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Lippia lacunosa AS A PROMISING SOURCE OF PHENYLETHANOID GLYCOSIDES WITH INHIBITORY ACTIVITY AGAINST SARS-COV-2 PROTEASES

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Lippia lacunosa Mart. & Schauer (Verbenaceae) is a native and endemic species of Brazil, traditionally used to treat respiratory disorders[1,2]. Considering that SARS-CoV-2 primarily affects the respiratory system, this species represents a promising candidate for COVID-19-related studies. Phytochemically, *L. lacunosa* is rich in phenolic metabolites, particularly phenylpropanoid glycosides (PhGs). Previous reports highlight the inhibitory potential of these compounds against viral targets such as the SARS-CoV-2 proteases 3CLpro and PLpro[3], which are essential for viral replication. Thus, this study aimed to evaluate the inhibitory activity of *L. lacunosa* extracts against these proteases, followed by metabolite fractionation using Countercurrent Chromatography (CCC) and chemical characterization by LC-MS/MS. Ethanolic and ethyl acetate (EtOAc) extracts were tested at 100 µg/mL in FRET-based enzymatic assays using recombinant SARS-CoV-2 proteases (3CLpro and PLpro). The ethanolic extract inhibited over 90% of both proteases, while the EtOAc extract showed 100% inhibition of 3CLpro and 55% inhibition of PLpro. The EtOAc extract was selected for CCC fractionation, employing the biphasic solvent system ethyl acetate-butanol-water (1:0.05:1), yielding 9 fractions. LC-MS/MS combined with Feature-Based Molecular Networking (FBMN) confirmed PhGs like *m/z* 665 $[M-H]^-$ (acetyl-verbascoside), *m/z* 755 $[M-H]^-$ (forsythoside B), and other glycosylated flavonoids. Perspectives include testing all fractions against proteases and isolating the most active metabolites. Despite its extensive popular use, research on *L. lacunosa* is scarce; to our knowledge, this is one of the first investigations into its antiviral potential, especially against SARS-CoV-2, reinforcing the importance of exploring Brazilian native plants as sources of bioactive compounds. The authors thank the support from their institutions and the financial support of FAPERJ, Capes and CNPq.

Keywords: *Verbenaceae, 3CLpro, PLpro, chemometrics, HSCCC, LC-MS/MS.*

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