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Predicting the potential absorption, distribution, metabolism and excretion of the aldehyde citral

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Citral is an acyclic monoterpene aldehyde that occurs in natural products in two forms: α-form (*trans*-3,7-dimethyl-2,6-octadiene-1-al) and β-form (*cis*-3,7-dimethyl-2,7-octadiene-1-al). The *trans*-form is also called geranial (citral a) and the *cis*-form neral (citral b). This aromatic substance is found in many essential oils - eucalyptus, lemongrass, citronella, lyceum, lemon wormwood, verbena, *etc.* It is mainly isolated from eucalyptus, lychee, lemongrass and other essential oils. For industrial purposes, however, it is synthesized. It has poor resistance to light, air and heat. Technical citral is more stable in soaps. It is used in perfumery and cosmetics, to flavor various food products and it is also used as a raw material for the synthesis of many other aromatic substances. The aim of the present study is to predict the biological effects of citral by applying an *in silico* approach.

Keywords: citral, absorption, distribution, metabolism, excretion

INTRODUCTION

Citral [CAS 106-26-3] is an acyclic monoterpene aldehyde that occurs in natural products as an isomeric mixture of geranial (*E*-3,7-dimethyl-2,6-octadienal) and neral (*Z*-3,7-dimethyl-2,6-octadienal). The *trans*-form is also called (citral a) and the *cis*-form (citral b). In the isomeric mixtures, geranial is usually the predominant one. It is usually isolated from different essential oils [1–3], for industrial purposes, however, it is synthesized from various other compounds, such as isoprene, methyl-heptenone, β-pinene, linalool or geraniol [1].

As an oxygen derivative, it exhibits antimicrobial properties against various test microorganisms, such as Gram-positive and Gram-negative bacteria, yeasts, molds [4–9], with pronounced antioxidant [5, 7, 8] and other biological properties [4, 7].

Technical citral is more stable in soaps. It is used in perfumery (with citrus, verbena, floral and fantasy notes) and cosmetics, to flavor various food products (with a citrus smell, as a substitute for lemon oil). Citral is also used as a raw material for the synthesis of many other aromatic substances [1, 3]. It is often encapsulated and, in combination with various polysaccharides, is used on one hand as a flavoring agent and preservative [6, 10–12], and on the other as a component of edible food coatings [10, 11, 13].

Findings have shown that for people with sensitive skin, it can cause allergies, resulting in skin redness, as well as breathing disorders [14–16]. Therefore, it is included in the list of 80 allergens of Regulation 2023/1554 of EC [17]. Its amount should be labeled on perfumery or cosmetic products when the content is more than 0.01% in rinse-off products for skin and hair (shampoos, shower gels, masks, *etc*.) and more than 0.001% in those that remain in contact with skin (creams, toilet milks, lotions, *etc*.).

The aim of the present study is to predict the biological effects of citral by applying an *in silico* approach, such as lipophilicity, water solubility, pharmacokinetics and other characteristic medicinal formulations.

MATERIALS AND METHODS

Compound data

Citral has been shown to exhibit apoptotic, anti-nociceptive and anti-inflammatory functions. These are compounds contaning a chain of two isoprene units [18].

SwissADME. This web tool grants free access to data regarding various properties and predictive models necessary in determining the physico-chemical parameters and for evaluating pharmaco-kinetics of various compounds [19].

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According to the "Rule of Five", a given molecule is orally active/absorbed when it does not violate any two or more of the rules. However, some complicated natural products are not suited to the rules. For that, a variety of other rules and filters regarding drug-likeness that are equal to the "Rule of Five" have been proposed [20–22].

Hopkins in 2012 developed the QED (quantitative estimate of drug-likeness) concept [23] which generated eight physicochemical properties, which include four of the five (MW, iLOGP, HBAs and HBDs) and four other parameters such as topological polar surface area (TPSA), number of rotatable bonds (ROTBs), number of aromatic rings (nAROMs), and number of alerts for undesirable substructures (ALERTs i.e. PAINS #alert and Brenk #alert) using 771 marketed oral drugs [23]. The concept of QED is the most flexible and adopted compared to ordinary drug-likeness rules [19].

RESULTS AND DISCUSSION

Some physicochemical parameters of citral are given in Table 1.

Lipophilic characteristics of citral are presented in Table 2.

