REBES **Revista Brasileira de Educação e Saúde**
Pombal, PB, Grupo Verde de Agroecologia e Abelhas
http://www.gvaa.com.br/revista/index.php/REBES
DOI: http://dx.doi.org/10.18378/rebes.v7i3.4705

ARTIGO CIENTÍFICO

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

Análise farmacológica e toxicológica de dois enantiômeros derivados do monoterpeno citronelal: Uma abordagem in sílico

Cássio Ilan Soares Medeiros
Mestre em Produtos Naturais e Sintéticos Bioativos, Universidade Federal da Paraíba. E-mail: cassioism@hotmail.com
Daniele de Figuêredo Silva
Mestre em Produtos Naturais e Sintéticos Bioativos, Universidade Federal da Paraíba. E-mail: danielefigueredo31@gmail.com
Abrahão Alves de Oliveira Filho
Doutor em Produtos Naturais e Sintéticos Bioativos, Universidade Federal da Paraíba. E-mail: abrahao.farm@gmail.com
Edeltrudes de Oliveira Lima
Doutora em Produtos Naturais e Sintéticos Bioativos, Universidade Federal da Paraíba. E-mail: edelolima@yahoo.com.br

Abstract: Monotherpenes 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 sílico*. 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 sílico*. Modelos *in sílico* 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.

Recebido em 28/01/2017
Aprovado em: 17/05/2017

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 terpenoides 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 monoterpene isolated as a non-racemic mixture of *R* and *S* enantiomers, common in the essential oils of plants of the genus *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 monoterpene 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-REHAILY 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; OPREA, 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 $\leq$ 5, molecular weight $\leq$ 500, number of hydrogen bond acceptors $\leq$ 10 (nALH $\leq$ 10) and the number of hydrogen bond donor's $\leq$ 5 (nDLH $\leq$ 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 Pa > 70% (Table 1) and numerous druglike properties in the Pa > 30%, for example: antifungal activity (Pa: 0.580 and Pi: 0.020), anthelmintic 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.

N° activities	Pa	Pi	Activity
1	0.747	0.032	Acrocylindropepsin 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	Antisecretoric
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 glycerophosphotransferase inhibitor
10	0.883	0.006	CYP2J substrate
11	0.843	0.002	Carboxylate 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-acyltransferase 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-opiomelanocortin 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 ADME-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 (HADDA et al., 2014).

The Osiris Property Explorer shown in this page is an integral part of Actelion'sinhouse 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).

The (*R*)-(+)- and (*S*)-(-)-citronellal was analyzed through Osiris tool for the determination of drug-relevant properties like mutagenic, irritant, reproductive effects, cLogP value, drug-score, druglikeness and their toxicity risks assessment. Osiris employed to predict the toxicity and carcinogenicity for antifungal agent was reported (TEKTO, 2005). The results showed this monoterpenes presents low theoretical risk of toxicity (Table 2) and has considerable values druglikeness (-6.97) and drug-score (0.26). "Drug score" (combining "druglikeness", cLogP, cLogS, mass molecular and risk of toxicity) that generates a value infers that the potential of a compound become a future drug.

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[a]				Drug score[b]						
	MUT	TUMO	IRRI	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

Nontoxic; Slighlytoxic; Highlytoxic; [a]MUT: Mutagenic; TUMO: Tumorigenic; IRRI: Irritant; REP: Reproductive effective. [b]CLP: cLogP; S: Solubility; DL: Drug-likeness; DS: Drug-Score; nALH: number of acceptors hydrogen bonding; nDLH: number of hydrogen bond donor groups; Da: Molecular Weight.

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 TPAS 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[a]						Drug-likeness[b]					
	TPSA	nON	miLogP	nV	nROTB	Vol	GPCRL	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	-3.59	-3.45	-2.45	-2.95
FLU	81.66	7.00	-0.12	0.00	5.00	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	607.90	-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	3.77	1.00	7.00	452.47	0.25	-0.14	-0.17	-0.32	-0.21	0.15

[a]TPSA: total polar surface area; nON: O/NH O-HN interaction; nV: number of violation; nROTB: number of rotation; Vol: volume. [b]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.

