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MARIA DE OLIVEIRA SANTOS

ANÁLISE DA VARIABILIDADE DAS INDICAÇÕES TERAPÊUTICAS E DOS COMPOSTOS QUÍMICOS DE ÓLEOS ESSENCIAIS DE *Copaifera langsdorffii* Desf. EM DIFERENTES FITOFISIONOMIAS

CRATO-CE
2022

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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 obtenção do título de doutora.

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Dedico a Deus por iluminar os meus passos e orientar as minhas decisões, e a minha família, pelo amor e apoio incondicional.

"Cada descoberta nova da
ciência é uma porta nova pela qual
encontro mais uma vez Deus,
o autor dela.".

Albert Einstein

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SUMÁRIO

RESUMO

SANTOS, Maria de Oliveira. Dra. Universidade Federal Rural de Pernambuco (UFRPE). Julho, 2022. Análise da variabilidade das indicações terapêuticas e dos compostos químicos de óleos essenciais de *Copaifera langsdorffii* Desf. em diferentes fitofisionomias. Dra. Marta Maria de Almeida Souza (Orientadora); Dr. José Galberto Martins da Costa (Coorientador).

Copaifera langsdorffii Desf. é uma espécie medicinal que pode ser encontrada em diferentes fitofisionomias. Estes diferentes ambientes influenciam tanto a composição química como o conhecimento local desta espécie, acarretando diferenças no número e concentração dos compostos, assim como, para o tratamento de doenças distintas junto as comunidades. Dentro deste contexto, com este estudo objetivou-se realizar um levantamento dos usos medicinais, da composição química e das atividades biológicas da *C. langsdorffii* nas distintas regiões brasileiras e verificar sua variação em diferentes fitofisionomias na Chapada do Araripe, Crato-CE. Para a revisão foram consultadas as seguintes bases: Scielo, Pub Med, Science Direct, Web of Science, Google scholar e Repositório Institucional da Universidade Estadual Paulista. Para o levantamento etnobotânico foram realizadas entrevistas semiestruturadas em comunidades da Chapada do Araripe, município de Crato, Nordeste do Brasil. O valor de diversidade de uso, valor de consenso da parte da planta e nível de fidelidade foram analisados para verificar o consenso das categorias de uso, parte da planta e doenças citadas nas diferentes fitofisionomias de Cerradão, Carrasco, Mata Úmida e Caatinga. Para a obtenção dos óleos essenciais, a resina coletada no Cerradão, Carrasco e Mata Úmida foram submetidos ao processo de hidrodestilação e componentes químicos foram analisados por cromatografia gasosa acoplada à espectrometria de massa. Para o Brasil, nos artigos científicos, foram catalogados 96 problemas de saúde, sendo inflamação em geral e cicatrizante os mais citados. Dos 277 compostos identificados, 91 foram exclusivos do óleo essencial, 58 da resina bruta e 57 do extrato. Foram registradas 28 atividades biológicas, sendo as mais testadas, antioxidante, citotóxica, anti-inflamatória e antibacteriana. Na Chapada do Araripe foram indicadas 61 indicações terapêuticas em fitofisionomias de Cerradão (38), Caatinga (33), Mata Úmida (20) e Carrasco (15), sendo cicatrizante, artrite reumática, dor nos ossos, problemas na coluna e inflamação na garganta as mais citadas. Para a química das diferentes fitofisionomias da Chapada do Araripe foram identificados 26 constituintes químicos, 12 registrados no Cerradão, 15 Carrasco e 18 Mata Úmida. Entre os compostos das três áreas, foi registrada uma variação na concentração de 0.60 % a 84.57 %, ambas registradas na Mata Úmida, com a maior para β-cariofileno e a menor para β-Elemeno e (1R)-2,6,6-Trimethylbicyclo[3.1.1]hept-2-eno. β-cariofileno foi o composto majoritário para todas as fitofisionomias e indivíduos estudados, com concentrações variando de 22.83 % a 84.57 %. Assim, os resultados obtidos são úteis para ampliar o conhecimento sobre a espécie e favorecer no desenvolvimento de padrões de coleta para obtenção de maiores concentrações de compostos aqui identificados, os quais são destinados ao uso terapêutico.

Palavras-chave: *Copaifera langsdorffii*; Medicina popular; Composição química; Chapada do Araripe.

ABSTRACT

SANTOS, Maria de Oliveira. Dra. Federal Rural University of Pernambuco (UFRPE). July 2022. Analysis of the variability of therapeutic indications and chemical compounds of essential oils from *Copaifera langsdorffii* Desf. in different phytophysiognomies. Dra. Marta Maria de Almeida Souza (Advisor); Dr. José Galberto Martins da Costa (Cosupervisor).

Copaifera langsdorffii Desf. is a medicinal species that can be found in different phytophysiognomies. These different environments influence both the chemical composition and the local knowledge of this species, causing differences in the number and concentration of compounds, as well as for the treatment of different diseases in the communities. Within this context, this study aimed to survey the medicinal uses, chemical composition and biological activities of *C. langsdorffii* in different Brazilian regions and verify its variation in different phytophysiognomies in Chapada do Araripe, Crato-CE. The following databases were consulted for the review: Scielo, Pub Med, Science Direct, Web of Science, Google scholar and Institutional Repository of Universidade Estadual Paulista. For the ethnobotanical survey, semi-structured interviews were carried out in communities in Chapada do Araripe, municipality of Crato, Northeastern Brazil. The value of diversity of use, consensus value of the plant part and level of fidelity were analyzed to verify the consensus of the categories of use, plant part and diseases cited in the different phytophysiognomies of Cerradão, Carrasco, Mata Úmida and Caatinga. To obtain the essential oils, the resin collected in Cerradão, Carrasco and Mata Úmida was submitted to the hydrodistillation process and chemical components were analyzed by gas chromatography coupled to mass spectrometry. For Brazil, in scientific articles, 96 health problems were cataloged, with inflammation in general and healing being the most cited. Of the 277 compounds identified, 91 were exclusive to the essential oil, 58 to the crude resin and 57 to the extract. Twenty-eight biological activities were recorded, the most tested being antioxidant, cytotoxic, anti-inflammatory and antibacterial. In Chapada do Araripe, 61 therapeutic indications were indicated in phytophysiognomies of Cerradão (38), Caatinga (33), Mata Úmida (20) and Carrasco (15), being healing, rheumatic arthritis, bone pain, spine problems and throat inflammation. the most cited. For the chemistry of the different phytophysiognomies of Chapada do Araripe, 26 chemical constituents were identified, 12 registered in Cerradão, 15 Carrasco and 18 Mata Úmida. Among the compounds from the three areas, a variation in concentration from 0.60 % to 84.57 % was recorded, both recorded in the Humid Forest, with the highest for β-caryophyllene and the lowest for β-Elemene and (1R)-2,6,6 -Trimethylbicyclo[3.1.1]hept-2-ene. β-caryophyllene was the major compound for all phytophysiognomies and individuals studied, with concentrations ranging from 22.83% to 84.57%. Thus, the results obtained are useful to expand knowledge about the species and favor the development of collection patterns to obtain higher concentrations of compounds identified here, which are intended for therapeutic use.

Keywords: *Copaifera langsdorffii*; Folk medicine; Chemical composition; Chapada do Araripe.

1. INTRODUÇÃO GERAL

1.1 OBJETIVOS E QUESTIONAMENTOS

As plantas medicinais se tornaram um tópico mundial (ULLAH *et al*., 2020), onde desempenham um papel fundamental no desenvolvimento e avanço dos estudos modernos, servindo como ponto de partida para o desenvolvimento de novidades em medicamentos (WRIGHT, 2005; IBRAHIM; KEBEDE, 2020), e exercem um papel vital na prevenção e tratamento de doenças (WANG *et al*., 2020). Segundo a Organização Mundial da Saúde (OMS), mais de 80% da população mundial usa rotineiramente medicamentos tradicionais para atender às necessidades de atenção primária à saúde (WHO, 2019). Além disso, mais de 50% dos novos medicamentos desenvolvidos e aprovados para comercialização são derivados de plantas medicinais ou dos constituintes ativos dessas plantas (TENG; SHEN, 2015).

Investigação sobre plantas medicinais e suas utilizações tem sido objeto de estudo em diferentes regiões geográficas. A realização de pesquisas etnobiológicas tem demonstrado o valor da biodiversidade para a bioprospecção (ALBUQUERQUE, 2010; RIBEIRO *et al*., 2014; ALMEIDA NETO; BARROS; SILVA, 2015), que surge como ferramenta importante ao acesso de novas estratégias para a investigação, desenvolvimento e exploração racional dos recursos medicinais derivados da flora (PATWARDHAN; MASHELKAR, 2009; ALBUQUERQUE; RAMOS; MELO, 2012).

Estudos etnobiológicos realizados nas diferentes formações vegetais do Brasil são instrumentos promissores na descoberta de novas drogas, uma vez que o Brasil possui elevada biodiversidade e endemismo associados a riqueza considerável de conhecimento sobre a sua flora (KONG; LI; ZHANG, 2009; ALVES; NASCIMENTO, 2010). É importante salientar que diferentes ambientes influenciam, tanto a composição química como o conhecimento local de espécies medicinais, causando diferenças no número e concentração dos compostos, muitos dos quais advindos do metabolismo secundário, bem como no número de doenças citadas nas comunidades (GOBBO-NETO; LOPES, 2007; BERNARDI *et al*., 2008; ALMEIDA *et al*., 2014; OLIVEIRA *et al*., 2017; EL-JALEL *et al*., 2018; MACÊDO *et al*., 2018; ARAÚJO; LIMA, 2019).

