042) and antioxidant activity (Pa: 0.409 and Pi: 0.011).

### Table 1. Predicted activities of the (R)-(+) and (S)-(−)-citronellal at Pa > 70% depicted through Pass online tool.

| No. | Activities | Pa   | Pi   | Activity                      |
|-----|------------|------|------|-------------------------------|
| 1   |            | 0.747| 0.032| Acrocyahidropsin inhibitor    |
| 2   |            | 0.797| 0.001| Alcohol dehydrogenase substrate |
| 3   |            | 0.904| 0.001| Aldose reductase substrate     |
| 4   |            | 0.704| 0.010| All-trans-retinyl-palmitate hydrolase inhibitor |
| 5   |            | 0.777| 0.004| Allyl-alcohol dehydrogenase inhibitor |
| 6   |            | 0.772| 0.005| Antisercretor                   |
| 7   |            | 0.758| 0.046| Aspulvinone dimethyl allyl transferase inhibitor |
| 8   |            | 0.823| 0.002| BRAF expression inhibitor       |
| 9   |            | 0.724| 0.048| CDP-glycerol glyceralphosphotransferase inhibitor |
| 10  |            | 0.883| 0.006| CYP2J substrate                |
| 11  |            | 0.843| 0.002| Carboxyly reductase inhibitor   |
| 12  |            | 0.747| 0.032| Chymosin inhibitor             |
| 13  |            | 0.768| 0.002| Dolichyl-phosphatase inhibitor  |
| 14  |            | 0.703| 0.005| Glutarate-semialdehyde dehydrogenase inhibitor |
| 15  |            | 0.781| 0.005| Limulus clotting factor B inhibitor |
| 16  |            | 0.729| 0.008| Limulus clotting factor C inhibitor |
| 17  |            | 0.781| 0.024| Mucomembranous protector       |
| 18  |            | 0.779| 0.041| Phobic disorders treatment     |
| 19  |            | 0.713| 0.014| Phosphatidylcholine-retinol O-acetyltransferase inhibitor |
| 20  |            | 0.756| 0.002| Plastoquinol-plastocyaninreductase inhibitor |
| 21  |            | 0.814| 0.017| Polyporopepsin inhibitor       |
| 22  |            | 0.824| 0.003| Prenyl-diphosphatase inhibitor  |
| 23  |            | 0.821| 0.012| Pro-opiocalcin converting enzyme inhibitor |
| 24  |            | 0.885| 0.004| Protein-disulfide reductase (glutathione) inhibitor |
| 25  |            | 0.747| 0.032| Saccharopepsin inhibitor       |
| 26  |            | 0.745| 0.018| TP53 expression enhancer       |
| 27  |            | 0.824| 0.020| Testosterone 17beta-dehydrogenase (NADP+) inhibitor |
| 28  |            | 0.838| 0.021| Ubiquinol-cytochrome-c reductase inhibitor |
| 29  |            | 0.769| 0.004| Undecaprenyl-phosphate mannosyltransferase inhibitor |

Pa: probability "being active" and Pi: probability "of being idle".

The in silico models are being applied for the assessment of the toxicity of organic compounds in the metabolic environment of mammals simulated in computers. Their use with the regulated environments has been encouraged by the recent legislation (MARCHANT, 2012).

However, the main limitation of the toxicity assessment in model animals is that they are efficient in the assessment of organic molecules with low average molecular weight (ANGELO et al., 2006; SRINIVAS et al., 2014).

Therefore, several efficient automatic learning statistical methods have been used to develop in silico tools to predict the toxicological hazards of molecular structures. This way, these tools are used to study existent hypothetical compounds, which are fast, reproducible and which are typically based on human biorregulators (MARCHANT, 2012; SRINIVAS et al., 2014).

This variety of possible effects to the (R)-(+) and (S)-(−)-citronellal are according to class of monoterpenes, secondary metabolites that have been proposed to exert beneficial effects in the prevention of a large number of diseases, including cancer, cardiovascular disease, neurodegenerative disorders and microbial infections (ROMANO et al., 2013). In addition, the results show that the monoterpenes followed the "Rule of Five" Lipinski which requires that the compound must possess at least three of four requisites (nDLH 5, nALH 10, Da 500 e cLogP 5), thus the (R)-(+) and (S)-(−)-citronellal may be active drug in humans by the oral route of administration (LIPINSKI et al., 2001; LIPINSKI, 2004) (Table 2).

Osiris calculation

Structure based designing is now a fairly routine procedure and many potential drugs do not qualify for clinic practice because of ADMET-Tox liabilities. One very important class of enzyme, responsible for many ADMET
problems, is the cytochromes P450. Inhibition of these or production of unwanted metabolites can result in many adverse drug reactions. Of the most important program, Osiris is already available online for its designing/prediction of various activities (HADDAA et al., 2014).

The Osiris Property Explorer shown in this page is an integral part of Actelion's inhouse substance registration system. It allows drawing chemical structures and also calculates various drug-relevant properties whenever a structure is valid. Prediction results are color coded in which the red color shows high risks with undesired effects like mutagenicity or a poor intestinal absorption and green color indicates drug-conform behavior (SAHU et al., 2016).

