TRITERPENES FROM MICONIA LANGSDORFFII AND EVALUATION OF SCHISTOSOMICIDAL ACTIVITY

TRITERPENOS DE MICONIA LANGSDORFFII E AVALIAÇÃO DA ATIVIDADE ESQUISTOSSOMICIDA

TRITERPENOS DE MICONIA LANGSDORFFII Y EVALUACIÓN DE LA ACTIVIDAD ESQUISTOSOMICIDA

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ABSTRACT

Neglected diseases affect thousands of people worldwide and lack adequate treatments, remaining one of the major public health problems and requiring new therapeutic alternatives. Among neglected diseases, schistosomiasis caused by the parasite Schistosoma mansoni stands out. Different chemical classes obtained from natural products have given rise to several drugs across therapeutic categories. In the present study, phytochemical investigations and the evaluation of the schistosomicidal activity of the crude hydroalcoholic extract from the aerial parts of Miconia langsdorffii are reported. The fractions obtained from extract fractionation were biomonitored for schistosomicidal activity. Fraction F2 was the most promising, showing 100% separated worm pairs, 100% high reduction in motor activity within only 24 hours, and 100% parasite mortality after 120 hours of incubation. In this fraction, a mixture of the triterpenes ursolic acid and oleanolic acid was identified. These triterpenes were isolated by HPLC and also evaluated. The mixture of the two triterpenes was able to potentiate schistosomicidal activity, thus demonstrating a possible synergistic effect. Ursolic acid showed better results when compared to oleanolic acid and, for this reason, aiming at a possible enhancement of activity, five semisynthetic derivatives were prepared. Among these

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derivatives, the potassium salt derivative of ursolic acid stood out, being the only one that potentiated the activity with 100% separated worm pairs after 120 hours of incubation, compared to ursolic acid, which showed 50% under the same conditions.

Keywords: *Schistosoma mansoni*. Ursolic Acid. Semisynthetic Derivatives.

RESUMO

Doenças negligenciadas afetam milhares de pessoas ao redor do mundo, e não dispõem de tratamentos adequados, permanecendo como um dos principais problemas de saúde pública, necessitando de novas alternativas para o tratamento. Dentre as doenças negligenciadas destaca-se a esquistossomose causada pelo parasita Schistosoma mansoni. Diferentes classes químicas obtidas de produtos naturais deram origem a diversos fármacos de categorias terapêuticas. Neste presente estudo são relatados estudos fitoquímicos e a avaliação da atividade esquistossomicida do extrato bruto hidroalcoólico das partes aéreas do vegetal Miconia langsdorffii. As frações obtidas no fracionamento do extrato foram biomonitoradas quanto à atividade esquistossomicida. A fração F2 foi a promissora apresentando 100% de casais separados, 100% de alta redução na atividade motora em apenas 24 horas e 100% de parasitas mortos em 120 horas de incubação. Foi identificada nesta fração a mistura dos triterpenos ácidos ursólico e oleanólico. Estes triterpenos foram isolados por CLAE e também avaliados. A mistura dois triterpenos foi capaz de potencializar a atividade esquistossomicida, demonstrando assim um possível efeito sinérgico. O ácido ursólico apresentou melhores resultados quando comparado com o ácido oleanólico e por esse motivo, para uma possível potencialização da atividade, foram preparados cinco derivados semissintéticos. Entre os derivados, destacou-se o derivado sal de potássio do ácido ursólico, o único que potencializou com 100% de casais separados em 120 horas de incubação quando comparado com o ácido ursólico, que foi de 50% nas mesmas condições.

Palavras-chave: *Schistosoma mansoni*. Ácido Ursólico. Derivados Semissintéticos.

