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ARTIGO

In silico study of the anti-obesity potential of *Baccharis trimera* phenolic compounds

Estudo em silico do potencial de compostos fenólicos de Baccharis trimera antiobesidade

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Abstract: Obesity is a worldwide public health problem. Regular exercises, balanced diet, allopathic and herbal medicines can be employed in the prevention and treatment of this pathological condition. Regarding the alternative treatment of obesity using medicinal plants, *Baccharis trimera* deserves attention due to the anti-obesity properties associated with its methanolic extracts. This *in silico* study aims to evaluate in which phenolic compounds of this plant the anti-obesity potential is most remarkable. According to the results obtained by the employment of some bioinformatics tools, the flavonoid known as epicatechin is probably the most important anti-obesity principle found in *Baccharis trimera*.

Key Words: Epicatechin; *Bacharis trimera*; Non-volatile compounds; Flavonoids.

Resumo: A obesidade é um problema da saúde pública em todo o mundo. Regular de exercícios, dieta equilibrada, alopática e fitoterápicos podem ser utilizados na prevenção e no tratamento desta condição patológica. Sobre a alternativa de tratamento da obesidade, uso de plantas medicinais, Baccharis trimera merece atenção devido às propriedades antiobesidade associado seus extratos metanólica. Em silico estudo visa avaliar em quais compostos fenólicos desta planta o potencial anti-obesidade é mais notável. De acordo com os resultados obtidos pelo emprego de algumas ferramentas de bioinformática, o flavonoide conhecido como epicatequina é provavelmente o mais importante princípio anti-obesidade encontrados em Baccharis trimera.

Palavras Chave: Epicatequina; Bacharis trimera Compostos não-voláteis; flavonoides.

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INTRODUÇÃO

Obesity is a public health problem that affects 27.5% of adults and 47.1% of children in the world. The amount of obese and overweight people reached the mark of 2.1 billion of people in 2013. Its prevention and treatment include the development of healthy habits, such as do regular exercises and ingest balanced diets, the use of allopathic medicines and the employment of alternative treatments with herbal medicines (CERCATO et al., 2015).

Currently, the importance of this last option has increased, mostly due to the lower cost of these natural products in comparison with the allopathic medicines. *Baccharis trimera* deserves a prominence place among the herbs that could be used in the treatment and control of obesity. *In vitro* studies have indicated that the methanolic extracts of this plant show inhibitory activity on pancreatic lipase. This enzyme is one of the main targets of the anti-obesity therapy (SOUZA et al., 2011).

However, until now nobody knows which substances are actually responsible for this anti-obesity property. Thus, this *in silico* study aims to evaluate in which phenolic compounds of *Baccharis trimera* (Table 1) the anti-obesity potential is most remarkable.

Table 1 - Phenolic compounds of *Baccharis trimera* and its pharmacological properties

Compounds	**Pharmacological properties**	**Authors**
Quercetin	Antioxidant, reduction of cardiovascular mortality, antiangiogenic activity, hepatoprotective and antifibrinogen effects, anti-inflammatory action; α and β glycosidase inhibitor	SILVA et al. (2016), JANUÁRIO *et al*. (2004) and ABOY et al. (2012)
Isoquercitin	Antioxidant	GONÇALVES (2014) and ABOY et al. (2012)
Cirsimaritin	Anti-inflammatory and antiplasmodial effects	SOICKE; LENG-PESCHLOW (1987) and ABOY et al. (2012)
Genkwanin	Antiplasmodial action	SOICKE; LENG-PESCHLOW (1987) and ABOY et al. (2012)
Quercitrin	Antioxidant	SILVA et al. (2016), GONÇALVES (2014) and ABOY et al. (2012)
Cirsiliol	Antimicrobial property	SOICKE; LENG-PESCHLOW (1987) and ABOY et al. (2012)
Eupatorin	Vasodilating, antioxidant and anti-inflammatory properties	ABOY et al. (2012), KIM et al. (1985) and KIM et al. (2016)
Epicatechin	Antioxidant	GONÇALVES (2014)
Catechin	Antioxidant	GONÇALVES (2014)
Kaempferol	Inhibitor of α and β glycosidase	SILVA et al. (2016) and GONÇALVES (2014)
Apigenin	Anti-inflammatory and antioxidant effects; α and β glycosidase inhibitor	KIM et al. (1985) and SOICKE; LENG-PESCHLOW (1987)
Luteolin	Neuroprotective and antioxidant effects, α and β glycosidase inhibitor	SILVA et al. (2016) and SOICKE; LENG-PESCHLOW (1987)
Rutin	Anti-inflammatory, antioxidant, neuroprotective effects; anti-Alzheimer activity; antidiabetic effects; anti-hypercholesterolemic effects; blood coagulation influence; α and β glycosidase inhibitor	SILVA et al. (2016) and GONÇALVES (2014)
5HTF	nd	SILVA et al. (2006)
Tricaffeoylquinic acid	Decreased glycemia, glycated hemoglobin and visceral fat; insulin secretagogue and antioxidant	SILVA et al. (2006) and ABOY et al. (2012)
3-Caffeoylquinic acid		
4-Caffeoylquinic acid		
5-Caffeoylquinic acid		
4-O-Feruloylquinic acid		
5-O-Feruloylquinic acid		
3,4-Dicaffeoylquinic acid		
3,5-Dicaffeoylquinic acid		
Ellagic acid	Antioxidant, anti-inflammatory and anti-atherosclerotic actions.	SILVA et al. (2016) and GONÇALVES (2014)
Caffeic acid	Antioxidant	SILVA et al. (2016) and GONÇALVES (2014)
Gallic acid	Antioxidant	SILVA et al. (2016) and GONÇALVES (2014)

