MINISTÉRIO DA EDUCAÇÃO

UNIVERSIDADE FEDERAL RURAL DA AMAZÔNIA

MUSEU PARAENSE EMÍLIO GOELDI

PROGRAMA DE PÓS GRADUAÇÃO EM CIÊNCIAS BIOLÓGICAS - BOTÂNICA TROPICAL

ELIZA DE JESUS BARROS DOS SANTOS

CARACTERIZAÇÃO ANATÔMICA, QUÍMICA E AVALIAÇÃO BIOLOGICA DAS FOLHAS DE *Myrcia sylvatica* (G. Mey): UMA ABORDAGEM INTEGRADA

BELÉM

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Dissertação apresentada à Universidade Federal Rural da Amazônia e ao Museu Paraense Emilio Goeldi, como parte das exigências do Programa de Pós-graduação em Ciências Biológicas: área de concentração: Botânica Tropical, para obtenção do título de mestre.

Orientador: Dr. Mozaniel Santana de Oliveira
Coorientadora: Dra. Eloisa Helena de Aguiar Andrade

BELÉM

2025

Dados Internacionais de Catalogação na Publicação (CIP)
Bibliotecas da Universidade Federal Rural da Amazônia
Gerada automaticamente mediante os dados fornecidos pelo(a) autor(a)

S237c Santos, Eliza de Jesus Barros dos
Caracterização Anatômica, Quimica e Avaliação Biológica das Folhas de Myrcia sylvatica (G.Mey) : Uma Abordagem Integrada / Eliza de Jesus Barros dos Santos. - 2025.
134 f. : il. color.

Dissertação (Mestrado) - Programa de PÓS-GRADUAÇÃO em Ciências Biológicas (CB), Campus Universitário de Belém, Universidade Federal Rural Da Amazônia, Belém, 2025.
Orientador: Prof. Dr. Mozaniel Santana de Oliveira
Coorientador: Prof. Dr. Eloisa Helena de Aguiar Andrade.

1. Óleo essencial. 2. Anatomia. 3. Histoquímica, . 4. Atividade antioxidante. 5. Toxicidade. . I. Oliveira , Mozaniel Santana de , *orient*. II. Título

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CDD 581

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Aprovado em: 01 / 08 / 2025

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Dedico este trabalho a mim mesma, pela coragem de persistir mesmo diante das dificuldades, e à minha mãe Maria Barros, que nunca deixou de acreditar em mim e sempre sonhou os meus sonhos como se fossem dela.

AGRADECIMENTOS

Primeiramente, agradeço a Deus, fonte de força, sabedoria e esperança, por me sustentar e iluminar cada passo desta caminhada acadêmica e pessoal.

Aos meus pais, Maria e Elias, minha base e inspiração. Obrigada pelo amor, paciência, dedicação e por nunca deixarem de acreditar em mim. À minha avó Luiza Aires (in memoriam), por todo carinho e amor. À Lorena Venâncio, pela presença constante e pelo apoio inestimável ao longo desta jornada.

Ao Museu Paraense Emílio Goeldi (MPEG) e à Universidade Federal Rural da Amazônia (UFRA), pela formação sólida e pelo suporte acadêmico e científico imprescindível à realização deste trabalho.

Agradeço a todos os docentes do PPGBot que contribuíram para a minha formação. Também agradeço à Dra. Ely Simone e à Zelina, pelas contribuições para a realização desta pesquisa. Aos colegas e amigos do programa, pelos momentos de apoio, risos e memórias compartilhadas, que tornaram o caminho mais leve.

Ao grupo de pesquisa de Fitoquímica, pela troca de conhecimentos, contribuições valiosas, apoio técnico e incentivo durante a escrita. Ao Anderson de Santana, Luiz e Carol, pela amizade, conselhos e contribuições para a minha pesquisa.

Ao meu orientador, Dr. Mozaniel Santana de Oliveira, pela orientação ética e respeitosa, pela confiança, autonomia concedida e incentivo contínuo. Às minhas coorientadoras, Dra. Karyme do Socorro e Dra. Eloisa Andrade, pelo valioso apoio e aprendizado ao longo da pesquisa.

À Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), pela concessão da bolsa, e ao Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), pelo financiamento. Por fim, agradeço a todos que, de alguma forma, contribuíram para a concretização deste trabalho. Minha eterna gratidão.

Muito obrigada!

Tudo tem o seu tempo determinado, e há tempo para todo proposito de baixo do céu

Eclesiastes 3:1

RESUMO

Os óleos essenciais (OEs) são compostos voláteis produzidos a partir do metabolismo secundário das plantas, que conferem aroma e têm diversas propriedades biológicas. O gênero *Myrcia* é uma importante fonte de OEs, que apresenta diversas espécies com potencial terapêutico e biotecnológico. Dentro deste gênero, a espécie *Myrcia sylvatica* desperta interesse científico devido à sua variabilidade química, que pode ser influenciada por fatores climáticos, disponibilidade de nutrientes foliares e ás técnicas de extração. Além disso, há lacunas na leitura sobre os aspectos anatômicos e histoquímicos foliares da espécie, o que dificulta a compreensão de quais estruturas especializadas a espécie apresenta, bem como os compostos bioativos. Este estudo teve como objetivo realizar uma revisão sobre o gênero *Myrcia* e a espécie *Myrcia sylvatica*, com foco na composição química e atividade biológica. Avaliando a anatomia, histoquímica e o potencial antioxidante, toxicidade e estudo *in silico* do óleo essencial das folhas de *Myrcia sylvatica*. Para isso, foi realizadoa uma compilação de informações na literatura sobre o gênero *Myrcia* e a espécie *M. sylvatica*, com foco na composição química e potencial biológico. Além disso, as folhas de *M. sylvatica* foram submetidas à anàlise anatômica e histoquímica, revelando estruturas secretoras associadas ao armazenamento, e à secreção de lipídios, terpenos, alcaloides e compostos fenólicos. Os óleos essenciais foram extraídos por hidrodestilação (HD) e destilação a vapor (SD) e caracterizados quimicamente por cromatografia gasosa acoplada à espectrometria de massa (CG-EM), mostrando a presença de sesquiterpenos como α-zingibereno, germacreno D e espatulenol como maiores concentrações. O óleo extraído por SD apresentou maior atividade antioxidante (CI_{50} ABTS = 6,8038 mg/mL; CI_{50} DPPH = 12,80 mg/mL) e maior toxicidade contra *Artemia salina* (CL_{50} = 4,1739 µg/mL) do que o óleo da HD. A análise de correlação indicou clusters biossintéticos distintos entre os 40 compostos. A docking molecular e a análise ADME destacaram o espatulenol e o globulol como moléculas bioativas promissoras com potencial inibitória sobre a acetilcolinesterase e perfis farmacocinéticos favoráveis. Os resultados desse estudo contribuem para o conhecimento biológico de *M. sylvatica*.

Palavras-chave: Óleo essencial, anatomia, histoquímica, atividade antioxidante, toxicidade.

ABSTRACT

Essential oils (EOs) are volatile compounds produced from the secondary metabolism of plants, which provide aroma and have various biological properties. The *Myrcia* genus is an important source of EOs and has several species with therapeutic and biotechnological potential. Within this genus, the species *Myrcia sylvatica* is of scientific interest due to its chemical variability, which can be influenced by climatic factors, availability of leaf nutrients and extraction techniques. In addition, there are gaps in the literature on the leaf anatomical and histochemical aspects of the species, which makes it difficult to understand which specialized structures the species has, as well as the bioactive compounds. The aim of this study was to review the genus *Myrcia* and the species *Myrcia sylvatica*, with a focus on their chemical composition and biological activity. The anatomy, histochemistry and antioxidant potential, toxicity and *in silico* study of the essential oil of *Myrcia sylvatica* leaves are relevant. To this end, information was compiled from the literature on the genus *Myrcia* and the species *M. sylvatica*, with a focus on chemical composition and biological potential. In addition, the leaves of *M. sylvatica* were subjected to anatomical and histochemical investigations, revealing secretory structures associated with the storage and distribution of lipids, terpenes, alkaloids and phenolic compounds. The essential oils were extracted by hydrodistillation (HD) and steam distillation (SD) and chemically characterized by gas chromatography coupled with mass spectrometry (GC-MS), showing the presence of sesquiterpenes such as α-zingiberene, germacrene D and spatulenol in the highest concentrations. The oil extracted by SD showed greater antioxidant activity (CI_{50} ABTS = 6.8038 mg/mL; CI_{50} DPPH = 12.80 mg/mL) and greater toxicity against *Artemia salina* (CL_{50} = 4.1739 µg/mL) than the HD oil. A Splendor analysis indicated different biosynthetic clusters among the 40 compounds. Molecular docking and ADME analysis highlighted spatulenol and globulol as promising bioactive molecules with acetylcholinesterase inhibitory potential and developed pharmacokinetic profiles. The results of this study provide details on the biological knowledge of *M. sylvatica*.

Keywords: Essential oil, anatomy, histochemistry, antioxidant activity, toxicity.

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1. CONTEXTUALIZAÇÃO

Os óleos essenciais (OEs) são substâncias voláteis naturais extraídas de plantas aromáticas, e têm sido alvo de extenso estudo devido às atividades biológicas que apresentam. Dentre as diversas espécies vegetais que produzem os OEs, o gênero *Myrcia* se destaca como uma fonte promissora, pois seus óleos essenciais possuem propriedades antioxidantes, antimicrobianas, inseticidas, fitotóxicas e hipoglicemiantes, entre outras, que são altamente valorizadas em setores como a indústria de alimentícias e farmacêuticas (Cascaes *et al.*, 2015; Scalvenzi *et al.*, 2017; De Oliveira *et al.*, 2021; De Moraes *et al.*, 2022; Dos Santos *et al.*, 2024).

O gênero *Myrcia* se caracteriza pela presença de monoterpenos, sesquiterpenos e outras classes químicas, apresentando uma variabilidade quimica significativa entre as espécies e até mesmo dentro da mesma espécie. Fatores como o ambiente em que a planta cresce, seu estágio de desenvolvimento, condições climáticas e até mesmo o momento da coleta, influenciam a composição química dos OEs. Essa complexidade na composição química dos OEs é importante, pois determina as propriedades biológicas do gênero, bem como as diferentes aplicações (Ferreira Macedo *et al.*, 2021; Costa *et al.*, 2022).

Espécies do gênero *Myrcia* são caracterizadas por apresentarem um perfil aromático, resultante da produção de terpenos que são armazenados e secretados por estruturas especializadas, como idioblastos, cavidade secretoras e tricomas (Gomes *et al.*, 2009; Pacheco-Silva; Donato, 2016; Costa *et al.*, 2020). Entre as diversas espécies do gênero, destaca-se *Myrcia sylvatica* (G. Mey), conhecida na região Amazônica como “murtinha” ou “murta”. Essa espécie é usada empiricamente pela comunidade local no tratamento do diabetes (Costa *et al.*, 2022).

Estudos mostram que *Myrcia sylvatica* apresenta um perfil químico rico em sesquiterpenos hidrocarbonetos e oxigenados, além de compostos fenólicos, o que confere potencial biológico, como anti-inflamatório, toxicidade e atividade antioxidante (Rosa *et al.*, 2016; Silva *et al.*, 2018; De Moraes *et al.*, 2022; Silva Júnior *et al.*, 2025). No entanto, ainda há lacunas na literatura para fundamentar quais estruturas especializadas a espécie apresenta, bem como os tipos de compostos bioativos.

A extração de óleos essenciais é fundamental para a investigação do potencial biológico das plantas. A hidrodestilação e o arraste a vapor são as técnicas mais convencionais para a extração de óleos essenciais, a caracterização química dos OEs por cromatografia gasosa

acoplada à espectrometria de massa é de suma importância para identificar e quantificar os compostos químicos presentes nos OEs (Stratakos; Koidis, 2016; Aparicio-Ruiz *et al.*, 2018). Além disso, métodos *in silico* como docking molecular e predição de propriedade (ADME) são importantes na análise de óleos essenciais, pois permitem uma avaliação preliminar do potencial terapêutico dos compostos bioativos, antes dos testes *in vitro* ou *in vivo* (Kotta *et al.*, 2020; Ralte *et al.*, 2022). A compreensão da composição química do OEs de *M. sylvatica* depende de técnicas, como hidrodestilação, arraste a vapor, cromatografia gasosa acoplada a espectrometria de massa e análise *in silico*, pois essas técnicas contribuem significativamente para o fornecer de informações sobre as propriedades biológicas da espécie.

A investigação do óleo essencial de *M. sylvatica* é importante não apenas pela sua atividade biológica, mas também pela sua potencial aplicação em diversos setores, como a indústria de cosméticos, alimentos e medicamentos. Além disso, a análise anatômica e histoquímico é fundamental para descrever quais estruturas especializadas a espécie apresenta, bem como os compostos bioativos que são armazenados e secretados por essas estruturas. Compreender os mecanismos de ação e os compostos responsáveis pelas atividades biológicas desse óleo essencial é fundamental para o desenvolvimento de novos produtos naturais e terapias alternativas, contribuindo assim para a saúde e o bem-estar da sociedade.

Com a finalidade de contribuir para o conhecimento científico, o estudo teve como objetivo realizar uma revisão sobre o gênero *Myrcia* e a espécie *Myrcia sylvatica*, com foco na composição química e atividade biológica. Avaliando a anatomia, histoquímica e o potencial antioxidante, toxicidade e estudo *in silico* do óleo essencial das folhas de *Myrcia sylvatica*.

O capítulo I apresenta a revisão de literatura que é apresentada em formato de um artigo publicado na Natural Products Chemistry Section of the jornal *Molecules* (percentil 87º), intitulada: “Exploring the Potential of *Myrcia* Essential Oils: A Review of Biological Activities and Recent Advances”. Essa revisão aborda o potencial dos óleos essenciais de *Myrcia*, destacando sua complexa composição química e suas propriedades biológicas, como antioxidante, antimicrobiana, anti-inflamatória e hipoglicemiante.

O Capítulo II apresenta a revisão de literatura intitulado Volatile Constituents and Chemometric Patterns of *Myrcia sylvatica* Essential Oils: A Systematic Review of Composition and Bioactivity, submetido na Natural Product Research (percentil 78º). O manuscrito está redigido em inglês e formatada conforme as normas do periódico. Esta revisão compila as

informações disponíveis na literatura sobre a composição e o potencial biológico dos compostos voláteis provenientes de 8 estudos com *M. sylvatica*.

O Capítulo III apresenta o estudo intitulado Integrated Anatomical, Chemical, Biological, and Computational Studies Approach of *Myrcia sylvatica* (G. Mey) DC. A Multifaceted Insight into a Promising Amazonian Species, submetido ao periódico *Flavour and Fragrance Journal* (percentil de 70º). O manuscrito está redigido em inglês e formatado com as normas do periódico. O estudo aborda a composição química do óleo essencial de *M. sylvatica*, fornece informações inéditas sobre as características anatômicas e histoquímicas foliares, e avalia o potencial antioxidante, toxicidade e estudo *in silico*.

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2. CAPITULO I

Exploring the Potential of *Myrcia* Genus Essential Oils: A Review of Biological Activities and Recent Advances

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Review

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Special Issue

Chemical Analyses and Applications of Essential Oils

Edited by

Prof. Dr. Anna Malm and Prof. Dr. Wirginia Kukula-Koch

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https://doi.org/10.3390/molecules29122720

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Review

Exploring the Potential of *Myrcia* Genus Essential Oils: A Review of Biological Activities and Recent Advances

Eliza de Jesus Barros dos Santos [1], Fernanda Wariss Figueiredo Bezerra [2], Luiz Renan Ramos da Silva [1], Marcilene Paiva da Silva [3], Oberdan Oliveira Ferreira [3], Luiza Helena da Silva Martins [2], Antônio Maia de Jesus Chaves-Neto [4], Anderson de Santana Botelho [3], Ravendra Kumar [5], Pooja Bargali [5], Karyme do Socorro de Souza Vilhena [3], Eloisa Helena de Aguiar Andrade [1,3] and Mozaniel Santana de Oliveira [1,3,*]

1 Graduate Program in Biological Sciences, Concentration Area—Tropical Botany, Federal Rural University of the Amazon and Museu Paraense Emílio Goeldi, Av. Perimetral, 1901, Terra Firme, Belém 66077-830, PA, Brazil; elizadejesus098@gmail.com (E.d.J.B.d.S.); luizrenan1@hotmail.com (L.R.R.d.S.); eloisa@museu-goeldi.br (E.H.d.A.A.)

2 Graduate Program of Food Science and Technology (PPGCTA), Institute of Technology (ITEC), Federal University of Pará (UFPA), Belém 66075-110, PA, Brazil; fernandawarissf@gmail.com (F.W.F.B.); luiza.martins@ufra.edu.br (L.H.d.S.M.)

3 Adolpho Ducke Laboratory—Coordination of Botany, Museu Paraense Emílio Goeldi, Av. Perimetral, 1901, Terra Firme, Belém 66077-830, PA, Brazil; arci_paiva@hotmail.com (M.P.d.S.); oberdan@museu-goeldi.br (O.O.F.); andersonbotelho10@hotmail.com (A.d.S.B.); karyme@ufpa.br (K.d.S.d.S.V.)

4 Laboratory of Preparation and Computation of Nanomaterials (LPCN), Federal University of Pará, C. P. 479, Belém 66075-110, PA, Brazil; amchaves@ufpa.br

5 Department of Chemistry, College of Basic Sciences and Humanities, G.B. Pant University of Agriculture and Technology, Pantnagar 263145, India; ravichemistry.kumar@gmail.com (R.K.); poojabargali8565@gmail.com (P.B.)

* Correspondence: mozaniel.oliveira@yahoo.com.br

Abstract: The present study provides a comprehensive analysis of the chemical composition of essential oils from species of the *Myrcia* genus and their applications. The compiled results highlight the chemical diversity and biological activities of these oils, emphasizing their potential importance for various therapeutic and industrial applications. The findings reveal that *Myrcia* essential oils present a variety of bioactive compounds, such as monoterpenes and sesquiterpenes, which demonstrate antimicrobial activities against a range of microorganisms, including Gram-positive and Gram-negative bacteria, as well as yeasts. Furthermore, this study highlights the phytotoxic activity of these oils, indicating their potential for weed control. The results also point to the insecticidal potential of *Myrcia* essential oils against a range of pests, showing their viability as an alternative to synthetic pesticides. Additionally, species of the genus *Myrcia* have demonstrated promising hypoglycemic effects, suggesting their potential in diabetes treatment. This comprehensive synthesis represents a significant advancement in understanding *Myrcia* essential oils, highlighting their chemical diversity and wide range of biological activities. However, the need for further research is emphasized to fully explore the therapeutic and industrial potential of these oils, including the identification of new compounds, understanding of their mechanisms of action, and evaluation of safety and efficacy in different contexts.

Keywords: *Myrcia*; natural products; essential oil; volatile compounds; biological applications

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Citation: dos Santos, E.d.J.B.; Bezerra, F.W.F.; da Silva, L.R.R.; da Silva, M.P.; Ferreira, O.O.; da Silva Martins, L.H.; de Jesus Chaves-Neto, A.M.; de Santana Botelho, A.; Kumar, R.; Bargali, P.; et al. Exploring the Potential of *Myrcia* Genus Essential Oils: A Review of Biological Activities and Recent Advances. *Molecules* **2024**, *29*, 2720. https://doi.org/10.3390/molecules29122720

Academic Editors: Francisco Leon, Anna Malm and Wirginia Kukula-Koch

Received: 24 April 2024
Revised: 30 May 2024
Accepted: 5 June 2024
Published: 7 June 2024

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1. Introduction

Myrcia, a genus within the Myrtaceae family, offers a wide range of species valued for their medicinal and culinary uses. With leaves and fruits as the primary components, *Myrcia* species are extensively employed in traditional medicine and as flavor enhancers

in culinary practices. In Brazil, where over 400 species thrive across diverse regions, *Myrcia* serves as a crucial reservoir of biodiversity, enriching the nation's natural heritage. A distinctive feature of *Myrcia* species is their abundant essential oil content, primarily composed of mono- and sesquiterpenes, alongside phenolics and others. These bioactive compounds confer a broad spectrum of biological properties to *Myrcia* extracts, including antioxidant, anti-inflammatory, antimicrobial, and antiviral effects. The prevalence of terpenoids underscores the therapeutic potential of *Myrcia* essential oils, offering benefits against oxidative stress, inflammation, and microbial infections [1–3].

The extraction technique can be one of the factors that influence the chemical composition of essential oils. Studies on obtaining essential oils from species of the *Myrcia* genus have reported that they are obtained using techniques such as hydrodistillation (HD) and steam distillation (SD). These studies indicate that the HD technique is the one with the higher mass yields when compared to SD. The maximum yield observed for HD extraction of *Myrcia multiflora* was 0.36% (*m*/*m*), while for SD extraction, the yield observed was 0.08% (*m*/*m*) for the same sample [4]; however, the sampling period of the species can be a determining factor that causes variation in the chemical composition of the essential oils. These variations can directly impact their biological activities, as well as their industrial and pharmaceutical applications. Research carried out by Ferreira et al. [5] analyzed the influence on the chemical composition of essential oils obtained from the species *Myrcia eximia* DC, collected in 2017 and 2018; the results obtained by the authors revealed that the time of collection can have a significant influence both qualitatively and quantitatively on the chemical composition of the essential oils of this species.

Among the applications are properties such as antioxidant, antimicrobial, insecticidal, hypoglycemic effects, and phytotoxic. In molecular biology, degenerative processes are associated with the occurrence of excess free radicals, which promote oxidative processes that are harmful to the human body. Plant species are capable of producing compounds such as terpenes, carotenoids, phenols, flavonoids, and anthocyanins, with antioxidant properties capable of neutralizing free radicals, which have a negative impact on the biological cells of living organisms [6]. Some species of the Myrtaceae family reported in the literature have exhibited strong antioxidant properties, which can be utilized in the pharmaceutical and cosmetic industries due to their antioxidant potential [3,7,8].

The genus *Myrcia* is widely acknowledged for its hypoglycemic properties, with numerous species being prominently utilized in traditional medicinal practices for managing diabetes. Research indicates that extracts derived from these plants possess inhibitory effects against the α-glucosidase enzyme, a pivotal player in carbohydrate metabolism. This suggests promising potential in regulating blood glucose levels, which is crucial in diabetes management [9].

Moreover, essential oils (EOs) obtained from species within the Myrtaceae family exhibit a spectrum of activities, including cytotoxicity. The essential oil of *M. floribunda* showed moderate phytotoxicity, in addition, when it came to assessing the toxic effect on the crustacean *Artemia salina*, and the essential oil of *M. floribunda* was classified as moderately toxic to *A. salina* (LC_{50} = 82.96 μg.mL^{-1}), while the essential oil of *Myrcia sylvatica* was classified as highly toxic (LC_{50} = 2.74 μg.mL^{-1}) [10]. According to Ramos et al. [11], an essential oil is classified as toxic when the LC50 is less than 80 μg.mL^{-1}; cytotoxicity is considered moderate when the LC_{50} is between 80 and 250 μg.mL^{-1}, and it is considered non-toxic or mildly toxic when the LC_{50} is greater than 250 μg.mL^{-1}. The essential oil of *M. floribunda* stood out due to its ability to neutralize the DPPH radical, showing a higher potential than that observed for the Trolox standard ($p < 0.0001$). This result indicated that the essential oil of *M. floribunda* has antioxidant potential, and its activity, according to the author, can be attributed to the chemical composition of the essential oil, which is rich in monoterpenes with antioxidant activity. These findings contribute significantly to our understanding of the genus; however, there remains a considerable need for further exploration to uncover the additional biological properties of *Myrcia* essential oils [10,12–14].

This study serves as a comprehensive compilation of the latest insights into the chemical composition and diverse biological activities associated with the essential oils derived from *Myrcia* species. By synthesizing this knowledge, it provides invaluable guidance for future research endeavors aimed at unraveling the full therapeutic potential of *Myrcia* essential oils.

2. Methods

Figure 1 shows the search and selection methodology for the articles cited in this paper. Different databases were used, and the selection was based on the relevance of the work and recommendations related to the topics covered in this paper.

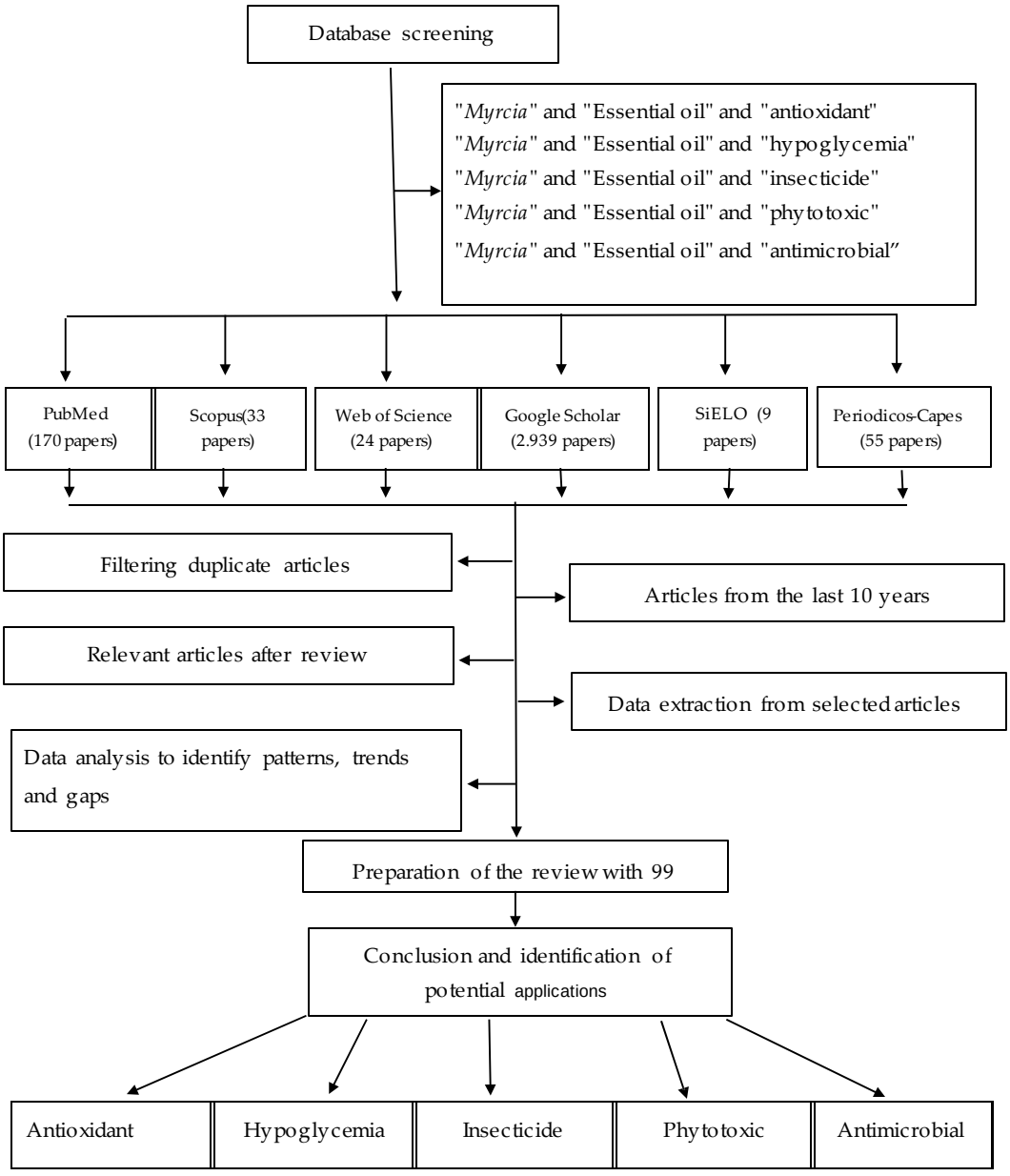

Figure 1. Flow chart of article selection process in the present review.

3. Botanical Characteristics

The Myrtaceae family is one of the most important in humid tropics and is widely distributed in South America, Australia, and tropical Asia [2]. Some authors claim that

besides the genus *Myrcia*, three other genera of Myrtaceae, namely *Calyptranthes*, *Marlierea*, and *Gomidesia*, are synonyms of this genus [15].

In Brazil, the genus *Myrcia* is represented by over 400 species, found in a variety of environments ranging from dense forests to drier areas. And 304 of these species are exclusive to Brazil, meaning they are not found anywhere else in the world [16]. This highlights not only the richness of *Myrcia* in the country but also the importance of the genus' diversity to the complexity of Brazilian ecosystems, for example, *Myrcia elevata*, *Myrcia cuprea*, *Myrcia intons*, *Myrcia fasciculata*, *Myrcia neospeciosa*, *Myrcia magna*, *Myrcia uaupensis*, *Myrcia cuspidata*, *Myrcia lepida*, *Myrcia laruotteana Myrcia revolutifolia*, *Myrcia clusiifolia*, *Myrcia saxatilis*, *Myrcia bicarinata*, *Myrcia neosuaveolens*, *Myrcia bicarinata*, *Myrcia* cf. *obversa*, *Myrcia hexasticha*, *Myrcia isaiana*, *Myrcia plusiantha*, *Myrcia tomentosa*, *Myrcia hatschbachii*, and *Myrcia pileata* [17–19].

The botanical genus *Myrcia* is monophyletic, meaning it shares a common ancestor and includes a large number of species. Its distribution is comprehensive, extensively occupying the American tropical territory and extending across almost all phytogeographical domains [20]. Diversity is a prominent characteristic of this genus, with approximately 800 species identified in a broad geographic area, from Central America to tropical re-gions [15,21].

Each species of the genus *Myrcia* displays significant variations in its phenological patterns, influenced by intrinsic factors such as genetic characteristics and extrinsic factors including climatic and microenvironmental conditions. Seasonal responses, such as flowering, fruiting, budding, and leaf fall, often adjust to climatic changes, revealing a temporal synchrony that can be interpreted as an adaptive strategy. Micro environmental conditions, such as cardinal orientation and surrounding vegetation structure, play a crucial role in these phenological patterns [22].

