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JULIMERY GONÇALVES FERREIRA MACEDO

ETNOBOTÂNICA, COMPOSIÇÃO QUÍMICA E ATIVIDADES BIOLÓGICAS DE ESPÉCIES MEDICINAIS DO GÊNERO *Psidium* L. (MYRTACEAE JUSS.)

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Tese apresentada ao Programa de Pós-Graduação em Etnobiologia e Conservação da Natureza (UFRPE, UEPB, URCA e UFPE) como parte dos requisitos para a obtenção do título de doutora em Etnobiologia e Conservação da Natureza.

Orientadora:
Dra. Marta Maria de Almeida Souza
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Tese Defendida e Aprovada em: 22 de fevereiro de 2022

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Dedico esse trabalho as pessoas que mais me ensinaram sobre a natureza, observando-a com respeito e cuidado; e mesmo não compreendendo direito o que eu fazia, tinham orgulho de dizer “minha neta será doutora dos matos”. Meus avós: Zulmira Pereira (Voinha) – *in memorian* e José Gonçalves (Duquinha) – *in memorian*.

Eu me lembro muito bem do dia em que cheguei
Jovem que desce do norte pra cidade grande
Os pés cansados e feridos de andar légua tirana
E lágrimas nos olhos de ler o Pessoa
E de ver o verde da cana

Em cada esquina que eu passava, um guarda me parava
Pedia os meus documentos e depois sorria
Examinando o três-por-quarto da fotografia
E estranhando o nome do lugar de onde eu vinha
...
A minha história é talvez,
É talvez igual a tua, jovem que desceu do norte...
...
Eu sou como você
Eu sou como você
Eu sou como você

Fotografia 3x4 – Belchior

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SUMÁRIO

RESUMO

MACEDO, Julimery Gonçalves Ferreira. Dra. Universidade Federal Rural de Pernambuco. Fevereiro, 2022. Etnobotânica, composição química e atividades biológicas de espécies medicinais do gênero *Psidium* L. (Myrtaceae Juss.); Orientação: Marta Maria de Almeida Souza e José Galberto Martins da Costa.

Espécies medicinais do gênero *Psidium* L. (Myrtaceae Juss.) têm longo histórico de uso na medicina popular para sanar ou tratar uma variedade de sintomas. A presença de óleos essenciais pode explicar as múltiplas atividades biológicas, como as antimicrobianas e antioxidantes. Esse estudo teve como objetivo levantar os usos medicinais de espécies nativas de *Psidium* e, analisar a composição química e atividades biológicas. Esse trabalho teve duas fases, na 1ª foi realizada uma revisão sistemática de artigos científicos que interligava os termos etnobotânica de plantas medicinais, composição química e testes farmacológicos, para o gênero, sendo utilizados 25 termos nas buscas. As publicações passaram por critérios de inclusão e exclusão, como ano, idioma, nome completo da espécie, bases de dados, tipo de publicação. A pesquisa gerou um total de 4.202 registros, que após passarem pelos filtros estabelecidos 70 artigos foram analisados. Essa análise possibilitou a identificação de 13 espécies nativas de *Psidium*, as quais seis eram mencionadas na medicina popular, com principal indicação dentro do sistema digestório. Do total de espécies, 12 apresentaram investigação de composição química e/ou atividade biológica, sendo seus compostos químicos apontados como os responsáveis pelas atividades aventadas. Na 2ª fase, foram realizadas análises químicas e atividade antibacteriana, moduladora e antioxidante das espécies medicinais *Psidium laruotteanum* Cambess., *Psidium salutare* (Kunth) O. Berg e *Psidium sobralianum* Landrum & Proença. As espécies foram coletadas em duas áreas de Cerrado disjunto da Chapada do Araripe (Brasil). A extração dos óleos essenciais das folhas, se deu por hidrodestilação e identificados por cromatografia gasosa acoplada a espectrometria de massas (CG/EM). A atividade antibacteriana foi avaliada pelo método de microdiluição seriada, determinando a concentração inibitória mínima (CIM) e atividade moduladora. No ensaio bacteriano foi usado *Escherichia coli* Ec 27, *Pseudomonas aeruginosa* ATCC 15442, *Staphylococcus aureus* Sa 358 e *Streptococcus mutans* INCQS 00446. O óleo essencial de *P. laruotteanum*, foi avaliado quanto ao efeito modulador frente aos antibióticos amicacina e cefalotina. O método DPPH (1,1-diphenyl-2-picrylhdrazine), foi utilizado para avaliar a atividade antioxidante. Os resultados foram analisados por ANOVA e teste de Tukey e Bonferroni. Um total de 26 compostos foram identificados para as espécies. Estas, demonstraram ser diferentes quimicamente, não apresentando nenhum composto comum as três espécies. Entre os majoritários tiveram destaque, 1,8-cineol (57,07%), α-phellandrene (14,62%) (*P. salutare*); Viridiflorol (27,89%), α-caryophyllene (27,62%) (*P. laruotteanum*); Viridiflorol (11,64%) e α-pinene (11,78%) (*P. sobralianum*). O óleo essencial de *P. laruotteanum* inibiu o crescimento de *E. coli* na concentração 96 µg/mL, e demonstrou efeito sinérgico quando associado a amicacina sobre *S. aureus*, com $p<0{,}001$. *Psidium salutare* e *P. sobralianum*, inibiram crescimento bacteriano em concentrações mais altas, entre 341,33 µg/mL e ≥ 1024 µg/mL, com pouca relevância do ponto de vista clínico. Em relação a atividade antioxidante, os resultados exibiram concentração dependente, sendo o melhor resultado para o óleo de *P. sobralianum* com IC_{50} de 5.99 mg/mL, quando comparado aos controles Ácido Ascórbico IC_{50} 0.02 mg/mL e Eugenol IC_{50} 0.04 mg/mL.

Palavras-chave: Araçá; Atividade Antibacteriana; Atividade Antioxidante; Atividade Moduladora; Medicina Popular; Óleos essenciais; *Psidium*.

ABSTRACT

MACEDO, Julimery Gonçalves Ferreira. Dra. Universidade Federal Rural de Pernambuco. February, 2022. Ethnobotany, chemical composition, and activites of medicinal species of the genus *Psidium* L. (Myrtaceae Juss.); Orientation: Marta Maria de Almeida Souza and José Galberto Martins da Costa.

Medicinal species of the genus *Psidium* L. (Myrtaceae Juss.) have a long history of use in folk medicine to cure or treat a variety of symptoms. The presence of essential oils can explain the multiple biological activities, such as antimicrobial and antioxidant. This study aimed to survey the medicinal uses of native species of *Psidium* and analyze the chemical composition and biological activities. This work had two phases in the 1st, a systematic review of scientific articles was carried out that linked the terms ethnobotany of medicinal plants, chemical composition, and pharmacological tests, for the genus, using 25 terms in the searches. The publications went through inclusion and exclusion criteria, such as year, language, the full name of the species, databases, type of publication. The research generated a total of 4.202 records, which, after passing through the established filters, 70 articles were analyzed. This analysis allowed the identification of 13 native species of *Psidium*, of which six were mentioned in folk medicine, with the main indication within the digestive system. Of the total number of species, 12 showed an investigation of chemical composition and/or biological activity, and their chemical compounds were identified as responsible for the activities suggested. In the 2nd phase, chemical analysis and antibacterial, modulating, and antioxidant activity of the medicinal species *Psidium laruotteanum* Cambess., *Psidium salutare* (Kunth) O. Berg and *Psidium sobralianum* Landrum & Proença were performed. The species were collected in two areas of Cerrado disjoint from Chapada do Araripe (Brazil). The extraction of essential oils from the leaves was carried out by hydrodistillation and identified by gas chromatography coupled to mass spectrometry (GC/MS). Antibacterial activity was evaluated by the serial microdilution method, determining the minimum inhibitory concentration (MIC) and modulating activity. In the bacterial assay, *Escherichia coli* Ec 27, *Pseudomonas aeruginosa* ATCC 15442, *Staphylococcus aureus* Sa 358, and *Streptococcus mutans* INCQS 00446 were used. The essential oil of *P. laruotteanum* was evaluated for its modulatory effect against the antibiotics amikacin and cephalothin. The DPPH method (1,1-diphenyl-2-picrylhdrazine) was used to evaluate the antioxidant activity. The results were analyzed by ANOVA and the Tukey and Bonferroni test. A total of 26 compounds were identified for the species. These were demonstrated to be chemically different, not presenting any compound common to the three species. Among the major ones, 1.8-cineole (57.07%), α-phellandrene (14.62%) (*P. salutare*); Viridiflorol (27.89%), α-caryophyllene (27.62%) (*P. laruotteanum*); Viridiflorol (11.64%) and α-pinene (11.78%) (*P. sobralianum*). The essential oil of *P. laruotteanum* inhibited the growth of *E. coli* at a concentration of 96 µg/mL, and showed a synergistic effect when associated with amikacin on *S. aureus*, with $p<0.001$. *Psidium salutare* and *P. sobralianum* inhibited bacterial growth at higher concentrations, between 341.33 µg/mL and ≥ 1024 µg/mL, with little clinical relevance. In relation to antioxidant activity, the results were concentration-dependent, with the best result for *P. sobralianum* oil with IC_{50} of 5.99 mg/mL, when compared to controls Ascorbic Acid IC_{50} 0.02 mg/mL and Eugenol IC_{50} 0.04 mg/mL.

Keywords: Araça; Antibacterial activity; Antioxidant activity; Modulating activity; Folk medicine; essencial oils; *Psidium*.

1. INTRODUÇÃO GERAL

1.1 OBJETIVOS E QUESTIONAMENTOS

As melhores opções para encontrar novos agentes eficazes contra uma variedade de doenças humanas, como as de origem antivirais, antiparasitárias, anticânceres, antioxidantes, antimicrobianas dentre outras, estão nas substâncias de fontes naturais (NEWMAN; CRAGG, 2020). Uma das principais causas de morte do mundo, são associadas a doenças infecciosas causadas por bactérias (DACOREGGIO; MORONI; KEMPKA, 2019), devido principalmente ao desenvolvimento de resistência por parte de microrganismos a produtos sintéticos, representando grave ameaça aos avanços da assistência médica mundial (GÓRNIAK; BARTOSZEWSKI; KRÓLICZEWSKI, 2018; WHO, 2021). Produtos naturais, podem desempenhar papel como agentes potencializadores de fármacos padrões, figurando como alternativa no combate a resistência antimicrobiana (LANGEVELD; VELDHUIZEN; BURT, 2014).

O envelhecimento e enfermidades como câncer, inflamação, doenças degenerativas e cardiovasculares, estão associadas ao estresse oxidativo, em decorrência do desequilíbrio no sistema oxidante-antioxidante, também correspondem a preocupações médicas mundiais (SUWANWONG; BOONPANGRAK, 2021). Em 2019, das 10 principais causas de morte no mundo, as doenças cardiovasculares lideravam o *ranking* (WHO, 2020). A presença de radicais livres e as espécies reativas de oxigênio (ROS) que são produzidos como subprodutos no corpo humano durante o metabolismo celular, se não eliminados, podem causar danos oxidativos e desencadear uma série de doenças, como as relacionadas acima. Nesse sentido, o consumo de substâncias com potencial antioxidante pela alimentação ou medicamentos, podem remover as ROS do sistema e fornecer benefícios à saúde (AMORATI; FOTI; VALGIMIGLI, 2013; ZHANG et al., 2011).

Substâncias naturais, como os óleos essenciais, oriundas do metabolismo secundário de plantas com usos na medicina popular em detrimento a produtos sintéticos, podem representar alternativas terapêuticas no tratamento ou cura de doenças e sintomas relacionados a infecções por bactérias ou excesso de substâncias oxidantes no corpo. Uma vasta literatura tem propagado plantas medicinais com essas atividades (NEWMAN; CRAGG, 2020; SOTTO et al., 2020; VALDIVIESO-UGARTE et al., 2019; VALUSSI et al., 2021; WELI et al., 2019; ZIVARPOUR et al., 2021).

Os diversos compostos químicos produzidos por espécies vegetais, estão diretamente associadas a atividades biológicas que essas desempenham (SOTTO et al., 2020; VALDIVIESO-UGARTE et al., 2019; VALUSSI et al., 2021). Em especial, os óleos essenciais ou óleos voláteis, estão presentes em cerca de 30% das espécies vegetais analisadas quanto a presença de compostos voláteis, com destaque para várias famílias de angiospermas eudicotiledôneas, tais como Apiaceae, Lamiaceae, Lauraceae, Piperaceae, Rutaceae e Myrtaceae, onde quase todas as espécies pertencentes a essas famílias, contêm óleos essenciais (HEINZMANN; SPITZER; SIMÕES, 2017).

Dentre as famílias botânicas produtoras de óleos essenciais, destacamos Myrtaceae Juss. e mais precisamente o gênero *Psidium* L. Espécies de *Psidium* têm histórico de uso na medicina popular para tratar uma variedade de sintomas, como dores de cabeça, gripe, doenças do sistema geniturinário (ABREU et al., 2015; SANTANA; VOEKS; FUNCH, 2016; SARAIVA et al., 2015). Todavia, as populações locais recorrem às espécies de *Psidium* mais frequentemente para combater sintomas relacionados ao sistema digestório. Os remédios caseiros são feitos a partir das folhas, cascas e frutos para tratar diarreias, dores de barriga, disenteria, dores de estômago e problemas intestinais (LOZANO et al., 2014; MACÊDO et al., 2015; PALHETA et al., 2017; PEDROLLO et al., 2016; RIBEIRO et al., 2014; YAZBEK et al., 2019).

Através dessas informações advindas do saber medicinal popular, várias pesquisas têm surgido na busca por substâncias ativas com propriedades biológicas para as espécies de *Psidium*. Em sua grande maioria, os trabalhos são realizados com *Psidium guajava* L., espécie cultivada em nosso país e a de maior destaque medicinal, alimentícia, presença de óleos essenciais e atividades biológicas (BEZERRA et al., 2018; MACHADO et al., 2018; MORAIS-BRAGA et al., 2016a, 2016b; WELI et al., 2019). Esta também é a única espécie do gênero a constar na Monografia de Plantas Medicinais da Farmacopeia Brasileira (ANVISA, 2019a), compêndio farmacêutico nacional, que estabelece os requisitos mínimos para a garantia da qualidade e da segurança dos medicamentos comercializados no país, sejam eles de referência, genéricos, similares, fitoterápicos, dentre outros.

As espécies nativas de *Psidium*, vem ganhando destaque em publicações científicas, principalmente *Psidium cattleyanum* Sabine (Araçá amarelo) e *Psidium guineense* Sw. (Araçá), usadas tanto na medicina popular quanto na alimentação (BEZERRA et al., 2018). Em recente publicação, Macedo et al. (2021) analisaram 13 espécies nativas do gênero para o Brasil, e retrataram os usos medicinais populares dessas espécies, que estão relacionados em grande parte a distúrbios digestivos, assim como composição química de extratos vegetais e óleos essenciais e suas aplicabilidades em atividades biológicas. As espécies são ricas em terpenos, compostos fenólicos, taninos e carotenoides. Essas substâncias conferem-lhes atividades biológicas como antiproliferativa, anti-inflamatória, antimicrobiana e antioxidante.

Quando destacamos os óleos essenciais, já foram relatados ao redor do mundo 110 registros para 18 espécies de *Psidium* (CAMPOS E SILVA et al., 2021). Estes apresentam significativa variabilidade de compostos químicos, sobressaindo-se a classe dos terpenos. Monoterpenos (limonene, α-pinene, 1,8-cineole) e sesquiterpenos (α-humulene, (E)-caryophyllene) são particularmente representativos nesse gênero (CAMPOS E SILVA et al., 2021; MACEDO et al., 2021). Esses compostos estão associados às atividades biológicas apresentadas pelas espécies, seja como componente majoritário ou levando em consideração todos os compostos presentes no óleo (CAMPOS E SILVA et al., 2021; JERÔNIMO et al., 2021; MACEDO et al., 2021; NASCIMENTO et al., 2018).

Pesquisas etnobotânicas em associação a estudos de composição química de espécies vegetais, têm trazido resultados promissores na descoberta de várias atividades biológicas, para espécies nativas da flora brasileira. Indo em direção a esse cenário, buscamos neste trabalho analisar a composição química de espécies medicinais nativas de *Psidium* para o Brasil e verificar as atividades biológicas, associando-as às indicações populares.

Considerando o uso medicinal popular e as atividades biológicas associadas aos compostos químicos das espécies de *Psidium*, levantamos os seguintes pressupostos: (1) As indicações terapêuticas relatadas para espécies de *Psidium*, podem ser comprovadas através da composição química e atividades biológicas. (2) Os óleos essenciais das folhas, apresentam resultados promissores contra bactérias tanto quanto antibióticos convencionais e, podem atuar como antioxidantes naturais.

1.2 ESTRATÉGIAS DE PESQUISA

O estudo foi realizado em áreas de Cerrado disjunto da Chapada Nacional do Araripe, no município de Crato, estado do Ceará. A Chapada do Araripe é um planalto localizado dentro do domínio da Caatinga no nordeste brasileiro, entre os estados do Ceará, Pernambuco e Piauí. Apresenta altitude variando de 700m a 1000m e área de aproximadamente 10.000 km^2. É uma área que desperta grande interesse econômico e biológico pela sua heterogeneidade ambiental e recursos naturais. Possui tipos vegetacionais de Savana (Cerrado), Savana estépica (Carrasco) e Floresta Estacional Sempre-Verde (Floresta úmida). Abriga duas unidades de conservação de uso sustentável, uma Floresta Nacional (FLONA Araripe-Apodi), uma Área de Proteção Ambiental (APA da Chapada do Araripe) e ainda um Geoparque (Geopark Araripe) (CORRÊA; CORRÊA, 2015; COSTA; ARAÚJO; LIMA-VERDE, 2004; LOIOLA et al., 2015).

Em áreas de Cerrado da Chapada do Araripe, Myrtaceae tem se destacado como uma das famílias botânicas mais ricas em números de espécies, assim como o gênero *Psidium* (COSTA; ARAÚJO; LIMA-VERDE, 2004; LOIOLA et al., 2015; RIBEIRO-SILVA et al., 2012). A escolha do gênero teve como base essas informações, assim como o fato dos integrantes apresentarem em suas folhas, estruturas morfológicas produtoras de óleos essenciais e investigações etnobiológicas dentro das comunidades da Chapada do Araripe. Essas espécies são conhecidas popularmente como Araçás ou Marangabas.

As quatro espécies de *Psidium* (*P. laruotteanum*, *P. myrsinites*, *P. salutare* e *P. sobralianum*) da Chapada do Araripe abordadas nessa pesquisa, foram mencionadas em entrevistas com formulário semiestruturado, com questões abertas e fechadas, sobre o conhecimento das comunidades a respeito das espécies de *Psidium* e seu uso medicinal (o artigo sobre esse tema não foi possível ser concluído, sendo interrompido devido a pandemia do novo coronavírus em 2020). Esse tipo de técnica apresenta vantagens para a coleta de dados, uma vez que questões fechadas possibilitam uniformidades de respostas, enquanto as abertas permitem maior liberdade ao entrevistado (ALBUQUERQUE et al., 2014). Para realização dessa etapa, a pesquisa foi cadastrada no Sistema Nacional de Gestão de Patrimônio Genético e do Conhecimento Tradicional Associado (SisGen), sob número de cadastro AE56B81 (ANEXO A) e aprovada pelo Comitê de Ética em Pesquisa (CEP) da Universidade Regional do Cariri (URCA) sob parecer 2.954.183 (ANEXO B).

As espécies medicinais em estágios reprodutivos e disponíveis na área foram coletadas através de turnê guiada, tanto com os entrevistados que indicaram as espécies, quanto com auxílio de mateiro. Essa aplicação metodológica é fundamental na validação dos nomes vernaculares atribuídos as espécies. Visto que uma determinada espécie pode apresentar variações de nomes populares, ou o mesmo nome ser utilizado para designar espécies distintas, tanto entre indivíduos de diferentes áreas, quanto entre indivíduos de uma mesma comunidade (ALBUQUERQUE et al., 2014). A coleta das espécies foi autorizada pelo Sistema de Autorização e Informação em Biodiversidade (SISBIO) do

Instituto Chico Mendes de Conservação da Biodiversidade (ICMBio), sob números, 63956-1 e 63956-2 (Renovação) (ANEXO C).

O material botânico coletado, foi tratado segundo as técnicas de herborização propostas por Mori et al. (1989), e enviado para identificação em herbários que possuíam especialistas na família (Myrtaceae) ou gênero (*Psidium*). Os especialistas a identificarem as espécies foram, a Dra. Carolyn Elinore Barnes Proenca da Universidade de Brasília (UnB) e o Dr. Marcos Eduardo Guerra Sobral da Universidade Federal de São João Del-Rei (UFSJ), sendo o material testemunho depositado nos respectivos herbários, Herbário da Universidade de Brasília (UB) e Herbário da Universidade Federal de São João Del Rei (HUFSJ).

As demais espécies apontadas nesse trabalho, foram levantadas através de revisão de literatura em quatro bases de dados, Scopus, ScienceDirect, PubMed e Web of Science. Estiveram incluídas nessa busca, espécies nativas de *Psidium* para a flora do Brasil que estavam identificadas com gênero e epíteto específico, registro de uso na etnobotânica médica, composição química e atividades biológicas. Estipulamos um intervalo de 10 anos (2010 a 2019), período que apresenta maiores índices de trabalhos publicados com o tema ‘plantas medicinais e produtos naturais biologicamente ativos’ (YEUNG et al., 2020), e apenas artigos científicos publicados nesse período, foram considerados. Trabalhos de revisão podem fornecer uma concepção mais clara e abrangente sobre determinado assunto, seu principal objetivo é viabilizar um resumo detalhado das pesquisas disponíveis a fim de responder uma pergunta de pesquisa. Além de preencher lacunas, deve possuir objetivos claros e critérios pré-determinados que sejam transparentes e reproduzíveis (CLARKE, 2011).

Com relação ao monitoramento dos compostos químicos dos óleos essenciais presentes nas folhas, selecionamos um indivíduo de cada espécie no interior da área, com características semelhantes em relação ao comprimento, diâmetro e em condições homogêneas.

As folhas frescas foram submetidas ao processo de hidrodestilação por 2h em aparelho tipo Clevenger modificado, para extração dos óleos essenciais. Posteriormente, os óleos foram tratados com sulfato de sódio anidro (Na_2SO_4) e mantidos sob refrigeração < 4º C até o momento das análises. A hidrodestilação é uma técnica laboratorial moderna para extração e determinação do teor de óleos voláteis. É bastante indicado para extrair óleos de plantas frescas, inclusive preconizado pela Farmacopeia Brasileira (ANVISA, 2019b; HEINZMANN; SPITZER; SIMÕES, 2017). A identificação dos componentes químicos ocorreu por cromatografia gasosa acoplada a espectrometria de massas (CG/EM). Esse método é utilizado para separar e quantificar substâncias componentes dos óleos essenciais. Apresenta vantagens pois permite a identificação e determinação dos teores dos compostos presente nos óleos. Em associação a espectrometria de massas, possibilita a separação dos componentes e fornece um espectro de massas para cada pico cromatográfico individual. A partir de uma espectroteca (espécie de biblioteca de referência que inclui o espectro de massas de uma grande variedade compostos) instalada a um computador, é possível comprar o espectro de massas do composto alvo com aquele de substâncias do banco de dados, permitindo assim a identificada (HEINZMANN; SPITZER; SIMÕES, 2017).

Para as análises das várias amostras dos ensaios antibacterianos, modulação e efeito antioxidante, foi utilizado análise de correlação, ANOVA, por meio de teste de Tukey e correção de Bonferroni. Estes métodos permitem a análise de apenas um valor de diferença mínima, a despeito da existência de várias médias. Essas análises são importantes, pois direcionam pesquisas para aquelas espécies que merecem mais atenção para serem usadas, por exemplo em investigações de bioprospecção.

1.3 ESTRUTURA DA TESE

A tese está estruturada em quatro capítulos, os quais discorrem sobre os seguintes assuntos:

Capítulo 1: refere-se à fundamentação teórica da tese, com abordagens pautadas na temática proposta na tese. Está dividida em dois tópicos. O primeiro, "Caracterização etnobiológica e química do gênero *Psidium* L.", fornece os principais aspectos etnobiológicos e de composição química da Família Myrtaceae e gênero *Psidium*. E de maneira mais detalhada, a caracterização desses aspectos para cada espécie da Chapada do Araripe abordadas nesse trabalho. Sendo elas, *Psidium laruotteanum* Cambess. (Marangaba peluda), *Psidium myrsinites* DC. (Marangaba amarela), *Psidium salutare* (Kunth) O. Berg (Marangaba vermelha) e *Psidium sobralianum* Landrum & Proença (Araçá de veado).

O segundo tópico, "Óleos essenciais e atividades biológicas", é pautado na conceituação e características de óleos voláteis, assim com sua aplicabilidade em investigações antibacterianas e antioxidantes.

Capítulo 2: intitulado "Therapeutic indications, chemical composition and biological activity of native Brazilian species from *Psidium* genus (Myrtaceae): A review", trata-se de uma revisão sistemática baseada na literatura disponível, em quatro bases de dados. Este versa sobre conhecimento popular do uso medicinal de espécies nativas do gênero *Psidium* para o Brasil, e riqueza de compostos químicos associados as atividades biológicas atrelada as espécies. Teve como objetivo: analisar as indicações terapêuticas, os principais constituintes químicos e as atividades biológicas das espécies nativas de *Psidium* para o Brasil. E assim, contribuir com um diagnóstico sobre os estudos destas espécies, bem como, mostrar se existe um padrão com relação a essas investigações, sugerindo futuras pesquisas de bioprospecção. Este capítulo foi publicado em forma de artigo científico no periódico Journal of Ethnopharmacology, em outubro de 2021 (DOI: 10.1016/j.jep.2021.114248) (ANEXO D).