Table 2. Osiris calculations of toxicity risks and drug-score of compounds (R)-(+) and (S)-(−)-citronellal compared to the standard antifungal drugs.

| Compounds         | Toxicity risk[6] | Drug score[7] |
|-------------------|------------------|---------------|
|                   | MUT   | TUMO | IRRRI | REP | CLP | S | D-L | D-S | nALH | nDLH | Da   |
| (R)-(+) CT         | [ ]   | [ ]  | [ ]   | [ ] | 3.13 | -2.36 | -6.97 | 0.26 | 1.00  | 0.00  | 154.25 |
| (S)-(−) CT         | [ ]   | [ ]  | [ ]   | [ ] | 3.13 | -2.36 | -6.97 | 0.26 | 1.00  | 0.00  | 154.25 |
| Amphotericin B     | [ ]   | [ ]  | [ ]   | [ ] | 0.32 | -5.07 | -0.13 | 0.27 | 18.00 | 12.00 | 924.09 |
| Fluconazole        | [ ]   | [ ]  | [ ]   | [ ] | -0.10 | -2.17 | 3.03  | 0.90 | 7.00  | 1.00  | 306.28 |
| Itraconazole       | [ ]   | [ ]  | [ ]   | [ ] | 5.15 | -7.30 | 7.61  | 0.07 | 12.00 | 0.00  | 705.64 |
| Miconazole         | [ ]   | [ ]  | [ ]   | [ ] | 4.85 | -5.08 | 4.72  | 0.49 | 3.00  | 0.00  | 416.13 |
| Ketoconazole       | [ ]   | [ ]  | [ ]   | [ ] | 3.36 | -2.99 | 8.14  | 0.60 | 8.00  | 0.00  | 531.44 |

In addition, the results show that the enantiomers followed the "Rule of Five" Lipinski, which requires that the compound must possess at least three of four requisites (nDLH ≤ 5, nALH ≤ 10, Da ≤ 500 and cLogP ≤ 5), thus the citronellal may be active drug in humans by the oral route of administration (Table 2) (LIPINSKI et al., 2001; ABHAY et al., 2007).

Molinspiration calculation

CLogP is calculated by the Molinspiration as a sum of contributions based on the molecular structure and correction factors (Table 2). This method is very robust and capable of processing all the organic molecules and many organometallic ones. The total polar surface area (TPSA) is calculated by the methodology published by Ertl et al. (2000) as being the addition of the contributions of the molecular fragments. Polar fragments of O and N are considered.

The PSA has shown to be a very good descriptor for the characterization of absorption of drugs, including intestinal absorption, bioavailability and penetration of the blood–brain barrier (ERTL et al., 2000). The prediction results for the compounds (R)-(+) and (S)-(−)-citronellal are given in Table 3. In addition, polar surface area (TPSA) is a determinant factor in the prediction of molecular bioavailability, which should be less than or equal to 140 Å2. Therefore, as can be seen in table 3, (R)-(+) and (S)-(−)-citronellal present the lowest values of TPSA compared to standard drugs (ERTL et al., 2000).

Table 3. Molinspiration calculations of compounds (R)-(+) and (S)-(−)-citronellal compared to the standard antifungal drugs.

| Compounds         | Physicochemical properties[8] | Drug-likeliness[9] |
|-------------------|--------------------------------|--------------------|
|                   | TPSA | nON | miLogP | nV | nROTB | Vol | GPCR | ICM | KI | NRL | PI | EI |
| (R)-(+) CT         | 17.07 | 1.00 | 3.60 | 0.00 | 5.00 | 175.95 | -0.83 | -0.08 | -1.30 | -0.61 | -0.50 | -0.03 |
| (S)-(−) CT         | 17.07 | 1.00 | 3.60 | 0.00 | 5.00 | 175.95 | -0.83 | -0.08 | -1.30 | -0.61 | -0.50 | -0.03 |
| AMB                | 319.61 | 18.0 | -2.49 | 3.00 | 3.00 | 865.48 | -3.06 | -3.53 | -3.45 | -2.45 | -2.95 |
| FLU                | 81.66 | 7.00 | -0.12 | 0.00 | 11.0 | 248.96 | 0.04 | 0.01 | -0.09 | -0.23 | -0.09 | 0.03 |
| ICZ                | 104.73 | 12.0 | 5.32 | 3.00 | 11.0 | 610.90 | -0.40 | -1.50 | -1.30 | -1.31 | -0.66 | -0.97 |
| MCZ                | 27.06 | 3.00 | 5.72 | 1.00 | 6.00 | 321.63 | 0.21 | -0.13 | 0.07 | -0.12 | -0.10 | 0.33 |
| KET                | 69.08 | 8.00 | 5.72 | 1.00 | 7.00 | 452.47 | -0.25 | -0.14 | -0.17 | -0.32 | -0.21 | 0.15 |

[6]TPSA: total polar surface area; nON: O/NH O-HN interaction; nV: number of violation; nROTB: number of rotation; Vol: volume. [7]ICM: ion channel modulator; KI: kinase inhibitor; NRL: nuclear receptor ligand; PI: protease inhibitor; EI: enzyme inhibitor.
CONCLUSION

The in silico study of monoterpenes (R)-(+) and (S)-(-)-citronellal demonstrates that this compound has several possible biological effects on the human body as well as good oral bioavailability and low toxicity theoretical risk.

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