

Molluscicidal activity of *Piper anisum* (Spreg.) Angely Essential Oil and of its 1-butyl-3,4-methylenedioxybenzene Major Compound

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Abstract

Schistosomiasis is a historically endemic disease in Brazil, which is caused by the trematode parasite *Schistosoma mansoni* hosted by the worm *Biomphalaria glabrata* snails. The searching for new environmental non-toxic active agents for *B. glabrata* control is emerging. Natural products as alternative drug lead can be justified by its low toxicity and environmental sustainability. In this work, *Piper anisum* essential oil (EO) and its major compound were investigated for molluscicidal activity against snails of the species *B. glabrata*, taking into account the seasonal variation of EO. Leaves of *P. anisum* were collected in different seasons and the EO was obtained by hydrodistillation. Chemical analysis of the EO by Gas Chromatography (GC) coupled to Mass Spectrometer (MS) and GC coupled to Flame Ionization Detector (FID) allowed identification and quantification of the EO compounds, respectively. The EO major compound 1-butyl-3,4-methylenedioxybenzene (BMDB) was also isolated from leaf *n*-hexane extract. The molluscicidal activity was determined by exposing snails to increasing concentrations of the EO and BMDB, and the lethal concentration (LC₅₀) was calculated. The chemical composition of the EO varied between seasons, with higher percentage (> 99%) of BMDB observed in the summer. The results showed molluscicidal activity against *B. glabrata*, of all EO samples at 100 µg/mL. The LC₅₀ was determined as 35 ppm for BMDB suggesting this compound as an alternative source of biocontrol agent against *B. glabrata*.

Introduction

Parasitic diseases are prevalent among the Brazilian population, especially in impoverished areas (Pereira et al., 2020). Due to a lack of effective treatment, inefficiency, or the use of poor and outdated methods, these diseases are classified as neglected diseases (Saucha et al., 2015). One of the parasitic infections promoted by worms is schistosomiasis, that is a disease caused by the trematode parasite *Schistosoma mansoni*, which has a high incidence in Brazil (Meireles et al., 2022). It is contracted through contaminated water, and the biological cycle of the worm requires the presence of the intermediate host, snails of the genus *Biomphalaria*, including the species *B. glabrata* (Carlos de Souza et al., 2011). The total number of deaths from schistosomiasis during the period from 2010 to 2022 was 6,130, representing an average annual mortality rate of 472 deaths. (Brasil, 2022). It was observed that there is a strong correlation between greater social vulnerability and high rates of the disease and mortality. The areas in Brazil endemic for schistosomiasis infection include Northeast region, as well as in the northern part of the Southeast region of Brazil (Pinheiro et al., 2020). According to Nascimento et al., (2019), the total cost of schistosomiasis in Brazil can be attributed to indirect expenses, which was estimated to be US\$ 41.7 million in 2015.

The World Health Organization (WHO) recommends the use of niclosamide, a synthetic chemical compound, for the biological control of *B. glabrata* snails as the only preventive measure against parasite maturation (WHO, 2017). However, the compound shows high toxicity to the aquatic ecosystem, resulting in the mortality of other organisms. While this preventive method has been a protocol at the WHO since

the 1960s, it is crucial to investigate new compounds that can act as biocontrols without posing risks to the environment (Ribeiro et al., 2021).

Natural products serve as significant sources for research in obtaining new chemical compounds with pharmacological interest and for conducting biological activity assays (Najmi et al., 2022). The genus *Piper* L. is a well-studied group known for its bioactivities, which include insecticidal, antibacterial, analgesic, and larvicidal properties (Peixoto et al., 2021; Ramos et al., 2021; Matias et al., 2022). A great number of metabolites, such as terpenes, amides, flavonoids, alkaloids, phenylpropanoids, and lignoids, have been isolated from *Piper* L. species (Ferraz et al., 2010; López et al., 2016; Mendes et al., 2017; Nascimento et al., 2020; Ramos and Moreira, 2019; Marques et al., 2022). Essential oils (EOs) from this genus have exhibited cytotoxic effects and demonstrated various properties, including insecticidal, bactericidal, leishmanicidal, antifungal, and larvicidal activities (Oliveira et al., 2014; da Silva et al., 2016; dos Santos et al., 2021; Machado et al., 2021).

