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Research Article

Characterization of Volatile Organic Compounds Profile and Prediction of Pharmacokinetic Properties by ADMET in Purple Passion Fruit (*Passiflora Edulis* Sims) Pulp at different Maturation Stages

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Abstract

Purple passion fruit (*Passiflora edulis* Sims) is characteristic of tropical and subtropical regions of the world and its pulp is widely used in the production of various food products. Purple passion fruit is also used in therapeutic and medicinal treatments, due to its rich phytochemical matrix, in which volatile organic compounds (VOC) are strongly present. In this study, we performed the VOC identification of purple passion fruit in three development stages using the headspace solid phase microextraction combined with gas chromatography-mass spectrometry technique. In order to evaluate the potential pharmacokinetic properties of these compounds as new drug and nutraceutical candidates, we employed a computational model of molecules that allows the prediction of pharmacokinetics. 31 distinct VOC were identified across the three developmental stages. The major compound found was the alcohol heptan-2-ol. 15 volatiles were classified as soluble and 16 as very soluble. The permeability of these compounds in the intestinal membranes was considered moderate. No VOC showed similarities to toxins or xenobiotics. Most of the compounds investigated showed values indicating relatively normal distribution in the plasma, rather than high distribution in tissues. Terpenes, the ketone β-Ionone, and the compound styrene were more promising. All compounds have the potential to enter the central nervous system, with emphasis on the terpenes β-Myrcene, (Z)-β-ocimene, (E)-β-ocimene and the compound styrene. Of the compounds evaluated, 13 esters, two alcohols, all terpenes, one ketone and styrene have a lower rate or speed of excretion. All VOC showed no capacity to cause or induce undesirable genetic mutations.

Keywords: Volatiles; Prediction; Metabolites; Pharmacological, Fruit; Development

Abbreviations

VOC: Volatile Organic Compounds; HS-SPME-GC-MS: Headspace Solid Phase Microextraction combined with Gas Chromatography--Mass Spectrometry); ADMET: Absorption, Distribution, Metabolism, Excretion and Toxicity

Introduction

Appreciated for its unmistakable flavor, purple passion fruit (*Passiflora edulis* Sims, Passifloraceae family) is characteristic of tropical and subtropical regions of the world [1]. Purple passion fruit pulp is used in the preparation of beverages and desserts, as well as in the production of various products in the agroindustry

[2], in addition to being highly appreciated for consumption *in natura*. Due to its nutritional and phytochemical richness, purple passion fruit is used in therapeutic and medicinal treatments [3]. Within this rich phytochemical matrix, volatile organic compounds (VOC) are strongly present, which contribute significantly to the perception of the characteristic aroma of purple passion fruit, its quality and attractiveness, both for animals and humans [4,5].

VOC have characteristics such as high vapor pressure, moderate hydrophilicity, and low molecular mass. The distinct aroma of foods is defined by the combined perception of their volatile profile [6], and in fruits, the volatile profile undergoes variations throughout development, being produced from different routes, and may derive from amino acids, sugars, and fatty acids [7,8]. Among the methods employed for VOC identification, headspace solid phase microextraction combined with gas chromatography--mass spectrometry (HS-SPME-GC-MS) is a well-established and reliable methodology with high sensitivity, reproducibility and robustness [9]. Generally, work with VOC in food matrices is based on the identification and quantification of these compounds and the evaluation of their odor impact.

Foods, such as fruits and vegetables, are important vehicles for phytochemicals, such as alkaloids and phenolic compounds, whose pharmacokinetic properties have been the subject of research [10,11]. Many compounds in these classes are also volatile, especially phenolic compounds such as thymol, eugenol and derivatives, vanillin, gingerol and estragole, for example [12,13]. Certainly, new drug and nutraceutical candidates can be discovered through scientific exploration of fruits produced by species distributed throughout the globe. On the other hand, molecules with properties incompatible with an acceptable pharmacokinetic profile may be discarded for human use. Approximately one-third of commercial drugs come from natural sources, and plant metabolites are the main targets in research into the invention of new drugs with pharmaceutical utility [14].