Os metabólitos secundários além de alcançarem diversas aplicações que representam grande importância ecológica, principalmente no desenvolvimento de defesas químicas, também podem agir em alvos celulares funcionando no tratamento ou cura de doenças e sintomas relacionados a infecções por bactérias ou excesso de substâncias oxidantes no corpo (FERREIRA; PINTO, 2010; VERMA; SHUKLA, 2015). Uma vasta literatura tem propagado plantas medicinais com essas atividades (GELMINI *et al*., 2013; ABRÃO *et al*., 2015;

ALENCAR *et al*., 2015; BATISTA *et al*., 2016; VALDIVIESO-UGARTE *et al*., 2019; WELI *et al*., 2019; NEWMAN; CRAGG, 2020; SOTTO *et al*., 2020; VALUSSI *et al*., 2021; ZIVARPOUR *et al*., 2021). Os diversos compostos químicos produzidos por espécies vegetais, estão diretamente associadas a atividades biológicas que essas desempenham (VALDIVIESO-UGARTE *et al*., 2019; SOTTO *et al*., 2020; VALUSSI *et al*., 2021).

As mudanças nos mecanismos bioquímicos das plantas ocorrem pela influência de inúmeros fatores que atuam correlacionados entre si ou isoladamente (GOBBO-NETO; LOPES, 2007a). Entre os principais fatores que interferem no metabolismo da planta e, consequentemente, no conteúdo químico total e nas proporções relativas dos compostos químicos estão a sazonalidade climática (GOUVEA *et al*., 2012; OLIVEIRA *et al*., 2017; RIBEIRO *et al*., 2020), disponibilidade de água, a radiação solar (GOUINGUENÉ; TURLINGS, 2002; ARAÚJO; SOUZA; GUARÇONI, 2015), radiação UV, o ritmo circadiano (BLANK *et al*., 2005; SOUSA *et al*., 2010), a fase fenológica (ÇIRAK *et al*., 2007; LAGO *et al*., 2007; OLIVEIRA *et al*., 2017; RIBEIRO *et al*., 2020), a composição do solo (DUARTE *et al*., 2010; BARBOSA *et al*., 2012) entre outros.

Vários estudos têm reconhecido a importância da variabilidade química de espécies vegetais utilizadas na terapêutica a fim de comparar estas variações nos componentes químicos ativos em diferentes períodos e ambientes, também para propor critérios de padronização (SOUSA *et al*., 2014; YAO *et al*., 2016). Conhecer os fatores que podem levar a variabilidade química de cada espécie vegetal é importante, principalmente, para aquelas destinadas ao uso terapêutico e que possuem interesse medicinal e comercial, colaborando com o desenvolvimento de padrões de coleta para a obtenção de maiores rendimentos de substâncias alvo com concentrações desejáveis de compostos químicos bioativos e que se encaixam nas necessidades das comunidades locais e do mercado (SOUSA *et al*., 2014; YAO *et al*., 2016).

O Brasil possui uma variedade de ambientes, apresentando diversidade de paisagens influenciadas principalmente por fatores abióticos como temperatura, umidade, radiação solar, entre outros. Estes ambientes mostram uma flora bastante particular caracterizando as diferentes fitofisionomias, como Cerradão, Caatinga, Carrasco e Mata Úmida. Entretanto, algumas espécies aparecem inseridas em mais de um tipo fitofisionômico e isto demostra a grande tolerância a modificações ambientais. Sabendo que fatores bióticos e abióticos interferem na composição química das espécies torna-se necessário estudos que mostrem a variação dos constituintes químicos das espécies de acordo com as características do ambiente e suas funcionalidades.

Das diversas espécies que surgem em diferentes fitofisionomias, pode-se destacar *Copaifera langsdorffii* Desf. que aparece no Sul do Ceará em áreas de Cerradão, Carrasco e

Mata Úmida da Chapada do Araripe (CARTAXO; SOUZA; ALBUQUERQUE, 2010; RIBEIRO *et al*., 2014; SARAIVA *et al*., 2015; SANTOS *et al*., 2019a). Essa espécie apresenta grande potencial medicinal, sendo de grande importância para as comunidades, indicada para o tratamento de gripes, tosses, expectorante, resfriados, dores no corpo, cicatrizante local e internamente, anti-inflamatório, diurético e alergias (VEIGA JUNIOR; PINTO, 2002; PASA; SOARES; GUARIM NETO, 2005; LEANDRO *et al*., 2012; RIBEIRO *et al*., 2014).

As inúmeras indicações terapêuticas de *C. langsdorffii* geralmente estão atreladas a um constituinte majoritário ou a um composto químico ou o sinergismo entre eles. Entender a variabilidade da composição química em diferentes fitofisionomias pode auxiliar na ampliação dos conhecimentos sobre o uso do vegetal nos distintos ambientes, além de propiciar um maior entendimento das interações ecológicas do vegetal (GOBBO-NETO; LOPES, 2007a), indicando ainda a melhor época para coleta de forma a se obter concentrações desejáveis de compostos químicos que se adequem às necessidades do mercado e das comunidades (FIGUEIREDO *et al*., 2009). Entretanto, poucos são os estudos que avaliam as variações químicas das espécies ocasionadas por fatores ambientais (MURAKAMI, 2009; VALENTINI *et al*., 2010; INÁCIO, 2013), principalmente em diferentes ambientes.

Considerando a importância medicinal da *C. langsdorffii* para as comunidades e tendo em vista a ausência de estudos referentes a variação da composição química do óleo essencial extraído da resina do caule de *C. langsdorffii* em diferentes fitofisionomias, as seguintes hipóteses são sugeridas: (1) As indicações terapêuticas de *C. langsdorffii* podem ser similares apesar do seu uso em diferentes fitofisionomias; (2) Ocorre variação dos compostos químicos e alterações da constituição e rendimento do óleo essencial da *C. langsdorffii* em diferentes fitofisionomias.

1.2 ESTRATÉGIAS DE PESQUISA

O estudo foi realizado em diferentes fitofisionomias da Chapada do Araripe, no município de Crato, Ceará. Localizada dentro da Caatinga no Nordeste Brasileiro, a Chapada do Araripe engloba os estados do Ceará, Pernambuco e Piauí, apresentando superfície tabular, com altitude que varia de 800 m a 900 m (MORO *et al*., 2015). A cobertura vegetal é composta por fitofisionomias de Cerrado, Cerradão, Carrasco, Floresta Subperenifolia (Floresta Ombrófila) e Caatinga Hipoxerófila (SOUZA; OLIVEIRA, 2006; MORO *et al*., 2015). Os solos predominantes são latossolos vermelho-amarelos, neossolos litólicos e argissolos vermelho-amarelos (MMA, 2004; SOUZA; OLIVEIRA, 2006; IPECE, 2016). Os latossolos presentes no topo da chapada, são profundos, de baixa fertilidade, apresentam cobertura vegetal do tipo Cerrado, Cerradão e Carrasco. Os neossolos recobrem as encostas e áreas de declive, solos muitos rasos e pedregosos de baixa fertilidade, apresentando faixa de transição da Floresta Subperenifolia (Floresta Ombrófila) para Caatinga Hipoxerófila. Por fim, os argissolos localizados nas partes medianas a baixas, solos rasos que possuem alta fertilidade e vegetação constituída pela Floresta Subperenifólia e Caatinga Hipoxerófila (SOUZA; OLIVEIRA, 2006). A tipologia da parte superior da Chapada do Araripe reflete numa permeabilidade das águas da chuva agindo como zona de infiltração e abastecimento para os aquíferos subterrâneos, os quais ressurgem como várias nascentes, riachos e rios nas partes medianas e baixas dessa chapada (SILVA; LINHARES, 2011). A Chapada do Araripe é protegida por uma Área de Proteção Ambiental (APA da Chapada do Araripe) e parte de seu território também é protegido pela Floresta Nacional do Araripe e pelo Parque Geológico do Araripe (COSTA; ARAÚJO; LIMA-VERDE, 2004). O clima predominante é o Tropical Quente Úmido, com precipitação média anual de aproximadamente 1090,9 mm, apresentando pouca variação térmica com temperatura média anual entre 24 ºC e 26 ºC (CAVALCANTI; LOPES, 1994; COSTA; ARAÚJO; LIMA-VERDE, 2004).

Na Chapada do Araripe existe uma fonte relevante de matéria prima para extração de recursos vegetais por parte das comunidades tradicionais locais e suas características econômicas incluem a colheita de produtos madeireiros e não madeireiros, principalmente para comércio, além de agricultura e pecuária (BEZERRA, 2004). Dos produtos naturais extraídos pode-se destacar *Caryocar coryaceum* Wittm., *Dimorphandra garderiana* Tul., *Himatanthus drasticus* (Mart.) Plumel, *Stryphnodendron rotundifolium* Mart. e *C. langsdorffii* que são explorados através da utilização de seus frutos, látex, cascas e resina principalmente para uso medicinal e comércio informal (BEZERRA, 2004).

Copaifera langsdorffii pode ser encontrada na região da Chapada do Araripe, em fitofisionomias de Cerradão, Carrasco e Mata Úmida (CARTAXO; SOUZA; ALBUQUERQUE, 2010; RIBEIRO *et al*., 2014; SARAIVA *et al*., 2015; SANTOS *et al*., 2019b). Essa espécie apresenta potencial medicinal, sendo de muita importância para as comunidades, indicada para o tratamento de diversas doenças (VEIGA JUNIOR; PINTO, 2002; PASA; SOARES; GUARIM NETO, 2005; RIBEIRO *et al*., 2014; SARAIVA *et al*., 2015; MACÊDO *et al*., 2018).