MATERIALS AND METHODS

The phenolic composition of *Baccharis trimera* was established by the analysis of articles that were screened from GOOGLE ACADEMIC, SCOPUS and PUBMED search platforms. For the study of molecular docking, the structure of the pancreatic lipase enzyme (2PPL) was obtained in the Protein Data Bank (PDB) (https://www.rcsb.org/) and the docking operation was performed in an online software known as SwissDock (http: // www .swissdock.ch /).

The drug orlistat (Xanical®) was used as a positive control of lipase inhibition. Toxicity, mutagenic, tumorigenic, irritant, reproductive and drug-relevant properties, such as cLogP, solubility, molecular weight (MW), polar topological surface area (TPSA), drug similarity, and drug classification for all new inhibitors were predicted using OSIRIS Property Explorer.

This OSIRIS program calculates the probability to use a compound as a drug based on a list of about 5,300 substructure fragments created for 3,300 drugs as well as 15,000 commercially available chemicals, producing a complete list of all available fragments that present potential to be used as a drug. The drug score was calculated using the toxicity risk, cLogP, logS and MW.

The biological activity spectra were obtained by the PASS web tool (http://www.pharmaexpert.ru/passonline/). This software predicts the pharmacological effects and biochemical mechanisms on the basis of the structural formula of a substance. The prediction process by the PASS was based on SAR analysis of the training set containing more than 205,000 compounds exhibiting more than 3,750 types of biological activities (GOEL et al., 2011; BALAKRISHNAN; RAJ; KANDAKATLA, 2015).

RESULT AND DISCUSSION

Twenty-five phenolic compounds were identified as *Baccharis trimera* constituents. These compounds can be classified as phenolic acids (KIM et al., 2015) and flavonoids (BALAKRISHNAN; RAJ; KANDAKATLA, 2015).

The employment of the bioinformatic tools known as Pass Online, OSIRIS Property Explorer and SwissDock was able to show the inhibition potential of the pancreatic lipase associated with eight of these compounds: apigenin, ellagic acid, epicatechin, gallic acid, isoquercetin, kaempferol, quercetin and rutin (Table 2).

These results corroborated with the findings of Souza et al. (2011) which attributed to the methanolic extracts of *Baccharis trimera* an inhibitory action on pancreatic lipase. The inhibitory potential of these eight compounds against the pancreatic lipase enzyme was weaker than that estimated for the reference compound (orlistat). Among the phenolic compounds of this plant, epicatechin (P = 0.162) appeared to be the most important inhibitory agent of the pancreatic lipase. It was also the compound with the highest value of drug score (0.87), indicating its potential to become a drug. This result was about eight times higher than that found for orlistat (0.11), the only clinically accepted anti-obesity drug that has been shown to act through inhibition of pancreatic lipase.

However, the binding affinity (ΔG = -7.80 kcal/mol) of epicatechin was estimated as being 11.6% lower than that established for orlistat (ΔG = -8.82 Kcal/mol). This inhibitory effect of epicatechin has already been reported by Siguemoto (2013). In this previous study, this researcher had noted an inverse correlation between the concentration of this flavonoid in the aqueous extract of *Byrsonima crassifolia* and the pancreatic lipase activity.