In silico methods, which combine biology, engineering and computation for simulation purposes, have been increasingly and efficiently employed in drug discovery. This potentially shortens the time and costs of studies by pre-screening prospective compounds [15]. Computational modeling of molecules allows the prediction of pharmacokinetics (ADMET: Absorption, Distribution, Metabolism, Excretion and Toxicity) and the description of drug interactions with target proteins [16]. *In silico* ADMET evaluation models were developed as an additional tool to aid in the design and optimization of leads, which are chemical compounds that demonstrate robust pharmacological and biological activity in a specific therapeutic target, functioning as a starting point for the design and optimization of future drugs [17].

Considering the scarcity of studies on the evaluation of volatile metabolites as drug or nutraceutical candidates and their pharmacokinetic properties, the present study investigated *Passiflora edulis* Sims (purple passion fruit) fruits at three ripening stages regarding their volatile profile and the pharmacokinetic properties of their VOC, by ADMET.

Materials and Methods

Collection, selection and definition of stages

P. edulis Sims fruits were harvested in a single day in the city of Santana do Garambéu, (21°34'30''S and 44°4'49''W) in the Campo das Vertentes region, southeast of the state of Minas Gerais, Brazil. The fruit were transported, on the same day, to the Post-harvest Fruit and Vegetable laboratory at the Federal University of Lavras, Minas Gerais, Brazil. They were separated into three stages of development, according to the roughness and external color of the peel. On the first stage, called immature, the fruit had completely green and smooth peel. On the second stage, called mature, the peel was purple and smooth, while on the third stage, called ripe, the peel presented more intense purple color than the second stage and it was wrinkled. The fruits in the three stages are shown in the upper part of figure 1. In the lower part there is an illustrative drawing of the opened fruits. The pulp, after filtration in a sieve, was packed in polyethylene bags and stored in ultra freezer at -80 ºC.

Volatile organic compounds

The technique applied followed the methodology by da Costa [18]. The volatile compounds of the *P. edulis* Sims samples were examined using HS-SPME-GC-MS. Samples weighing 2 g were placed in 20 mL headspace bottles and heated to 40 ºC in an aluminum block. Volatile compounds were extracted using a 50/30 µm DVB/CAR/

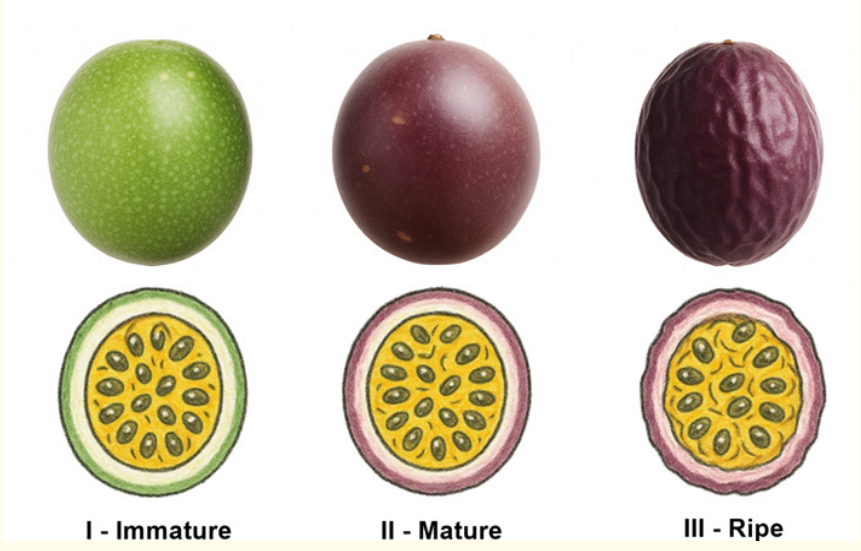

Figure 1: Purple passion fruit on three stages of development classified according to the color and texture of the peel. I (immature) - green and smooth peel; II (mature) – pale purple and smooth peel; III (ripe) – intense purple and wrinkled peel. Source: authors.

PDMS fiber. Volatile compounds were detected by GC-MS (Shimadzu CG-17 A, Shimadzu, Japan) equipped with an Rtx-5MS column 30 m x 0.25 mm internal diameter x 0.25 µm film thickness (bound phase; 5% diphenyl, 95% dimethyl polysiloxane). The carrier gas (helium) flow rate was a constant flow of 1.0 mL min^{-1}. The column initial temperature was 40 °C for 30 minutes, with subsequent ramp rate of 3 °C per minute until reaching a temperature of 220 °C. The interface temperature for the MS was 240 °C and the ion source 220 °C. The volatile compounds were tentatively identified by matching mass spectra with spectra of reference compounds in the NIST mass spectral library. The retention indices (RI) were calculated and compared with the literature (RI Lit) to ensure correct identification of the compounds. The RI of the compounds was calculated using an alkane standard (C5-C20) obtained from Sigma-Aldrich Company (St. Louis, MO, USA).