Capítulo 3: intitulado "Chemical composition, antioxidant, antibacterial and modulating activity of the essential oil of three species of *Psidium* L. (Myrtaceae Juss.) from northeastern Brazil", traz uma análise sobre três espécies medicinais nativas de *Psidium* que ocorrem na Chapada do Araripe e em outros domínios fitogeográficos brasileiros. O objetivo desse estudo foi: analisar a composição química do óleo essencial das folhas de *Psidium laruotteanum* Cambess. (Marangaba-peluda), *Psidium salutare* (Kunth) O. Berg (Marangaba-vermelha) e *Psidium sobralianum* Landrum & Proença (Araçá-de-veado), e investigar o potencial antibacteriano e antioxidante, assim como capacidade moduladora de antibióticos, atrelado a seus óleos essenciais. Este capítulo encontra-se nas normas do periódico Biocatalysis and Agricultural Biotechnology, ao qual está submetido (ANEXO E).

Capítulo 4: "Considerações finais", aborda as principais conclusões da tese, relacionando os resultados aos objetivos propostos para cada um dos artigos elaborados.

2. CAPÍTULO 1: FUNDAMENTAÇÃO TEÓRICA

2.1. CARACTERIZAÇÃO ETNOBIOLÓGICA E QUÍMICA DO GÊNERO *Psidium* L.

2.1.1. FAMÍLIA MYRTACEAE JUSS.

A família Myrtaceae Juss. está inserida na ordem Myrtales, distribuída nas regiões tropicais e subtropicais do globo, com picos de diversidade na América do Sul, Austrália, sudeste da Ásia e em partes da África. É considerada umas das famílias mais ricas do mundo em número de espécies, representada por 6019 espécies, 144 gêneros e 17 tribos (PROENÇA et al., 2020; WCSP, 2017; WILSON, 2011). No Brasil, os representantes de Myrtaceae abrigam 29 gêneros e somam 1193 espécies, sendo 784 endêmicas (PROENÇA et al., 2020). Suas espécies podem apresentar-se em forma de árvores, arbustos ou subarbustos com córtex liso ou rugoso; flores com coloração predominantemente branca; frutos do tipo baga, podendo conter uma ou várias sementes com testa membranácea a óssea; geralmente as folhas são opostas, sem estípulas, pecioladas, com pontuações translúcidas que apontam a presença de cavidades secretoras de óleos essenciais (HEINZMANN; SPITZER; SIMÕES, 2017; PROENÇA et al., 2020).

Estudos ecológicos com Myrtaceae tem demonstrado sua importância para a funcionalidade ambiental, salientando que a produção contínua de seus frutos é um recurso fundamental durante períodos de escassez de alimentos, evidenciando o papel chave dessa família para a manutenção da fauna frugívora (STAGGEMEIER; CAZETTA; MORELLATO, 2017). Para a espécie humana é uma família de destaque, apresentando elevado valor econômico por compreender um grande número de espécies com potencial alimentar, podendo ser comercializadas *in natura* para uso na fabricação de doces, geleias, licores, sorvetes, dentre outros. Os principais gêneros de interesse econômico são *Eugenia*, *Myrciaria* e *Psidium* (FRANZON et al., 2009; PEREIRA et al., 2012).

Myrtaceae, além de evidenciar uma rica flora frutífera com potencial ecológico e comercial, é significativamente reconhecida por populações tradicionais na utilização de suas espécies na medicina popular (ARAÚJO et al., 2019; MACEDO et al., 2021). Dessas, *Capomanesia xanthocarpa* O. Berge. (Guabiroba), *Eugenia uniflora* L. (Pitanga), *Eucalyptus globulus* Labill. (Eucalipto), *Myrciaria tenella* (DC.) O. Berg (Cambuí/murta) e espécies do gênero *Psidium* como, *Psidium cattleyanum* Sabine (Araçá amarelo), *Psidium guajava* L. (Goiaba) e *Psidium guineense* Sw. (Araçá) são exemplos culturalmente usados na medicina por diversas comunidades (ARAÚJO et al., 2019; CRUZ; KAPLAN, 2004; FRANZON et al., 2009; MORAIS-BRAGA et al., 2016b; PEREIRA et al., 2012; YAZBEK et al., 2019).

2.1.2. GÊNERO *Psidium* L.

O gênero *Psidium*, pertencente à família Myrtaceae, abriga 185 espécies em todo o mundo, com destaque para o Brasil, país com maior número de ocorrência dessas espécies, 26458 (GBIF, 2020). Precisamente, em território Brasileiro já foram catalogadas para o gênero 60 espécies, sendo 39 endêmicas (TULER; PROENÇA; COSTA, 2020). Dos gêneros com maior números de espécies da família Myrtaceae identificados na Flora do Brasil, *Psidium* fica atrás apenas de *Eugenia* L., constituído por 407 espécies, representando o gênero de maior riqueza dentro da família (MAZINE et al., 2020; TULER; PROENÇA; COSTA, 2020).

Psidium possui distribuição Neotropical, podendo ser encontrado do Sul do México à Argentina, na Índia e em arquipélagos do Pacífico (FRANZON et al., 2009). O Brasil é considerado um dos centros de diversidade para o gênero, estando representado em todos os domínios fitogeográficos, com destaque para a Mata Atlântica e Cerrado, ambos somam mais de 60% do total das espécies para o país (FRANZON et al., 2009; TULER; PROENÇA; COSTA, 2020).

Morfologicamente o gênero pode ser caracterizado por folhas simples e opostas com nervura submarginal, apresentando forma de vida desde árvores de grande porte a pequenos arbustos. Flores pentâmeras; sépalas livres ou totalmente fundidas; pétalas livres de cor branca ou creme; frutos com variações de cores, como verdes, verde-amarelados ou amarelos; muitas sementes por furto; sementes com testa óssea (TULER et al., 2017; TULER; PROENÇA; COSTA, 2020).

As espécies de *Psidium* têm grande relevância ecológica, econômica e medicinal. Ecologicamente, seus frutos carnosos com sementes pequenas, servem de alimentos para diversos animais, como pássaros e mamíferos. Essa relação ecológica tem promovido a conservação de diversidade do gênero, uma vez que os animais atuam como agentes dispersores de sementes (GRESSLER; PIZO; MORELLATO, 2006; STAGGEMEIER; CAZETTA; MORELLATO, 2017). As propriedades organolépticas dos frutos e o elevado teor de vitamina C, confere as espécies de *Psidium* grande interesse econômico, podendo ser consumidos *in natura* ou processados na forma de doces, geleias e sucos. *Psidium guajava* L. (goiaba, espécie naturalizada) é a representante de maior interesse econômico, já as espécies nativas destacam-se *Psidium cattleyanum* Sabine e *Psidium guineense* Sw., conhecidas popularmente como araçazeiros (FRANZON et al., 2009).

Na medicina popular, espécies de *Psidium* são utilizadas como agentes terapêuticos, através do aproveitamento de partes como caule, raiz, folhas e flores, preparadas principalmente através de infusões e decocções. Sua utilização tem histórico no tratamento de doenças e sintomas associadas a vários sistemas corporais, com indicações para dores de cabeça, gripes, problemas geniturinários e principalmente a distúrbios do sistema digestório como dores estomacais, intestinais, diarreias e disenteria (MACEDO et al., 2021; MORAIS-BRAGA et al., 2016b).

As diversas indicações terapêuticas de espécies medicinais nativas de *Psidium*, têm despertado a atenção da indústria farmacêutica por serem ricas em substâncias antioxidantes, antimicrobianas, antiflamatórias e atnociceptivas de extratos vegetais e óleos essenciais (CAMPOS E SILVA et al., 2021; FRANZON et al., 2009; MACEDO et al., 2021).

2.1.3. *Psidium laruotteanum* CAMBESS.

Psidium laruotteanum é uma espécie encontrada no continente Americano, principalmente em países da América no Sul (TROPICOS, 2021a). No Brasil, ocorre em forma de arbusto, medindo de 1 a 3 metros, com ocorrência registrada em todos as regiões brasileiras em domínios fitogeográficos como Mata Atlântica, Pampa e Cerrado (PROENÇA; COSTA; TULER, 2020d). É conhecida popularmente como Araçá-cascudo, no Brasil central e Marangaba na região Nordeste (FAGG et al., 2015; PROENÇA; COSTA; TULER, 2020d).

Para populações do Cerrado, a espécie é fonte de alimento tanto humano quanto animal. O sabor exótico de seus frutos, a torna muito apreciada para consumo *in natura* e em formas de doces e geleia (FRANZON et al., 2009; MEDEIROS et al., 2018). Nas áreas de ocorrência natural de *P. laruotteanum* e outros araçazeiros, estes representam (embora pequena) uma fonte adicional de renda para as populações locais. No entanto, essa atividade está ameaçada, haja vista os avanços da agricultura empresarial intensiva, colocando em risco a existência e manutenção das espécies (BEZERRA et al., 2018). Na etnobotânica médica, ainda é uma espécie desconhecida.

Estudos com abordagens de composição química, têm descrito *P. laruotteanum* com teor de compostos fenólicos totais, a partir da infusão das folhas, de 576,56 mg de ácido gálico equivalentes por gramas de extrato seco (TAKAO; IMATOMI; GUALTIERI, 2015). A composição do óleo essencial, é rica em monoterpenos e monoterpenóides, onde o composto p-cimeno figura como o majoritário, com concentração variando de 19,4 % a 34, 8 %. Outros compostos merecem destaque, 1,8 cineol (6,9 % - 19,2 %), α-pinene (9,2 % - 13,4 %) e γ-terpinene (3,6 % - 14 %) (MEDEIROS et al., 2018).

Com relação a atividade biológica, possui resultados promissores. Atividade antioxidante, associada ao alto teor de conteúdo fenólico em sua composição (TAKAO; IMATOMI; GUALTIERI, 2015). Atividade antiparasitária, onde os extratos de hexano (IC_{50} 3,9 µg / mL) e acetato de etila (IC_{50} 6,8 µg / mL) das folhas foram os mais ativos contra *Trypanosoma brucei gambiense*, e contra *Plasmodium falciparum*, o extrato de acetato de etila (IC_{50} 16,3 µg/mL) se mostrou mais eficaz (CHARNEAU et al., 2016). Os mesmos autores atestaram que os extratos não apresentaram citotoxicidade contra células L6. Atividade microbiana e inseticida de extratos botânicos contra *Diabroica speciosa* e bactérias isoladas do seu intestino. Sendo o extrato de acetato de etila capaz de controlar o desenvolvimento e a população de *D. speciosa*, principalmente pela presença de β'-chalcanone, composto que atua como defesa química contra insetos (LUIZ et al., 2017). O óleo essencial, testado contra o fungo xilófago *Gloeophyllum trabeum*, demostrou inibição muito pequena, cerca de 9 %, na maior concentração testada (MEDEIROS, 2014).

2.1.4. *Psidium myrsinites* DC.

Psidium myrsinites conhecida popularmente como Araçá, é encontrada na natureza em forma de árvore ou arbusto. Espécie frutífera nativa do Brasil, alcançando até seis metros de altura e circunferência do tronco com cerca de 21 cm. É extensamente distribuída pelas regiões brasileiras, exceto a região Sul, com ocorrência em domínios de Caatinga e Cerrado, áreas de constante estresse abiótico, incluindo água e temperaturas extremas (BEZERRA et al., 2018; FRANZON et al., 2009; PROENÇA; COSTA; TULER, 2020a). Alguns indivíduos possuem glândulas laminares visíveis (tecido especializado em secretar óleos e outros produtos) e suas folhas ao serem trituradas exalam cheiro agradável, constatando a presença de óleos essenciais (BEZERRA et al., 2018; GONÇALVES; LORENZI, 2011; SILVA JÚNIOR, 2005).

Folhas, frutos e casca do caule de *P. myrsinites*, são utilizados na preparação de medicamentos caseiros no sistema médico local de populações de Cerrado da Chapada do Araripe na porção do Ceará. Através de infusão das folhas e imersão da casca do caule em água, as comunidades tratam sintomas como diarreias e dores de estômago, inerentes ao sistema digestório (LOZANO et al., 2014; RIBEIRO et al., 2014). Como em outras espécies de *Psidium*, seus frutos são valorizados na alimentação humana, sendo utilizados na fabricação de geleias e sucos, além de serem consumidos *in natura* (FRANZON et al., 2009).

Um importante constituinte químico usado em cosméticos e perfumes para fixar a fragrância na pele, o linalol, é encontrado no óleo essencial das folhas de *P. myrsinites*. A presença desse composto nesta espécie, e em outros *Psidium*, *P. sartorianum* (O. Berg) Nied. e *P. salutare* (BEZERRA et al., 2018; MACÊDO et al., 2018), podem representar uma alternativa sustentável para a exploração desse recurso, visto que a principal fonte de linalol é *Aniba rosiodora* Ducke (Pau-rosa), onde o óleo é extraído do tronco, colocando as populações dessa espécie em risco eminente (BEZERRA et al., 2018; CASTELO; MENEZZI; RESCK, 2010; FRANZON et al., 2009).

Extraído principalmente das folhas, o óleo essencial de *P. myrsinites* apresenta predomínio de derivados caryophyllenes (CAMPOS E SILVA et al., 2021; MACEDO et al., 2021). Análises químicas de diferentes regiões do Brasil, têm demostrado constância nos constituintes químicos majoritários da espécie. Por exemplo, no Centro-oeste do Brasil houve preponderância de *E*-cariofileno (31 %), α-humuleno (12,3 %), óxido de cariofileno (7,3 %) (DURÃES et al., 2017) e óxido de cariofileno (26,1 %), epóxido de humuleno (8,8 %), β-cariofileno (7,4 %), α-cariofileno (5,4 %), mirceno (5,4 %) (MEDEIROS et al., 2015). Assim como no Nordeste, onde os compostos *(E)*-β-cariofileno (26,1 %), α-humuleno (23,9 %), óxido de cariofileno (10,1 %), epóxido de humuleno II (6,4 %), e cariofiledienol II (5,66 %) figuram como os majoritários (DIAS et al., 2015).

Pesquisas têm apontado atividades biológicas para o óleo essencial de *P. myrsinites*, principalmente como inseticida. A espécie apresentou atividade larvicida frente a larvas de *Aedes aegypti* L. (vetor transmissor da dengue e da Chikungunya) com concentração letal (CL) de CL_{50} 292 mg/L (DIAS et al., 2015), sendo esta, considerada uma concentração eficaz desenvolvida a partir de produtos naturais, com potencial larvicida contra mosquitos, segundo critérios estabelecidos por Komalamisra et al. (2005).

Investigações antibacterianas indicam que os compostos químicos presentes nos extratos etanoico e cetônicos das folhas de *P. myrsinites* frente a cepas de *Staphylococcus aures* e *S. epidermidis,* podem ser substâncias usadas no tratamento de patologias causadas por agentes microbianos (DURÃES et al., 2017), visto que as concentrações testadas foram sensíveis aos extratos com intensidade moderada (HOLETZ et al., 2002). O mesmo não aconteceu com o óleo essencial, apresentando concentração inibitória mínima com valores > 2.000 µg.mL^{-1} contra todas as bactérias testadas (DURÃES et al., 2017). Resultado divergente, quando analisada outra espécie nativa do gênero com composição química semelhante a *P. myrsinites,* rica em derivados cariofilanos. Por exemplo *P. myrtoides* O. Berg. apresenta entre os compostos majoritários trans-*β*-cariofileno (30,09 %), α-humuleno (15, 9 %) e oxido de cariofileno (7,3 %) e demostrou moderada atividade antibacteriana frente a *Streptococcus mitis*, *S. sanguinis*, *S. sobrinus*, *S. salivarius*, e forte atividade frente a *S. mutans* com MIC 62,5 µg/mL (DIAS et al., 2019).

2.1.5. *Psidium salutare* (KUNTH) O. BERG

Psidium salutare é amplamente distribuída nas Américas, indo do México ao Uruguai, sendo endêmica da parte ocidental de Cuba (PINO; QUERIS, 2008; TROPICOS, 2021b). Nativa da flora brasileira, forma de vida arbustiva ou subarbustiva, com tamanho variando entre um e três metros de altura. É distribuída em todas as regiões do Brasil, com ocorrência em domínios fitogeográficos de Cerrado, Amazônia, Mata Atlântica e Pampas. Possui vários sinônimos e uma variedade, *Psidium salutare* var *pohlianum* (O. Berg) Landrum, distinguindo-se pelo tamanho, até 10 metros, folhas maiores e casca ásperas com fendas profundas (LANDRUM, 2003; PROENÇA; COSTA; TULER, 2020e).

São escassos registros na literatura que aponte *P. salutare* sendo empregada por populações locais para alguma utilização. As informações são vagas ou referências utilizadas não direcionam para afirmações precisas. Bezerra et al. (2018); Franzon et al. (2009), indicam que esta, encontra-se entre uma das principais espécies do gênero na Região Centro-Oeste do Brasil, mas não especificam em quais quesitos. Macêdo et al. (2018), afirmam que na Região do Cariri (Nordeste do Brasil) a mesma é utilizada na alimentação e na medicina popular para tratar doenças e sintomas associadas ao sistema digestório, porém as referências utilizadas para tal afirmação, mostra espécies de *Psidium* identificadas apenas a nível de gênero. Não sendo, portanto, uma informação consistente. A informação mais próxima a uma utilização popular é a da comunidade La Lechura, município de Los Palacios em Cuba, onde possui uma área produtora de Guayabita del Pinar (nome vernáculo para a espécie, na referida localidade), utilizada com recurso florestal não madeireiro, vindo a se tornar uma bebida, conhecida pelo mesmo nome popular (ÁVILA-GARCÍA; MEZQUÍA-MESA; VALDÉS-RODRIGUEZ, 2018).

Análises químicas do óleo essencial de *P. salutare*, demonstra que as folhas da espécie são ricas em terpenos, com maiores concentrações para p-cimeno (17,83%), γ-terpineno (17,09%), terpinoleno (16,99%), τ-cadinol (15,20%) (MACÊDO et al., 2018) e Caryophyllene oxide (39,8 %) e ar-turmerone (17,3 %) (PINO et al., 2003). Para os frutos, 109 compostos voláteis foram identificados, sendo encontrados terpenoides, ésteres e derivados cinamila. Os compostos majoritários dessas análises foram, limone (17,3%), mirceno (16,2%), α-pineno (9,3%), viridiflorol (37,28 mg / l), epi-α-cadinol (28,79 mg / l), linalol (12,88 mg / l) e α-cadinol (12,34 mg / l) (PINO; MARBOT; BELLO, 2002; PINO; QUERIS, 2008).

Atividades antifúngicas têm sido evidenciadas para o óleo essencial de *P. salutare*, quando testadas frente a cepas do gênero *Candida*. O óleo apresenta atividade modulatória, principalmente para *C. albicans* 40006 com IC_{50} variando de 2,7 µg/mL a 8,0 µg/mL, exibindo concentrações menores do que o fluconazol (antifúngico sintético) com IC_{50} 16,7 µg/mL (MACÊDO et al., 2018).

Outras atividades farmacológicas têm sido demostradas para *P. salutare*. Atividade antioxidante do extrato de acetato de etila foi demostrado por Simonetti et al. (2016), com inibição de 94,08 % do radical DPPH a uma concentração de 50 µg/mL e IC_{50} de 13,63 ± 0,51 µg/mL do extrato etanoico. E ainda, atividade antibacteriana do extrato hexânico frente a *Listeria monocytogenes*, com concentração inibitória mínima (CIM) de 312, 5 µg/mL e concentração bactericida mínima (CBM) de 625 µg/mL.

2.1.6. *Psidium sobralianum* LANDRUM & PROENÇA

Psidium sobralianum é uma espécie endêmica do Brasil, recém descrita (2015), com forma de vida arbustiva ou arbórea, com altura variando de três a 25 metros de altura. Tem ocorrência confirmada região Norte (Pará) e mais amplamente no Nordeste (Ceará, Maranhão, Pernambuco), em domínios fitogeográficos de Caatinga, Cerrado e Carrasco (LANDRUM; PROENÇA, 2015; PROENÇA; COSTA; TULER, 2020b). É estreitamente relacionada com *P. bahianum* (espécie que ocorre na Mata Atlântica Baiana) e os autores as consideram espécies alopátricas, ambas ocorrendo no Nordeste Brasileiro, que concentra uma grande diversidade de Myrtaceae de modo geral (LANDRUM; PROENÇA, 2015; PROENÇA; COSTA; TULER, 2020c, 2020b).

Na medicina popular, é comumente conhecida como Araçá de veado e tem sido usada pela população local da Chapada do Araripe para tratar transtornos do sistema digestório, como disenteria (LOZANO et al., 2014), e no alívio de sintomas respiratórios, como dores de garganta e gripe (Beatriz M. Gomes, comunicação pessoal - LANDRUM; PROENÇA, 2015). A população ainda a utiliza na alimentação, especialmente devido a características específicas dos frutos de muitas espécies nativas de *Psidium*, com sabor exótico e elevado teor de vitamina C (ASSIS et al., 2020; BEZERRA et al., 2018; FRANZON et al., 2009).

Psidium sobralianum, está entre as frutas da sociobiodiversidade do Nordeste do Brasil com quantidades variáveis de vitaminas importantes para a saúde humana, como por exemplo vitamina B5, B6 e principalmente vitamina C, com valores variando de 2,03 mg/100g a 4,13 mg/100g da fração comestível. Além de ser fonte de carotenoides, conhecidos por desempenhar relevante papel na prevenção de câncer e atividade antioxidante (ASSIS et al., 2020).

A presença de compostos fenólicos no extrato hidroalcóolico das folhas de *P. sobralianum*, foi responsável pela atividade antioxidante com teor de compostos fenólicos de 417,48 mg/g e flavonoides de 12,54 mg/g (SOBRAL-SOUZA et al., 2014). É uma espécie com poucos relatos bibliográficos sobre atividades biológicas, assim como, análise de composição química, principalmente do óleo essencial.

2.2. ÓLEOS ESSENCIAIS E ATIVIDADES BIOLÓGICAS

Os óleos essenciais podem ter diversas nomenclaturas, sendo chamados de óleos voláteis, óleos etéreos ou essências. São misturas complexas de substâncias voláteis, obtidas de matérias-primas vegetais. Entre suas principais características estão, a volatilidade, aroma agradável e intenso (na maioria das espécies), solubilidade em solventes orgânicos apolares (HEINZMANN; SPITZER; SIMÕES, 2017).

Os componentes químicos presentes nos óleos essenciais podem variar de 20 a 200 compostos, e cerca de 3.000 substâncias químicas distintas já foram detectadas em óleos essenciais (HEINZMANN; SPITZER; SIMÕES, 2017). Embora exista uma grande diversidade química observada para os óleos essenciais, as classes mais encontradas são os fenilpropanoides e os terpenos. Estruturalmente os terpenos são formados pela combinação de unidades de isopreno ($C_5 H_8$), resultando na produção de hidrocarbonetos. Os principais terpenos oriundos dessas combinações são os monoterpenos ($C_{10} H_{16}$) e sesquiterpenos ($C_{15} H_{24}$) ou cadeias mais longas, como diterpenos ($C_{20} H_{32}$) e triterpenos ($C_{30} H_{40}$). Quando há adição de moléculas de oxigênio, esses passam a ser chamados de terpenoides. Os fenilpropanoides, são menos variados do que os terpenos. São caracterizados por um anel aromático ligado a uma hidroxila e uma cadeia de três átomos de carbonos (CARSON; HAMMER, 2010; HEINZMANN; SPITZER; SIMÕES, 2017).

Os óleos essenciais têm sido usados há séculos como remédios terapêuticos. Nas últimas décadas, pesquisas têm revelado diversas atividades biológicas relacionadas ao seu uso. Atividades com efeitos antibacterianos, antifúngicos, anti-inflamatórios, antirreumáticos, antitússicos, antioxidantes, expectorantes, imunomoduladores e sedativos, têm sido evidenciadas (AMORATI; FOTI; VALGIMIGLI, 2013; CARSON; HAMMER, 2010). Estes, podem atuar ainda, na cognição, memória e humor. Os meios de aplicação dependem da fisiopatologia. Para sintomas respiratórios e nervosos, o tratamento pode ser feito por meio de inalação, enquanto doenças de pele, por exemplo herpes labial e herpes genital, a aplicação tópica é a melhor forma de terapia. Essas atividades podem ser atribuídas, aos principais grupos de compostos encontrados nos óleos essenciais, os monoterpenos e sesquiterpenos, presentes em proporções significativas (CARSON; HAMMER, 2010).

A quantidade dos diferentes componentes dos óleos essenciais, podem variar entre as partes da planta (folha, flor, casca, raiz e semente), assim como entre espécies de plantas (CHALCHAT; ÖZCAN, 2008; HEINZMANN; SPITZER; SIMÕES, 2017; MAGGIONI et al., 2018). Diferentes técnicas são empregadas para extração de óleos essenciais, como destilação a vapor, extração de solvente e extração de fluido supercrítico (HEINZMANN; SPITZER; SIMÕES, 2017). Entre suas características e de seus componentes está a hidrofobicidade, o que favorece seu mecanismo de ação causando danos irreversível na parede e membrada celular bacterina, tornando-as mais permeáveis. Isso pode resultar na morte da célula bacteriana devido ao vazamento de proteínas e moléculas de DNA e RNA (CHOUHAN; SHARMA; GULERIA, 2017; VALDIVIESO-UGARTE et al., 2019).

