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Study of physicochemical and pharmacokinetic properties of flavonoids from *Euterpe oleracea Martius*

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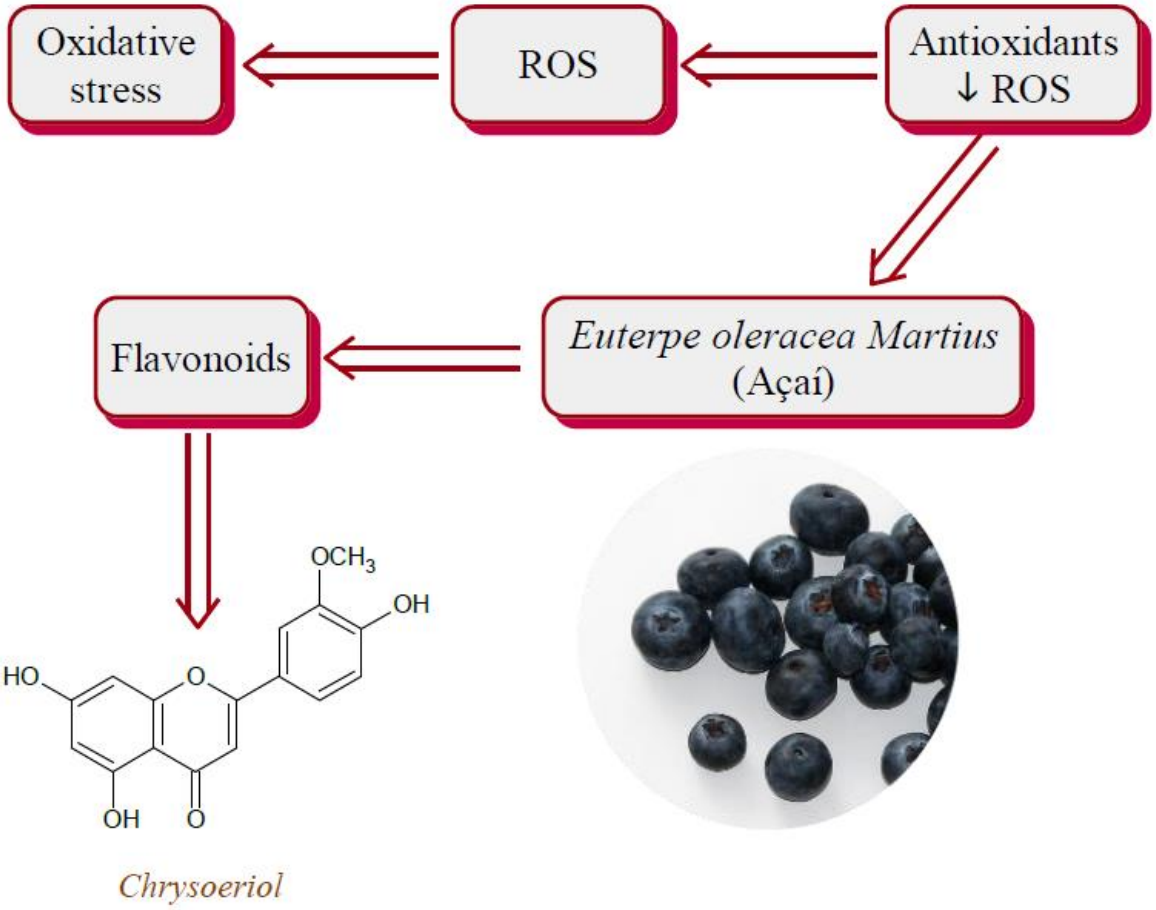


Abstract

Neurodegenerative disorders prevalence is growing due to life expectancy increase, thus the passage signs of time are clearly visible in the brain. Oxidative stress is a factor that contributes to the organic defenses imbalance, producing free radicals, brain-aging progression and various degenerative diseases. Macromolecules oxidative damage increases with age, leading to a progressive decline in cell and tissue function. Antioxidants reduce these free radicals formation or react with them by neutralizing them. *Euterpe oleracea Martius*, popularly known as açaí, is rich in α-tocopherol, fibers, lipids, polyphenols and mineral ions. Believes that polyphenols high content, among them flavonoids, confers to açaí fruits a variety of health promoting effects, including anti-inflammatory, immunomodulatory, antinociceptive and antioxidant properties. The present study aims to analyze, *in silico*, flavonoids physicochemical, pharmacokinetic and toxicological properties present in *Euterpe oleracea Martius.* **Methodology:** Initially, selected 16 molecules present in *Euterpe oleracea Martius*, divided into açaí pulp and oil. The physicochemical properties of the flavonoids were analyzed by the rule of 5, pharmacokinetic properties in the QikProp module of the Schrödinger software and the toxicity profile using the DEREK program. **Results:** Among physical-chemical properties, the flavonoid compounds catechin, epicatechin, luteolin, chrisoeriol, taxifolin, apigenin, dihydrocaempferol, isovitexin and vitexin presented good oral bioavailability. In pharmacokinetic properties, the molecules catechin, epicatechin, isovitexin, luteolin, chrisoeriol, taxifolina and isorhamnetina rutinosídeo presented the best results and high human oral absorption. In toxicological properties prediction the compounds presented good results, except for the isorhamnetina rutinoside and rutin compounds that presented alert about the mutagenicity for hydroxynaphthalene or derivative. **Conclusion:** Catechin, chrysoerythol and taxifolin flavonoids presented the best results, but other computational and experimental methods are needed to identify these compounds biological activity.

