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COMPARATIVE ANALYSIS OF THE PHYTOCHEMICAL PROFILE AND ANTI-SARS-COV-2 POTENTIAL OF Siparuna bifida LEAF EXTRACTS FROM THE AMAZON AND ATLANTIC FOREST BIOMES

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The genus *Siparuna* (Siparunaceae), widely distributed across the tropical Americas, includes aromatic species traditionally used in Brazilian folk medicine to treat colds and flu. Several species have demonstrated antiviral activity, attributed mainly to alkaloids and flavonoids, reinforcing the therapeutic relevance of this genus. Despite this, *Siparuna bifida* (Poepp. & Endl.) A.DC. remains poorly studied in terms of its chemical composition and biological properties. This study aimed to investigate the phytochemical profile and antiviral potential of *S. bifida* leaf extracts, focusing on the inhibition of the SARS-CoV-2 papain-like protease (PL_{pro}), a key enzyme involved in viral replication and immune evasion. Specimens were collected from two ecologically distinct Brazilian biomes—the Amazon Rainforest and the Atlantic Forest—to evaluate the influence of environmental factors on metabolite composition and bioactivity. Dried leaves were exhaustively macerated in ethanol, and the crude extract was subjected to liquid–liquid partitioning with solvents of increasing polarity (hexane, dichloromethane, ethyl acetate, and n-butanol), yielding four extracts. These were analyzed by UHPLC-DAD-MS/MS, and data processing using MZmine enabled metabolite annotation. Antiviral activity was assessed through a FRET-based enzymatic assay targeting PL_{pro}, and Feature-Based Molecular Networking (FBMN) was applied to visualize metabolite clustering based on MS/MS fragmentation patterns. The hexane extracts of Atlantic Forest and Amazon exhibited the most pronounced inhibitory effect, with 87% and 58.2% inhibition at 100 µg/mL, respectively, suggesting a correlation between low-polarity constituents and antiviral activity. This enhanced activity may be related to the higher relative abundance of annotated compounds in hexane and dichloromethane extracts from Atlantic Forest biome. Chemical analysis led to the annotation of eleven isoquinoline alkaloids, including reticuline and its derivatives. These compounds formed a distinct molecular network in FBMN analysis, allowing a clear association between chemical structure and biological activity. The results underscore the potential of *S. bifida* as a source of bioactive alkaloids with antiviral properties and demonstrate the effectiveness of molecular networking as a tool for the targeted screening of complex natural matrices.

Keywords: *Brazilian biomes; Siparunaceae; Benzyltetrahydroisoquinoline alkaloids; FRET; SARS-CoV-2.*

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