Pharmacokinetic properties by ADMET

To evaluate the pharmacokinetic properties of VOC identified in purple passion fruit pulp, the *in silico* ADMET methodology was used, based on the chemical structure (SMILE model input) of each compound. The digital platform http://www.swissadme.ch/[19] was used to measure the variables Water solubility, P-glycoprotein substrate, CYP substrate, CYP inhibitor and production of the BOILED-Egg graph. The variables Caco-2 permeability, VDss, Fraction unbound, CNS permeability, Total Clearance, Renal OCT2 substrate and Ames toxicity were analyzed using the digital platform https://biosig.lab.uq.edu.au/pkcsm/prediction [20].

Statistic

Data were analyzed using the SISVAR 5.8 version software. Analysis of variance (ANOVA) and the Scott-Knott method ($p < 0.05$) were used to compare the possible significant differences between the three developmental stages. Values were expressed as mean ± standard deviation for volatile compounds. The analyses were performed in six repetitions for each stage. Each repetition was composed of twelve fruits, totaling 216 fruits in the study.

Results and Discussion

VOC identified in purple passion fruit

Table 1 presents the 31 VOC identified in *P. edulis* Sims fruits at three developmental stages. These VOC are presented with their respective area percentages per stage and are organized into different groups according to their chemical structure.

Compounds	RI	RI Lit	Immature	Mature	Ripe
Ester					
(2S)-2-methyl-ethyl ester-butanoic acid	847	848	3,48 ± 0,12	ND	ND
Isopentyl acetate	876	876	0,82 ± 0,08^{a}	0,47 ± 0,04^{b}	0,14 ± 0,01^{c}
2-Methylbutyl acetate	881	881	0,13 ± 0,04	ND	ND
Methyl hexanoate	924	927	4,79 ± 0,00^{a}	ND	0,12 ± 0,01^{b}
Ethyl 3-hydroxybutanoate	935	935	ND	0,49 ± 0,02^{b}	1,99 ± 0,24^{a}
Ethyl hexanoate	1000	1002	6,77 ± 0,13^{c}	7,88 ± 0,41^{b}	8,87 ± 0,76^{a}
Ethyl 3-hexenoate	1005	1004	ND	ND	0,24 ± 0,01
cis-3-Hexenyl acetate	1007	1009	0,49 ± 0,04^{c}	5,53 ± 0,42^{a}	1,13 ± 0,13^{b}
Hexyl acetate	1013	1014	ND	2,56 ± 0,27^{a}	1,09 ± 0,1^{b}
Ethyl hex-(2E)-enoate	1045	1044	ND	0,47 ± 0,01^{b}	0,78 ± 0,07^{a}
Ethyl 3-hydroxyhexanoate	1129	1124	ND	ND	0,62 ± 0,09
Hexenyl butanoate <(3Z)->	1187	1186	ND	0,32 ± 0,03^{a}	0,13 ± 0,02^{b}
Ethyl cis-4-octenoate	1189	1187	ND	0,29 ± 0,05^{a}	0,22 ± 0,01^{b}
Hexyl butanoate	1193	1192	ND	1,61 ± 0,07^{a}	0,78 ± 0,08^{b}
Ethyl octanoate	1197	1197	ND	0,55 ± 0,00^{b}	0,58 ± 0,05^{a}
(Z)-3-hexenyl hexanoate	1382	1381	ND	0,87 ± 0,06^{a}	0,50 ± 0,01^{b}
Hexyl hexanoate	1387	1383	ND	3,28 ± 0,28^{a}	1,95 ± 0,12^{b}
Alcohol					
cis-3-Hexen-1-ol	859	858	ND	0,99 ± 0,07^{a}	0,17 ± 0,03^{b}
Hexan-1-ol	870	870	0,69 ± 0,16^{c}	4,59 ± 0,4^{a}	3,59 ± 0,33^{b}
Heptan-2-ol	904	896	1,01 ± 0,19^{c}	31,64 ± 1,83^{b}	42,05 ± 4,04^{a}
2-heptanol, acetate	1043	1043	ND	0,91 ± 0,07^{b}	1,21 ± 0,1^{a}
Octan-1-ol	1073	1072	ND	1,25 ± 0,15^{b}	1,42 ± 0,18^{a}
Nonan-2-ol	1104	1098	ND	2,06 ± 0,16^{b}	3,11 ± 0,17^{a}
Terpene					
β-Myrcene	991	992	0,30 ± 0,01	ND	ND
Limonene	1032	1033	0,38 ± 0,03	ND	ND
(Z)-β-ocimene	1037	1037	ND	0,27 ± 0,03	ND
(E)-β-ocimene	1049	1050	0,27 ± 0,06^{c}	2,92 ± 0,04^{a}	1,11 ± 0,16^{b}
Linalool	1102	1100	6,44 ± 0,33^{a}	1,62 ± 0,2^{c}	1,94 ± 0,02^{b}
Ketone					
2-heptanone	891	892	0,11 ± 0,02^{c}	1,18 ± 0,18^{b}	2,75 ± 0,25^{a}
β-Ionone	1486	1488	ND	3,19 ± 0,13^{a}	0,42 ± 0,04^{b}
Others					
Styrene	894	893	0,25 ± 0,01^{b}	ND	0,58 ± 0,06^{a}