Table 1. Physicochemical properties of citral

Molecular weight (g/mol)	Number of heavy atoms	Number of aromatic heavy atoms	Fraction Csp^3	Number of rotatable bonds	Number of H-bond acceptors	Number of H-bond donors	Molar refractivity	TPSA ($Å^2$)
152.23	11	0	0.50	4	1	0	49.44	17.07

Table 2. Lipophilic characteristics of citral.

iLOGP	XLOGP3	WLOGP	MLOGP	SILICOS-IT	Consensus Log $P_{o/w}$
2.47	3.03	2.88	2.49	2.65	2.71

* XLOGP3, an atomistic accost including corrective factors and knowledge based library; WLOGP, application of purely atomistic method stationed on fragmental system; MLOGP, an archetype of topological method suggested on a linear relationship with implemented 13 molecular descriptors; SILICOS-IT, an mongrel method entrust on 27 fragments and 7 topological descriptors; iLOGP, a physics-based method lean on free energies of solvation in n-octanol and water calculated by the generalized-born and solvent accessible surface area (GB/SA) model [19].

Table 3. Water solubility characteristics of citral

ESOL				Ali *et al.* [24]				SILICOS-IT			
Log *S* (ESOL)	Solubility		Class	Log *S*	Solubility		Class	Log *S* SILICOS-IT	Solubility		Class
	mg/ml	mol/L			mg/ml	mol/L			mg/ml	mol/L	
-2.43	5.67e-01	3.73e-03	S	-3.05	1.34e-01	8.83e-04	S	-1.96	1.66e+00	1.09e-02	S

*I – insoluble; PS – poorly soluble; S – soluble; VS – very soluble.

Table 4. Pharmacokinetic parameters of citral

GI absorption	BBB permeant	P-gp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Log *Kp* (Skin permeation) (cm/s)
High	Yes	No	No	No	No	No	No	-5.08

Table 5. Drug-likeness rules and bioavailability score of citral

Lipinski *et al.* [20]	Ghose *et al.* [21]	Veber *et al.* [28]	Egan *et al.* [29]	Muegge *et al.* [30]	Bioavailability score
Yes; 0 violation	No; 1 violation MW < 160	Yes	Yes	No; 2 violation:MW < 200; Heteroatoms < 2	0.55

Table 6. Medicinal chemistry properties of the compound citral

Pains	Brenk *et al.* [32]	Leadlikeness	Synthetic accessibility (SA)
0 alert	3 alerts: aldehyde, isolated_alkene, michael_acceptor_1	No; 1 violation: MW < 250	2.49

Log P data define citral as lipophilic. Two different topological approaches predicting water solubility are included in SwissADME, with the first one applying an ESOL model. (Solubility class: Log S Scale: Insoluble & lt; -10 weakly & lt; -6, moderately & lt; -4 soluble & lt; -2 very & lt; 0 & lt; high), and the second was adapted by Ali *et al.* [24]. A third predictor of SwissADME has been developed from SILICOS-IT (Solubility class: Log S Scale: Insoluble & lt; - 10 weakly & lt; -6, moderately & lt; -4 soluble < -2 very & lt; 0 & lt; high), the linear coefficient being corrected by molecular weight ($R^2 = 0.75$).

Water solubility characteristics of citral are presented in Table 3. Citral has high water solubility. For the prediction of passive absorption in the gastrointestinal tract, as well as in drug development, the BOILED-Egg model is used, which is very rapid, spontaneous and effective [25]. The space of molecules with a greater degree of absorption from the gastrointestinal tract is colored white, and this is most likely to penetrate the brain – in yellow [19]. It is known that between 50 and 90% of molecules with therapeutic properties from the five main isoforms of citral are biotransformed from cytochrome P450 (CYP) isoenzymes [26, 27].

Pharmacokinetics parameters of citral are presented in Table 4. The data indicate a high level of absorption of the gastrointestinal tract and a high BBB, i.e. citral is not the substrate for P-gp. The data show that citral cannot be a substrate of P-gp, it is also a non-inhibitor of the cytochrome P450 isozymes. Citral is weak in permeability which is determined by the skin permeability coefficient (Log Kp) [27]. Access to five different filters, which are based on rules with different ranges of properties, and define the molecule as a drug, is given by section SwissADME. The Lipinski *et al.* [20] (Pfizer) filter is the pioneer for rule-of-five along with Ghose *et al.* [21] (Amgen), Veber *et al.* [28] (GSK), Egan *et al.* [29] (Pharmacia) and Muegge *et al.* [30] (Bayer) methods. The specific needs of the end-user with respect to the chemical space are formed by different evaluations which allow a choice of diverse methods. A description of each rule violation appears in the output panel [19].