RESUMEN

Las enfermedades desatendidas afectan a miles de personas en todo el mundo y carecen de tratamientos adecuados, permaneciendo como uno de los principales problemas de salud pública y requiriendo nuevas alternativas terapéuticas. Entre las enfermedades desatendidas se destaca la esquistosomiasis causada por el parásito Schistosoma mansoni. Diferentes clases químicas obtenidas de productos naturales han dado origen a diversos fármacos de distintas categorías terapéuticas. En el presente estudio se reportan investigaciones fitoquímicas y la evaluación de la actividad esquistosomicida del extracto crudo hidroalcohólico de las partes aéreas de Miconia langsdorffii. Las fracciones obtenidas a partir del fraccionamiento del extracto fueron biomonitoreadas en cuanto a la actividad esquistosomicida. La fracción F2 fue la más prometedora, presentando 100% de parejas separadas, 100% de alta reducción de la actividad motora en solo 24 horas y 100% de parásitos muertos tras 120 horas de incubación. En esta fracción se identificó una mezcla de los triterpenos ácido ursólico y ácido oleanólico. Estos triterpenos fueron aislados por HPLC y también evaluados. La mezcla de ambos triterpenos fue capaz de potenciar la actividad esquistosomicida, demostrando así un posible efecto sinérgico. El ácido ursólico presentó mejores resultados en comparación con el ácido oleanólico y, por este motivo, con el fin de una posible potenciación de la actividad, se prepararon cinco derivados semisintéticos. Entre los derivados, se destacó el derivado sal de potasio del ácido ursólico, siendo el único que potenció la actividad con 100% de parejas separadas tras 120 horas de

incubación, en comparación con el ácido ursólico, que presentó un 50% en las mismas condiciones.

Palabras clave: *Schistosoma mansoni*. Ácido Ursólico. Derivados Semisintéticos.

1 INTRODUCTION

Over the centuries, all populations used plants to cure some disease. The use of medicinal plants is of human heritage, and this situation is still found in communities that are geographically isolated, where there are difficulties in society, such as few doctors due to the limitation of economic factors. In these areas, the treatment of diseases is based exclusively on medicines of natural origin [1].

Secondary metabolites produced by plants are a source of bioactive substances. Nowadays, scientific interest in these metabolites has increased because of the search for new drugs originating from plants [2]. Biodiversity, in general, is responsible for the production of most of the known organic substances. However, the plant kingdom is responsible for the largest portion of the chemical diversity known and recorded in the literature [3].

In economic terms, biodiversity crosses borders, offering conventional industries a valuable source of biological and chemical data on the large use of discovered drugs. Certainly, the use of natural products has been one of the strategies in the discovery of new drugs. Half of the twenty best-selling drugs are of natural origin, and their total sales reach 16 billion, demonstrating the importance of natural products in the world [4].

Biological diversity is not evenly distributed across the planet. The world's tropical forests have the richest biomes and probably include the largest number of species on earth [5]. Approximately 70% of the world's species are distributed in only a few countries, such as; Australia, Brazil, China, Colombia, Ecuador, India, Indonesia, Madagascar, Mexico, Peru, Zaire [6].

Brazil's biodiversity is considered a source of biologically active substances for isolation, and its preservation is fundamental, both for the intrinsic value of this immense biological wealth and for its enormous potential [7]. It is the country that has the greatest biodiversity in the world, estimated at about 20% of the total number of species on the planet [8].

The Melastomataceae family has about 4200 to 5000 species distributed throughout tropical and subtropical regions around the globe, with approximately 166 genera. It is one of the most important families of the neotropical flora [9], abundant in diversity. In Brazil, there are about 1500 species, distributed in 66 genera and occurring mainly in tropical areas [10,11]. *Miconia* it is undoubtedly the largest genus, with approximately 1000 species distributed throughout tropical America and especially concentrated in the Andes [12, 13]. Several studies related to the description of biological activities of the species *Miconia* have shown promising results [14-18]. Among the classes of isolated substances, triterpenes [19], flavonoids [20], coumarins and benzoquinones [21] stand out.

According to the World Health Organization, schistosomiasis affects more than 207 million people worldwide, and about 779 million people are at risk of contracting one of the schistosomiasis. In Brazil, the endemic area covers 19 states with approximately 42 million inhabitants exposed to risk, and about 7 million infected individuals, who in many cases have severe deficiencies, compromising the development of young people and the productivity of adults and making this disease one of the most serious health problems [22-24].

