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Natural Product Research
Formerly Natural Product Letters

ISSN: 1478-6419 (Print) 1478-6427 (Online) Journal homepage: http://www.tandfonline.com/loi/gnpl20

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To cite this article: Alex Gutterres Taranto, Sônia Carine Cova Costa, Franco Henrique Andrade Leite, Matheus Santos de Sá, Milena Botelho Pereira Soares, Miriam Moreira Mussi & Alexsandro Branco (2016): Caffeoylquinic acids from antiplasmodial active extract of Xanthium cavanillesii fruits and their molecular modelling studies, Natural Product Research, DOI: 10.1080/14786419.2016.1219856

To link to this article: http://dx.doi.org/10.1080/14786419.2016.1219856

NATURAL PRODUCT RESEARCH, 2016
http://dx.doi.org/10.1080/14786419.2016.1219856

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SHORT COMMUNICATION

Caffeoylquinic acids from antiplasmodial active extract of *Xanthium cavanillesii* fruits and their molecular modelling studies

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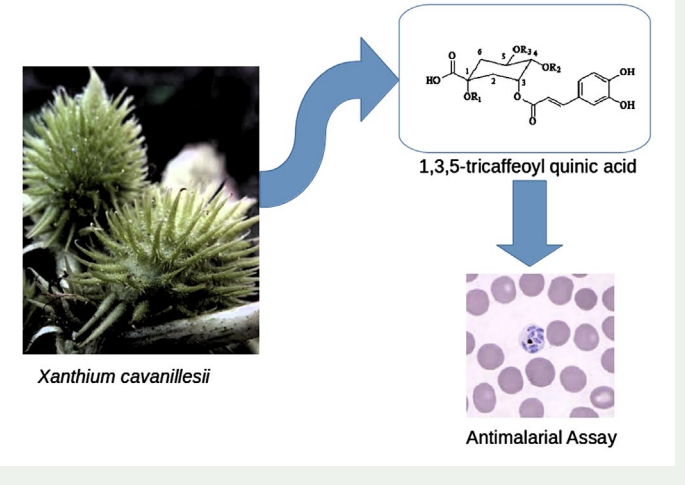
ABSTRACT

The antiplasmodial active extract of *Xanthium cavanillesii* contains 3,4-dicaffeoyl quinic acid (3,4-DCQA), 3,5-dicaffeoyl quinic acid (3,5-DCQA) and 1,3,5-tricaffeoyl quinic acid (1,3,5-TCQA). These results inspired us to investigate the interaction of these molecules with a promising validated target of Plasmodium, PfATP6 orthologue of mammalian Ca^{+2}-ATPase. Models of this receptor were obtained through comparative modelling. Afterwards, molecular docking studies were used to identify possible interaction modes of these caffeoyl quinic derivatives on the binding site. The 1,3,5-TCQA had the best energy, but all of these had better energy than thapsigargin, a non-competitive inhibitor of the sarco/endoplasmatic reticulum Ca^{+2}-ATPase (SERCA).



ARTICLE HISTORY
Received 22 October 2015
Accepted 6 July 2016

KEYWORDS
Xanthium cavanillesii; caffeoyl quinic acid; antiplasmodial activity; PfATPase