The genus *Myrcia* comprises shrubs or small- to medium-sized trees, whose branching follows a dichotomous pattern. Young branches exhibit varied characteristics, such as being flattened, ridged, winged, or pubescent. Their leaves are opposite or simple, with well-defined veins and entire margins, and can be leathery or membranous, without stipules. Trichomes are generally simple, although some species may have bifurcations. Flowers are often arranged in panicles. Before flowering, the calyx of the flowers is closed, opening during flowering, with petals usually absent or small. The reproductive organs have numerous stamens and an ovary with two cells, each containing two ovules. The fruits are berries with 1 to 4 seeds, covered by the basal portion of the calyx, and the seeds tend to be subglobose, with large, thin, and often twisted cotyledons [17,23,24].

Myrcia presents its inflorescence in the form of a panicle, which refers to an arrangement of flowers where multiple branches radiate from a central point, presenting a structure resembling a panicle. This structural characteristic facilitates flower distribution, contributing to pollination and, consequently, promoting a high plant reproduction rate. Additionally, the panicle-type inflorescence can exhibit a variety of sizes and shapes, contributing to morphological diversity within the genus [25,26].

Species of the genus *Myrcia* exhibit aromatic characteristics due to the production of essential oils as part of their secondary metabolism. These essential oils are composed of volatile substances that impart fragrance to the plants and are stored in specialized structures called secretory cavities. These cavities are found in various parts of the plant, such as leaves, flowers, fruits, stems, or roots, and are responsible for the production, storage, and release of these aromatic substances. Secretory cavities are essential for the adaptation and survival of *Myrcia* species in their natural habitats [27–31]. The genus *Myrcia* is recognized for the presence of several species that produce volatile compounds [32], such as *M. palustres*, *M. guianensis*, *M. sylvatica*, *M. rostrata*, among others [33–36].

4. Chemical Composition of Essential Oils

The essential oils of the *Myrcia* genus exhibit chemovariability, which may be associated with factors such as climatic data, foliar nutrients, aerial parts, habitat, collection time,

and also the different types of extraction techniques for these volatile oils [37]. Regarding this diversity in chemical profile, it is possible to observe in Table 1 the major compounds found in the essential oils of some species of the genus, with the presence of monoterpenes, sesquiterpenes, and other chemical classes.

Monoterpenes are natural organic compounds that represent a large group in the field of chemistry [38]. In this study, it was possible to observe that this chemical class characterized the profile of the essential oils of *Myrcia lundiana* (MLUN19), *M. lundiana* (MLUN23), *M. mollis*, *M. ovata*, and *M. Paivae* [7,13,39,40].

Sesquiterpenes are classes of compounds found in nature, which are present in both aromatic plants and marine life [41]. In this research, these organic compounds were found to be predominant in the essential oils of various species such as *Myrcia eximia* (Specimen B) [5], *M. hatschbachii* [42], *M. loranthifolia* [43], *M. multiflora* (Specimen A, B and C) [4], *M. oblongata* [44], *M. sylvatica* [10,45], *M. rostrata* [46], *M. splendens* [47,48], *M. vitoriana* [49], and finally, the samples of *M. tomentosa* [3,50].

Table 1. Main major compounds of *Myrcia* essential oils. The analyses of the essential oils presented in the table were carried out using Gas Chromatography Coupled with Mass Spectrometry (GC/MS).

Species	Collection Site	Plant Part	Extraction Type	Major Components	References
Myrcia eximia (Specimen A)	Magalhães Barata, Pará, Brazil	Leaves	HD	hexanal (26.09%), (*E*)-Caryophyllene (20.3%), and (2E)-hexenal (6.63%).	[5]
M. eximia (Specimen B)	Magalhães Barata, Pará, Brazil	Leaves	SD	Caryophyllene oxide (22.16%), α-Copaene (10.98%), and 14-Hydroxy-9-epi-(E)-caryophyllene (7.84%)	[5]
M. guianensis	Rio Verde, Goiás, Brazil.	Flores	HD	methyl salicylate (11.13%), geraniol (8.03%), and eugenol (8.12%)	[51]
M. hatschbachii	Parana, Curitiba, Brazil	Leaves	HD	trans-calamenene (19.10%), (E)-caryophyllene (10.96%), and spathulenol (5.03%).	[42]
M. ovata	Japaratuba, in the state of Sergipe, Brazil	Leaves	HD	nerolic acid (50.56–60.63%), geraniol (73.64–77.07%) neral (18.21–28.39%), geranial (36.96–48.48%), and (*E*)-nerolidol (26.97–58.27%)	[43]
M. lundiana chemotypes isopulegol (MLUN19)	Itabaiana, Sergipe, Brazil.	Freshly leaves	HD	Isopulegol (40.29%), Iso isopulegol (15.49%), and 1,8-cineol (14.16%)	[13]
M. lundiana chemotype citral (MLUN23)	Itabaiana, Sergipe, Brazil.	Freshly leaves	HD	Citral (23.43%), 1,8-cineol (16.43%), and Nerolic acid (16.42%)	[13]
M. mollis,	Gonzanamá, province of Loja, Equador	Leaves	SD	limonene (5.3–5.2%), 1,8-cineole (10.4–11.6%), and (Z)-caryophyllene (16.6–16.8%)	[39]
M. multiflora (Specimen A)	Magalhães Barata, Pará, Brazil	Leaves	HD	α-bulnesene (26.79%), pogostol (21.27%), and δ-amorphene (6.76%)	[4]
M. multiflora (Specimen B)	Magalhães Barata, Pará, Brazil	Leaves	HD	(E)-nerolidol (44.4%), (E)-γ-bisabolene (10.64%), and (E,E)-α-farnesene (8.19%)	[4]

Table 1. *Cont.*

Species	Collection Site	Plant Part	Extraction Type	Major Components	References
M. multiflora (Specimen C)	Magalhães Barata, Pará, Brazil	Leaves	HD	(E)-nerolidol (92.21%), (E,E)-α-farnesene (3.28%), and E-caryophyllene (1.11%)	[4]
M. oblongata	Cascavel, Paraná, Brazil.	Leaves	HD	caryophyllene oxide (22.03%), and trans-verbenol (11.94%).	[44]
M. ovata	Japaratuba, Sergipe, Brazil	Leaves	HD	Geranial (40.10%), Neral (28.39%), and Citronellal (9.19%)	[40]
	Guaramiranga, Ceará, Brazil	Leaves	HD	Geranial (52.60%) and neral (37.14%)	[52]
M. paivae	Peixe-Boi, Pará, Brazil	Leaves	HD	terpinolene (14.70%), α-phellandrene (14.69%), and γ-terpinene (9.64%)	[7]
M. sylvatica	Santarém, Pará, Brazil	Leaves	HD	β-selinene (9.96%), cadalene (9.36%), α-calacorene (9.17%)	[45]
	Bujaru, Pará, Brazil	Leaves	HD	(Z)-α-trans-bergamotene(24.57%), α-sinensal (13.44%), and (Z)-α-bisabolene (8.33%)	[10]
M. rostrata	Alagoinhas, Bahia, Brazil	Leaves	HD	carotol (17.68%), germacreno B (7.28%), and (*E*)-caryophyllene (6.45%)	[46]
M. splendens	Manaus, Amazonas, Brazil	Leaves	HD	trans-nerolidol (67.81%), α-bisabolol (17.51%), and β-caryophyllene (4.21%	[48]
	Sergipe, Brazil	Fresh leaves	HD	bicyclogermacrene (15.4%), germacrene D (8.9%), and E-caryophyllene (10.1%)	[47]
M. vittoriana	community in southeastern Brazil	Fresh leaves	HD	germacrene D (21.90%), germacrene B (17.30%), and bicyclogermacrene (11.90%)	[49]
M. tomentosa (specimen A)	Magalhães Barata, Pará, Brazil	Leaves	HD	γ-elemene (12.52%), germacrene D (11.45%), and (E)-caryophyllene (10.22%)	[3]
M. tomentosa (specimen B)	Magalhães Barata, Pará, Brazil	Leaves	HD	spathulenol (40.70%), α-zingiberene (9.58%), and γ-elemene (6.89%).	[3]
M. tomentosa	Belo Horizonte, Minas Gerais	Fresh leaves	SD	germacrene D (17.62%), (E)-caryophyllene (15.05%), and δ-cadinene (6.42%)	[50]

HD: Hydrodistillation; SD: Steam distillation.

Table 1 presents a comprehensive view of the diversity of plant species of the genus *Myrcia*, collected in various regions, along with the main chemical components extracted and their percentages. Among the species listed, *M. eximia* (Specimen A and B) from Magalhães Barata, Pará, Brazil, stands out, with hexanal (26.09%) and (*E*)-caryophyllene (20.3%) as major compounds, respectively. *M. guianensis*, collected in Rio Verde, Goiás, Brazil, presents methyl salicylate (11.13%) and Geraniol (8.03%) as predominant components. Another notable species is *M. hatschbachii*, from Paraná, Curitiba, Brazil, with trans-calamenene (19.10%) and (*E*)-caryophyllene (10.96%) as main compounds. Furthermore, *M. loranthifolia*, from Igarassu, Pernambuco, Brazil, is marked by (E)-caryophyllene (47.54%) and α-Humulene (9.22%) as major components. This chemical diversity reflects the

influence of environmental and geographic factors on the chemical composition of plants, highlighting the importance of an integrated approach to understanding their biology and potential application.

Other species include *M. lundiana*, collected in Itabaiana, Sergipe, Brazil, presenting Isopulegol (40.29%) and Iso isopulegol (15.49%) as the main compounds in the chemotype isopulegol (MLUN19) and Citral (23.43%) and 1,8-Cineole (16.43%) in the citral chemotype (MLUN23). *M. mollis*, from Gonzanamá, Loja Province, Ecuador, has (*Z*)-caryophyllene (16.6–16.8%) and 1,8-Cineole (10.4–11.6%) as highlighted components. *M. multiflora*, collected in Magalhães Barata, Pará, Brazil, presents different specimens, with (*E*)-nerolidol (44.4%) and (*E*)-γ-Bisabolene (10.64%) in Specimen B and (*E*)-nerolidol (92.21%) in Specimen C, among other compounds. This variety of chemical composition highlights the richness and complexity of plants of the *Myrcia* genus, offering vast potential for applications in various areas, from the pharmaceutical industry to cosmetology and aromatherapy.

Other chemical classes were also observed, such as aldehydes characterizing the essential oils of *Myrcia eximia* (Specimen A) [5] and phenylpropanoids in the oils of *M. guianensis* [51]. In summary, this research highlights the relevance of the volatile oils of this genus and their main implications in future studies, particularly in biological applications such as antimicrobial [53], antileishmanial [52], and insecticidal [54].

5. Antioxidant Activity

Antioxidant activity refers to the ability of certain substances to inhibit the damaging effects of free radicals and oxidative stress in biological systems. Free radicals are highly reactive molecules that can cause damage to cells, proteins, DNA, and other biomolecules, leading to various diseases and aging processes. This activity helps protect cells and tissues from oxidative damage and is associated with various health benefits, including reducing the risk of chronic diseases such as cardiovascular disease, cancer, and neurodegenera-tive disorders.

The antioxidant potential of the investigated substances was assessed by comparing them to Trolox, a water-soluble synthetic analog of vitamin E. This evaluation was based on their ability to inhibit the radical cation $ABTS^{+\bullet}$, which is formed by the reaction between 2,2 -azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt and potassium persulfate. The antioxidants reduce the $ABTS^{+\bullet}$ to ABTS, and the extent of this reduction depends on factors such as antioxidant capacity, concentration, and reaction time. Both TEAC and DPPH assays were employed to evaluate the antioxidant capacities of the essential oils. The DPPH method assesses the ability of EOs to neutralize 1,1-diphenyl-2-picrylhydrazyl. The EO of *M. tomentosa* exhibited significant inhibition of both $ABTS^{+\bullet}$ and $DPPH^{\bullet}$ radicals by 53.6% and 213%, respectively. This study represents the first report on the antioxidant activity of EOs extracted from *Myrcia tomentosa* reported by Franco et al. [3].

De Moraes et al. [7] reported the antioxidant activity of *Myrcia floribunda* and *Myrcia sylvatica* essential oil via $ABTS^{\bullet+}$ and $DPPH^{\bullet}$ methods. The results of their study indicated that the essential oil (EO) of *M. floribunda* exhibited an $ABTS^{\bullet+}$ inhibition rate of 53.27 ± 8.27%, comparable to Trolox (45.74 ± 4.16%) in terms of antioxidant potential. In the DPPH assay, the EO showed an AIR of 81.91 ± 3.46%, surpassing Trolox (50.53 ± 0.52%) significantly ($p < 0.0001$), suggesting excellent antioxidant activity attributed to its high levels of antioxidant monoterpenes. Conversely, *M. sylvatica* EO had a lower $ABTS^{\bullet+}$ AIR of 7.20 ± 0.72% compared to *M. floribunda* and Trolox. However, in the DPPH assay, *M. sylvatica* EO showed comparable AIR (80.55 ± 2.00%) to *M. floribunda* and superior to Trolox ($p < 0.0001$), possibly due to the presence of reactive oxygenated sesquiterpenes. Table 2 summarizes the antioxidant efficacy of various *Myrcia* species using different methods.

Table 2. Antioxidant activity of *Myrcia* genus.

Myrcia Species	Major Components of EO	Method	(%) Inhibition	References
M. tomentosa	γ-elemene (12.52%), germacrene D (11.45%), and (*E*)-caryophyllene (10.22%)	Trolox equivalent antioxidant capacity (TEAC) by 1,1-diphenyl-2-picrylhydrazyl (DPPH)	0.333 ± 0.247% (ABTS) and 208.5 ± 0.940% (DPPH)	[3]
M. hatschbachii D. Legrand	*trans*-calamenene (19.10%), (*E*)-caryophyllene (10.96%), and spathulenol (5.03%)	DPPH scavenging method; phosphomolybdenum complex formation assay	9.14 ±0.33% (DPPH) (DPPH)	[42]
M. floribunda	α-phellandrene (22.19%), 1,8-cineole (23.30%), terpinolene (22.23%), o-cymene (7.04%), and γ-terpinene (5.87%)	2,2′-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt (ABTS) and DPPH Assay	53.27 ± 8.27% (ABTS) and 81.91 ± 3.46% (DPPH)	[10]
M. sylvatica	(*Z*)-α-*trans*-bergamotene (24.57%), α-sinensal (13.44%), (*Z*)-α-bisabolene (8.33%), α-*trans*-bergamotene (7.06%), and β-*trans*-bergamotene (5.07%)	ABTS and DPPH assay	7.20 ±0.72% (ABTS) and 80.55 ± 2.00% (DPPH)	[10]
M. paivae O.Berg	terpinolene (14.70%), α-phellandrene (14.69%), γ-terpinene (9.64%), sylvestrene (7.62%), α-thujene (6.46%), α-pinene (6.39%)	(ABTS) and (DPPH) assay	0.886 ± 0.226% (ABTS) and 2.90 ± 0.083% (DPPH)	[7]
M. oblongata	not analyzed	free radical reduction method using DPPH radical	90.18	[55]
M. oblongata	α-pinene (36.81%), β-myrcene (13.99%), silvestrene (11.28%), and β-pinene (9.74%),	DPPH (2,2-diphenyl-1-picrylhydrazyl) and ABTS (2,2′-azino-di-(3-ethylbenzthiazoline sulfonic acid)) radical scavenging methods and antioxidant power were assessed by Ferric reducing antioxidant power (FRAP)	88.08 ±1.3% (ABTS) and 55.74 ±2.4% (DPPH)	[56]
M. splendens	*trans*-nerolidol (67.81%), α-bisabolol (17.51%), and β-caryophyllene (4.21%)	DPPH-HPTLC (1,1-diphenyl-2-picrylhydrazil—high performance thin layer chromatography) bioautographic assay and Spectrophotometric DPPH assay	43,537.00 ± 15% (DPPH)	[48]

Table 2. *Cont.*

Myrcia Species	Major Components of EO	Method	(%) Inhibition	References
M. splendens	myrcene (7.9%), α-copaene (4.5%), *E*-caryophyllene (45.8%), α-humulene (5.0%), and germacrene B (5.9%)	DPPH Radical Scavenging Assay	28.4 ± 7.1 (DPPH)	[57]
M. sylvatica	*E*-caryophyllene (10.0%), γ-elemene (12.5%), bicyclogermacrene (5.0%), and germacrene B (24.5%)	DPPH Radical Scavenging Assay	18.5 ± 3.5 (DPPH)	[57]

6. Biological Activities

6.1. Antimicrobial (Fungi and Bacteria)

Essential oils are associated with various biological activities, as seen in species of *Myrcia* (Myrtaceae family), which have been reported to possess antioxidant, anticancer, antiparasitic, anti-inflammatory, antiproliferative, cytotoxic, insecticidal, anticholinesterase, sedative, anesthetic, and antimicrobial properties [40,58,59]. It is important to highlight that these activities may be related to genetic or environmental (edaphoclimatic) variations, such as ambient temperature, light incidence, rainfall, and soil characteristics, which influence the plant's metabolism and, consequently, the concentration of its secondary metabolites [59].

Essential oils from various *Myrcia* species have been investigated for their use against pathogenic microorganisms affecting humans, animals, and plants. Nine essential oils from *M. ovata* Cambessedes were studied and showed inhibitory and bactericidal effects against *Staphylococcus aureus*, *Bacillus cereus*, *Bacillus subtilis*, *Enterococcus faecalis*, and *Pseudomonas aeruginosa* at concentrations ranging from 3.13 to 25 µL/mL. Gram-positive bacteria were more susceptible to the essential oil than Gram-negative ones. The study emphasized the inhibition and elimination effects of most essential oils against *P. aeruginosa*, a bacterium known for its high resistance to other essential oils and even synthetic antibiotics [40].

The antibacterial activity of the essential oil from *M. hatschbachii* D. Legrand leaves was studied using the Minimum Inhibitory Concentration (MIC) test. The essential oil showed moderate activity against *E. faecalis* (500 µg/mL) and weak activity against *S. aureus* (1000 µg/mL) [42].

Three specimens of *Myrcia multiflora* (A, B, C) had their essential oils evaluated for antifungal activity against *Candida albicans*, *C. tropicalis*, *C. famata*, *C. krusei*, and *C. auris*. In other studies, it was found that specimen B showed greater sensitivity against the studied yeasts, with inhibition halos ranging from 9 to 11 mm. Specimen A showed an MIC of 0.78 µL/mL against *C. famata* growth and a minimal fungicidal concentration (MFC) of 12.5 against *C. auris*, while specimen C showed a minimal inhibitory concentration of 5 µL/mL against *C. auris* growth and an MFC greater than or equal to 50 against the studied yeasts [4].

The essential oil of *M. oblongata* was studied for its MIC and Minimum Bactericidal Concentration (MBC) against ten *Salmonella* spp. serotypes (*S. Albany*, *S. braenderup*, *S. gafsa*, *S. heidelberg*, *S. idikan*, *S. lexington*, *S. livingstone*, *S. montevideo*, *S. saintpaul*, and *S. senftenberg*). In the study, Santana et al. [55] showed that the essential oil exhibited an MIC and MBC ranging from 437.5 to 7000 µg/mL for the ten serotypes, with better activities against *S. Lexington* (MIC = 437.5 and MBC = 3500) and *S. Saintpaul* (MIC = 875 and MBC = 1750).

The essential oil of *M. ovata* was first evaluated in 2010 for its antimicrobial activity against *Enterococcus faecalis*, *Escherichia coli*, *Helicobacter pylori*, *Pseudomonas aeruginosa*, *Salmonella choleraesuis*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Candida parapsilosis*, as well as biofilm formation by *Enterococcus faecalis*. The authors reported that the essential oil exhibited antimicrobial activity against all tested microorganisms (diameter

of inhibition zone = 16 to 36 mm), except for *Helicobacter pylori* (0 mm), and was effective against biofilm formation compared to the control (sterile saline) [60].

The antibacterial activity of the essential oil of *M. splendens* was evaluated against Gram-positive and Gram-negative bacteria, with the MIC determined by the serial microdilution method. The oil showed more satisfactory effects against phytopathogen strains, with greater sensitivity and, consequently, lower MIC value (125 µg/mL) for the Gram-positive *C. michiganensis* subsp. *Nebraskensis*; all Gram-negative bacteria showed resistance to the essential oil, except for *P. syringae* pv. *seringas*, which showed an MIC value of 250 µg/mL. These effects were attributed to the major compounds, the sesquiterpenes trans-nerolidol (67.81%) and α-bisabolol (17.51%) [48].

The antimicrobial activity of essential oils from *Myrcia* species, as well as from other essential oils, is mainly related to the presence of their volatile compounds such as terpenes (mono-, sesqui-, and diterpenes), alcohols, acids, esters, epoxides, aldehydes, ketones, amines, and sulfides [3,5,61].

The antifungal activity is attributed to the lipophilic nature and low molecular weight of these compounds, which can lead to the inhibition of sporulation, germination, and cell death [4,62]. Meanwhile, the antibacterial activity is associated with the ability of essential oils to penetrate the lipid membrane of bacteria, leading to leakage of intracel-lular components, inhibiting their functional properties and, eventually, leading to cell death [40,61].

It is important to highlight that the antifungal and antibacterial activities of essential oils are also attributed to the synergistic action of minor concentration compounds with the major compounds. Table 3 presents the antifungal and antibacterial activities of essential oils from *Myrcia* species, along with the main chemical compounds found in these oils.

Table 3. Synthesis of antifungal and antibacterial activities and the main constituents of essential oils from *Myrcia* species.

Species	Main Constituents (%Area)	Activity Against	Reference
Nine plants of *M. ovata* Cambessedes	Geraniol (74.37 to 0.45%) Nerolic acid (73.97 to 6.33%) Geranial (40.10 to 0.10%) 1,8-Cineole (33.03 to 0.75%) Neral (28.39 to 0.11%) Isopulegol (27.50 to 2.30%) (*E*)-Nerolidol (20.24 to 0.29%) Linalool (19.61 to 0.53%) Citronellal (0 to 9.19%) Iso-isopulegol (0 to 10.29%)	Results of diameters of inhibition zone in mm Gram-positive bacteria *Staphylococcus aureus* (11–28.5) *Bacillus cereus* (10–25.5) *Bacillus subtilis* (13.5–30) *Enterococcus faecalis* (7.5–22) Gram-negative bacteria *Pseudomonas aeruginosa* (8–30) *Serratia marcensces* (6–27) *Escherichia coli* (8–24) *Salmonella enteritidis* (6–26.5)	[40]
M. hatschbachii D. Legrand	Trans-calamanene (19.10) (*E*)-Caryophyllene (10.96) Spathulenol (5.03)	Results of MIC in µg/mL Gram-positive bacteria *Enterococcus faecalis* (500) *Staphylococcus aureus* (1000)	[42]
M. multiflora	(A) α-Bulnesene (26.79%) Pogostol (21.27%) δ-Amorphene (6.76%) (B) (*E*)-Nerolidol (44.4%) (*E*)-γ-Bisabolene (10.64%) (*E*,*E*)-α-Farnesene (8.19%) (C) (E)-Nerolidol (92.21%)	Results of diameters of inhibition zone in mm Leveduras (A–B–C) *Candida albicans* (8–9–7) *C. tropicalis* (8–11–8) *C. famata* (6–10–8) *C. krusei* (9–10–8) *C. auris* (9–10–8)	[4]

Table 3. *Cont.*

Species	Main Constituents (%Area)	Activity Against	Reference
M. oblongata DC	Uninformed	Results of MIC/MBC in µg/mL Gram-negative bacteria *Salmonella Albany* (3500/7000) *S. braenderup* (3500/7000) *S. gafsa* (1750/3500) *S. heidelberg* (3500/7000) *S. idikan* (1750/3500) *S. Lexington* (437.5/3500) *S. livingstone* (3500/3500) *S. montevideo* (3500/-) *S. saintpaul* (875/1750) *S. senftenberg* (3500/7000)	[55]
M. ovata	Geranial (50.4%) Neral (35.8%) 1,8-Cineole (4.8%) α-Terpineol (1.1%)	Results of diameter of inhibition zone in mm/MIC (%)/MBC (%) Gram-positive bacteria *Enterococcus faecalis* (36/0.031/0.031) *Staphylococcus aureus* (23/0.25/−0.5) *Streptococcus pneumoniae* (25/0.0625/0.25) Gram-negative bacteria *Escherichia coli* (21/1/1) *Helicobacter pylori* (0/0/0) *Pseudomonas aeruginosa* (16/>1/>1) *Salmonella choleraesuis* (26/0.5/0.5) *Salmonella choleraesuis* (26/0.5/0.5) Yeast *Candida parapsilosis* (30/0.031/-)	[60]
M. splendens (Sw.) DC. (sin. *M. fallax* (Rich.) DC.)	Trans-nerolidol (67.81%) α-Bisabolol (17.51%)	Results of MIC in µg/mL Gram-positive bacteria *Clavibacter michiganensis* subsp. *nebraskensis* (125) *Enterococcus faecalis* (2000) *Listeria grayi* (1000) *Staphylococcus aureus* (1000) *Staphylococcus epidermidis* (1000) Gram-negative bacteria *Agrobacterium tumefaciens* (500) *Agrobacterium vitis* (2000) *Pseudomonas syringae* pv. *syringae* (250) *Escherichia coli* (>2000) *Pseudomonas aeruginosa* (>2000)	[48]

MIC = Minimum Inhibitory Concentration; MBC = Minimum Bactericidal Concentration.

6.2. Phytotoxic Activity of Myrcia Genus

Allelochemicals, compounds produced by plants and other species, induce allelopathic (phytotoxic) activity by affecting the growth and development of nearby plants. Allelochemicals can intervene in physiological processes in different ways and exhibit diversified mechanisms of action. Some substances may inhibit seed germination by interfering with water absorption or cell division. Other compounds affect root growth, so plants are unable to absorb nutrients from the soil, or photosynthesis, reducing energy production. Allelochemicals can also affect the metabolism of the host plant, hindering the production of essential enzymes or hormones. Studies also indicate that some of these compounds limit the production of reactive oxygen species, creating conditions of oxidative stress. The effectiveness of allelochemicals varies based on environmental conditions or the concentrations in which they are found [63,64].

Phytotoxic activity refers to the ability of certain substances, such as plant extracts, essential oils, etc. to inhibit the growth of other plants. This activity is often studied in the context of weed control or understanding the interactions between different plant species in ecosystems. Phytotoxic compounds can affect various processes in plants, including germination, root growth, shoot development, and overall plant health. Studying phytotoxic activity helps in identifying natural or synthetic compounds that could potentially be used for weed management or understanding ecological relationships between plants. Vasconcelos et al. [49] reported a macroscopic analysis that involved assessing the germination of *Lactuca sativa* and *Allium cepa*, followed by evaluating germination percentage and root growth. Notably, the essential oil of *Myrcia vittoriana* decreased the germination rate of *A. cepa*. All essential oil concentrations except 375 $\mu g.mL^{-1}$ reduced the germination speed index of *A. cepa*, with the highest concentration showing the most substantial reduction. The essential oil strongly inhibited aerial growth in *L. sativa* across all concentrations compared to water, with a dose–response relationship evident. At the highest concentration, it caused a 54.8% inhibition in aerial growth, accompanied by yellowish seedling coloration and leaf necrosis. The growth of the aerial part of *Lactuca sativa* was strongly inhibited by the essential oil of *M. vittoriana*.

The phytotoxic activity was assessed by examining the impact of *Myrcia hatschbachii* essential oil on the germination and growth of *Lactuca sativa* seeds. Results revealed that the highest concentration (1%) of the EO exhibited the most pronounced effects on both hypocotyl and radicle growth. All concentrations of the EO hindered hypocotyl growth in *L. sativa*. For the radicle, the EO showed significant growth inhibition at the 1% concentration, while concentrations of 0.001% and 0.01% also displayed adverse effects compared to the control groups (water and 1% polysorbate in water), as presented by Gatto et al. [42]. The study investigated the allelopathic effects of extracts, fractions, essential oils, and isolated chemical compounds (gallic acid and protocatechuic acid) on the germination, radicle, and hypocotyl growth of weed species *Mimosa pudica* and *Senna obtusifolia*. Extracts and fractions were examined at a concentration of 1%, while essential oils and isolated chemical compounds were tested at 15, 30, 45, and 60 ppm. Interestingly, the essential oil inhibited the germination of *M. pudica* [65].

6.3. Insecticide

Several plants possess defense mechanisms against insects that can harm their growth and development [66]. Among them is the production of chemical compounds with insecticidal properties that are capable of repelling, incapacitating, or even killing insects [67,68]. These compounds can be found in various parts of the plant, such as leaves, flowers, stems, and roots, and play a crucial role in protecting plants against herbivorous insects, helping them survive and successfully reproduce in their natural environment [69–72].

Many of these natural insecticidal compounds, in addition to protecting the plant itself, can also be used for pest control in agriculture, gardening, and forestry management and can be applied directly to plants as natural extracts, essential oils, or plant-based products [73,74]. Thus, studies of plant insecticidal compounds have been developed to obtain safer and more sustainable pesticides, reducing dependence on environmentally harmful synthetic chemicals and human health risks.

Among these studies are some conducted with the genus *Myrcia*, which demonstrate the insecticidal potential of the species. In a study conducted with extracts and essential oil from the leaves of *Myrcia oblongata* DC, for example, the insecticidal effect on the beetle *Alphitobius diaperinus* was evaluated. In the study, the hexane extract, composed of steroids, triterpenoids, alkaloids, tannins, and flavonoids, and the essential oil showed the highest mortality rates (<95%) against *A. diaperinus* larvae, while the other extracts showed mortality rates above 50%, and the aqueous extract showed no activity. The highest lethality against adult *A. diaperinus* was observed for the essential oil (92.5%), while the extracts had mortality values below 20% [55].

In another study conducted with the methanolic extract of *Myrcia* splendens leaves, insecticidal action against the *Ceratitis capitata* fly species was observed. The activity was observed in extract fractions obtained by HPLC, which had their compounds isolated and identified as myricetin-3-*O*-(6″-*O*-galloyl)-β-galactopyranoside, myricitrin, and quercitrin. Among these, the compound myricetin-3-*O*-(6″-*O*-galloyl)-β galactopyranoside showed moderate activity at 2500 ppm [75].