The species *Miconia langsdorffii* Cogn. (Figure 1) was selected for the present study in order to evaluate extracts and major chemical constituents in relation to schistosomicidal activity.

Figure 1

Miconia langsdorffii Cogn. Source: Durigan et al. 2004 [25]

2 MATERIAL AND METHODS

2.1 COLLECTION AND IDENTIFICATION OF PLANT MATERIAL AND OBTAINING THE EXTRACT

The aerial parts of *M. langsdorffii* Cogn. (Melastomataceae) were collected in March 2009 at the Palmira Farm, Serra Azul, São Paulo State, Brazil. The collection and identification were carried out by Valéria M. M. Gimenez and deposited in the Herbarium of the Department of Biology, Faculty of Philosophy, Sciences and Letters of Ribeirão Preto – USP (Herbarium SPFR) with registration number 12288.

The aerial parts of the vegetable were dried and stabilized in a circulating air oven (40ºC) and crushed into powder in a knife mill. The resulting powder (0.5 kg) was extracted with ethyl alcohol/water (96:4 v/v) at an interval of three days, and repeated three times. The solvent was removed using a rotaevaporator, obtaining 7.81g of dry hydroalcoholic crude extract.

2.2 ANALYSIS OF THE CRUDE EXTRACT OF *M. LANGSDORFFII*

Part of the extract (6.7g) was submitted to a vacuum liquid chromatography (CLV), using n-hexane (Hex), ethyl acetate (AcOEt), ethanol (EtOH) and mixtures of these as mobile phase in increasing polarity gradient. Six fractions were collected (Table 1) and these were biomonitored for their schistosomicidal activities *in vitro*.

Table 1

Fractionation of the hydroalcoholic extract of M. langsdorffii

Fraction	**Mobile phase**	**Volume** (L)	**Mass obtained** (g)
F1	Hex/AcOEt 25%	3,0	0,36
F2	Hex/AcOEt 50%	3,0	1,51
F3	AcOEt	2,0	1,40
F4	AcOEt/EtOH 25%	2,0	0,43
F5	AcOEt/EtOH 50%	2,0	0,71
F6	EtOH	2,0	0,35

All fractions were analyzed through HPLC. The NMR-1H $^{and\ 13C\ data}$ of the F2 fraction revealed the presence of the mixture of the triterpenes ursolic acid (**1**) and oleanolic acid (**2**) [26]. An aliquot of this fraction (500 mg) was filtered into 60 g of the celite:activated carbon mixture (3:1 m/m) and eluted with ethyl acetate. This was later purified through HPLC, enabling the purification of the two triterpenes (Figure 2). Ursolic acid was subjected to derivatization reactions, and it was possible to obtain five derivatives (**1a-1e**) [26].

2.3 IN *VITRO EVALUATION* OF SCHISTOSOMICIDAL ACTIVITY

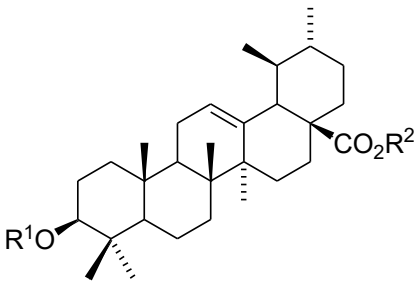
The *in vitro* schistosomicidal evaluation assays were carried out at the Antiparasitic Testing Laboratory of the Natural Products Research Group of the University of Franca, according to standardized methodologies in published works [27,28].