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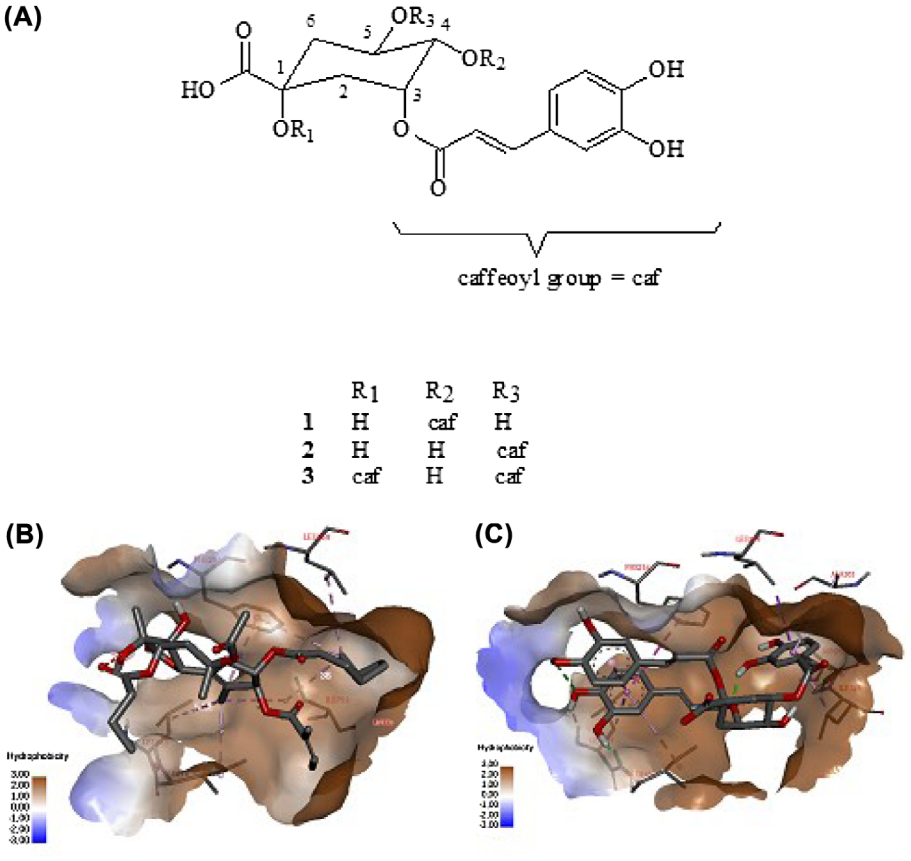
Supplemental data for this article can be accessed at http://dx.doi.org/10.1080/14786419.2016.1219856.

1. Introduction

Malaria is an infectious, non-contagious disease with chronic evolution and acute manifestations affecting 97 countries and territories in tropical and subtropical areas worldwide. In 2013,198 million cases were reported leading to 584,000 deaths. It is more prevalent in lower and middle-income countries, with Africa being the most affected continent with 90% of the deaths occurring in children under five years (WHO 2014).

Xanthium cavanillesii (Asteraceae) is an herbaceous annual plant that is extremely competitive with other crops; it has been considered to be the worst weed on plantations. This plant is known for intoxicating several ruminant animals mainly in the south and south-east of Brazil. Toxicity generally occurs in spring and early summer due to the ingestion of seedlings in the cotyledonary stage. Seeds are also toxic and cause intoxication when the fruits are mixed with foodstuffs or hay (Mendez et al. 1998). Previous studies have shown that the compound responsible for this mortality is the diterpene kaurene called carboxyatractyloside (Obatomi & Bach 1998; Chen et al. 2015).

In this study, we described the characterisation, the docking studies and the antimalarial assay (Mendiola et al. 2014; Mollinedo et al. 2015) of three caffeoyl quinic acid derivatives of an antimalarial active extract from *X. cavanillesii* (Figure 1). These structures have a caffeoylquinic acid scaffold (Manohar et al. 2013), inspiring us to perform docking studies



	R_1	R_2	R_3
1	H	caf	H
2	H	H	caf
3	caf	H	caf

Figure 1. Caffeoyl quinic acid scaffold: (1) 3,4-dicaffeoyl quinic acid (3,4-DCQA); (2) 3,5-dicaffeoyl quinic acid (3,5-DCQA) and (3) 1,3,5-tricaffeoyl quinic acid (1,3,5-TCQA).

on the PfATP6 model, which was previously constructed by comparative homology modelling (Guimarães et al. 2015). The experimental details are described in the Supplementary Material.