Piper anisum (Spreng.) Angely, sin. *Ottonia anisum* (Spreng.) Angely, commonly known as “jaborandi”, which has been extensively studied for its various medicinal properties, including analgesic, bactericidal, insecticidal, and antifungal activities (Marques and Kaplan, 2015; López et al., 2016; Marques et al., 2017; Batista et al., 2020; Soares et al., 2022). This species is native to the Northeast and Southeast regions of Brazil and is used by traditional “Quilombola” communities for religious practices, as well as for its anesthetic and diuretic properties. The Pataxó Indians in Bahia State of Brazil, also utilize *P. anisum* for its tooth anesthetic properties (Lopez et al., 2016; Batista et al., 2020). Despite extensive research, the variation in its essential oil (EO) content across different seasons and its molluscicidal activity has never been evaluated in the literature. The study conducted by Moreira and Kaplan (1997) identified a butyl derived compound, 1-butyl-3,4-methylenedioxybenzene (BMDB), as the major component in the EO of *P. anisum*. Other compounds derived from the same biosynthetic pathway, such as dillapiole (Maia and Andrade, 2009), safrole (Do Carmo et al., 2012), eugenol (Kumar et al., 2008), apirole, and myristicin (Sousa et al., 2014), have had their molluscicidal activities confirmed.

Therefore, the objective of this study is to assess the molluscicidal activity of the EO and its major compound BMDB from *P. anisum* against snails of the species *B. glabrata*.

Materials and Methods

Plant material

Leaves of *Piper anisum* (Spreng.) Angely were collected from adult individuals located in Raiz da Serra, Magé municipality, Rio de Janeiro (S 22°33'20.50" / 43°10'44.68" W) at 10:00 am, during the months of November (spring), February (summer), May (autumn), and August (winter) of 2019. The plant was in vegetative stage in the autumn and winter and in reproductive stage in the spring and summer. A voucher specimen (HRJ13453) was deposited in the Bradeanum Herbarium of State University of Rio de Janeiro and the plant identification was confirmed by taxonomist expert Elsie Franklin Guimarães from Rio de

Janeiro Botanical Garden Research Institute. Legal access to the genetic heritage component was authorized and registered under AE4E953 and the collection license was obtained through the Biodiversity Authorization and Information System with number 57296-4.

Extraction of the Essential Oil

The essential oil (EO) was extracted from 150 g of fresh leaves, which were chopped manually with the help of scissors and subjected to the hydrodistillation method in a modified Clevenger-type apparatus (Wasichy, 1963). The plant material was placed in a 2 L round bottom volumetric flask and 700 mL of distilled water were added. The flask containing the cut leaves and water was placed on the heating mantle, initiating the hydrodistillation process that lasted 2 h. The EO was collected, dried with anhydrous sodium sulfate, and transferred to a 2 mL amber vial, which was sealed and kept at -20 °C until analysis (Oliveira et al., 2013; Ramos et al., 2021; Costa-Oliveira et al. 2023). The yield was calculated by dividing the mass of the obtained EO by the mass of the leaves used for extraction (w/w), multiplied by 100 to show in percentage.

Isolation and identification of 1-butyl-3,4-methylenedioxybenzene (BMDB)

Fresh leaves (100 g) of *P. anisum* were reduced in size using scissors and then extracted by dynamic maceration with *n*-hexane at room temperature. The resulting material was filtered, and the solvent was evaporated under reduced pressure, yielding 2.8 g of a non-polar extract. The fractionation of the *n*-hexane extract of *P. anisum* was carried out using column chromatography over silica gel (60 mesh, Sigma-Aldrich, Brazil). A gradient of increasing polarities with *n*-hexane-ethyl acetate-methanol was used as the mobile phase. A total of 89 fractions were collected, and all samples were analyzed by TLC (silica gel 60 F₂₅₄ aluminium sheets, Sigma-Aldrich, Brazil). Fractions 12–27 (120 mg) were combined based on their TLC similarity profiles and then subjected to GC-MS analysis (HP Agilent GC 6890 – MS 5973, see below for the GC-MS parameters) for the characterization of the isolated compound. The structure of the pure compound was determined by the analysis of its MS fragmentation pattern, as well as ¹H and ¹³C NMR analysis (CDCl₃ as solvent; TMS as internal standard; Bruker DRX 400 spectrometer). The obtained data were compared with previously reported data (Moreira and Kaplan, 1997). The structure of the identified compound is shown in Fig. 1.

