Revista Brasileira de Farmacognosia (2020) 30:118–122
https://doi.org/10.1007/s43450-020-00017-5

SHORT COMMUNICATION

# Pharmacological properties of specioside from the stem bark of *Tabebuia aurea*

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Received: 5 July 2019 / Accepted: 19 September 2020 / Published online: 25 February 2020


## Abstract

Iridoids are secondary metabolites with several biological activities. They are often found in species of the genus *Tabebuia* Gomes ex A.P. de Candolle. *Tabebuia aurea* (Silva Manso) Benth. & Hook. F. ex S. Moore, Bignoniaceae, is used to treat snake bites in traditional medicine. This study aimed to isolate the specioside - an the iridoid glycoside - from *T. aurea*, as well as investigate its potential biological properties, including anti-inflammatory, antibacterial, antibiofilm, cytotoxic, anti-*Trichomonas vaginalis* and antitrypanosomal activities. Specioside inhibited leucocyte recruitment into the peritoneal cavity in mice injected with carrageenan, data that demonstrated its anti-inflammatory potential. However, the additional evaluated biological properties were negligible.

**Keywords** Iridoid · Anti-inflammatory · Chemical identification · Leucocyte recruitment · Cytotoxic

## Introduction

Iridoids are natural constituents in a large number of plant families, including Bignoniaceae, Scrophulariaceae, Rubiaceae, Verbenaceae, Oleaceae, Acanthaceae, Pedaliaceae, Labiatae, Loganiaceae, Ericaceae, Liliaceae, Apocynaceae and Euphorbiaceae (Cao et al. 2019). These compounds are exhibit a wide range of biological and pharmacological activities, such as anti-inflammatory, antiamoebic, anti-diabetic, neuroprotective, anti-cancer, anti-obesity, hepatoprotective and cardiovascular (hypotensive, antiarrhythmic, increase in coronary perfusion rate) properties (Ghisalberti 1998; Bharti et al. 2006; Dinda et al. 2007; Huang et al. 2019).

Specioside (**1**), 6-*O*-(*p*-coumaroyl)-catalpol was first isolated from the bark of *Catalpa speciosa* (Warder ex Barney) Warder ex Engelm., Bignoniaceae (El-Naggar and Doskotch 1980). It is an important iridoid of the *Tabebuia* Gomes ex A.P. de Candolle genus, Bignoniaceae, having been described from *T. argentea* Britt., *T. rosea* (Bertol.) DC., *T. pentaphylla*

**Electronic supplementary material** The online version of this article (https://doi.org/10.1007/s43450-020-00017-5) contains supplementary material, which is available to authorized users.

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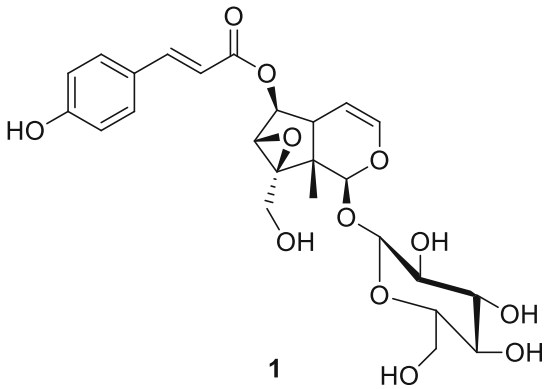
Hemsl. and *T. aurea* (Silva Manso) Benth. & Hook. F. ex S. Moore (Cao et al. 2019; Malange et al. 2019). This compound has already been identified in some species from other genera, including *Ailanthus integrifolia* Lamk, *Buddleja alternifolia* Maxim, *Kigelia africana* (Lam.) Benth, *Verbascum phlomoides* L. and *Veronica peregrina* L., amongst others (Cao et al. 2019). In addition, specioside shows antioxidant activity (Elusyian et al. 2011); in the free-living nematode *Caenorhabditis elegans*, it alleviates stress and prolongs lifespan (Ashtana et al. 2015).