Yun (2010), in his review about natural products with anti-obesity activity also mentioned a strong inhibition action of epicatechin, isolated from tea leaves, against pancreatic lipase. Thus, the results found in the present *in silico* study suggest that the anti-obesity activity attributed to *Baccharis trimera* can be explained, at least in part,by the presence of epicatechin in its constitution. However, the contribution of apigenin, ellagic acid, gallic acid, isoquercetin, kaempferol, quercetin and rutin to this inhibitory effect could not be discharged.

Table 2 - Results of the *in silico* tests with the phenolic compounds of *Baccharis trimera*

Compounds	cLogP	MM (g.mol-1)	TPSA (Å²)	logS	Drug score	M	T	I	R	ΔG	P
3,4,5-TRICQA	2,36	678	257,8	-4,21	0,33	N	N	N	N	-	-
3,4-DICQA	0,8	516	211,2	-2,85	0,53	N	N	N	N	-	-
3,5-DICQA	0,80	516	211,2	-2,85	0,52	N	N	N	N	-	-
3-CQA	-0,77	354	164,7	-1,5	0,7	N	N	N	N	-	-
4-CQA	-0,77	354	164,7	-1,5	0,7	N	N	N	N	-	-
4-OFA	-0,49	368	153,7	-1,81	0,65	N	N	N	N	-	-
5-CQA	-0,77	354	164,7	-1,5	0,7	N	N	N	N	-	-
5-HTF	2,75	358,35	83,45	-3,52	0,28	Y	Y	N	N	-	-
5-OFA	-0,49	368	153,7	-1,81	0,68	N	N	N	N	-	-
Apigenin	2,34	270,0	86,99	-2,86	0,47	Y	N	N	N	-7,29	0,013
Caffeic acid	0,78	180,16	77,75	-1,41	0,19	Y	Y	N	Y	-	-
Cirsiliol	2,2	330,0	105,4	-2,89	0,48	Y	N	N	N	-	-
Cirsimaritin	2,54	314,0	85,22	-3,19	0,74	N	N	N	N	-	-
Ellagic acid	1,28	302,19	133,5	-3,29	0,51	N	N	N	N	-7,36	0,032
Epicatechin	1,51	290,0	110,3	-1,76	0,87	N	N	N	N	-7,80	0,162
Eupatorin	2,47	344	94,45	-3,21	0,28	Y	Y	N	N	-	-
Gallic acid	0,11	170	97,99	-0,74	0,27	Y	N	N	Y	-10,60	0,039
Genkwanin	261	284	75,99	-3,17	0,77	N	N	N	N	-7,62	-
Isoquercetin	-0,35	484	206,6	-2,19	0,43	N	N	N	N	-8,60	0,043
Kaempferol	1,84	286	107,2	-2,79	0,46	Y	N	N	N	-7,36	0,032
Orlistat (Xanical®)	**7,62**	**495,75**	**81,75**	**-6,86**	**0,11**	**N**	**N**	**N**	**N**	**-8,82**	**0,470**
Quercetin	1,49	302,0	127,4	-2,49	0,3	Y	Y	N	N	-7,61	0,036
Rutin	-1,26	610,0	265,5	-2,4	0,57	N	N	N	N	-8,91	0,099

P = Pa-Pi; Pa = probability to be active; Pi = probability to be inactive; ΔG (Kcal/mol). M: mutagenic; T: tumorigenic; I: irritant; R: reprodutive effect; Y: Yes; N: no; TRICQA: tricaffeoylquinic acid; 3,4-DICQA: 3,4-Dicaffeoylquinic acid; 3,5-DICQA: 3,5-Dicaffeoylquinic acid; 3-CQA: 3-Caffeoylquinic acid; 4-CQA: 4-Caffeoylquinic acid; 4- OFA: 4-O-Feruloylquinic acid; 5-CQA: 5-Caffeoylquinic acid; 5-OFA:5-O-Feruloylquinic acid.

CONCLUSION

The results of this *in silico* study showed that epicatechin is probably the most important antiobesity phenolic compound of *Baccharis trimera*. This flavonoid can become an important phytotherapic agent due to its inhibitory effect against pancreatic lipase and, also, to its well-recognized antioxidant potential.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

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