



***Eco-friendly approaches to malaria and dengue control: larvicidal, antiparasitic and antiviral activities of *Piper alatipetiolatum* essential oil***

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In Brazil, malaria and dengue are diseases caused by *Plasmodium* and DENV, respectively, and primarily transmitted by *Anopheles darlingi* and *Aedes aegypti* mosquitoes that have developed resistance to insecticides often toxic to non-target organisms. In May 2025, over 1,242,400 probable cases of dengue and 29,955 confirmed cases of malaria have been reported. In response, eco-friendly vector control strategies have increasingly focused on natural products from Amazonian plants, particularly *Piper* species. This study aimed to investigate the essential oil (EO) and its major compounds from *P. alatipetiolatum* as potential agents against mosquito vectors and the etiologic agents of malaria and dengue. The EOs were extracted by hydrodistillation and characterized using GC-based techniques. The major compounds were isolated by column chromatography and identified by HRMS, GC-MS, GC-FID, and <sup>1</sup>H and <sup>13</sup>C NMR. These products were evaluated against *An. darlingi* and *Ae. aegypti* larvae, *P. vivax*, and DENV. Toxicity was also assessed in non-target aquatic organisms, including *Hemiptera*, *Coleoptera*, and *Diptera*. For the first time, the sesquiterpene 6-ishwarone was isolated from essential oil, as well as ishwarol B and ishwarane. The EO and the compounds 6-ishwarone, ishwarol, and ishwarane showed larvicidal activity (LC<sub>50</sub> from 29.31 to 40.76 µg/mL), with cellular damage and changes in antioxidant enzymes such as SOD, CAT, GST, and α- and β-esterases. Antiparasitic (IC<sub>50</sub> from 3.7 to 11.2 µg/mL) and antiviral (IC<sub>50</sub> from 5.8 to 13.24 µg/mL) activities were also observed, with no cytotoxicity to VERO or PBMC cells. These products showed toxicity to non-target organisms only at high concentrations (LC<sub>50</sub> from 2,098.80 to 7,707.13 µg/mL), indicating environmental safety. Thus, EOs and compounds from *P. alatipetiolatum* and *P. purusianum* may serve as eco-friendly alternatives for controlling mosquito vectors and the pathogens of malaria and dengue.

**Keywords:** *Piper*, sesquiterpenes, mosquitoes, <sup>13</sup>C NMR, dengue, malaria.