Table 1: The values shown are the mean and standard deviation of the volatile organic compounds identified in the fruit pulp of *P. edulis* Sims at three stages: immature, mature and ripe. The results obtained were expressed in area percentage. Different letters indicate significant differences ($p< 0.05$) by ANOVA analysis followed by the Scott-Knott test. ND: Not Detected; RI: Retention Index Calculated; RI Lit: Retention Index Found in Literature.

Of the 31 VOC identified, there were 17 esters (54.84%), 6 alcohols (19.35%), 5 terpenes (16.13%) and 2 ketones (6.45%), in addition to phenylbenzene, also known as styrene. Ethyl hexanoate was the major VOC in immature purple passion fruit, followed by linalool, methyl hexanoate and heptan-2-ol. In mature fruits, heptan-2-ol stood out as the major VOC, followed by ethyl hexanoate, cis-3-hexenyl acetate, hexan-1-ol, Hexyl hexanoate, β-Ionone, (E)--β-ocimene, Hexyl acetate, Nonan-2-ol, Linalool, Hexyl butanoate, Octan-1-ol and 2-heptanone. Heptan-2-ol also stood out as the major VOC in ripe fruits, followed by Ethyl hexanoate, Hexan-1-ol, Nonan-2-ol, 2-heptanone, Hexyl hexanoate, Linalool, Octan-1-ol, 2-heptanol, acetate and (E)-β-ocimene. The other VOC identified presented areas smaller than 1%.

Esters are usually the group of volatile chemical compounds most abundantly synthesized in fruits, and are responsible for the fruity aroma, in addition to being critical structural elements and synthetic intermediates [21]. However, the major compound found in the volatile profile of purple passion fruit was the alcohol heptan-2-ol, with an area of 42.05% in the ripe fruit, followed by the ester ethyl hexanoate, with an area of 8.87% , also in the ripe fruit. Heptan-2-ol showed an exacerbated increase in area of approximately 31 times between the immature and mature stages, while from the second to the third stage this compound had an increase in area of 32.9%.

When studying the volatile profile of ripe fruits of purple passion fruit, yellow passion fruit and banana passion fruit, Pontes, Marques and Câmara [22] identified heptan-2-ol only in purple passion fruit, but with a much lower area percentage than that detected in our study. Ethyl hexanoate was also identified by these authors in purple passion fruit, with an area of 9.31% , similar to that observed in the ripe fruits in the present study. Heptan-2-ol was previously classified as part of a group that plays an important role within the aromatic compounds in purple passion fruit [23], and was also identified as the key compound for the aroma of coffee and some tropical fruits, and is generally related to the aroma of "fresh-fruity", "lemon" and "citrus" [24].

Passion fruit has been known for thousands of years as a fruit with therapeutic properties in traditional medicine and as a powerful natural sedative. Although the aromatic compounds in passion fruit are essential for its sensory appeal, it also has potential health-promoting properties [25].