Drug-likeness rules and bioavailability score of citral are presented in Table 5.

Citral expressed and followed the rule invoked in SwissADME, the violation shown by it is minimal [31]. In the model of Brenk *et al.* [32] components, which are smaller and less hydrophobic, are considered rather than those defined by "Lipinski's rule of 5" to extend the possibilities of optimization of lead. For example, lead optimization was developed by a method where molecular weight between 100 and 350 Da, ClogP between 1 and 3.0 is taken [33]. A fingerprint-based approach was used to estimate Synthetic accessibility (SA) [34].

The medically important properties of citral are presented in Table 6. No reaction alerts were observed for PAIN alert, but were observed for Brenk *et al.* [32]. Therefore, there is some deviation of citral in terms of its drug similarity. It is seen that the molecule is at the prediction site, i.e. in the yolk (high brain penetration) of BOILED-Egg (Fig. 1). The molecule of citral is depicted as red indicating non-substrate of P-gp (PGP-).

Citral was evaluated for drug-likeness by bioavailability radar (Figure 2).

Six physicochemical properties: lipophilicity (from -0.7 to +5.0), molecular mass (from 150 to 500 g/mol), polarity (of 20 and 130Å), insolubility (log S not higher than 6), saturation (the fraction of carbons in sp^3 hybridization not less than 0.25)

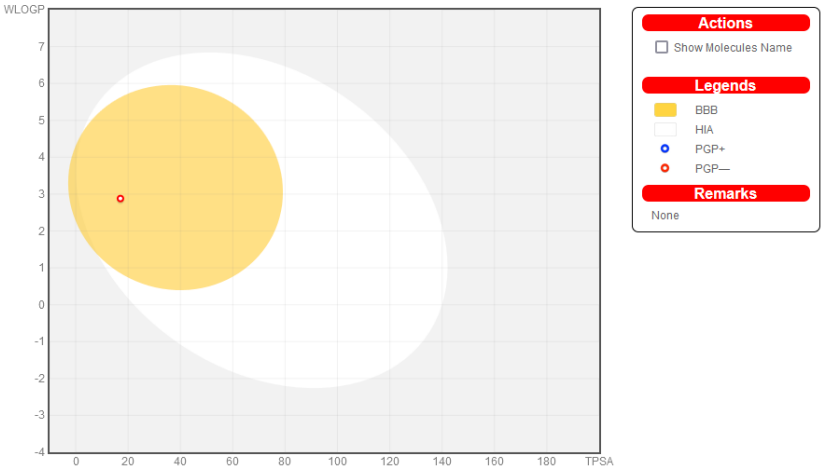

Fig 1. Schematic representation of perceptive evaluation of passive gastrointestinal absorption (HIA) and brain penetration (BBB) with the three molecules using BOILED-Egg (WLOGP *vs*. TPSA).

and flexibility (no more than 9 rotating connections) outline an optimum space (pink area) which predict its bioavailability when consumed orally [19].

Bioavailability radar gives the most general idea of the drug-likeness of a molecule. The compound is in the optimal range of the pink zone with small deviations in some parameters (Fig. 2).

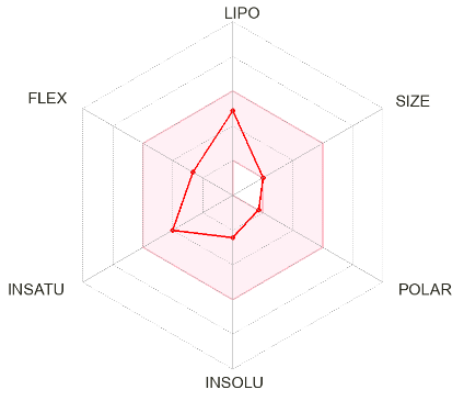

Fig. 2. Schematic diagram of bioavailability radar for drug likeness of citral.

CONCLUSIONS

In order to act as a drug, citral must meet certain requirements that will allow the relevant biological events to take place. The SwissADME tool makes it possible to calculate medically important physicochemical, pharmacokinetic and other parameters of flavoring substances.

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