REFERENCES

ABDEL-RAHMAN, A.; ANYANGWE, N.; CARLACCI, L.; CASPER, S.; DANAM, R. P.; ENONGENE, E.; ERIVES, G. FABRICANT, D.; GUDI, R.; HILMAS, C. J.; HINES, F.; HOWARD, P.; LEVY, D.; LIN, Y.; MOORE, R. J.; PFEILER, E.; THURMOND, T. S.; TURUJMAN, S.; WALKER, N. J. The Safety and Regulation of Natural Products Used as Foods and Food Ingredients. Toxicological Sciences, v.123, n.2, p.333-348, 2011.

ABHAY, T. S.; UDAY, D. D.; SANJAY, S. P.; SUDHIR, M. V. Improving decision making for drug candidates: A computational approach for benzthiazoles as antifungal. Indian Journal of Biotechnology, v.6, n.1, p.389-396, 2007.

AL-REHAILY, A. J.; AHMAD, M. S.; MUSTAFA, J.; AL-OQAIL, M. M.; HASSAN, W.; KHAN, S. I.; KHAN, I. A. Solanopubamine, a rare steroidal alkaloid from *Solanum schimperianum*: Synthesis of some new alkyl and acyl derivatives, their anticancer and antimicrobial evaluation. Journal of Saudi Chemical Society, In Press, Corrected Proof, Oct 2011.

ANGELO, V.; MAX, D.; MARKUS, A. L. The Challenge of Predicting Drug Toxicity *in silico*. Basic & Clinical Pharmacology & Toxicology, v. 99, n.1, p.195-208, 2006.

BOERSMA, M. G.; VERVOORT, J.; SZYMUSIAK, H.; LEMANSKA, K.; TYRAKOWSKA, B.; CENAS, N.; SEGURA-AGUILAR, J.; RIETJENS, I. M.. Regioselectivity and reversibility of the glutathione conjugation of quercetin quinone methide. Chemical Research in Toxicology, v.13, n.1, p.185-191, 2000.

CHAND, B. Structure-Bioactivity-Relationships and Crystallographic Analysis of Secondary Interactions in Pregnane-Based Steroids. Journal Chemical Crystallography, v.41, n.12, p.1901-1926, 2011.

DOLDER, S.; HOFSTETTER, W.; WETTERWALD, A.; MÜHLBAUER, R. C.; FELIX, R. Effect of Monoterpenes on the Formation and Activation of Osteoclasts *In Vitro*. Journal Bone end Mineral Research, v.21, n.4, p.1-9, 2006.

ERTL, P.; ROHDE, B.; SELZER, P. Fast calculation of molecular polar surface area (PSA) as a sum on fragment-based contributions and its application to the prediction of drug transport properties. Journal of Medicinal Chemistry, v.43, n.1, p.3714-3717, 2000.

HADDA, T. B.; AHMAD, M.; SULTANA, S.; SHAHEEN, U.; BADER, A.; SRIVASTAVA, S. POM analyses for antimicrobial evaluation of thienopyrimidinones derivatives: a rapid method for drug design. Medicinal Chemistry Research, v.23, n.1, p.16-24, 2014.

HANSCH, C.; LEO, A.; MEKAPATI, S. B.; KURUP, A.; BIOORG. QSAR and ADME. Journal of Medicinal Chemistry, v.12, n.1, p.3391-3400, 2004.

KHURANA, N. I.; MOHAN, P. S.; GAJBHIYE, A.; GOEL, R. K. PASS assisted prediction and pharmacological evaluation of novel nicotinic analogs for nootropic activity in mice. European Journal of Pharmacology, v.662, n.1-3, p.22-30, 2011.

KOUTSOUKAS, A.; SIMMS, B.; KIRCHMAIR, J.; BOND, P. J.; WHITMORE, A. V.; ZIMMER, S.; YOUNG, M. P.; BENDER, A. From *in silico* target prediction to multi-target drug design: Current databases, methods and applications. Journal of Proteomics, v.74, n.12, p.2554-2574, 2011.

KUMAR, P.; MISHRA, S.; MALIK, A.; SATYA, S. Housefly (*Musca domestica* L.) control potential of *Cymbopogon citratus* Stapf. (Poales: Poaceae) essential oil and monoterpenes (citral and 1,8-cineole). Parasitology Research, v.112, n.1, p.69-76, 2013.

LANGE, B. M. Biosynthesis and Biotechnology of High-Value *p*-Menthane Monoterpenes, Including Menthol, Carvone, and Limonene. Biotechnology of Isoprenoids, v.148, n.1, p.319-353, 2015.