Prediction of pharmacokinetic properties by ADMET

Table 2 presents different predictive descriptors that make up the pharmacokinetic properties of each volatile compound, considering its chemical structure. The first parameter presented, water solubility, follows a qualitative estimation scale of the solubility class according to the following log S scale: insoluble < -10 < poorly < -6 < moderately < -4 < soluble < -2 < very < 0 < highly [19]. Therefore, of the 31 VOC identified, 15 volatiles are classified as soluble and 16 as very soluble. In this first group of compounds classified as soluble, the greatest representation is given by esters (40%), followed by terpenes (33.33%), while among the 16 very soluble compounds, 68.75% are esters and 25% are alcohols.

Approximately 80% of active pharmaceutical ingredients are poorly soluble in water, including natural bioactive compounds. This directly affects the bioavailability of these compounds when ingested orally. Thus, industries are always looking for soluble compounds or applying techniques that make the structure of poorly soluble compounds of interest soluble [26]. The ability of the molecule to solubilize in water makes its use, formulation and various stages in drug development simpler. In the case of drugs administered orally, this aqueous solubility becomes a fundamental characteristic that influences drug absorption [27]. This is because only after dissolution in the gastrointestinal fluid can the compounds be absorbed by the intestine. The greater the water solubility capacity, the stronger its bioavailability to the body [26]. Therefore, all 31 VOC identified in purple passion fruit present, in this aspect, a desirable property for use in orally administered medications. In addition, they also have a great capacity for natural absorption through consumption of the juice, with emphasis on the 16 highly soluble compounds.

	Absorption			Distribution			Metabolism		Excretion		Toxicity
Compounds	**Water solubility (log mol L^{-1})**	**Caco-2 permeability (log P_{app} 10^{-6} cm s^{-1})**	**P-glycoprotein substrate (Yes/No)**	**VDss (log L kg^{-1})**	**Fraction unbound (F_u)**	**CNS permeability (Log PS)**	**CYP substrate(Yes/No)**	**CYP inhibitior(Yes/No)**	**Total Clearence(log ml min^{-1} kg^{-1})**	**Renal OCT2 substrate (Yes/No)**	**AMES toxicity (Yes/No)**
(2S)-2-methyl-ethyl ester--butanoic acid	-1,57	1.611	No	-0,09	0.631	-2,55	No	No	0,458	No	No
Isopentyl acetate	-1,8	1.628	No	-0,095	0,596	-2,191	No	No	0,4555	No	No
2-Methylbutyl acetate	-1,73	1.616	No	-0,09	0,644	-2.545	No	No	0,485	No	No
Methyl hexanoate	-1,89	1.61	No	-0,053	0,57	-2,244	No	No	0,517	No	No
Ethyl 3-hydroxybutanoate	-0,5	1.172	No	-0,247	0.774	-2,935	No	No	0,829	No	No
Ethyl hexanoate	-1,89	1.606	No	-0,004	0.543	-2,343	No	No	0.558	No	No
Ethyl 3-hexenoate	-1,58	1.613	No	-0,035	0.552	-2,290	No	No	0,501	No	No
Hexenyl acetate	-1,58	1,617	No	-0,035	0,565	-2,290	No	No	0,542	No	No
Hexyl acetate	-1,86	1.611	No	-0,004	0.556	-2,343	No	No	0.537	No	No
Ethyl hex-(2E)-enoate	-1,83	1.613	No	-0,035	0.552	-2,290	No	No	1	No	No
Ethyl 3-hydroxyhexanoate	-1,1	1.232	No	-0,129	0.653	-2,763	No	No	0,521	No	No
Hexenyl butanoate <(3Z)->	-2,14	1.573	No	0.066	0.446	-2,201	No	No	0.601	No	No
Ethyl cis-4-octenoate	-2,15	1.61	No	0.083	0.433	-2.161	No	No	0.607	No	No
Hexyl butanoate	-2,43	1.226	No	0.052	0.461	-2.233	No	No	1.619	No	No
Ethyl octanoate	-2,61	1.604	No	0.115	0.424	-2.214	No	No	1.64	No	No
(Z)-3-hexenyl hexanoate	-2,87	1.571	No	0.154	0.338	-2.052	No	No	1.761	No	No
Hexyl hexanoate	-3,16	1.153	No	0.125	0.354	-2.109	No	No	1.696	No	No
cis-3-Hexen-1-ol	-1,09	1.48	No	0.024	0.615	-2.250	No	No	0.452	No	No
Hexan-1-ol	-1,49	1.474	No	0.055	0.606	-2.303	No	No	0.439	No	No
Heptan-2-ol	-1,75	1.476	No	0.081	0.577	-2.349	No	No	1.483	No	No
2-heptanol, acetate	-1,99	1.375	No	-0,674	0.552	-2.772	No	No	1.65	No	No
Octan-1-ol	-2,14	1.471	No	0,183	0,488	-2,174	No	No	1.558	No	No
Nonan-2-ol	-2,51	1.474	No	0.209	0.459	-2,220	No	No	1.56	No	No
β-Myrcene	-3,05	1.4	No	0.363	0.39	-1.902	No	No	0.438	No	No
Limonene	-3,5	1.401	No	0.396	0.480	-2,370	No	No	0.213	No	No
(Z)-β-ocimene	-3,17	1.406	No	0.336	0.387	-1,848	No	No	0.441	No	No
(E)-β-ocimene	-3,17	1.406	No	0.336	0.387	-1.848	No	No	0.441	No	No
Linalool	-2,4	1.493	No	0.152	0.484	-2.339	No	No	0.446	No	No
2-heptanone	-1,53	1.491	No	0.075	0.551	-2.176	No	No	0.448	No	No
β-Ionone	-2,73	1.513	No	0.319	0.373	-2.304	No	No	1.315	No	No
Styrene	-2,83	1.544	No	0.403	0.331	-1.577	No	No	0.265	No	No