A escolha da espécie para essa pesquisa teve como base essas informações, assim como o fato de ser produtora de resina, a qual apresenta importante valor medicinal, rico em óleo essencial e investigações etnobiológicas, dentro das comunidades da Chapada do Araripe. Essa espécie é conhecida popularmente como copaíba, podói, pau d'óleo, cupaúba e cupiúva.

Levando em consideração a importância medicinal da *C. langsdorffii* para as comunidades e a falta de estudos que tratem especificamente essa espécie em diferentes fitosifionomias, um estudo etnobiológico foi realizado na Chapada do Araripe, município do Crato, em áreas de Cerradão, Carrasco, Mata Úmida e Caatinga por meio de entrevistas semiestruturada com o auxílio de um formulário padronizado (artigo II), com questões abertas e fechadas, sobre o conhecimento das comunidades a respeito da *C. langsdorffii* e seu uso medicinal. 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).

Ramos reprodutivos (flor ou fruto) de *C. langsdorffii* foram coletados nas quatro fitosifionomias estudadas (Cerradão, Carrasco, Mata Úmida e Caatinga) através de turnê guiada, tanto com os entrevistados que indicaram a espécie, 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). O material coletado foi levado ao Laboratório de Ecologia Vegetal da Universidade Regional do Cariri, acondicionado em sacos plásticos e tratado segundo as técnicas usuais de herborização (MORI *et al*., 1989). Posteriormente identificado e incorporado ao acervo do Herbário Caririense Dárdano de Andrade-Lima da Universidade Regional do Cariri (HCDAL/URCA). A identificação ocorreu através de bibliografia especializada e comparações com exsicatas de herbário. O sistema de classificação adotado foi o Angiosperm Phylogeny Group IV (APG IV, 2017). Para confirmação do nome científico da espécie foi consultado a lista de espécies da flora do Brasil (FLORA DO BRASIL, 2022). A autorização para coleta do material botânico foi fornecida pelo Sistema de Autorização e Informação em Biodiversidade (SISBIO) do Instituto Brasileiro do Meio Ambiente e dos Recursos Renováveis (IBAMA).

Com relação ao monitoramento dos compostos químicos dos óleos essenciais presentes na resina, indivíduos de *C. langsdorffii* foram marcados no interior das fitofisionomias de Cerradão, Carrasco e Mata Úmida da Chapada do Araripe, município do Crato, com características semelhantes em relação ao comprimento, diâmetro e visivelmente saudáveis. A extração da resina foi realizada perfurando o tronco das árvores com um trado de 2 cm de diâmetro a uma altura de 1,30 m do solo. Um pedaço de tubo de PVC (¾) foi inserido no orifício para drenar a resina. A tubulação foi conectada a um recipiente coletor com capacidade de aproximadamente 250 ml por meio de uma mangueira plástica (¾). Toda resina extraída foi acondicionada em potes plásticos e coberta com papel alumínio para um transporte mais seguro ao laboratório de Pesquisa de Produtos Naturais da Universidade Regional do Cariri.

As amostras de resina devidamente pesadas foram submetidas ao processo de hidrodestilação por 2 h cada, em aparelho tipo Clevenger, para extração dos óleos essenciais. Posteriormente, os óleos voláteis 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 para extração de óleos voláteis. É bastante indicado para extrair óleos de plantas, inclusive preconizado pela Farmacopeia Brasileira (HEINZMANN; SPITZER; SIMÕES, 2017; ANVISA, 2019). A identificação dos componentes químicos ocorreu por cromatografia gasosa acoplada a espectrometria de massas (CG/EM). A partir de uma espectroteca (espécie de biblioteca) instalada a um computador, o espectro da amostra é comparado com as substâncias do banco de dados e a substância é identificada (HEINZMANN; SPITZER; SIMÕES, 2017).

Por se tratar de uma das espécies mais abundantes do gênero (TROPICOS, 2021a), *C. langsdorffii* se destaca, devido seu acentuado uso nas comunidades e, por ser alvo de pesquisa química e farmacológica em diferentes regiões do Brasil. Diante da carência de pesquisas que reúnam e analisem as variações das informações disponibilizadas desta espécie foi realizada uma revisão de literatura em seis bases de dados, Pub Med, Science Direct, Scielo, Web of Science, Google scholar e Repositório Institucional da Universidade Estadual Paulista (UNESP). Estiveram incluídos nessas buscas artigos científicos publicados em periódicos em um intervalo de 20 anos (2000 à 2019). Estudos que não abordavam a etnofarmacologia, composição química e atividades biológicas desta espécie foram excluídos, assim como artigos de revisão, pesquisas provenientes de livros, teses, dissertações, monografias e resumos. Na compilação dos dados foram registrados estudos desenvolvidos no Brasil.

1.3 ESTRUTURA DA TESE

Para testar as hipóteses levantadas foram realizadas pesquisas etnobiológicas com a espécie *C. langsdorffii* em diferentes fitofisionomias da Chapada do Araripe, assim como análises químicas do seu óleo essencial extraído da resina coletada em áreas de Cerradão, Carrasco e Mata Úmida, município de Crato-CE, o que resultou em três produções científicas, as quais estão listadas na Tabela 1.

Tabela 1. Produções científicas originadas da tese de doutorado intitulada: Análise da variabilidade das indicações terapêuticas e dos compostos químicos de óleos essenciais de *Copaifera langsdorffii* Desf. em diferentes fitofisionomias, autoria de Maria de Oliveira Santos, do Programa de Pós-graduação em Etnobiologia e Conservação da Natureza.

Título	Periódico	Percentil	Fator de Impacto
Artigo 1: *Copaifera langsdorffii* Desf.: A chemical and pharmacological review (capítulo 2)	Biocatalysis and Agricultural Biotechnology	79%	3.281
Artigo 2: Consensus of the medicinal use of *Copaifera langsdorfflii* Desf. in different phytophysiognomies (capítulo 3)	Acta Botanica Brasilica	58%	1.268
Artigo 3: Chemical composition variation of essential oils of *Copaifera langsdorffii* Desf. from different vegetational formations (capítulo 4)	Natural Product Research	76%	2.861

A tese está estruturada em cinco 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 três tópicos. O primeiro, "A etnobiologia na seleção de plantas para a bioprospecção", é pautado na conceituação e fornece os principais aspectos etnobiológicos, químicos e farmacológicos. O segundo tópico, "Caracterização botânica de *Copaifera langsdorffii* Desf.", está dividido em dois subtópicos: "Família Fabaceae Lindl." descreve a família Fabaceae, sua riqueza de espécies e distribuição; "*Copaifera langsdorffii* Desf." caracteriza a espécie em estudo e fornece seus principais usos medicinais, comprovações farmacológicas e aplicações na indústria, além da sua distribuição (ocorrência) em diferentes ambientes. O terceiro tópico, "Influência dos fatores ambientais no rendimento e na composição química das espécies" mostra as características de óleos voláteis, e como estes podem variar qualitativamente e quantitativamente a depender das condições ambientais das áreas coletadas como, precipitação, temperatura, solo, diferentes fases fenológicas e diferentes indivíduos em uma mesma área.

Capítulo 2: intitulado "*Copaifera langsdorffii* Desf.: uma revisão química e farmacológica", trata-se de uma revisão de literatura sobre a *C. langsdorffii* disponível em seis bases de dados. Este relata sobre o conhecimento popular do uso medicinal dessa espécie em diferentes regiões do Brasil, assim como a respeito da riqueza de compostos químicos associados as atividades biológicas. Teve como objetivo: verificar se existe consenso na utilização medicinal, componentes químicos e atividades biológicas de *Copaifera langsdorffii*

Desf. em diferentes regiões do Brasil. Com isso, os seguintes questionamentos foram levantados: Quais os usos e/ou conhecimento das indicações terapêuticas, da composição química e da atividade biológica de *C. langsdorrffii* e qual a variabilidade destas informações em todo o Brasil? Existe consenso sobre a sua utilização na medicina tradicional, nos componentes químicos e sobre suas atividades biológicas? Qual a relevância etnofarmacológica de *C. langsdorrffii* e as possibilidades para futuras pesquisas com esta planta? Pesquisas dessa natureza permitem análise do padrão e variação das características da espécie, além de indicar lagunas de conhecimentos para melhores avaliações e sugestões de futuras pesquisas. Este capítulo foi publicado no formato de artigo de revisão no periódico Biocatalysis and Agricultural Biotechnology, em Janeiro de 2022 (DOI: 10.1016/j.bcab.2021.102262).

Capítulo 3: intitulado "Consensus of the medicinal use of *Copaifera langsdorffii* Desf. in different phytophysiognomies", mostra a concordância de uso medicinal de *C. langsdorffii* em diferentes fitofisionomias da Chapada do Araripe, município do Crato, Ceará. O objetivo desse estudo foi: realizar um levantamento etnobotânico de *C. langsdorffii* em fitofisionomias de Cerradão, Carrasco, Mata Úmida e Caatinga na Chapada do Araripe, Nordeste, Brasil. Considerando que cada região e cada formação vegetacional tem suas características específicas e consequentemente cultura, comportamentos diferenciados e que isto pode influenciar no tipo das indicações terapêuticas, bem como nas partes utilizadas, formas de preparo, etc, realizou-se um estudo para verificar o número de indicações terapêuticas em diferentes fitofisionomias (Cerradão, Carrasco, Mata Úmida e Caatinga) e avaliar a concordância de uso/conhecimento entre os informantes sobre as indicação terapêutica nas comunidades nos diversos ambientes. Isto é de suma importância pois irá indicar para qual patologia a espécie apresenta maior consenso entre os informantes para a cura e assim sugerir estudos direcionados e mais aprofundados para *C. langsdorffii*. Este capítulo está submetido e em processo de revisão no periódico Acta Botanica Brasilica no formato de artigo original.