In another study on the insecticidal potential of the *Myrcia* genus, the insecticidal action of the essential oil from the leaves of two chemotypes of *Myrcia lundiana* and their major compounds, isopulegol and citral, against the *Acromyrmex balzani* ant species was evaluated. Other essential oils from *M. lundiana* showed activity. The oil from the isopulegol chemotype presented LC_{50} values of 2.29 µL/L (CI 2.08–2.49) and LC_{95} of 6.28 µL/L (CI 5.32–7.97), and its major compound, isopulegol (40.29%), presented LC_{50} and LC_{95} values equal to 0.16 µL/L (CI 0.14–0.19) and 1.08 µL/L (0.81–1.58), respectively, while the citral chemotype presented LC_{50} values of 2.35 µL/L (CI 2.13–2.61) and LC_{95} of 9.14 µL/L (CI 7.25–12.61), and its major compound, citral (23.43%), presented LC_{50} and LC_{95} values equal to 0.59 µL/L (CI 0.48–0.69) and 3.83 µL/L (2.87–5.77), respectively [13].

Another species from the genus that had its insecticidal potential evaluated was *Myrcia dictyophylla*. A study conducted with the species' essential oil against *Aedes aegypti* observed insecticidal action against the arbovirus vector, where an LC_{50} value of 17.6 µg/mL for mosquito larvae after 24 h of exposure and 92.5% knockdown was observed in adult mosquitoes after 4 h of exposure, in addition to repellent action. The studied oil presented three major sesquiterpenes: α-amorphene (19.8%), δ-cadinene (12.5%), and germacrene-D (10.3%) [76].

Although incipient, these studies demonstrate the insecticidal potential of the genus *Myrcia*, especially its essential oils, not only in pest control for agriculture but also in controlling disease vector insects. These studies reveal the genus as a promising sustainable strategy in insect control and as a natural alternative to synthetic compounds in the biological control of parasites, highlighting the need for further studies to explore and better elucidate this potential.

6.4. Hypoglycemic Potential of Myrcia Species

Diabetes refers to a group of diseases characterized by high blood glucose levels. Generally, it results from a deficiency in the production or action of insulin, resulting in metabolic disorders. Type 2 diabetes mellitus (DM) is the most common form of diabetes, and its main characteristics are insulin resistance, chronic hyperglycemia, and inefficient insulin secretion and action. According to the World Health Organization (2017), diabetes is responsible for the deaths of around 1.6 million people worldwide [77].

The main drugs used to treat DM2 include insulin sensitizers, glucosidase inhibitors, incretin-based therapies, and sodium-glucose co-transporter 2 inhibitors. Some species of plants, fruits, and teas, for example, may emerge as an alternative to traditional pharmacological therapy. So-called dietary supplements can be recommended to prevent and also improve disorders caused by DM2. The treatment of DM2, in an advanced phase, with synthetic drugs and compounds of natural origin cause synergistic interactions resulting in a more efficient treatment [78].

Therefore, knowledge about the properties, chemical composition, and beneficial characteristics of *Myrcia* species, popularly used to treat diabetes, can help offer a complementary natural alternative to the use of synthetic drugs [79].

Among the species of *Myrcia*, plants known as "pedra-hume-caá", "pedra-ume-caá", or "insulin plant" are noteworthy. They are known by these designations due to their use by indigenous communities in Brazil to lower blood sugar levels and are commonly used in the treatment of diabetes. In the literature, several species are related to the term "pedra-hume-caá", including: *Myrcia guianensis* (Aubl.) DC., *Myrcia punicifolia* (Kunth) DC., *Myrcia citrifolia* (Aubl.) Urb., *Myrcia uniflora* DC., *Myrcia multiflora* (Lam.) DC., *Myrcia salicifolia* DC., *Myrcia speciosa* (Amsh.) Mc Vaugh, *Myrcia rubella* Cambess., *Myrcia virgata*

Cambess., *Myrcia paivae* O. Berg., *Myrcia laruotteana* Camb., and *Myrcia sylvatica* (G. Mey) DC [37,80–82].

A study has shown that extracts obtained from the leaves of *M. guianensis* exhibit inhibition against α-glucosidase, which is the enzyme responsible for the metabolism of carbohydrates and a known target for type 2 diabetes mellitus (DM2), alongside demonstrating nephroprotective and hepatoprotective action. The ethyl acetate extract of *M. guianensis* showed the greatest potential for inhibiting both alpha-glucosidase and PTP1B (protein tyrosine phosphatase). The extract showed IC_{50} values for alpha-glucosidase of 7.80 μg/mL, while for the enzyme PTP1B, the value observed was 3.26 μg/mL [81]. This same chemical extract has been shown to be active against the protein tyrosine phosphatase (PTP1B), which is a recent target for DM2 and is involved in insulin signaling [9].

Another species of the genus, also known as the insulin plant, is *M. multiflora* (Lam.) DC., a shrubby species, also known as "pedra-ume-caá", typical of the Brazilian Amazon region, occurring in the states of Amazonas, Pará, and Amapá [9]. This species is also found in regions of the Brazilian Cerrado, characteristic of mountainous terrain, poor soils, and margins of sandy or non-floodable fields [4]. *M. multiflora* produces a globose fruit, with succulent and edible pulp, highly appreciated by children [83]. The fruits range in color from dark red to purple when ripe, containing one, two, or three seeds, with a bitter taste [84].

Studies involving ripe fruits of *M. multiflora* have shown that they have a high antioxidant potential, supporting the idea that their consumption may result in health benefits for humans. Samples obtained from the fruits were analyzed for non-enzymatic antioxidant content and showed significant amounts of vitamin C, alongside being rich in anthocyanins, flavonoids, and polyphenols [4,84]. Another study has indicated the presence of a substance beneficial for preventing obesity, capable of reducing intestinal lipid absorption [83].

Research involving the use of substances known as myrciacitrins obtained from the leaves of *M. multiflora* has shown, in rats, activity against the enzyme aldose reductase, which is responsible for catalyzing and reducing glucose. The dry extract obtained from the infusion of *M. multiflora* leaves showed a glycemic effect in animals induced for 28 days. In the group of animals whose glucose levels were measured at the beginning of and during treatment with 50 mg/kg (body weight of dry extract), there was a 74.5% reduction in glucose levels when compared to the results of the levels before the start of treatment. At the end of the treatment, after 28 days, the author reported that there was an 11% reduction in glucose levels compared to the beginning of the tests. According to him, this result indicated that the use of the dry extract of *M. multiflora* is capable of maintaining the hypoglycemic effect [85,86].

In a study involving the essential oil obtained from the leaves of three species of *M. multiflora* (referred to as A, B, and C) collected in different areas of a secondary forest in the coastal region of the state of Pará in the city of Magalhães Barata, the essential oils obtained from the species referred to as A (collected in 2017 in an area of the secondary forest -capoeira-), B (collected in 2017 in areas of swidden planting exposed to sunlight), and C (collected in 2019 in an area of the secondary forest -capoeira-) were characterized as having α-bulnesene (26.79%), pogostol (21.27%), and δ-amorphene (6.76%) as major compounds for chemical type A, (*E*)-nerolidol (44.4%), (*E*)-γ-bisabolene (10.64%), and (*E*,*E*)-α-farnesene (8.19%) for chemical type B, and the substances (*E*)-nerolidol (92.21%), (*E*,*E*)-α-farnesene (3.28%), and (*E*)-caryophyllene (1.11%) were the major constituents identified in the essential oil of *M. multiflora*—chemical type C. The research also reported a significant difference between the chemical profiles of the *M. multiflora* species studied [4]. The chemical structures of the main constituents of *M. multiflora* (A, B, and C) are shown in Figure 2.

The essential oils of *M. multiflora* are rich in (*E*)-nerolidol, which is the main component of the essential oil of two chemotypes (B and C) collected in the state of Pará [41]. A study showed that nerolidol significantly improved insulin levels and body weight when administered to obese and diabetic animals at a dose of 25 mg/kg (body weight/day) for 28 days.

As a result, high glucose and glycated hemoglobin levels were reduced. In addition, the study reported that during the use of nerolidol, liver integrity was preserved, and the regulation of insulin-dependent glucose transport was improved in skeletal muscles due to the activation of GLU4 (Glucose transporter type 4) [87,88]. It is also worth mention-ing that another substance with reported antihyperglycemic activity in the literature is caryophyllene, also identified in the essential oil of *M. multiflora*, which showed significant antidiabetic effects on glucose homeostasis in diabetic rats at a dose of 200 mg/kg (body weight) [89].

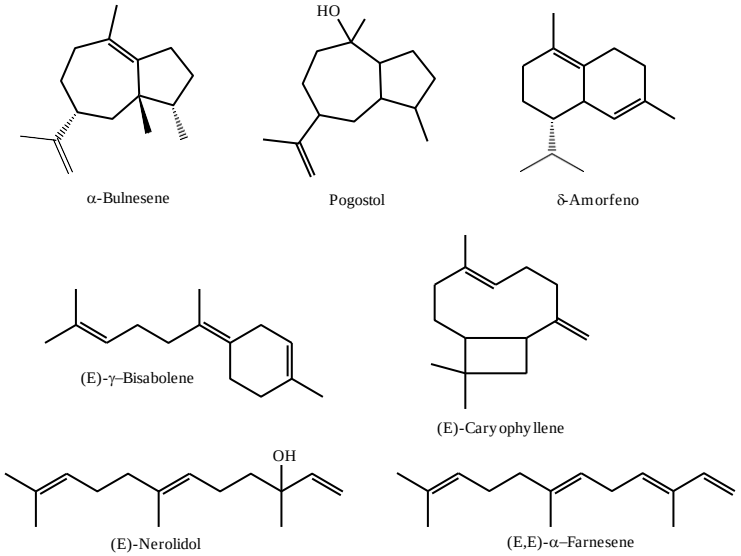

Figure 2. Major constituents of essential oils from *M. multiflora* species collected in the state of Pará.

M. bella Cambess., also popularly known as "mercurinho", is a common species in savanna fragments and easily found in the Brazilian Cerrado [86]. This species is widely used in traditional medicine due to its use as a phytotherapeutic medication for the treatment of gastrointestinal disorders and diabetes mellitus [90]. The species is a source of phenolic compounds and flavonoids, with fractions rich in flavonoids showing cytotoxic effects against osteosarcoma cells [91].

In a recent study, the chemical composition of the essential oil obtained from the leaves of an *M. bella* specimen collected during the rainy season in the Assis State Forest, São Paulo State, Brazil, was analyzed. The research indicated that the essential oil of *M. bella* is mainly composed of oxygenated sesquiterpenes α-cadinol (14.4%), ledol (12.2%), and the sesquiterpene hydrocarbon germacrene D (11.8%) [92]. The chemical structures of α-Cadinol, Ledol, and Germancrene D from *M. bella* are shown in Figure 3.

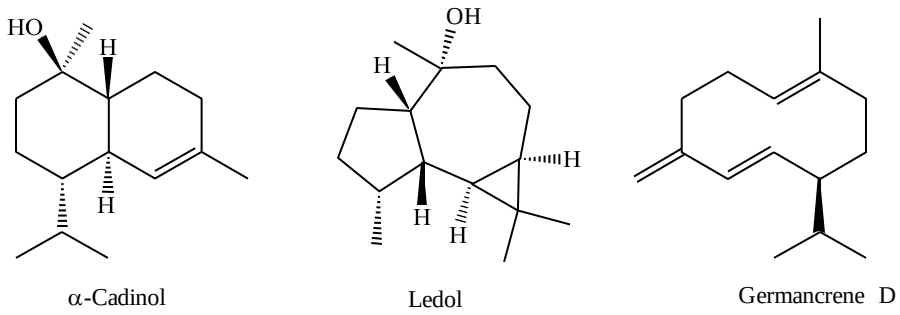

Figure 3. Major constituents of essential oil of *M. bella* leaves.

The species *M. laruotteana* Camb. is commonly known as "cambuí" in the southern and southeastern regions of Brazil. In the Amazon, it is also recognized by popular names such as "murta" and "smooth-skinned guava". The species is a shrub or small tree that

not only occurs in the southern, southeastern, and central-western regions of Brazil but also has a wide distribution in the states of Pará, Tocantins, Maranhão, Mato Grosso, Goiás, Distrito Federal, Mato Grosso do Sul, Minas Gerais, Espírito Santo, São Paulo, Paraná, and Santa Catarina [18].

The flowers of *M. laruotteana* are white and strongly aromatic, while the green fruits contain essential oil, which decreases as they ripen, giving rise to small edible fruits with a purple color. This species occurs in upland areas and floodplain forests, and morphological variations associated with different environments where individuals occur are observed. The study of the essential oil obtained by hydrodistillation from the green fruits of the species *M. laruotteana* Camb. showed that the major constituents are α-bisabolol (23.6%) and α-bisabolol oxide B (11.5%) [93]. Chemical structures of the compounds α-Bisabolol and α-Bisabolol oxide B are shown in Figure 4.

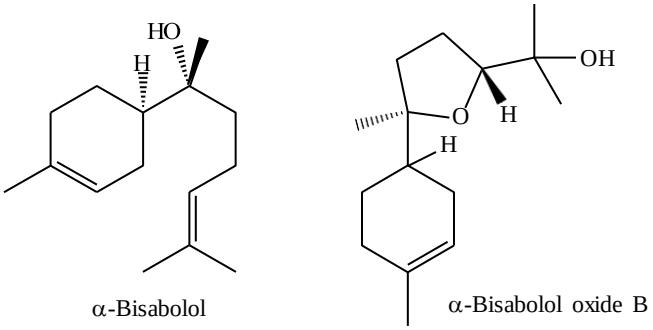

Figure 4. Main chemical constituents of the essential oil from *M. laruotteana* fruits.

α-Bisabolol is the main constituent of the *M. laruotteana* essential oil and is also reported to have hypoglycemic properties. A study reports that α-bisabolol has antidiabetic properties related to reducing insulin resistance, glucose intolerance, plasma triacylglycerol, and LDL/VLDL cholesterol. Other factors such as the modulation of molecular pathways involved in the expression of target genes such as PPARs (Peroxisome proliferator-activated receptors) are among the properties described for this molecule [94].

The species *M. pubiflora* DC. is widely found in South America, especially in the region ranging from Brazil to Paraguay. It is a shrub that predominantly occurs in tropical and humid biomes [86]. The essential oil obtained from the fresh leaves of *M. pubiflora* shows the oxygenated sesquiterpene caryophyllene oxide as the major component (22.2%), with other components present in smaller amounts, such as mustakone (11.3%), 1,8-cineole (5.4%), and tryciclene (5.3%) [95]. The chemical structures of the main constituents of the essential oil from *M. pubiflora* leaves are shown in Figure 5.

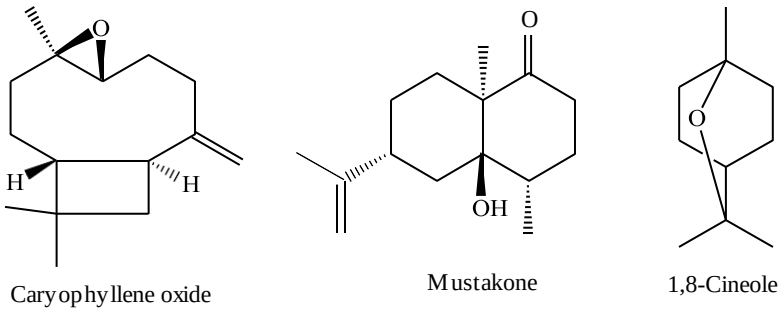

Figure 5. Major constituents of the essential oil of *M. pubiflora*.

The main constituent of the *M. publiflora* essential oil is caryophyllene oxide (caryophyllene-type structure). The antihyperglycemic activity of compounds with a caryophyllene-type structure has been reported in the literature. One study evaluated the activity of the compound β-caryophyllene in streptozotocin (STZ)-induced diabetic rats. The results

showed that administration of β-caryophyllene at a dose of 200 mg/kg (body weight) had significant antidiabetic effects, demonstrating beneficial effects on glucose homeostasis in diabetic rats. Therefore, the hypoglycemic activity may be associated with the presence of a compound with a similar structure to this one but not only this one [89].

Myrcia sylvatica (G. Mey) DC. is a species widely distributed in South America, from the Guianas to Brazil. This species is popularly known in the Amazon region as "murta", "kumate-folha-miúda", or "murtinha", and it is also known as the "insulin plant" because local communities empirically use infusions of various parts of these plants to treat diabetes [82]. Res Research carried out with *Myrcia loranthifolia* grown in Atlantic Forest and Dry Forest forests in Brazil, showed that the essential oil of this species has an average yield of 0.23 to 0.33%, with the major compounds identified being (*E*)–caryophyllene (47.80%), Cis-calamenene (11.40%), and germacrene D (10.07%) [96]. The chemical structure of the main constituents of the essential oil of fresh *M. sylvatica* leaves are shown in Figure 6.

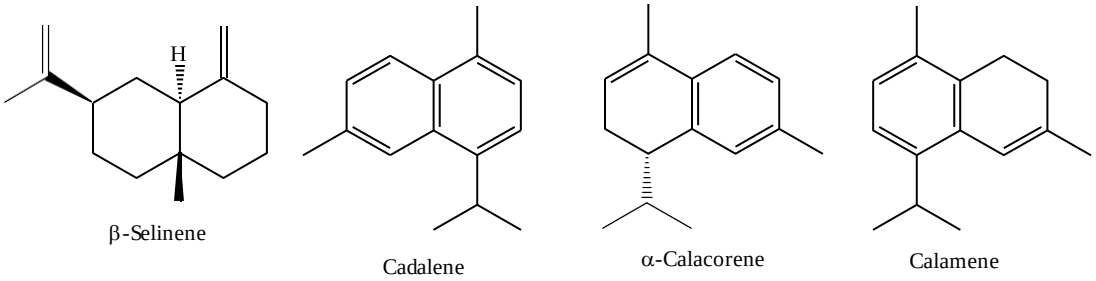

Figure 6. Major constituents of the essential oil of *M. sylvatica* fresh leaves.

Another species known for its traditional use as a hypoglycemic agent is *Mycia*. It is a tree species that occurs in the Amazon biome in the northern regions, especially in the states of Amazon [9]. In the central-western region, it is commonly found in the state of Mato Grosso, in both upland forest and floodplain areas. This species is considered a medicinal plant in the Amazon region, and infusions of its leaves are used to prepare teas that are beneficial for consumption during pregnancy and for treating diabetes [9].

A study evaluating the chemical composition of the essential oil obtained by hydrodistillation of the leaves of a *Myrcia paivae* specimen collected in the municipality of Peixe-boi, Pará State, Brazil, identified the main constituents as compounds of the class of monoterpene hydrocarbons (77.93%), followed by sesquiterpene hydrocarbons (10.16%) and oxygenated monoterpenes (7.97%). In this study, the compounds α-phellandrene (14.69%), terpinolene (14.70%), and γ-terpinene (9.64%) were identified as the major ones [7]; the majority compounds can be seen in Figure 7.

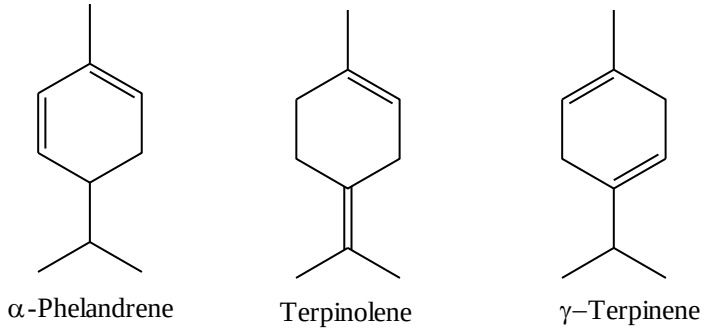

Figure 7. Major constituents of the essential oil of *M. paivae* leaves.

In a study investigating the effect of α-Phelandrene, a major constituent in the essential oil of *M. paivae*, on the function of adipocytes under conditions of insulin resistance, the reduction in glucose uptake by insulin-resistant 3T3-L1 adipocyte cells was evaluated. The

3T3-L1 adipocytes were exposed to 25 μM glucose and insulin (0.6 nM) for 24 h. The author reported that α-Phelandrene contributed to benefiting the functions of adipocytes under conditions of insulin resistance. Cells treated with alpha-Phelandrene (65 μM) for 24 h showed a significant improvement in glucose uptake in the adipocytes of 3T3-L1 cells, with values of 11.31 mm/L, a result similar to that presented by the group treated with rosiglitazone [97]. Terpinolene, which is the second main constituent of the *Myrcia paivae* essential oil, is a substance whose activity in reducing blood glucose levels (mg/dL) has been described in the literature. The author reported that an extremely significant reduction in blood glucose levels was observed in diabetic female rats treated with 12.5 and 25.0 mg/kg of the terpene terpinolene for 4 weeks. In the group treated with 12.5 mg/kg of the substance, the animals had a blood sugar level of 580 mg/dL, and after treatment, the value was reduced to approximately 290 mg/dL. A similar result was observed for the group treated with 25 mg/kg of the terpene; the value before treatment was approximately 500 mg/dL and after treatment, 200 mg/dL [98]. In in vitro research involving various types of terpenes commonly found in essential oils, such as myrcene, eugenol, eucalyptol, β-pinene, citrol and terpineol, the effect and potential benefits in the prevention and treatment of diabetes were evaluated based on the action of these compounds against the α-amylase enzyme (enzyme responsible for hydrolyzing oligosaccharides into monosaccharides, increasing blood sugar levels). In this study, solutions were prepared containing different concentrations ($\mu M.cm^{-3}$) of the selected terpenes. The results indicated that terpenes, which are the primary components of essential oils, have the potential to inhibit α-amylase to a significant degree, with the most efficient terpene concentrations ranging from 1.16 $\mu mol.cm^{-3}$ for β-pinene to 5.50 $\mu mol.cm^{-3}$ for eugenol [99].

The species mentioned above are particularly noteworthy for their popular uses by traditional indigenous communities and for their hypoglycemic activity. Studies highlighting the chemical composition of the leaves, flowers, and fruits, as well as the essential oils of these species, provide the scientific community with knowledge about this natural wealth. Most of these *Myrcia* species, as the text highlights, occur in Brazilian biomes, being predominantly distributed in the Cerrado, Caatinga, and the Amazon, and constitute a natural wealth that is still little known.

The data cited in the previous text reveal interesting activities for the essential oils obtained from *Myrcia* species as natural pharmacological agents, which could be important for the development of phyto-formulations against diseases such as DM2. The essential oils from the leaves of these *Myrcia* species, popularly used as hypoglycemic agents, can be considered a potential source of pharmacological agents, which could be used in formulations for the treatment of diabetes, Alzheimer's, and diseases linked to oxidative stress and applied as active ingredients in phyto-formulations as an alternative to the use of synthetic drugs.

7. Conclusions

The *Myrcia* genus is a promising source of essential oils, whose chemical composition is characterized by great complexity, which depends on climate location and seasonal factors, among others. The results obtained by the consulted studies indicate that *Myrcia* essential oils can constitute a promising source of bioactive compounds such as monoterpenes and sesquiterpenes with different biological activities including antioxidant, antimicrobial, phytotoxic, insecticidal, and hypoglycemic. All these effects can attract the attention of several industrial sectors, such as the pharmaceutical and cosmetic industries, which open up a vast field of therapeutic possibilities. The *M. eximia* sample A shows a high quantity in percentage of hexanal (26.09%) and (*E*)-caryophyllene (20.3%), and sample B, caryophyllene oxide (22.16%) and α-copaene. Furthermore, *M. hatschbachii* exhibits trans-calamenene (19.10%) and (*E*)-caryophyllene (10.96%), whilst *M guianensis* is notable for its methyl salicylate (11.13%) and Geraniol (8.03%). Among the variety of *Myrcia* species, (*E*)-caryophyllene and caryophyllene oxide are substances most commonly found in the various *Myrcia* species. These complex chemical compositions are present in several *Myrcia*

plant species and sections, demonstrating the genetics and environmental complexity of plants, as well as the impact of geographical and climatic variables. Understanding these intricacies is vital for pragmatic implementations in the fields of medicine, cosmetics, and other domains. Promoting the sustainable use of these vital resources all depends on protecting these species and their habitats.

Author Contributions: Conceptualization, E.d.J.B.d.S., L.R.R.d.S., F.W.F.B., M.P.d.S., O.O.F., L.H.d.S.M., A.M.d.J.C.-N., A.d.S.B., R.K., P.B., K.d.S.d.S.V., E.H.d.A.A. and M.S.d.O.; methodology, E.d.J.B.d.S.; validation, E.H.d.A.A. and M.S.d.O.; formal analysis, E.d.J.B.d.S., F.W.F.B., M.P.d.S., O.O.F., L.H.d.S.M., A.M.d.J.C.-N., A.d.S.B., R.K., P.B., K.d.S.d.S.V. and E.H.d.A.A.; investigation, E.d.J.B.d.S., L.R.R.d.S., F.W.F.B., M.P.d.S., O.O.F., L.H.d.S.M., A.M.d.J.C.-N., A.d.S.B., R.K., P.B., K.d.S.d.S.V., E.H.d.A.A. and M.S.d.O.; resources, E.d.J.B.d.S.; data curation, E.d.J.B.d.S.; writing—original draft preparation, E.d.J.B.d.S.; writing—review and editing, E.H.d.A.A. and M.S.d.O.; visualization, E.H.d.A.A. and M.S.d.O.; supervision, M.S.d.O.; project administration, M.S.d.O.; funding acquisition, M.S.d.O. All authors have read and agreed to the published version of the manuscript.

Funding: CAPES process number 001.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data are contained within the article.

Acknowledgments: The author Mozaniel Santana de Oliveira thanks PDPG-POSDOC—Programa de Desenvolvimento da Pós-Graduação (PDPG) Pós-Doutorado Estratégico, as well as CAPES for the scholarship (process number: (88887.852405/2023-00). The authors thank CAPES process number 001.

Conflicts of Interest: The authors declare no conflicts of interest.

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3. CAPITULO II

Volatile Constituents and Chemometric Patterns of *Myrcia sylvatica* Essential Oils: A Systematic Review of Composition and Bioactivity

Volatile Constituents and Chemometric Patterns of *Myrcia sylvatica* Essential Oils: A Systematic Review of Composition and Bioactivity

Eliza de Jesus Barros dos Santos[1], Mateus Machado Lima[2], Leonardo Souza da Costa[2], Ravendra Kumar[3], Pooja Bargali[3], Hayet Edziri[4], Karyme do Socorro de Souza Vilhena[5], Eloisa Helena de Aguiar Andrade[1,2] e Mozaniel Santana de Oliveira[1,2*]

[1] Postgraduate program in biological sciences - tropical botany. Universidade Federal Rural da Amazônia and Museu Paraense Emílio Goeldi, Av. Terra Firme, 66075-900 Belém, Pará, Brazil.

[2]Adolpho Ducke Laboratory - Botany Coordination, Museu Paraense Emílio Goeldi, Av. Perimetral, 1901, Terra Firme, 66077-830, Belém PA, Brazil.

[3] Department of Chemistry, College of Basic Sciences and Humanities, G.B. Pant University of Agriculture and Technology, Pantnagar, U.S. Nagar-263145, Uttarakhand, India.

[4]Laboratory of Transmissible Diseases and Biologically Active Substances (LR99 ES27), Faculty of Pharmacy, University of Monastir 5000, Monastir Tunisia.

[5]Department of Chemistry, Institute of Exact and Natural Sciences, Universidade Federal do Pará, Augusto Corrêa Rua, S/ N, Guamá, Belém 66075-900, Pará, Brazil.
Hayet Edziri

*Corresponding author: mozaniel.oliveira@yahoo.com.br

Abstract

This systematic review compiles the chemical composition, chemometric patterns, and biological activities of essential oils from *Myrcia sylvatica* (G. Mey) DC., a species of the Myrtaceae family with wide distribution in South America. A total of 216 volatile constituents have been identified, mainly hydrocarbon and oxygenated sesquiterpenes such as (E)-caryophyllene, germacrene B, spathulenol, and (*Z*)-α-trans-bergamotene. Chemometric analyses revealed distinct chemical clusters and potential chemotypes, influenced by genetic and environmental factors. Biological assays demonstrated antioxidant potential, antimicrobial activity against Gram-positive bacteria, and toxicity to *Artemia salina* larvae, indicating promising pharmacological and agrochemical applications. Despite advances, studies remain limited and reveal substantial chemical variability. These findings highlight the need for further integrative research combining phytochemistry, bioassays, and ecological assessments to better understand the bioactive potential and ensure sustainable use of *M. sylvatica*.

Keyword: *Myrcia sylvatica*; Essential oils; Chemometric analysis; Antioxidant activity; Biological potential.

1. Introduction

The Myrtaceae family has 142 genus and 6000 species that occur in tropical and subtropical regions, including Amazonia (Silva et al. 2023). Essential oils of Myrtaceae species

have a wide range of biological activities, including antioxidant, antimicrobial and insecticidal properties. (Barbosa et al. 2019). The chemical composition and concentration of the main compounds can vary depending on the geographical location (Anjos da Silva et al. 2023). The Myrtacea family has bioeconomic potential and is used in wastewater phytoremediation. Some species of the family, such as Leptosperum scoparium and Kunzea robusta, have the ability to tolerate contaminated environments and act in phytoremediation (Meister et al. 2023) and traditional medicine (Farias et al. 2020).

The *Myrcia* genus, which is part of the Myrtaceae family, is made up of more than 400 shrub and tree species that are native to tropical and subtropical regions. This genus has aromatic plants, resulting from the presence of secondary metabolites such as monoterpenes and sesquiterpenes, which are secreted and stored by specialized structures, this chemical characteristic confers pharmacological properties to the genus (Cascaes et al. 2015; Santos et al. 2018).