Table 2: Pharmacokinetic properties measured by ADMET of the 31 volatile organic compounds identified in the pulp of *P. edulis* Sims at three maturation stages.

Citation: Eduardo Valério de Barros Vilas Boas, *et al.* "Prediction of Pharmacokinetic Properties by ADMET in Purple Passion Fruit (*Passiflora Edulis* Sims) Pulp at different Maturation Stages". *Acta Scientific Nutritional Health* 9.9 (2025): 04-15.

In addition to the ability to solubilize in water, another important parameter in assessing the bioavailability of compounds is the permeability of this compound in the intestinal membranes. There are several possible assessments to quantify permeability, such as the use of Caco-2 cells. Caco-2 is the human epithelial colorectal adenocarcinoma cell and its permeability is used in calculating the intake of oral medications. These cells are recognized as a gold standard in research due to their ability to mimic the phenotype of enterocytes. Enterocytes are epithelial cells located in the outermost layer of the small intestine and large intestine, playing a fundamental role in the absorption of nutrients. [28,29]. Caco-2 permeability is determined by calculating the apparent permeability coefficient (P_{app}). A low permeability compound (0 to 20%) presents P_{app} below 1 x 10^{-6} cm s^{-1}, while moderate permeability compounds (20 to 70%) have a value between 1 a 10 x 10^{-6} cm s^{-1}, and finally, high permeability compounds (70 to 100%) have P_{app} above 10 x 10^{-6} cm s^{-1} [30]. All VOC present in purple passion fruit presented P_{app} values (Table 2) that fit into the moderate permeability range.

Some disadvantages in applying permeability prediction by Caco-2 are the low permeability of hydrophilic compounds with low molecular weight in Caco-2 cells, such as VOCs, and the fact that the natural intestinal epithelium contains more cell types, in addition to enterocytes [31]. However, taking the Caco-2 results together with the solubility presented, it is possible to classify the 16 volatile compounds of purple passion fruit that are highly soluble into one of the four proposed classes of the biopharmaceutical classification system (BCS). This method classifies drugs intended for gastrointestinal absorption, correlating the solubility and permeability of the drug with the rate and extent of oral absorption. However, in addition to being used for pharmaceuticals, BCS is also useful for measuring the bioactive constituents of foods to understand their nutraceutical potential [32].

Class I drugs have a high absorption rate and solubility. For this reason, they are rapidly biotransformed in first-pass metabolism, so that small amounts of the active drug are released into the circulatory system, significantly reducing their bioavailability. In Class II, the compounds are easily absorbed but have low solubility, which restricts their absorption *in vivo*, except at high doses. However, their absorption occurs more slowly compared to Class I drugs, resulting in a prolonged action. Class III drugs, in turn, have low permeability, which results in limited absorption in the body. Despite being highly soluble and dissolving quickly, their activity is not influenced by the dose. Finally, Class IV compounds, which have both low solubility and low permeability, face difficulties for effective oral administration due to their restricted bioavailability [32]. Although the 16 very soluble compounds have moderate and not low permeability, their values are close to the minimum thresholds, so we relate such VOC to class III of the BCS method.