Capítulo 4: intitulado "Chemical composition variation of essential oils of *Copaifera langsdorffii* Desf. from different vegetational formations". Traz uma análise comparativa da composição química e dos principais compostos em diferentes fitofisionomias. Objetivo: considerando a importância medicinal de *C. langsdorffii* para as comunidades e a ausência de informações científicas relacionadas a dados químicos em diferentes tipos vegetacionais, esse estudo trata da análise do perfil químico do óleo essencial extraído da resina do caule de *C. langsdorffii* em áreas de Cerradão, Carrasco e Mata Úmida, na Chapada do Araripe, Nordeste do Brasil, com o intuito de investigar a variação química da espécie em diferentes áreas e indicar em qual ambiente a espécie produz maior teor químico. Este capítulo foi publicado no periódico

Natural Product Research no formato de comunicação curta, em Maio de 2022 (DOI: 10.1080/14786419.2022.2081849).

Capítulo 5: "Considerações finais", aborda as principais conclusões da tese, relacionando os resultados aos objetivos propostos para cada um dos artigos elaborados.

As etapas do desenvolvimento desse trabalho foram pensadas com o propósito de investigar se existe variação nas indicações terapêuticas, assim como na composição química do óleo essencial extraído da resina de *C. langsdorffii* em diferentes fitofisionomias, como forma de indicar os usos com maior consenso nas diferentes áreas e a melhor ambiente para coleta da resina, para subsidiar estudos farmacológicos com essa espécie.

2. CAPÍTULO 1: FUNDAMENTAÇÃO TEÓRICA

2.1 A ETNOBIOLOGIA NA SELEÇÃO DE PLANTAS PARA A BIOPROSPECÇÃO

No âmbito etnobiológico, uma ferramenta necessária para conhecer e classificar o uso dos recursos naturais é a valorização da riqueza biológica e cultural, bem como o conhecimento adquirido por várias práticas tradicionais (ALBUQUERQUE; HANAZAKI, 2006; RIBEIRO *et al*., 2014). A realização de estudos com produtos naturais, especialmente com plantas, sofreu enorme avanço, propiciando a descoberta de diversas substâncias químicas utilizadas atualmente na terapêutica (DIEGUES; ARRUDA, 2001; CRAGG; NEWMAN, 2013; KHAN; AHMAD, 2019).

O avanço ocorrido na área científica permitiu o desenvolvimento de fitoterápicos confiáveis e eficientes, embora ainda faltem estudos científicos que comprovem a utilização segura e eficaz de várias plantas (VIEIRA *et al*., 2010).

O Brasil apresenta uma flora bastante diversificada, com vegetações de diferentes características e muitos princípios ativos ainda desconhecidos, o que justifica o crescimento significativo de estudos com produtos de origem vegetal objetivando a obtenção de novos potenciais fitoterápicos (CALIXTO, 2003; NAPOLITANO *et al*., 2005). Além disso, é considerado o país mais rico em biodiversidade, atualmente são reconhecidas 49.979 espécies para a flora brasileira (FLORA E FUNGA DO BRASIL, 2020), das quais poucas foram estudadas em termos biológicos, químicos e farmacológicos.

A biodiversidade é uma imensa fonte de informação e matéria-prima que suporta vários sistemas médico-tradicionais ao redor do mundo. A importância da natureza como fonte de medicamentos tradicionais é demonstrada muitas vezes por meio do conjunto de conhecimento associado ao uso de recursos da flora que se destacam pela diversidade de formas de uso e pelo alto número de doenças e/ou sintomas que são tratadas (ALMEIDA; ALBUQUERQUE, 2002).

O acúmulo de práticas e de conhecimento formam sistemas médicos empíricos baseados muitas vezes no uso de recursos naturais vegetais (MONTEIRO *et al*., 2008). O estudo destes mecanismos oferece para a etnofarmacologia uma suposta eficácia das plantas que são selecionadas dependendo do conceito de doença e saúde (BERLIN; BERLIN, 2005; ALBUQUERQUE, 2010), e esta identificação também auxilia no aprimoramento de outras abordagens que utilizam plantas medicinais como objeto de pesquisa (ALMEIDA *et al*., 2010).

As plantas com potencial terapêutico são objeto de análise em várias abordagens etnobiológicas e apresentam dentre várias possibilidades de estudos, os métodos de extração e caracterização de diferentes classes de compostos presentes nestas plantas que formam os pilares da fitoquímica (ALMEIDA *et al*., 2010). A elucidação estrutural dos princípios ativos de uma planta medicinal constitui um passo indispensável para a compreensão do seu mecanismo de ação (HOSTETTMANN; QUEIROZ; VIEIRA, 2003), por esta razão o entendimento e isolamento dos princípios ativos das plantas é uma das prioridades da farmacologia (CRAGG; NEWMAN, 2013).

Averiguações etnobotânicas têm sido realizadas em conjunto com abordagem química ecológica (ALMEIDA *et al*., 2005; MELO *et al*., 2017). Ao empregar a abordagem etnobotânica e/ou etnofarmacológica, as informações sobre uso de plantas medicinais fornecidas pela comunidade são combinadas aos resultados obtidos em estudos químicos e farmacológicos (ELISABETSKY; SOUZA, 2010) e caso os dados sejam positivos e efetivos, o entendimento da ecologia química das plantas investigadas se torna essencial.

Estudos comparativos com diferentes indivíduos em um mesmo ambiente ou em ambientes distintos são necessários para confirmar se esta relação das plantas com o ambiente pode ser bem sucedida como os estudos etnodirigidos (ALBUQUERQUE; RAMOS; MELO, 2012). Desta forma, é fundamental entender como as plantas medicinais se comportam no ambiente, como estes recursos são utilizados e como esta informação pode contribuir para estratégias de uso sustentável. A partir da concepção de conhecimento local, é possível desenhar estratégias que levam a alternativas que respeitem a necessidade de conservação, juntamente com as tradições das pessoas que usam esses recursos e o conhecimento cientifico (ALBUQUERQUE *et al*., 2011), podendo fornecer informações de melhor época de coleta e melhor período em que a mesma produz alto rendimento de substâncias essenciais para o tratamento medicinal e posteriores utilizações farmacológicas.

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

As plantas são conhecidas por produzirem uma grande diversidade de metabólitos secundários, mostrando inúmeros efeitos farmacológicos (NEWMAN; CRAGG, 2020; SALM *et al*., 2021). As plantas medicinais podem atuar por meio de diferentes mecanismos de ação (ZIMMERMANN *et al*., 2013; FOKOU *et al*., 2015; MONTESINO *et al*., 2015; SALM *et al*., 2021). A etnofarmacologia continua a inspirar a bioprospecção à medida que investiga o consenso de tratamento de drogas naturais entre grupos étnicos com indicações terapêuticas para eficácia farmacológica presumida (BUENZ; VERPOORTE; BAUER, 2018; SALM *et al*., 2021).

Algumas das plantas medicinais indicadas em levantamentos etnobotânicos já tiveram suas indicações terapêuticas comprovadas e foram alvo de estudos farmacológicos *in vitro* e *in vivo*. A exemplo, *C. langsdorffii* com importante atividade anti-inflamatória (PAIVA *et al*., 2003), *Croton zehntneri* (velame) com ação anti-inflamatória, antinoceptivo (OLIVEIRA *et al*., 2001), anti-hipertensivo (SIQUEIRA *et al*., 2006) e cicatrizante (CAVALCANTI *et al*., 2012), *Hancornia speciosa* atividade anti-úlcera (MORAES *et al*., 2008), *Lantana camara* (camará) atividade antibacteriana (COSTA *et al*., 2009), *Solanum paniculatum* (jurubeba) atividade antibacteriana (LÔBO *et al*., 2010), *Stryphnodendron adstringens* ação anti-inflamatória (LIMA; MARTINS; SOUZA, 1998) e *Bowdichia virgilioides* também apresentando atividade anti-inflamatória (VELOZO; SILVA; BERNARDO, 1999).

2.2 CARACTERIZAÇÃO BOTÂNICA DE *Copaifera langsdorffii* DESF.

2.2.1 Família Fabaceae Lindl.

A família Fabaceae é uma das maiores entre as angiospermas existentes no mundo (SILVEIRA; MIOTTO, 2013), sendo dominante em diversos ambientes, cuja distribuição varia de florestas tropicais a desertos, planícies, regiões alpinas e ambientes aquáticos (DOYLE; LUCKOW, 2003; FERNANDES; GARCIA, 2008). Esta alta capacidade de distribuição de suas espécies lhes confere uma grande relevância ecológica, tornando-se indispensáveis a manutenção do equilíbrio dos ecossistemas como um todo (AMORIM *et al*., 2016).