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*Tabebuia aurea* is used in traditional medicine to treat snake bites. In experimental mice, its hydroethanolic extract decreases the inflammatory, haemorrhagic and myotoxic activities induced by the venom of *Bothrops neuwiedi* Wagler, 1824 (Reis et al. 2014). Additionally, this extract reduces the paw edema induced by the venom of *Bothrops moojeni* Hoge, 1966 (Carollo et al. 2015), as well as the hyperalgesia and neuronal injury induced by *Bothrops mattogrossensis* Amaral, 1925 venom (Malange et al. 2019). Although *T. aurea* extracts are effective in reducing inflammation caused by snake venom, specioside, present in these extracts, had not yet been tested as anti-inflammatory agent.

Although iridoids have a wide range of biological activities, including anti-diabetic, anti-inflammatory, immunosuppressive, neuroprotective, anti-cancer and anti-obesity, there are few studies on the biological activities of specioside. Thus, the present study aimed to isolate the specioside from the barks of *T. aurea* and evaluate its pharmacological potential in series of simple bioassays to examine its anti-inflammatory, cytotoxic, antibacterial, antibiofilm, cytotoxic, anti-*Trypanosoma cruzi* and anti-*Trichomonas vaginalis* activities.

## Material and methods

Stem barks from *Tabebuia aurea* (Silva Manso) Benth. & Hook. F. ex S. Moore, Bignoniaceae, were collected in 2017 in Campo Grande, MS, Brazil (20°44′28”S, 54°64′64”W) at an altitude of 615 m above sea level. A voucher specimen was deposited in the CGMS herbarium at the Federal University of Mato Grosso do Sul (number 74328). It was identified by Professor Flavio Macedo Alves, based on the comparison with herbarium samples, a specialised bibliography (Gentry 1992) and the type specimens. The material was dried, powdered and 2.90 kg was extracted with ethanol:water (7:3, *v*/v; 2.16 l) by percolation. The extract was concentrated and lyophilised to yield a crude extract (606.49 g). A portion of this extract (189.11 g) was solubilised in methanol and maintained in contact with Amberlite XAD2 for 2 h with agitation. Subsequently, the Amberlite XAD2 was washed with deionised water (approximately 5 l) to remove the sugars, followed by washing with methanol (approximately 5 l) to obtain the methanolic fraction. This fraction was concentrated and precipitated using deionised water. The precipitate was removed and dried by lyophilisation to obtain the iridoid specioside (18.65 g).

The iridoid was analysed by liquid chromatography-diode array detection-tandem mass spectrometry (LC-DAD-MS/MS) with UFLC Shimadzu Prominence equipment coupled to a DAD and MicrOTOF mass spectrometer, using a Kinetex C18 column (2.6 μm, 100 × 3.01 mm, Phenomenex) and the following elution gradient profile 0–10 min: 6.0% B; 10–12 min: 6.0–40.0% B; 12–13 min: 40.0–100.0% B; 13–15 min: 100.0–6.0% B (solvent B: acetonitrile, solvent A: water; both solvents were added to 0.1% formic acid). The analyses were acquired in negative and positive ion modes. Nitrogen was applied as a nebuliser gas (4 Bar), dry gas (9 l/min) and collision gas. The capillary voltage was 3.5 kV. The compound was solubilised at 0.3 mg/ml (methanol and water, 6:4 *v*/v), filtered (Millex, PTFE, 0.22 μm × 3.0 mm, Millipore) and injected on the system. The injection volume, flow rate and oven temperature were 1 μl, 0.3 ml/min and 50 °C, respectively. The iridoid was also analysed by nuclear magnetic resonance (NMR; $^{1}H$, $^{13}C$, DEPT 135°, COSY, HMQC and HMBC) on a Bruker DRX500 spectrometer ($^{1}H$ at 500 MHz and $^{13}C$ at 125 MHz). Chemical shifts (δ) were expressed in ppm value relative to TMS. The sample was solubilised in $CD_3OD$ (δ 3.31). NMR data are included as Supplementary Material.