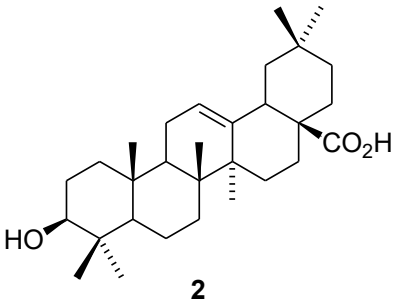
The Schistossoma mansoni *eggs* present in the feces of mice previously infected with the parasite were collected by the Hoffmann method and exposed for approximately 1 hour under light, for the release of miracidia. The miracidia were used to infect the intermediate host, which after 38 to 43 days released the infective form of the parasite, cercariae, which in turn infected the vertebrate host. The cercariae were inoculated into the mice

subcutaneously and after approximately 45 days the adult worms were recovered from the hepatic portal system by infusion [29]. After collection, the parasites were maintained in RPMI 1640 medium buffered with HEPES 20 μM, pH 7.5; supplemented with penicillin (100 U/mL), streptomycin (100 μg/mL) and 10% fetal bovine serum until the moment of use. A pair of adult worms was transferred to a 24-well culture dish (1couple/well) containing the same medium described above and incubated in a humidifying atmosphere at 37ºC in the presence of 5% CO2. After 24 hours of incubation, the compounds previously dissolved in DMSO were added to the RPMI 1640 medium at a final concentration between 10, 50, 100 and 150 μg/mL for fractions and extract, and 10, 50 and 100 μM for pure substances. The parasites were incubated under the same conditions described above for 120 hours and monitored every 24 hours using an inverted microscope to evaluate the general conditions of the parasites such as: pairing, motor activity, tegument alteration and death [27]. Death of the parasites was defined as absence of movement for more than 2 minutes of observation [30]. Adult worms kept in RPMI 1640 medium or RPMI medium with 1% DMSO were used as negative control, and adult worms incubated with 10 μM praziquantel were used as positive controls. Two independent experiments were carried out, and four pairs of worms were evaluated by concentration in each experiment.

Figure 2

*Chemical structures of ursolic acid (**1**), oleanolic acid (**2**) and semisynthetic derivatives of ursolic acid (**1a**, **1b**, **1c**, **1d**, and **1e**)*





2

	R^1	R^2
1	H	H
1a	$COCH_3$	H
1b	$CO(CH_2)_{10}CH_3$	H
1c	$CO(CH_2)_{16}CH_3$	H
1d	H	CH_3
1e	H	K

3 RESULTS AND DISCUSSION

In our studies evaluating schistosomicidal activity, adult *S. mansoni* worm couples were incubated with the compounds to be tested and monitored every 24 hours for 120 hours, using an inverted microscope to evaluate the general conditions of the parasites. In this study, the pure substances were tested at concentrations of 10, 50 and 100 μM and the fractions and extract were tested at concentrations of 10, 50, 100 and 150 μg/mL. No relevant results were obtained at concentrations lower than 150 μg/mL and 100 μM, therefore, the results taken into account were concentrations of 150 μg/mL for fractions and extract, and 100 μM for pure substances.

As observed (Table 2), the crude extract (coded as EHML) at 120 hours of treatment showed an interesting result, demonstrating 100% death of male and female parasites and 100% reduction in motor activity. The fraction **F2** It was the most active, causing the separation of 100% of adult worm couples in 24 hours of incubation, leading to the death of 100% of male and female parasites in 120 hours, and stood out in just 24 hours, triggering a high reduction in the motor activity of the parasites of 100%. The fraction **F3** It also stood out, but not as interesting as the fraction **F2**, as it showed a high reduction in motor activity of 75% only for females, in 24 hours of incubation. The fraction **F4** It demonstrated 100% separation of pairs, death of 50% of male and female parasites, and high reduction in motor activity of 100% of parasites only in 120 hours of incubation.