A família engloba 795 gêneros e quase 20.000 espécies (LEWIS *et al*., 2005; LPWG, 2017; FLORA E FUNGA DO BRASIL, 2020) e se destaca por ser a terceira maior família de plantas do mundo, perdendo apenas para Asteraceae e Orchidaceae (AMORIM *et al*., 2016). A família pertence à ordem das Fabales juntamente com Polygalaceae, Surianaceae e Quilajaceae (DOYLE; LUCKOW, 2003; JUCHUM, 2007a), sendo depois de Poaceae, a segunda maior em importância econômica, medicinal, alimentícia, ornamental e madeireira (CIPRIANO *et al*., 2014). Atualmente a família é dividida em seis subfamílias (LPWG 2017), das quais, apenas a subfamília monoespecífica africana Duparquetioideae (*Duparquertia orchidacea* Baill.) não é representada no Brasil. As subfamílias presentes no Brasil são: Cercidoideae, Detarioideae, Dialioideae, Caesalpinioideae e Papilionoideae (LPWG 2017). A subfamília Papilionoideae está distribuída através do mundo, em diferentes habitats, enquanto Caesalpinioideae se sobressaem nas regiões tropicais e subtropicais (COSTA, 2012). O maior grupo dessas subfamílias é Papilionoideae constituída por 503 gêneros e 14.000 espécies (LPWG 2017).

A família Fabaceae reúne representantes dos mais diversos hábitos, desde árvores de grande porte até ervas (anuais e perenes), trepadeiras e lianas (SILVEIRA; MIOTTO, 2013). As plantas herbáceas do grupo Fabaceae são mais distribuídas em regiões temperadas enquanto que as plantas lenhosas são mais representativas em regiões tropicais e subtropicais (SOUZA, 2012). São extremamente variadas na morfologia de suas folhas e flores e exibe geralmente um fruto típico, o legume, que é característico deste grupo, cujo fruto apresenta variações: legume bacóide, nucóide, samaróide e também lomento, folículo, sâmara e drupa (FERNANDES; GARCIA, 2008; AMORIM *et al*., 2016). Essa expressiva variação morfológica de seus frutos e sementes tem contribuído para o seu sucesso evolutivo e ecológico. As Leguminosas, cosmopolita em distribuição, constituem o elemento principal de vários tipos vegetacionais existentes em várias regiões do mundo (PETERLE *et al*., 2015). São adaptadas a solos de baixa fertilidade, pobres em nitrogênio, onde estabelecem uma relação de simbiose com bactérias em nódulos radiculares permitindo a fixação de nitrogênio atmosférico (LEWIS *et al*., 2005).

No Brasil, Fabaceae é abundante em todos os biomas, apresentando-se sempre com um conjunto de espécies e gêneros endêmicos (GIULIETTI; HARLEY, 2005), abrangendo 3.026 espécies, das quais 1.577 são endêmicas (FLORA E FUNGA DO BRASIL, 2020). No domínio Cerrado, a família encontra-se dentre as mais representativas em número, representando cerca de 777 espécies, distribuídas em aproximadamente 101 gêneros (SANTOS, 2010), sendo um dos grupos botânicos que mais se sobressai nas pesquisas etnobotânicas (RIBEIRO *et al*., 2014; SARAIVA *et al*., 2015; MACÊDO *et al*., 2015, 2018; SANTOS *et al*., 2018, 2019a; ALMEIDA *et al*., 2022).

No semiárido nordestino, no domínio Caatinga, a família Fabaceae está bem representada com aproximadamente 600 espécies distribuídas em 120 gêneros, fazendo parte da maior diversidade da flora da região (AMORIM *et al*., 2016).

2.2.2 *Copaifera langsdorffii* Desf.

Copaifera langsdorffii é uma espécie arbórea pertencente à família Fabaceae e subfamília Detarioideae (CHASE *et al*., 2016; LPWG, 2017; GBIF, 2021a), encontrada desde o Nordeste da Argentina até a Venezuela (ALMEIDA *et al*., 1998; LORENZI, 2000), mostrando ampla distribuição. No Brasil estende naturalmente pelas regiões Nordeste, Norte, Centro-Oeste, Sudeste e Sul, e pode ser encontrada em diferentes fitofisionomias, como Campo

Rupestre, Cerrado (*lato sensu*), Floresta Ciliar ou Galeria, Floresta de Terra Firme, Floresta Estacional Semidecidual e Floresta Ombrófila (Floresta Pluvial), e em áreas antropizadas (COSTA, 2020). *C. langsdorffii* é uma espécie adaptável às condições edáficas, ocorrendo tanto em áreas de solo fértil e bem drenado quanto em áreas de solo pobre, ácido e álico. É uma espécie heliófita não pioneira, podendo ser utilizada em programa de recuperação de áreas desmatadas ou em matas com dossel em fechamento (SALGADO *et al*., 2001).

Levantamentos e inventários florísticos no Nordeste registram a ocorrência de *C. langsdorffii* em Pernambuco (COSTA JUNIOR *et al*., 2008), Piauí (ALVES *et al*., 2013a), Maranhão (CONCEIÇÃO; CASTRO, 2009) e Ceará (OLIVEIRA *et al*., 2021). No Ceará (Chapada do Araripe) podemos encontrar em áreas de Cerradão (RIBEIRO *et al*., 2014; MACÊDO *et al*., 2015, 2016, OLIVEIRA *et al*., 2017, 2021), Carrasco (SOUZA *et al*., 2014b; OLIVEIRA *et al*., 2021) e Mata Úmida (SANTOS *et al*., 2019b), onde é conhecida popularmente como pau d´óleo, copaíba ou podói. Nas demais regiões é chamada vulgarmente de copaíba, cupaúba e cupiúva (CORRÊA, 1984; LORENZI, 1992; RIBEIRO *et al*., 2017; MESQUITA; TAVARES-MARTINS, 2018; OLIVEIRA-SILVA *et al*., 2018; SILVA; RORIZ; SCARELI-SANTOS, 2018).

Na maioria dos estudos etnobotânicos, *C. langsdorffii* é uma das plantas mais citada pelas populações entrevistadas, devido os benefícios oferecidos pela resina extraída do caule (RIBEIRO *et al*., 2014; MACÊDO *et al*., 2015, 2016, 2018; PEREIRA *et al*., 2016; OLIVEIRA-SILVA *et al*., 2018; RONCHI *et al*., 2016). O óleo (resina) de copaíba, como é popularmente chamado (VEIGA JUNIOR; PINTO, 2002), é um fitoterápico utilizado para os tratamentos de gripes, tosses, resfriados, dores no corpo, cicatrizante local e internamente, inflamação, diurético e alergias (VEIGA JUNIOR; PINTO, 2002; PASA; SOARES; GUARIM NETO, 2005; LEANDRO *et al*., 2012; RIBEIRO *et al*., 2014; MACÊDO *et al*., 2018; ARAÚJO; LIMA, 2019; SANTOS *et al*., 2019a).

Algumas das indicações terapêuticas de *C. langsdorffii* já tiveram suas indicações terapêuticas comprovadas através da bioprospecção, com estudos farmacológicos mostrando importantes atividades anti-inflamatória (PAIVA *et al*., 2003, 2004; SILVA *et al*., 2009; GELMINI *et al*., 2013), gastroprotetora (LEMOS *et al*., 2015; MOTTA *et al*., 2017), antimicrobiana (PIERI *et al*., 2011; SOUZA *et al*., 2011a), antineoplásica (SENEDESE *et al*., 2013), antitumoral (OSHAKI *et al*., 1994), diurética (PAIVA *et al*., 2003; BRANCALION *et al*., 2012), antioxidante (COSTA *et al*., 2015; BATISTA *et al*., 2016; CARMO *et al*., 2016), cicatrizante (PAIVA *et al*., 2002; MASSON-MEYERS *et al*., 2013), antinociceptivo (GOMES *et al*., 2007) e citotóxico (LEMOS *et al*., 2015; VARGAS *et al*., 2015; FARIAS *et al*., 2019).

Além da sua grande importância medicinal *C. langsdorffii* também já apresenta resultado bastante favorável como biocombustível (SOARES, 2008), sendo utilizado pelas populações do interior na iluminação doméstica, substituindo o óleo diesel.

De modo geral, os óleos essenciais são utilizados, principalmente, para conferir aromas a produtos alimentícios e de perfumaria, em produtos domissanitários e na conservação de produtos alimentícios (CRAVEIRO; FERNANDES; ANDRADE, 1981; SANTOS, 2002). Além disso, os óleos essenciais podem ter um papel ecológico, especialmente como inibidores da germinação, na proteção contra perda de água e no aumento da temperatura, na atração de polinizadores, na defesa contra herbívoros e como reguladores de decomposição da matéria orgânica no solo (CRAVEIRO; MACHADO, 1986).

2.3 INFLUÊNCIA DOS FATORES AMBIENTAIS NO RENDIMENTO E NA COMPOSIÇÃO QUÍMICA DAS ESPÉCIES

Plantas que ocorrem em diferentes condições ambientais apresentam variação qualitativa e quantitativa dos constituintes químicos responsáveis pelas atividades biológicas (DUARTE *et al*., 2004; JORGE *et al*., 2004; HIRUMA-LIMA *et al*., 2006; LIMA *et al*., 2006; CERQUEIRA *et al*., 2009; OLIVEIRA *et al*., 2017). Considerando que essa variação decorre da interação entre as plantas e o ambiente, a síntese de compostos químicos é frequentemente afetada por condições ambientais (KUTCHAN, 2001; GOBBO-NETO; LOPES, 2007).

Fatores como temperatura, precipitação, ventos fortes, altitude, solo, radiação, época de coleta e outros fatores de estresse (LIMA; KAPLAN; CRUZ, 2003; GOBBO-NETO; LOPES, 2007; OLIVEIRA *et al*., 2017; RIBEIRO *et al*., 2020), bem como os eventos fenológicos e a sazonalidade (ALMEIDA *et al*., 2014; OLIVEIRA *et al*., 2017; RIBEIRO *et al*., 2020), podem ocasionar variabilidade no conteúdo total bem como nas proporções relativas dos compostos químicos, principalmente de óleos essenciais. Essa variação tem grande importância porque as substâncias químicas presentes nos óleos têm significado biossistemático, fisiológico, ecológico, terapêutico e implicações evolutivas (LAHLOU, 2004; BAKKALI *et al*., 2008; EDRIS, 2008).