Keywords: Flavonoids. Acai. *Euterpe oleracea Martius*. Antioxidants.

Introduction

Medicinal plants in Brazil

SOURCE: http://www.pronoticia.com

It is the country that has the highest biodiversity on the planet, estimated at around 20% of the total of existing plant species (NUNES & MACIEL, 2016)

Currently, more than 45% of pharmaceutical products come from natural products (NUNES & MACIEL, 2016)

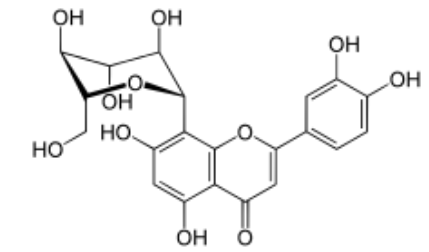
In Amapá, floodplain forest occupies 4.8% of the State, this ecosystem presents a wealth of palm trees, emphasizing the *Euterpe oleracea Martius* (açaí) (SILVA, 2002).

Introduction

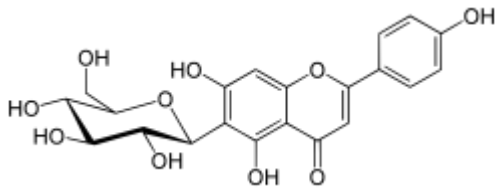
Phytochemical composition of *Euterpe Oleracea Martius*

Euterpe Oleracea Martius

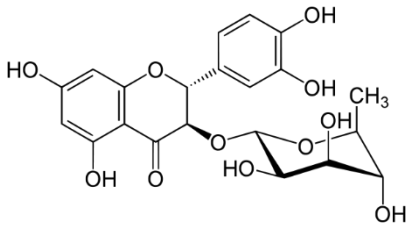
Rich in bioactive polyphenols, especially flavonoids (YAMAGUSHI et al., 2015).



Orientin



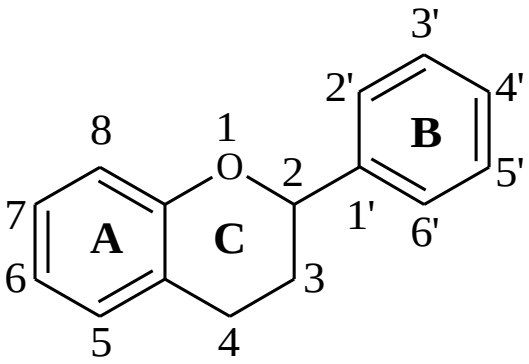
Isovitexin



Taxifolin deoxyhexose

Introduction

Flavonoids



Basic flavonoid structure (PANCHE et al., (2016)

They may be subdivided into flavones, flavanones, flavanoids, isoflavones, flavonols and anthocyanins (LI et al., 2009).

They are antioxidant molecules, of vegetal origin that offer perspectives in oxidative damages prevention (JIT et al., 2016).

In the açaí pulp, the most abundant phenolic compounds are anthocyanins, proanthocyanidins, other flavonoids and lignans (KANG et al., 2011).

Results and discussion

- **Physicochemical Properties**

Table 1 – Physicochemical properties of flavonoids present in *Euterpe oleracea* pulp.

	Inhibitor	Molecular weight (Dalton)	Hydrogen bond donor	Hydrogen bond acceptor	LogP	RO5 violations
1	CID 9064	290.271	5	6	0.4	0
2	CID 72276	290.271	5	6	0.4	0
3	CID 162350	432.381	7	10	0.2	1
4	CID 5280441	432.381	7	10	0.2	1
5	CID 5280445	286.239	4	6	1.4	0
6	CID 5383409	462.407	7	11	0.2	2
7	CID 5280666	300.266	3	6	1.7	0
8	CID 439533	304.254	5	7	1.5	0
9	CID 5481663	624.548	9	16	-1	3
10	CID 5280443	270.240	3	5	1.7	0
11	CID 5280805	610.521	10	16	-1.3	3
12	CID 122850	288.255	4	6	1.8	0

Results and discussion

- Most of selected flavonoids did not violate Lipinski's Rule.

- The compounds 9 and 11, present in the pulp of açaí,1 presented 3 violations not favoring the bioavailability in the organism.

- Compound 6 showed 2 violations.

- Only compounds 1, 2, 5, 7, 8, 10, 12, and compounds 3 and 4 which have had a violation have physicochemical properties deemed necessary for a good bioavailability in the body for planning of a future drug candidate by oral route.

- Dos Santos (2014) stated in his study that the phenolic compounds luteolin and taxifolina also did not violate any parameter of the Lipinski rule, having a good oral bioavailability.