LIPINSKI, C. A. Drug discovery today. Technologies, v.1, n.1, p.337-341, 2004.

LIPINSKI, C. A.; LOMBARDO, F.; DOMINY, B. W.; FEENEY, P. J. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Advanced Drug Delivery Reviews, v.46, n.1-3, p.3-26, 2011.

MARCHANT, C. A. Computational toxicology: a tool for all industries. WIREs Computational Molecular Science. v.2, n.1, p.424-434, 2012.

NIGSCH, F.; LOUNKINE, E.; MCCARREN, P.; CORNETT, B.; GLICK, M.; AZZAOUI, K.; URBAN, L.; MARC, P.; MULLER, A.; HAHNE, F.; HEARD, D. J.; JENKINS, J. L. Computational methods for early predictive safety assessment from biological and chemical data. Expert Opinion on Drug Metabolism & Toxicology, v.7, n.12, p.1497-1511, 2011.

OUÉDRAOGO, I. W. K.; WINTER, J. D.; GERBAUX, P.; BONZI-COULIBALY, Y. L. Volatility profiles of monoterpenes loaded onto cellulosic-based materials. Industrial Crops and Products, v.51, n.1, p.100-106, 2013.

PATHIPATI, U. R. Fumigant and contact toxic potential of essential oils from plant extracts against stored product pests. Journal of Biopesticides, v.5, n.2, p.120-128, 2012.

ROMANO, B.; PAGANO, E.; MONTANARO, V.; FORTUNATO, A. L.; MILIC, N.; BORRELLI, F. Novel Insights into the Pharmacology of Flavonoids. Phytother research, v.27, n.1, p.1588-1596, 2013.

SAHU, P. K.; SAHU, P. K.; SAMADHIYA, P.; SAHU, P. L.; AGARWAL, D. D. POM analyses and evaluation of *in vitro* antimicrobial, antitumor activity of 4H-pyrimido[2,1-b] benzothiazole derivatives. Medicinal Chemistry Research, v.1, n.1, p.1-13, 2016.

SHIKATA, S.; WATANABE, T.; HATTORI, K.; AOYAMA, M.; MIYAKOSHI, T. Dissolution of polystyrene into cyclic monoterpenes present in tree essential oils. Journal Material Cycles and Waste Management, v.13, n.1, p.127, 2011.

SRINIVAS, N.; SANDEEP, K. S.; ANUSHA, Y.; DEVENDRA, B. N. *In Vitro* Cytotoxic Evaluation and Detoxification of Monocrotaline (Mct) Alkaloid: An *In Silico* Approach. International Invention Journal Biochemistry Bioinformatics, 2014.

SRIVIDYA, N.; DAVIS, E. M.; CROTEAU, R. B.; LANGE B. M. Functional analysis of (4S)-limonene synthase mutants reveals determinants of catalytic outcome in a model monoterpene synthase. Proceedings of the National Academy of Sciences, v.112, n.11, p.3332-3337, 2015.

TEKTO, I. V. Drug Discov. Computing chemistry on the web. Today, v.10, n.22, p.1497-1500, 2005.

TRINDADE, L. A.; OLIVEIRA, J. A.; CASTRO, R. D.; LIMA, E. O. Inhibition of adherence of C. albicans to dental implants and cover screws by Cymbopogon nardus essential oil and citronellal. Clinical Oral Investigations, v.19, n.9, p.2223-2231, 2015.

URSU, O.; OPREA, T. I. Model-Free Drug-Likeness from Fragments. Journal Chemical Information and Modeling, v.50, n.8, p.1387-1394, 2010.

URSU, O.; RAYAN, A.; GOLDBLUM, A.; OPREA, T. I. Understanding drug-likeness. Wiley Interdisciplinary Reviews: Computational Molecular Science, v.1, n.5, p.760-781, 2011.

VERMA, A. Lead finding from *Phyllanthus debelis* with hepatoprotective potentials. Asian Pacific Journal Tropical Biomedicine, v.3, n.1, p.1735-1737, 2012.

YILDIRIM, E.; EMSEN, B.; KORDALI, S. Insecticidal effects of monoterpenes on *Sitophilus zeamais* Motschulsky (Coleoptera: Curculionidae). Journal Applied Botany and Food Quality, v.86, n.1, p.198-204, 2013.