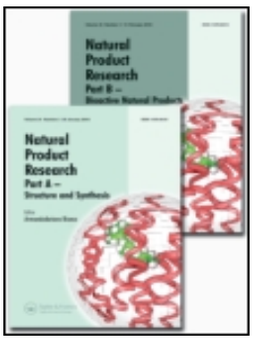

Natural Product Research

Formerly Natural Product Letters

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

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To cite this article: Yanna C. F. Teles, Jaime Ribeiro-Filho, Patrícia T. Bozza, Maria de Fátima Agra, Weam Siheri, John O. Igoli, Alexander I. Gray & Maria de Fátima V. de Souza (2016) Phenolic constituents from *Wissadula periplocifolia* (L.) C. Presl. and anti-inflammatory activity of 7,4′-di-*O*-methylisoscutellarein, Natural Product Research, 30:16, 1880-1884, DOI: 10.1080/14786419.2015.1081196

To link to this article: https://doi.org/10.1080/14786419.2015.1081196

NATURAL PRODUCT RESEARCH, 2016
VOL. 30, NO. 16, 1880–1884
http://dx.doi.org/10.1080/14786419.2015.1081196

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SHORT COMMUNICATION

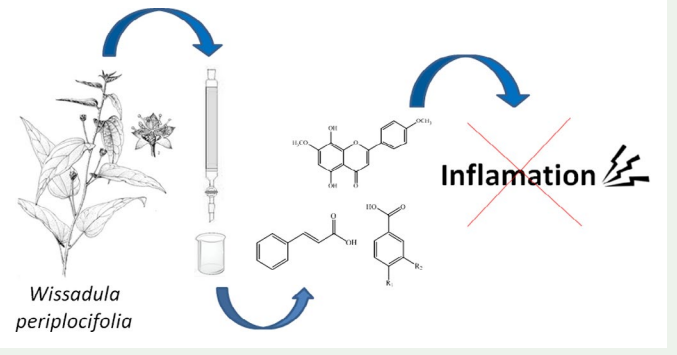
Phenolic constituents from *Wissadula periplocifolia* (L.) C. Presl. and anti-inflammatory activity of 7,4′-di-*O*-methylisoscutellarein

Yanna C. F. Teles[a], Jaime Ribeiro-Filho[b], Patrícia T. Bozza[c], Maria de Fátima Agra[d], Weam Siheri[e], John O. Igoli[e], Alexander I. Gray[e] and Maria de Fátima V. de Souza[a]

[a]Pós-graduação em Desenvolvimento e Inovação Tecnológica em Medicamentos, Centro de Ciências da Saúde, Universidade Federal da Paraíba, João Pessoa, Brazil; [b]Faculdade Leão Sampaio, FLS, Juazeiro do Norte, Brazil; [c]Instituto Oswaldo Cruz, FIOCRUZ, Rio de Janeiro, Brazil; [d]Centro de Biotecnologia, Universidade Federal da Paraíba, João Pessoa, Brazil; [e]Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, UK

ABSTRACT

This study reports the first phenolics from *Wissadula* genus (Malvaceae) and the anti-inflammatory activity of 7,4′-di-*O*-methylisoscutellarein. Using chromatographic methods, five phenolic compounds were isolated from aerial parts of *Wissadula periplocifolia* (L.) C. Presl. The compounds were identified as 4-hydroxybenzoic acid, 3-hydroxybenzoic acid, *trans*-cinnamic acid, tamgermanetin and 7,4′-di-*O*-methylisoscutellarein using spectroscopic methods. The flavone 7,4′-di-*O*-methylisoscutellarein showed anti-inflammatory activity by inhibiting neutrophils recruitment in a mice model of pleurisy and by decreasing significantly the production of cytokines IL-1β and TNF-α.



ARTICLE HISTORY
Received 18 January 2015
Accepted 31 July 2015

KEYWORDS
Malvaceae; *Wissadula periplocifolia*; 7,4′-di-*O*-methylisoscutellarein; anti-inflammatory activity

1. Introduction

Species in the Malvaceae family are known to produce phenolic compounds. Phytochemical investigations have described the isolation of flavonoids (Gomes et al. 2011), coumarins,

CONTACT Maria de Fátima V. de Souza mfvanderlei@ltf.ufpb.br
The supplemental data for this article is available online at http://dx.doi.org/10.1080/14786419.2015.1081196

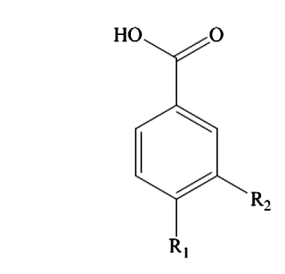
phenolic acids (Silva et al. 2006) along with non-phenolics (Teles et al. 2014). The use of these plants in folk medicine may be due to their anti-inflammatory properties, and they have been reportedly used for the treatment of gastrointestinal diseases, bee stings, asthma, bronchitis and skin infections (Chaves et al. 2013). *Wissadula periplocifolia* (L.) C. Presl. is used in folk medicine to treat snake bites and indigestion (Rahmatullah et al. 2010). The species is reported to possess better antioxidant potential among several studied Malvaceae plants (Oliveira et al. 2012), supporting the search for its phenolic constituents and the anti-inflammatory investigation.