Compostos químicos do tipo terpenoides como mentol, timol, carvacrol, geraniol e linalol, que apresentam em sua estrutura átomos de oxigênio ou grupo metila, apresentam maior atividade antibacteriana. Estando esse fato relacionado aos seus grupos funcionais, sendo o grupo hidroxila e a presença de elétrons desemparelhados, elementos importantes para a ação antimicrobiana (NAZZARO et al., 2013). Já hidrocarbonetos como terpineno, limoneno, pineno e 1,8-cineol (presente em muitas espécies de *Psidium*, as vezes como compostos majoritários), demonstram atividade antibacteriana elevada, no entanto menos eficientes quando comparadas aos terpenoides (BASAVEGOWDA; BAEK, 2021; NAZZARO et al., 2013). De maneira geral, a eficácia antibacteriana depende de diferentes características dos óleos essenciais e seus componentes, como por exemplo a presença de determinados grupos químicos, estruturas em anel e cadeias laterais (BASAVEGOWDA; BAEK, 2021).

Além de atividade antibacteriana, os óleos essenciais desempenham papel importante em atividades antioxidantes, o que é justificado pelo envolvimento do estresse oxidativo na doença. Essas propriedades se deve ao modo de ação de alguns de seus componentes, em especial os compostos fenólicos, com capacidade de interromper ou retardar a oxidação, prevenção de iniciação de cadeia, sequestradores de radicais livres, agentes redutores, dentre outras (AMORATI; FOTI; VALGIMIGLI, 2013). Os constituintes do tipo fenólicos, são compostos orgânicos formados por um grupo hidroxila (-OH) ligado diretamente a um átomo de carbono no anel aromático. O átomo de hidrogênio do grupo hidroxila pode ser doado aos radicais livres, evitando assim que outros compostos sejam oxidados (TONGNUANCHAN; BENJAKUL, 2014).

Outras substâncias naturais presentes nos óleos essenciais, sem o grupo fenol, expressam comportamento antioxidante. Por exemplo, terpenoides com estrutura de ciclohexadieno, como o γ-terpineno (AMORATI; FOTI; VALGIMIGLI, 2013) presente no óleo essencial de várias espécies botânicas incluído as do gênero *Psidium* (CAMPOS E SILVA et al., 2021; MACEDO et al., 2021), causam aumento na taxa de terminação da cadeia oxidativa, encurtando dessa maneira o comprimento da cadeia e reduzindo a taxa geral de oxidação. Exibindo portanto, comportamento antioxidante (AMORATI; FOTI; VALGIMIGLI, 2013).

Alguns fatores como a espécie botânica, genética, variação geográfica, condições ambientais, dentre outros, podem afetar a composição química dos óleos essenciais, refletindo em diferentes atividades antioxidantes. Isso também se aplica a óleos obtidos por diferentes técnicas de extração. Por exemplo, o teor de eugenol no óleo essencial das folhas de *Pimenta dioica* (L.) Merr. (Myrtaceae) foi de 77,4 % quando obtido por extração com fluido supercrítico (EFS), e de apenas 45,4 % por hidrodestilação (MARONGIU et al., 2005).

Espécies de *Psidium* têm demonstrado atividade antioxidante atrelada a seus compostos químicos, tanto por extração de solvente usando hexano, metanol, etanol, acetona, quanto por hidrodestilação, no caso dos compostos voláteis. Como exemplo podem ser citadas as espécies *P. brownianum, P. cattleyanum, P. grandifolium, P. guajava, P. guineense, P. laruotteanum, P. salutare* (CAMPOS E SILVA et al., 2021; MACEDO et al., 2021).

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3. CAPÍTULO 2: MANUSCRITO I

Título: Therapeutic indications, chemical composition and biological activity of native Brazilian species from *Psidium* genus (Myrtaceae): A review

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Therapeutic indications, chemical composition and biological activity of native Brazilian species from *Psidium* genus (Myrtaceae): A review.

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Abstract
Ethnopharmacological importance: Brazilian medicinal species of the *Psidium* genus are rich in secondary metabolites such as terpenes and phenolic compounds and present biological activities for several human diseases. For the native *Psidium* species, there are no specific research reports for any member of the genus about ethnobotanical research, hindering the joint analysis of its therapeutic indications together with the scientific evidence already investigated.

Study objective: Analyze the therapeutic indications, the main chemical constituents, and the biological activities of native species of the *Psidium* to Brazil.

Materials and methods: Systematic research was carried out in the Scopus, ScienceDirect, PubMed, and Web of Science databases over a period of ten years. Articles in English, Portuguese and Spanish were used. The research was divided into three phases, seeking information on ethnobotany, chemical composition and biological activities. The words were combined to structure the descriptors used in the search.

Results: A total of 13 native species belonging to the *Psidium* genus were identified in this analysis, *Psidium acutangulum* DC., *Psidium brownianum* Mart. ex DC., *Psidium cattleyanum* Sabine, *Psidium densicomum* Mart. ex DC., *Psidium grandifolium* Mart. ex DC., *Psidium guineense* Sw., *Psidium laruotteanum* Cambess., *Psidium myrsinites* DC, *Psidium myrtoides* O. Berg, *Psidium salutare* (Kunth) O. Berg, *Psidium schenckianum* Kiaersk., *Psidium sobralianum* Proença & Landrum, *Psidium striatulum* Mart. ex DC. Of these, six were indicated in folk medicine, digestive system disorders being their main therapeutic indication. Most species presented an investigation of chemical composition and biological activity. They are rich in phenolic compounds, flavonoids, and terpenes and have antimicrobial, antioxidant, antiproliferative, and repellent activities.

Conclusions: Native species of the *Psidium* genus are important sources of active ingredients in combating adversities that affect the human health, especially regarding the digestive system. They have a rich chemical composition, responsible for the biological activities demonstrated for the species.

Keywords: Ethnobotanical survey; Medicinal plants; Chemical characterization; Biological activity; *Psidium*.

1. Introduction

The richness of Brazilian medicinal species has contributed considerably to the development of therapeutic alternatives through the identification of secondary metabolites, which present activity for several diseases that affect human health (Zivarpour et al., 2021). Among these species, the Myrtaceae family stands out, one of the ten angiosperms families with the most diversity, with 1,028 species and 27 genera (BFG et al., 2015; Flora do Brasil, 2020). The *Psidium* genus, belonging to this family, is well distributed with around 185 species in the world (GBIF, 2021). It houses species in all phytogeographic domains of the Brazilian territory, presenting a wealth of 60 species, of which more than 65% (39 species) are considered endemic (Flora do Brasil, 2021).

Members of this genus are indicated in ethnobotanical research for curing various human diseases (Abreu et al., 2015; Santana et al., 2016; Yazbek et al., 2019) and some have already proven their popular uses through investigations (Macaúbas-Silva et al., 2019; Macêdo et al., 2018). They present of fruits of commercial interest for the food industry (Franzon et al., 2009) and leaves rich in essential oils (Weli et al., 2019). Species of this genus, such as *Psidium guajava* L., have stood out in research in several areas (Ribeiro et al., 2017; Souza et al., 2018; Weli et al., 2019) probably for being distributed thoughout the entire Brazilian territory, despite being naturalized (Flora do Brasil, 2020).

For native species, some works with chemical and pharmacological research are reported (Dias et al., 2015; Houël et al., 2016; Macêdo et al., 2018; Schiassi et al., 2018; Vinholes et al., 2017). However, there are no specific researches for any native member of the genus regarding to ethnobotanical research, as they are found in surveys (checklists) along with several other species. Scientific research with native species popularly used to cure diseases can benefit both the health of communities and enhance the development, management and commercialization of these plants and their by-products by the food, phytotherapy and pharmaceutical industries.

The medicinal importance of the *Psidium* genus, the relevance of chemical and pharmacological properties linked to the need for further studies that gather information on species of this genus native to Brazil, this research aimed to analyze its therapeutic indications, main chemical constituents and biological activities, thus contributing to a diagnosis on the studies of these species, as well as possibly identifying the presence of a pattern in relation to these investigations, suggesting future bioprospecting researches.

2. Materials and methods

2.1. Search strategy

The research was carried out in four databases: Scopus, ScienceDirect, PubMed and Web of Science. Three parallel searches were carried out, the first sought information on medicinal ethnobotanical use of the *Psidium* genus for Brazil using the following descriptors: 'Ethnobotany, medicinal plants and Brazil', 'Ethnobotany, medicinal plants, *Psidium* and Brazil', 'Traditional medicinal use, *Psidium* and Brazil' and 'Ethnobotany, *Psidium* and Brazil'; the second, information on chemical composition and biological activities of the species found in the first search (*Psidium acutangulum* DC., *Psidium* *cattleyanum* Sabine, *Psidium densicomum* Mart. ex DC., *Psidium guineense* Sw., *Psidium myrsinites* DC., *Psidium sobralianum* Proença & Landrum) , and then combined with the descriptors 'chemical composition', 'biological activity' and 'pharmacological tests'. A third search was carried out on chemical composition and biological activities, in the search for species that were not found in previous searches, because their studies are not directly related to ethnobotany, but that presented the mentioned data (chemical composition and biological activities) (*Psidium brownianum* Mart. Ex DC., *Psidium grandifolium* Mart. Ex DC., *Psidium laruotteanum* Cambess., *Psidium myrtoides* O. Berg, *Psidium salutare* (Kunth) O. Berg, *Psidium schenckianum* Kiaersk., *Psidium striatulum* Mart. Ex DC.). Using the descriptors '*Psidium* and chemical composition', '*Psidium* and biological activity' and '*Psidium* and pharmacological tests'.

2.2. Study selection and inclusion/exclusion criteria

Titles, abstracts and full articles were analyzed according to the research objectives. The selected articles were required to have an ethnobotanical application for medical use and only native species of *Psidium* for Brazil, according to the Flora do Brasil 2020 database (Flora do Brasil, 2020) and those that were correctly identified, genus + specific epithet , were selected. For the correct spelling of scientific names, the websites Flora do Brasil 2020 (Flora do Brasil, 2020) and Tropicos (Tropicos, 2020) were consulted.

The search for descriptors was limited to an interval of 10 years, from January 1, 2010 to December 31, 2019, a period that presents the highest indexes of works published with the theme 'medicinal plants and biologically active natural products' (Yeung et al., 2020). Articles in English, Portuguese and Spanish were used. The articles with information on chemical composition and biological activity were not limited by territory, but followed the same time interval.

Monograph works, dissertations, theses, abstracts published in events, bibliographic reviews, exotic species or naturalized to Brazilian flora, as well as articles that did not present native *Psidium* species or were outside the databases, were not considered in this research.

2.3. Data organization and extraction

The data were organized in Excel spreadsheets. The extracted information included *Psidium* species found in the articles, vernacular names, medicinal use, part used, method of preparation, region of Brazil and later chemical composition and biological activities. Representations of chemical structures were developed in the ChemDraw Ultra v. 12.0.

3. Results and discussion

3.1. Analysis of bibliografic data

The database search generated 4,202 records, using the descriptors already mentioned. After applying the inclusion and exclusion criteria, 1,882 remained, of which 1,750 were excluded based on the title, abstract and duplicates. A total of 132 complete articles were evaluated and 65 were excluded for not meeting the review objectives. Of the 67 articles included for analysis in the present review, 19 were found for descriptors referring to ethnobotany and 48 for those of chemical components, biological activities and pharmacological tests (Fig. 1).

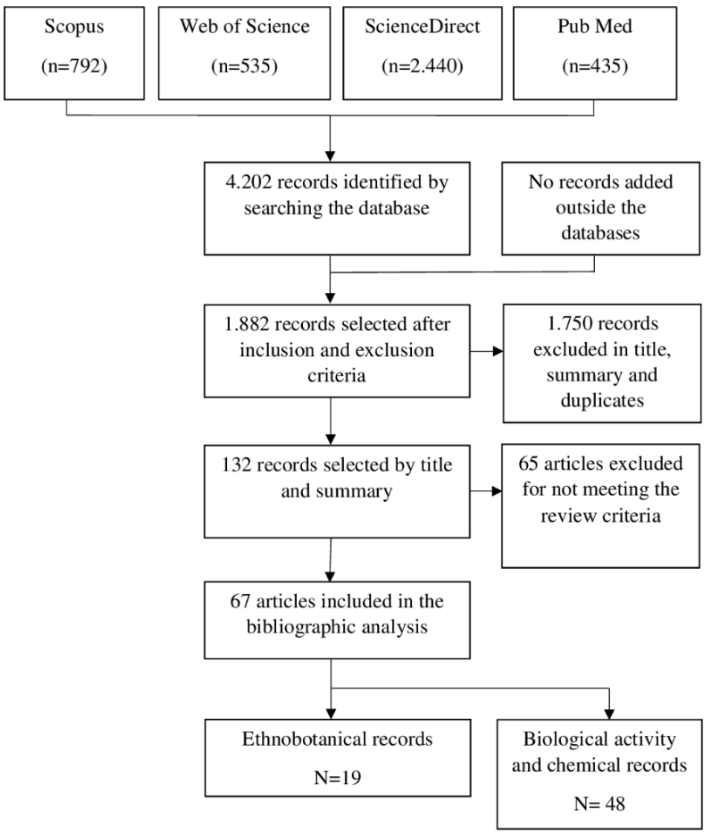

Fig. 1. Diagram of bibliographic records obtained from the review.

3.2. Species, ethnobotany and distribution

A total of 13 native species belonging to the *Psidium* genus were registered in this analysis, *P. acutangulum*, *P. brownianum*, *P. cattleyanum*, *P. densicomum*, *P. grandifolium*, *P. guineense*, *P. laruotteanum*, *P. myrsinites*, *P. myrtoides*, *P. salutare*, *P. schenckianum*, *P. sobralianum*, *P. striatulum*. Of these, six are used in folk medicine, *P. acutangulum*, *P. cattleyanum*, *P. densicomum*, *P. guineense*, *P. myrsinites* and *P. sobralianum* (Table 1). With the exception of *P. sobralianum*, all of them presented research studies on chemical composition and/or biological activity.

The number of species found for the genus *Psidium* was discreet. This number corresponds to just over 20% of the species richness registered in the Flora do Brasil portal, which contains a total of 59 species native to the genus (Flora do Brasil, 2021). Possibly one of the causes to justify this finding is the difficulty in identifying the species, since in many articles some specimens were identified only at the level of genus, and therefore disregarded for this research.

The 19 ethnobotanical articles reviewed varied from 31 to 231 species, where only one (Lozano et al., 2014) registered two *Psidium* species, while the others, one each. It is worth mentioning that, within the investigation criteria, no specific ethnobotanical studies on medicinal uses were found for native species of the *Psidium* genus.

Reports indicate 12 different therapeutic indications and 30 citations for use. *P. cattleyanum* stood out with 16 citations, followed by *P. guineense*, *P. myrsinites* and *P. acutangulum* with six, five and two, respectively. *P. densicomum* and *P. sobralianum* were mentioned only once each. Most of the therapeutic indications found for the species are related to disorders of the digestive system (58.33%), treated by decoctions (63.63%) of the leaves (50%). The species *P. cattleyanum* and *P. guineense* were indicated to treat other systems other systems (although with few indications) such as disorders in the respiratory system (influenza and sore throat), nervous system (headaches) and genitourinary system, deserving more studies that investigate these therapeutic indications, and chemical and biological studies that can validate the mentioned uses.

Regarding the quantitative ethnobotanical indices, 14 articles report the use of some. The most common were Informant Consensus Factor - FIC (8 articles), Use Value - UV (6 articles) and Main Use Agreement - MUA (3 articles). These indices are important to assess the informants' agreement regarding medical use. The more a plant or body system has agreement of use among the informants, the "safer" or more used for a

Table 1: *Psidium* species with therapeutic indications found in the literature.

Scientific name	Vernacular name	Therapeutic indication	Body system	Part Used	Preparation method	Region of Brazil	References
Psidium acutangulum DC.	Goiaba araçá, Goiabarana	Diarrhea, dysentery	DSD (2)	Lb, St	De	N (2)	Palheta et al., 2017; Pedrollo et al., 2016.
Psidium cattleyanum Sabine	Araçá (6), Araçá-roxo, Araçá-do-brejo, Araçá branco	Diarrhea (6), stomach pain (3), digestive system diseases (2), sore throat, stomach pains, genitourinary system diseases, dysentery, respiratory system diseases.	DSD (13), RSD (2) GSD (1)	Le (5), Fr (2), St, Lb	De (5), Sy	NE (4), S (2), SU (2), MW	Abreu et al., 2015; Baptista et al., 2013; Bieski et al., 2015; Bolson et al., 2015; Brito et al., 2017; Castro et al., 2011; Macêdo et al., 2015; Tomazi et al., 2014; Tribess et al., 2015; Yazbek et al., 2019.
Psidium densicomum Mart. ex DC.	-	Diarrhea	DSD	Lb	Ma	N	Santos et al., 2014.

Scientific name	Vernacular name	Therapeutic indication	Body system	Part Used	Preparation method	Region of Brazil	References
Psidium guineense Sw.	Araçá (2), Araçá-mirim	Dysentery (2), influenza, sore throat, bowel problems, stomach pains, diarrhea, headaches	DSD (5), RSD (2) NSD (1)	Le (2)	De, *In*	NE (4)	Beltreschi et al., 2019; Santana et al., 2016; Silva et al., 2012, 2018.
Psidium myrsinites DC.	Araçá, Araçá vermelho, Goiabinha	Diarrhea (2), stomach pain	DSD (3),	Le, Fr	*In*, If	NE (2)	Lozano et al., 2014; Ribeiro et al., 2014.
Psidium sobralianum Proença & Landrum	Goiabinha	Dysentery	DSD	-	-	NE	Lozano et al., 2014.

Subtitle: Body system (DSD: Digestive system disease; GSD: Genitourinary system disease; NSD: Nervous system disease; RSD: Respiratory system disease).
Part used: (Lb: Leaf bud; St:Stem; Le: Leaf; Fr: Fruit).
Preparation method: (De: Decoction; If: Infusion; *In*: *In Natura*; Ma: Maceration; Sy: Syrup).
Region of Brazil: (MW: Midwest; N: North; NE: Northeast; S: South; SE: Southeast).

given purpose that plant is.

The species indicated in popular medicine are distributed in all Brazilian regions, being *P. acutangulum* and *P. densicomum* exclusive to the North region; *P. guineense, P. myrsinites* and *P. sobralianum* exclusive to the Northeast and *P. cattleyanum* was present in almost all regions, except in the North region. Ethnobotanical studies stood out in the Northeast (11 articles), followed by North (3 articles), South and Southeast (2 articles each) and Midwest (1 article).

3.3. Psidium species: ethnobotany, chemical composition and biological activity

Of the species reported in the ethnobotanical studies, *P. acutangulum, P. cattleyanum, P. densicomum, P. guineense* and *P. myrsinites* have some chemical or biological investigation. The others, *P. brownianum, P. grandifolium, P. laruotteanum. P. myrtoides, P. salutare, P. schenckianum, P. sobralianum, P. striatulum*, were recorded only within studies with chemical or biological research, and are not associated with popular use (Table 2). Figure 2 shows the structural representations of the substances identified in the referred species.

Of the 48 articles, 33 presented information on chemical composition and biological activities, ten only chemical, and five biological activities. From these findings, it can be seen that most researchers strive to extract the compounds from the species and investigate whether they have any activity.

The chemical compounds of the *Psidium* species are extracted by different types of solvents. Aqueous extracts were the most used, 19 articles. Then the methanolic and ethanolic extracts, mentioned in ten and six articles, respectively. Fifteen articles used volatile extracts for their analysis.

Chemical compounds extracted from fixed extracts include phenolic content (15 articles), flavonoids (7 articles), catechins, anthocyanins, and B-carotene (4 articles each). For volatile extractions, the content of essential oils has prominent compounds, β-caryophyllene, a-humulene, and α-pinene.

Psidium species were tested for 13 biological activities. Research on antioxidant and antimicrobial activities corresponds to almost 70% of the total. Activities such as antiproliferative, antiplasmodial, anti-inflammatory, antiparasitic are linked to *Psidium* species.

Table 2: Chemical composition and biological activities of species of the *Psidium* genus.

Species	Part used	Extract type	Component identified / isolated	Activities tested / Concentration	Study location	Reference
Psidium acutangulum DC.	Leaves	Aqueous	Myricetin*	-	Venezuela	Rivero-Maldonado et al., 2013.
	Leaves, stem and fruits	Decoction	3'-formyl-2 ', 4', 6'-trihydroxy-5'-methyldydrochalcone *	Antimalarial: IC_{50} 3.3 µg / mL Cytotoxicity: IC_{50} > 100 µg / mL Antioxidant: NO (-13%) a 50 µg / mL	French Guiana	Houël et al., 2015.
	Leaves, caule and fruits	Ethyl acetate	Catechin: 9.1% p / p; Guaijaverin (quercetin-3-O-α-L-arabinopyranoside 0.7% p / p); Wayanin (quercetin-3-O-β- D-xylofuranoside 9.1% p / p); Reynoutrin (quercetin-3-O -β-D xylopyranoside 1.8% p / p); Avicularin (quercetin-3-O-β-L-arabinofuranoside1.5% p / p); Quercitrin (quercetin-3-O-α-L rhamnopyranoside 0.7% p / p).	Antiplasmodial: IC_{50} <1 µg / mL; Cytotoxicity: IC_{50} = 57.4 µg / mL; Anti-inflammatory: 50 µg / mL	French Guiana	Houël et al., 2016.
		Decoction	-	-		

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Species	Part used	Extract type	Component identified / isolated	Activities tested / Concentration	Study location	Reference
		Aqueous	-			
		Hexanic				
				Antiplasmodial: IC_{50} of 3.3 µg / mL;		
				Antiplasmodial: IC_{50} = 2.7 µg / mL;		
				Antiplasmodial: IC_{50} = 32.3 µg / mL		
Psidium brownianum Mart. ex DC.	Leaves	Aqueous	-	Antiparasitic: 1000 µg / mL 100% inhibition; Cytotoxicity: 90.85%	Brazil	Machado et al., 2018.
		Hydroethanolic	-	Antiparasitic: 1000 µg / mL 100% inhibition Cytotoxicity: 59.73%.		
	Leaves	Aqueous	Luteolin: 10.34 mg / g. Quercetin: 7.08 mg / g; Kaempferol: 6.97 mg / g; Quercitrin: 4.32 mg / g; Rutin: 4.29 mg / g;	Antimicrobial: IC_{50} 2924.15 µg / mL	Brazil	Morais-Braga et al., 2016a.

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Species	Part used	Extract type	Component identified / isolated	Activities tested / Concentration	Study location	Reference
			Chlorogenic acid: 4.05 mg / g;			
			Ellagic acid: 3.84 mg / g;			
			Coumarin: 3.10 mg / g;			
			Gallic acid: 2.98 mg / g;			
			Caffeic acid: 1.76 mg / g;			
			Catechin: 1.70 mg / g;			
		Hydroethanolic	Quercetin: 11.54 mg / g;	Antimicrobial:		
			Kaempferol: 8.93 mg / g;	IC_{50} 1056.82 µg / mL;		
			Coumarin: 7.18 mg / g;			
			Quercitrin: 5.63 mg / g;			
			Luteolin: 5.61 mg / g;			
			Caffeic acid: 5.41 mg / g;			
			Ellagic acid: 4.35 mg / g;			
			Catechin: 4.28 mg / g;			
			Gallic acid: 3.15 mg / g;			
			Rutin: 2.67 mg / g;			
			Chlorogenic acid: 0.09 mg / g;			

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Species	Part used	Extract type	Component identified / isolated	Activities tested / Concentration	Study location	Reference
	Leaves	Aqueous Hydroethanolic	Phenolic content: 80.77 GAE / g. Phenolic content: 49.25 GAE / g	Antimicrobial: IC_{50} 2.05 µg / mL Antimicrobial: IC_{50} 8.30 µg / mL	Brazil	Morais-Braga et al., 2016b.
	Leaves	Hydroethanolic	-	Antimicrobial: CIM 512 µg / mL	Brazil	Morais-Braga et al., 2016c.
	Leaves	Ethanolic	Flavonoids: 70.97 µg / g of quercetin.	Antioxidant: Fe^{2+}: EC_{50} 360.66 µg / g; Fe^{3+}: EC_{50} 756.20 µg / g; FRAP: EC_{50} 23.27 mmol/g; Antimicrobial: MIC ≥ 1024 µg / mL.	Brazil	Sobral-Souza et al., 2019.
Psidium cattleyanum Sabine	Leaves	Essential oil	β-caryophyllene: 31.5%; α-humulene: 4.4%	-	Tahiti	Adam et al., 2011.
	Seeds	Methanolic	Total phenolic: 501.33 mg / 100 g GAE of d. w.; Total flavonoid: 100.20 mg / 100 of quercetin of d. w.	Antioxidant: TEAC: 156 µM/g	Brazil	Biegelmeyer et al., 2011.