The genus *Myrcia* shows chemical variability in the composition of its essential oil. In a study carried out with *M. splendens*, the compounds trans-nerolidol and α-bisabolol were identified as the main constituents of the essential oil. The presence of these compounds was associated with the antibacterial activity demonstrated by the essential oil of the species (Scalvenzi et al. 2017). In the studies by Franco et al. (2021) the essential oil of the *M. tomentosa* specimen showed antioxidant properties, inhibiting the ABTS and DPPH radicals by 53.6% and 213%, respectively. The antioxidant activity of the specimen resulted from the presence of γ-elemene, germacrene D and (*E*)-caryophyllene in the chemical composition of its essential oil. Species of the genus also have antifungal, insecticidal, phytotoxic and hypoglycemic properties (Santos et al. 2024).

Although the genus *Myrcia* is widely studied due to its pharmacological and economic potential, there are still species that are little explored. Among them is *M. sylvatica*, a species native to Brazil and not endemic, with a distribution throughout South America, from the Guianas to Brazilian territory. In Brazil, its phytogeographic domains are the Amazon, Caatinga, Cerrado and Atlantic Rainforest (Santos et al. 2020). This species has pharmacological potential and is known in the Amazon empirically as "myrtle". In popular medicine, tea made from this species is used by local communities to treat diabetes (Cascaes et al. 2015; Costa et al. 2022). The essential oil of the species has a chemical variability that may be associated with abiotic and biotic factors and the different types of method used to extract these volatile compounds (Cascaes et al. 2015; Raposo et al. 2018).

This systematic review aims to synthesize and critically analyze the available literature on the chemical composition, chemometric patterns, and biological activities of volatile compounds from *Myrcia sylvatica* (G. Mey) DC. By integrating data from eight studies, we seek to highlight chemical variability, identify potential chemotypes, and evaluate the pharmacological and ecological relevance of this species, thereby providing a foundation for future research and sustainable applications.

2. Methodology

2.1. See supplemental material.

3. Results and discursion

3.1. Chemical composition

M. sylvatica is a species that produces essential oil in its secondary metabolism that is rich in bioactive compounds that have antioxidant, antimicrobial and toxic properties (Rosa et al. 2016; Silva et al. 2016; de Moraes et al. 2022). A detailed table of the constituents and metabolic classes of the volatile compounds of *M. sylvatica* specimens described in the literature is shown in Supplementary Table S1 and the two-dimensional structures of the main chemical

constituents of the species are shown in Figure S3. A total of 216 constituents were characterized and the specimens were collected in Santarém, Caratateua, Bujaru, cities in the state of Pará, Brazil and Carolina, a city in the state of Maranhão, Brazil, as shown in Figure S3, the full list of compounds can be reviewed in supplementary material S1.

The chemical profile of the volatile compounds of *M. sylvatica*, is mainly characterized by hydrocarbon and oxygenated sesquiterpenes and, among these metabolic classes, it was possible to observe a higher concentration of hydrocarbon sesquiterpenes in the specimens of *M. sylvatica* recorded in the literature. It is possible to observe a higher content of hydrocarbon sesquiterpenes in the specimens collected in Carolina Maranhão, Brazil and Bujaru, Pará, Brazil (Rosa et al. 2016; Moraes et al. 2022).

The constituent found in highest concentration among the volatile compounds of *M. sylvatica* was (*E*)-caryophyllene (45.88%), identified in the specimen collected in Carolina, Maranhão, Brazil (Rosa et al. 2016). It is a hydrocarbon sesquiterpene found in essential oils of the genus *Myrcia*, with pharmacological relevance due to their antimicrobial and antioxidant activities (Gatto et al. 2020; Franco et al. 2021). Germacrene-B (24.5%) and spathulenol (16%) were identified in specimens from the island of Caratateua Belém, Pará, Brazil. (Costa et al. 2022). In addition, germacrene-B, a sesquiterpene hydrocarbon, has been reported as one of the major constituents in the essential oil of *M. rostrata*. Studies have shown that the chemical constituents of the essential oil of this species have antinociceptive activity (Silva et al. 2018). This sesquiterpene also has phytotoxic and cytotoxic potential (Vasconcelos et al. 2022).

The main oxygenated sesquiterpene identified in this study was spathulenol, which has also been found in other studies with species of the *Myrcia* genus. The essential oil of *M. tomentosa* had a high concentration of this compound (40.70%) and showed potential for inhibiting free radicals (Franco et al. 2021). The essential oil of *M. hatschbachii* leaves, collected

in Curitiba, Paraná, Brazil, had spathulenol and (*E*)-caryophyllene as its main constituents, in addition to showing significant antioxidant activity, moderate toxicity against Artemia salina and phytotoxic potential (Gatto et al. 2020).

The (*Z*)-α-trans-bergamotene (24.57%), a hydrocarbon sesquiterpene identified in the essential oil of the specimen collected in the city of Bujaru, Pará, Brazil, was associated with the antioxidant activity and toxicity of the essential oil extracted from the leaves (de Moraes et al. 2022). This compound was also found among the predominant constituents of the essential oil of Santalum album (Indian sandalwood), which showed antifungal and cytotoxic action. The essential oil composed of (*Z*)-α-trans-bergamotene showed efficacy against the fungi *Aspergillus niger*, *Candida albicans* and *Cryptococcus neoformans*, as well as cytotoxic activity against the human breast tumor cell lines MCF-7 (estrogen receptor positive breast adenocarcinoma) and MDA-MB-231 (estrogen receptor negative breast adenocarcinoma) (Powers et al. 2018).

3.1. Chemometric analysis

In order to gain a better understanding of the similarities and differences between the chemical compositions observed for the essential oils of *Myrcia* species published in the literature, correlation analysis was applied between the volatile chemical compounds, shown in figure 1. The analysis revealed important patterns in the joint variation of the constituents of the matrices of the species studied. In general, clusters of highly correlated compounds were observed, as well as antagonistic relationships between certain metabolites. Compounds such as (*Z*)-β-bisabolene and germacrene-D showed a perfect correlation ($r = 1.00$), suggesting that both share a common biosynthetic origin or are formed simultaneously in specific physiological responses of the plant (Pazouki and Niinemets 2016; Vattekkatte A and Boland W 2020; Wu et al. 2025). This relationship indicates that the presence or increase of one of these compounds can

be a strong indication of the presence of the other, which can be exploited for the use of chemical markers in chemotyping studies or for quality control purposes.

Similarly, compounds such as cis-calamenene and β-Calacorene (r = 0.85), and 14-Hydroxy-(*Z*)-cadalene and Cadalene (r = 0.92) also showed high positive correlations, reinforcing the hypothesis that specific sets of sesquiterpenes share metabolic pathways or are synthesized from common precursors (May et al. 2013). This behavior is consistent with the knowledge that many sesquiterpenes are derived from farnesyl pyrophosphate (FPP) and can diverge through specific enzymatic reactions (Tholl 2006).

On the other hand, marked negative correlations were also observed (Figure 1), such as the relationship between Allo-cedrol and (*Z*)-β-Bisabolene (r = -0.99). This negative correlation suggests a possible metabolic exclusion mechanism, in which the synthesis route of one compound inhibits or reduces the production of the other, this behavior may be due to competition for common substrates or the differential regulation of biosynthetic pathways in response to environmental or ontogenetic factors (Asakawa and Noma 2010; Varenikov et al. 2021).

The presence of several weak or zero correlations between other compounds indicates that not all volatile metabolites follow co-production patterns. These results can be attributed to factors such as genetic variability between the individuals analyzed, differences in environmental conditions (light, soil, humidity), and the influence of the plant's stage of development on the expression of certain metabolic pathways (Alami et al. 2024). These findings have relevant implications for practical applications. The identification of strongly correlated compounds can guide the selection of chemotypes for pharmacological or agricultural applications. In addition, understanding the antagonistic relationships between metabolites can be useful in breeding for specific chemical profiles (Wainwright et al. 2022).

The multivariate analysis combining Principal Component Analysis (PCA) and Hierarchical Cluster Analysis (HCA) revealed informative and complex patterns in the chemical variability of the samples studied. PCA proved to be efficient in reducing the dimensionality of the chemical composition data, retaining most of the explained variance, as shown in figure 5. The first two principal components explained approximately 46.5% of the total variance, while five principal components accumulated around 71.4% of the variability. These results indicate a relatively complex chemical structure, in which several compounds contribute simultaneously to the differentiation between the samples.

Analysis of the eigenvalues showed that eleven principal components had values greater than 1.0, reinforcing the significant contribution of multiple axes to the variability of the data. However, from the fifth component onwards, the variance explained fell sharply, justifying the concentration of interpretation on the first components. Compounds such as (*E*)-caryophyllene, γ-elemene, germacrene D, bicyclogermacrene and germacrene-B exhibited high factor loadings in PC1, indicating their fundamental role in separating the samples. This co-occurrence of compounds in the same principal component suggests that these metabolites share biosynthetic routes or are modulated by similar environmental factors. In contrast, compounds such as β-(Z)-bergamotene, α-(Z)-bergamotene and (Z)-α-bisabolene stood out in PC2, representing a second dimension of variability associated mainly with sesquiterpene hydrocarbons (Figure 5).

A clear separation was also observed between hydrocarbon compounds and oxygenated compounds, such as caryophyllene oxide, spathulenol and globulol, indicating differences possibly related to plant material maturation factors or responses to biotic and abiotic stresses. These results corroborate previous findings demonstrating metabolic plasticity in the biosynthesis of terpenoids in plants under different environmental conditions.

Hierarchical Cluster Analysis (HCA) complemented these findings by revealing clusters of samples with similar chemical patterns, as shown in figure 3. At the start of the clustering, there was high similarity between the samples (>97%), confirming the partial homogeneity suggested by the PCA (Figure 2). However, as the number of clusters was reduced, the similarity decreased, showing substantial chemical heterogeneity, especially from the formation of fewer than twenty clusters. The final partition resulted in thirteen clusters, most of which were made up of just one observation, highlighting the uniqueness of some samples. Only three clusters grouped together multiple samples, with Cluster 12 being the most expressive, bringing together 22 observations and showing low intra-group variability.

Analysis of the centroids of the clusters enabled the identification of key compounds in differentiating the clusters. Compounds such as δ-selinene, β-selinene and δ-cadinene characterized Cluster 1, while Cluster 2 was strongly influenced by high concentrations of (*E*)-caryophyllene. Cluster 3 stood out for the presence of (*Z*)-α-trans-bergamotene and α-sinensal, compounds often associated with the maturation of plant tissues. The high distance between centroids, especially between Clusters 1 and 2, reinforced the substantial chemical differences between the groups.

The combination of PCA and HCA proved effective in discriminating between samples with distinct chemical profiles, allowing not only the identification of similarity groups, but also compounds that could act as potential chemical markers. The results suggest the existence of distinct chemotypes, reflecting genetic variability, environmental variations or differences in metabolic processes. This study highlights the importance of multivariate analysis in characterizing essential oils and identifying compounds of pharmacological, cosmetic or agricultural interest. Future studies could integrate this chemical characterization with bioactivity

data and genetic information, deepening the understanding of the factors that shape the observed chemical diversity.

4.Antioxidant activity

The physicochemical tests are used to measure the antioxidant activity of a substance, such as the ABTS•+ radical test. This method is based on the generation of the ABTS•+ radical cation, a blue-green compound. This radical also determines the antioxidant capacity of hydrophilic and lipophilic compounds. The DPPH test is also used to determine the antioxidant capacity of a substance. This method is based on the donation of electrons from antioxidants to neutralize the DPPH• radical. For quantification, Trolox, a water-soluble synthetic analog of vitamin E, is used as a reference standard, allowing the results to be expressed in Trolox equivalents (TEAC) (Munteanu and Apetrei 2021).

Substances synthesized by plants have been widely evaluated as alternatives to synthetic substances due to their antioxidant potential (Costa et al. 2024). In this context, the *Myrcia* genus is rich in essential oil-producing species that may offer a promising source of these compounds (Santos et al. 2024). According to (Moraes et al. 2022), the essential oil of *M. sylvatica*, consisting solely of sesquiterpenes, showed a significant capacity to inhibit the DPPH• radical (80.55 ± 2.00%) when compared to the Trolox standard (45.74 ± 4.16%), although it did not show a significant capacity to inhibit the ABTS•+ radical (7.20 ± 0.72%) when compared to the same standard (Moraes et al. 2022). The authors emphasize that the high antioxidant potential can be attributed mainly to the high concentration of oxygenated sesquiterpenes present in the oil, in addition, (Ferreira et al. 2021) cite that the results obtained against DPPH• and ABTS•+ radicals can differ greatly due to differences in the reaction mechanisms between the antioxidant substances present in the oil and each of the free radicals.

5. Biological activities

The biological properties of species from the Myrtaceae family are attributed to the various bioactive compounds they produce, which have the potential to be exploited in a wide variety of areas, such as food, cosmetics and pharmacology (Ferreira et al. 2020). Within this family, the genus *Myrcia* stands out as the most representative in terms of number of species, as well as having high phytochemical variability, with the presence of compounds such as mono- and sesquiterpenes in the secondary metabolism of plants of the genus (Santos et al. 2024). The biological potential of the *M. sylvatica* species is described as particularly promising due to the complex chemical composition of the species' essential oils, which, in general, cannot be summarized as just a few major compounds in high concentration, but as a volatile concentrate of different substances in significant quantities, which may lead the oil to present, by virtue of synergistic and antagonistic effects, a range of biological activities that have not yet been investigated to date (Moraes et al. 2022; Costa et al. 2022; Silva Júnior et al. 2025).

Moraes et al. (2022), evaluated the toxicity of the essential oil of *M. sylvatica* leaves from the Brazilian Amazon against larvae of the microcrustacean *Artemia salina* Leach, and found a Mean Lethal Concentration (CL_{50}) of 2.74 µg.mL-1, which indicates the high toxicity of the oil. The authors attribute the result to the sesquiterpenes, unique constituents of the oil analyzed, a class of substances described as toxic in different studies found in the literature (Costa et al. 2022; Mustapha et al. 2023; Cruz et al. 2024). The majority compound found in the essential oil, (*Z*)-α-trans-bergamotene (24.57%), oils with this constituent have shown biological activities, such as antimicrobial, cytotoxic and antiproliferative activities (Annaz et al. 2024). On the other hand, interactions with other substances present in the mixture must be taken into account to explain the oils high toxicity.

In another study, the essential oil from the leaves of a specimen of *M. sylvatica* from the Brazilian Cerrado, with a chemical composition characterized by a high concentration of (E)-

caryophyllene (45.55%), was tested for toxicity against *Artemia salina* and *Aedes aegypti* larvae, showing moderate toxicity (79.44 µg.mL-1) against *A. salina* larvae and no effect on *A. aegypti* larvae at the concentrations tested (Rosa et al. 2016). Lima et al. (Lima et al. 2024) analyzed the toxicity of the essential oil of *Piper tuberculatum*, rich in (*E*)-caryophyllene, and of (*E*)-caryophyllene isolated against *A. aegypti* larvae, both substances showed high toxicity, although the essential oil was more effective, indicating the importance of interactive effects in the properties of the oil, which may have been decisive for the result described for the oil of *M. sylvatica*.

The essential oil of a specimen of *M. sylvatica* from the Brazilian Amazon was tested for antibacterial potential and showed an effect against the bacteria *Staphylococcus aureus* (MIC = 2.5 µL. mL^{-1}), *S. epidermidis* (MIC = 20.0 µL.mL^{-1}), *Bacillus cereus* (MIC = 0.2 µL.mL-1) and *Enterococcus faecalis* (MIC = 20.0 µL.mL^{-1}), but it was not effective against the yeasts and Gram-negative bacteria tested. The oil had a high concentration of sesquiterpenes, with ar-curcumene (7.6%) and cubenol (6.9%) as the major ones, in line with the study by Moraes et al. (2022) para o perfil químico de espécime proveniente do mesmo bioma.

5. Conclusion

Myrcia sylvatica essential oils exhibit remarkable chemical diversity dominated by sesquiterpenes, whose composition varies with geographic and environmental factors. Chemometric analysis confirmed the presence of distinct chemical profiles, supporting the existence of chemotypes within the species. The biological assays demonstrated antioxidant, antimicrobial, and toxicological potential, suggesting promising applications in pharmacology, agriculture, and biotechnology. However, the pronounced chemical variability indicates that synergistic and antagonistic interactions between compounds must be further investigated. Future studies integrating ecological context, seasonal variation, and in vivo bioassays are crucial to deepen understanding of this species' metabolic plasticity. Overall, M. sylvatica represents a valuable source of bioactive molecules, with high potential for sustainable exploitation and innovation in natural product research.

Acknowledgments

The authors thank CAPEs for the scholarship and financing code 001.

Declaration of Interest statement

There are no conflicts of interest for the present work.

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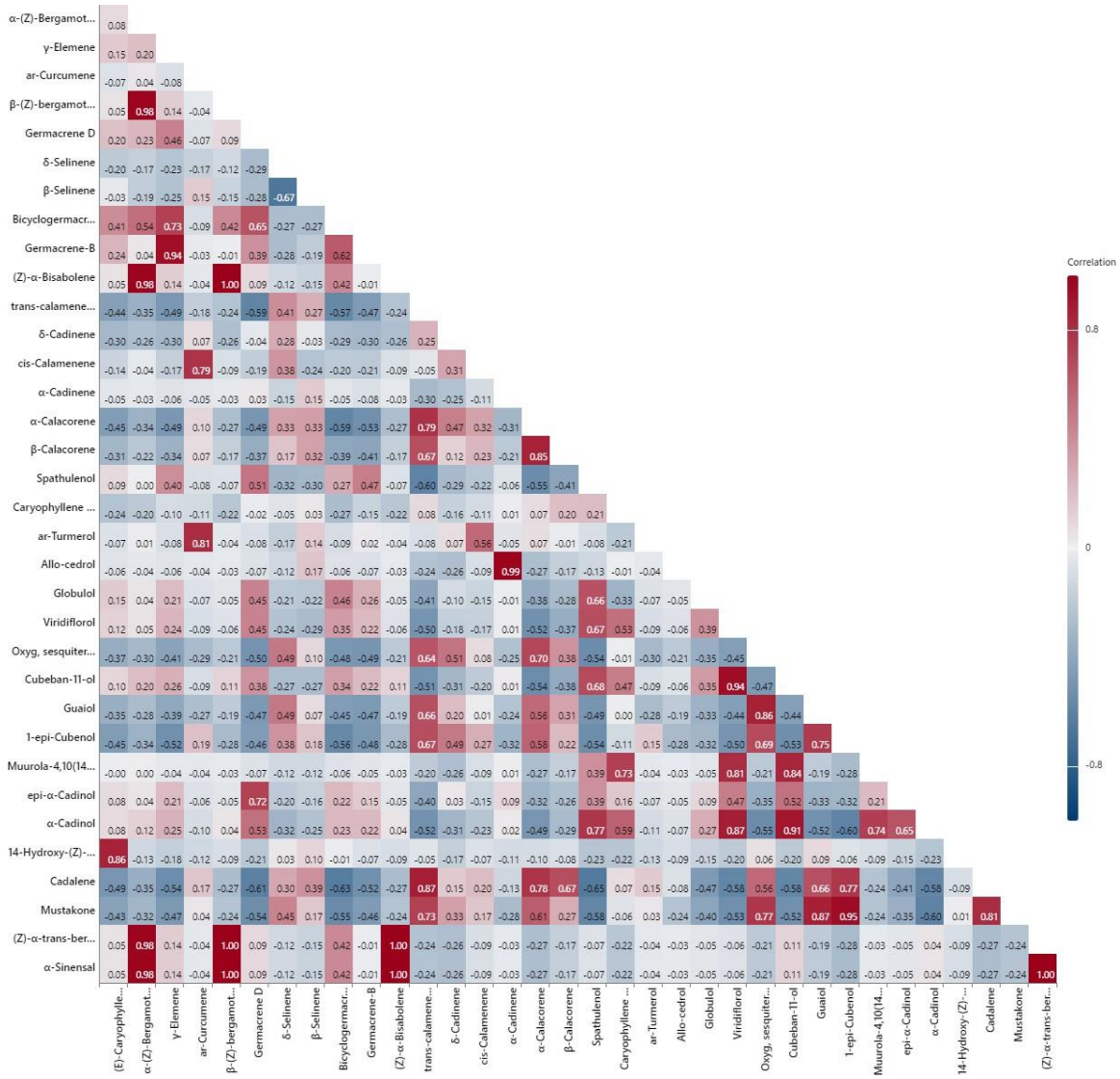

Figure 1. Correlation analysis between the volatile chemical compounds of *Myrcia sylvatica* (G.Mey) DC. collected in Brazil.

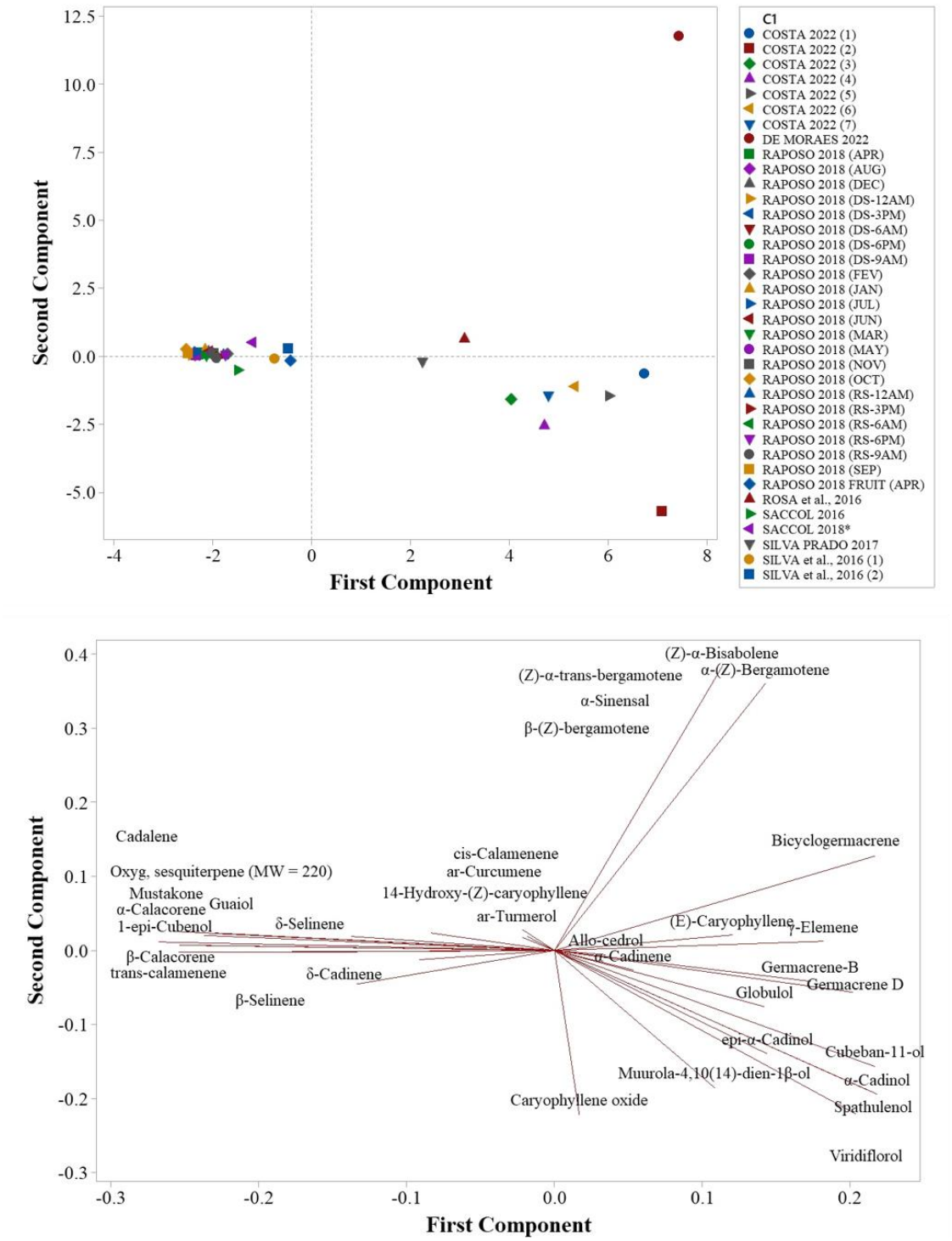

Figure 2. Biplot (PCA) obtained as a result of the analysis of *Myrcia sylvatica* (G.Mey) DC. volatile compounds in different studies. (Silva et al. 2016); (Saccol et al. 2018); (Raposo et al. 2018); (Prado et al. 2017); (Saccol et al. 2017); (Moraes et al. 2022); (Costa et al. 2022); (Rosa et al. 2016).

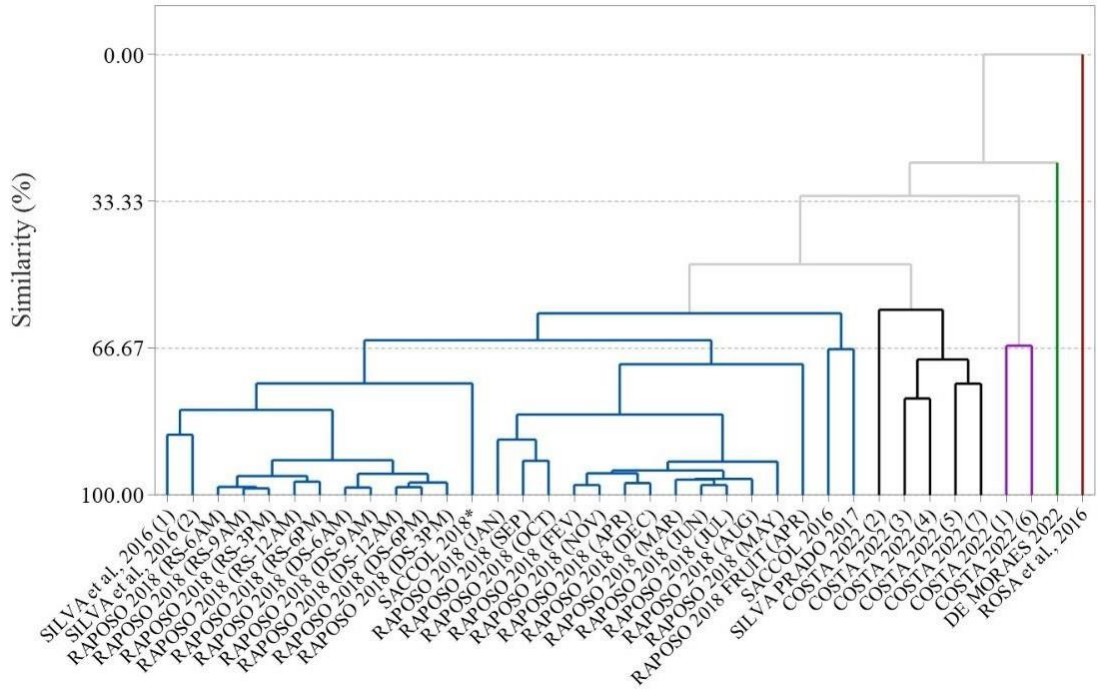

Figure 3. Hierarchical Cluster Analysis of the compounds identified in the essential oil of *Myrcia sylvatica* (G.Mey) DC. in different studies. (Silva et al. 2016); (Saccol et al. 2018); (Raposo et al. 2018); (Silva Prado et al. 2017); (Saccol et al. 2017); (de Moraes et al. 2022); (Costa et al. 2022); (Rosa et al. 2016).

Supplementary material

Volatile Constituents and Chemometric Patterns of *Myrcia sylvatica* Essential Oils: A Systematic Review of Composition and Bioactivity

Eliza de Jesus Barros dos Santos[1], Mateus Machado Lima[2], Leonardo Souza da Costa[2], Ravendra Kumar[3], Pooja Bargali[3], Hayet Edziri[4], Karyme do Socorro de Souza Vilhena[5], Eloisa Helena de Aguiar Andrade[1,2] e Mozaniel Santana de Oliveira[1,2*]

[1] Postgraduate program in biological sciences - tropical botany. Universidade Federal Rural da Amazônia and Museu Paraense Emílio Goeldi, Av. Terra Firme, 66075- 900 Belém, Pará, Brazil.

[2]Adolpho Ducke Laboratory - Botany Coordination, Museu Paraense Emílio Goeldi, Av. Perimetral, 1901, Terra Firme, 66077-830, Belém PA, Brazil.

[3] Department of Chemistry, College of Basic Sciences and Humanities, G.B. Pant University of Agriculture and Technology, Pantnagar, U.S. Nagar-263145, Uttarakhand, India.

[4]Laboratory of Transmissible Diseases and Biologically Active Substances (LR99 ES27), Faculty of Pharmacy, University of Monastir 5000, Monastir Tunisia.

[5]Department of Chemistry, Institute of Exact and Natural Sciences, Universidade Federal do Pará, Augusto Corrêa Rua, S/ N, Guamá, Belém 66075-900, Pará, Brazil.
Hayet Edziri

*Corresponding author: mozaniel.oliveira@yahoo.com.br

Abstract

This systematic review compiles the chemical composition, chemometric patterns, and biological activities of essential oils from *Myrcia sylvatica* (G. Mey) DC., a species of the Myrtaceae family with wide distribution in South America. A total of 216 volatile constituents have been identified, mainly hydrocarbon and oxygenated sesquiterpenes such as (E)-caryophyllene, germacrene B, spathulenol, and (*Z*)-α-trans-bergamotene. Chemometric analyses revealed distinct chemical clusters and potential chemotypes, influenced by genetic and environmental factors. Biological assays demonstrated antioxidant potential, antimicrobial activity against Gram-positive bacteria, and toxicity to *Artemia salina* larvae, indicating promising pharmacological and agrochemical applications. Despite advances, studies remain limited and reveal substantial chemical variability. These findings highlight the need for further integrative research combining phytochemistry, bioassays, and ecological assessments to better understand the bioactive potential and ensure sustainable use of *M. sylvatica*.

Keyword: *Myrcia sylvatica*; Essential oils; Chemometric analysis; Antioxidant activity; Biological potential.