The last parameter related to absorption is the permeability glycoprotein (P-gp) substrate. This is one of the most valuable pharmacokinetic parameters measured, as it allows us to assess whether a compound is a substrate for P-gp or not. P-gp acts as a physiological barrier, transporting toxins, xenobiotics, and natural compounds out of cells, acting to protect the central nervous system (CNS) [33]. Figure 2 shows the BOILED-Egg graph with all the volatile compounds identified in purple passion fruit. This graph is used to predict the absorption of small molecules by the gastrointestinal tract (light region) and their passive penetration of the blood-brain barrier (yellow region). The representation of the compound as a blue or red circle means that it is or is not a substrate for P-gp, respectively. Therefore, when marked in blue, it means that such compound presents similarities to toxins or xenobiotics, serving as a substrate for P-gp. Thus, no volatile compound identified in purple passion fruit showed similarities to toxins or xenobiotics that could cause damage to the CNS. All compounds, except for Ethyl 3-hydroxybutanoate, the only compound present in the light part of the graph, have passive brain penetration capacity.

The parameters volume distribution in a stable state (VDss), Fraction unbound, blood-brain barrier (BBB) and CNS permeability are essential in the evaluation of a compound in relation to its diffusion capacity in the cellular environment, defining the potential of drug or nutraceutical candidates.

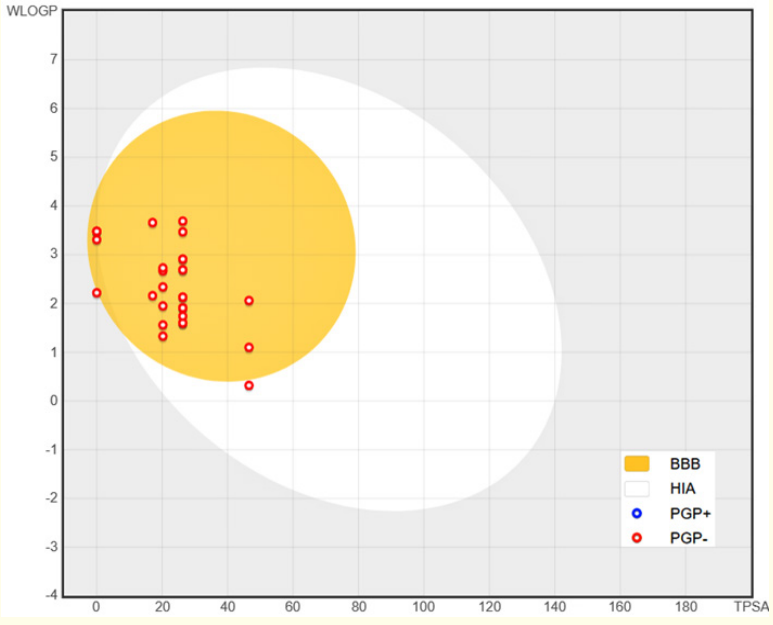

Figure 2: BOILED-Egg graph with volatile compounds identified in purple passion fruit at all stages of development. The clear region of the egg shows the predicted absorption of small molecules by the gastrointestinal tract. Compounds in the yellow region have the capacity for passive penetration of the blood-brain barrier. The representation of the compound as a blue or red circle means that it is a substrate or not permeability glycoprotein (P-gp), respectively.

VDss indicates a uniform distribution of the drug to all tissues. The drug will be more distributed in the tissue than in the plasma for higher VDss [34]. A VDss value >0.5 suggests that a drug candidate is sufficiently distributed in the plasma, while a value below -0.5 indicates that a drug has a low ability to cross the cell membrane [35]. Of all the compounds (Table 2), only 2-heptanol acetate had a low VDss, and no compound had a high VDss value. Therefore, all the other compounds investigated showed values indicating relatively normal distribution in the plasma, rather than high distribution in tissues. In general, terpenes, the ketone β-Ionone, and the compound styrene were more promising in this pharmacokinetic property than the other compounds.