O rendimento dos óleos essenciais de espécies vegetais costuma variar dependendo do ambiente e do período coletado. Com isso podemos citar *C. langsdorffii*, onde seu óleo essencial ocorre nos diversos órgãos da planta e o seu rendimento pode variar entre as diversas partes, assim como em um mesmo órgão quando analisado em diferentes ambientes e em diferentes períodos sazonais. Como por exemplo temos o estudo do rendimento das diversas partes de um indivíduo (resina, folhas, casca da raiz, casca do fruto, casca do tronco, madeira do tronco, madeira da raiz e fruto) de *C. langsdorffii* onde apresentaram uma variação de 0,008% à 7,3% (GRAMOSA; SILVEIRA, 2005). Já um estudo analisando o rendimento médio das partes (folhas, ramos, pericarpos e sementes) de cinco indivíduos foi observado valores variando de 0,05% a 2,33% (NASCIMENTO *et al*., 2012). A sazonalidade também influencia no rendimento, como pode ser observado nos estudos de Oliveira *et al*. (2017) e Almeida *et al*. (2014) com o óleo resina e folhas de *C. langsdorffii* respectivamente, onde apresentaram um maior rendimento dos seus óleos essenciais na época chuvosa. Tanto a sazonalidade como diferentes áreas podem contribuir para um rendimento diferenciado, como no estudo de Almeida *et al*. (2014), onde a Floresta Estacional Semidecidual apresentou 0,380 % no período chuvoso e 0,296% na estação seca, já no Cerrado *sensu stricto* apresentou 0,6% na época chuvosa e 0,456% na seca.

Além da variação existente no rendimento, quando relacionado a sazonalidade e os diferentes ambientes nos óleos essenciais de *C. langsdorffii*, existe também uma variação com relação a quantidade de compostos presentes. Em estudos analisados, observa-se uma variação de seis a 58 constituintes (GRAMOSA; SILVEIRA, 2005; NASCIMENTO *et al*., 2012; OLIVEIRA *et al*., 2017). Os majoritários podem variar dependendo da parte da planta, como folhas (β- cariofileno, espatulenol, óxido cariofileno, germacreno D, γ-muurolene) (GRAMOSA; SILVEIRA, 2005; NASCIMENTO *et al*., 2012; ALMEIDA *et al*., 2014), resina (β-cariofileno, germacreno B, óxido cariofileno) (GRAMOSA; SILVEIRA, 2005; OLIVEIRA *et al*., 2017), fruto (α-copaeno, β-cubebene, , espatulenol, óxido cariofileno, β- cariofileno, γ-muurolene) (GRAMOSA; SILVEIRA, 2005; NASCIMENTO *et al*., 2012), ramo (β-cariofileno, óxido cariofileno, germacreno D) (NASCIMENTO *et al*., 2012), semente (espatulenol e óxido cariofileno (NASCIMENTO *et al*., 2012); raiz (óxido cariofileno e 4-α-copaenol) (GRAMOSA; SILVEIRA, 2005), madeira do tronco (óxido cariofileno, kaurene, kaurenol e β-bisabolol) (GRAMOSA; SILVEIRA, 2005). O β- cariofileno e óxido cariofileno são os compostos encontrados em todos os órgãos de *C. langsdorffii*, sendo este último majoritário em todas as partes. O Sesquiterpeno β-cariofileno é o composto majoritário também em outras espécies do gênero *Copaifera*: em *C. duckei* (LAMEIRA *et al*., 2009); *C. reticulata* (ZOGHBI *et al*., 2009); *C. pubiflora* (ZOGHBI; MARTINS-DA-SILVA; TRIGO, 2009); e *C. multijuga* (CASCON; GILBERT, 2000).

É importante ressaltar que alguns fatores apresentam correlações entre si e não atuam isoladamente, podendo influenciar em conjunto na composição química, como por exemplo, a fase fenológica e sazonalidade (GOBBO-NETO; LOPES, 2007a). Entre os estudos considerando as variações químicas ocasionadas por fatores ambientais, em conjunto com os eventos fenológicos, podem ser referidos os realizados com *Chromolaena laevigata*

(MURAKAMI, 2009), *Hypericum perforatum* (SCHWOB *et al*., 2004) e *Guarea macrophylla* (LAGO *et al*., 2007). Os óleos essenciais das duas primeiras espécies extraídos das folhas na fenofase de frutificação e de *G. macrophylla* na fenofase de floração, apresentaram maior número de compostos químicos em relação a quantidade de constituintes identificados nos outros eventos fenológicos. Tais resultados podem estar relacionados com o favorecimento da polinização e dispersão (LAGO *et al*., 2007), já que, a produção de compostos voláteis, como os terpenos oxigenados, são reconhecidos pelo aparelho olfativo de alguns agentes polinizadores (GERSHENZON; DUDAREVA, 2007). Pesquisa realizada com *Lipia alba*, em condições de cultivo semelhantes, demonstrou que os teores dos componentes majoritários são maiores na fase de crescimento vegetativo (TAVARES *et al*., 2005). Com relação a influência da sazonalidade na composição química, alguns autores relatam variações na quantidade de compostos presentes em suas amostras em função da sazonalidade, como por exemplo, Oliveira *et al*. (2017) e Ribeiro *et al*. (2020) verificaram que na época chuvosa existe uma maior quantidade de compostos presentes quando comparado com o período seco. Estudos enfocando a composição química de óleos essenciais das mesmas espécies em diferentes áreas ou tipos vegetacionais são mais escassos, mesmo assim podemos destacar o de Oliveira *et al*. (2017) que analisaram a variabilidade química dos óleos essenciais de *C. langsdorffii* em diferentes fases fenológicas em áreas conservada e antropizada, onde constataram que houve alteração qualitativa e quantitativa na composição química dos óleos essenciais provindos dos diferentes ambientes, entre os períodos de estiagem e chuvoso, nas diferentes fases fenológicas. Estudos desta natureza são muito importantes para o desenvolvimento de padrões de coleta para obter maiores concentrações de compostos e que são destinados ao uso terapêutico. Como pode-se observar, vários trabalhos associam as variações químicas aos eventos de variações sazonais (MACHADO; ZOGHBI; ANDRADE, 2003; FRIZZO; LORENZO; DELLACASSA, 2004; SCHWOB *et al*., 2004; BARROS *et al*., 2009; BARBOSA *et al*., 2012; SILVA *et al*., 2013a; OLIVEIRA *et al*., 2017; RIBEIRO *et al*., 2020). Entretanto, no estudo de Oliveira, Lameira e Zoghbi (2006), os óleos essenciais extraídos de resinas de *Copaifera reticulata*, *Copaifera duckei* e *Copaifera martii* apresentaram variações das concentrações das substâncias independentemente do período de chuvas, embora os maiores teores do composto β-cariofileno tenham sido observados em março a abril, período de maior precipitação pluviométrica. Assim como em um estudo em três áreas em São Paulo (duas áreas de floresta estacional semidecídua e uma área de cerrado *strictu sensu*), Almeida *et al*. (2014) compararam os perfis fitoquímicos dos óleos essenciais das folhas de *C. langsorffii* na estação seca e chuvosa. As plantas das florestas estacionais semidecíduais mostraram diferenças no perfil fitoquímico obtido em períodos secos e chuvosos. Os teores de monoterpenos e sesquiterpenos diminuíram na estação chuvosa. No cerrado *strictu sensu* não houve diferenças significativas na composição química dos compostos voláteis. Os mesmos autores concluíram que fatores ecofisiológicos devem ser considerados ao se discutir variações químicas em plantas, já que a sazonalidade não foi a principal causa da variação na composição dos óleos essenciais das folhas de *C. langsdorffii,* em diferentes formações do cerrado.

Existe ainda variação dos compostos químicos em uma mesma parte da planta a depender do ambiente coletado, como por exemplo, as folhas de *C. langsdorffii* coletadas no Nordeste por Gramosa e Silveira (2005) apareceu com 24 compostos, onde os majoritários foram γ-muuroleno (25,2%) e β-cariofileno (16,6%), já para Nascimento *et al*. (2012) no Sudeste, foram identificados 47 compostos, onde os majoritários foram o óxido cariofileno (47,3%) e o β-cariofileno (10,5%). Assim como o óleo essencial extraído da resina dessa mesma espécie variou quando analisada no Nordeste por Gramosa e Silveira (2005), onde apareceu 13 compostos, enquanto que em áreas conservada e antropizada também no Nordeste, Oliveira *et al*. (2017), mostrou 36 compostos em cada área, sendo 28 em comum para as duas áreas (conservada e antropizada) e oito exclusivos de cada área (exclusivos da área conservada: Aristoleno, 3,7 (11)-selinadieno, δ-muruleno, α-selina-4,(19),11-dieno, isospatulenol, patchulano, cis-cariofileno, epóxido aromadendreno; e da área antropizada: Cicloisosativeno, α-cubebeno, aloaromadendreno, junipeno, humuladienono, caurano-18-al, α-cadinol, óxido aromadendreno). O β-cariofileno é considerado o composto majoritário do óleo essencial extraído da resina de *C. langsdorffii*, pois apresentou as maiores porcentagens entre os compostos presentes nas áreas analisadas (GRAMOSA; SILVEIRA, 2005; OLIVEIRA *et al*., 2017 - antropizada e conservada) com 53,3%, 46,4% e 38,5% respectivamente. Conhecer essas variações da composição química das espécies em diferentes áreas é importante, pois determinados constituintes muitas vezes de grande interesse medicinal têm preferência por determinados ambientes.