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Species	Part used	Extract type	Component identified / isolated	Activities tested / Concentration	Study location	Reference
	Fruits	Essential oil	β-caryophyllene: 22.5%;			
			β-selinene: 10.1%;	-		
			α-selinene: 9%.			
	Fruits	Aqueous	(-) - Epicatechin: 1059.3 µg g^{-1};	Antioxidant: DPPH: 39.89%	Brazil	Medina et al., 2011.
			Gallic acid: 637.1 µg g^{-1};	Antiproliferative:		
			Coumaric acid: 31.7 µg g^{-1};	MCF-7: 82 % of cel. Sur.		
			Ferulic acid: 6.0 µg g^{-1};	Caco - 2: 63.3 % of cel. sur.		
			Myricetin: 14.0 µg g^{-1};	Antimicrobial: MIC: 16 %.		
			Quercetin: 6.6 µg g^{-1};			
		Ketone	(-) - Epicatechin: 2659.5 µg g^{-1};	Antioxidant: DPPH: 45.32%		
			Gallic acid: 801.0 µg g^{-1};	Antiproliferative:		
			Coumaric acid: 49.1 µg g^{-1};	MCF-7: 73.7 % de sob. cel.		
			Ferulic acid: 8,1 µg g^{-1};	Caco - 2: 66.3 % de sob. cel.		
			Myricetin: 3.8 µg g^{-1};	Antimicrobial: MIC: 5 %.		
			Quercetin: 6.8 µg g^{-1}			
	Leaves	Ethanolic	β-sitosterol: 51.0 mg;	-	Brazil	Moresco et al., 2012.
			Catechin: 18.7 mg;			

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Species	Part used	Extract type	Component identified / isolated	Activities tested / Concentration	Study location	Reference
			β-sitosterol-3-*O*-*β*-D glucopyranoside: 14.3 mg			
	Fruits	Fixed oil	Lutein: 26.380 g / g in d. m.; *β*-carotene: 0.492 g / g in d. m.	Antioxidant: ABTS: 242.30 Trolox μM equiv/g in d. mat.	Brazil	Pereira et al., 2012.
	Leaves	Aqueous Methanolic	-	Repellent: 85.00 mg / mL; Repellent:100.00 mg / mL	South Africa	Chalannavar et al., 2013.
	Fruits	*In Natura*	-	Antioxidant *	Brazil	Nora et al., 2014a.
	Fruits	Methanolic	*β*-cryptoxanthin: 1029.77 μg 100 g^{-1} d. f. All-*trans*-lutein: 557.79 μg 100 g^{-1} d. f.; *β*-carotene: 512.60 μg 100 g^{-1} d. f.; Cyanidin 3-glucoside: 354.66 μg g^{-1} d. f.; Malvidin 3-glucoside: 243.58 μg g^{-1} d. f.	Antioxidant: ABTS: 150.17 μM Trolox g^{-1} d. fru. DPPH: EC_{50} 16713.20 g^{-1} d. fru.	Brazil	Nora et al., 2014b.
	Fruits	Methanolic	Malvidin 3-glucoside: 67.7%; *β*-cryptoxanthin: 50.4%; Lutein: 37.8%;	Antioxidant:	Brazil	Nora et al., 2014c.

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Species	Part used	Extract type	Component identified / isolated	Activities tested / Concentration	Study location	Reference
			Cyanidin 3-glucoside: 51.7%.	ABTS: 248.6 μMTE / g in d. fru. DPPH: EC_{50} 548.4 g in d. fru.		
	Bark	Hydroalcoholic	Tannins, saponins, flavonoids and terpenes*	Antimicrobial: MIC 100 μg / mL	Brazil	Alvarenda et al., 2015.
	Fruits	-	Phenolic content: 177.59 mg GAE $100g^{-1}$ f. w. Anthocyanins: 2.47 mg of cyanidin 3-glucoside $100g^{-1}$ f. w. Carotenoids: 26 μg of β-carotene g^{-1} f. w.; Ascorbic acid: 2.67 mg $100g^{-1}$ L-ascorbic acid f. w.	Antioxidant: DPPH: 405.61 mg TE $100g^{-1}$ of p. fre. ABTS: 49.82 mg TE $100g^{-1}$ of p. fre.	Brazil	Reissig et al., 2016.
	Leaves	Aqueous	Tannins, flavonoids and triterpenoids*	Antioxidant: DPPH: IC_{50} 17.57 mg / mL; Antimicrobial: MIC: 6.25 mg / mL	Brazil	Scur et al., 2016.
		Ethanolic	Tannins, flavonoids and triterpenoids *	Antioxidant: DPPH: IC_{50} 13.90 mg / mL;		

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Species	Part used	Extract type	Component identified / isolated	Activities tested / Concentration	Study location	Reference
				Antimicrobial: MIC: 0.78 mg / mL		
		Essential oil	*α*-copaene: 21.96%; Eucalyptol: 15.05%; *δ*-cadinene: 9.63%.	Antioxidant: DPPH: IC_{50} 171.14 mg/mL; Antimicrobial: MIC: 200 mg/mL		
	Leaves	Essential oil	*β*-Caryophyllene: 28.83%; *α*-pinene: 28%; *β*-myrcene: 13.40%.	Antimicrobial: MIC: 13.01 µg/mL	Brazil	Soliman et al., 2016.
	Fruits	Ethanolic	Total phenolic: 606.1 mg of chlorogenic acid/100 g f. w.; Anthocyanins: 29.3 mg of cyanidin-3-glucoside / 100 g f. w.; Carotenoids: 364.4 µg of *β*-carotene/100 g f. w.	Antioxidant: *α*-glucosidase: IC_{50} 25.4 µg / mL; DPPH: IC_{50} 334.3 µg / mL; RSA: IC_{50} 173.3 µg / mL; RH: IC_{50} 245.9 µg / mL; NO: IC_{25} 1360.0 µg / mL.	Brazil	Vinholes et al., 2017.

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Species	Part used	Extract type	Component identified / isolated	Activities tested / Concentration	Study location	Reference
	Fruits	Methanolic	Total phenolic: 7190 mg kg^{-1} f. f.; Anthocyanin: 1.7 mg kg^{-1} f. f.; Cyanidin-*O*-glucoside: 11.7 mg kg^{-1} f. f.	Antioxidant: DPPH: EC_{50} 60.11 mg / mL^{-1}; ABTS: EC_{50} 141 mg / mL^{-1}.	Brazil	Chaves et al., 2018.
	Fruits	-	Total phenolic: 625.34 mg GAE / 100 g Pr; Anthocyanin: 4.99 mg / 100 g Pr; Quercetin: 7.621 mg / 100 g Pr; Coumaric acid: 5.583 mg / 100 g Pr; Gallic acid: 40.955 mg / 100 g Pr; Catechin: 4.287 mg / 100 g Pr; Vescalagin: 10.012 mg / 100 g Pr; Limonene: 51.319 mg / 100g Pr; *γ*-terpinene: 43.005 mg / 100g Pr.	Antioxidant: FRAP: 25.50 mmol Fe^{2+} / kg pr^{-1}	Comoros Islands	Donno et al., 2018.

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Species	Part used	Extract type	Component identified / isolated	Activities tested / Concentration	Study location	Reference
	Leaves	Methanolic	Phenolics, flavonoids and triterpenes *	Antioxidant: DPPH: IC_{50} 40.11 µg /mL	Egypt	Saber et al., 2018.
	Fruits	Methanolic	Total phenolic: 85.30 mg GAE / 100 g e. f.; (all-*E*)-lutein: 38.3 µg / 100 g e. f.; (all-*E*)-β-carotene: 47.55 µg / 100 g e. f.	-	Brazil	Biazotto et al., 2019.
	Leaves	Aqueous	Total phenolic: 123 mg of GAE g^{-1}	Antioxidant: DPPH: IC_{50} 37.3 µg / mL Antimicrobial: MIC: 6.3 µg / mL	Brazil	Dacoreggio et al., 2019.
Psidium densicomum Mart. ex DC.	Leaves and flowers	Aqueous	-	Antimicrobial: MIC: 5.000 < MIC < 12.500 µg / mL.	Brazil	Castilho et al., 2014.
Psidium grandifolium Mart. ex DC.	Fruits	Ethanolic	Total phenolic: 136.95 mg GAE / 100 g	Antioxidant: DPPH: EC_{50} 6.37 mg / mL; Antimicrobial: MIC 3.91 mg / mL	Brazil	Bittencourt et al., 2019.
		Essential oil	α-pinene: 20.75%;	-		

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Species	Part used	Extract type	Component identified / isolated	Activities tested / Concentration	Study location	Reference
			p-cymene: 20.50%; o-cymene: 20.05%; E-caryophyllene: 17.56%; α-humulene: 16.26%.			
Psidium guineense Sw.	Fruits	Aqueous	Total phenolic: 754.4 mg GAE / 100 g d. m.; Ascorbic acid: 101.3 mg / 100 g d. m.	Antioxidant: Peroxyl radical: IC_{50} 1.58 g/L; Peroxynitrite: IC_{50} 4.0 g/L.	Brazil	Gordon et al., 2011.
	Fruits	Essential oil	β-caryophyllene: 8.6%; Butanol: 7.4%.	-	Colombia	Peralta-Bohórquezo et al., 2010.
	Fruits	Aqueous Ethanolic Ethereal	Total phenolic: 18.4 mg GAE $100g^{-1}$ - -	Antioxidant DPPH: 18.43%; DPPH: 13.47%; DPPH: 15.45%.	Brazil	Damiani et al., 2012.
	Leaves	Aqueous	Tannins, flavonoids, leucoanthocyanidins and condensed proanthocyanidins*	Antimicrobial: 250-500 µg / mL	Brazil	Fernanda et al., 2017.
	Leaves	Aqueous	-	Repellent: 95.00 mg/mL;	South Africa	Chalannavar et al., 2013.

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Species	Part used	Extract type	Component identified / isolated	Activities tested / Concentration	Study location	Reference
		Methanolic		100.00 ± 0.0 mg/mL.		
	Leaves	Aqueous	Myricetin, Kaempferol, Luteolin*	-	Venezuela	Rivero-Maldonado et al., 2013.
	Fruits	Methanolic	Total phenolic: 316.5 mg GAE / g.	Antioxidant: TEAC: 1339.5 µmol ET / g; ORAC: 359.1 µmol ET / g; Anti-collagenase: 100.0 µg / mL; Anti-elastase: 95.3 µg / mL; Anti-hyaluronidase: 100.0 µg / mL; Anti-tyrosinase: 92.9 µg / mL.	Colombia	Bravo et al., 2016.
	Leaves	Aqueous	Guajaverin (3-*O*-arabinopyranoside); * Avicularin (3-*O*-arabinofuranoside).	Antiviral: IC_{50} 8.5 µg/mL	Venezuela	Ortega et al., 2017.
	Leaves	Essential oil	Limonene: 47.4%; *β*-caryophyllene: 24%;	-	Brazil	Figueiredo et al., 2018.

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Species	Part used	Extract type	Component identified / isolated	Activities tested / Concentration	Study location	Reference
			α-pineno: 35.6%; *epi*-β-bisabolol: 18.1%; Caryophyllene oxide: 14%.			
	Leaves	Essential oil	Spathulenol: 80.71%.	Antioxidant: DPPH: IC_{50} 63.08 µg / mL; ABTS: $IC_{50} \geq$ 780.13 µg / mL; MDA: IC_{50} 37.91 µg / mL; Anti-inflammatory: 48.48 %; Antiproliferative: $GI_{50} <$ 9.84 µg/mL; Antibacterial: MIC 126.4 µg / mL	Brazil	Nascimento et al., 2018.
	Fruits	Fruit pulp	Total phenolic: 89.14 mg GAE /100g f. w.	Antioxidant: ABTS: 10.92 µmol TE / g of p. fre. DPPH: EC_{50} 721.85 g / p. fre;	Brazil	(Schiassi et al., 2018)
	Leaves	Phenolic	Gallic acid: 8749 mg kg^{-1}; Chlorogenic acid: 657 mg kg^{-1};	Antioxidant: DPPH: 25.76 µmol L^{-1} ABTS: 14.06 µmol L^{-1}.	Sri Lank	Senanayake et al., 2018.

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Species	Part used	Extract type	Component identified / isolated	Activities tested / Concentration	Study location	Reference
			p-hydroxy benzoic acid: 1217 mg kg^{-1};			
			Caffeic acid: 3234 mg kg^{-1};			
			Vanillic acid: 961 mg kg^{-1};			
			Syringic acid: 1597 mg kg^{-1};			
			Ferulic acid: 4556 mg kg^{-1};			
			p-coumaric acid: 1258 mg kg^{-1};			
			Ellagic acid: 171 mg kg^{-1};			
			Catechin:1491 mg kg^{-1};			
			Daidzein: 1774 mg kg^{-1};			
			Epigallocatechin: 142 mg kg^{-1};			
			Naringenin: 600 mg kg^{-1};			
			Genistein: 309 mg kg^{-1};			
			Apigenin: 1440 mg kg^{-1}.			
	Leaves	Ethyl acetate	Araçain.	Antimicrobial: MIC 64 µg / mL.	Brazil	Macaúbas-Silva et al., 2019.
		Hexanic	Sitosterol; 17^3 -etoxiphaeophorbide a; Ursolic acid.	-		

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Species	Part used	Extract type	Component identified / isolated	Activities tested / Concentration	Study location	Reference
		Methanolic	Kaempferol; Rutin; Quercetin. *	-		
Psidium laruotteanum Cambess.	Leaves	Essential oil	*p*-cimene: 34.8 %; 1,8-cineole: 19.2 %; *γ*-terpinene: 14 %; *α*-pinene: 13.4 %.	-	Brazil	Medeiros et al., 2018.
Psidium myrsinites DC.	Leaves	Essential oil	Linalool *	-	Brazil	Castelo et al., 2010.
	Leaves	Essential oil	(*E*)-*β*-caryophyllene: 26.5%; *α*-humulene: 23.92%; Caryophyllene oxide: 10.09%.	Larvicide: LC_{50} 292 mg/L	Brazil	Dias et al., 2015.
	Leaves and flowers	Essential oil	Caryophyllene oxide: 6.1%; Humulene epoxide II: 8.8%; *β*-caryophyllene: 7.4%; *α*-caryophyllene: 5.4%.	-	Brazil	Medeiros et al., 2015.
Psidium myrtoides O. Berg	Leaves	Essential oil	*trans*-β-caryophyllene: 30.9 %; *α*-humulene: 15.9 %; *α*-copaene: 7.8 %; Caryophyllene oxide: 7.3 %;	Antimicrobial: MIC = 62.5 µg/mL; Antiproliferative: M059J: EC_{50} 289.3 µg/mL	Brazil	Dias et al., 2019.

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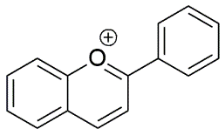
Species	Part used	Extract type	Component identified / isolated	Activities tested / Concentration	Study location	Reference
			α-bisabolol: 5.3 %.			
Psidium salutare (Kunth) O. Berg	Leaves	Essential oil	p-cimene: 17.83 %; γ-terpinene: 17.09 %; terpinolene: 16.99 %; τ-cadinol: 15.20 %.	Antimicrobial: IC_{50} 2.6 µg / mL	Brazil	Macêdo et al., 2018.
	Leaves	Aqueous	Luteolin, Myricetin *.	-	Venezuela	Rivero-Maldonado et al. 2013.
Psidium schenckianum Kiaersk.	Fruits	Ketone	Carotenoids: 7.90 Beta-carotene µg / g; Flavonols: 24.59 of quercetins / 100 g	-	Brazil	Nascimento et al., 2011.
Psidium striatulum Mart. ex DC.	Leaves	Essential oil	α-humulene: 13 %; α-copaeno: 8.4 %; 1,8-cineole: 8.1 %; Aromadendrene: 6.3 %; α-terpinenol: 5.7 %.	Antimicrobial: IC_{50} a 250 µg / mL	Brazil	Moniz et al., 2019.

Subtitles: * The authors do not report values for compound / class / activity; -: Not applicable; d. m.: dry matter; d. w.: dry weignt; d. f.: dry fruit; f. f.: fresh fruit; f. w.: fresh weight; e. f.: edible fraction; MTE/g: µM Trolox Equivalents (TE) / g of dried fruit.; MCF-7: human cancer cells (breast); Caco - 2: human cancer cells (colon); cel. sur.: cell survival; M059J: human glioblastoma; GAE: gallic acid equivalent; TEAC: Trolox equivalent antioxidant capacity; ORAC: oxygen radicals absorbing capacity; MDA: Malondialdehyde; ET: electronic transfer; Pr: Product; RSA:

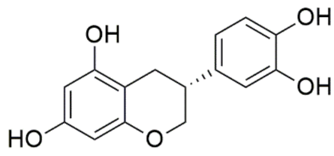
Radical anionic superoxide; RH: Hydroxyl radical; NO: Nitric oxide; MIC: minimal inhibitory concentration; TE: trolox equivalent; edi.. frac.: edible fraction.

PHENOLIC COMPOUNDS

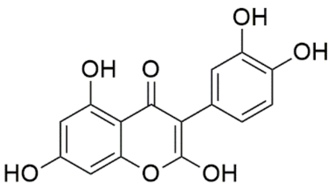


Anthocyanin

Kaempferol



(-)-Epicatechin



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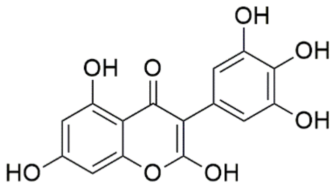

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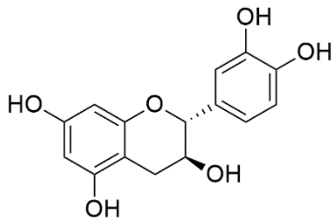

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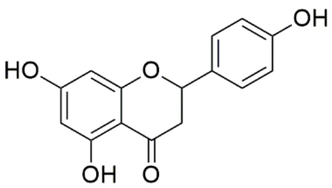

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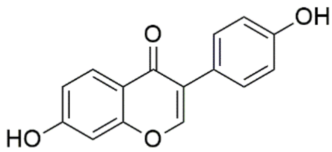
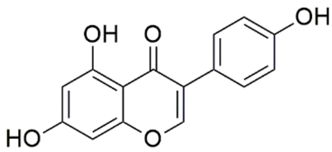
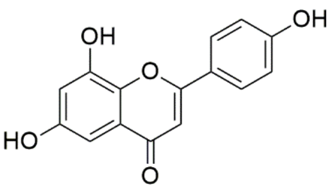


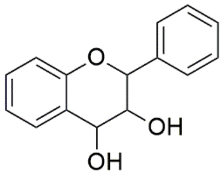
Daidzein



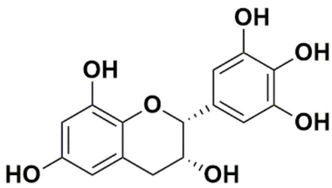
Genistein



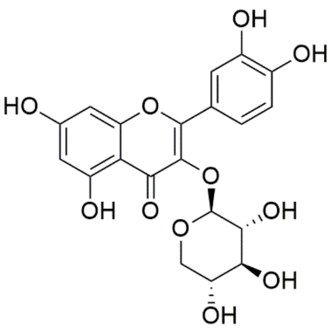
Apigenin



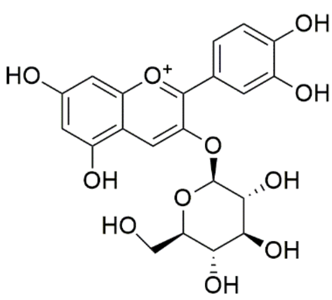
Leucoanthocyanidin



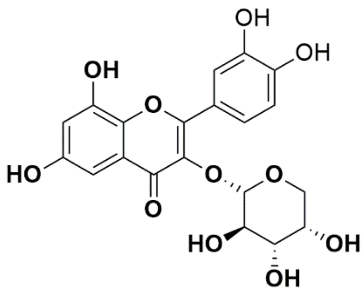
Epigallocatechic



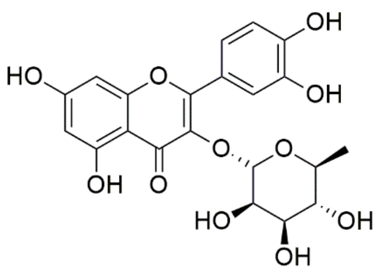
Reynoutrin (quercetin3-O-β-D-xilopiranosideo)



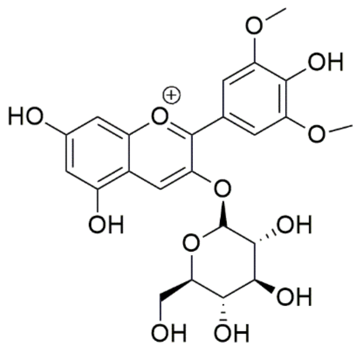
Cyanidin 3-glucoside



Guaijaverin (quercetin-3-O-L-α-arabinopyranoside)



Quercitrin



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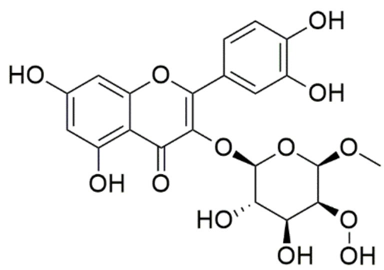
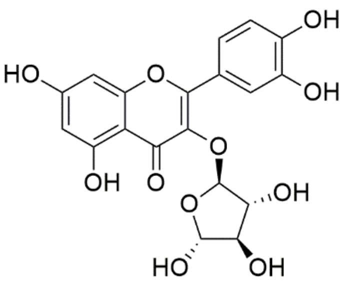
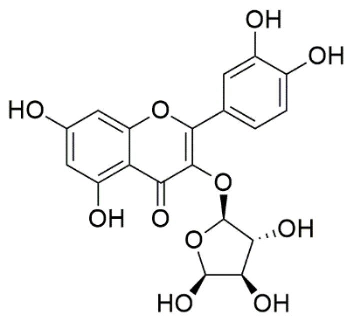


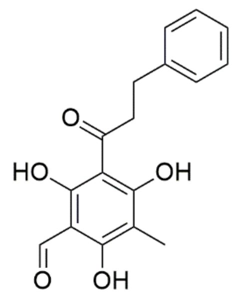
Quercitrina
(quercetin 3-O-α-L-ramnopiranosideo)



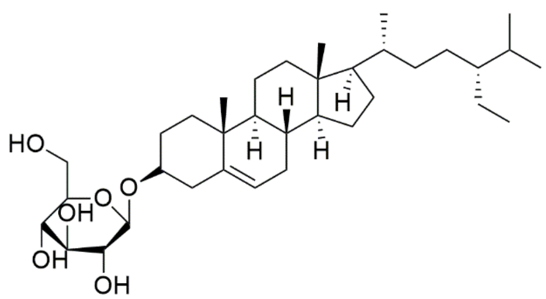
Avicularin (quercetin-3-0-β-L-arabinofuranoside)



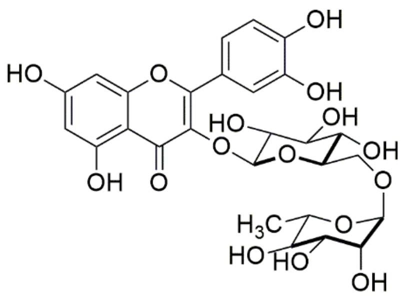
Wayanina (quercetin-3-0-β-D-xilofuranosideo)



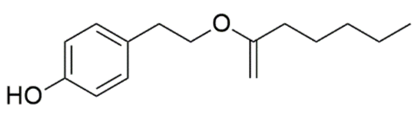
3'-formyl-2', 4', 6'-trihydoxy-5'-methyldydrochalcon