Watanabe [36] proposed a global classification model of the pharmacokinetic property Fraction unbound into three classes with Fu,p threshold values (low < 0.05 < medium > 0.20 > high). In this classification, all 31 VOCs showed high values of unbound fraction, indicating better permeation of the cell membrane. On the contrary, compounds with a low unbound fraction have strong binding affinity to plasma proteins, which may impact the efficacy of this compound, since the unbound fraction of a compound is the portion that can exert therapeutic effects [33]. Therefore, only the unbound (free) drug is capable of interacting with pharmacological target proteins, such as receptors, channels, and enzymes, and is capable of diffusing between plasma and tissues [36]. When analyzing the VDss result with fraction unbound, we concluded that the volatile compounds of purple passion fruit do not have a great capacity for diffusion between the tissues of the organism, being limited to the blood plasma. However, these compounds tend to act more effectively if they are used for therapeutic purposes, since they do not have an affinity to bind to plasma proteins, which would impair their effects.

Regarding CNS, a log PS value >-2 indicates that the drug molecule can enter the CNS, while a value <-3 suggests that the drug molecule cannot easily reach the CNS [35]. Therefore, all compounds have the potential to enter the CNS, with emphasis on the terpenes β-Myrcene, (Z)-β-ocimene, (E)-β-ocimene and the compound styrene, as their log PS values are greater than -2.

No compound showed activity as a substrate or inhibitor of human cytochrome P450 (CYP) enzymes. In the CYP substrate column, the isoforms CYP2D6 and CYP3A4 were considered for prediction, and in the CYP inhibitor column, the isoforms CYP1A2, CYP2C19, CYP2C9, CYP2D6 and CYP3A4. CYP constitutes a superfamily of heme-thiolate monooxygenases that plays an essential role in the detoxification of xenobiotics, participating in the metabolism of many structurally divergent compounds [37]. CYP oxidizes xenobiotics or drugs, which are subsequently conjugated and excreted. CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4 are the five main CYP isoforms, therefore used in *in silico* studies on interactions with xenobiotics and drugs. There is evidence that CYP and P-gp may process small molecules synergistically to enhance tissue and organism protection [19].

The total clearance parameter and renal organic cation transporter 2 (OCT2) describe the excretion rate of compounds. The higher the total clearance value, the faster the rate of elimination of the drug from the body [38]. Total clearance refers to a combination of hepatic and renal clearance processes, in which such interaction is associated with bioavailability and is essential to define the dose required to achieve an equilibrium concentration in the body. OCT2 is a transporter present in the kidneys that plays a crucial role in the elimination and clearance of drugs and substances produced by the body itself [16]. Of the compounds evaluated, 13 esters, two alcohols (cis-3-Hexen-1-ol and Hexen-1-ol), all terpenes, one ketone (2-heptanone) and the compound styrene had a total clearance value equal to or below 1 (Table 2). About the other compounds, this means that these volatiles, when absorbed by the organism, have a lower rate or speed of excretion. No compound showed activity as a substrate for OCT2 (Table 2). Due to this possibility of greater permanence, such compounds can be more easily metabolized in several other biological processes, being used as metabolites in the synthesis or conversion of other compounds, supplying several metabolic pathways, or being able to generate therapeutic effects, when applicable.

Among the different in silico methods to assess the toxicity potential of a compound, one of the most widely used is the Ames test, developed based solely on the chemical structure of the compound. This test uses bacteria to determine whether a chemical compound is likely to induce genetic mutations, such as structure changes and base pair substitutions, for example [24]. All 31 VOC showed negative interaction for the Ames test (Table 2), thus, these volatiles cannot cause or induce undesirable genetic mutations.

Conclusion

The VOC identified in purple passion fruit showed, to varying degrees, desirable properties such as good bioavailability and passive penetration of the blood-brain barrier. They were not substrates or inhibitors of P-gp and CYP proteins, and presented high values of unbound fraction and excretion considered adequate, in addition to not showing any toxicity. When comparing the classes, although esters have greater solubility than terpenes, the latter presented a greater potential capacity to enter the CNS and better uniform distribution to all tissues.

In general, we did not identify any volatile compound as a fully ideal drug candidate based on the set of pharmacokinetic properties measured, since no compound stood out with better indices in all properties investigated. Although we did not highlight a compound as globally ideal for a drug among the 31 VOC identified, the information provided may help future studies on the compounds exposed in this work, such as molecular docking with target proteins, for example, which require knowledge of the pharmacokinetic properties to be performed.

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Conflict of Interest

The authors declare no conflict of interest.

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