This work reports the first phenolic compounds from *W. periplocifolia* and the anti-inflammatory evaluation of the isolated flavone 7,4′-di-*O*-methyl isocutellarein. Isoscutellarein derivatives, including new glucosides, have been recently identified from Lamiaceae species (Venditti, Serrilli et al. 2013; Venditti et al. 2013; Leporini et al. 2015), and studies have demonstrated relevant biological activities for these compounds, i.e. leishmanicide and antiofidic (Urs et al. 2014; Teles et al. forthcoming) justifying the interest on the pharmacological potential of 7,4′-di-*O*-methyl isocutellarein.

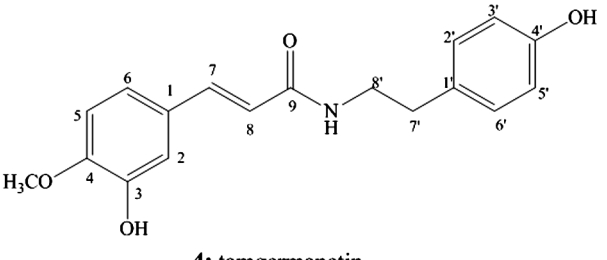
2. Results and discussion

2.1. Identification of purified compounds

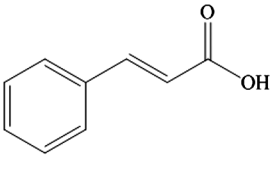
From the aerial parts of *W. periplocifolia,* five phenolic compounds were isolated (Figure 1). Compounds **1**–**3** were obtained as white crystalline solids, and after analysis of their spectral data, they were identified as 4-hydroxybenzoic acid (**1**); 3-hydroxybenzoic acid (**2**); and *trans*-cinnamic acid (**3**) (Canuto & Silveira 2010). Compound **4** was obtained as a pale



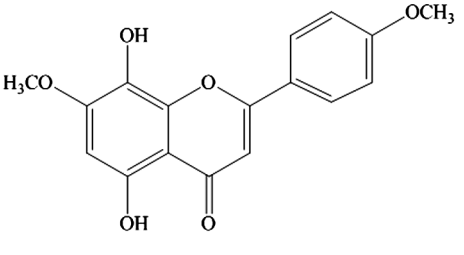
1: R_1= OH; R_2 =H; 4-hydroxybenzoic acid
2: R_1= H; R_2= OH; 3-hydroxybenzoic acid



4: tamgermanetin



3: *trans*-cinnamic acid



5: 7,4'-di-*O*-methylisoscutellarein

Figure 1. Structures of compounds isolated from *W. periplocifolia*.

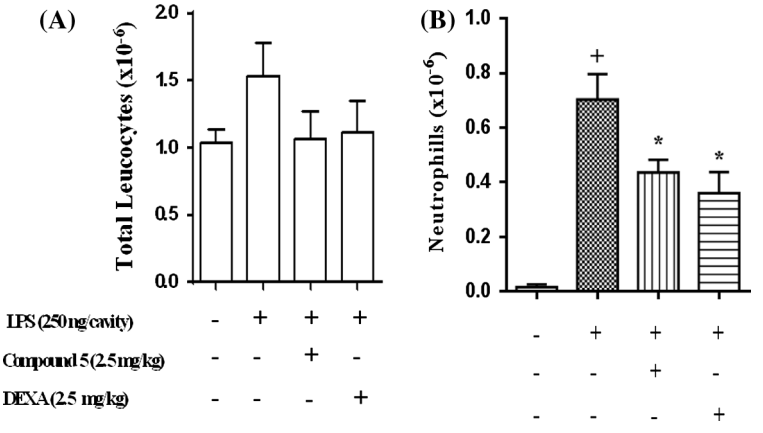


Figure 2. The effect of compound **5** on neutrophil recruitment in LPS-induced Pleurisy. (A) Number of total leucocytes; (B) number of neutrophils; + significantly different ($p < 0.05$) from the unchallenged group; * significantly different from the untreated, LPS-challenged group.

amorphous solid. Its ^{1}H and ^{13}C NMR and the correlations observed in the COSY, HMQC and HMBC spectra allowed identification of compound 4 as *N-trans*-3-hydroxy-4-methoxy cinnamoyltyramine (tamgermanetin) first isolated as a cytotoxic compound from *Myricaria germanica* (Tamaricaceae) (Nawwar et al. 2013).