The *in vivo* study was approved by the Ethics Committee on Animal Experimentation of the UFMS (Protocol 588/2014; May, 52,014) and was conducted in accordance with the National Institutes of Health regulations on the use and care of animals for scientific purposes. For carrageenan-induced leucocyte recruitment into the peritoneal cavity assay, male Swiss mice (18–25 g; $n = 9$ per group; four groups) were used. The animals were obtained from the Central Animal House of UFMS and housed under a 12 h light:12 h dark cycle before starting the experiments, at 22 ± 2 °C, with food and water available ad libitum. Six hours before each experiment, the animals received only water to avoid food interference with substance absorption. To induce leucocyte recruitment into the peritoneal cavity, the animals were pre-treated for

60 min with vehicle (water), specioside (50 mg/kg, *p.o.*) or indomethacin (15 mg/kg, *p.o.*). Subsequently, carrageenan 1% (*w*/*v*, 0.5 ml, *i.p.*) diluted in 0.9% sterile saline solution was injected. Four hours post-injection of stimulus, the mice were euthanised in a $CO_2$ chamber, and the cells from the peritoneal cavity were harvested by injecting 3 ml phosphate-buffered saline (PBS) that contained 30 U (units) heparin (Basel, Switzerland). The suspension was aspirated with a syringe, diluted (1:20, *v*/v) in Turk's solution (0.2% crystal violet dye in 30% acetic acid), and the total cells were counted in a Neubauer chamber. For differential cell counts, the preparations were stained with Instant-Prov (Newprov). These cells were classified as either polymorphonuclear or mononuclear based on conventional morphological criteria.

The data of carrageenan-induced leucocyte recruitment assay are shown as the mean ± S.E.M. Statistical differences were analysed by one way ANOVA followed by the Tukey's test.

The specioside cytotoxicity was examined using a MTT assay (Invitrogen, Eugene, OR, USA) (Mosmann 1983). HeLa cells (cervical cancer cell line) and HaCaT (human keratinocytes cell line) were kindly provided by Dr. Luisa L. Villa (ICESP, School of Medicine, University of São Paulo/Brazil) and Dr. Silvya S. Maria-Engler (Faculty of Pharmaceutical Sciences, University of São Paulo), respectively. Cells were cultured in Dulbecco's modified Eagle's medium (D6429; Sigma-Aldrich).

For the antibacterial, biofilm formation and eradication of established biofilm assays, *Staphylococcus aureus* (*S. aureus*) ATCC 25904 (clumping factor positive variant), *Staphylococcus epidermidis* (*S. epidermidis*) ATCC 35984 (isolated from catheter sepsis in the state of Tennessee, USA) and *Pseudomonas aeruginosa* (*P. aeruginosa*) ATCC 27853 (isolated from blood culture) were cultivated in Mueller Hinton (MH) agar at 37 °C. Bacterial suspensions ($3 \times 10^8$ colony-forming units [CFU]/ml) were prepared in 0.9% sterile saline. Antibiofilm activity was evaluated using a crystal violet assay according to Trentin et al. (2011), whilst the viability of biofilm cells was measured by the MTT assay. Dimethyl sulfoxide (DMSO) was used as negative control, and vancomycin (for *S. aureus*), rifampicin (for *S. epidermidis*) and gentamycin (for *P. aeruginosa*) were included as positive controls.

The antitrypanosomal assay utilised *T. cruzi* isolated from *Didelphis marsupialis*. The isolation was performed at the University of Carabobo, Venezuela. Axenic culture was established in liver infusion tryptose (LIT) medium, and a clonal population was obtained. The *T. cruzi* clone Dm28c was biologically characterised, and an aliquot was kindly provided by the Carlos Chagas-Fiocruz Institute/PR.

Epimastigote forms of *T. cruzi*, clone Dm28c, were kept at 28 °C in LIT medium supplemented with 10% inactivated foetal bovine serum. Parasites in the exponential growth phase were used for the experiments. The antiproliferative activity evaluated by the MTS (3-(4,5-dimetilthyazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium) assay, according to Henriques et al. (2011). The cells were seeded in 96-well tissue plates at $1 \times 10^6$ cells/ml and incubated with specioside (93 or 290 μM; contained 1.5% DMSO) at 28 °C for 72 h. A negative control (1.5% DMSO) and positive controls with different benznidazole concentrations (5 to 80 μM) were also included. Then, MTS/PMS (40 μg and 0.92 μg per well, respectively) were added to each well, and the plate was incubated at 28 °C for 4 h. The absorbance was evaluated at 490 nm. In parallel, we performed tests of each treatment fixed with 4% paraformaldehyde prior to the addition of MTS/PMS (basal absorbance control).