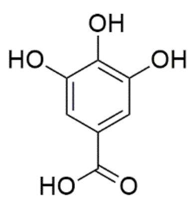
β-sitosterol-3-O-β-D-glucopyranoside



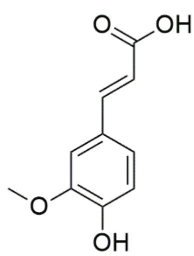
Rutin



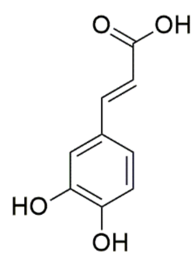
araçain



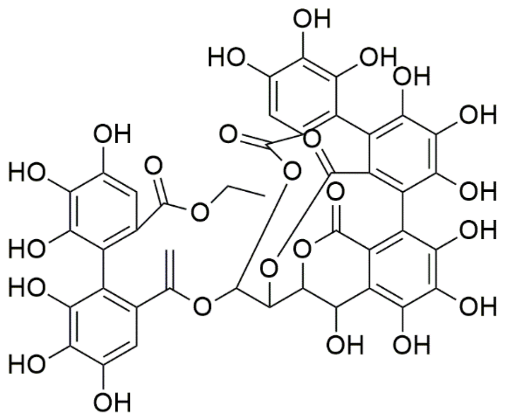
Gallic acid



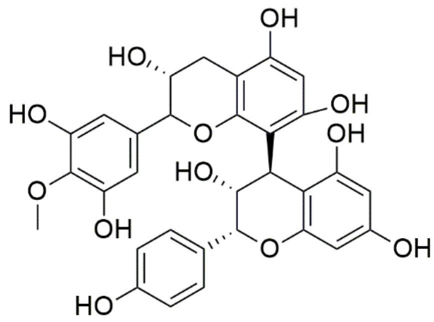
Feluric acid



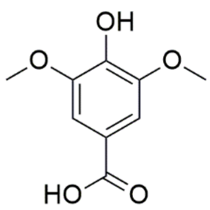
Caffeic acid



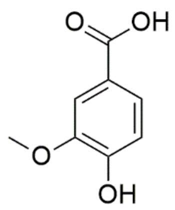
Vescalagin



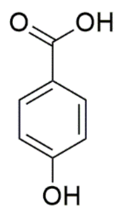
Proanthocyanidin



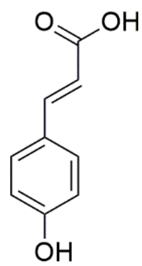
Syringic acid



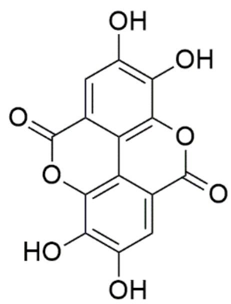
Vanillic acid



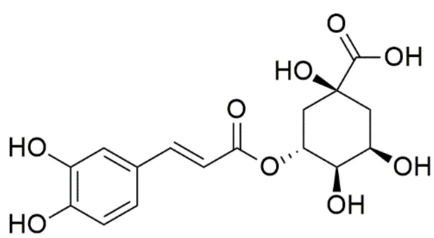
p-hidroxy benzoic acid



p-coumaric acid

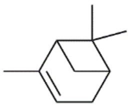


Ellagic acid

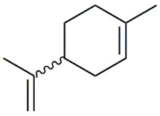


Chlorogenic acid

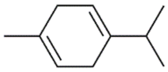
TERPENES



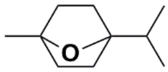
α-pinene



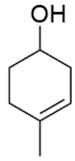
Limonene



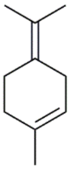
γ-terpinene



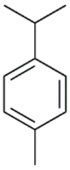
1,8-cineole



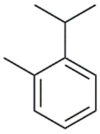
α-terpineol



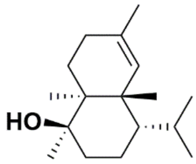
Terpinolene



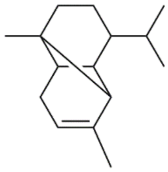
p-cymene



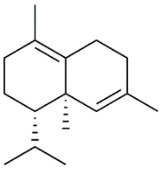
o-cymene



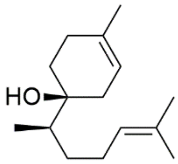
τ-cadinol



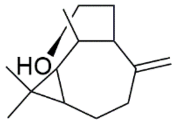
α-copaene



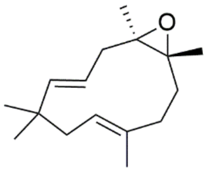
δ-cadinene



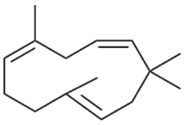
epi-β-bisabolol



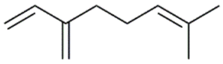
Spathulenol



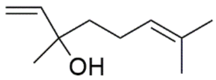
Humulene epoxide II



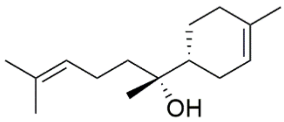
α-humulene



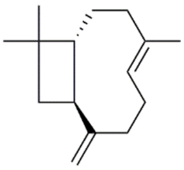
β-myrcene



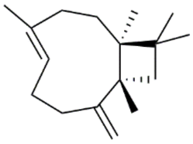
Linalool



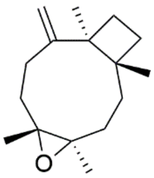
α-bisabolol



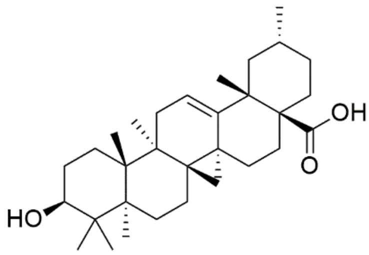
(*E*)-β-caryophyllene



β-caryophyllene

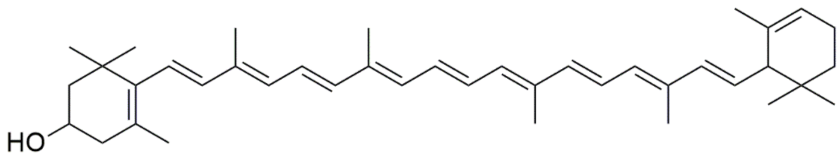


Caryophyllene oxide

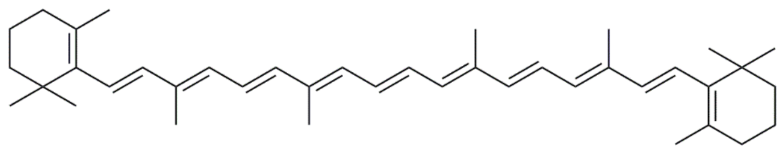


Ursolic acid

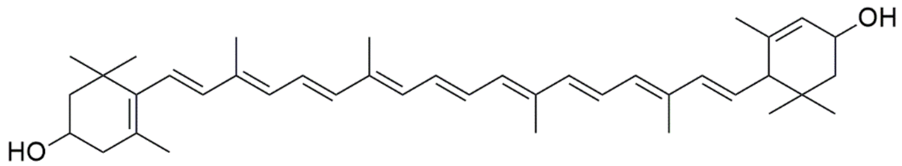
VITAMINS



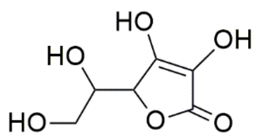
β-cryptoxanthin



β-carotene

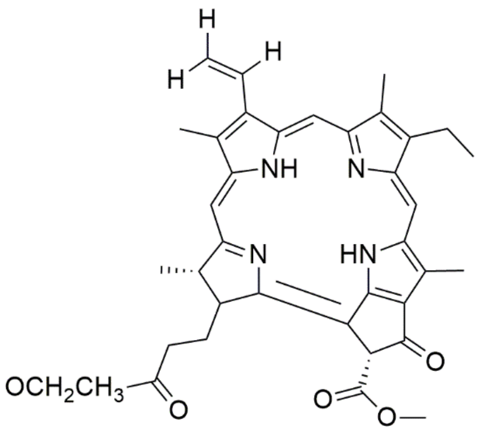


Lutein

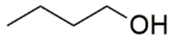


Ascorbic acid

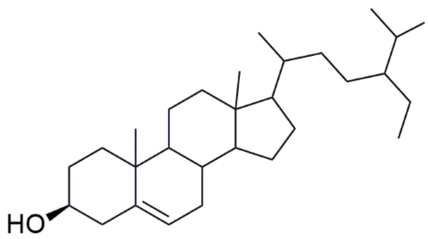
OTHERS



17^3-Etoxiphaeophorbide a



Butanol



β-sitosterol

Figure 2: Molecular structures of *Psidium* species

3.3.1. Psidium acutangulum DC.

Psidium acutangulum is rarely cited in ethnobotanical works, being mentioned in only twice (Palheta et al., 2017; Pedrollo et al., 2016) in Northern Brazil. Its leaf buds and stems are prepared as decoctions to exclusively treat digestive system disorders such as diarrhea and dysentery. There are few investigations on chemical compounds and biological activities, although its leaves, stem and fruit have been chemically characterized through aqueous, hexane and ethyl acetate extracts, highlighting the components myricetin, catechin, quercetin-3-O-β- D-xylofuranoside (9.1%), quercetin-3-O -β-D xylopyranoside (1.8%), 3'-formyl-2 ', 4', 6'-trihydroxy-5'-methyldydrochalcone, all belonging to the flavonoid class (Houël et al., 2016, 2015; Rivero-Maldonado et al., 2013). The compound 3'-formyl-2 ', 4', 6'-trihydroxy-5'-methyldydrochalcone, was found in another species of *Psidium, P. guineense*. The authors demonstrated that this compound showed strong bacterial activity against *Pseudomonas aeruginosa*, being promising for the development of new antibacterial drugs (Lima et al., 2020).

Psidium acutangulum extracts were tested against *Plasmodium falciparum* (which causes malaria) (Houël et al., 2016, 2015) and presented good *in vitro* antiplasmodial activity with IC_{50} <1 µg / mL (ethyl acetate extract), IC_{50} 3.3 µg / mL (decoction of leaves, stem and fruit) and IC_{50} = 32.3 µg / mL (hexane extract). It presented decoction antioxidant potential (NO (-13%) at 50 µg / mL) (Houël et al., 2015) and anti-inflammatory potential in ethyl acetate (50 µg / mL), inhibiting the secretion of IL-1β (-46 %) and NO production (-21%) (Houël et al., 2016). These results demonstrate that the ethyl acetate extract showed excellent activity. The authors suggest that these effects may be related to possible synergistic interactions between two flavonoids, Guaijaverin (quercetin-3-O-α-L-arabinopyranoside) and Wayanin (quercetin-3-O-β-D-xylofuranoside), found in *P. acutangulum*. Flavonoids are known to have anti-inflammatory properties, antioxidant potential, radical scavengers, among others (Azevedo et al., 2016). The mentioned compounds (Guaijaverin and Wayanin) are present in the chemical characterization of other species of Myrtaceae, as in *Myrcia bella* (Saldanha et al., 2013) and *Plinia edulis* (Azevedo et al., 2016). The latter showed anti-inflammatory and anti-nociceptive activity through leaf infusion, and the authors associated these activities with the presence of triterpenoids and flavonoids in their composition, including Guaijaverin.

Psidium acutangulum extracts were tested for cytotoxicity and showed non-cytotoxic results, with IC_{50} > 100 µg / mL (Houël et al., 2015) and IC_{50} 57.4 µg / mL (Houël et al., 2016). This inconsistency between the IC_{50} values may be related to the different extracts tested. Houël et al. (2015) tested the cytotoxic effect of *P. acutangulum* in aqueous extract and Houël et al. (2016) in a fraction of ethyl acetate. These results are promising with regard to the search for herbal medicines with few adverse effects.

Psidium acutangulum demonstrated promising results from its extracts for some biological activities, which may favor its use as a herbal medicine. However, there is still a lack of research that identifies the chemical components of its essential oil, in addition to pharmacological tests directed to the mosts reported uses in the literature, such as those related to the digestive system.

3.3.2. Psidium brownianum Mart. ex DC.

Within the criteria established in this analysis, there were no articles on medicinal use for *P. brownianum*. However, (Jesus, 2012) found it to be used in food and folk medicine to treat influenza. This work is used as an ethnobotanical reference for the analysis of chemical and biological data of the species (Machado et al., 2018; Morais-Braga et al., 2016b; Morais-Braga et al., 2016).

The aqueous and hydroalcoholic extracts of *P. brownianum* leaves showed phenolic levels ranging from 49.25-80.77 GAE / g (Morais-Braga et al., 2016b). Further compounds like Quercetin 11.54 mg / g; Luteolin: 10.34 mg / g; Kaempferol: 8.93 mg / g; Coumarin: 7.18 mg / g, among others, were identified in its ethanolic extract (Morais-Braga et al., 2016), in addition to the quantification of flavonoid contents with 70.97 μg / g of quercetin (Sobral-Souza et al., 2019). Articles on essential oil extraction for *P. brownianum* were not found in this analysis, however, as several species of the genus are rich in these volatile compounds, it is to infer the same about this particular species. In this sense, investigations with this approach are necessary.

Biological activities, *P. brownianum* demonstrated excellent parasitic activity against *Trypanosoma cruzi* with a 100% inhibition percentage at 1000 µg / mL concentration. In cytotoxic tests, it presented high toxicity, killing 90.85% of fibroblasts (Machado et al., 2018).

Psidium brownianum was investigated against bacteria and fungi *Staphylococcus* and *Candida* genera, respectively. In general, the authors state that *P. brownianum* extracts have significant antimicrobial activity. And when associated with synthetic drugs, they cause synergism, potentiate the effect, and reduce the MIC of drugs against these pathogens. These effects are possibly associated with the presence of phenolic compounds and flavonoids present in their extracts (Morais-Braga et al., 2016a, 2016b, 2016c).

The ethanolic extract of *P. brownianum* showed cytoprotective properties against mercury and aluminum toxicity (Sobral-Souza et al., 2019). The authors correlated this finding with the antioxidant effects observed by different methods (Fe^2 +: EC_{50} 360.66 μg / g; Fe^3 +: EC_{50} 756.20 μg / g; FRAP: EC_{50} 23.27 mmol / g) and associated it with the presence of secondary metabolites, mainly flavonoids.

Psidium brownianum presented five articles in this analysis that demonstrate its chemical and / or biological potential, but further studies are needed to trace its chemical profile, especially on its essential oil. From the information already acquired, it is a promising species for bioprospecting, and it may yet prove to be an alternative to solve environmental problems caused by toxic metals.

3.3.3. Psidium cattleyanum Sabine

Psidium cattleyanum appears in folk medicine as one of the native species of the genus most cited by traditional populations (10 articles), for the treatment of diseases of the digestive system such as diarrhea, stomach pains, belly aches and dysentery (Baptista et al., 2013; Bieski et al., 2015; Brito et al., 2017; Castro et al., 2011; Tomazi et al., 2014), for disorders of the genitourinary system (Abreu et al., 2015) and respiratory system such as sore throats (Bolson et al., 2015; Castro et al., 2011). These symptoms are mainly treated by the decoction of the leaves. Other parts of the plant such as fruits, stem and leaf bud are mentioned, although less used.

Regarding the evaluation of secondary metabolites, *P. cattleyanum* presents good indicators, with 16 articles mentioning its constituents. Chemical compounds present in its leaves, barks, fruits, and seeds were identified through volatile and fixed extracts (Table 2). (Table 2).

The analysis of *P. cattleyanum* essential oil shows β-caryophyllene as the major component in most of the reported studies, with 22.5%, 28.83%, 31.5% (Adam et al., 2011; Biegelmeyer et al., 2011; Soliman et al., 2016) respectively. Other compounds also stand out, α-pinene (28%) (Soliman et al., 2016), α-copaene (21.96%), Eucalyptol (15.05%) (Scur et al., 2016), β-myrecene (13.40%) and β-selinene (10.1%) (Biegelmeyer et al., 2011; Soliman et al., 2016). Other researches refer to the chemical composition of the essential oil of *P. cattleyanum*, highlighting the substances α-tujene (25.2%), 1.8-cineole (16.4%) and β-caryophyllene (10.2%) (Marques et al., 2008) and 1,8-cineole (55.8%), α-pinene (31.8%), (E) -caryophyllene (20.7%) (Rocha et al., 2020). Rocha et al. (2020) drew attention to the *P. cattleyanum* leaf oil collected in other parts of the world, not presenting a record for the occurrence for 1.8 cineol (Adam et al., 2011; Pino et al., 2004; Tucker et al., 1995). This compound has been registered, so far, only for species of *P. cattleyanum* occurring in Brazilian territory.

Meroterpenoids are another chemical class elucidated for *P. cattleyanum*, although there is little investigation or identification of these compounds for the species. Zhu et al. (2019) recently discovered a new meroterpenoid with a 6/8/9/4 - tetracyclic nucleus, Littordial F, isolated from *Psidium littorale* leaves (synonymous with *P. cattleyanum*) and exhibited potential cytotoxic activities in vitro, in cancer cell lines. Several meroterpenoids have been identified for *P. guajava* as guadial A, psiguadials C and D (Shao et al., 2012), Psidials A - C (Fu et al., 2010), Psiguajadials AK (Tang et al., 2017), (+) - Psiguadial B (Chapman et al., 2018), Psiguajdianone (Ning et al., 2019). These meroterpenoids are responsible for anti-inflammatory and antiproliferative activities against the cancer cell line.

Research on the biological activity of *P. cattleyanum* essential oil demonstrates an antimicrobial effect with MIC 13.01 µg / mL (Soliman et al., 2016) and MIC 200 mg / mL and antioxidant potential by the DPPH method with IC_{50} 171.14 mg / mL (Scur et al., 2016).

The ethanolic extract of *P. cattleyanum* acts on α-glucosidase inhibitory activity with IC_{50} 25.4 µg / mL, MIC antimicrobial activity = 0.78 mg / mL, in addition to presenting antioxidant potential with DPPH = IC_{50} 13.90 mg / mL and superoxide anion radical with IC_{50} 173.3 µg / mL (Scur et al., 2016; Vinholes et al., 2017). These results can be explained by the combination of phenolic compounds, anthocyanins, carotenoids and reducing sugars present in the species extract (Vinholes et al., 2017).

Psidium cattleyanum has an antioxidant effect by several tested methods, highlighting a greater number of publications for methanolic extractions. Some of the results of these extractions are values of ABTS 150.17 µM Trolox g^{-1} (Nora et al., 2014b), ABTS EC_{50} 141 mg / mL^{-1} (Chaves et al., 2018); DPPH IC_{50} 40.11 µg / mL (Saber et al., 2018); TEAC: 156 µM / g (Biegelmeyer et al., 2011). Some other methods showed the antioxidant effect of the species, FRAP: 25.50 mmol Fe^{2+} / kg_{Pr}^{-1} (aqueous extracts) (Donno et al., 2018); RSA: IC_{50} 173.3 µg / mL, RH: IC_{50} 245.9 µg / mL and NO: IC_{25} 1360.0 µg / mL (ethanolic extracts) (Vinholes et al., 2017). The authors consider that these effects are attributed to the presence of health-promoting substances, evidenced in the metabolic profile of this species, such as phenolic compounds, flavonoids and triterpenes.

Other important activities are evidenced for *P. cattleyanum*, such as antiproliferative against, human cancer cells (breast) with 73.7% - 82% cell survival and human cancer cells (colon) with 63.3% - 66.3% cell survival (Medina et al., 2011). The species also shows antimicrobial activity (Alvarenda et al., 2015; Dacoreggio et al., 2019; Medina et al., 2011; Scur et al., 2016; Soliman et al., 2016), a finding which may be related to the content of volatile substances, tannins and phenolic compounds present in the species, which can act as inhibitors of enzymatic expression and exert antimicrobial action.

Repellent activity was observed for *P. cattleyanum* against *Anopheles arabiensis*, repelling 80-100% of mosquitoes through aqueous (85.00 mg / mL) and methanolic (100.00 mg / mL) extracts (Chalannavar et al., 2013). The 1,8 cineole and β-caryphyllene compounds present in the essential oil of *P. cattleyanum*, previously mentioned, showed effectiveness in repelling some mosquitoes (Rocha et al., 2020; Wang et al., 2009).

Although being widely explored in terms of chemical composition and biological activities, both being directly related, no phytotherapic treatment from *Psidium cattleyanum* has yet been proposed. It was also noticed that there is a deficiency in cytotoxicity data and *in vivo* research, which is one of the steps for the formulation of new drugs. This could strengthen the information and place the species as a potential vegetable drug.

3.3.4. Psidium densicomum Mart. ex DC.

Psidium densicomum was registered in only one study (Santos et al., 2014), in which the popular use of seedlings is indicated in the form of maceration for diarrhea. There is still no information on chemical composition and we found only one studywith biological research (Castilho et al., 2014). The authors evaluated the antimicrobial activity of the species against *Enterococcus faecalis* (bacteria present in the gastrointestinal and genitourinary tracts causing pathogenicity) and the aqueous extract proved to be more effective than SH1% C (Commercial sodium hypochlorite 1% - Asfer, São Paulo, SP, Brazil) with $p < 0.05$. *P. densicomum* obtained MIC between 5.000 < 12.500 μg / mL in the work of Castilho et al. (2014). These were the inhibitory concentrations that showed antimicrobial activity.

Although the aqueous extract of *P. densicomum* presents promising results against *E. faecalis*, which causes gratointestinal disorders, researches that demonstrates its biological potential, as well as the metabolites responsible for its action, are still incipient or, frequently, nonexistent.

3.3.5. Psidium grandifolium Mart. ex DC.

There is little information on the chemical composition and biological activity of *P. grandifolium*, only one study was found within the analysis. Thus, a greater effort of investigation regarding this species is necessary.

The chemical composition of *P. grandifolium* was analyzed using an ethanolic extract, with a phenolic content of 136.95 mg EGA / 100 g, and a volatile composition with major compounds α-pinene (20.75%), p-cymene (20.50%), o-cimene (20.05%), E-caryophyllene (17.56%) and α-humulene (16.26%) (Bittencourt et al., 2019).

The species has antioxidant potential with DPPH: EC_{50} 6.37 mg / mL and antimicrobial potential against *Pseudomonas aeruginosa* (MIC 15.62 mg / mL), *Staphylococcus aureus* (MIC 15.62 mg / mL), *Bacillus cereus* (MIC 7.81 mg / mL) and *Listeria monocytogenes* (MIC 3.91 mg / ml). The chemical composition of the species is rich in several compounds that offer health benefits (Bittencourt et al., 2019), which may be associated with their biological properties.

3.3.6. Psidium guineense Sw.

Ethnobotanical data showed the use of *P. guinense* by populations in the Northeast, being indicated for dysentery, intestinal problems, belly pain, diarrhea (digestive system), influenza, sore throat (respiratory system), headaches (nervous system) (Beltreschi et al., 2019; Santana et al., 2016; Silva et al., 2012, 2018). The exclusive use of the leaves was reported in the form of decoction.

The volatile composition of *P. guineense* varied from 38 to 181 compounds (Figueiredo et al., 2018; Nascimento et al., 2018; Peralta-Bohórquezo et al., 2010) with a predominance of terpenes as major components, Spathulenol (80.71%) (Nascimento et al., 2018), Limonene (47.4%), α-pinene (35.6%) (Figueiredo et al., 2018), β-caryophyllene (8.6% -24.4%) (Figueiredo et al., 2018; Peralta-Bohórquezo et al., 2010) and epi-β-bisabolol (18.1%) (Figueiredo et al., 2018). According to Figueiredo et al. (2018) these elements form, so far, four chemical types for *P. guineense*: (I) α-pinene / Limonene; (II) epi-β-bisabolol; (III) β-caryophyllene / caryophyllene oxide; (IV) Spathulenol. This finding may contribute to the specific selection of compounds with significant biological activities.

Nascimento et al. (2018) demonstrated the effectineness of *P. guineense* leaves essential oil for antioxidant (DPPH: IC_{50} 63.08 μg / mL; ABTS: $IC_{50} \geq$ 780.13 μg / mL; MDA: IC_{50} 37.91 μg / mL), antiproliferative (GI_{50} <9.84 μg) / mL), anti-inflammatory

(48.48%) and antimicrobial (MIC 126.4 µg / mL). These same authors suggested that the predominance of Spathulenol, corresponding to more than 80% of its composition, is partly responsible for the therapeutic effects associated with the species.

For fixed extracts, *P. guineense* presented chemical constituents such as phenolic compounds, tannins and flavonoids, responsible for biological activities linked to the species. It showed a high content of phenolic compounds ranging from 18.4-8749 mg/g, extracted by different solvents: water, methanol, ethanol and phenol (Bravo et al., 2016; Damiani et al., 2012; Gordon et al., 2011; Schiassi et al., 2018; Senanayake et al., 2018). According to Senanayake et al. (2018), these values are significantly high compared to many other species and similar to those of the *Psidium* genus.

The antioxidant capacity of *P. guineense* can be affirmed by several DPPH methods: 25.76 µmol L^{-1} and ABTS: 14.06 µmol L^{-1} (Senanayake et al., 2018), Peroxyl radicals: IC_{50} 1.58 g / L (Gordon et al., 2011), TEAC: 1339.5 µmol ET / g and ORAC: 359.1 µmol ET / g (Bravo et al., 2016). The greater antioxidant capacity of *P. guineense* extracts may arise from the presence of a wide variety of phenolic compounds in their composition acting synergistically (Senanayake et al., 2018), or even some specific component such as ascorbic acid (101.3 mg / 100 g d.m.) contributing to the antioxidant property of the fruits (Gordon et al., 2011).

Antimicrobial activity was evaluated against *Staphylococcus aureus* and *Klebsiella pneumonia*, both pathogenic to humans and resistant to antibiotics. For *S. aureus*, the aqueous extract showed strong activity against strains tested with MIC 250-500 µg / mL. The combination of the extract with the beta-lactam cephalothin showed a lower fractional inhibitory concentration index (FICI) with a range from 0.125 to 0.5 µg / mL, demonstrating that the natural product potentiated the effect of the synthetic drug (Fernandes et al., 2012). The authors state that the content of polyphenols (21.62 g%) determined in the plant extract plays an important role in its biological properties. Regarding *K. pneumonia*, the ethyl acetate extract showed the best antimicrobial result with MIC 64 µg / mL (Macaúbas-Silva et al., 2019). The presence of tyrosol-derived araçain for *P. guineense* may be responsible for the demonstrated antimicrobial potential.

The aqueous extract of *P. guineense* leaves showed anti-HIV activity, from the mixture of two quercetin-derived flavonoids, Guajaverin and Avicularin with IC_{50} 8.5 µg / mL (Ortega et al., 2017). It is reported in the literature that the leaves of species of the genus, like *P. guajava*, are rich in flavonoids as the main active substance, particularly quercetin, and that the spasmodic and antidiarrheal effects, listed in the popular indications, are associated with the flavonoids and glycosides derived from quercetin present in its chemical composition (Joseph and Priya, 2011; Lozoya et al., 2002).

3.3.7. Psidium laruotteanum Cambess.

Psidium laruotteanum was chemically analyzed by Medeiros et al. (2018), and the volatile composition of the leaves presents Terpenes, p-cymene (34.8%), 1.8-cineole (19.2%), γ-terpinene (14%), and α-pinene (13.4%) as major components. These compounds are commonly found in the chemical composition of the essential oil of various *Psidium* species.

Other investigations demonstrate high phenolic content (576.56 mg GAE / g of extract) and antioxidant potential (IC_{50} = 3.86 μg.mL^{-1}) for *P. laruotteanum* (Takao et al., 2015). Antiparasitic activity, through hexane and ethyl acetate extracts with IC_{50} values of 3.9 and 6.8 μg / mL, with additional verification of the extracts' atoxicity (TC_{50}> 100 μg / mL) (Charneau et al., 2016). Luiz et al. (2017) demonstrated antimicrobial activity of the tested extracts inhibited microbial growth at least 70% of the tested bacterial species.