As classes de sesquiterpenos e diterpenos caracterizam o óleo essencial extraído da resina de *C. langsdorffii* (VEIGA JUNIOR; PINTO, 2002; GRAMOSA; SILVEIRA, 2005; YAMAGUCHI; GARCIA, 2012; OLIVEIRA *et al*., 2017), onde os principais sesquiterpenos encontrados são: β-cariofileno, óxido de cariofileno, α-humuleno, δ-cadineno, α-cadinol, α-cubebeno, α- e β-selineno, β-elemeno, α-copaeno, trans-α-bergamoteno e β-bisaboleno. Já os diterpenos mais citados são os ácidos: copálico, polialtico, hardwickiico, caurenóico e ent-caurenóico, juntamente com os seus derivados, os ácidos: 3-hidróxi-copálico, 3-acetóxi-copálico, e entagático (VEIGA JUNIOR; PINTO, 2002; LEANDRO *et al*., 2012; OLIVEIRA *et al*., 2017).

Sabendo-se dos inúmeros fatores que podem levar a variação qualitativa e quantitativa de compostos químicos, fica clara a necessidade de estudos visando detectar as condições, o ambiente e épocas para cultivo e/ou coleta que conduzam a uma matéria-prima vegetal com concentrações desejáveis de princípios ativos (GOBBO-NETO; LOPES, 2007a).

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3. CAPÍTULO 2: Artigo I

Título: *Copaifera langsdorffii* Desf.: a chemical and pharmacological review

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Copaifera langsdorffii Desf.: a chemical and pharmacological review

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Abstract

The chemical composition of *Copaifera langsdorffii* Desf. is rich in sesquiterpenes and diterpenes, and is mainly indicated for healing and inflammation in general. Considering the medicinal importance of this species and the lack of research that gathers and analyzes the available information, this study aimed to verify if there is consensus on the medicinal use, chemical components and biological activities. A search was conducted in Pub Med, Science Direct, Scielo, Web of Science, Google Scholar and Institutional Repository of the Universidade Estadual Paulista. A total of 96 health problems were catalogued, of which inflammation in general and healing were the most cited, along with with resin-oil and stem bark. Of the 277 compounds recorded, 91 were specific to the essential oil, 58 to the crude resin, and 57 to the extract. Caryophyllene oxide was the most frequent constituent. The major constituents presented variation in the essential oil, crude resin, extract and different parts of the plant. A total of 28 proven activities were recorded, of which the most tested were antioxidant, cytotoxic, anti-inflammatory and antibacterial. *C. langsdorffii* shows important sources of active principles in the combat of diseases which affect human health, mainly

regarding the Skin, General, and Nonspecific systems. Its chemical composition is responsible for the biological activities demonstrated for the species. Further investigations are necessary, mainly regarding *in vitro* and *in vivo* pharmacological properties, isolation of substances, mechanism of action, and bioavailability, in order to provide subsidies for the development of new drugs.

Keywords: *Copaifera langsdorffii*; Ethnobotany; Chemical composition; Biological activity.

1. Introduction

The genus *Copaifera* L. belongs to the family Fabaceae (Chase et al., 2016; GBIF, 2021a) and the subfamily Detarioideae (AZANI et al., 2017). This botanical group is one of the most evaluated, from ethnobiological, chemical, and pharmacological perspectives (CAVALCANTE; CAVALCANTE; BIESKI, 2017; MACEDO et al., 2018; NEVES et al., 2017; WINK, 2003). This is probably related to the presence of important chemical components, such as flavonoids, alkaloids, coumarins, among other metabolites (WINK, 2003), which treat and/or cure diseases.

Copaifera spp. have a cosmopolitan distribution they are not only widespread in West Africa, but also in the tropical region of America, from northern Argentina to Mexico (GBIF, 2021a). Sixteen species can be found in Brazil (TROPICOS, 2021b; VEIGA JUNIOR; PINTO, 2002), of which *Copaifera langsdorffii* Desf. is one of the most abundant species (TROPICOS, 2021a). It is naturally spread throughout the Northeast, North, Central-West, Southeast and South regions, and can be found in different phytophysiognomies, such as Campo Rupestre, Cerrado (lato sensu), Ciliary or Gallery Forest, Terra Firme Forest, Semidecidual Seasonal Forest, and Ombrophylous Forest (Rain Forest), as well as being widely distributed in anthropized areas (ZAPPI et al., 2015). Due the fact that it is widely spread and hence found under different environmental pressures and stresses, *C. langsdorffii* is an excellent model to assess the consequences of climate change on natural populations, since significant changes are observed in functional characteristics in a manner favorable to environmental pressures imposed on different populations (GIANOLI; GONZÁLEZ-TEUBER, 2005; LÁZARO-NOGAL et al., 2015).

C. langsdorffii stands out due to its widespreadl use in communities, and for being the target of chemical and pharmacological research. It is popularly known as copaíba, podói, pau d'óleo, cupaúba, and cupiúva, and it is an arboreal species which can reach 36 m in height and 140 cm in diameter (LISBOA et al., 2018; ZAPPI et al., 2015). This species is frequently used in popular medicine and the pharmaceutical industry, noted mainly for being a producer of resin-oil, a secondary metabolite extracted from the stem with phytotherapeutic effects of great economic value (Gama and Nascimento Júnior, 2019; Nisgoski et al., 2012; Stupp et al., 2008; Veiga Junior and Pinto, 2002), prompting interest in scientific research to prove the mentions of its activities. In addition to the resin-oil, other structures of this species, such as the bark, leaf, inner bark, fruit, seed, root, and sap, are indicated in the communities for curing diseases.

Different environments and regions influence both the chemical composition and local knowledge of medicinal species, causing differences in the number and concentration of compounds, as well as the number of diseases cited in communities (ALMEIDA et al., 2014; ARAÚJO; LIMA, 2019; EL-JALEL et al., 2018; GOBBO-NETO; LOPES, 2007a; MACEDO et al., 2018; OLIVEIRA et al., 2017). Differences in chemical composition as a function of geographic location have been reported for different species, including *C. langsdorffii* (ALMEIDA et al., 2014; OLIVEIRA et al., 2017). However, these studies refer to this variation only in a restricted area, within the same locality. This is very significant from a scientific point of view, but there is still a lack of research that gathers and analyzes information about the differences, both from an ethnobiological and chemical point of view of this species and given its wide distribution.

Thus, considering the importance of *C. langsdorffii*, the wide geographical distribution in Brazil and the lack of research that gathers and analyzes the variations in the information available on this species, the present study was conducted. As a result, the following questions were raised: What are the uses and/or knowledge of the therapeutic indications, chemical composition and biological activity of *C. langsdorffii* and what is the variability of this information throughout Brazil? Is there a consensus about its use in traditional medicine, its chemical components and its biological activities? What is the ethnopharmacological relevance of *C. langsdorffii* and the possibilities for future research with this plant? Research of this nature enables analysis of the pattern and variation of the species characteristics, as well as indicating knowledge gaps for better evaluations and suggestions for future research.

2. Material and Methods

The following databases were consulted: Pub Med, Science Direct, Scielo, Web of Science, Google Scholar, and Institutional Repository of the Universidade Estadual Paulista (UNESP). The inclusion criteria were scientific articles present in journals published between the years 2000 to 2019, derived from the keywords "*Copaifera langsdorffii*" or the combination of the words "GC *Copaifera langsdorffii*", "*Copaifera langsdorffii* biological activity" and "ethnobotany of *Copaifera langsdorffii*". A total of 94 original articles published in the last 20 years were consulted, including 46 on ethnobotany, 17 on chemistry and 38 on pharmacological evidence. Studies which did not address the ethnopharmacology, chemical composition and biological activities of this species were excluded, including review articles, research from books, theses, dissertations, monographs and abstracts. In the compilation, studies developed in Brazil were registered.

The therapeutic indications of *C. langsdorffii* were grouped into 14 body system categories based on the International Primary Care Classification (ICPC-2) proposed by the International Committee on Classifications (WONCA, 2000): Circulatory System (K); Digestive System (D); Endocrine/Metabolic and Nutritional System (T); Female Genital System (X); Male Genital System (Y); General and Nonspecific System (A); Musculoskeletal (L); Neurological System (N); Skin System (S); Psychological System (P); Respiratory System (R); Urinary System (U); Pregnancy, Childbirth and Family Planning (W); Blood, Hematopoietic System, Lymphatic System, Spleen (B).

3. Results and Discussion

3.1 Tradicional Uses

C. langsdorffii was reported to treat 96 health problems, encompassing 14 body systems. The number of ailments varied from 2 to 45 among different Brazilian regions, with the Northeast (45) and Central-West (33) of Brazil where this species was indicated for curing the greatest number of ailments, with the highest number of surveys 16 and 18, respectively (Table 1). This is probably related to a greater distribution and density of this species in these regions (ZAPPI et al., 2015), providing greater accessibility to communities and consequently greater use, due to its effectiveness in treating different diseases that affect different body systems. The accentuated medicinal use of this species is possibly associated with its wide distribution, in which its numerous phytotherapeutic activities are determinants for its intensified use (BRUNETON et al., 2001; SARAIVA et al., 2015). The abundance of its individuals, as well as its distribution in the environment, raises the probability of use by human populations that use resources from its flora (GUARIM NETO; MORAIS, 2003; PINTO et al., 2013a).

