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SHORT COMMUNICATION

Antileshimania, anti-*Trypanosoma cruzi* and antimicrobial activities of scandenin and 4′-O-methylderrone from *Deguelia costata*

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ABSTRACT

Scandenin and 4′-O-methylderrone were isolated from the ethanol extract of the roots and dichloromethane extract of the leaves of *Deguelia costata* (Benth.) A.M.G. Azevedo & R.A. Camargo, respectively. These compounds and their extracts had their antiprotozoal, antibacterial, antifungal, and cytotoxic activities tested. All samples were active for amastigotes of the *T. cruzi*, with EC_{50} values varying from 34.5 to 9.8 μg mL^{-1}. The 4′-O-methylderrone and scandenin showed better leishmanicidal action against the promastigote of *L. amazonensis*, with EC_{50} of 43.3 and 45.9 μg mL^{-1}, respectively, when compared to their extracts. All extracts and scandenin showed activities against *Staphylococcus* sp, *Bacillus* sp, and *Candida* sp. The compounds did not show cytotoxicity on rat macrophages. As confirmed by spectroscopic analyses, the extracts are rich in phenolics, mainly isoflavonoids. The study of *D. costata* is a promising strategy for discovering isoflavones and 4-hydroxy-3-phenylcoumarins with antiprotozoal, antibacterial, and antifungal activities.

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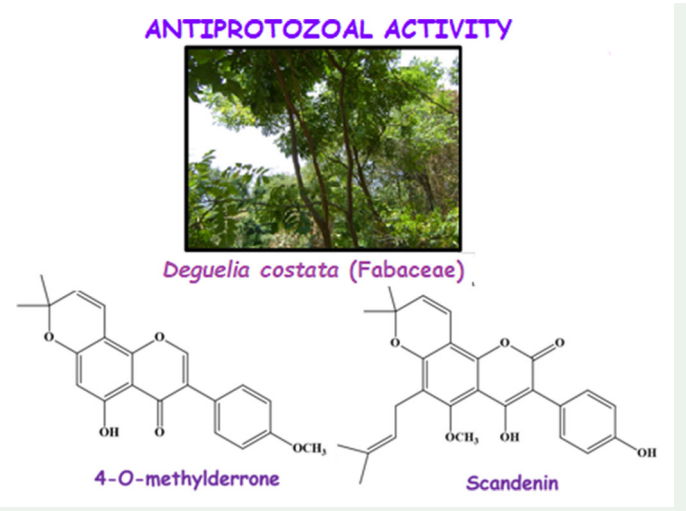

1. Introduction

Leishmaniasis and Chagas disease are Neglected Tropical Diseases (NTDs), and they are in many countries. These diseases affect low-income people, mainly those who live in precarious housing conditions, where access to basic sanitation is still inadequate (WHO 2021a, 2021b). Cutaneous leishmaniasis (American cutaneous leishmaniasis) and mucocutaneous leishmaniasis have, as etiological agents, *L. braziliensis*, *L. amazonensis*, respectively. In turn, protozoan *Trypanosoma cruzi* is the etiologic agent of the Chagas disease. Chemotherapy for treating these diseases has high toxicity and several side effects. Additionally, the emergence of resistant protozoan strains reinforces the need for new chemotherapeutic agents to treat NTDs (Santos et al. 2020). In this context, natural products of plant origin are a promising source of bioactive compounds (Newman and Cragg 2020).

Compounds and extracts of Fabaceae species show recognized antiprotozoal (Bortoluzzi et al. 2021); antifungal (do Nascimento et al. 2020) and antibacterial properties (Cuellar et al. 2020; do Nascimento et al. 2020; Erhabor et al. 2020), among others. The study of species of the genus *Deguelia*, subfamily Papilonoideae (Fabaceae), is a promising strategy for the discovery of isoflavonoids with antiprotozoal and antimicrobial activities (Marques et al. 2015).

Deguelia costata (Benth.) A.M.G. Azevedo & R.A. Camargo, that belongs to the *Multiovulis* section of the *Deguelia*, in a previous phytochemical study, showed the presence of three 4-hydroxy-3-phenylcoumarins (scandenin, robustin and isorobustin), six isoflavones (4′-O-methylderrone, 5-hydroxy-3′,4′-dimethoxy-2",2"-dimethylpyrano [5",6":7,6] isoflavone, 4′-O-methylalpinumisoflavone, gancaonin M, costatin A and costatin B) (Lemes et al. 2019). Some of these compounds showed several biological properties, such as antiprotozoal, antibacterial and antifungal (Magalhães et al. 2006; Tamfu et al. 2020).

Given the need to discover new therapies to treat infectious diseases, mainly NTDs, this unprecedented study evaluated the anti-*Trypanosoma cruzi*, anti-*Leishmania*

amazonensis, antibacterial, antifungal, antioxidant and cytotoxic activities of leaf dichloromethane extract and root ethanolic extract of *D. costata,* as well as its compounds 4′-O-methylderrone and scandenin. Moreover, this study determined the total contents of phenolics and tannins in the extracts.