The *T. vaginalis* isolate 30236 (JH 31A #4, from the American Type Culture Collection ([ATCC], USA) was used in the anti-*Trichomonas vaginalis* assay. Parasites were cultured in vitro in trypticase-yeast extract-maltose (TYM) medium (pH 6.0) supplemented with 10% (*v*/v) heat-inactivated adult bovine serum, and incubated at 37 °C (Diamond 1957). Trophozoites in the logarithmic growth phase - and exhibiting more than 95% viability and normal morphology - were harvested, centrifuged and resuspended in the new TYM medium for the experimental assays. In the 96-well microplate, 50 μl specioside (at 100 μM) was added to 150 μl of a trophozoite suspension ($2 \times 10^5$ trophozoites/ml). The plate was incubated for 24 h at 37 °C with 5% $CO_2$. Subsequently, the exclusion dye trypan blue was added, and the viable number of trophozoites was counted with a Neubauer camera. Three controls were performed: negative control (trophozoites without treatment), vehicle control (0.6% DMSO) and positive control (100 μM metronidazole).

## Results and discussion

Extracts from *Tabebuia* species have shown anti-inflammatory, antioxidant, anti-hemorrhagic, anti-diabetic, anti-cancer, anti-obesity, antibacterial and antihyperalgesic activities (Ospina et al. 2013; Huang et al. 2019; Malange et al. 2019). The *Tabebuia* genus has a storage capacity for iridoid glycosides, which has been described as important chemotaxonomy markers (Santos et al. 2017).

In the present study, compound **1**, namely the iridoid isolated from *T. aurea*, was identified as specioside by comparison of its physical and spectroscopic properties with those previously reported in the literature (Compadre et al. 1982). This compound was analysed by NMR (Supplementary Material) and LC-DAD-MS. In the LC-DAD-MS/MS analysis, the compound showed a retention time of 21.9 min, two absorption bands at 299 and 312 nm in its UV spectrum and the deprotonated molecule anion at *m/z* 507.1498 $[M-H]^-$, which was compatible with the molecular formula

$C_{24}H_{28}O_{12}$. The $[M-H]^-$ yielded the fragment ions at *m/z* 345.0997 and 163.0391 (coumaric acid moiety), which are relative to the eliminations of a hexose molecule and a glycosylated iridoid, respectively. Notably, in the present study, specioside (**1**) was isolated from *T. aurea* with a yield 20-times higher than that reported by Compadre et al. (1982).

Previous studies reported a wide range of bioactivities for iridoids, including antimicrobial, cytotoxic, hypotensive, sedative, choleretic, hepatoprotective, anti-inflammatory, antiallergic, anti-arthritic, wound-healing, antispasmodic and antioxidative (Ghisalberti 1998; Bharti et al. 2006; Dinda et al. 2007). Thus, it is crucial to explore the biological potential of these compounds because they may represent a relevant starting point for the development of novel drugs. Few studies have investigated the potential activities of specioside, the iridoid isolated in this study.

The effect of specioside on leucocyte recruitment into the peritoneal cavity was evaluated in mice injected with 1% carrageenan (Fig. 1). Treatment with specioside (50 mg/kg) resulted in an 80.0% inhibition of leucocyte infiltration, whilst indomethacin (15 mg/kg) reduced the leucocyte migration by 56% when compared to the vehicle (water 10 ml/kg). Reis et al. (2014) evaluated the effect of the hydroethanolic extract from *T. aurea* on polymorphonuclear recruitment into the peritoneal cavity in mice injected with *B. neuwiedi* snake venom and observed that 100 mg/kg of this extract reduced the recruitment by 32.2%. Thus, our result demonstrates the anti-inflammatory potential of specioside and highlights that the isolated compound presents a promising activity.