3.3.8. Psidium myrsinites DC.

In folk medicine, *P. myrsinites* is used to treat diarrhea and stomach pains inherent to the digestive system. The preparation of home remedies is done by infusing the leaves, along with *in natura* comsumption of the fruits. There is still little data on the medical systems of which the species is part, it was only mentioned in two studies published in the Northeast (Lozano et al., 2014; Ribeiro et al., 2014).

Only the essential oil of the leaves and flowers of *P. myrsinites* was chemically analyzed. These analyzes show richness of terpenes (which is characteristic for *Psidium* species), with emphasis on (E) -β-caryophyllene as the major compound, ranging from 7.4% to 26.5% of the oil composition (Dias et al., 2015; Medeiros et al., 2015). Other compounds such as α-humulene (23.92%), caryophyllene oxide (6.1% to 10.09%), humulene epoxide II (8.8%), α-caryophyllene (5.4%) and Linalol, are present in its composition (Castelo et al., 2010; Dias et al., 2015; Medeiros et al., 2015). (E) -β-caryophyllene has been found as a major component in most *Psidium* species (Vasconcelos et al., 2019) and may be a potential chemical marker for the genus.

Data on biological activities are insufficient, *P. myrsinites* was analyzed for its larvicidal activity against the mosquito *Aedes aegypti* L. and demonstrated effective results with LC_{50} 292 mg / L (Dias et al., 2015). Durães et al. (2017), analyzing the antimicrobial activity of the essential oil, showed values> 2,000 µg. mL-1.

3.3.9. Psidium myrtoides O. Berg

Among the criteria established for this analysis, only the study by Dias et al. (2019) refers to the chemical and biological properties of *P. myrtoides*. After analyzing the leaves' essential oil, the authors found trans-β-caryophyllene (30.9%), α-humulene (15.9%), α-copaene (7.8%), caryophyllene oxide (7.3%), and α-bisabolol (5.3%) as major components. These compounds were previously detected in the essential oils of other *Psidium* species (Medeiros et al., 2015; Scur et al., 2016). Other authors (Macêdo et al., 2020; Vasconcelos et al., 2019) demonstrate the variation and richness of chemical compounds for the essential oil of *P. myrtoides*.

The species essential oil has *in vitro* antibacterial activity against cariogenic bacteria, mainly *Streptococcus mutans* with MIC = 62.5 µg / mL (Dias et al., 2019). Interesting result according to Melo et al. (2017), since few natural compounds are known to inhibit *S. mutans*, one of the main causes of tooth decay.

Psidium myrtoides also demonstrated antiproliferative activity against human breast adenocarcinoma cells (MCF-7: EC_{50} 254.5 µg / mL), human cervical adenocarcinoma (HeLa: EC_{50} 324.2 µg / mL) and human glioblastoma (M059J: EC_{50} 289.3 µg / mL) (Dias et al., 2019).

The reported results highlight *P. myrtoides* as a potential source for new antibacterial and antitumor agents. However, studies that identify the chemical constituents responsible for its biological activity are still scarce.

3.3.10. Psidium salutare (Kunth) O. Berg

Only the work of Macêdo et al. (2018) was found for *P. salutare*, considering the criteria established in this analysis. The authors analyzed the chemical composition of the leaves' essential oil and obtained the constituents p-cymene (17.83%), γ-terpinene (17.09%), Terpinolene (16.99%), and τ- cadinol (15.20%) as major components. Secondary metabolites present in the fruits of *P. salutare* were also identified.

Quantitatively, the most abundant class of compounds were terpenoids, among them limone (17.3%), myrcene (16.2%) and α-pinene (9.3%) as major constituents (Pino et al., 2002). Pino and Queris (2008) detected in their research 109 volatile constituents for the fruits of *P. salutare*. The fruit macerates were rich in mono and sesquiterpenes, esters, and cinnamyl derivatives. The compounds viridiflorol (37.28 mg / l), epi-α-cadinol (28.79 mg / l), linalool (12.88 mg / l), and α-cadinol (12.34 mg / l) were among the highest reported quantities.

The fixed chemical composition of *P. salutare* has shown interesting biological activity. According to Simonetti et al. (2016), the ethyl acetate extract of the leaves has high antioxidant action, 94.08%, and moderate antimicrobial action against *Listeria monocytogenes* with MIC = 312.5 µg / mL. The leaves' essential oil has antifungal activity against fungi of the *Candida* genus, especially for *Candida albicans* with IC_{50} 2.6 µg / mL, showing lower concentrations when compared to fluconazole with IC_{50} 16.7 µg / mL (Macêdo et al., 2018).

These results point to *P. salutare* as a possible complementary therapy to diseases of bacterial and fungal origin, however further *in vitro* and *in vivo* tests are needed, as well as analyzes of its chemical composition to better understand the therapeutic effects associated with the species.

3.3.11. Psidium schenckianum Kiaersk.

Psidium schenckianum is used as food by local populations in the Northeast (Nascimento et al., 2011), however, it is poorly investigated in any aspect. Nascimento et al. (2011), report the presence of Carotenoids (7.90 Beta-carotene µg / g) and Flavonoids (24.59 mg of quercetin / 100 g), and based on that the species is interesting for future studies of antioxidant activity.

3.3.12. Psidium sobralianum Proença & Landrum

In ethnobotanical research, *P. sobralianum* is indicated only in the work of Lozano et al. (2014) being used to treat diarrhea in northeastern Brazil. It appears to be used in the food of local populations (Campos et al., 2016, 2015), which may be linked to the fact that many species of the *Psidium* genus produce edible fruits with an exotic flavor and a high content of vitamin C (Franzon et al., 2009). There are no chemical or biological descriptions for *P. sobralianum*.

The lack of data may be due to its recent description (2015), as it is distributed in northeastern Brazil in areas of mountainous forests, such as in Chapada do Araripe and Chapada da Ibiapaba in Ceará, and in low land areas of Pará. All these citations are of landscape with elevations of 90 to 760 m (Landrum and Proença, 2015).

3.3.13. Psidium striatulum Mart. ex DC.

Analysis of the essential oil from *P. striatulum* leaves allowed the identification of the major compounds α-humulene (13%), α-copaene (8.4%), 1.8-cineole (8.1%), Aromadendrene (6.3%) and α-terpinenol (5.7%) (Moniz et al., 2019b). Silva et al. (2003) identified different terpenes as the major components in the essential oil of the leaves and stems of *P. striatulum* (β-caryophyllene: 28.6%; α-selinene: 7.7%; caryophyllene oxide: 7.6%; β-selinene: 7.4%; selin -11-en-4α-ol: 6.0%). For the fruits (Moniz et al., 2019a), the major compounds are the compounds α-pinene (12%), humulene (10.4%), α-copaene (7.1%).

Although the analyzes have shown different chemical compositions of the leaves, fruits and bark of *P. striatulum*, many of these constituents are present (sometimes as majorities) in other species of the genus (Biegelmeyer et al., 2011; Dias et al., 2019; Moniz et al., 2019b; Soliman et al., 2016)

Regarding biological activity, *in vitro* tests with *P. striatulum* essential oil revealed inhibition of the microorganisms *Salmonella typhimurim*, *Bacillus cereus* and *Staphylococcus aureus*, in addition to having an effect on the acetylcholinesterase enzhyme (Moniz et al., 2019b)

The fixed composition of *P. striatulum* is still unknown, and further studies with this bias are needed, in addition to studies of biological activities to establish the safety and efficacy of its secondary metabolites as possible pharmaceutical agents.

3.4. Traditional use and scientific investigations

The native species of *Psidium*, covered in this review, used in traditional medicine, have therapeutic indications mainly linked to the digestive system. All six species indicated in traditional medicine indicate within this system. Five of them have indications for diarrhea, and four for dysentery, showing the prevalence of these therapeutic uses within the genus. Digestive disorders are associated with issues of basic sanitation and water treatment (Ortega-Cala et al., 2019; Tangjitman et al., 2015), affecting the most vulnerable part of society. According to the World Health Organization (WHO) (WHO, 2020), diseases of the digestive system, mainly diarrhea, are among the main causes of death in the world, occupying the eighth position. The use of native *Psidium* species for this system may appear as a therapeutic alternative for communities more susceptible to these diseases.

The traditional uses identified are associated with symptoms or causes and not with specific diseases. Symptoms such as dysentery, diarrhea, headaches, breathing problems, inflammation indicate a range of illnesses. None of these therapeutic uses have been tested directly in biological tests. Researchers perform the studies based not only on popular indications but in general due to tested microorganisms that affect human health. However, studies carried out against bacteria of the genera *Salmonella, Staphylococcus, Bacillus, Pseudomonas, Staphylococcus, Listeria, Klebsiella* (Alvarenda et al., 2015; Durães et al., 2017; Macaúbas-Silva et al., 2019; Melo et al., 2017; Moniz et al., 2019b) and fungi of the genus *Candida* (Macêdo et al., 2020, 2018; Morais-Braga et al., 2016a), may be associated with traditional uses of popular medicine, since these microorganisms are capable of causing diseases and infections with the same symptoms reported in ethnobiological research: diarrhea, dysentery, and belly pain.

The medicinal uses indicated for disorders of the respiratory and nervous systems have no biological investigation. This may be because they are less evident systems among *Psidium* species. On the other hand, antiproliferative investigations in breast, ovarian, and colon cancer cells (Dias et al., 2019; Medina et al., 2011; Nascimento et al., 2018), may be associated with indications for the genitourinary system (Abreu et al., 2015).

Although the research is not directly related to the traditional uses reported, the species most used in folk medicine are also the most analyzed in terms of biological activity, such as *P. cattleyanum* and *P. guineense*. Thus, the traditional knowledge associated with the number of therapeutic indications seems to be a criterion for the selection of species to be investigated in ethnopharmacology. This connection between the lines of research shows the importance of ethnobiology as a premise for testing species with therapeutic indications reported by communities, and directing species for bioprospecting.

Malaria was the only disease reported for *Psidium* species (specifically *P. acutangulum*) and tested directly because of its popular indications, either in the treatment of the disease (Houël et al., 2016, 2015) or in the form of prevention against transmitting mosquitoes (Chalannavar et al., 2013). However, this information is not present in the ethnobotanical data of this analysis, because the research was carried out in French Guiana in the years 2003 and 2007 (Fleury, 2007, 2003) and is not part of the criteria established in this investigation. *P. acutangulum* indications against malaria need further investigation because despite the decline in malaria cases reported in the 20th century, this disease still represents a public health problem in most developing countries in tropical and subtropical areas. In these countries, factors such as temperature and rainfall are preponderant for the development of vectors and parasites (Greenwood et al., 2008). Plants are the richest sources of active ingredients, many identified compounds are used as herbal agents (Lee, 2010).

The chemical composition of *Psidium* species may be related to the success of biological activities. Most studies analysed show that they are part of the compounds found in plant extracts in the species already described: the total phenolic content, the richness of flavonoids (catechins and anthocyanins), essential oils (β-caryophyllene) and the meroterpenoids, identified mainly in *P. guajava*.

In *Psidium* species, metabolites (vitamins, phenolic compounds, carotenoids, and flavonoids) constitute an important source of antioxidant compounds (Batista et al., 2018; Pereira et al., 2012; Trueba, 2003). The antioxidant capacity of the species is mainly associated with the richness of flavonoids. They are one of the groups most present in the *Psidium* species investigated in this analysis (Chaves et al., 2018; Donno et al., 2018; Saber et al., 2018). Both popular medicine and human food use its fruits (Franzon et al., 2009). Fruits and vegetables are sources of nutritional resources. Their consumption is related to a reduction of the incidence of diseases such as cancer, cardiovascular dysfunctions, inflammation, the decline of the immune system (Schiassi et al., 2018; Steinmetz and Potter, 1996).

The tested concentrations of plant extracts of *Psidium* species influence biological activities. In general, the reported studies make the concentrations viable for application, because they present significant biological activity, either in the synergistic interaction between chemical compounds, compounds, and synthetic drugs or isolated compounds (Castilho et al., 2014; Chalannavar et al., 2013; Charneau et al., 2016; Gordon et al., 2011;

Houël et al., 2016; Luiz et al., 2017; Morais-Braga et al., 2016a; Nascimento et al., 2018; Ortega et al., 2017).

Cytotoxicity tests are important to make the concentrations used in biological assays feasible, however, they are still incipient. Only two of the analyzed species provide this information. The tested concentrations of *P. acutangulum* do not show cellular cytotoxicity (Houël et al., 2016, 2015), however *P. brownianum* (Machado et al., 2018) has a high toxic effect on fibroblasts, although it has shown excellent biological activity.

It is difficult to provide a direct answer about the effectiveness of the concentrations tested in the research analyzed since different means of testing and units of measurement are used in the conduct of the experiments. One of the examples that can be cited is the results of antioxidant tests through the DPPH method expressed in different forms, percentage, µmol L-1, µg / mL, mg / mL, g / dry fruit. It would be ideal to establish a standardized range of effectiveness for each biological activity, as well as for the methods tested.

Seven species in the group of species analyzed in this investigation do not have ethnobotanical reports. Among these seven species, five of these denote biological activities. We found that some studies justify carrying out biological tests based on popular indications. However, these studies do not investigate the therapeutic uses indicated by local populations (Macêdo et al., 2020; Moniz et al., 2019b; Morais-Braga et al., 2016b). Other studies support their research based on the use of species for human consumption (Bittencourt et al., 2019), or seek to understand their chemical composition based on the scarcity of reports in the scientific literature (Dias et al., 2019; Medeiros et al., 2018; Nascimento et al., 2011). It would be interesting if future studies of biological activities were directed to the same therapeutic indications reported in the communities, being able to assure if a given treatment used empirically brings benefits or harms.

In this context, ethnobotanical data still need to be better targeted, to point out species with pharmacological potential, as this facilitates the emergence of biological activity research that is directly related to the therapeutic uses indicated by the communities.

4. Conclusions

Few *Psidium* species have been registered with therapeutic indications, most of which were included in ethnobotanical surveys in lists with several other species.

Most of the investigated species present studies on chemical composition and / or biological activities, with the exception of *P. sobralianum*, which has not presented any record with this scientific approach.

Psidium species are indicated in Brazilian folk medicine almost exclusively for disorders in the digestive system, although they are used for other systems such as respiratory, nervous and genitourinary. However, there is little research on chemical composition and biological activity aimed directly at these therapeutic indications.

The *Psidium* species studied are rich in terpenes, phenolic compounds, tannins and carotenoids and these substances are directly responsible for the biological activities conferred on the species, such as antioxidant, antimicrobial, antiproliferative and anti-inflammatory.

Psidium cattleyanum and *P. guineense* are the most investigated species in terms of ethnobiological research, chemical composition and biological activities. The commercial exploitation of its fruits can be one of the determining factors for these investigations.

Psidium acutangulum, P. brownianum, P. densicomum, P. grandifolium, P. laruotteanum, P. myrsinites, P. myrtoides, P. salutare, P. schenckianum, P. striatulum and *P. sobralianum*, appear less frequently in investigations in scientific studies. However, these are species that deserve attention, as some already register the presence of flavonoids and terpenes, two chemical classes proven to be responsible for biological activities.

Native species of the *Psidium* genus are important sources of active ingredient, however new research on bioprospecting is relevant and necessary to carry out a diagnosis within the genus, and help in the development of effective herbal medicines to combat human diseases.

Authors contributions

Julimery Gonçalves Ferreira Macedo collected the information, wrote the paper. Juliana Melo Linhares Rangel contributed editorial comments and corrections. Maria de Oliveira Santos prepared the tables. Cicera Janaine Camilo prepared the figures. Marta Maria de Almeida Souza and José Galberto Martins da Costa conceptualized the study and suggested several improvements for the first version and later.

Declaration of competing interest

The authors declare no conflict of interst.

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4. CAPÍTULO 3: MANUSCRITO II

Título: Chemical composition, antioxidant, antibacterial and modulating activity of the essential oil of *Psidium* L. species (Myrtaceae Juss.)

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Chemical composition, antioxidant, antibacterial and modulating activity of the essential oil of *Psidium* L. species (Myrtaceae Juss.)

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Abstract

This work aimed to analyze the chemical composition of the essential oils from *Psidium laruotteanum* Cambess. (Marangaba-peluda), *Psidium salutare* (Kunth) O. Berg (Marangaba-vermelha) and *Psidium sobralianum* Landrum & Proença (Araçá-de-veado), and to investigate their antibacterial and antioxidant activities. Twenty-six chemical compounds were identified, with a predominance of hydrocarbon sesquiterpenes (38.46%). The essential oils presented different compounds, with the majorities being Viridiflorol (27.89%), α-caryophyllene (27.62%) and Isocaryophyllene (10.16%) for *P. laruotteanum*; 1,8-Cineole (57.07%) and α-phellandrene (14.62%) for *P. salutare* and α-pinene (11.78%), Viridiflorol (11.64%), δ-amorphene (9.93%) and γ-eudesmol (9.44%) for *P. sobralianum*. The essential oil of *P. laruotteanum* showed the best antibacterial results, inhibiting the growth of *E. coli* at concentration 96 µg/mL, and demonstrating synergistic effect when associated with amikacin on *S. aureus*, with $p<0.001$. The dominance of Caryophyllene derivatives may be responsible for the activity. *P. salutare* and *P. sobralianum*, were only able to inhibit bacterial growth at higher concentrations, between 341.33 µg/mL and ≥ 1024 µg/mL. Regarding antioxidant activity, the three species were able to inhibit DPPH in a concentration-dependent manner, with the best result for *P. sobralianum* oil with IC_{50} of 5.99 mg/mL.

Keywords: *Psidium laruotteanum*; *Psidium salutare*; *Psidium sobralianum*; Terpenes; Volatile oils; Biological activities.

1. Introduction

Human infectious diseases, such as those caused by bacteria, are associated with high rates of mortality and morbidity, being one of the leading causes of death worldwide (Dacoreggio et al., 2019). Multidrug-resistant strains are emerging from the indiscriminate and/or inappropriate use of synthetic antimicrobials, representing a serious public health problem worldwide (Górniak et al., 2018). Medicinal plants are prospective sources of antimicrobial agents. The presence of secondary metabolites in their chemical composition figure as alternative products used against pathogenic microorganisms, many showing efficient antimicrobial activity (Campos e Silva et al., 2021; Górniak et al., 2018).

Besides the use of medicinal plants for the treatment of infectious diseases, they are also used for the treatment of neurodegenerative, cardiovascular and cancer diseases. The presence of excessive free radicals in the body or insufficient production of antioxidants leads to oxidative stress in cells and favors the development of these latter diseases (Suwanwong and Boonpangrak, 2021).

The therapeutic activities of medicinal plants are largely attributed to bioactive compounds present in their metabolism. Flavonoids, phenolic compounds, tannins, and volatile terpenes present in the chemical composition of plant species are directly responsible antimicrobial and antioxidant activities (Chouhan et al., 2017; Górniak et al., 2018; Vinholes et al., 2017).

Volatile terpenes, especially monoterpenes and sesquiterpenes, present in essential oils of plant species, represent alternatives of biological (natural) sources in the development of new drugs both in fighting infectious diseases (Tariq et al., 2019) and attacking free radicals (Valdivieso-Ugarte et al., 2019). These metabolites can act synergistically with synthetic drugs potentializing their effect when used in combination with plant extracts, or interfering with the resistance mechanism of microorganisms or cellular oxidation (Kalan and Wright, 2011).

Medicinal plant species found in the Brazilian flora have contributed to the development of therapeutic alternatives through the identification of their secondary metabolites. Botanical species belonging to the Myrtaceae family, especially in the genus *Psidium* L., are used in the treatment of diseases and symptoms associated with various body systems (Macedo et al., 2021).

The therapeutic potential of these species may be related to the richness of chemical compounds present in the essential oil, demonstrating to be effective against several bacteria (Dias et al., 2019; Durães et al., 2017; Moniz et al., 2019) and in helping to eliminate of free radicals present in the body (Jerônimo et al., 2021; Nascimento et al., 2018; Nora et al., 2014). Taking into consideration the ethnopharmacological potential of *Psidium* species and the presence of essential oils in their chemical composition, the aim of this study is to analyze the chemical composition of the essential oil of *Psidium laruotteanum* Cambess. (Marangaba-peluda), *Psidium salutare* (Kunth) O. Berg (Marangaba-vermelha) and *Psidium sobralianum* Landrum & Proença (Araçá-de-veado), and to investigate their antibacterial and antioxidant potential. These species are present in several Brazilian phytogeographic domains and are used in traditional medicine, but there is little information about these investigations.

2. Materials and methods

2.1. Collection and identification of botanical material

The collection of plant material took place in two areas of disjunct Cerrado in the Chapada Nacional do Araripe, Barreiro Grande and Malhada Bonita, located about 26 km from the municipality of Crato, Ceará, in Northeastern Brazil.

The study was carried out with young and healthy leaves of the shrubby species *Psidium sobralianum* Landrum & Proença (07º 21’ 43.22" S and 039º 28’ 34.2" W), *P. laruotteanum* Cambess. (07º 21’ 23.2" S and 039º 26’ 17.6" W) and *P. salutare* (Kunth) O. Berg. (07º 23’ 25.8" S and 039º 26’ 53.4" W), with the respective herbarium accession numbers, IPA: 92709, UB: 217278 and UB: 217277, all collected by the first author.

The botanical material was collected and processed according to classic herborization techniques (Mori et al., (1989) and identified by Dra. Carolyn Elinore Barnes Proenca of the Universidade de Brasília (UnB) and by Dr. Marcos Eduardo Guerra Sobral of the Universidade Federal de São João Del-Rei (UFSJ). The voucher material was deposited at the Dárdano de Andrade Lima Herbário of the Instituto Agronômico de Pernambuco (IPA), at the Herbarium of the Universidade Federal of São João Del Rei (HUFSJ) and at the Herbário da Universidade of Brasília (UB). The survey is registered in the National System for the Management of Genetic Heritage and Associated Traditional Knowledge (SISGEN), registration number AE56B81. Authorization for the collection of botanical material was provided by the Information System on Authorization and Biodiversity (SISBIO) of the Chico Mendes Institute for Biodiversity Conservation (ICMBio), under authorization number 63956-1.

2.2. Extraction and analysis of essential oils

The chemical profile of the species was evaluated from the collection of leaves extracted from a single individual (per species) and collected preferably in the morning, around 9 am. The leaves collected from each individual ranged from 204g to 380g in weight.

Fresh leaves with a mass of 204g (*P. laruotteanum*), 336g (*P. salutare*), and 380g (*P. sobralianum*) were submitted to the hydrodistillation process for 2 h in a modified Clevenger apparatus. After this process, the essential oils were collected and treated with anhydrous sodium sulfate (Na_2SO_4) and kept under refrigeration at < 4° C until analyzed.

The essential oils were analyzed by gas chromatography coupled with mass spectrometry (GC/MS) in a Shimadzu QP 2010 spectrometer, operating with ionization energy of 70 eV. A capillary column of fused silica Rtx – 5MS (30 m x 0.25 mm i.d., 0.25 μm film thickness) and a helium gas carrier with a flow of 1 mL/min with split was used. Injector and detector temperatures were programmed at 250 °C and 200 °C, respectively. The column temperature was determined from 35°C to 180°C at 4°C/min and then from 180 °C to 280 °C at 10 °C/min. Mass spectra were obtained from 30 to 450 m/z. Individual components were identified by matching their mass spectra with those in the database, as well as by visually comparing the fragmentation pattern with those reported in the literature (Adams, 2001). The representation of chemical structures was developed in ChemDraw 18.1.

2.3. Antibacterial test

2.3.1. Determination of minimum inhibitory concentration (MIC)

The antibacterial activity of essential oils was evaluated by the serial microdilution method, using the M02-M11 model as a reference (CLSI, 2018). The assay was performed with the bacteria *Escherichia coli* Ec 27 and *Pseudomonas aeruginosa* ATCC

15442 gram-negative and *Staphylococcus aureus* Sa 358, and *Streptococcus mutans* INCQS 00446 gram-positive. Table 1 shows the bacterial resistance profile.

Table 1: Profile of bacterial resistance to antibiotics (Sobral et al., 2016).

Bacteria	Source	Antibiotic resistance
Staphylococcus aureus Sa 358	surgical wound.	Oxa, Gen, Tob, Amk, Lex, Neo, Paro, But, Sis, Net
Escherichia coli Ec 27	surgical wound.	Azm, Amx, Amp, Amk, Lex, Cec, Cef, Caz, Cip, Chl, Ipm, Kan, Sxt, Tet, Tob

Subtitle: Amk: Amikacin; Amp: Ampicillin; Amx: Amoxicillin; Azm: Azithromycin; But: Butirosin; Caz: Ceftazidime; Cec: Cefaclor; Cef: Cephalothin; Chl: Chloramphenicol; Cip: Ciprofloxacin; Gen: Gentamicin; Ipm: Imipenem; Kan: Kanamycin; Lex: Cephalexin; Neo: Neomycin; Net: Netilmicin; Oxa: Oxacillin; Paro: Paromomycin; Sis: Sisomicin; Sxt: Sulfamethoxazole; Tet: Tetracycline; Tob: Tobramycin.

Essential oils were diluted in sterile distilled water and dimethylsulfoxide (DMSO) at a concentration of 1024 μg/mL. Serial dilutions were performed to obtain concentrations ranging from 512 to 8 μg/ml. Tests were performed in triplicate and plates incubated at 35 ± 2 °C for 24 h. The analysis of the results was carried out by colorimetry with the addition of 25 μL of resazurin solution (0.01%) to each well after incubation. The minimum inhibitory concentration (MIC) was defined as the lowest concentration of essential oil capable of inhibiting bacterial growth.

