Abstract

This thesis builds upon previous research into the antiplasmodial properties of plants from the *Strychnos* genus (Loganiaceae family), focusing on several species that have shown promising potential, including *Strychnos icaja* Baill., *Strychnos usambarensis* Gilg ex Engl., and *Strychnos variabilis* De Wild. The initial phase of this study involved an *in vitro* screening of 43 methanolic crude extracts from 28 *Strychnos* species for their antiplasmodial activity against the 3D7 strain of *Plasmodium falciparum*. This screening was complemented by an exploration of the metabolites from these extracts, as well as an alkaloidic extract, using molecular networking, a chemometric method that maps metabolites and visualizes their relationships based on MS/MS spectra. The application of spectral databases allowed for the rapid differentiation of known and unknown compounds, thereby facilitating the bio- and mass-guided fractionation process. This study initially highlighted the importance of further exploring the *Strychnos* genus, revealing clusters of previously unidentified metabolites that may exhibit antiplasmodial properties. Consequently, several species with promising (IC_{50} ≤ 5 µg/mL) or good (IC_{50} between 5 and 15 µg/mL) antiplasmodial activity were selected, notably the leaves of *S. usambarensis* Gilg ex Engl. and *S. phaeotricha* Gilg, as well as the trunk barks of *S. longicaudata* Gilg.

The second phase of the study focused on validating one of the database identifications, strychnine, which was detected in seven species not previously recognized as producers of this compound. Various analyses confirmed its presence, providing proof of concept for the molecular networking methodology.

The final part of the study centered on isolating and identifying novel antiplasmodial metabolites through bio- and mass-guided fractionation. Analyses of *S. usambarensis* leaves revealed unknown compounds with masses above *m/z* 900. One metabolite, with a mass of *m/z* 944, was isolated. It could be a dimeric or trimeric alkaloid containing a glycosidic moiety. However, its antiplasmodial activity could not be evaluated due to its limited quantity and structural fragility. In the case of *S. longicaudata* trunk barks, fractionation led to the isolation of alstonine and seven unknown metabolites, five of which demonstrated promising antiplasmodial activities and three of which were subjected to structural elucidation. Lastly, a preliminary study on *S. phaeotricha* leaves revealed good antiplasmodial activity despite the low quantity of alkaloids it contains. The results suggest that the activity may be attributed to compounds from either the alkaloid or terpene classes. Bio- and mass-guided fractionation has been initiated, and further enrichment of the fractions is necessary to progress this research.

Exploring the chemodiversity from the *Strychnos* genus using molecular networking to unveil and identify novel antiplasmodial compounds

O. Bonnet

Exploring the chemodiversity from the *Strychnos* genus using molecular networking to unveil and identify novel antiplasmodial compounds

Olivier Bonnet

University of Liège
Faculty of Medicine
Center for Interdisciplinary Research on Medicines
Laboratory of Pharmacognosy (Pr. M. Frédérich)

Thesis submitted for the degree of PhD in Biomedical and Pharmaceutical Sciences

Supervisor: Pr. Michel Frédérich

2024-2025

LIÈGE université
Center for Interdisciplinary Research on Medicines