Table 3 shows the results of pure substances at a concentration of 100 μM. As observed, compound **2** (oleanolic acid) did not show activity, on the other hand, compound **1** (ursolic acid), and its derivatives **1d** and **1e** caused 50% separation of adult worm couples and showed a high reduction in motor activity of 50% of the parasites in 24 hours. Derivative **1e** stands out, the only one that enhanced 100% of couples separated in 120 hours of incubation when compared to ursolic acid **1**, which was 50% under the same conditions. Derivatives **1b** and **1c** only showed a high reduction in motor activity of 75 and 100% of the parasites in 120 hours, respectively. When the assay was carried out with the mixture of the triterpenes ursolic acid and oleanolic acid **(1+2),** it was observed the separation of 100% of the adult worm couples and a high reduction in the motor activity of 100% of the parasites in 24 hours, a factor suggesting a possible synergistic effect. Considering the results obtained, further studies are needed to clarify the mechanism of action of these compounds, as well as to broaden the conclusions regarding the structure-activity relationships.

Table 2

In vitro schistosomicidal activity of hydroalcoholic extract and fractions of Miconia langsdorffii

Samples	Incubation time (hours)	Number of separated couples %	Number of dead parasites %		Reduction in motor activity	
			M	F	% M	% F
Control[a]	24	0	0	0	0	0
	120	0	0	0	0	0
DMSO at 1.5%	24	0	0	0	0	0
	120	0	0	0	0	0
PZQ[b]	24	0	100	100	100	100
	120	0	100	100	100	100
EHML	24	0	0	0	25	25
	120	0	100	100	100	100
F1	24	0	0	0	0	0
	120	25	0	0	50	100
F2	24	100	0	0	100	100
	120	100	100	100	100	100
F3	24	100	0	0	0	75
	120	100	100	100	100	100
F4	24	50	0	0	0	0
	120	100	50	50	100	100
F5	24	0	0	0	0	0
	120	0	0	0	75	75
F6	24	0	0	0	0	0
	120	0	0	0	100	100

[a] RPMI 1640
[b] PZQ Praziquantel [3.1μg/mL,(10μM)]
M: male parasites, F: female parasites
EHML Miconia langsdorffii *hydroacoolic extract* [150μg/mL]
Fractions: F1 *n-hex*/AcOEt 75:25, F2 *n-hex*/AcOEt 50:50, F3 AcOEt, F4 AcOEt/EtOH 75:25, F5 AcOEt/EtOH 50:50, F6 EtOH – all fractions at 150μg/mL.

Table 3

In vitro schistosomicidal activity of substances isolated from M. langsdorffii and semisynthetic derivatives of ursolic acid

Samples	Incubation time (hours)	Number of separated couples %	Number of dead parasites %		Reduction in motor activity	
			M	F	% M	% F
Control[a]	24	0	0	0	0	0
	120	0	0	0	0	0
DMSO at 1.5%	24	0	0	0	0	0
	120	0	0	0	0	0
PZQ[b]	24	0	100	100	100	100
	120	0	100	100	100	100
1	24	50	0	0	50	50
	120	50	0	0	50	50
2	24	0	0	0	0	0
	120	0	0	0	0	0
1+2	24	100	0	0	100	100
	120	100	0	0	100	100
1a	24	0	0	0	0	0
	120	0	0	0	0	0
1b	24	0	0	0	50	50
	120	0	0	0	75	75
1c	24	0	0	0	0	0
	120	0	0	0	100	100
1d	24	50	0	0	50	50
	120	50	0	0	50	50
1e	24	50	0	0	50	50
	120	100	0	0	50	50

[a]RPMI 1640
[b] PZQ Praziquantel [3.1μg/mL,(10μM)]
M male parasites, F female parasites
1 Ursolic acid [45.7μg/mL,(100μM)]
2 Oleanolic acid [45.7μg/mL,(100μM)]
1+2 Ursolic Acid and Oleanolic Acid Mixture [91.3μg/mL,(100μM)]
1a acetylation derivative of ursolic acid with acetic anhydride and pyridine [49.9μg/mL,(100μM)]
1b acetylation derivative of ursolic acid with lauric acid [63.9μg/mL,(100μM)]
1c acetylation derivative of ursolic acid with stearic acid [72.3μg/mL,(100μM)]
1d methylated derivative of ursolic acid [47.1μg/mL,(100μM)]
1e salt derived from ursolic acid [49.5μg/mL,(100μM)].

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