2. Results and discussion

The known compounds 4′-O-methylderrone and scandenin were previously isolated of the extracts leaf dichloromethane (E1) and root ethanolic (E2) from *D. costata*, respectively. Your identifications were based on the NMR data (Figures S1 and S2, Table S1) and comparison with literature values (Lemes et al. 2019). The anti-*T. cruzi* activity these compounds and extracts were evaluated against the trypomastigote form and the intracellular form (amastigote) (Table S2). Regarding activity against amastigotes, 4′-O-methylderrone, scandenin and extracts were active, with EC_{50} values in the range 34.5 to 9.8 $\mu g\ mL^{-1}$ (EC_{50} benznidazole = 1.4 μM). 4′-O-methylderrone and scandenin had best leishmanicidal action against the promastigote of *Leishmania amazonensis*, with an $EC_{50} = 43.3\ \mu g\ mL^{-1}$ and $EC_{50} = 45.9\ \mu g\ mL^{-1}$, respectively, when compared with their extracts (range EC_{50}: 182.3 − 145.5). Compounds had an SI (selectivity index), above 1 for both parasites, confirming their greater activity against protozoa in relation to cytotoxicity against mammalian cells. The SI consists of the ratio between the Cytotoxic Concentration 50% (CC_{50}) for murine cells and EC_{50} for protozoa, reveals how specific the extract or substance is for the parasite, that is, values greater than 1 indicate that the treatment is more active against the parasite than toxic to the host cells, a characteristic that makes it a promising compound for drug development (de Almeida et al. 2014). Scandenin showed antifungal activity against *C. albicans* and *C. glabrata* (MIC = 50 $\mu g\ mL^{-1}$ for both yeasts) and antibacterial against *S. epidermidis* (MIC = 12.5 $\mu g\ mL^{-1}$; MBC = 50 $\mu g\ mL^{-1}$) and *B. cereus* (MIC = 6.25 $\mu g\ mL^{-1}$), while 4′-O-methylderrone showed only a fungiostatic effect for *C. albicans* (Table S3). *S. epidermidis* was most sensitive to all extracts, followed by *B. subtilis* and *B. cereus*. The E1 was bacteriostatic and bactericidal against *M. luteus* (MBC = 500 $\mu g\ mL^{-1}$) and *B. subtilis* (MIC = MBC = 62.5 $\mu g\ mL^{-1}$) and fungiostatic for *C. glabrata* (MIC = 500 $\mu g\ mL^{-1}$). While, E2 was active against all tested fungi (range MICs: 500 − 125 $\mu g\ mL^{-1}$). In view of these results, was observed that E1 is more selective in relation to the antifungal effect that E1. Regarding the antibacterial action, both were selective for Gram-positive strains. In the ^1H NMR spectrum of the E1 (Figure S3), signals at 8.01-7.88 suggested the presence of proton in position 2, ring C of isoflavone, among others. Intense singlet signals were observed at δ 13.09 − 12.64 and δ 13.71 − 13.69 of the proton of hydroxyl groups, in A-rings of isoflavone, in intramolecular hydrogen bonding with the carbonyl group in the C-ring. Additionally, singlets with lower intensities were observed in the range of δ 11.19 − 9.01, indicating the presence of the hydroxyl group in position 4, ring C of 4-hydroxy-3-phenylcoumarins. In the ^1H NMR spectrum of E2 (Figure S4) were observed singlet signals between at δ 10.23 − 9.93, suggesting the presence of hydroxyl group (-OH), in position 4 of the C-ring of 4-hydroxy-3-phenylcoumarins, among others. In addition, the most intense signals at

δ 7.43 – 6.90; δ 5.69, δ 6.90, δ 1.47; δ 5.17, δ 3.33; δ 1.71 and δ 1.79 and δ 4.02 – 3.92 indicated the majority presence of scandenin. These isoflavonoids suggested a positive correlation between the phenolic contents and DPPH and ABTS radical scavenging activity in the extracts (Table S4). These findings were in agreement with the chemosystematics of the *Deguelia* genus, which must be related to the presence of isoflavonoid derivatives, as indicated in the ^{1}H NMR data (Marques et al. 2015; Lemes et al. 2019) and suggest that the antiprotozoal effect of the extracts, especially against *T. cruzi*, should be mainly due to the presence of isoflavonoids, in these extracts, since the antiparasitic, antifungal and antibacterial potential of this class of compounds has already been reported in the literature (Magalhães et al. 2006; Al-Maharik 2019; Kalli et al. 2020; Chang et al. 2021; Pontes et al. 2021; Ito et al. 2022).

The antioxidant defense system can be targeted by some antiprotozoal drugs, which may interfere with the function of antioxidant enzymes such as catalase, glutathione peroxidase or other targets. Polyphenolic compounds are recognized for their ability to induce the production of reactive oxygen species (ROS) in host cells, in infectious processes, and also in the protozoan cell [Fonseca-Silva et al. 2011; Mohseni et al. 2022]. In view of the results obtained, studies on the mechanisms of action of *D. costata* extracts and their polyphenolics should be conducted in the future in order to set relationships between their antioxidant, antimicrobial and antiprotozoal properties. However, the anti-*T. cruzi* and antileishmanial effects of scandenin are being reported for the first time in this work. In this way, given the anti-*T. cruzi* effect obtained for scandenin, future studies should be encouraged to evaluate the antiprotozoal effect of 4-hydroxy-3-phenylcoumarins derivatives, which are compounds of rare occurrence in nature.

3. Experimental

The methodology is in the supplementary material.

4. Conclusion

The results suggested that scandenin showed antimicrobial potential, especially for *S. epdermidis* and yeasts. In relation to antiprotozoal effect, scandenin and root extract showed selectivity for amastigote forms of *T. cruzi*, associated with their low cytotoxicity in uninfected macrophages. Thus, the study showed that isoflavonoids from the *D. costata* are potential drug discovery candidates for the treatment of neglected and infectious diseases.

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Disclosure statement

The authors declare no conflict of interest.

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