2.1. See supplemental material methodology

The literature search was conducted in six databases: A comprehensive list of relevant bibliographic databases includes PubMed, Scopus, Web of Science, Google Scholar, SciELO, and Periódicos-CAPES. The initial identification of articles yielded a total of 752, which were distributed as follows: The following databases were searched: PubMed (5), Scopus (0), Web of Science (10), Google Scholar (712), SciELO (2), and Periódicos-CAPES (23). The present study exclusively considered articles published in the last ten years (2015-2025). Subsequently, duplicates were filtered and titles, abstracts, and full texts were analyzed to verify relevance. The present study exclusively included investigations that presented information on chemical composition and/or biological activities. Following the application of the eligibility criteria and the removal of duplicates, articles relevant to the review topic were selected. The information related to the discussion of the statistical analysis was supported by other articles. The selected articles were then subjected to a qualitative analysis, with a focus on identifying patterns, trends, and gaps related to chemical composition and biological activities. The flowchart illustrating the methodology employed in this study can be found in Figure S1.

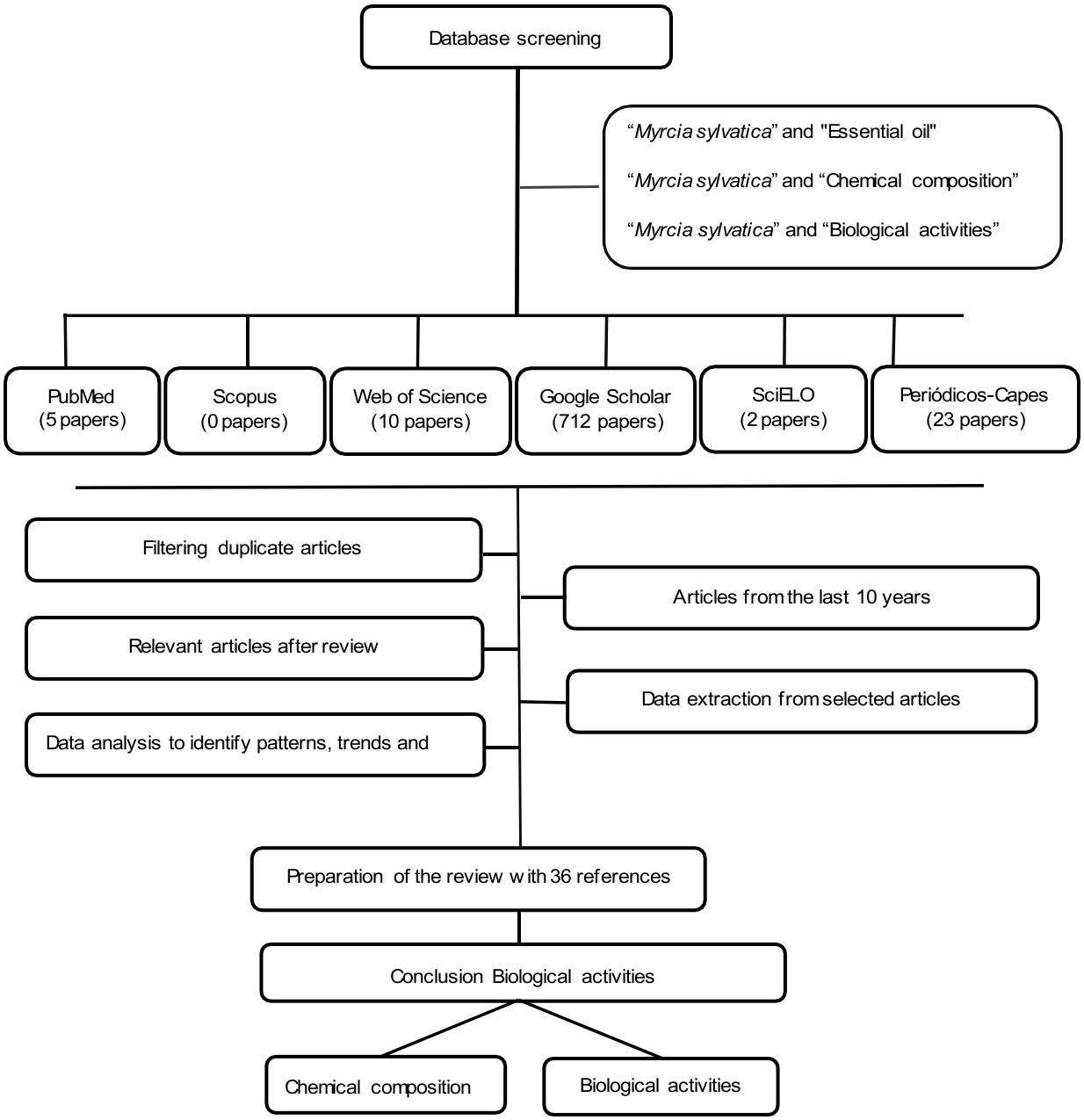

Figure S1. Flowchart of the screening, selection and analysis process of articles included in the review.

In figure 2 we have the main occurrence locations of the *Myrcia sylvatica* species, we can observe that until now this species has only been found in the Amazon.

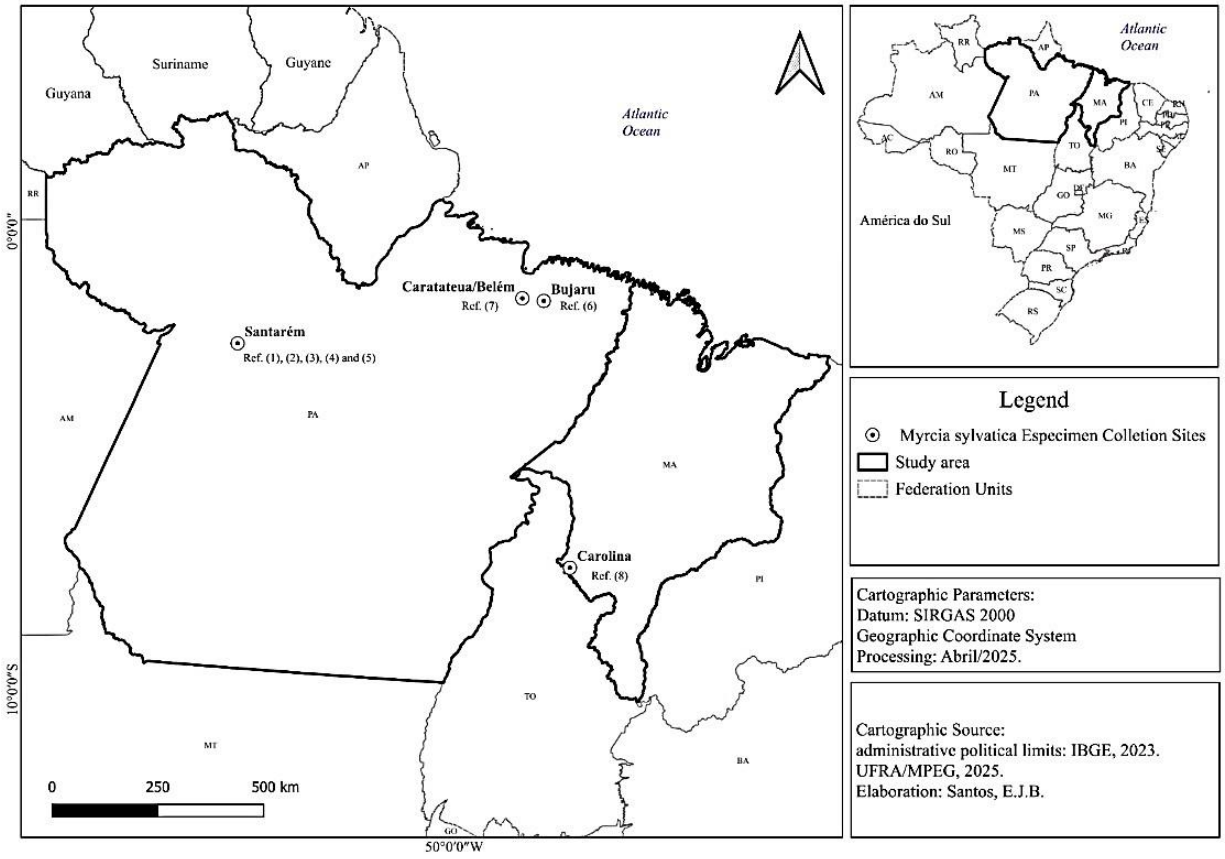

Figure S2. Collection sites of *Myrcia sylvatica* (G.Mey) DC. specimens, collected in Brazil. Ref **(1)** =(Silva et al. 2016); **(2)** =(Saccol et al. 2018); **(3)** = (Raposo et al. 2018); **(4)** = (Silva Prado et al. 2017); **(5)** =(Saccol et al. 2017); **(6)** = (de Moraes et al. 2022); **(7)** = (Costa et al. 2022); **(8)** = (Rosa et al. 2016).

2.2. Statistical analysis

The data regarding the composition of volatile compounds were subjected to multivariate statistical analyses to identify patterns of variability, similarity, and clustering among the samples. Prior to the analyses, the data were standardized using z-score transformation (mean = 0; standard deviation = 1) to minimize the influence of differences in variable scales. Initially, a Pearson correlation analysis was performed to evaluate the degree of linear association between chemical constituents. The correlation coefficients were used to identify pairs of compounds with similar or antagonistic

behaviors. These values were visually represented using a correlation plot (correlogram), which applied a diverging color scale (from blue to red) to indicate negative and positive correlations, respectively. Numerical values of the correlation coefficients were also displayed to facilitate the identification of statistically relevant relationships among compounds. A Principal Component Analysis (PCA) was carried out to reduce data dimensionality and highlight the main axes of chemical variation among the samples. PCA was based on the correlation matrix, and principal components with eigenvalues greater than 1.0 were retained according to the Kaiser criterion. Factor loadings (eigenvectors) were examined to determine which compounds contributed most significantly to each principal component, enabling the identification of chemical groupings and shared structural or biosynthetic patterns. Additionally, a Hierarchical Cluster Analysis (HCA) was performed to investigate the similarity of chemical profiles among the samples. The analysis employed the Euclidean distance as a dissimilarity measure, and clustering was based on the Complete Linkage method, which considers the maximum distance between pairs of elements in distinct clusters. The results were visualized through a dendrogram, and the optimal number of clusters was defined by examining the levels of similarity during the amalgamation steps and the distances between cluster centroids. All statistical analyses were performed using Minitab® 22 Free Version (Minitab LLC, State College, PA, USA).

3.1. See supplemental material results.

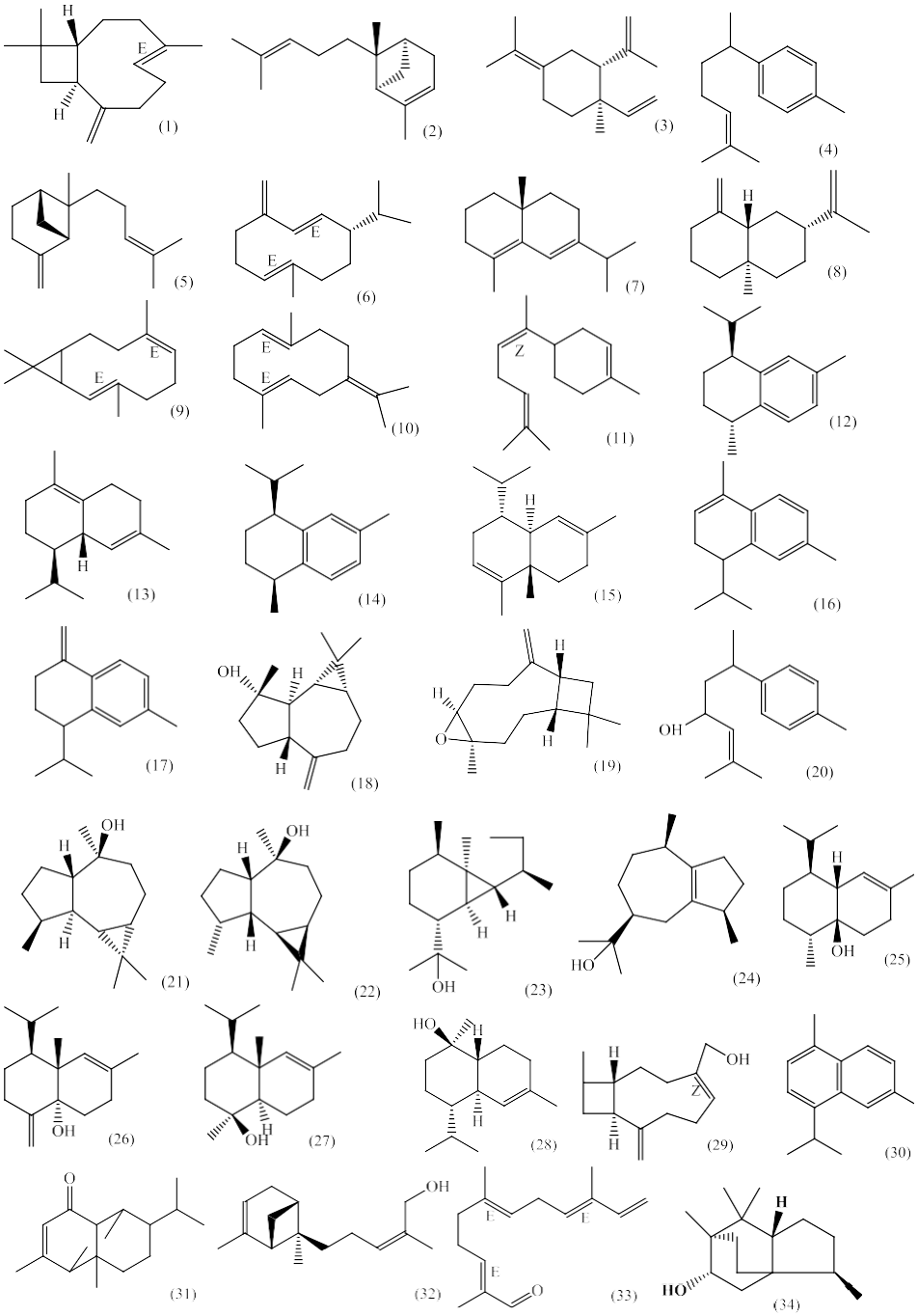
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Figure S3. Structure of the main compounds in the essential oil of *Myrcia sylvatica* (G.Mey) DC.., (>5%) (Constituents: **(1)** (*E*)-Caryophyllene; **(2)** α-(*Z*)-Bergamotene; **(3)** γ-Elemene; **(4)** *ar*-Curcumene; **(5)** β-(*Z*)-Bergamotene; **(6)** Germacrene D; **(7)** δ-Selinene; **(8)** β-Selinene; **(9)** Bicyclogermacrene; **(10)** Germacrene-B; **(11)** (*Z*)-α-Bisabolene; **(12)** trans-Calamenene; **(13)** δ-Cadinene; **(14)** cis-Calamenene; **(15)** α-Cadinene; **(16)** α-Calacorene; **(17)** β-Calacorene; **(18)** Spathulenol; **(19)** Caryophyllene oxide; **(20)** *ar*-Turmerol; **(21)** Globulol; **(22)** Viridiflorol; **(23)** Cubeban-11-ol; **(24)** Guaiol; **(25)** 1-epi-Cubenol; **(26)** Muurola-4,10(14)-dien-1β-ol; **(27)** epi-α-Cadinol; **(28)** α-Cadinol; **(29)** 14-Hydroxy-(*Z*)-caryophyllene; **(30)** Cadalene; **(31)** Mustakone; **(32)** (*Z*)-α-trans-bergamotene; **(33)** α-Sinensal; **(34)** Allo-Cedrol.

Table S1 of the compounds organized in the Excel file is available at the link bellow:

https://docs.google.com/spreadsheets/d/1gHnQ4wOdHvnluzv685qFZ6ddiJI4jrRA/edit?usp=sharing&ouid=110622141983870347106&rtpof=true&sd=true

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4. CAPITULO III

Integrated Anatomical, Chemical, Biological, and Computational Studies Approach of *Myrcia sylvatica* (G. Mey) DC. A Multifaceted Insight into a Promising Amazonian Species

Flavour and Fragrance Journal

Original Article

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Submission ID a8c3e229-2227-4ad8-babb-48039ffcaf8a

Submission Version Initial Submission

PDF Generation 04 Jun 2025 12:18:17 EST by Atypon ReX

Authors

Miss Eliza de Jesus Barros dos Santos

Affiliations

- Graduate Program in Biological Sciences - Tropical Botany. Universidade Federal Rural da Amazônia and Museu Paraense Emílio Goeldi, Av. Perimetral, 1901. Terra Firme, 66075- 900 Belém, Pará, Brazil

Dr. Zelina Ataíde Correia

Affiliations

- Graduate Program in Biological Sciences - Tropical Botany. Universidade Federal Rural da Amazônia and Museu Paraense Emílio Goeldi, Av. Perimetral, 1901. Terra Firme, 66075- 900 Belém, Pará, Brazil

Dr. Ely Simone Cajueiro Gurgel

Affiliations

- Graduate Program in Biological Sciences - Tropical Botany. Universidade Federal Rural da Amazônia and Museu Paraense Emílio Goeldi, Av. Perimetral, 1901. Terra Firme, 66075- 900 Belém, Pará, Brazil

Mr. Leonardo Souza da Costa

Affiliations

- Adolpho Ducke Laboratory - Botany Coordination, Museu Paraense Emílio Goeldi, Av. Perimetral, 1901, Terra Firme, 66077-830, Belém PA, Brazil

Prof. Mabrouk Horchani

Affiliations
- Laboratory of Heterocyclic Chemistry, Natural Products and Reactivity, Medicinal Chemistry and Natural Products (LR11ES39), Faculty of Sciences of Monastir, University of Monastir, Monastir 5000, Tunisia

Prof. Hayet Edziri

Affiliations
- Laboratory of Transmissible Diseases and Biologically Active Substances, Faculty of Pharmacy, 5000, University of Monastir, Monastir, Tunisia

Prof. Ravendra Kumar

Affiliations
- Department of Chemistry, College of Basic Sciences and Humanities, G.B. Pant University of Agriculture and Technology,Pantnagar, U.S. Nagar-263145, Uttarakhand, India

ORCiD
https://orcid.org/0000-0002-0296-5231

Dr. Anderson de Santana Botelho

Affiliations
- Adolpho Ducke Laboratory - Botany Coordination, Museu Paraense Emílio Goeldi, Av. Perimetral, 1901, Terra Firme, 66077-830, Belém PA, Brazil
- Graduate Program in Chemistry - Federal University of Pará - Rua Augusto Corrêa S/N, Guamá, 66075-900, Belém, Pará, Brazil

Dr. Karyme do Socorro de Souza Vilhena

Affiliations
- Faculty of Chemistry, Institute of Exact and Natural Sciences, Federal University of Pará, Augusto Corrêa Rua, S/ N, Guamá, Belém 66075-900, Pará, Brazil

Prof. Eloisa Helena de Aguiar Andrade

Affiliations
- Graduate Program in Biological Sciences - Tropical Botany. Universidade Federal Rural da Amazônia and Museu Paraense Emílio Goeldi, Av. Perimetral, 1901. Terra Firme, 66075- 900 Belém, Pará, Brazil
- Adolpho Ducke Laboratory - Botany Coordination, Museu Paraense Emílio Goeldi, Av. Perimetral, 1901, Terra Firme, 66077-830, Belém PA, Brazil

Prof. Mozaniel Santana de Oliveira

Corresponding Author Submitting Author

Affiliations
- Graduate Program in Biological Sciences - Tropical Botany. Universidade Federal Rural da Amazônia and Museu Paraense Emílio Goeldi, Av. Perimetral, 1901. Terra Firme, 66075- 900 Belém, Pará, Brazil
- Adolpho Ducke Laboratory - Botany Coordination, Museu Paraense Emílio Goeldi, Av. Perimetral, 1901, Terra Firme, 66077-830, Belém PA, Brazil

ORCiD
https://orcid.org/0000-0002-4076-2443

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Integrated Anatomical, Chemical, Biological, and Computational Studies Approach of *Myrcia sylvatica* (G. Mey) DC. A Multifaceted Insight into a Promising Amazonian Species

Eliza de Jesus Barros dos Santos[1], Zelina Ataíde Correia[1], Ely Simone Cajueiro Gurgel[1], Leonardo Souza da Costa[2], Mabrouk Horchani[3], Hayet Edziri[4], Ravendra Kumar[5], Anderson de Santana Botelho[2,6], Karyme do Socorro de Souza Vilhena[7], Eloisa Helena de Aguiar Andrade[1,2], and Mozaniel Santana de Oliveira[1,2]*

[1]Graduate Program in Biological Sciences - Tropical Botany. Universidade Federal Rural da Amazônia and Museu Paraense Emílio Goeldi, Av. Perimetral, 1901. Terra Firme, 66075- 900 Belém, Pará, Brazil.

[2]Adolpho Ducke Laboratory - Botany Coordination, Museu Paraense Emílio Goeldi, Av. Perimetral, 1901, Terra Firme, 66077-830, Belém PA, Brazil

[3] Laboratory of Heterocyclic Chemistry, Natural Products and Reactivity, Medicinal Chemistry and Natural Products (LR11ES39), Faculty of Sciences of Monastir, University of Monastir, Monastir 5000, Tunisia.

[4] Laboratory of Transmissible Diseases and Biologically Active Substances, Faculty of Pharmacy, 5000, University of Monastir, Monastir, Tunisia.

[5]Department of Chemistry, College of Basic Sciences and Humanities, G.B. Pant University of Agriculture and Technology,Pantnagar, U.S. Nagar-263145, Uttarakhand, India.

[6]Graduate Program in Chemistry - Federal University of Pará - Rua Augusto Corrêa S/N, Guamá, 66075-900, Belém, Pará, Brazil.

[7]Faculty of Chemistry, Institute of Exact and Natural Sciences, Federal University of Pará, Augusto Corrêa Rua, S/ N, Guamá, Belém 66075-900, Pará, Brazil.

*Corresponding author: mozaniel.oliveira@yahoo.com.br

Abstract

Myrcia sylvatica (G. Mey) DC., a native aromatic species from the Brazilian Amazon, was comprehensively studied for its anatomical, histochemical, chemical, and biological characteristics, including an in silico evaluation. Leaves were subjected to anatomical and histochemical analysis, revealing secretory structures associated with the accumulation of

lipids, terpenes, alkaloids, and phenolic compounds. Essential oils were extracted by hydrodistillation (HD) and steam distillation (SD), and chemically characterized via GC-MS, revealing sesquiterpenes such as α-zingiberene, germacrene D, and spatulenol as major constituents. The SD-extracted oil presented higher antioxidant activity (ABTS IC_{50} = 6.80 mg/mL; DPPH IC_{50} = 12.80 mg/mL) and greater toxicity against Artemia salina (LC_{50} = 4.17 µg/mL) than the HD oil. Correlation analysis indicated distinct biosynthetic clusters of compounds. Molecular docking and ADME analysis highlighted spathulenol and globulol as promising bioactive molecules with potential acetylcholinesterase inhibitory activity and favorable pharmacokinetic profiles. These results provide unprecedented insights into the bioactive potential and chemical ecology of *M. sylvatica*, supporting its application in natural product development.

Keywords: *Myrcia sylvatica*; Essential oils; Sesquiterpenes; Molecular docking; Antioxidant activity

1. Introduction

The Myrtaceae family has a great diversity of species, with around 142 genus and 6000 species distributed throughout tropical and subtropical regions. In Brazil, the family has a remarkable number of native and endemic species, with confirmed occurrences in the North, Northeast, Midwest, Southeast and South [1,2] . Mytaceae plays a significant role in traditional medicine due to the bioactive potential of many of its species [3] .

Among the species of the Myrtaceae family, the *Myrcia* genus stands out due to its therapeutic properties, as it produces a large amount of essential oil in its secondary metabolism, rich in compounds such as monoterpene, sesquiterpene and phenolic compounds, making the genus have great biological potential, such as antimicrobial, phytotoxic, antioxidant, insecticide and hypoglycemic, among others [4,5].

Within this context, *Myrcia sylvatica* (G.Mey) DC., popularly known as "Pedra-ume-caá", stands out for its chemical and biological properties. Studies indicate that *M. sylvatica* produces essential oils with variations in chemical composition influenced by extrinsic factors, such as environmental conditions [6]. Several studies have been conducted to investigate the chemical composition and biological properties of *M. sylvatica* [7–11].

Research has identified the main compounds present in the plants essential oil, including hydrocarbon and oxygenated sesquiterpenes and phenolic compounds [7–11]. These compounds have been associated with antioxidant, anti-inflammatory and toxicity activities [9,10,12], which may be useful in the treatment of various diseases.

However, there are gaps in the literature on the anatomical and histochemical aspects and biological properties of *M. sylvatica*. Filling these gaps is important because a detailed understanding of the anatomy and histochemistry of the species can provide information on the production and storage sites of the metabolites that the species presents. In addition, the chemical characterization of the essential oil of *M. sylvatica* is fundamental to understanding its chemical variability, which can contribute to the development of new natural products with medicinal applications.

The aim of this study was to characterize the chemical composition of the essential oil of *M. sylvatica*, to provide unpublished information on its anatomical and histochemical characteristics, and to evaluate its antioxidant potential, toxicity and In silico study, thus contributing to knowledge of the species biological potential.

2. Material and methods

2.1 Sample collection and processing

M. sylvatica leaves were collected in the environmental preservation area of the Utinga State Park, located in Belém, Pará, Brazil (Figure 1). This site was chosen due to its representativeness of floodplain and terra firme forest ecosystems, typical of the Amazon,

where the species is native. In addition, the park offers a protected and monitored area, which guarantees the integrity of the botanical material collected.

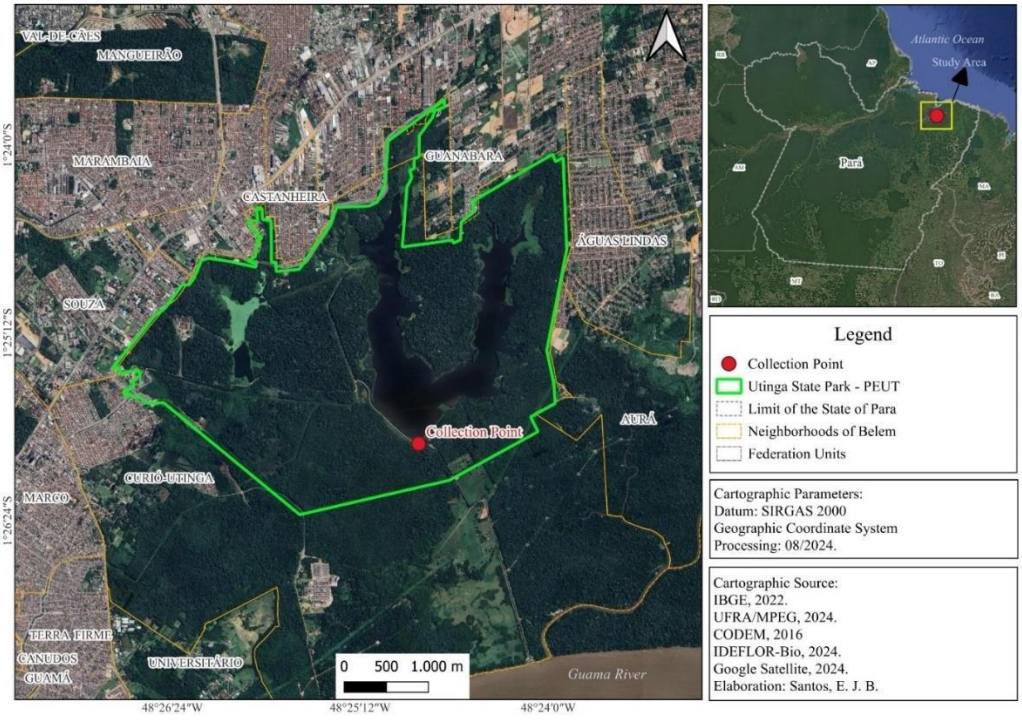


Figure 1 - Map illustrating the collection site in Utinga State Park (PEUT).

The species was collected following the protocols for field collection and herborization. The exsiccate, botanical identification and registration of the species were deposited in the João Murça Pires Herbarium of the Museu Paraense Emílio Goeldi, Belém, Pará, with the following registration number MG254169, the species is also registered in SisGen A965505.

2.2 Anatomical Analysis of the Leaf Blade by Light Microscopy (LM)

Parts of the leaf blade of *M. sylvatica* in natura, including the median region, central vein, margin and petiole, as shown in Figure 2, were fixed in formaldehyde, acetic acid and 50% ethanol (FAA)[13] for 24 hours for structural analysis. For the histochemical tests, the samples were fixed in FAA to check for hydrophilic substances, neutral buffered formalin (NTF) to check for lipophilic substances and ferrous sulphate in formalin (SFF) to determine total phenolic compounds [13,14].

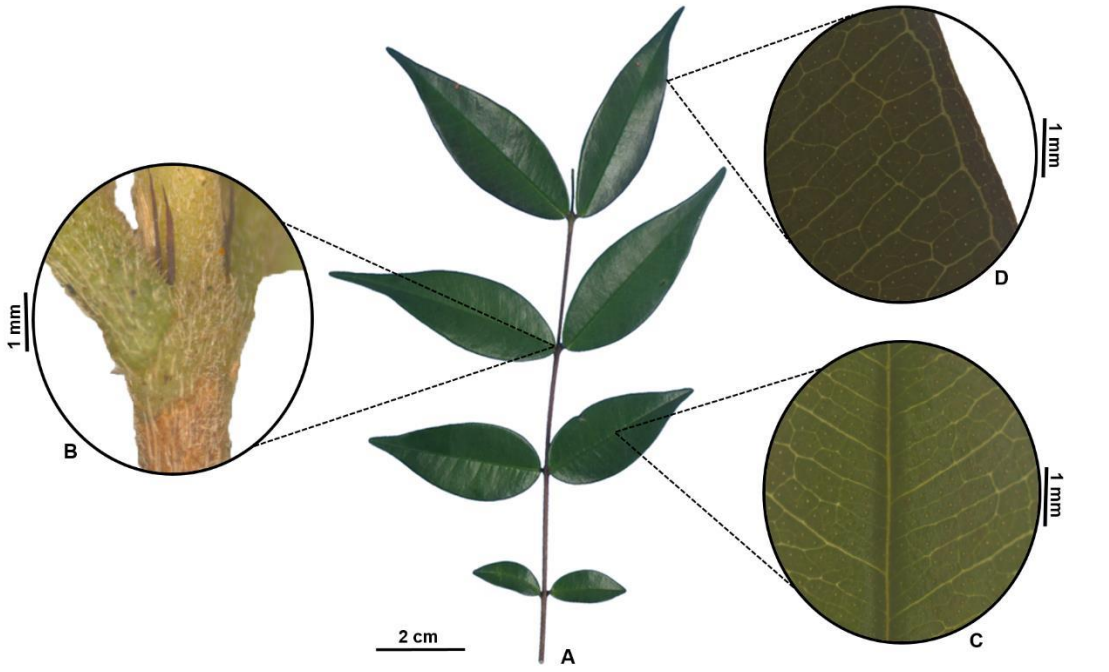


Figure 2 - Leaf structure of *Myrcia sylvatica* (G.Mey) DC. (A) General view of the branch, (B) Petiole (C) Median region and central vein, (D) Margin.