Compound **5** was isolated as a yellow powder, and from its ^{1}H, ^{13}C and 2D NMR spectra, it was identified as 7,4′;-di-*O*-methylisoscutellarein. Previous studies have reported the isolation of compound **5** from *Sidastrum micranthum* and *Sidastrum paniculatum* (Malvaceae), demonstrating its biological activity as antibiotic-resistant *Staphylococcus aureus* modulator and antileismanial agent (Gomes et al. 2011; Teles et al. forthcoming). Other isoscutellarein derivatives have been reported from Malvaceae species: *Malope trifida* (glucuronides), *S. micranthum* (sulphated derivative), *Abutilon pakistanicum* (methoxyl derivatives) and *Althaea officinalis* (glucosides) (Sikorska et al. 2004; Buchholz et al. 2007; Ali et al. 2010; Zoobi & Mohd 2011). Furthermore, recent researches have successfully isolated isoscutellarein derivatives from *Galeopsis angustifolia* and *Siderites italica* (Lamiaceae) (Venditti, Serrilli et al. 2013; Venditti, et al. 2013).

2.2. Anti-inflammatory activity of 7,4′-di-O-methylisoscutellarein (5)

2.2.1. Neutrophil recruitment inhibition in LPS-induced pleurisy

An intrapleural injection of LPS in mice induced an intense influx of neutrophils into the pleural cavity that was associated with the development of pleural inflammation. Macrophages and neutrophils play key roles in inflammation conditions by producing mediators that amplify the inflammatory response, including cytokines, lipid mediators and reactive oxygen species (Rainsford 2007). To demonstrate the anti-inflammatory effects, the animals were pre-treated orally with compound **5** (2.5 mg/kg) or dexamethasone (DEXA) (2.5 mg/kg) 1 h before the LPS challenge. This treatment significantly reduced the total number of neutrophils in the pleural lavage (Figure 2) compared with the untreated LPS-challenged group, demonstrating that compound **5** plays an inhibitory role on neutrophil recruitment.

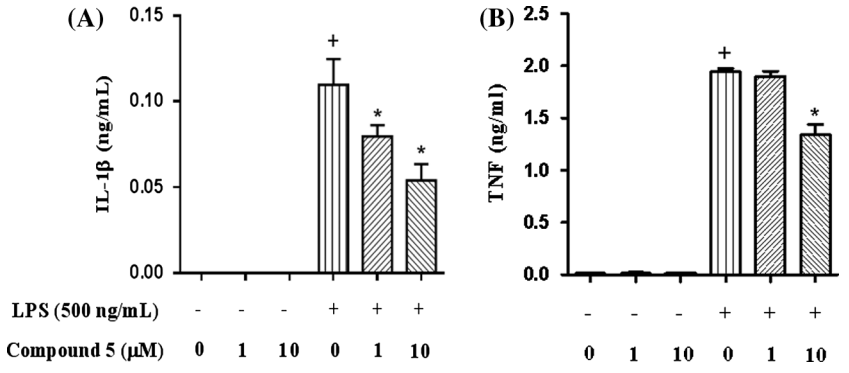


Figure 3. The effects of compound **5** on cytokine production *in vitro*. + Significantly different ($p < 0.05$) from non-stimulated cells; *significantly different from the untreated, LPS-stimulated cells.

2.2.2. The effects of 7,4′-di-O-methylisoscutellarein (5) on cytokine production in vitro

Compound **5** was examined for a direct inhibitory effect on macrophage activation by analysing the production of inflammatory cytokines *in vitro*. As shown in Figure 3(A) and (B), the addition of LPS in peritoneal macrophage culture induced an expressive production of IL-1β and TNF-α that was significantly inhibited by pre-treatment with compound **5**, indicating its inhibitory effect on neutrophil recruitment may be associated with inhibition of cytokine production (Libby 2007).

3. Conclusions

The phytochemical investigation of *W. periplocifolia* has led to the first phenolic constituents from *Wissadula* genus: 4-hydroxybenzoic acid, 3-hydroxybenzoic acid, *trans*-cinnamic acid, tamgermanetin and 7,4′-di-*O*-methylisoscutellarein. Isoscutellarein derivatives have been previously reported from some Malvaceae species; thus, this study contributes to the chemotaxonomy of the family by supporting the close botanical relationship between *Wissadula*, *Sidastrum, Abutilon, Malope* and *Althaea* genera. Furthermore, the flavone 7,4′-di-*O*-methylisoscutellarein showed anti-inflammatory activity by inhibiting the recruitment of neutrophils and decreasing the production of IL-1β and TNF-α *in vitro*, thus it could be a potential candidate for anti-inflammatory drug development.

Funding

Coordenação de Aperfeiçoamento de Pessoal de Nível Superior and Conselho Nacional de Desenvolvimento Científico e Tecnológico with grant number Universal 14/2011 – CNPq Process (Nº 481625/2011).

Disclosure statement

No potential conflict of interest was reported by the authors.

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