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ANTI-*Leishmania infantum* ACTIVITY OF ACETOGENINS FROM *Porcelia macrocarpa* (ANNONACEAE)

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Visceral leishmaniasis is a neglected disease with a significant public health impact, with approximately 30,000 new cases reported annually[1]. In this context, discovering new drugs to treat this disease is crucial. As part of our ongoing research on *Porcelia macrocarpa*,[2] five chemically related acetogenins (**1–5**, Figure 1) were isolated from the seeds of this specie. ^{1}H NMR spectra of **1-5** showed characteristic signals of the γ-lactone ring at δ 2.56–2.57 (dt, J = 9.9 and 4.8 Hz, H-2), 4.30–4.38 (dd, J = 4.8 and 3.1 Hz, H-3), 4.44–4.45 (dq, J = 6.5 and 3.1 Hz, H-4) and 1.43 (d, J = 6.5 Hz, H-5).[2] To compounds **1–4**, a triplet at δ 2.13 was also observed, assigned to the propargylic hydrogens H-10' and H-13'. Additionally, in the ^{1}H NMR spectra of **2–4**, were observed signals at δ 5.80–5.81 (ddt, J = 16.9, 10.2 and 6.6 Hz) and 4.95–4.96 (m), indicating the presence of a terminal double bond in the side chain. These signals were absent from the ^{1}H NMR spectra of compounds **1** and **5**, which showed one broad singlet at δ_H 1.27 and one triplet at δ 0.85 (J = 6.8 Hz), which is characteristic of a terminal methyl group.[2] Analysis of ^{13}C NMR spectra of **1-5** confirmed the presence of γ-lactone ring due to the signals at δ 177 (C-1), 47 (C-2), 71 (C-3), 78 (C-4) and 13 (C-5). In the ^{13}C NMR spectra of **1–4**, were observed signals at δ 81 (C-11') and 80 (C-12'), characteristic of sp carbons, while spectra of **2–4**, signals at δ 139 and 114, characteristic of terminal double bonds were detect. On the other hand, except to the signals of γ-lactone ring, no signals of sp and sp^2 carbons were observed in the ^{13}C NMR spectrum of **5**, indicating a saturated side chain. Analysis by ESI-HRMS showed $[M+H]^+$ ions at *m/z* 393.3382 ($C_{25}H_{45}O_3$, **1**), 391.3227 ($C_{25}H_{43}O_3$, **2**), 363.2900 ($C_{23}H_{39}O_3$, **3**), 419.3522 ($C_{27}H_{47}O_3$, **4**) and 397.3681 ($C_{25}H_{49}O_3$, **5**). Additionally, fragmentation patterns at *m/z* 143, 255 and 307, observed in the MS/MS spectra, indicated that the triple bond in compounds **2–4** are located at C-11'. Initially, no toxicity against NCTC cells was observed for compounds **1-5** (CC_{50} > 200 μM). Their antileishmanial effect was then evaluated *in vitro* against the amastigote form of *L. infantum*. Among compounds with a C_{20} side chain, **2** displayed activity (EC_{50} = 23.5 μM), while **1** and **5** were inactive (EC_{50} > 150 μM). These results suggest that the terminal double bond in the side chain plays an important role in activity. Based on this profile, the effects of **2 – 4** on *L. infantum* suggested that elongating the side chain (C_{22} - compound **4**) decreased activity (EC_{50} > 150 μM), while reducing it (C_{18} - compound **3**) enhanced the potency (EC_{50} = 11.3 μM). Interestingly, compound **3** showed similar effect of that determined to the positive control, miltefosine (EC_{50} = 17.8 μM). Therefore, these data suggest that the antileishmanial activity of acetylenic acetogenins depends on a combination of double and triple bonds in the side chain and an appropriate side-chain length.

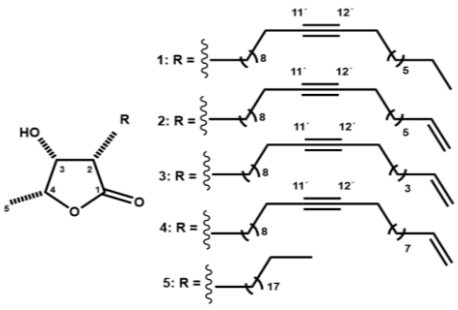

Figure 1. Molecular structures of the acetogenins **1 - 5** isolated from *P. macrocarpa*

Keywords: Porcelia macrocarpa*, acetogenins, antileishmanial activity.*

References: [1]WHO, *Leishmaniasis* **2023**; [2]Brito et al., *Phytochemistry* **2025**, *231*, 114360.

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