2.3.2. Evaluation of the modulating effect

The modulating effect of essential oils from *Psidium laruotteanum* Cambess., *P. salutare* (Kunth) O. Berg, and *P. sobralianum* Landrum & Proença were analyzed by combining them with the aminoglycoside amikacin and the beta-lactam cephalothin, according to the methodology proposed by Coutinho et al. (2008).

The essential oils that obtained the best MIC were used in sub-inhibitory concentrations (MIC/8) in 10% BHI. The solutions were distributed in microdilution plates, followed by the addition of different concentrations of antimicrobials obtained by serial dilution from an initial solution of 1024 μg/mL. In the negative control, antibiotics were not added to the strains. The plates were incubated at 35 ± 2 °C for 24 h and read by colorimetry by adding 25 μL of resazurin solution (0.01%). As a positive control, the MICs of the antibiotics used were used.

2.4. Antioxidant test

2.4.1 DPPH free radical scavenging activity

The free radical scavenging activity of essential oils was determined by the photocolorimetric method of DPPH (1,1, diphenyl-2-picrylhydrazyl), according to Choi et al. (1994), with modifications using ascorbic acid and eugenol as standard antioxidants.

In 96-well plates, triplicate volumes of 20μL of ascorbic acid and eugenol dissolutions and oils were added to 80μL of 99.5% ethanol and 100μL of 0.4 mM DPPH ethanolic radical solution; generating final concentrations of standards and oils of 1.37-88.11 mg/mL. After 1 h of incubation at room temperature and in the dark, absorbance measurements were taken at 518 nm. The absorbance readings of the respective blanks of the oils and standards were carried out under the same working conditions, 20µL of dissolution of oils and standards, 180µL of 99.5% ethanol, obtaining the same final concentrations.

The percentages (%) of DPPH radical inhibition were expressed as a percentage compared to the control, consisting of 100µL of 0.4 mM DPPH ethanolic solution and 100µL of 99.5% ethanol, and calculated using the equation:

$$\% \text{ DPPH inhibition} = \frac{[(\text{Abs.}_{\text{Control}} - (\text{Abs.}_{\text{Extract}} - \text{Abs.}_{\text{White}})] \times 100\%}{\text{Abs.}_{\text{Control}}}$$

Where, $\text{Abs.}_{\text{Control}}$ is the absorbance of the extract-free DPPH solution; $\text{Abs.}_{\text{Extract}}$ is the absorbance of the extract with DPPH; $\text{Abs.}_{\text{White}}$ is the absorbance of the extract without DPPH.

2.5. Statistical analysis

Antioxidant assay results were analyzed using ANOVA and Tukey tests, and microbiological results were analyzed using a one-way ANOVA with the Bonferroni correction using GraphPad Software Prism 8.0. Results with $p < 0.05$ were considered statistically significant.

3. Results and discussion

3.1. Chemical analysis

The essential oil yields of *P. sobralianum* and *P. salutare* were higher than those obtained from *P. laruotteanum* (0.52%, 0.51% and 0.05%, respectively). According to the literature the essential oil of *P. salutare* and *P. laruotteanum* showed yield variations between 0.15%-0.73% for the former; 0.3%-0.4% and 0.4 ± 0.0 for the latter two (Camara et al., 2020; Macêdo et al., 2018; Medeiros et al., 2018). No chemical yield was found in the literature for the essential oil of *P. sobralianum*, this is the first extraction reported for this species.

The variation in essential oil yield may be related to the quantity of times that the same plant individual is submitted to the leaf removal process (among other factors), since these factors were directly proportional. Once the leaves are removed (an important element in photosynthesis), the species may invest more energy resources to produce new leaves and perhaps make fewer resources available for essential oil production (a process with significant energy investment; Taiz et al., 2017). This process can be aggravated if the withdrawal intervals are too short. In this way, the species will not have enough time to produce new leaves, and consequently essential oil production will be affected.

The analyses performed in GC-MS revealed qualitative and quantitative variations of the oils. Twenty-six compounds corresponding to 80%, 96.62% and 100.00% of *P. sobralianum, P. laruotteanum* and *P. salutare* were identified, respectively (Table 2). Of the identified compounds, 84.61% were present in only one species, 15.38% were shared between two species, and none o were shared among the three species. The chemical composition of plant essential oils is genetically determined; however, environmental conditions such as the vegetative cycle, and extrinsic factors, as well as different extraction methods can cause significant variation (Heinzmann et al., 2017).

Table 2: Chemical composition of essential oils from leaves of *Psidium laruotteanum*, *Psidium salutare*, *Psidium sobralianum*, analyzed by gas chromatography coupled with mass spectrometry (GC/MS).

Nº	Compounds	*Psidium laruotteanum*		*Psidium salutare*		*Psidium sobralianum*	
		RT (min.)	%	RT (min.)	%	RT (min.)	%
1	α-pinene	-	-	3.896	4.48	3.887	11.78
2	β-pinene	-	-	-	-	4.790	8.13
3	β-myrcene	5.008	3.56	-	-	-	-
4	α-phellandrene	-	-	5.398	14.62	-	-
5	Terpinolene	-	-	5.640	2.06	-	-
6	Limonene	-	-	5.878	8.37	-	-
7	1,8-Cineole	-	-	5.969	57.07	5.948	7.10
8	γ-terpinene	-	-	6.378	4.85	-	-
9	Linalool	6.989	7.26	6.990	5.74	-	-
10	L-α-Terpineol	-	-	-	-	8.158	2.02
11	α-terpinyl acetate	-	-	9.618	2.82	-	-
12	Isocaryophyllene	10.370	10.16	-	-	-	-
13	Bicyclosesquiphellandrene	-	-	-	-	10.450	2.74
14	α-caryophyllene	10.718	27.62	-	-	-	-
15	Germacrene D	-	-	-	-	10.837	6.18
16	β-selinene	11.051	2.12	-	-	-	-
17	Viridiflorene	11.128	4.04	-	-	-	-
18	γ-elemene	-	-	-	-	11.140	6.32
19	δ-amorphene	-	-	-	-	11.363	9.93

Nº	Compounds	*Psidium laruotteanum*		*Psidium salutare*		*Psidium sobralianum*	
		RT (min.)	%	RT (min.)	%	RT (min.)	%
20	10-epi-Elemol	-	-	-	-	11.689	4.72
21	Palustrol	12.053	3.06	-	-	-	-
22	Aromadendrene	12.273	3.42	-	-	-	-
23	Cycloheptane, 4-methylene-1-methyl 2-(2-methyl-1-propen-1-yl)-1-vinyl-	12.391	4.78	-	-	-	-
24	Viridiflorol	12.570	27.89	-	-	13.247	11.64
25	Caryophyllene oxide	12.654	2.71	-	-	-	-
26	γ-eudesmol	-	-	-	-	12.908	9.44
	Hydrocarbon monoterpenes	-	9.09	-	62.5	-	18.18
	Oxigenated monoterpenes	-	9.09	-	37.5	-	18.18
	Hydrocarbon sesquiterpenes	-	54.54	-	-	-	36.36
	Oxigenated sesquiterpenes	-	27.27	-	-	-	22.27
	Total identificado (%)		96.62		100.00		80

Subtitle: -: not detected; %: Concentration; RT: Retention time; min.: minute.

Psidium essential oils have a terpene chemical profile, with a predominance of hydrocarbon sesquiterpenes (38.46%), followed by hydrocarbon monoterpenes (26.92%), oxygenated sesquiterpenes (19.23%), and oxygenated monoterpenes (15.38%). Figure 1 shows the structural representations of the substances identified in the study species. These results are similar to those reported in the literature for native Brazilian species of *Psidium* (Campos e Silva et al., 2021; Macedo et al., 2021).

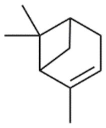
It was observed that the essential oil of *P. laruotteanum* and *P. sobralianum* are richer in sesquiterpenes (hydrocarbonated and oxygenated) while that of *P. salutare* is composed exclusively of monoterpenes (hydrocarbonated and oxygenated). It can be seen that the predominance of chemical classes of the species are not invariable. For example, Medeiros et al. (2018) notes that the essential oil of *P. laruotteanum* is rich in monoterpenes, whereas Camara et al. (2020) recorded richness in sesquiterpenes. The same distinction can be made for the essential oil of *P. salutare*, rich in sesquiterpenes in the study by Pino et al. (2003) and in monoterpenes in Macêdo et al. (2018). This distinction may be related to the presence of the dominant compound, since this compound stands out due to its high percentage in relation to the others.

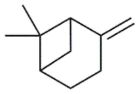
Eleven compounds were identified in *P. laruotteanum* oil, where the dominat compounds were Viridiflorol (27.89%), α-caryophyllene (27.62%) and Isocaryophyllene (10.16%). In the literature about 79 compounds have already been recorded in the essential oil of *P. laruotteanum* (Camara et al., 2020; Medeiros et al., 2018). However, the chemical composition of our analysis incorporate new elements to the species, since of the compounds found, only 3.79% had already been identified in the species.

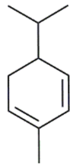
The discrepancy in the composition of the essential oil of *P. laruotteanum*, is also demonstrated for the majority compounds found in the literature. In this analysis the majority compounds cited in the previous paragraph, differ from those reported by Medeiros et al. (2018) (p-cymene: 34.8%; 1,8-cineole: 19.2%; y-terpinene: 14%; a-pinene: 13.4%) and Camara et al.

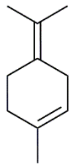
(2020) ((E)-Nerolidol: 9.6%; y-terpinene: 9.4%; Caryophyllene oxide: 7.3%). Although there is difference between the chemical profile of the species, it shows similarity with other *Psidium* species, such as *P. myrsinites* DC. and *P. myrtoides* O. Berg (Camara et al., 2020; Dias et al., 2020) showing richness of caryophyllene derivatives.

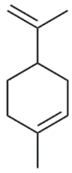
Monoterpenes hydrocarbons

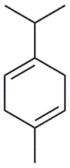

α-pinene

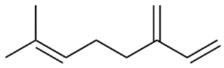

β-pinene


α-phellandrene

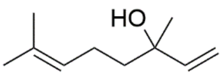

Terpinolene


Limonene

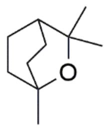

γ-terpinene


β-myrcene

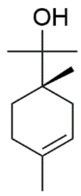
Oxygenated monoterpenes



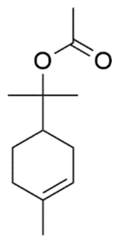
Linalool



1,8-cineole

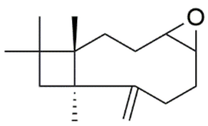


L-α-terpineol

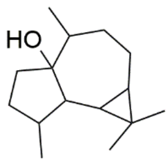


α-terpinyl acetate

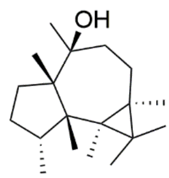
Oxygenated sesquiterpenes



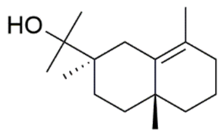
Caryophyllene oxide



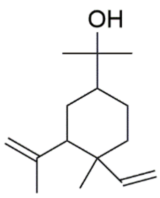
Palustrol



Viridiflorol



γ-eudesmol



10-epi-elemol

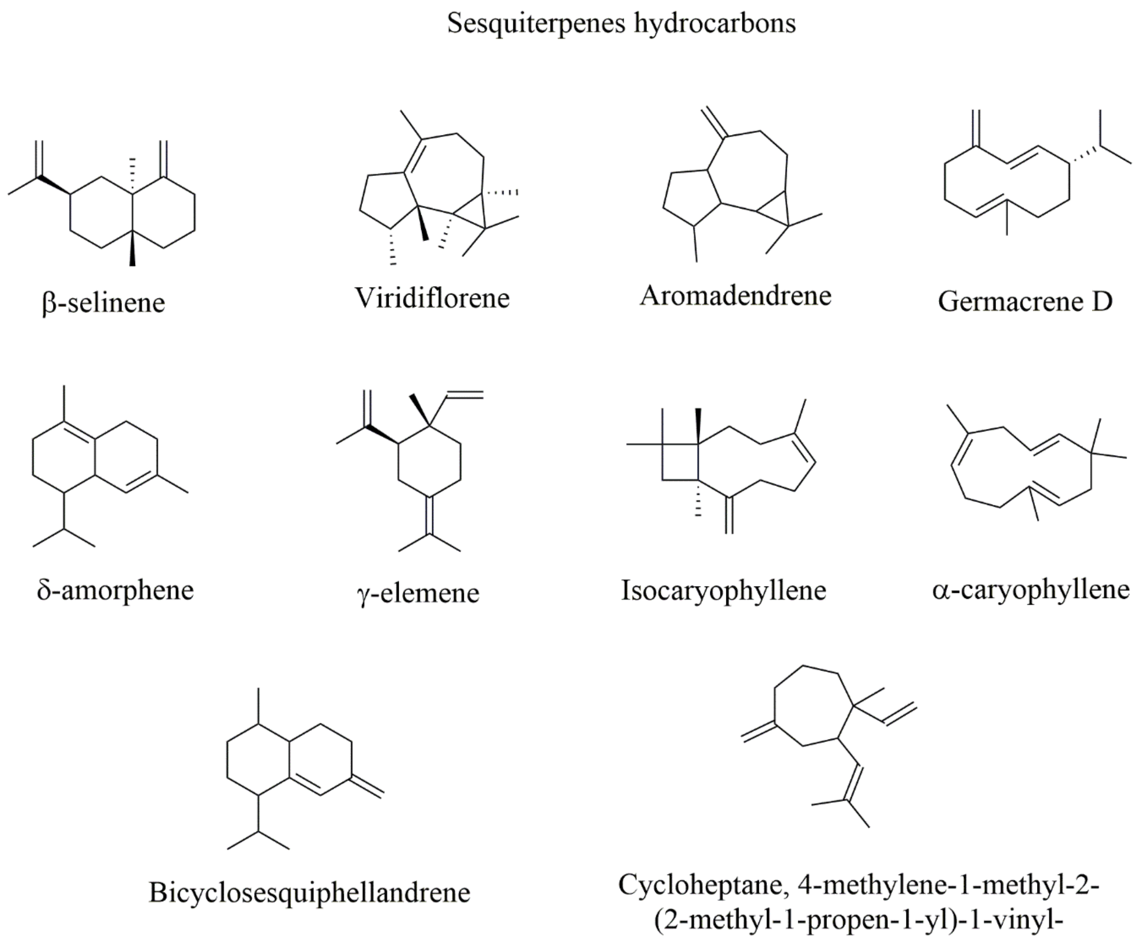


Fig. 1: Structural representation of the chemical compounds of essential oils from *Psidium* species.

For *P. salutare*, eight compounds were identified in essential oil. Of these, only two (α-phellandrene and α-terpinyl acetate) had not been reported for this species, showing that it presents a similar profile to other populations previously analyzed. However, the monoterpenes 1,8-cineole (57.07%) and α-phellandrene (14.62%) figure as the majority compounds, a result different from that found in the literature. Macêdo et al. (2018) recorded p-cymene (17.83%), γ-terpinene (17.09%), terpinolene (16.99%), and t-cadinol (15.20%) as the majority compounds. Pino et al. (2003) reported the compounds Caryophyllene oxide (39.8%) and ar-turmerone (17.3%) as the majority compounds.

For *P. salutare*, the he high concentration of 1,8-cineole (above 50%) in its essential oil is noteworthy. High concentrations might have potential therapeutic value, as it is a component that frequently appears in myrtle oils (Dhakad et al., 2018). Eucalyptol or 1,8-cineole is the active compound of many *Eucalyptus* species (also Myrtaceae), with concentrations ranging from 60% to 95% and can act as an antimicrobial, anti-inflammatory, antioxidant, bronchodilator, and antiviral (Dhakad et al., 2018). In a recent research developed by Valussi et al. (2021), the authors demonstrate that the use of Eucalyptol (as an isolated substance or as a main compound of essential oils) seems to be a useful remedy for the treatment of respiratory symptoms, as well as in patients with mild uncomplicated infections caused by coronaviruses such as SARS-CoV-2.

For *P. sobralianum*, a total of 11 compounds were identified essential oil, with α-pinene (11.78%), Viridiflorol (11.64%), δ-amorphene (9.93%) and γ-eudesmol (9.44%) as the major components. This analysis provides unprecedented information in the literature on the chemical composition of the essential oil of *P. sobralianum*, a species endemic to Brazilian. The chemical characterization of the species expands our knowledge of the volatile compounds within the genus, Macedo et al. (2021), state that some species of *Psidium* are unknown or that on their chemical profiles information is often scarce.

The chemical composition of the essential oil of *P. sobralianum* is similar to some *Psidium* species cited in the literature, such as *P. brownianum* Mart. ex DC. (Sampaio et al., 2020), *P. guineense* Sw., *P. laruotteanum*, and *P. salutare* (Campos e Silva et al., 2021; Macêdo et al., 2018; Medeiros et al., 2018) presenting as characteristic in their essential oils the presence of α-pinene, β-pinene and 1,8-cineole. In some of these species these compounds figure as the dominant compounds. The voucher specimen cited by Sampaio et al. (2020) as *P. brownianum* was Morais-Braga s.n., depositad in HCDAL (Accession 10671) and UB (Barcode UB0038996), from the same locality as our study. This voucher has since been re-identified as *P. sobralianum* Landrum & Proença, described in 2015 after the study by Sampaio et al. (2020). The name *P. brownianum* was poorly understood at the time of their study, and was applied to what is now understood as three different species (Landrum and Proença, 2015; Tuler et al., 2019).

Compounds such as Bicyclosesquiphellandre (2.74 %), Germacrene D (6.18 %), δ-amorphene (9.93 %), 10-epi-elemol (4.74 %) and γ-eudesmol (9.44 %) that appear in the essential oil of *P. sobralianum,* are less frequent in other *Psidium* species. Of these, δ-amorphene and γ-eudesmol stand out, corresponding to more than 19% of the total concentration of compounds.

3.2. Antibacterial assay

The values of inhibitory concentrations obtained from the bacterial strains tested are shown in table 3.

Table 3: Minimum inhibitory concentration (MIC) of essential oil from leaves of *Psidium* species on bacterial strains.

Tested microorganisms	MIC (µg/mL)		
	EOPL	EOPSA	EOPSO
Gram$^-$			
Escherichia coli Ec 27	96	≥ 1024	768
Pseudomonas aeruginosa ATCC	426.67	853.33	341.33
Gram+			
Staphylococcus aureus Sa 358	512	853.33	512
Streptococcus mutans INCQS 00446	170.67	≥ 1024	597.33

Subtitle: ATCC: American Type Culture Collection; INCQS: National Institute for Quality Control in Health. EOPL: essential oil of *P. laruotteanum*; EOPSA: essential oil of *P. salutare*; EOPSO: essential oil of *P. sobralianum*.

The essential oil of *P. laruotteanum* showed the best MIC results, thus having the modulating activity analyzed. It was able to inhibit the growth of *Escherichia coli* and

Streptococcus mutans bacteria at concentrations of 96 µg/mL and 170.67 µg/mL, respectively. This effect on *E. coli* is an important finding, since it shows that the essential oil was able to inhibit the action of a multidrug-resistant bacterium that has a multilayer membrane structure, which is difficult to be broken by conventional antibiotics (Madigan et al., 2016).

The dominant presence of Caryophyllenes derivatives, such as Isocaryophylle, α-caryophyllene, Caryophyllene oxide (lower amount) (Sotto et al., 2020), in addition to considerable amount of Viridiflorol (27.89%), could be responsible for the antibacterial activity of *P. laruotteanum* essential oil. Or even, by higher and lower levels of different compounds, could be responsible for the effective synergistic effect on *E. coli* and *S. mutans*.

This is the first report of antibacterial activity of *P. laruotteanum* oil. An acaricidal action of its oil on *Tetranychus urticae* has already been verified (Camara et al., 2020). Although there are no reports of antibacterial action of *P. laruotteanum* essential oil, research with hexane and ethyl acetate extracts from the leaves, revealed significant activity on *Trypanosoma brucei gambiense* (Charneau et al., 2016).

The oils from *P. salutare* and *P. sobralianum*, were only able to inhibit bacterial growth at higher concentrations, 853, 33 µg/mL to ≥ 1024 µg/mL for the former and 341.33 µg/mL to 768 µg/mL for the latter. The species showed richness of 1,8-cineole (57.07 %) (*P. salutare*) and α-pinene (11.78 %) (*P. sobralianum*), compounds that are generally considered bacterial growth inhibitors (for both gram+ and gram- bacteria) as demonstrated by Elaissi et al. (2012), in assays with *Eucalyptus* L'Hér species. which show abundance of these compounds, especially 1,8-cineole. However, this is not a general rule. Cimanga et al. (2002), investigating the relationship between chemical composition and antibacterial activity of aromatic oils from medicinal species, observed that there was no significant correlation between antibacterial activity and the percentage of major compounds. This suggests that the compounds present in greater proportions are not necessarily responsible for the greater portion of the total activity. Thus, the less abundant constituents should be considered, and the activity may be attributed to the presence of these compounds or a synergistic capacity among all compounds in the essential oils.

Other *Psidium* species are pointed out presenting antibacterial activity. Soliman et al. (2016), argued that *P. guajava* L. and *P. cattleyanum* Sabine species showed potent bacterial inhibition on *Staphylococcus aureus* (6.75 µg/mL) and *Neisseria gonorrhoeae* (13.01 µg/mL), suggesting medicinal use and possible therapeutic application of their essential oils for the treatment of various diseases. *Psidium myrtoides* O. Berg was found to have moderate activity against some bacteria of the genus *Streptococcus*, with strong activity against *Streptococcus mutans* as MIC of 62.5 µg/mL (Dias et al., 2019). Still regarding *P. myrtoides*, Macêdo et al. (2020) verified in antifungal tests that the essential oil potentiated the effect of fluconazole (a commercial antifungal agent) on *Candida albicans* strains.

3.2.1. Modulation

The analysis of the antibiotic modulating activity of *P. laruotteanum* oil on bacterial strains showed that the oil had a synergistic effect, as shown (Fig. 2). The essential oil showed synergism especially when associated with amikacin on *S. aureus*, with $p<0.001$, demonstrating that it potentiated the action of the antibiotic on the bacteria tested. There was no modulation when the oil was associated with cephalothin. Synergism was also found in the association of essential oil with amikacin and cephalothin antibiotics on *E. coli*, although not statistically significant. These data are important, since these microorganisms are resistant to the antibiotics tested (Table 1).

Gram-negative bacteria are less susceptible to essential oil components than Gram-positive bacteria, in general. This is due to the outer membrane of lipopolysaccharides (LPS) present in Gram-negative bacteria, which act as a barrier to macromolecules and hydrophobic compounds, thus providing greater tolerance to hydrophobic antimicrobial compounds (Madigan et al., 2016), such as those found in oils essential.

Aminoglycosides, the class to which amikacin belongs, in general, present characteristic cellular toxicity due to their absorption in the intracellular medium (Oliveira et al., 2006). The association of this class of antibiotics and natural products may be an alternative to mitigate their side effects, since a reduction in the MIC may also represent a reduction in the therapeutic dose (Figueredo et al., 2013).

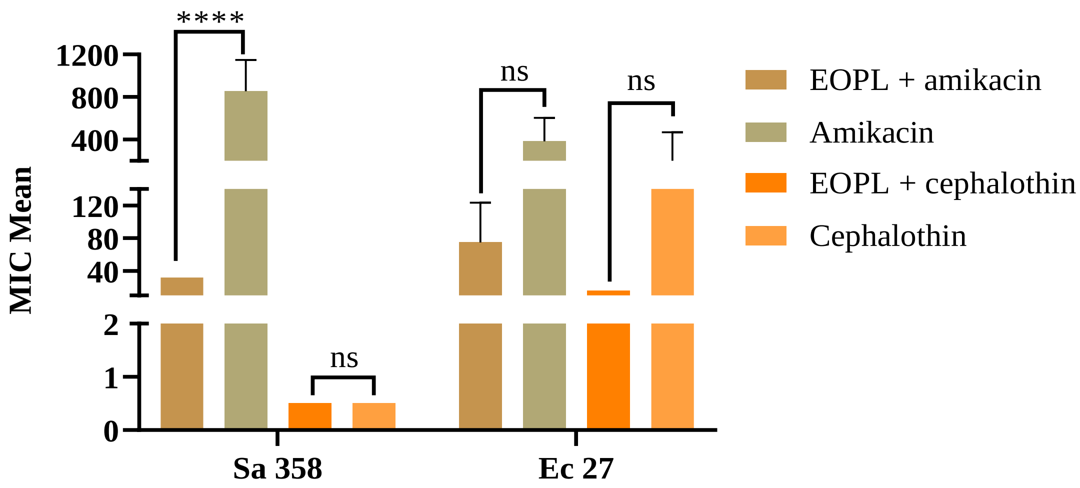


Fig. 2: Modulating effect of *Psidium laruotteanum* (OEPL) essential oil on the antibacterial activity of amikacin and cephalothin on Sa 358 and Ec 27 strains. **** statistically significant p value < 0.001; ns: not significant. Sa 358: *Staphylococcus aureus*; Ec 27: *Escherichia coli*. Data were analyzed by ANOVA and Bonferroni test.

The major compounds of *P. laruotteanum* oil (Viridiflorol: 27.89%; α-caryophyllene: 27.62%; Isocaryophyllene: 10.16%) or the rich mixture of various compounds may be responsible for the antibacterial and modulating activity of this species.