Essential Oil Analysis

The EO obtained by hydrodistillation was dissolved in dichloromethane (Tedia[®], Brazil) to a final concentration of approximately 1000 ppm and subjected to Gas Chromatography (GC) coupled to Mass Spectrometry (MS) analysis using an HP Agilent GC 6890 – MS 5973 equipment, to acquire mass spectra. The percentage and Retention Index (RI) were obtained by GC coupled to a Flame Ionization Detector (FID) on an HP-Agilent 6890 equipment.

The conditions for GC-MS analysis were HP-5MS column (30 m x 0.25 mm i.d. x 0.25 µm, film thickness), temperature program from 60°C to 240°C, with an increment of 3°C/min, and using helium (~ 99.99%) as

the carrier gas, with a constant flow rate of 1.0 mL/min, mass scans between m/z 40–600 u.m.a., with an impact energy of 70 eV, in positive mode. A sample of 1 μ L of the EO solution was injected splitless, with an injector temperature of 270°C. The GC-FID analysis was done under the same conditions as the GC-MS analysis, except for the carrier gas used, which was hydrogen (Oliveira et al., 2013).

The Retention Indices (RI) were determined from the retention time (Rt) of a series of saturated aliphatic hydrocarbons (C₈-C₂₈, Sigma-Aldrich, Brazil) obtained by CG-FID, under the same conditions as the EO analyses. The compounds present in the EO were identified by comparison of their mass spectra with equipment database records (Wiley 7n; NIST) and by comparison of the calculated RI (Dool and Kratz, 1963) with those from the literature (Adams, 2017). All analyzes were performed in triplicate.

Molluscicidal bioassay

The molluscicidal activity of the samples was performed according to the protocol described by Oliveira-filho (2003). For each assay, 400 mL of synthetic soft water containing 10 snails of the *B. glabrata* species were placed in a 600 mL beaker. A 100 μ L aliquot of the EO was dissolved in distilled water, and then, emulsified to facilitate solubilization in the biological assay environment. The control group consisted only of synthetic soft water, while the tested groups had a final concentration of 100 μ g/mL of *P. anisum* EO for each season of the year. The same procedure was carried out with BMDB at final concentrations of 25, 36, 50, and 75 μ g/mL. The animals were exposed to the EO and BMDB for 96 h, after which they were transferred to beakers containing only synthetic soft water and kept under observation for an additional 10 days. The soft water was prepared using 20 mL of solution 1 and 10 mL of solution 2 in 970 mL of distilled water. Solution 1 was prepared with 1.5 g of calcium sulfate in 1000 mL of distilled water, and solution 2 with 0.02 g of potassium chloride, 4.8 g of sodium bicarbonate, and 6.1 g of magnesium sulfate in 1000 mL of distilled water (Oliveira-Filho et al., 2010).

Data Analysis

Probit regression analysis in Excel Office software was used to determine the LC₅₀ values, which denote effective doses for 50% mortality. These are the endpoints commonly used in modern dose-response experiments (Ali et al., 2016). The associated Chi-Square (χ^2) values were used to evaluate the quality of Pearson's goodness-of-fit for the adequacy of the probit model to these specific data.

Results and Discussion

The hydrodistillation of fresh leaves of *P. anisum* resulted in four EO with yields of 0.22% for spring (EO-Sp), 0.26% for summer (EO-S), 0.27% for autumn (EO-A), and 0.21% for winter (EO-W). Compounds identification ranged from 16 to 3 different ones and from 93.29 to 99.49% of identification (Table 1). BMDB (Figure 1) is reported as the major compound for all samples.

As published in the literature, EO are associated with plant communication, attraction of pollinators, seed dispersers, and defense against microorganisms, and herbivory (Machado et al., 2021). Various factors affect the qualitative and quantitative production of EO, and these changes are related to the genotype of

the species, which has undergone several plastic adaptations throughout the evolutionary process due to interactions with biotic and abiotic factors (Pereira et al., 2021).