The samples were then dehydrated in an increasing series of tertiary butyl alcohol for inclusion in histological paraffin with dimethyl sulfoxide (DMSO) (Paraplast® , ©Leica Biosystems, Teaneck, NJ, USA)[13] . Transverse and longitudinal sections of 11 µm were obtained using a rotary microtome (Leica model® RM 2245, Leica® Biosystems, Heidelberg, Germany). Part of the samples were stained with astra blue and safranin[15], the rest were used for histochemical tests. The slides were mounted in colorless Canada balsam [16].

2.3 Dissociation of the epidermis

To dissociate the epidermis, fractions of leaves were sectioned with a steel blade and immersed in a solution of hydrogen peroxide and acetic acid for 24 hours[17]. After this period, the samples were washed in distilled water and stained with Safranin[15]. Subsequently, the slides were mounted in aqueous glycerin (1:1), with the edges duly sealed using colorless enamel, as described by Purvis et al. [18].

2.4 Histochemistry

In the analysis of the metabolic groups present in the samples, different reagents were used to identify and characterize the compounds. For the detection of total lipids, the Sudan Black reagent was used, as described by Pearse [19]. Acid lipids were identified using Nile blue sulphate, following the methodology of Cain [20] . Terpenes were visualized using the Nadi reagent, which followed the protocol described by David and Carde [21] .

The presence of phenolic compounds was determined using the (SFF) reagent, as described by Johansen [13], while tannins were detected using hydrochloric vanillin solution, using the method described by Mace and Howell [22].

Lignin was analyzed using the phloroglucinol reagent, following the studies of Johansen [13]. For the detection of acid mucilage, the ruthenium red reagent was used, following the studies of Gregory and Baas [23]. Total polysaccharides were detected using the PAS reagent (Periodic Acid Schiff's reagent), according to the studies of McManus [24], and for the identification of starch, the lugol reagent was used, following the methodology of Johansen [13] . Alkaloids were detected using the Wagner reagent, based on the studies of Furr and Mahlberg [25], and the presence of crystals was detected using 5% hydrochloric acid, as described in the studies of Chamberlain [26].

Photographic records of both anatomy and histochemistry were taken on a Leica microscope (DM6B, Wetzlar, Germany W) coupled to a digital camera (Leica application suite LAS V4. 12) in the Botany Microscopy Laboratory at the Museu Paraense Emílio Goeldi (MPEG), calibrated with suitable micrometer slides as specified by the manufacturer.

2.5 Extraction methods

The *M. sylvatica* leaves were dried in an air-conditioned room with temperature and humidity control using air conditioning and a dehumidifier. The material was ground in a knife mill.

For the essential oil extraction process, the dried leaves were subjected to two distillation methods: steam (SD) and hydrodistillation (HD). Both methods used a modified Clevenger-type glass system with an extraction time of 3 hours. The AV method used 1.666 kg of dried leaves, while the HD method used 1.415 kg of material, following the methods described by Santana de Oliveira et al. [27].

The EOs were centrifuged for 5 min at 3000 rpm, dehydrated with anhydrous sodium sulfate (Na_2SO_4) and centrifuged again under the same conditions. They were then stored in amber glass ampoules and kept refrigerated at a constant temperature of -5 °C. The percentage of water in the samples studied was determined using an infrared moisture analyzer. The EO yield was calculated on a moisture-free basis using the ratio between mass, oil and moisture, as established by Santos et al. [28].

$$\%\,\acute{o}leoBLU = \left(\frac{V}{m-\left(\frac{mxU}{100}\right)}\right) x100 \quad (1)$$

Where: V is the volume of oil obtained, in milliliters (mL); (m) is the mass of sample weighed for hydrodistillation, in grams (g); (U) is the humidity of the samples, on a decimal basis.

2.6 Identification of chemical components by GC/MS

The chemical composition of the EOs was analyzed by gas chromatography coupled to mass spectrometry (GC/MS) on a SHIMADZU QP Plus-2010 system equipped with a DB-5MS silica capillary column (30 m × 0.25 mm; film thickness 0.25 µm) under the following operating conditions: carrier gas: helium, linear velocity 36.5 cm.s $^{-1}$; injection mode: splitless (2 µL of oil in 0.5 mL of hexane); injector temperature: 250 °C, temperature program: 60-250 °C with a gradient of 3 °C min $^{-1}$; the temperature of the ion source for other parts was kept at 220 °C. The scan time of the quadrupole was 39 to 500 daltons.s^{-1}. Ionization was carried out in electron impact mode at 70 eV. Identification of the volatile components was based on the linear retention index (RI) and the mass spectral fragmentation pattern, comparing the data with

164 authentic samples from the Adams library [29]. The IRs were obtained using the homologous
165 series of n-alkanes (C_8- C_{40}) from Sigma-Aldrich (San Luis, AZ, USA).

166 *2.7 Preliminary toxicity bioassay with Artemia*

167 For the toxicity tests, the essential oil of *M. sylvatica* obtained by HD and AV was
168 evaluated in relation to the larvae of the microcrustacean *Artemia salina*, as described in the
169 literature [27,30]. The *A.salina* eggs were incubated at room temperature (27-30 °C) in an
170 aquarium containing artificial salt water made up of a mixture of 46 g of NaCl, 22 g of $MgCl_2$
171 $.6H_2O$, 8 g of Na_2SO_4, 2.6 g of $CaCl_2$ $.6H_2O$, 1.4 g of KCl in 2.0 L of distilled water. The pH
172 was adjusted to between 8.0 and 9.0 using Na_2CO_3. 24 hours after the eggs hatched, oil solutions
173 were prepared at concentrations of 100, 50, 25, 10, 5 and 1 µg/mL, using brine water and 5%
174 DMSO as a diluent. In each tube containing the solutions, 10 *A. salina* larvae were added and,
175 after 24 hours, the mortality rate of the larvae was calculated, estimating the average lethal
176 concentration (LC_{50}), using the Probitos statistical method.

177 *2.8 Testing the antioxidant capacity of essential oils*

178 *2.8.1 $ABTS^{\bullet+}$ test*

179 The radical inhibition activity (AIR) of the diammonium salt 2,2'-azino-bis (3-
180 ethylbenzothiazoline-6-sulfonic acid) ($ABTS^{-+}$) was analyzed according to the study by
181 Kuskoski et al., [31], with modifications. Initially, ABTS (7 $mM.L^{-1}$) and potassium persulfate
182 (140 $mM.L^{-1}$) were mixed and left in the dark for 16 hours to form the $ABTS^{\bullet+}$ radical (2.45
183 $mM.L^{-1}$). The radical was then diluted in phosphate-buffered saline until it reached an
184 absorbance of 0.700 ± 0.05 in a Genesys50 spectrophotometer (Thermo Scientific) at 734 nm.
185 Next, 30 µL of samples at concentrations of 4, 8, 12, 16 and 20 mg/mL of the HD and AV oils
186 prepared in ethanol or the positive control (Trolox) at concentrations of 2, 4, 6, 8 and 10 µg/mL
187 were added to 2 mL of the $ABTS^{\bullet+}$ solution. The absorbance was read after 6 minutes of reaction

188 at 743 nm. This procedure was carried out in duplicate and ethanol was used as a negative
189 control. AIR was calculated according to the equation:

190 $$AIR\ (\%) = \frac{(A\ controle - A\ amostra)}{A\ controle \times 100} \quad (2)$$

191 where $A_{control}$ represents the absorbance of the $ABTS^{-+}$ radical ($^{2}.5\ mM.L^{-1)}$, A_{sample} the
192 absorbance of the sample and $A_{control}$ the absorbance of the negative control.

193 *2.8.2 DPPH• test*

194 The AIR of 2,2-diphenyl-1-picrylhydrazyl ($DPPH^{(-)}$) was determined according to the
195 studies by Brand-Williams et al.,[32] , with modifications. Firstly, a solution of DPPH• 60 µM.L
196 $^{-1}$was prepared in ethanol (PA; C_2H_6O; Sigma-Aldrich; 216224; São Paulo/SP, Brazil). The
197 absorbance of the DPPH• solution was then read on a Genesys50 spectrophotometer (Thermo
198 Scientific) at 517 nm. Next, 50 µL of the samples at concentrations of 4, 8, 12, 16 and 20 mg/mL
199 and the positive control (Trolox) at concentrations of 2, 4, 6, 8 and 10 µg/mL were added to
200 1.95 mL of the DPPH• solution and stored away from light for 1 hour. The test was carried out
201 in duplicate and ethanol was used as a negative control. The calculation was carried out
202 according to equation (2).

203 The antioxidant activity data was processed and presented as mean ± standard deviation,
204 inhibitory concentration (IC_{50}) and trolox equivalent antioxidant capacity (TEAC). The
205 IC_{50} values of the samples and trolox were calculated using non-linear regression analysis,
206 respectively. The statistical treatment and graphs were carried out and generated using
207 GraphicPad Prism 10 software. Tukey's statistical test was also carried out where the statistical
208 difference was considered significant when $p < 0.050$.

209 *2.9. Estatistical*

210 Correlations among the chemical compounds were evaluated using Pearson's linear
211 correlation, considering only compounds with a minimum concentration of 0.5 in at least one
212 of the analyzed samples. The aim was to identify patterns of direct or inverse association among

213 the metabolites present in the samples. The correlation matrix was constructed based on the
214 quantitative values of the relative concentrations of the compounds, allowing the identification
215 of groups of substances with similar or antagonistic chemical behavior. Analyses were
216 performed using Minitab® version 22 (free version, Minitab LLC), and the results were
217 presented as a correlogram, in which the intensity and direction of the correlations are
218 represented by a bidirectional color scale.

219 *2.10 Materials and Methods*

220 *2.10.1. Molecular docking procedure*

221 Molecular docking simulations were carried out by the Auto Dock 4.2 program package
222 [33]. The X-ray crystal structure of AChE complexed with « donepezil » was sourced from
223 Protein Data Bank (PDB code: 1EVE) [34]. The water molecules (H_2O) in the protein's
224 structure were removed and the steps were done: add the missing hydrogens in addition to
225 assigning the partial charges (Gasteiger). The AutoDock Tools were used to prepare the ligands
226 and protein files (PDBQT). The optimization of all the geometries of ligands was conducted by
227 using ACD (3D viewer) software (http://www.filefacts.com/acd3d-viewer-freeware-info) and
228 the visualization and analysis of interactions were carried out *via* Discovery Studio 2017R2
229 (https://www.3dsbiovia. com/products/collaborative-science/biovia-discovery-studio/).

230 *2.10.2. ADME Properties*

231 The pharmacokinetic and druglikeness properties of the main phytocompounds were
232 estimated by using ADME (absorption, distribution, metabolism and excretion) descriptors *via*
233 a SwissADME online server (http://www.swissadme.ch/).

234 **3. Results and discussion**

235 *3.1 Anatomical characterization*

236 As a result of the anatomical characterization of *M. sylvatica*, it was observed that, in
237 frontal view, the epidermis on both sides consists of cells with sinuous anticlinal walls (Figures

3-A, B, C, and D). In cross section, it was observed that the mesophyll epidermis is unistratified, consisting of tabular cells, and the margin has the same epidermal characteristics as the mesophyll (Figure 4-A and B). The epidermal cells present in the adaxial part of the central vein of *M. sylvatica* are large and tabular, while in the abaxial phase the cells are rounded and small (Figure 4-C and E).

The epidermis is covered by a thick, smooth cuticle (Figures 4-A, B, C, and F). The stomata are located at the same level as the other epidermal cells and are anomocytic, with a hypoestomatic arrangement (Figures 3-A, B, and 4-A). In addition, the epidermis contains unicellular trichomes with sharp apices (Figures 3 and 4) and unicellular and multicellular glandular trichomes (Figures 4-A and F).

These anatomical structures are characteristic of *Myrcia* DC. species, reflecting their ability to adapt to different environments. For example, the hypostome minimizes water loss from the plant, while the paracytic stomata have subsidiary cells aligned parallel to guard cells, allowing greater control over the opening and closing of stomatal pores and enabling water homeostasis. Another adaptation observed in *M. sylvatica* is the sinuous anticlinal walls that contribute to the flexibility and support of the epidermis [35,36].

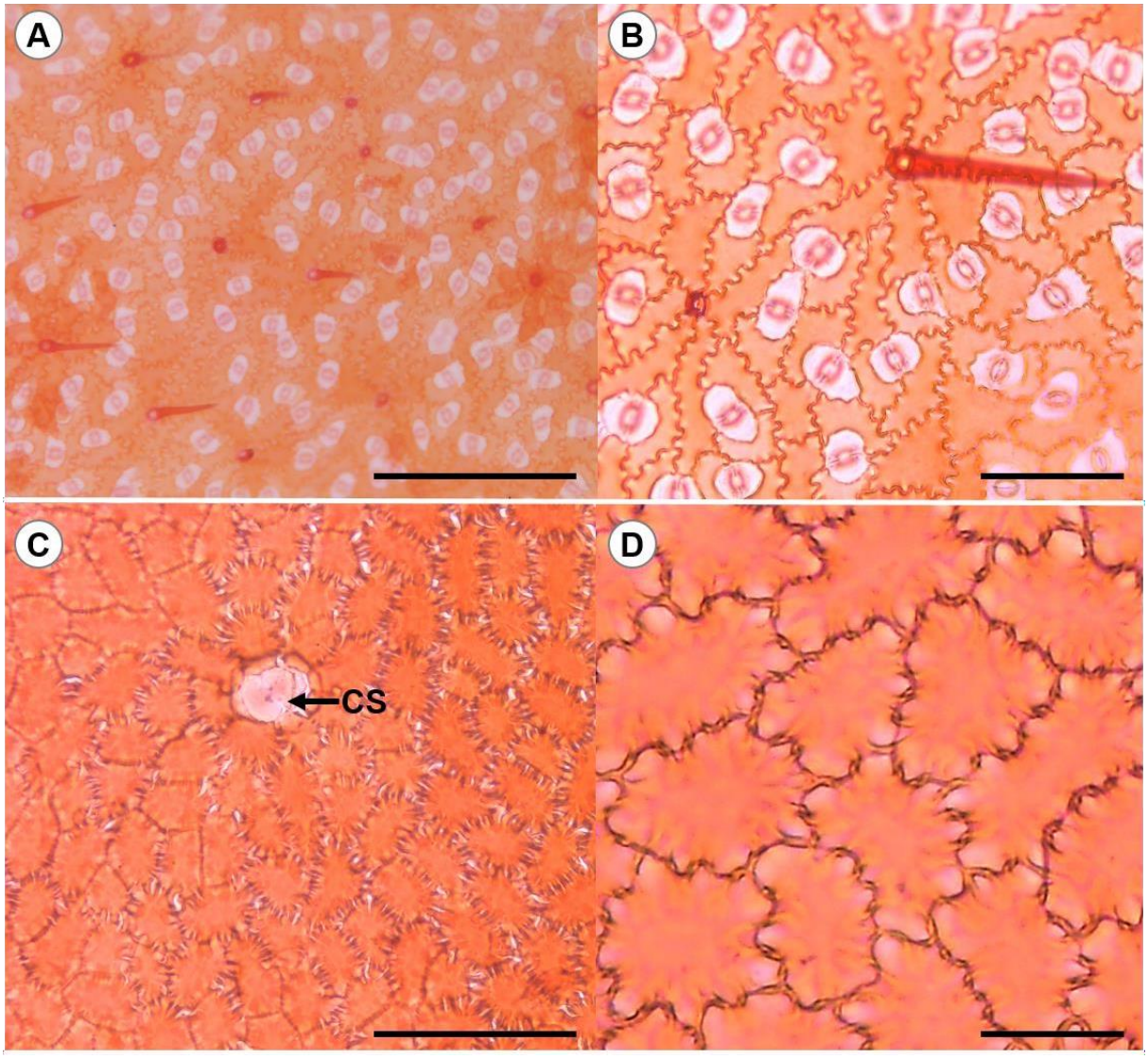


Figure 3 - Front view of the leaf of *Myrcia sylvatica* (G. Mey) DC. **(A-E)**. **(A)** General view of the abaxial surface. **(B)** Paracytic stomata on the abaxial surface. (C) General view of the adaxial surface with secretory cavity (arrow). **(D)** Adaxial surface with detail of cells with sinuous anticlinal walls. Scale bar: 100 µm **(B, D)**, 200 µm **(A, C)**.

The mesophyll of *M. sylvatica* is dorsiventral, presenting palisade parenchyma with two layers of cells and lacunar parenchyma with 5 to 6 layers of cells. In addition, secretory idioblasts, prismatic crystals, and secretory cavities are found in the lacunar parenchyma (Figure 4-A). The secretory cavities were located in the palisade and lacunar parenchyma and consisted of a single-layered secretory epithelium of thin-walled tabular cells delimiting the lumen (Figure 4-A). These characteristic anatomical structures are associated with the

311 production, storage, and secretion of bioactive compounds and are found in some species of the
312 genus *Myrcia* [35,36]. This dorsiventral organization of the mesophyll aids in the absorption
313 of light and the circulation of oxygen and carbon dioxide, which are essential for maximizing
314 the efficiency of photosynthesis in high-light environments. This characteristic aids in the
315 classification and taxonomic identification within the Myrtaceae family [36,38].

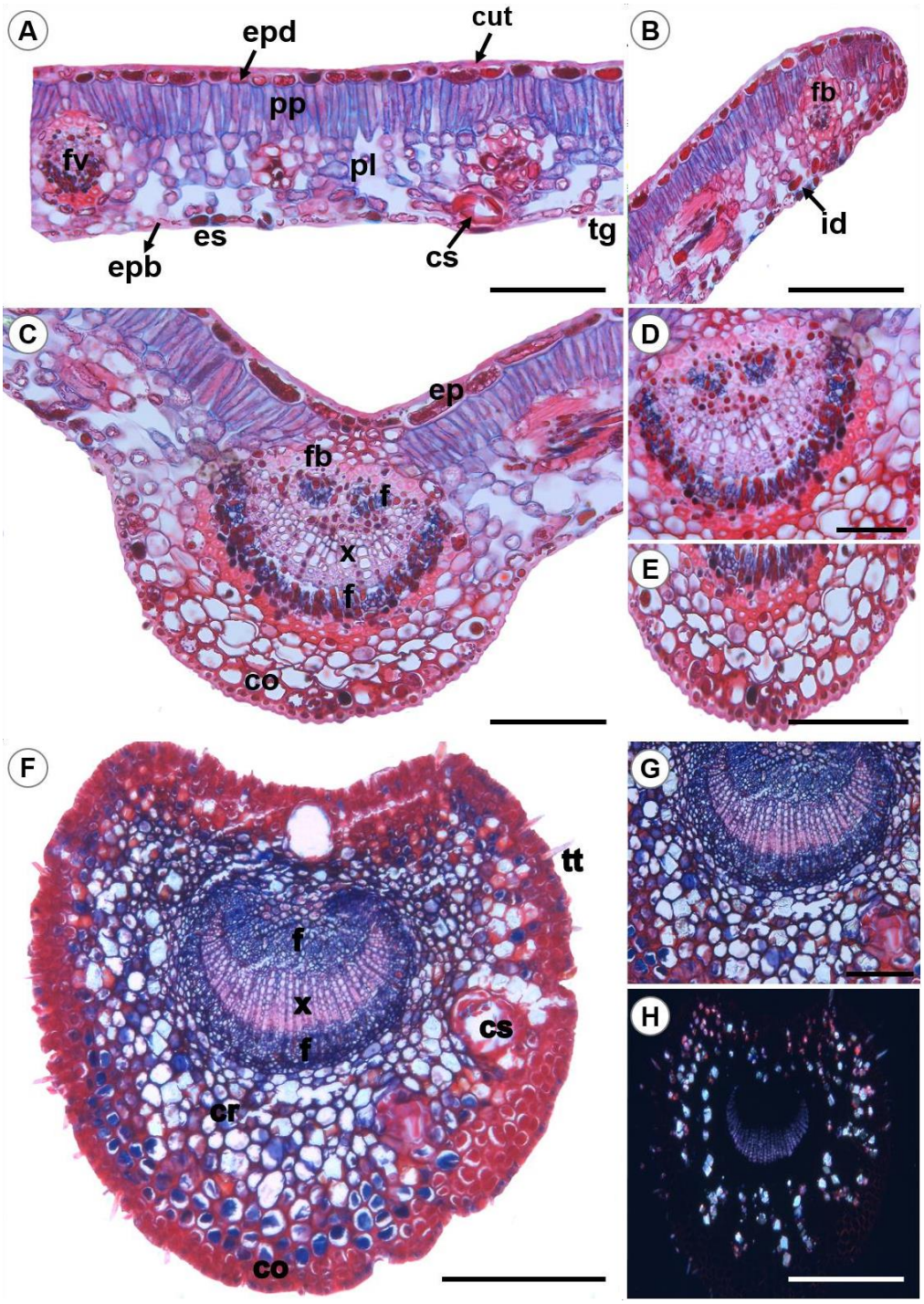
316 The margin has a structure similar to the midrib, but the mesophyll region has rounded
317 cells with the same characteristics as the mesophyll. However, the cells of the palisade and
318 spongy parenchyma are more compact (Figure 4-B). In the lacunar parenchyma, there are
319 collateral vascular bundles surrounded by sclerenchymatic fibers. These fibers help filter light
320 in the inner layers of the mesophyll during photosynthesis [39].

321 The midrib has a flat convex shape (Figure 4-C). The flat convex shape of the midrib of
322 *M. sylvatica* is a characteristic that can vary among species of the genus, and this variation
323 reflects the morphological diversity of *Myrcia*, reinforcing the phenotypic plasticity and
324 adaptive capacity of the genus [43,44].

325 The cortex of the rib is formed by 1-2 layers of angular collenchyma (Figure 4-C and
326 E). The parenchymatic tissue is formed by polygonal cells with spaced walls and intracellular
327 spaces containing numerous secretory idioblasts. The vascular system is organized into a
328 bicolateral vascular bundle surrounded by a sheath of sclerenchymatic fibers (Figure 4-D). The
329 vascular system, organized into a bicolateral bundle, is a characteristic commonly found in the
330 genus *Myrcia* [43,44].

331 The petiole in cross section is flat and convex with a single-layered epidermis consisting
332 of rectangular cells with glandular trichomes and tectorial trichomes. It is also covered by a
333 smooth, spaced cuticle (Figure 4-F). In the cortex, there are 2-3 layers of lamellar collenchyma,
334 and the parenchymatic tissue is formed by polygonal, heterodimeric cells with thick walls
335 (Figure 4-F). In the parenchymatic tissue, there are secretoid idioblasts, secretory cavities, and

prismatic crystals (Figures 4-F, G, and H). The vascular bundle is bicolateral (Figure 4-F, G, and H). The petiole and midrib of the species under study differ from other species of the genus in terms of the shape and organization of the vascular system [35,44,45].



356

357 **Figure 4.** Transverse section of the leaf of *Myrcia sylvatica* (G.Mey) DC. (**A**) General view of
358 the mesophyll, (**B**) Margin, (**C**) General view of the central vein. (**D**) Detail of the vascular
359 bundle. (**E**) Detail of the epidermis and collenchyma. (**F**) General view of the petiole. (**G**) Detail
360 of the vascular bundle. (**H**) General view of the petiole under polarized light. Legend: co-
361 colenchyma, **cut** - cuticle, cr - crystals, **cs** - secretory cavity, **epd** - adaxial epidermis, **epb** -
362 abaxial epidermis, ep - epidermis, **es** - stomata, **fv** - vascular bundle, **fb** - sclerenchymatous
363 fiber, **f-** phloem, **id-** secretory idioblast, **tt** - tectores trichome, tg - glandular trichome. Scale
364 bar: 50µm (**D, G**), 100µm (**A, B, C, E, H**), 200µm (**F**).

365 **3.2 Histochemistry**

Histochemical tests performed on *M. sylvatica* leaves reacted to different metabolic classes, testing positive in idioblasts, secretory cavities, secretory epidermis, and glandular trichomes. These structures store and secrete bioactive metabolites, which perform functions related to growth, protection, and defense against pathogens and herbivores. [35,46,47].

The histochemistry results are shown in Table 1, and the reactions are shown in Figures 5 and 6.

Table 1- Results of the histochemical tests on the leaf lamina and petiole of *Myrcia sylvatica* (G.Mey) DC.

		Structures				
Reagent	Metabolites	Idioblast	Secretory cavities	Secretory epidermis	Secretory trichomes	Other structures
Sudan Black	Total lipids	+	+	+	+	-
Nile blue sulphate	Acid lipids	+	+	+	+	-
Nadi's reagent	Terpenes	+	+	+	+	-
SFF (iron sulphate in formalin)	Phenolic compounds	+	+	+	+	-
Hydrochloric vanillin	Tannin	+	-	-	-	-
Floroglucinol	Lignin	-	-	-	-	+
Ruthenium red	Acid mucilage	+	+	+	+	-
PAS (Periodic Acid Schiff's reagent)	Total polysaccharides	+	+	+	+	-
Lugol's reagent	Starch	-	-	-	-	+
Wagner	Alkaloid	+	+	+	+	-
Hydrochloric acid 5%	Crystals of Calcium oxalate	+	-	-	-	-

(+) positive reaction, (-) negative reaction.