2. Results and discussion

The *X. cavanillesii* fruit extract was assayed *in vitro* against the W2 strain of *Plasmodium falciparum*, which showed antiplasmodial activity, with IC_{50} values of 65.8 µg/mL, against artemisinin with 0.0022 µg/mL. The phytochemical study indicated the possibility to obtain 3,4-DCQA (compound **1**), 3,5-DCQA (**2**) and 1,3,5-TCQA (**3**) (Figure 1(A)). Structural elucidation of the isolated natural products was achieved through spectrometric analyses, such as hydrogen nuclear magnetic resonance and high performance liquid chromatography coupled to a mass spectrometry detector (HPLC-Ms^n, Figure S1)). These compounds have not been previously reported in *X. cavanillesii* although they have already isolated from other species of the *Xanthium* (Mahmoud et al. 2005).

The above results inspired us to investigate the pharmacological mechanism by evaluating the affinity of these compounds against the PfATP6 model using docking routine (Trott & Olson 2010). As a result, all caffeoylquinic acid derivatives had better binding energies than thapsigargin (–7.4 kcal/mol). Furthermore, 1,3,5-TCQA had the highest energy (–8.6 kcal/mol). Moreover, 3,4-DCQA and 3,5-DCQA had binding energies of –8.1 and –7.7 kcal/mol, respectively. These findings suggested that caffeoylquinic acid is a pharmacophoric moiety of this class of compounds.

In addition, thapsigargin could complex with the PfATP6 model through hydrophobic interactions with Phe254, Leu258, Ile752, Leu815 and Ile816 (Figure 1(B)). Similarly, 1,3,5-TCQA could have hydrophobic interactions with Phe254, Leu258, Ala303, Asn755and Ile756. Furthermore, 1,3,5-TCQA could bind, as a hydrogen bond donor, to Leu815 and Ile816, increasing the affinity profile (Figure 1(C)).

Finally, despite the fact that biological assays were not performed for isolated compounds, the experimental and *in silico* data have showed that quinic acid derivatives are promising antimalarial lead compounds and previously published studies have identified antimalarial properties on those compounds (Carbonara et al. 2012). Further assays to confirm and explain the biological properties of *X. cavanillesii* extracts are in progress.

3. Experimental

3.1. Plant material

X. cavanillesii was collected from São Lourenço do Sul, Rio Grande do Sul State, Brazil. A voucher specimen was deposited at the Herbarium of the Department of Biology of the State University of Feira de Santana (HUEFS 139439).

3.2. Preparation of the ethanolic extract

The fruits of *X. cavanillesii* (3.9 kg) were manually separated, dried at 45 °C and pulverised. Extraction commenced with ethyl acetate, which was aimed at removing the waxes, which was followed by the use of ethanol for 72 h at room temperature. The respective solvent was filtered and evaporated using a rotaevaporator apparatus, resulting in the ethanol (50 g) extract.

4. Conclusions

The ethanolic extract of *X. cavanillesii* had significant activity against the *P. falciparum* W2 strain. The chemical investigation of this extract allowed for characterisation of 3,4-DCQA, 3,5-DCQA and 1,3,5-TCQA. Comparing the calculated structures, 1,3,5-TCQA had the same interaction pattern as thapsigargin. As a result, 1,3,5-TCQA can be used as a lead compound for further biological studies against PfATP6. These computational studies not only shed light on the mechanism of PfATP6 inhibition, but also provide insight for the rational improvement of inhibitory potency. Consequently, these strategies can be used to identify novel antimalarial drug candidates from natural sources.

Supplementary material

Experimental details relating to this article are available on line.

Acknowledgements

The authors wish to thank Prof Dr Rodrigo Bagueira (UFF) for technical assistance with the NMR analysis.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by FAPESB [grant number SEMIÁRIDO - PET0018/2007]; CAPES [grant number PROCAD 2007]; FAPEMIG [grant number APQ-00557-14]; CNPq [grant number 475512/2010-3], [grant number 449984/2014-1]; PPGBiotec/UFSJ.

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