3.3. Antioxidant test (DPPH)

The DPPH elimination index and the value of half inhibitory concentration (IC_{50}) were determined to evaluate the antioxidant capacity of *P. laruotteanum*, *P. salutare* and *P. sobralianum* essential oils.

In the results of free radical scavenging percentage, *P. sobralianum* oil exhibited the highest antioxidant activity, with 53.55 % DPPH inhibition, followed by *P. salutare* with 24.46 % and *P. laruotteanum with* 23, 72 %. These values are lower when compared to the Eugenol and ascorbic acid controls, at 85 % and 88 %, respectively.

When analyzing the IC_{50} values, *P. laruotteanum*, *P. salutare* and *P. sobralianum* oils were able to eliminate DPPH in a concentration-dependent manner (Fig. 3), with IC_{50} ranging from 5.99 mg/mL to 54.34 mg/mL. All oils showed lower inhibition when compared to the positive controls, ascorbic acid (IC_{50} 0.02 mg/mL) and eugenol (IC_{50} 0.04 mg/mL), capable of inhibiting 88.77 % and 85.74 % of the radical, respectively.

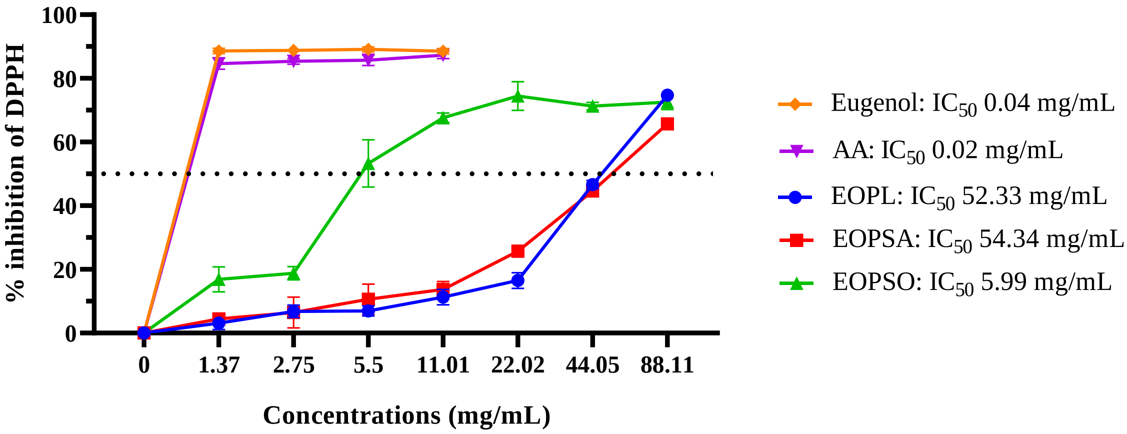


Fig. 3: Antioxidant effect of *Psidium laruotteanum* (EOPL), *Psidium salutare* (EOPSA), and *Psidium sobralianum* (EOPSO) essential oils; of ascorbic acid (AA) and eugenol on the DPPH radical.

The oil of *P. sobralianum* was the most effective against the DPPH radical, with IC_{50} of 5.99 mg/mL. This result places the species in prominence among the native species of the genus, since the IC_{50} of 5.99 mg/mL, is within the established dosage range for antioxidant activity of essential oils, which is 0.01 and 10 mg/mL (Valdivieso-Ugarte et al., 2019). The other *Psidium* species analyzed, although they showed some antioxidant activity, showed IC_{50} values that are not relevant from a clinical point of view, since high doses of the natural product would be needed to have the desired effect.

The essential oil of other *Psidium* species, such as *P. cattleyanum* shows low antioxidant effect, ranging from 16.19 % to 4.01% (Scur et al., 2016). In some cases, such as the essential oil of *P. grandifolium* Mart. Ex DC., the IC_{50} cannot be determined, because even at high concentrations they were not able to reduce DPPH levels by 50% (Bittencourt et al., 2019). On the other hand, *P. guajava*. demonstrates significant antioxidant activity (Jerônimo et al., 2021), a result that may be linked to the high content of oxygenated sesquiterpenes (44.7%), since this class of compounds generally exerts good free radical scavenging activity.

The chemical composition of *Psidium* essential oils may have affected the antioxidant capacity of the species. Good antioxidant behavior can be expected from essential oils with high phenolic content and modest unsaturated terpene content; large amounts of phenolic compounds and significant amounts of cyclohexadiene-like components, e.g. γ-terpinene (Amorati et al., 2013). Although the chemical composition of the essential oil of the studied species shows unsaturated terpenes, it does not reveal any components with predictable antioxidant activity (e.g. phenols). The absence of phenolic compounds (such as thymol, carvacrol or eugenol) in *Psidium* essential oils are characteristic of many native species of the genus (Dias et al., 2020, 2019; Figueiredo et al., 2018; Medeiros et al., 2015, 2018; Soliman et al., 2016). These compounds are largely responsible for the antioxidant activities of the species.

Essential oils from various plants present different degrees of antioxidant activity, according to a table formulated by Amorati et al. (2013). From this data compilation, the authors found that some of the essential oils linked to *Psidium* species in this study show good, low, or pro-oxidant activity using BHT as a reference. For example, the compounds γ-terpinene and 1,8-cineole showed good antioxidant activity; in contrast, the compounds α-phellandrene, Linalool, Germacrene D, α-pinene, Viridiflorol, and Limonene showed very low pro-oxidant or antioxidant activity.

Although the essential oil from *Psidium* species present, in some cases, low capacity to capture free radicals, this does not mean that the species do not have antioxidant potential. Other secondary metabolites, obtained from, for example, aqueous, ethanolic, and methanolic extracts may reveal chemical compounds different from those obtained from essential oils extraction methods. This occurs because while in the latter volatile terpenes predominate, the former may record phenolic compounds rich in flavonoids that are natural sources of antioxidant substances.

Several examples in the literature point out that the aqueous, ethanolic, or methanolic plant extracts of *P. acidum* (DC.) Landrum (originally identified as *P. acutangulum* but see Landrum, 2016), *P. brownianum*, *P. cattleyanum*, or *P. guineense* were rich in phenolic compounds, flavonoids, quercetins, luteins, and tannins showing antioxidant activity (Macedo et al., 2021).

Besides the different methods of extraction, the quantitative and qualitative variation of secondary metabolites found in both essential oils and plant extracts of *Psidium* species can be affected by different conditions, whether genetic, developmental, or environmental.

4. Conclusion

Analysis of the chemical composition of the essential oils of *P. laruotteanum*, *P. salutare* and *P. sobralianum* revealed qualitative and quantitative variations and none of the compounds appeared simultaneously in the three species.

Of the compounds identified, there was a predominance of hydrocarbon terpenes and new elements were identified in the chemical profiles of *P. laruotteanum* and *P. salutare*, while for *P. sobralianum* the information of its essential oil constituents is new.

Antibacterial and modulating effects were observed for *P. laruotteanum* essential oil. The effects presented by this species may be associated with the majority presence of Caryophyllenes compounds.

Antioxidant activity was evidenced in a concentration-dependent manner, with *P. sobralianum* showing the best activity. The other species did not have clinically relevant concentrations, requiring high doses of the natural product for the desired effect. The absence of phenolic compounds in the chemical composition of essential oils may be responsible for this.

CRediT authorship contribution statement

Julimery Gonçalves Ferreira Macedo: Conceptualization, Methodology, Validation, Investigation, Writing – review & editing, Formal analysis, Writing – original draft, Data curation, Resources. Maria de Oliveira Santos: Investigation, Validation. Carla de Fátima Alves Nonato, Gerson Javier Torres Salazar, Fábio Fernandes Galvão Rodrigues and José Weverton Almeida-Bezerra: Software, Formal analysis, Investigation. Ângela Maria de Miranda Freitas: Investigation, Validation. Carolyn Elinore Barnes Proenca: Supervision, Writing – review & editing, Writing – original draft. Marta Maria de Almeida Souza and José Galberto Martins da Costa: Conceptualization, Methodology, Resources, Project administration, Writing – review & editing, Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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5. CAPÍTULO 4: CONSIDERAÇÕES FINAIS

5.1. PRINCIPAIS CONCLUSÕES

Espécies nativas de *Psidium*, ainda são pouco investigadas quanto suas propriedades terapêuticas. Em contraste com a riqueza de espécie dentro do gênero (o segundo maior entre Myrtaceae) seis espécies, *P. acutangulum*, *P. cattleyanum, P. densicomum, P. guineense, P. myrsinites* e *P. sobralianum* tiveram indicações terapêuticas vinculadas a alguma prática da medicina popular. Entretanto, a grande maioria dos trabalhos está direcionado a duas espécies, *P. cattleianum* e *P. guineense*, a exploração comercial de seus frutos pode ser um dos fatores responsáveis por maiores interesses de investigação.

Em sua grande maioria, espécies de *Psidium* são usadas sobretudo para tratar sintomas associados a transtornos do sistema digestório como diarreia, disenteria, problemas estomacais. De forma mais discreta são utilizadas para os sistemas respiratório, nervoso e geniturinário. Os tratamentos medicinais mencionados pelas populações são feitos principalmente pelo uso das folhas em forma de decocção.

Quimicamente apresentam variações qualitativas e quantitativas de compostos químicos. Diferentes partes das plantas além de díspares solventes utilizados nos extratos vegetais conferem essa variabilidade. O óleo essencial extraído das folhas é rico em terpenos, as vezes variando entre monoterpenos e sesquiterpenos, tanto hidrocarbonados quanto oxigenados. Os compostos 1,8-cineole, Viridiflorol, α-caryophyllene, β-caryophyllene, Isocaryophyllene, α-humulene e α-pinene têm aparecido com os majoritários dentro do gênero. Além desses, novos elementos químicos foram adicionados as espécies *P. laruotteanum* e *P. salutare* e relatado pela primeira vez na literatura a composição química de *P. sobralianum*.

Os compostos químicos presentes nos extratos vegetais e óleos essenciais, são diretamente responsáveis por conferirem as espécies diferenciadas atividades biológicas como anti-inflamatória, antiproliferativa, antimicrobiana e antioxidante. Destacando as duas últimas e associado a atividade dos óleos essenciais, verificamos que estes podem ser mais eficazes para atividades antibacterianas, visto que o óleo de *P. laruotteanum* inibiu o crescimento de *E. coli* demostrou efeito sinérgico quando associado a amicacina sobre *S. aureus*. Já para a atividade antioxidante os resultados foram dependentes de concentração, com resultados promissores para *P. sobralianum*.

O fato de as indicações terapêuticas das espécies de *Psidium* estarem associadas a sintomas ou causas e não a doenças específicas, levam muitas vezes a investigações de atividades biológicas que não estejam associadas diretamente com as indicações relatadas pelas comunidades locais pesquisadas. No entanto, estudos realizados com diferentes bactérias e fungos podem estar associados aos usos tradicionais da medicina popular, uma vez que esses microrganismos podem causar infecções apresentando os mesmos sintomas relatados nos trabalhos de investigações etnobiológicas.

Espécies nativas do gênero *Psidium* são importantes fontes de substâncias promissoras para a bioprospecção, sendo necessárias mais investigações para que se possa perfazer um diagnóstico dentro do gênero. Pesquisas associando etnobotânica médica, composição química e atividades biológicas são indispensáveis. Uma vez que a conexão entre o saber popular e o saber científico, podem convergir para o desenvolvimento de medicamentos fitoterápicos ou fitofármacos, eficazes no combate a enfermidades humanas.

5.2. CONTRIBUIÇÕES TEÓRICAS E/OU METODOLÓGICAS DA TESE

A presente pesquisa destacou o conhecimento etnobotânico, composição química e atividades biológicas de espécies medicinais nativas do gênero *Psidium* (Myrtaceae), tanto em um contexto local como nacional. Teve como principal objetivo levantar os usos medicinais, analisar a composição química e atividades biológicas de espécies nativas do gênero *Psidium* para o Brasil. Os resultados encontrados em cada um dos capítulos são pertinentes, ao mesmo tempo que propicia um melhor entendimento dessas características dentro do gênero, preenchendo lacunas de conhecimento. Vinculado a isso, essa tese trouxe elementos semelhantes aqueles que têm sido associados as espécies de *Psidium*, como as substâncias presentes em sua composição química sendo responsáveis diretamente pelas atividades biológicas relatadas. Assim como, contribuiu com novos achados químicos, com constituintes ainda não vinculados ao gênero, como também resultados importantes na inibição do crescimento bacteriano, sinergismo frente a antibióticos sintéticos e potencial antioxidante.

No campo metodológico, a tese traz um arranjo de revisão sistemática delineada de uma maneira clara de ser compreendida e passível de ser replicada em investigações que busquem compreender característica etnobotânicas, química e biológicas dentro de um gênero e de forma mais específica para espécies. Além disso, para o estudo local das espécies, utilizamos uma metodologia acessível em relação a outras existentes para determinar os constituintes químicos, assim como compreender seu papel em atividades exercida por essas espécies.

5.3. PRINCIPAIS LIMITAÇÕES DO ESTUDO

Os desafios logísticos, especialmente idas ao campo para a coleta das espécies *in situ*, podem ter influenciado no número da amostra. A escassez de referências bibliográficas sobre estrutura de vegetação na área pesquisada, como os fitossociológicos, assim como trabalhos de outra natureza (por exemplo etnobiológicos) que trazem a identificação das espécies de *Psidium* apenas em nível de gênero, podem ter sido uma barreira na localização de mais espécies. Caso conseguíssemos uma amostra maior poderíamos efetivar um melhor diagnóstico para o gênero nas abordagens propostas.

O fato de termos realizados apenas dois testes na busca por atividades biológicas, talvez não tenhamos dado uma compreensão mais apurada sobre o potencial das espécies. No entanto, essa questão pode ser atribuída a crise sanitária causada pelo coronavírus SARS-CoV-2 causador da COVID-19 que atingiu todo o mundo, levando os países a decretarem *lockdown*. Dessa maneira, com o fechamento e confinamento, ficamos impossibilitados de realizar novas análises que poderia dar um melhor direcionamento para o uso dos óleos essenciais das espécies de *Psidium* e onde estes, poderiam serem melhor aplicados.

5.4. PROPOSTAS DE INVESTIGAÇÕES FUTURAS

Investigações etnobotânicas destinadas especificamente ao gênero *Psidium*, através da utilização dos nomes populares conhecidos nas comunidades locais, podem dar um melhor direcionamento de como essas espécies são utilizadas na prática. No decurso de nossas investigações bibliográficas, percebemos que espécies nativas de *Psidium* além do uso medicinal, são usadas também na alimentação humana. Análises que compreendam essas duas características, podem vir a colocar o gênero em destaque tanto do ponto de vista fitoterápico quanto como sendo adicionado no cardápio alimentar.

Os constituintes químicos presentes nos óleos essenciais das espécies são variáveis, tanto qualitativa quanto quantativamente, sendo essa variação influenciada por diversos fatores. Análises que possam compreender a diferença entre essas variáveis, como temperatura, pluviosidade, eventos fenológicos, tipos de solo, dentre outros, poderiam trazer luz aos principais constituintes presentes nas espécies, assim como entender quais fatores são determinantes para a variação desses compostos. Dessa maneira, poderíamos estabelecer um padrão na composição química de gêneros e mais especificamente espécies botânicas, em razão da presença de determinados compostos em sua constituição, os marcadores químicos. Além de, selecionar as espécies mais indicadas para determinadas atividades biológicas, com base no seu padrão químico.

Extrair compostos químicos de diferentes partes das plantas e analisar por diferentes técnicas de extração, seria importante pela mesma questão apresentada no parágrafo anterior. Pois enquanto determinadas técnicas podem apresentar limitações, outras poderiam trazer novos aspectos a determinado respeito, e melhores respostas a certas investigações. No entanto, essa proposta precisa de incentivo financeiro para pesquisadores e instituições, uma vez que se trata de análises que requerem equipamentos sofisticados e caros, o que torna impraticável o custeio por parte do aluno ou professor, quando as instituições não detêm os recursos necessários para realização de análises como essas.

Testes de citotoxicidade e análises *in vivo* para as espécies de *Psidium*, constituem outro horizonte a ser investigado. Pesquisas com esses objetivos fornecem materialidade para que se possa avançar na busca por novos agentes eficazes contra doenças humanas. Devido principalmente a resistência microbiana a produtos sintéticos, as substâncias de fontes naturais, como os constituintes químicos extraídos de espécies vegetais, são as melhores opções para esse tipo de investigação.

5.5. ORÇAMENTO

Essa pesquisa foi realizada com apoio financeiro da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) e Fundação Cearense de Apoio ao Desenvolvimento Científico e Tecnológico (FUNCAP) por meio de concessão de bolsa de doutorado (proc. 88887.190974/2018-00) a aluna Julimery Gonçalves Ferreira Macedo. As despesas para o desenvolvimento da pesquisa incluem compra de material de papelaria e de campo, abastecimento de veículo, alimentação, pagamento de pessoal de campo. Foram gastos cerca de R$ 2.280,00 em 22 dias a campo, representando uma média de R$ 103, 63 por dia. Com esse investimento diário foi possível coletar folhas para a extração de óleo essencial de seis espécies de *Psidium*, além de observações fenológicas. Foi possível ainda, iniciar um levantamento etnobotânico de uso medicinal do gênero em duas localidades da Chapada do Araripe, sendo possível identificar (até a realização da pesquisa) cinco espécies de *Psidium* (pesquisa interrompida devido a pandemia do COVID 19). Esse trabalho também recebeu auxílio concedido pelo programa de Pós-Graduação em Etnobiologia e Conservação da Natureza, dos recursos do PROAP no valor de R$ 1.160,00. Esse valor foi utilizado para custeio de hospedagem na participação do 70º Congresso Nacional de Botânica em Maceió-AL e para compra de solventes, reagentes e material de uso não permanente, para utilização em laboratório.

ANEXOS

ANEXO A: Documento de cadastro da pesquisa no SisGen.

Ministério do Meio Ambiente
CONSELHO DE GESTÃO DO PATRIMÔNIO GENÉTICO
SISTEMA NACIONAL DE GESTÃO DO PATRIMÔNIO GENÉTICO E DO CONHECIMENTO TRADICIONAL ASSOCIADO

Comprovante de Cadastro de Acesso
Cadastro nº AE56B81

A atividade de acesso ao Patrimônio Genético/CTA, nos termos abaixo resumida, foi cadastrada no SisGen, em atendimento ao previsto na Lei nº 13.123/2015 e seus regulamentos.

Número do cadastro:	**AE56B81**
Usuário:	**Julimery Gonçalves Ferreira macedo**
CPF/CNPJ:	**053.354.563-37**
Objeto do Acesso:	**Patrimônio Genético/CTA**
Finalidade do Acesso:	**Pesquisa**

Espécie

Impossibilidade de identificação

Não se aplica

Fonte do CTA

CTA de origem não identificável

Título da Atividade:	**Marcadores químicos de espécies medicinais do gênero Psidium (Myrtaceae).**

Equipe

Julimery Gonçalves Ferreira macedo	**URCA**
Marta Maria de Almeida Souza	**Urca**

Data do Cadastro:	**09/07/2018 12:03:38**
Situação do Cadastro:	**Concluído**

Conselho de Gestão do Patrimônio Genético
Situação cadastral conforme consulta ao SisGen em **12:04** de **09/07/2018**.

SISTEMA NACIONAL DE GESTÃO DO PATRIMÔNIO GENÉTICO E DO CONHECIMENTO TRADICIONAL ASSOCIADO - **SISGEN**

ANEXO B: Documento de aprovação da pesquisa no CEP-URCA.

UNIVERSIDADE REGIONAL DO CARIRI - URCA

PlataForma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Marcadores químicos de espécies medicinais do gênero Psidium (Myrtaceae).
Pesquisador: Julimery Gonçalves Ferreira Macedo
Área Temática:
Versão: 2
CAAE: 94494418.2.0000.5055
Instituição Proponente: Universidade Regional do Cariri - URCA
Patrocinador Principal: FUND COORD DE APERFEICOAMENTO DE PESSOAL DE NIVEL SUP

DADOS DO PARECER

Número do Parecer: 2.954.183

Situação do Parecer:
Aprovado
Necessita Apreciação da CONEP:
Não

CRATO, 10 de Outubro de 2018

Assinado por:
cleide correia de Oliveira
(Coordenador(a))

ANEXO C: Documento de autorização para coleta das espécies pelo SISBIO.

Ministério do Meio Ambiente - MMA
Instituto Chico Mendes de Conservação da Biodiversidade - ICMBio
Sistema de Autorização e Informação em Biodiversidade - SISBIO

Autorização para atividades com finalidade científica

Número: 63956-1	Data da Emissão: 10/07/2018 10:21	Data para Revalidação*: 09/08/2019
* De acordo com o art. 28 da IN 03/2014, esta autorização tem prazo de validade equivalente ao previsto no cronograma de atividades do projeto, mas deverá ser revalidada anualmente mediante a apresentação do relatório de atividades a ser enviado por meio do Sisbio no prazo de até 30 dias a contar da data do aniversário de sua emissão.		

Dados do titular

Nome: Julimery Gonçalves Ferreira Macedo	CPF: 053.354.563-37
Título do Projeto: Marcadores químicos de espécies medicinais do gênero Psidium (Myrtaceae).	
Nome da Instituição : Universidade Regional do Cariri	CNPJ: 06.740.864/0001-26

Ministério do Meio Ambiente - MMA
Instituto Chico Mendes de Conservação da Biodiversidade - ICMBio
Sistema de Autorização e Informação em Biodiversidade - SISBIO

Autorização para atividades com finalidade científica

Número: 63956-2	Data da Emissão: 01/11/2018 11:18:38	Data da Revalidação*: 01/06/2020
De acordo com o art. 28 da IN 03/2014, esta autorização tem prazo de validade equivalente ao previsto no cronograma de atividades do projeto, mas deverá ser revalidada anualmente mediante a apresentação do relatório de atividades a ser enviado por meio do Sisbio no prazo de até 30 dias a contar da data do aniversário de sua emissão.		

Dados do titular

Nome: Julimery Gonçalves Ferreira Macedo	CPF: 053.354.563-37
Título do Projeto: Marcadores químicos de espécies medicinais do gênero Psidium (Myrtaceae).	
Nome da Instituição: UNIVERSIDADE REGIONAL DO CARIRI URCA	CNPJ: 06.740.864/0001-26

ANEXO D: Artigo publicado a partir dos dados referentes ao capítulo 2 da tese. Therapeutic indications, chemical composition and biological activity of native Brazilian species from *Psidium* genus (Myrtaceae): A review.

Journal of Ethnopharmacology 278 (2021) 114248

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Therapeutic indications, chemical composition and biological activity of native Brazilian species from *Psidium* genus (Myrtaceae): A review

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ARTICLE INFO

Keywords:
Ethnobotanical survey
Medicinal plants
Chemical characterization
Biological activity
Psidium

ABSTRACT

Ethnopharmacological importance: Brazilian medicinal species of the *Psidium* genus are rich in secondary metabolites such as terpenes and phenolic compounds and present biological activities for several human diseases. For the native *Psidium* species, there are no specific research reports for any member of the genus about ethnobotanical research, hindering the joint analysis of its therapeutic indications together with the scientific evidence already investigated.
Study objective: Analyze the therapeutic indications, the main chemical constituents, and the biological activities of native species of the *Psidium* to Brazil.
Materials and methods: Systematic research was carried out in the Scopus, ScienceDirect, PubMed, and Web of Science databases over a period of ten years. Articles in English, Portuguese and Spanish were used. The research was divided into three phases, seeking information on ethnobotany, chemical composition and biological activities. The words were combined to structure the descriptors used in the search.
Results: A total of 13 native species belonging to the *Psidium* genus were identified in this analysis, *Psidium acutangulum* DC., *Psidium brownianum* Mart. ex DC., *Psidium cattleyanum* Sabine, *Psidium densicomum* Mart. ex DC., *Psidium grandifolium* Mart. ex DC., *Psidium guineense* Sw., *Psidium laruotteanum* Cambess., *Psidium myrsinites* DC, *Psidium myrtoides* O. Berg, *Psidium salutare* (Kunth) O. Berg, *Psidium schenckianum* Kiaersk., *Psidium sobralianum* Proença & Landrum, *Psidium striatulum* Mart. ex DC. Of these, six were indicated in folk medicine, digestive system disorders being their main therapeutic indication. Most species presented an investigation of chemical composition and biological activity. They are rich in phenolic compounds, flavonoids, and terpenes and have antimicrobial, antioxidant, antiproliferative, and repellent activities.
Conclusions: Native species of the *Psidium* genus are important sources of active ingredients in combating adversities that affect the human health, especially regarding the digestive system. They have a rich chemical composition, responsible for the biological activities demonstrated for the species.

1. Introduction

The richness of Brazilian medicinal species has contributed considerably to the development of therapeutic alternatives through the identification of secondary metabolites, which present activity for several diseases that affect human health (Zivarpour et al., 2021). Among these species, the Myrtaceae family stands out, one of the ten angiosperms families with the most diversity, with 1028 species and 27 genera (BFG et al., 2015; Flora do Brasil, 2020). The *Psidium* genus, belonging to this family, is well distributed with around 185 species in the world (GBIF, 2021). It houses species in all phytogeographic domains of the Brazilian territory, presenting a wealth of 60 species, of

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Available online 28 May 2021

ANEXO E: Artigo submetido a partir dos dados referentes ao capítulo 3 da tese. Chemical composition, antioxidant, antibacterial and modulating activity of the essential oil of *Psidium* L. species (Myrtaceae Juss.)