



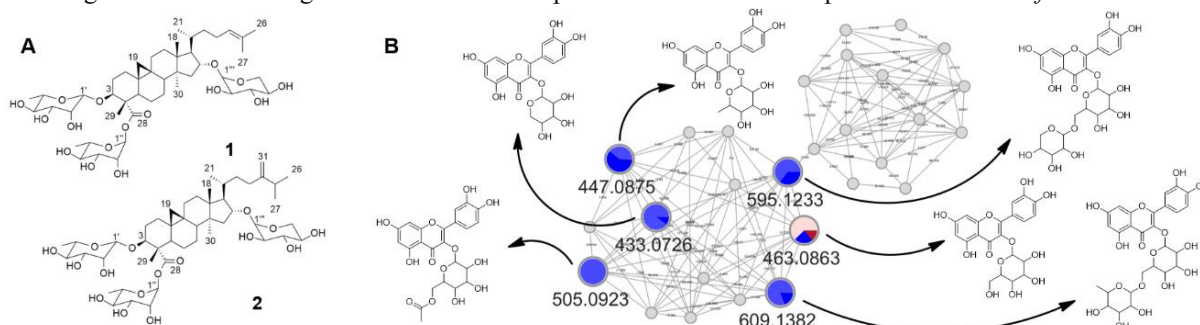
**NEW TRITERPENE SAPONIN, METABOLOMIC PROFILE, CYTOTOXICITY AND ANTIPLASMODIAL ACTIVITIES OF *Combretum mellifluum***

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Numerous species from *Combretum* (Combretaceae) genus are used in folk medicine, including for malaria treatment. *Combretum mellifluum* Eichler (“mofumbo-da-chapada”), found in various regions of Brazil, contains steroids, triterpenes, lignans, flavonoids, and other phenolics, with reported antioxidant and cytotoxic activities. This study reports the isolation of a mixture of two triterpene saponins (**1+2**) and their cytotoxic potential. The metabolomic profile of the leaves and stem bark from *C. mellifluum* as well as its antiplasmodial activity were analyzed. The mixture was isolated by column chromatography, NMR, and MS identified a new saponin 28-*O*- $\alpha$ -rhamnopyranosyl 3-*O*- $\alpha$ -rhamnopyranoside-16-*O*- $\alpha$ -arabinopyranoside-3 $\beta$ ,16 $\alpha$ -dihydroxy-24-methylenecycloartan-28-oate (**1**) and amphipaniculoside C (**2**) (Fig.1A). The mixture showed cytotoxicity against SW-480 and MDA-MB-231 cancer cell lines (IC<sub>50</sub> = 14.83 and 15.06  $\mu$ g/mL) but no effect on L929 non-tumoral cells (>25  $\mu$ g/mL). LC-MS profiling of hexane, ether, ethyl acetate, and hydromethanol fractions (from ethanolic extracts) was obtained via MZmine 3.9 and GNPS molecular networking, being annotated 28 metabolites distributed in nine classes, including *O*- and *C*-glycosylated flavonoids (Fig. 1B), proanthocyanidins, *O*-methylated flavonoids, flavan-3-ols, triterpene saponins, an ellagic acid derivative, a flavonol, and a chlorophyll derivative. Antiplasmodial tests against *Plasmodium falciparum* (W2 strain) showed activity for the hexane (9.8  $\pm$  2.02  $\mu$ g/mL) and ether (8.91  $\pm$  1.75  $\mu$ g/mL) leaf fractions, and the ethyl acetate bark fraction (13.44  $\pm$  2.35  $\mu$ g/mL). The findings advance knowledge on the chemical composition and antimalarial potential of *C. mellifluum*.



**Figure 1:** Mixture of saponins (**1+2**) isolated from the ethanolic extract from *C. mellifluum* leaves (A). Flavonoid glycoside cluster in negative ionization mode (B).

**Keywords:** *Combretum mellifluum*; Triterpene saponin; Molecular Networking; Cytotoxicity; Antiplasmodial activity

<sup>1</sup>Silva, J. S. et al. *Toxicol. Environ. Health, Part A* **2021**, 85(9), 364.

<sup>2</sup>Mirowski, P. S. et al. *Nat. Prod. Res.* **2022**, 36(24), 6224.