- Regarding molecular weight, Vetrova et al. (2017) disagree with the present results, stating in their studies that rutin has antioxidant activity with broad potential for protection, low molecular weight and is widely distributed in vegetables and fruits.

Results and discussion

Table 2 - Physicochemical properties of flavonoids present in *Euterpe oleracea* oil.

	Inhibitor	Molecular weight (Dalton)	Hydrogen bond donor	Hydrogen bond acceptor	LogP	RO5 violations
13	CID 5281675	448.380	8	11	-0.2	2
14	CID 114776	448.380	8	11	-0.2	2
15	CID 441667	449.388	8	10	-3.94	1
16	CID 441674	595.530	10	14	-4.37	3

Results and discussion

- According to Silva and Rogez (2013), in fixed oils of E. oleracea there is a flavonoid profile similar to that described for pulps, where the main phenolic compounds are gallic acid, cyanidin-3-O-glucoside and cyanidin-3- O-rutinoside.

- Thus, 4 molecular structures of flavonoids present in açaí oil (Euterpe oleracea) were selected.

Results and discussion

Table 3 - Prediction of Pharmacokinetic Properties of Pulp Molecules.

	Compound	Stars	P_{CaCO2} (nm/sec)	P_{MDCK} (nm/sec)	HOA (%)	QLogBB
1	CID 9064	0	75.329	30.233	64	-1.629
2	CID 72276	0	62.186	24.574	61	-1.790
3	CID 162350	0	67.382	26.801	62	-1.714
4	CID 5280441	2	10.708	3.670	29	-3.002
5	CID 5280445	0	28.575	10.603	53	-2.092
6	CID 5383409	1	11.536	3.978	28	-2.640
7	CID 5280666	0	130.332	54.680	74	-1.367
8	CID 439533	0	49.583	19.238	62	-1.837
9	CID 5481663	0	134.248	56.457	75	-1.482
10	CID 5280443	9	1.008	0.285	0	-4.741
11	CID 5280805	1	18.335	6.564	22	-2.798
12	CID 122850	8	4.175	1.326	0	-4.063

PCaco2 = Caco2 Cell Permeability; PMDCK = MDCK Cell Permeability; HOA = Human Oral Absorption.

Results and discussion

- Compounds 1, 7, 8 and 9 showed high AOH;
- Compounds 2, 3, 4, 5 and 6 had mean AOH;
- Compounds 10, 11 and 12 have low AOH, indicating that oral to the latter route would not be a good choice.

- A study of açaí pulp and clarified E. oleracea juice by oral route, observed that total anthocyanin levels reached maximum concentrations of 2321ng / L in time of 2.2 hours and 1138ng / L in 2.0 hours, respectively , and plasma antioxidant capacity increased significantly after the pulp ingestion (MERTENS-TALCOTT et al., 2008).

Results and discussion

- Compounds 1, 2, 3, 4, 5, 6, 7, 8 and 9 presented mean % AOH;
- Compounds 10, 11 and 12 had low % AOH.
- It is observed that compounds 10, 11 and 12 are weak candidates in this respect, presenting disadvantage in relation to the others in the pulp (MERTENS-TALCOTT et al., 2008).
- For drugs that act on the central nervous system, penetration into the blood-brain barrier (BBB) is essential.
- Compounds that have Cbrain / Cblood> 1 values are able to cross BHE and compounds with values below 1 do not act on the CNS (MA; CHEN; YANG, 2005). As observed in Table 3, only compounds 4, 10 and 12 presented values that were not recommended. In contrast, most compounds are promising for CNS activity.

Results and discussion

Table 4 - Prediction of pharmacokinetic properties of oil molecules.

	Compound	Stars	P_{CaCO2} (nm/sec)	P_{MDCK} (nm/sec)	HOA (%)	QLogBB
13	CID 5281675	-	-	-	-	-
14	CID 114776	4	4.499	1.438	5.384	-3.482
15	CID 441667	-	-	-	-	-
16	CID 441674	3	5.632	1.833	7.004	-2.977

PCaco2 = Caco2 Cell Permeability; PMDCK = MDCK Cell Permeability; HOA = Human Oral Absorption.

Results and discussion

- Lipophilicity, measured by logP, is one of the physicochemical properties that most influence a molecule ability to move through biological compartments (CLEMENTE, 2011).

- The results found (Table 4) show that açaí oil flavonoid molecules are more lipophilic than hydrophilic, meaning that the plasma proteins are more easily bound, facilitating the compound distribution by biological organism.

Results and discussion

- The acai oil has a high content of unsaturated fatty acids.
- It is great interest to the food and beverage industries that seek alternatives to produce healthier products (HORNSTRA, 1999).
- The fixed oil contained in açaí tree fruits represents approximately 50% of the total dry matter of the pulp and presents a lipid profile.
- Acai oil is a valuable byproduct because of its unique sensory properties and potential health benefits (BICHARA; ROGEZ, 2011).

Conclusions

- Catechin, chrysoerythol and taxifolin flavonoids presented the best results, but other computational and experimental methods are needed to identify these compounds biological activity.

Acknowledgments