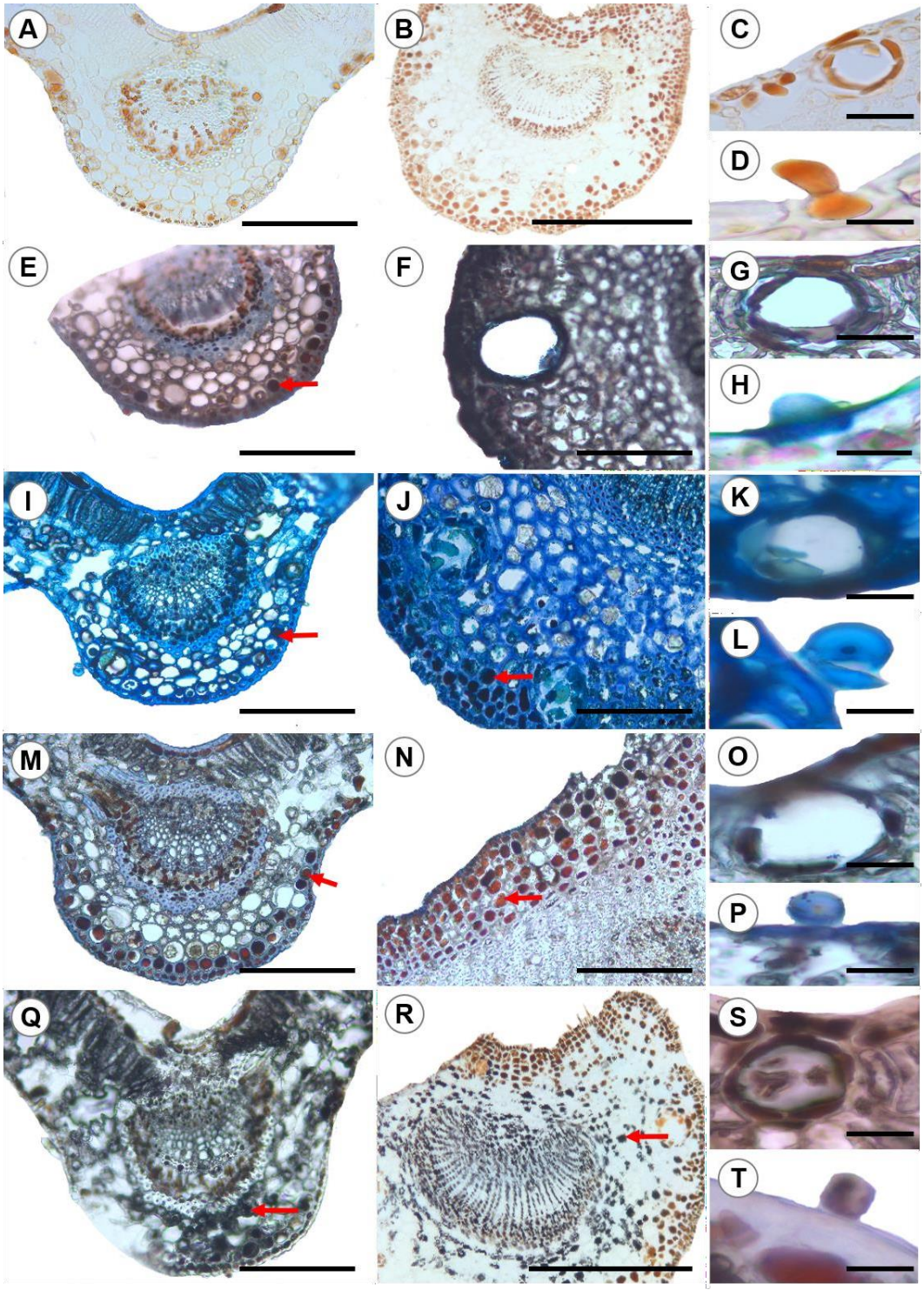


Figure 5 - Histochemical tests applied to the leaf of *Myrcia sylvatica* (G.Mey) DC. **(A)** Blank midrib – secretory epidermis and idioblast. **(B)** Petiole in white – secretory epidermis and idioblast. **(C)** Secretory cavity in white. **(D)** Trichome in white. **(E, F, G, H)** Positive reaction for total lipids. **(I, J, K, L)** Positive reaction for fatty acids**. (M, N)** Positive reaction for terpenes showing resin oil. **(O, P)** Positive reaction for terpenes showing essential oil. **(Q, R, S, T)** Positive reaction for phenolic compounds. Arrow indicating the reaction in secretory idioblasts. Scale bar: 50µm **(C, D, G, H, K, L, O, P, S, T)** 100µm **(A, E, I, M, Q)** 200µm **(B, F, J, N, R).**

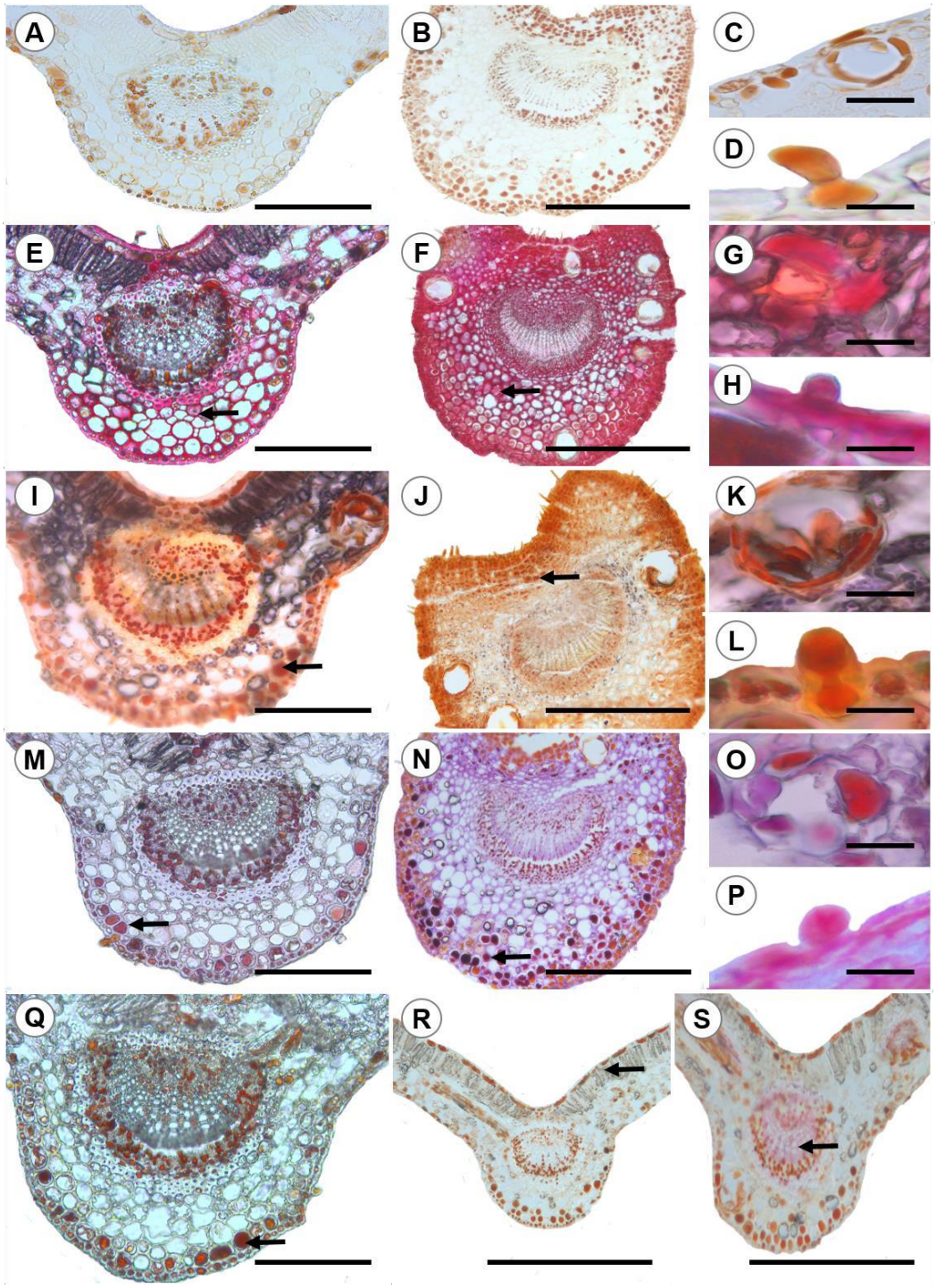


Figure 6 - Histochemical tests applied to the leaf of *Myrcia sylvatica* (G.Mey) DC. **(A)** Central vein in white – secretory epidermis and idioblast. **(B)** Petiole in white – secretory epidermis and idioblast. **(C)** Secretory cavity in white, **(D)** Trichome in white. **(E, F, G, H)** Positive reaction to acid mucilage. **(I, J, K, L)** Positive reaction to alkaloids. **(M, N, O, P)** Positive reaction to total polysaccharides. **(Q)** Positive reaction to tannin. **(R)** Positive reaction to starch. **(S)** Positive reaction to lignin. Arrow indicating reaction in idioblasts. Scale bar: 50µm **(C, D, G, H, K, L, O, P)**, 100µm **(A, E, I, M, Q)**, 200µm **(B, R, J, N, R, S)**.

393 The positive reaction of total lipids, acid lipids, terpenes, and phenolic compounds in
394 specialized structures such as idioblasts, secretory cavities, secretory epidermis, and glandular
395 trichomes. The identification of the secretory epidermis in *M. sylvatica* is heterogeneous, which
396 is an unprecedented characteristic for the genus *Myrcia*. The positive reaction of these bioactive
397 compounds in these specialized structures indicates that these compounds play important roles
398 in defense and metabolism regulation, contributing to the growth and development of *M.*
399 *sylvatica* [5,40–42,45,48].

400 Lipophilic compounds such as total lipids, acid lipids and terpenes are metabolites found
401 in species of the Myrtaceae family [40,41,45]. These compounds play important roles,
402 especially in defense against biotic and abiotic factors[42]. Species of the *Myrcia* genus are
403 known for producing volatile compounds in their secondary metabolism, such as essential oil,
404 which has terpenes as its main constituents. Terpenes play an important role in the ecosystem,
405 as they act in defense against herbivores and pathogens, and also have antimicrobial,
406 phytotoxic, antioxidant and hypoglycemic activities, among others.[5,49] .

407 Histochemical tests also demonstrated the presence of phenolic compounds in the
408 idioblasts, secretory cavities, secretory epidermis, and glandular trichomes of M. sylvatica. The
409 presence of phenolic compounds indicates the therapeutic potential of this species, especially
410 in the prevention of diseases related to oxidative stress [7,49,50]. This data corresponds with
411 the metabolic profile of other species of the *Myrcia* genus, which is known for the presence of
412 phenolic compounds [5,49].

413 The tests qualitatively show that *M. sylvatica* presented acid mucilage, alkaloids, and
414 total polysaccharides in the idioblasts, secretory cavities, secretory epidermis, and glandular
415 trichomes. Acid mucilage aids in water retention and protection against environmental stresses
416 [51] . Alkaloids are important for protection against herbivores and are known for their
417 antimicrobial and anticancer properties [52,53] . Total polysaccharides have

418 immunomodulatory properties, i.e. they are able to regulate the immune system's response [54]
419 , and have anti-inflammatory potential [55].

420 The positive result for hydrochloric vanillin indicated the presence of tannins in the
421 idioblasts of *M. sylvatica*. Souza-Moreira et al.,[56] observed that the polar extracts of *Plinia*.
422 *cauliflora* (Myrtaceae), rich in tannins, showed activity against Candida species. This
423 corroborates the literature reports on the antifungal potential of species from the Myrtaceae
424 family [57–59] . Idioblasts have also been shown to contain calcium oxalate crystals, which are
425 commonly found in the leaves of species from the Myrtaceae family, such as *Eucalyptus saligna*
426 Sm. [60], *Myrcia hatschbachii* D. Legrand [35], *Myrcia multiflora* (Lam.) DC. [44], *Plinia*
427 *cauliflora* (DC.) Kausel .[56].

428 Although *M. sylvatica* has several secretory structures, starch and lignin were detected
429 in the xylem and palisade parenchyma. Lignin and starch are two essential substances for plant
430 physiology and development, providing functions such as maintaining cell structure, defense
431 against pathogens and energy reserves [61,62] .

432 *3.3 Chemical composition of the essential oil*

433 In total, 57 constituents were identified in HD and 84 were identified in steam
434 distillation, both quantified by gas chromatography coupled with mass spectrometry (GC/MS),
435 as shown in Table 2. The yield of essential oil from the dried leaves of *M. sylvatica* obtained
436 by steam distillation was 0.24%, while by hydrodistillation it was 0.41%. The difference in the
437 yields of the essential oils may be related to the extraction technique used. Studies on other
438 species have shown that both hydrodistillation (HD) and steam distillation (SD) influence the
439 yield of essential oil [63,64].

440 **Table 2 -** Chemical composition of the essential oils of *Myrcia sylvatica* (G.Mey) DC extracted by
441 steam distillation and hydrodistillation.

		Extraction method	**Steam distillation**	**Hydrodistillation**
		Yield	**0.24%**	**0.41%**
IR_L	**IR_C**	**Chemical component**		

844[a]	842	Hex-(3*E*)-enol		0.08
853[a]	850	Hex-(3*Z*)-enol		034
864[a]	851	Hex-(2E)-enol	1.55	
866[a]	863	Hex-(2*Z*)-enol		0.09
941[a]	944	2-Acetoxyhexane		0.07
988[a]	988	Mircene		0.03
1187[b]	1183	Hex-(3Z)-enyl butyrate		0.01
1195[b]	1193	α-Terpineol		0.02
1335[a]	1331	δ-Elemene	1.71	1.24
1345[a]	1345	α-Cubebene	0.52	0.28
1371[a]	1367	Cycloactive	0.21	0.19
1374[a]	1373	α-Copaene	0.95	0.55
1378[b]	1378	(3*Z*)-Hexenyl hexenoate	0.11	
1382[a]	1381	β-Bourbonene	0.36	0.33
1389[a]	1388	β-Elemene	2.33	1.95
1405[a]	1401	Sesquithujene		0.02
1406[b]	1404	α-Gurjunene	0.17	0.15
1416[a]	1412	α-(*Z*)-Bergamotene	0.06	0.06
1424[b]	1420	(*E*)-Caryophyllene	7.24	4.89
1430[b]	1424	γ-Maaliene		0.09
1432[a]	1428	γ-Elemene	2.43	2.66
1432[a]	1431	α-(*E*)-Bergamotene	0.7	0.45
1439[a]	1437	Aromadendrene	1.08	0.92
1442[a]	1439	6,9-Guaiadiene	0.72	0.23
1447[a]	1443	Isogermacrene D		0.28
1451[a]	1447	(*Z*)-Muurola-3,5-diene	0.56	0.5
1454[a]	1450	(*E*)-β-Farnesene	0.55	
1454[b]	1454	α-Humulene	0.87	1.22
1458[a]	1458	*allo*-Aromadendrene	1.4	1.09
1475[a]	1469	γ-Gurjunene	0.86	
1478[b]	1475	γ-Muurolene	1.83	2.34
1480[a]	1481	Germacrene D	10.72	5.52
1483[b]	1484	β-(*E*)-Bergamotene		0.21
1492[b]	1490	β-Selinene	3.16	3.92
1496[a]	1492	Viridiflorene	3.04	2.05
1496[b]	1497	α-Zingiberene	14.27	9.14
1500[a]	1498	α-Muurolene	2.66	
1506[a]	1503	δ-Amorphene	1.26	0.81

1508[b]	1507	β-Bisabolene	0.78	0.49
1512[a]	1513	γ-Cadinene	1.55	1.25
1518[a]	1519	δ-Cadinene	4.25	3.81
1521[a]	1520	(E)-Calamenene	0.57	
1523[a]	1524	β-Sesquifelandrene	2.7	2.41
1529[a]	1526	(*E*)-γ-Bisabolene	0.57	0.35
1536[b]	1531	(*E*)-Cadine-1,4-diene	0.43	0.45
1538[a]	1535	α-Cadinene	0.43	0.43
1544[a]	1540	α-Calacorene	0.56	0.67
1557[b]	1557	Germacrene B	0.92	0.87
1558[a]	1560	epi-Longipinanol	0.37	0.56
1561[a]	1563	(E)-Nerolidol		0.11
1567[a]	1569	Palustrol	0.7	1.61
1577[a]	1580	Spathulenol	7.56	7.58
1582[a]	1582	Caryophyllene oxide	0.51	0.52
1590[a]	1588	Globulol	2.72	5.74
1594[a]	1596	Viridiflorol	1.34	2.95
1595[a]	1598	Cubeban-11-ol	1.07	1.75
1602[a]	1604	Ledol	0.26	0.66
1609[b]	1607	Rosifoliol	0.84	1.52
1618[a]	1614	1,10-di-epi-Cubenol		0.3
1619[b]	1622	Junenol	0.91	1.11
1627[b]	1624	Eremoligenol	0.93	1.48
1627[a]	1627	1-epi-Cubenol	1.03	1.77
1632[b]	1633	Muurola-4,10(14)-dien-1-β-ol	0.72	1.3
1639[a]	1637	aromadendrene *allo-epoxide*		0.14
1640[b]	1642	*epi*-α-Cadinol	0.95	1.68
1640[a]	1644	*epi*-α-Muurolol	1	2.4
1644[a]	1648	α-Muurolol	0.64	0.98
1650[b]	1650	Himachalol	0.11	0.31
1652[a]	1659	α-Cadinol	1.83	5.2
1658[a]	1662	Selin-11-en-4-α-ol	1.1	1.28
1658[b]	1666	neo-Intermedeol		0.1
1664[b]	1670	Allohimachalol	0.06	0.86
1671[a]	1677	14-hydroxy-9-*epi*-(*E*)-caryophyllene		0.26
1679[a]	1685	*epi*-α-Bisabolol		0.33
1685[a]	1686	α-Bisabolol		0.15
1685[b]	1689	Germacra-4(15),5,10(14)-trien-1-α-ol		0.19

1698[a]	1693	(2Z,6Z)-Farnesol		0.27
1700[a]	1697	Eudesm-7(11)-en-4-ol		0.47
1713[a]	1713	(2*E*,6Z)-Farnesal		0.02
1714[a]	1716	Nootkatol		0.13
1730[b]	1722	γ-Costol		0.12
1730[a]	1727	Vetiselinenol		0.05
1733[a]	1729	Isobicyclogermacrenal		0.07
1740[a]	1735	Mint sulphide		0.08
1751[b]	1741	Xanthorrizol		0.1
1752[b]	1754	7,14-Anidro-Amorfo-4,9-dieno		0.12
1767[a]	1762	13-Hydroxyvalencene		0.17
1769[b]	1766	Drimenol		0.22
1779[a]	1770	14-hydroxy-α-muurolene		0.16
1793[a]	1790	(*E*)-Isovalencenol		0.1
		Monoterpene hydrocarbons		0.03
		Oxygenated monoterpenes		0.02
		Sesquiterpene hydrocarbons	72.54	52.16
		Oxygenated sesquiterpenes	24.28	44.12
		Others	1.91	1.05
		Total	98.73	97.38

IRL, retention index of a = Adams library [29]; b = FFNCS library [65]. IRC, retention index calculated from a homologous series of n-alkanes (C8- C40) on a DB5-MS column.

Figure 7 shows the two-dimensional structures of the constituents with the highest concentration identified in the essential oils of *M. sylvatica* from the SD and HD extraction techniques. With regard to the chemical profile of *M. sylvatica*, the essential oil obtained by VA was characterized as consisting mainly of sesquiterpene hydrocarbons (72.42%) and oxygenated sesquiterpenes (24.65%), while the essential oil obtained by HD also showed a predominance of sesquiterpene hydrocarbons (51.82%) and oxygenated sesquiterpenes (45.02%).

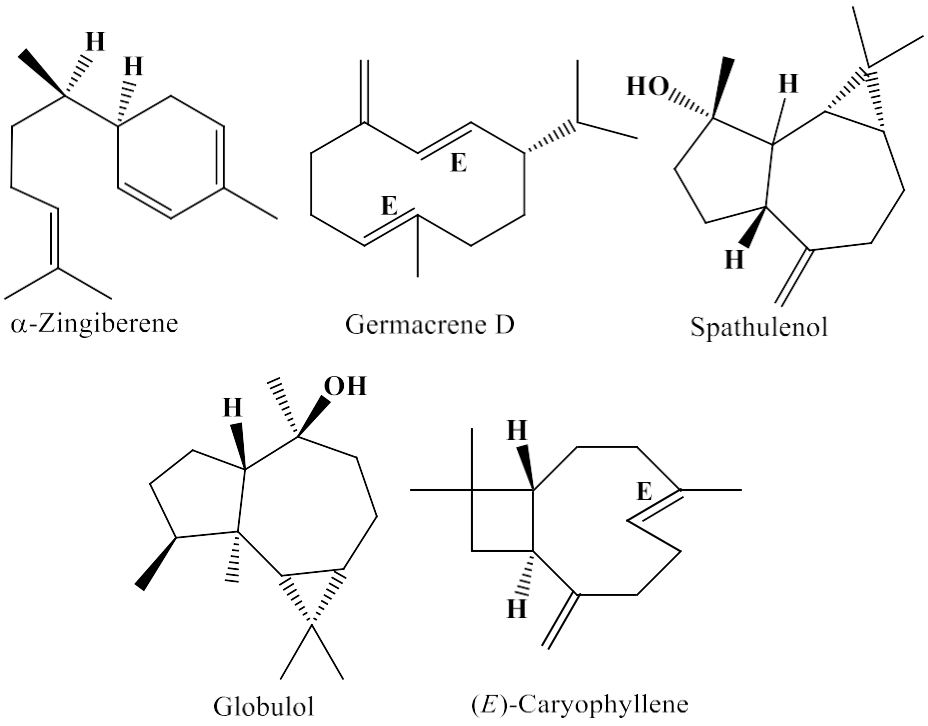


Figure 7 - Two-dimensional chemical structure of the main constituents identified in the essential oil of *M. sylvatica*.

The α-zingiberene was identified at a concentration of 14.27% in the essential oil obtained by steam distillation, and 9.14% in the essential oil obtained by hydrodistillation, and the same compound was identified in the essential oil of other specimens of *M. sylvatica*, albeit in lower concentrations. In the studies by Silva *et al* [66] , α-zingiberene had a concentration of 0.2%, while in the studies by Sacool *et al* [67] α-zingiberene had a concentration of 0.41%. The variation in the concentration of α-zingiberene shows the chemical variation of the species, which is caused by the influence of environmental and genetic factors.

In the studies by Costa et al., [6], the chemical characterization of the essential oil of seven specimens of *M. sylvatica* was carried out, showing a chemical variability in the essential oil of the species, which was evidenced by the presence of four chemical profiles. These findings show that seasonality, collection site, genetics and plant part can contribute to variations in the chemical profile of *M. sylvatica*.

Essential oils containing high concentrations of α-zingiberene may have the potential to inhibit the production of aflatoxins and other fungal mycotoxins. Nerilo *et al* [68] evaluated the efficacy of the essential oil of ginger (*Zingiber officinales* Roscoe), rich in α-zingiberene with a concentration of 23.85%, the study showed that the mycelial growth of *Aspergillus flavus* reduced at a concentration of 150 $\mu g.mL^{-1}$ of essential oil, and inhibition of the germination of conidia was shown at a concentration of 10 $\mu g.mL^{-1}$. In addition, ergosterol biosynthesis was inhibited at a concentration of 10 $\mu g.mL^{-1}$, and 15 $\mu g.mL^{-1}$ of essential oil was able to inhibit aflatoxin production by *A. flavus*.

Vasconcelos et al [69] analyzed the chemical composition of the essential oil of *M. vittoriana*, with Germacrene D (21, 90%) being the main constituent. According to the authors, the essential oil caused a reduction in the germination rate of *Allium cepa* at concentrations of 187.5, 1500 and 3000 $\mu g.mL^{-1}$. At the highest concentration tested, there was a 61.6% increase in germination inhibition.

(*E*)-caryophyllene is a hydrocarbon sesquiterpene. In the steam distillation extraction technique, it had a concentration of 7.22%, and in hydrodistillation its concentration was 4.88%. The difference in concentration suggests that steam distillation favors the retention of this compound, minimizing the thermal degradation of volatile compounds [27,70] Furthermore, in a previous study, (*E*)-caryophyllene was characterized as the majority compound in the essential oil of *M.* sylvatica leaves [10]

Spatulenol, an oxygenated sesqueterpene, showed significant concentrations in both extraction techniques, with 8.07% in steam distillation and 7.57% in hydrodistillation. The small variation in concentrations suggests that spatulenol maintains its properties and concentrations in a similar way in steam distillation and hydrodistillation [27,70].

Globulol, an oxygenated sesquiterpene, showed a concentration of 5.74% in hydrodistillation compared to 2.72% in steam distillation. This result shows that the extraction

493 method influences the chemical composition of the essential oil [71] , as each extraction
494 technique can favor or reduce the concentration of the constituents depending on their volatility
495 and solubility.

496 *3.3.1. Statistical analysis*

497 The correlation matrix reveals highly organized structural patterns of interdependence
498 among the analyzed chemical compounds, uncovering relationships that go beyond simple
499 linear associations (Figure 8). Two major variable clusters are observed, displaying strong
500 positive correlations within each group and negative correlations between distinct groups.
501 Compounds such as α-Cubenene, δ-Bemene, β-Bisabolene, α-Cadinene, γ-Muurolene, and
502 Germacrene-D form a tightly intercorrelated set, with correlation coefficients close to 1 among
503 themselves. This systematic co-occurrence suggests that these compounds likely share common
504 biosynthetic pathways or are products of the same enzymatic lineage. The high correlation
505 between α-Cubenene and δ-Bemene, for instance, may reflect a metabolic origin from a shared
506 precursor, such as farnesyl pyrophosphate (FPP), via the mevalonate pathway, which often
507 yields cyclic sesquiterpenes.

508 On the other hand, compounds like Caryophyllene, Spathulenol, Palustrol, Globulol,
509 epi-α-Cadinol, Selina-6-en-4-ol, and α-Muurolol exhibit similarly high positive correlations
510 among themselves, forming a distinct, metabolically related group. The simultaneous presence
511 of Palustrol and Spathulenol, with their strong correlation, suggests either sequential
512 biosynthetic conversion or shared intermediate byproducts in oxidative processes of alcoholic
513 sesquiterpenes. Even more intriguing is the fact that these two major groups are negatively
514 correlated with each other. For example, Caryophyllene shows a negative correlation of −1 with
515 α-Cubenene and δ-Bemene, indicating not only distinct metabolic pathways but also a form of
516 metabolic exclusivity or biochemical antagonism between the biosynthetic routes responsible
517 for their production. This could imply that the production of compounds like Caryophyllene

518 occurs at the expense of Cubenene biosynthesis, possibly due to direct competition for limiting
519 precursors or opposing regulation of key enzymes.

520 Furthermore, the negative correlation between β-Bisabolene and Globulol indicates that
521 these compounds are not only formed independently but that the presence of one is
522 systematically associated with the absence of the other. This exclusivity may reflect ecological
523 or adaptive factors, such as chemical specializations driven by different environmental selective
524 pressures (e.g., defense against herbivores, pollinator attraction, etc.). Compounds like epi-
525 Cubenol and epi-α-Muurolol, which are also highly correlated with each other, show marked
526 negative correlations with δ-Cadinene and Caryophyllene oxide, suggesting that beyond the
527 differentiation between major groups, there are even more specific subdivisions within
528 biosynthetic trajectories.

529 Overall, the structure of the matrix reveals that the analyzed chemical system is highly
530 compartmentalized, with strongly structured relationships between compounds. The
531 polarization in correlations (extreme values with no intermediates) suggests a tightly regulated
532 biochemical system in which groups of compounds are synthesized in a coordinated and
533 mutually exclusive manner. This organization not only reflects metabolic compartmentalization
534 but may also indicate functional modularity, with significant implications for chemical ecology,
535 chemotaxonomy (chemotyping), and potential biotechnological applications. Understanding
536 this chemical architecture, based on the observed correlations, provides a solid foundation for
537 future investigations into metabolic regulation, functional diversity, and the biosynthetic origin
538 of the compounds in question.

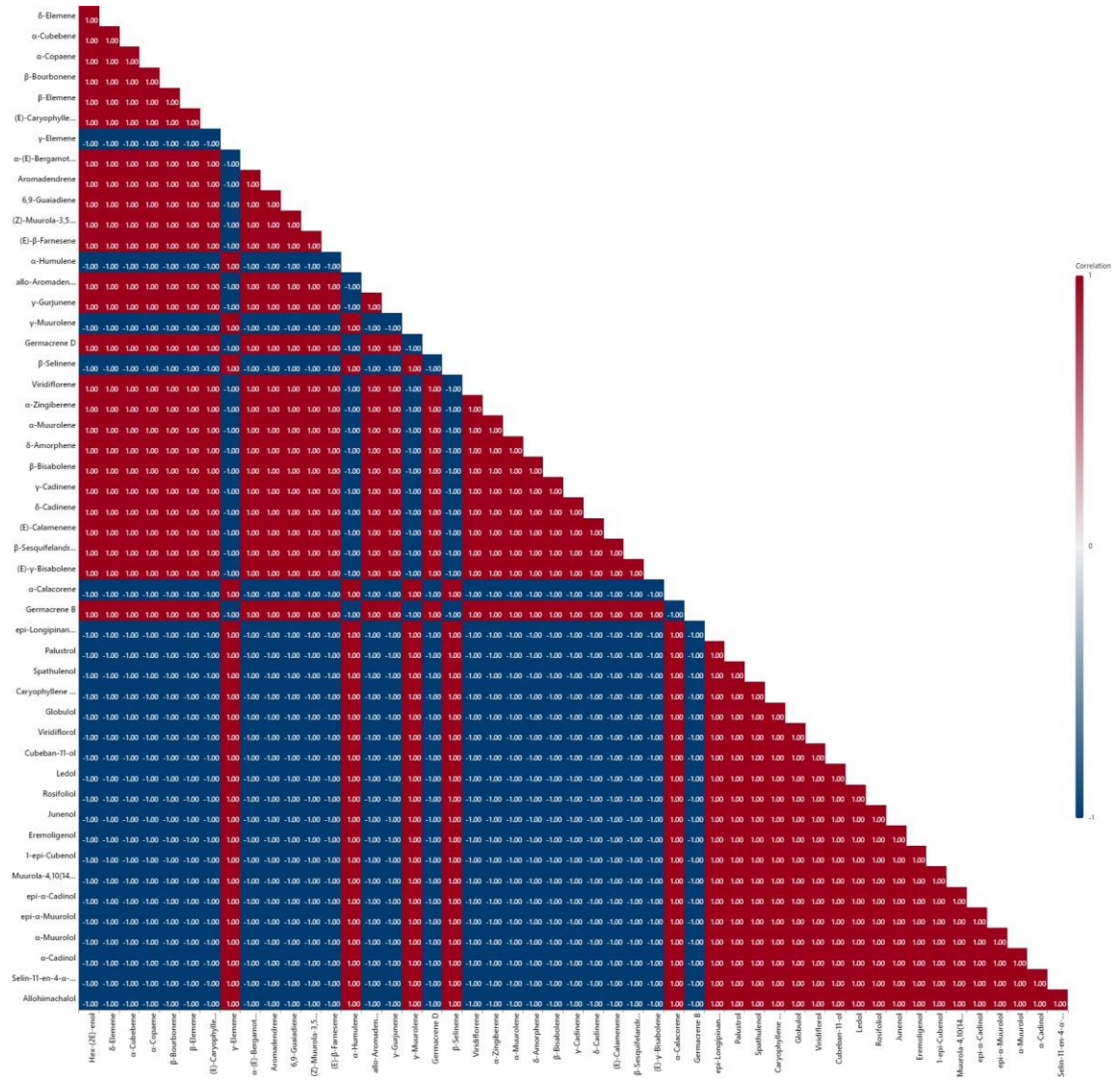


Figure 8. Correlogram of the correlation matrix between the identified chemical compounds. The color represents the strength and direction of the Pearson correlation between pairs of compounds, with shades of red indicating positive correlations and shades of blue indicating negative correlations. Values equal to 1 indicate maximum positive correlation, while values equal to -1 indicate maximum negative correlation. The formation of distinct blocks of compounds with high correlation within the groups and negative correlation between different groups is observed, indicating possible coordinated biosynthetic relationships and metabolic exclusivity between chemical sets.

3.4 Preliminary toxicity

In the control test there was no mortality, showing that the use of DMSO is viable as a solvent for the test. The LC_{50} values were obtained by converting the *A. salina* mortality rates into probit units, allowing the regression curve to be drawn as a function of the oil concentrations expressed on a logarithmic scale. Table 3 shows the mortality results and the LC_{50} concentrations.

Table 3. Preliminary toxicity of *Myrcia sylvatica* (G.Mey) DC. essential oil to *Artemia salina*.

Essential Oil	Concentration (µg.mL^{-1})	Mortality (%)	$LC_{(50)}$ (µg.mL^{-1})
HD	100	100	5.83 ± 0.31
	50	100	
	25	90	
	10	46.67	
	5	33.33	
	1	13.33	
SD	100	100	4.17± 1.16
	50	100	
	25	96,67	
	10	70	
	5	43.33	
	1	10	

Values are expressed as mean and standard deviation (n = 3) of preliminary toxicity.

The essential oils of *M. sylvatica* leaves extracted by hydrodistillation and steam distillation showed LC_{50} of 5.83 µg.mL^{-1}, and 4.17 µg.mL^{-1}, respectively. The oils were toxic to *A. salina*. According to Nguta et al. [72] products that show activity < 100 µg.mL^{-1} have high toxicity compared to products that are > 1000 µg.mL^{-1} which are considered to have low toxicity.