In the present study, the specioside did not show activity against HeLa and HaCaT cells. Xu et al. (2016) also noted that

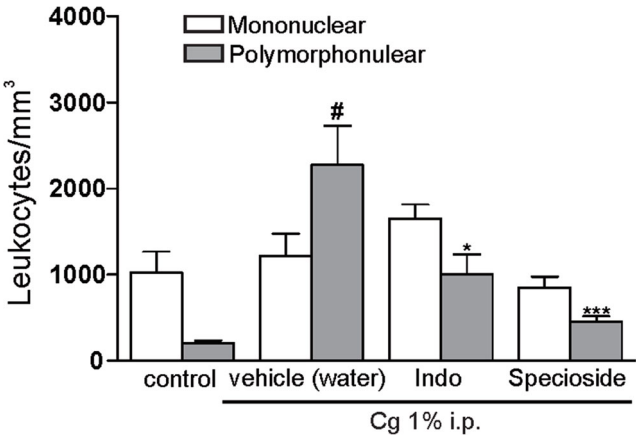


**Fig. 1** Effect of specioside on leucocyte recruitment into the peritoneal cavity in mice injected with carrageenan (1%, *i.p.*, 0.5 ml). The control group was injected *i.p.* with 0.9% sterile saline solution. Indomethacin (15 mg/kg, *p.o*, positive control), specioside (50 mg/kg, *p.o.*) or water (10 ml/kg, *p.o.*, vehicle) were administered 60 min before injection of the stimulus. Cells number is expressed as the mean ± S.E.M. ($n = 9$). $^{\#}p < 0.001$ when compared to the saline group. $^{*}p < 0.05$ and $^{***}p < 0.001$ when compared to the vehicle (water group). Data were analysed using ANOVA followed by the Tukey's Test

no cytotoxic activity by specioside on HepG2 and HeLa cells. Additionally, although some studies demonstrated that the antimicrobial activity of iridoids, specioside did not show antibacterial effects against planktonic cells of *S. aureus*, *S. epidermidis* or *P. aeruginosa* (Tab. 1). It was also unable to inhibit biofilm formation or eradicate the biofilm already formed by these bacterial strains. Our results are consistent with Compadre et al. (1982), who demonstrated that specioside is not effective against *Escherichia coli*, *Sarcina lutea*, *Candida albicans* and *S. aureus*.

Concerning the antitrypanosomal property, compound **1** did not show activity at the tested concentrations. Furthermore, in the anti-*T. vaginalis* assay, it also failed to inhibit this protozoan.

**Acknowledgements** The authors are grateful to Carlos Chagas-Fiocruz Institute/PR for the donation of clone Dm28c of *T. cruzi*, Dr. Luisa L. Villa (ICESP, School of Medicine, University of São Paulo/Brazil), and Dr. Silvya S. Maria-Engler (Faculty of Pharmaceutical Sciences, University of São Paulo) for the donation of culture cells (HeLa and HaCaT cells).

**Authors' contributions** SRN was responsible for conception, design, data analysis and preparation of the manuscript; NNK was responsible for the preparation of extract and isolation of specioside; JMA and AMTF performed the anti-*Trypanosoma.cruzi* assays; MCT-Ki contributed with anti-inflammatory experiments; LEFM, GMZFD and MELC were responsible for evaluation of cytotoxicity; SVR and AJM contributed with antibacterial and antibiofilm assays; TT and GVR evaluated the anti-*Trichomonas vaginalis* activity; FMA was responsible for identification and harvest of plant material; CAC and DBS were responsible for conception and design the study, and the spectroscopic elucidation of specioside. All the authors have revised and approved the final manuscript as submitted and take full responsibility for the contents reported in the manuscript.

**Funding information** This work was supported by INAU (Instituto Nacional de Áreas Úmidas), FUNDECT (Fundação de Apoio ao Desenvolvimento do Ensino, Ciência e Tecnologia do Estado de Mato Grosso do Sul), CNPq, and CAPES.

## Compliance with ethical standards

**Conflict of interest** The authors declare no conflicts of interest.

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