The spring essential oil showed greater chemical diversity (16 identified compounds) and lower BMDB percentage (51.34%) compared to other seasons. In spring, the specimens were at the beginning of the reproductive period, with flowers and fruits, and the end was recorded in summer. According to Machado et al. (2021), during the reproductive period, in order to ensure the completion of the reproductive cycle, specimens of the genus *Piper* L. synthesize compounds with anti-herbivory and pollinator-attracting action. The author highlights the presence of linalool and *E*-nerolidol in the reproductive phenophase of *Piper mollicomum* Kunth as powerful attractors, as well as 1,8-cineol as a significant herbivore repellent. This may justify the greater chemical diversity of the EO from spring. The same was observed in the spring EO of *P. anisum*, with a great relative percentage of 1,8-cineol (17.64%) and the lowest content of BMDB (51.34%) compared to other seasons. According to Giuliani et al. (2018), the ecological demands experienced by plants produce responses that are modulated in terms of energy economy, which has been categorized as the drain effect. The competition between the mevalonic acid and/or 2-C-methyl-D-erythritol 4-phosphate and shikimic acid pathways takes place to mediate microclimatic factors (Ramos et al., 2020). Furthermore, the relatively low percentage (78.41%) recorded for BMDB in the autumn sample, compared to the samples collected during summer (99.12%) and winter (96.86%), could potentially be attributed to the presence of 1-propyl-3,4-methylenedioxybenzene. This compound shares the same biosynthetic pathway as BMDB.

Insert Fig. 1 here

Insert table 1 here

It is noteworthy that the seasonal variation of the EO from this species has not been previously studied. As formerly mentioned, BMDB compound has been identified in the chemical composition of the EOs of *P. anisum* from different locations (Moreira and Kaplan, 1997; Pereira et al., 2021). Also, BMDB has been described in the chemical composition of the EO of *Piper corcovadensis* (Miq.) C.DC., a species taxonomically very similar to *P. anisum* (de Lira Pimentel et al., 2021).

Regarding molluscicidal activity, the mortality rate of snails was lower for EO-Sp (30% mortality), whereas EO-S, EO-A, and EO-W led to 100% mortality, all samples at a concentration of 100 mg/mL. The isolated BMDB at a concentration of 25 µg/mL (BMDB25) caused 10% mortality, while at 38 µg/mL (BMDB38) resulted in 70% mortality. At concentrations of 50 and 75 µg/mL (BMDB50 and BMDB75), the mortality rate reached 100% (Table 2, Fig. 2).

Considering these results, molluscicidal assays performed with BMDB at concentrations of 25, 38, 50, and 75 µg/mL resulted in an LC₅₀ value of 35.05 ppm, demonstrating significant molluscicidal action against snails of the *B. glabrata*. This is the first report of this biological activity for BMDB in the literature.

Insert table 2 here

Insert Fig. 2 here

The lowest activity observed for the spring EO can be explained in terms of a higher relative percentage of 1,8-cineole, as well as a lower of BMDB. According to studies carried out with the species *Eugenia punicifolia* (HBK) DC. and *Hyptis dilatata* Benth, both of which contain 1,8-cineol as the major compound, they did not exhibit any biological activity against the snail species *B. glabrata*. In contrast, *Lippia acutidens* Mart. and *Lippia gracilis* Schauer, species that do not contain this terpenoid, showed bioactivity against the mollusk (Ribeiro et al., 2021). Although Ribeiro et al. (2021) isolated 1,8-cineol for direct testing on *B. glabrata* snail species, no biological activity was observed.