The toxicity of the essential oils of *M. sylvatica* on *A salina* may be related to the place of collection and, consequently, to the chemical composition of the essential oils, for example, essential oils of *M. sylvatica* collected in the municipality of Bujaru in the state of Pará by Moraes et al, [12] rich in (*Z*)-α-trans-bergamotene (24.57%), α-sinensal (13.44%) and (*Z*)-α-bisabolene (8.33%) showed greater toxicity with a LC_{50} of 2.74 µg.mL^{-1} than the essential oil collected by Rosa et al., [10] in Carolina, Maranhão, in Carolina, Maranhão, which showed a

lower toxicity LC_{50} of 79.44 µg.mL^{-1}, being an oil rich in (*E*)-caryophyllene (45.88%) and 14-hydroxy-(*Z*)-caryophyllene (10.15%).

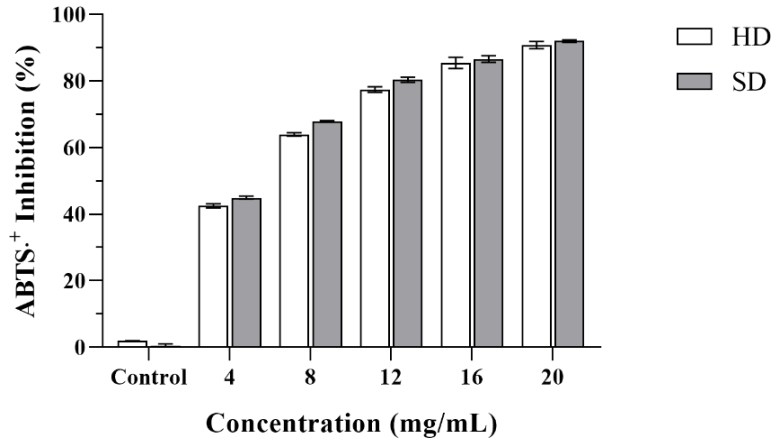
This activity may also be related to the presence of the compounds (*E*)-caryophyllene and spatulenol, which show toxic activity in *A. salina*[73]. Germacrene D also shows toxic bioactivity [74]. As well as α-Zingiberene, which has the ability to interact with biological systems, causing adverse effects [75,76]. According to the literature, essential oils rich in sesquiterpenes have toxicological potential in *A. salina* [77,78].

3.5 Antioxidant capacity

Table 4 shows the antioxidant activity of the essential oils. In the $ABTS^{\bullet+}$ radical scavenging test, the essential oil extracted by HD showed an IC_{50} of 8.36 ± 0.50 mg/mL and a Trolox Equivalent Antioxidant Capacity (TEAC) of 834.63± 56.85 µg TE/g of essential oil (EO). The essential oil extracted by SD had an IC_{50} of 6.80± 0.08 mg/mL and a TEAC of 1026.77 ± 2.96 µg TE/g OE. In the test against $DPPH^{\bullet}$ radicals, the essential oil extracted by HD showed a CI_{50} of 24.62 ± 1.58 mg/mL and the TEAC value was 116.98 ± 7.47 µg TE/g OE, while the essential oil extracted by SD showed a CI_{50} of 12.80± 0.19 mg/mL and TEAC 225.00± 3.25 µg TE/g OE. These results are illustrated in Figures 9 and 10, which show the percentage of radical inhibition as a function of the essential oil concentrations. There was no significant difference in the percentage of free radical inhibition by the essential oils obtained from HD and SD at the concentrations tested.

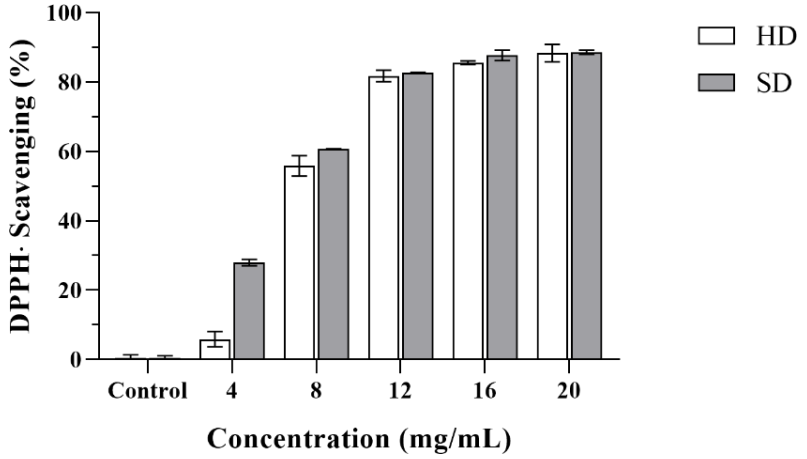
Table 4. Antioxidant activity of *Myrcia sylvatica* (G.Mey) DC. essential oil.

Essential oil	IC_{50} (mg/mL)		TEAC (µg TE/g OE)	
	ABTS	DPPH	ABTS	DPPH
HD	8.36 ± 0.50	24.62 ± 1.58	834.63± 56.85	116.98 ± 7.47
SD	6.80 ± 0.08	12.80 ± 0.19	1026.77± 2.96	225.00± 3.25



587

588 **Figure 9.** Antioxidant activity of the essential oil of *Myrcia sylvatica* (G.Mey) DC., obtained
589 by hydrodistillation (HD), assessed by the ABTS$^{\bullet+}$ assay, expressed as mean and standard
590 deviation (n=2).



591

592 **Figure 10.** Antioxidant activity of *Myrcia sylvatica* (G.Mey) DC. essential oil, obtained by
593 steam distillation (SD), assessed by the DPPH$^{\bullet}$ assay, expressed as mean and standard deviation
594 (n=2).

595

596 The antioxidant activity displayed by the essential oils can be attributed to their
597 constituents. In particular, the oil obtained by SD, characterized by a high percentage of
598 sesquiterpene hydrocarbons (72.42%) and oxygenated sesquiterpenes (25.65%), was more
599 efficient in inhibiting both types of radical. These results can be attributed mainly to the
600 oxygenated compounds present in the oil, which generally have greater antioxidant activity than
601 hydrocarbons of the same class [79]. Although isolated sesquiterpene hydrocarbons such as

602 Germacrene D and (*E*)-caryophyllene do not show considerable antioxidant activity, essential
603 oils rich in sesquiterpenes have shown considerable antioxidant activity against $ABTS^{\bullet+}$ and
604 $DPPH^{\bullet}$ radicals [80–82].

605 The germacrene D, a sesquiterpene hydrocarbon, is one of the main constituents of *M.*
606 *sylvatica* essential oil, with a concentration of 10.72% in steam distillation and 5.51% in
607 hydrodistillation. In a study carried out with *Eugenia patrissi*, the essential oil showed
608 germacrene D (20.03%) as the majority compound, the essential oil of the species obtained
609 significant antioxidant activity, with inhibition of 31.4 ± 0.1 $ABTS^{\bullet+}$ and 99.0 ± 0.099 ($DPPH^{\bullet}$
610), antioxidant capacity equivalent to the trolox standard in the $DPPH^{\bullet}$ assay [83].

611 On the other hand, even with a higher percentage of oxygenated sesquiterpenes
612 (45.02%), the essential oil obtained by HD showed lower antioxidant activity in the two
613 methods analyzed, indicating the antagonistic and/or synergistic influences that each
614 antioxidant compound present in the mixture can exert on the others and, consequently, on the
615 overall effect of the interaction with the free radical [84,85] . De Moraes et al.[12] analyzed the
616 antioxidant potential of *M. sylvatica* essential oil, rich in sesquiterpene hydrocarbons (51.60%)
617 and oxygenated sesquiterpenes (46.52%), which showed greater antioxidant activity (AIR =
618 80.55±2.00%) than the standard antioxidant Trolox (50.53±0.53%) in inhibiting $DPPH^{\bullet}$ radicals.

619 The oils obtained by the two extraction techniques were more effective in the $ABTS^{\bullet+}$
620 radical scavenging tests than in the $DPPH^{\bullet}$ radical scavenging tests. The difference in results can
621 be attributed to the nature of the reaction mechanism for eliminating each of the radicals,
622 considering that, although both tests involve the transfer of a single electron (SET) and the
623 transfer of a hydrogen atom (HAT) from the antioxidant substances, both types of mechanism
624 can occur simultaneously at different rates during the reaction, depending on the nature of the
625 radical and the antioxidant, and the conditions of the reaction medium [86–89].

626 *3.6. Computational Approach*

627 *3.6.1. Docking Validation*

To enhance our understanding of the intricate ligand-protein binding interactions, the *in silico* docking simulations were performed. To validate the procedure of this technique, the docked 'donepezil' (Figure 11: B) structure was overlayed to 'donepezil' obtained from the crystal structure of the AChE (Figure 11: A). We displayed the interactions formed originally between the co-crystallized molecule with the targeted enzyme in order to show the similarity through the positioning and the residues involved in the interactions. From the molecular docking outcomes, it should be noted that the redocked 'donepezil' interacts favourably with the receptor, this ligand exhibited similar interactions those found originally in the crystal structure. Furthermore, the result of superposition figure displays that the root mean square deviation ''RMSD'' between the two ligands (cyan: re-docked and yellow: co-cristallized) is minimal.

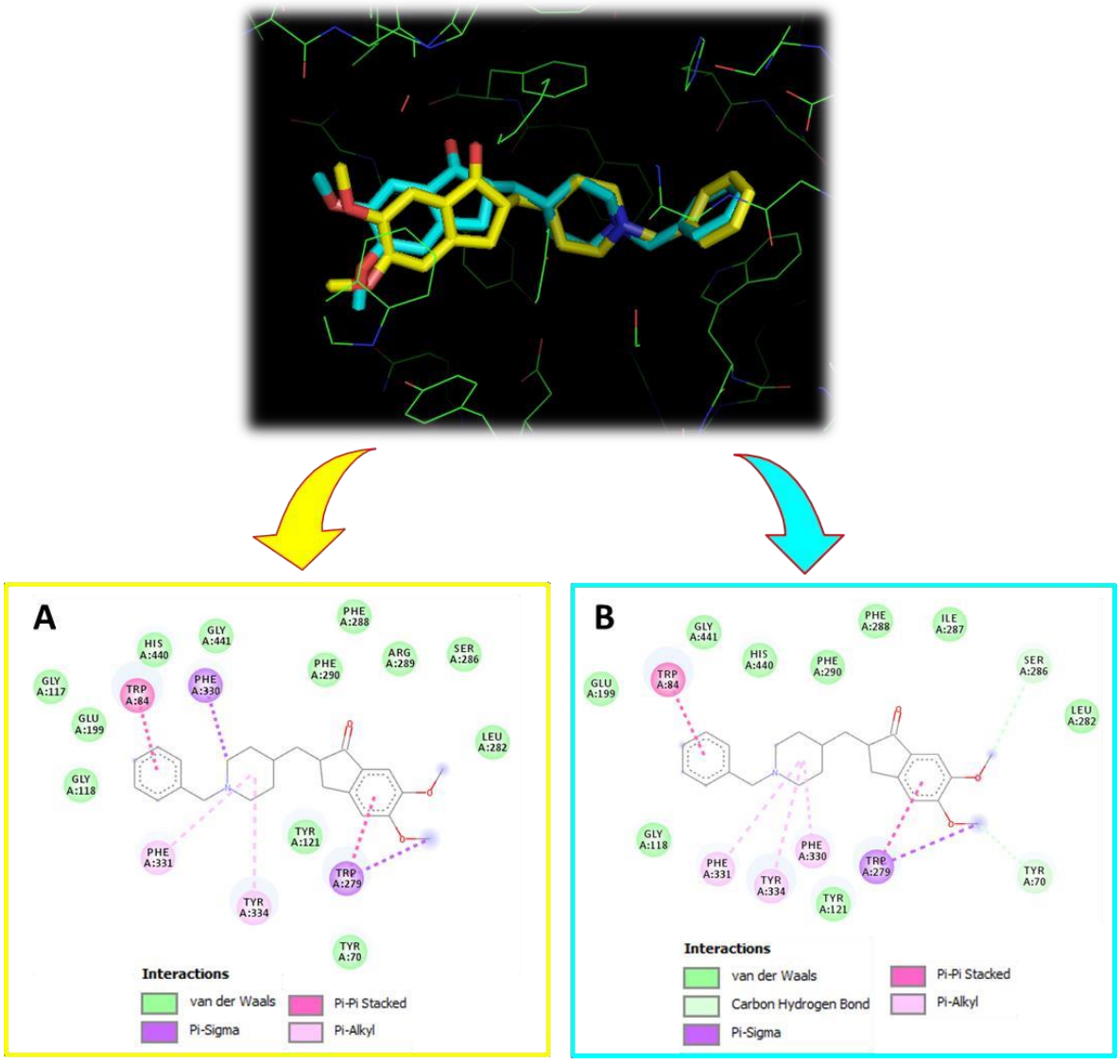


Figure 11. 2D model of different interactions formed by the co-cristallized 'Donepezil' (yellow color) (**A**) and the re-docked 'Donepezil' (cyan color) (**B**) within the active site of AChE (pdb : 1EVE).

3.6.2. Docking Results Analysis

Based on the free-binding energy values, the obtained outcomes indicate that the ligands 'Spathulenol' (-8.9 kcal mol^{-1}) was found to be the most bioactive compound as Table 5 shows. This docked molecule is involved in a conventional hydrogen bond with Tyr121. The interesting potential of 'Spathulenol' is also explained by the formation of some other contacts as Pi-Sigma with Phe330 and Pi-Alkyls with Trp84, Phe330, Phe331 and His440 (figure 12 (C)). By showing almost the same interactions, as figure 12 (D) exhibites, 'Globulol' was considered as the second effective ligand while the two phytocompounds 'alpha-Zingiberene' and '(E)-Caryophyllene' displayed the third best anti-AChE potentials by the formation of some hydrophobic contacts: Alkyl and Pi-Alkyl as detailed in figure 12 (A and E). On another hand, Germacrene D was found to be the least active compound by showing a Pi-Sigma interaction with Trp84 besides to Pi-Alkyl contacts with Phe330, Phe331, Tyr334 and His440 respectively.

Although all docked phytoligands cannot showed scores comparable to the reference (co-crystallized ligand), they were able to form very interesting interactions in comparison with the interactions formed by Donepezil, in particular with the two alcohols: 'Spathulenol' and 'Globulol' which formed H-bonds. All these outputs and findings display the importance of the tested phytocompounds in the inhibition of AChE.

Table 5. Docking results of the docked ligands with their binding energy scores.

Docked ligand	**binding energies (kcal mol^{-1})**
alpha-Zingiberene	-8.1
Germacrene D	-8.0
Spathulenol	-8.9
Globulol	-8.3
(*E*)-Caryophyllene	-8.1
Co-crystallized ligand « Donepezil »	-9.6

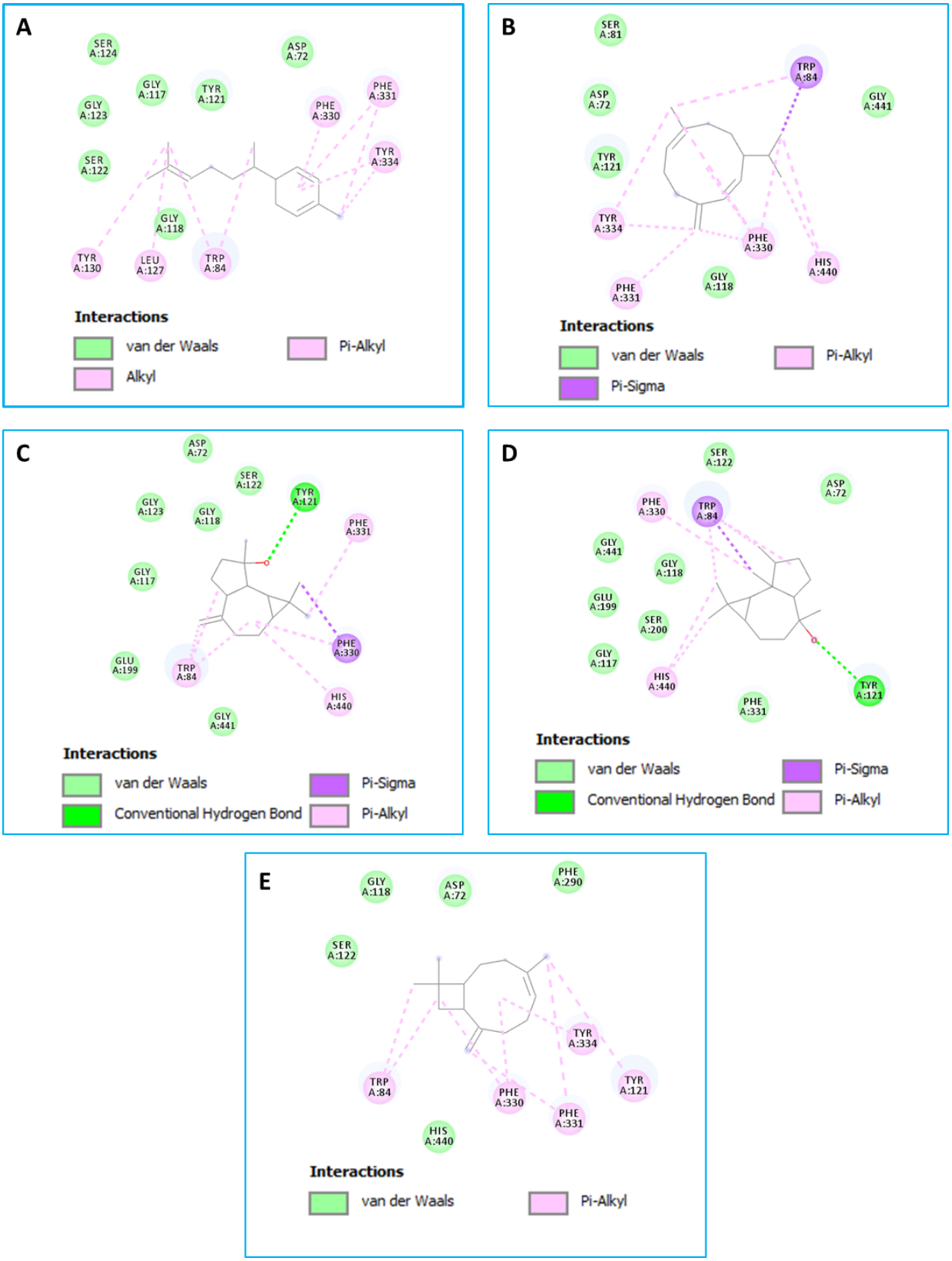


Figure 12. 2D binding modes of the most bioactive compounds: A: alpha-Zingiberene, B: Germacrene D, C: Spathulenol, D: Globulol and E: (*E*)-Caryophyllene

669 *3.6.3. Predictive ADME Analysis*

670 The forecasting of ADME (absorption, distribution, metabolism and excretion) data of
671 the major phytocompounds have been estimated. The predicted descriptors including their
672 pharmacokinetic and druglikeness properties are showed in Table 6. All tested ligands were
673 found to correctly meet the Lipinski's rule, and so share 'topological polar surface area' (TPSA)
674 values of 00.00 to 20.23Å^2, supporting the probability to have predicted high passive oral
675 absorption, and that is expressed by the consensus Log Po/w in the range 3.29 to 4.44.
676 Furthermore, the bioavailability score of 0.55 indicates higher bioactivity of the molecule. As
677 noticed in the table 6, there is no P-glycoprotein (P–gp) substrate, this finding suggestes the
678 good intestinal absorption of compounds and bioavailability. Additionally, all tested ligands
679 displayed low gastrointestinal absorption (GI) except Globulol. This compound in addition to
680 Spathulenol were predicted to cross the blood–brain barrier (BBB). Further, almost all tested
681 compounds were found to no inhibit the main cytochrome (CYP 450) enzymes; CYP1A2,
682 CYP2C19, CYP2C9, CYP2D6 and CYP3A4. The radar plot (Figure 13), shows that all tested
683 molecules are in the pink zone, confirming their better drug-likeness with a good bioavailability
684 profile. On another hand, the figure 14 exhibites the BOILED-EGG curve and the BBB
685 penetration, GI absorption (HIA) of the substances may be predicted by this method. Indeed,
686 there are two areas: one for the GI absorption zone (HIA) and the other for BBB penetration
687 (yolk). Neither 'GI absorption' nor 'BBB penetration' is indicated if any component is found
688 in the gray zone. According to the results obtained, two out of five phytoligands: the two
689 alcohols: 'Spathulenol' and 'Globulol' are appeared in the yellow region (yolk) with a red
690 points that indicated their high probability of brain penetration (BB) acting as a non-substrate
691 of P–gp.

692 **Table 6.** *In silico* ADME analysis of the main phytoligands.

Entry	**A**	**B**	**C**	**D**	**E**
GI absorption*	Low	Low	High	High	Low
P–gp substrate*	No	No	No	No	No
BBB permeant*	No	No	Yes	Yes	No
CYP1A2 inhibitor*	No	No	No	No	No
CYP2C19 inhibitor*	Yes	No	Yes	Yes	Yes
CYP2C9 inhibitor*	Yes	Yes	No	Yes	Yes
CYP2D6 inhibitor*	No	No	No	No	No
CYP3A4 inhibitor*	No	No	No	No	No
Log Kp (cm/s) [a*]	-3.88	-4.18	-5.44	-4.81	-4.44
Lipinski**	Yes	Yes	Yes	Yes	Yes
Veber**	Yes	Yes	Yes	Yes	Yes
Egan**	Yes	Yes	Yes	Yes	Yes

Bioavailability Score**	0.55	0.55	0.55	0.55	0.55
TPSA (Å^2)***	00.00	00.00	20.23	20.23	00.00
Consensus Log *P*o/w****	4.44	4.30	3.29	3.73	4.24

a: skin permeability, A: alpha-Zingiberene, B: Germacrene D, C: Spathulenol, D: Globulol and E: (E)-Caryophyllene, Pharmacokinetics*, Druglikeness**, Physicochemical Properties*** and Lipophilicity****

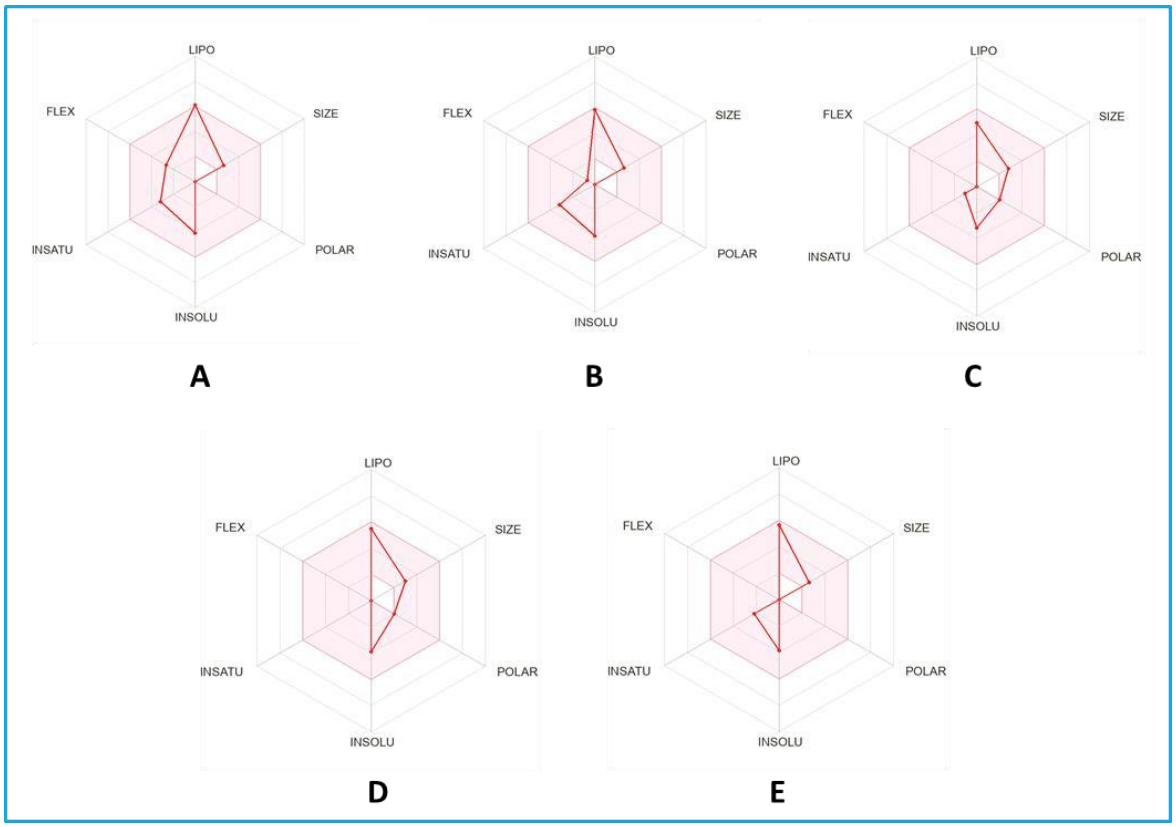


Figure 13. Bioavailability radar of the main phytoconstituants: A: alpha-Zingiberene, B: Germacrene D, C: Spathulenol, D: Globulol and E: (E)-Caryophyllene

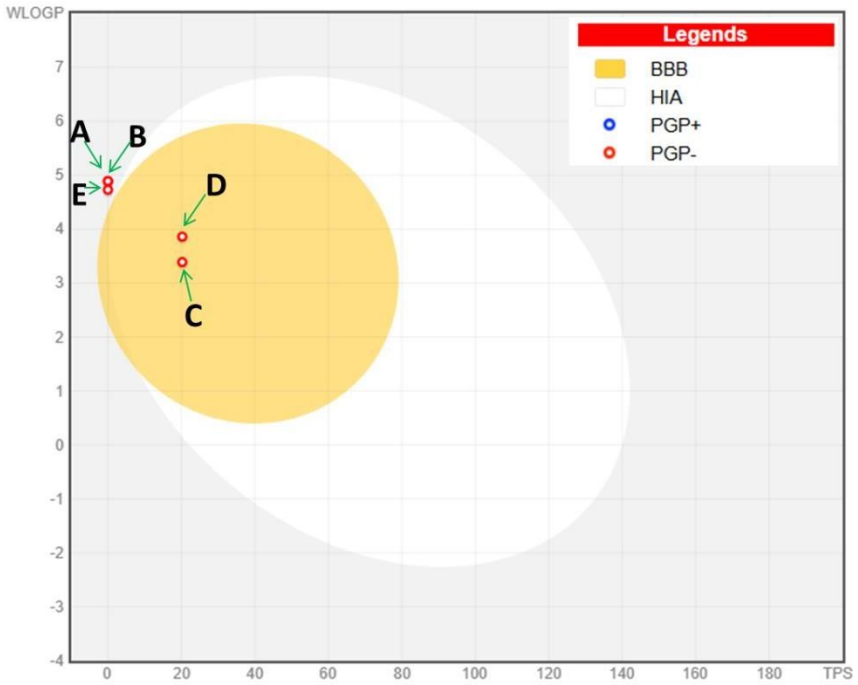


Figure 14. Boiled-egg graph of the main phytoconstituants: A: alpha-Zingiberene, B: Germacrene D, C: Spathulenol, D: Globulol and E: (*E*)-Caryophyllene.

4. Conclusion

This study offers a pioneering and integrative characterization of *Myrcia sylvatica*, demonstrating its taxonomically relevant anatomical features and revealing secretory structures associated with a diversity of bioactive metabolites. The essential oils showed chemical variability depending on the extraction method, with a predominance of sesquiterpenes that strongly influenced both antioxidant and toxicological profiles. The steam-distilled oil exhibited superior biological activity, particularly in radical scavenging and toxicity assays. Furthermore, molecular docking simulations and ADME predictions revealed that compounds such as spathulenol and globulol possess strong potential as acetylcholinesterase inhibitors, with desirable pharmacokinetic properties. These novel findings not only deepen our understanding of the chemical ecology of M. sylvatica but also highlight its potential for pharmaceutical and biotechnological applications. This work expands the scientific basis for the valorization and sustainable use of Amazonian biodiversity.

Acknowledgments

The author Mozaniel Santana de Oliveira thanks PDPG-POSDOC—Programa de Desenvolvimento da Pós-Graduação (PDPG) Pós-Doutorado Estratégico, as well as CAPES for the scholarship (process number: (88887.852405/2023-00). The authors thank CAPES process number 001.

Funding information

This project did not receive funding.

Author Contributions (CRediT taxonomy)

E.J.B.S., Z.A.C., E.S.C.G., L.S.C., M.H., H.E., R.K., A.S.B., K.S.S.V., E.H.A.A. and M.S.O. contributed to conceptualization, investigation, methodology, and writing of the original draft, as well as reviewing and editing the manuscript. M.H. and H.E. also contributed to computational analyses and in silico validation. R.K. additionally contributed to obtaining resources. E.H.A.A. and M.S.O. also contributed to project supervision and administration.

Conflict of interests

Authors state no conflict of interest.

Ethical approval:

The conducted research is not related to either human or animal use**.**

Data availability statement - choosing one of the following:

Data are however available from the authors upon reasonable request and with permission of corresponding author.

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5. CONSIDERAÇÕES FINAIS

O levantamento bibliográfico sobre o gênero *Myrcia* mostra a diversidade química e o potencial biológico dos óleos essencias do gênero, com destaque para as atividades antioxidante, inseticida, fitotóxica e hipoglicimiante. A espécie *M. sylvatica* apresenta variabilidade química em seu óleo essencial, influenciada por fatores ambientais e metodológicos. As folhas de *M sylvatica* possuem estruturas especializadas, como cavidade secretoras, idioblastos, epiderme secretora e tricomas secretores, que sintetizam, armazenam e secretam composto bioativos. Além disso, a espécie apresenta óleo essencial com atividade antioxidante e toxicidade. As analises *in silico* mostram que ó óleo essencial de *M. sylvatica* apresenta compostos promissores com potencial farmacológico, como o espatulenol e o globulol. Esses resultados contribuem para o conhecimento biológico e para a valorização biotecnológica de *M. sylvatica*