Compounds with a C₆-C₃ chemical skeleton, known as arylpropanoids, have been demonstrated to be effective molluscicides in several studies (Kumar et al., 2008; Maia and Andrade, 2009; Do Carmo et al., 2012; Sousa et al., 2014). The compound BMDB, which has a C₆-C₄ skeleton, is synthesized through the same biosynthetic pathway as the C₆-C₃ compounds and are chemically related to arylpropanoids. In a biological assay against the snail species *B. glabrata*, eugenol obtained from the species *Cinnamomum zeylanicum* Blume, resulted in an LC₅₀ of 18.62 µg/mL (Gomes et al., 2019). These data suggest that aromatic rings, methylenedioxy group, and lateral carbon chains (allyl and/or alkyl) may contribute to the biological action against the snail species *B. glabrata*. Compounds with methoxy or hydroxy groups in place of methylenedioxy are demonstrated to be more active, such as eugenol (Gomes et al., 2019).

Nevertheless, the biological mechanisms leading to the death of snails of the species *B. glabrata* are still unclear. Despite that, cellular-level actions, inhibition of enzymatic action, or electrostatic interactions with phospholipids in the cytoplasm are suggested as possible causes (Ribeiro et al., 2021).

Conclusion

This study found that *Piper anisum* essential oil has molluscicidal activity against *B. glabrata*, a known intermediate host of *Schistosoma mansoni*. Essential oil from spring season showed the lowest activity. BMDB was identified as the main compound in all tested samples, and it demonstrated dose-dependent snail mortality. These findings suggest that the essential oil and BMDB could be studied as molluscicides to control schistosomiasis.

Declarations

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Authors' contributions

Conceptualization, R. D. C. C. and D. L. M., Methodology, R. D. C. C., R. R. C., A. M. M. and D. L. M.; Formal Analysis, R. D. C. C. and Y. J. R.; Investigation, R. D. C. C.; Resources, D. L. M., R. R. C., A. M. M. and R. D. C. C.; Writing – Original Draft Preparation, R. D. C. C. and Y. J. R.; Writing – Review & Editing, R. D. C. C., Y. J. R., A. M. M. and D. L. M.,

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Tables

Table 1 and 2 are available in the Supplementary Files section.

Figures

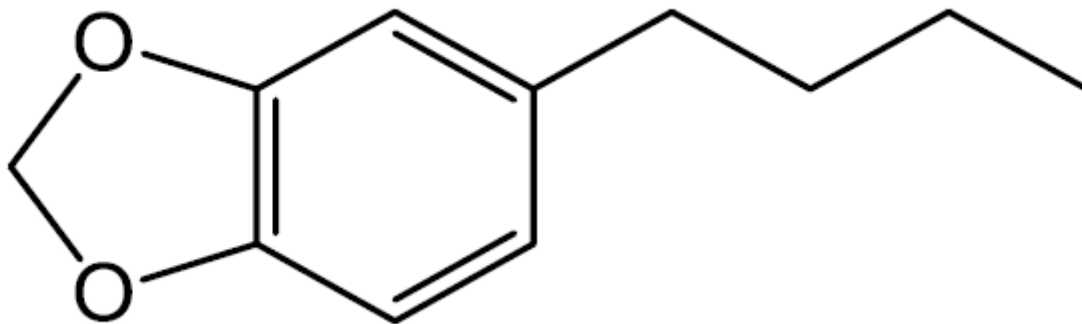


Figure 1

Chemical structure of 1-butyl-3,4-methylenedioxybenzene, the main compound identified in the essential oil from

leaves of *Piper anisum*.

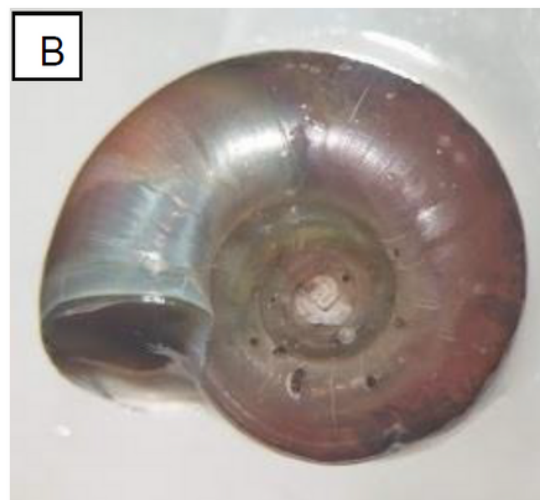


Figure 2

A: control snail; B: snail treated with 25 µg/mL of 1-butyl-3,4-methylenedioxybenzene

Supplementary Files

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