In addition to the number of body systems and diseases varying among Brazilian regions, a greater concentration of a certain type of disease per region was notable. Even so, the diseases recorded in all Brazilian regions and present in a greater number of studies were cicatrization (30 surveys) and inflammation in general (26), which belong to the Skin and General and Nonspecific systems, respectively (Table 1). These systems also comprise the largest numbers of records in the analyzed surveys.

Some ailments were unique to certain regions, such as indications for high blood pressure, malaise and birth control (North); loss of synovial fluid, arthritis, pain in the lower

Table 1: Ethnopharmacological studies of the species *Copaifera langsdorffii* Desf.

Reference	Research location	Part used	Preparing	Form of use	Therapeutic indications/body systems
Araújo and Lima, 2019	Floriano- Piauí	Resin-oil	Syrups	Form of use was not mentioned	Burns (S14) and throat irritation (2) (R21)
Santos et al., 2019	Parnaíba-Piauí	Bark		Form of use was not mentioned	Throat (R21) and inflammation (2) (A29)
Fagundes et al., 2017	Claro dos Poções – Minas Gerais	Resin-oil, inner bark	Tea	Form of use was not mentioned	Healing (S18), loss of synovial fluid (W99), arthritis (L88), rheumatism (L88), bronchitis (R78), pain in the lower limbs (L14) and anti-flu (8) (R80)
Macêdo et al., 2018	Nova Olinda-Ceará, Crato-Ceará, Barbalha-Ceará, Moreilândia-Pernambuco and Exu- Pernambuco	Leaf, fruit, resin-oil, stem bark, inner stem bark, Root	Mode of preparation was not mentioned	Form of use was not mentioned	Influenza (R80), rheumatism (L88), headache (N01), general pain (A01), uterine inflammation (X29), bone fracture (L76), wounds (S18), kidney complications (U14), gastritis (D99), angina (K74), knee swelling (L15), blows (S18), rheumatism (L88), cough (R05), healing (S18), rheumatic pain (L88), bellyache (D29), fever (A03), allergy (A92), swelling (A08), kidneys (U14), back pain (L29), rheumatism (L88), indigestion (D07), epilepsy (N88), blood purifier (B04), swelling in the belly (D29), stomachache (D29), general pain (A01), wounds (S18), cancer (A79), inflammation (A29), constipation (D29), depression (P03), nerves (P01), stomach pain (D29), gastritis (D99), flu (39) (R80)
Mesquita and Tavares-Martins, 2018	Belém-Pará	Bark	Tea	Drink	Pain (A01), inflammation (A29) and healing (3) (S18)

Oliveira-Silva et al., 2018	Rio de Janeiro	Resin-oil	*In natura*	Form of use was not mentioned	Bruises (S29), internal infections (A78) and healing (3) (S18)
Silva et al., 2018	Araguaína-Tocantins	Leaf, stem bark, resin-oil	Tea	Form of use was not mentioned	Flu (R80), inflammation (A29), infection (A78) and healing (3) (S18)
Ribeiro et al., 2017	North Araguaia Microregion - Mato Grosso	Bark, resin-oil, seed	Decoction, maceration, fresh, syrup	Form of use was not mentioned	Inflammation in general (A29), prostate inflammation (Y06), intestinal inflammation (D29), diuretic infection (U29), uterus (X29) and ovary (X29), urinary tract infection (U29), kidney stones (U14), prostate (Y06), kidney infection (U14), wound healing (S18), skin wound healing (S18), stomach wound healing (D29), snake bites (S13), burns (S14), headaches (N01), throat (R21), infection (A78) and insect repellent (20) (S12)
Franco and Souza, 2016	Porto Velho-Rodônia	Bark, resin-oil	Syrup	Form of use was not mentioned	Throat infection (R21), infections (A78) and inflammation in general (3) (A29)
Souza et al., 2016	Jataí-Goiás	Resin-oil, stem	Drops in the water, dripping on the area, powder in the food, decoction	Form of use was not mentioned	Anti-Diabetes (T89, 90), healing (S18), healing newborn's navel (S18), prostate (Y06) and inflammation in general (5) (A29)
Penido et al., 2016	Imperatriz-Maranhão	Barks	Decoction	Form of use was not mentioned	General inflammation (A29) and healing (2) (S18)
Macedo et al., 2016	Barbalha-Ceará	Leaf, stem bark, fruit, resin-oil	Decoction	Drink	Spine (L29), rheumatism (L88), indigestion (D07), epilepsy (N88), blood thinning (B04), swelling in the belly (D29), stomach pain (D29), generalized pain (A01) and injuries (9) (A80)

Ronchi et al., 2016	São Paulo	Resin-oil	Mode of preparation was not mentioned	Form of use was not mentioned	Wounds (S18) and healing newborn's navel (2) (S18)
Pereira et al., 2016	Cuiabá-Mato Grosso	Resin-oil	Mode of preparation was not mentioned	Topic	Gastritis (D99), general inflammation (A29) and sore throat (3) (R21)
Araújo et al., 2015	Bacabal-Maranhão	Resin-oil	Mode of preparation was not mentioned	Form of use was not mentioned	Healing (1) (S18)
Mariano et al., 2015	Cuiabá-Mato Grosso	Resin-oil	Mode of preparation was not mentioned	Form of use was not mentioned	Healing (1) (S18)
Bitu et al., 2015	Crato, Juazeiro do Norte, Barbalha-Ceará	Resin-oil	Mode of preparation was not mentioned	Form of use was not mentioned	Skin Inflammation (S29), bronchitis (R78) and venereal disease (3) (X29)
Pasa et al., 2015	Nossa Senhora do Livramento-Mato Grosso		Mode of preparation was not mentioned	Form of use was not mentioned	General inflammation (A29) and skin problems (2) (S29)
Ferreira et al., 2015	Cuiabá-Mato Grosso		Mode of preparation was not mentioned	Form of use was not mentioned	General inflammation (A29) and skin problems (2) (S29)
Macêdo et al., 2015	Moreilândia-Pernambuco	Inner bark, bark, oil-resin, leaf	In sugarcane liquor, Infusion, oil in the skin	Form of use was not mentioned	Cough (R05), healing (S18), rheumatic pain (L88), bellyache (D29), fever (A03), allergy (A92), swelling (A08) and kidneys (8) (U14)
Saraiva et al., 2015	Exu-Pernambuco	Leaf, bark, stem inner bark, oil-resin	Decoction, immersed in water, diluted in water	Oral ingestion, bathing, washing	Cancer (A79), general pain (A01), inflammation in general (A29), constipation (D29), depression (P03), nerves (P01), stomach pain (D29), gastritis (D99), influenza (R80) and lung inflammation (10) (R29)

Silva et al., 2015a	Luís Correia-Piauí	Stem bark	Mode of preparation was not mentioned	Form of use was not mentioned	Gastritis (1) (D99)
Silva et al., 2015b	Curitiba-Paraná		Mode of preparation was not mentioned	Form of use was not mentioned	Inflammation in general (A29) and healing (2) (S18)
Baptistel et al., 2014	Currais-Piauí	Resin-oil	Mode of preparation was not mentioned	Form of use was not mentioned	Cough (R05), flu (R80), asthma (R96), sexually transmitted diseases (STDs) (X29), wounds (S18), healing (S18), sore throat (R21), body pain (A29), chronic flu (R80), epilepsy (N88), migraine (N89) and hip fracture (13) (L76)
Ferrão et al., 2014	Buritis-Minas Gerais	Resin-oil and/or Stem resin	Oil *in natura*, syrup, decoction	Form of use was not mentioned	Healing (S18) and respiratory conditions (2) (R29)
Linhares et al., 2014	São Luís-Maranhão		Mode of preparation was not mentioned	Form of use was not mentioned	Inflammation in general (1) (A29)
Ribeiro et al., 2014	Crato-Ceará, Nova Olinda-Ceará	Leaf, stem bark, resin-oil	Immersed in water, decoction	Oral ingestion, applied to the affected site	Influenza (R80), rheumatism (L88), headache (N01), pain (A01), inflammation of the uterus (X29), bone fractures (L76), wounds (S18), kidney complications (U14), gastritis (D99), angina (K74), knees (L15) and murmur (12) (K81)
Santos et al., 2014	Ariquemes, Buritis, Candeias do Jamari, Cujubim and Itapoa do Oeste-Rondônia	Leaves, inner bark, resin-oil	Decoction, infusion, mixed with coffee	Form of use was not mentioned	Soothing (P01), high blood pressure (K86), infection (A78), flu (R80), malaise (A29) and contraceptive (6) (W14)
Souza et al., 2014	Crato-Ceará, Santana do Cariri-Ceará	Bark, green leaf	Mode of preparation was not mentioned	Form of use was not mentioned	General inflammation (A29), wound (S18), healing (S18), stomach pain (D29) and uterine inflammation (5) (X29)

Alves and Povh, 2013	Ituiutaba-Minas Gerais	Sap	Diluted with water	Ingestion	Ophidian accident (1) (S13)
Ferreira et al., 2013	Baependi-Minas Gerais		Mode of preparation was not mentioned	Form of use was not mentioned	General inflammation (A29) and body pain (2) (A29)
Pinto et al., 2013a	Cuiabá-Mato Grosso	Stem resin	Mode of preparation was not mentioned	Form of use was not mentioned	Gastritis (D99) and prostatitis (2) (Y06)
Pinto et al., 2013b	Três Lagoas-Mato Grosso do Sul, Porto Velho-Rondônia, Rio Verde-Goiás	Stem oil	Mode of preparation was not mentioned	Form of use was not mentioned	Throat (R21), urinary tract infection (U29), body (B29) and immunity strengthening (4) (B29)
Souza and Pasa, 2013	Rondonópolis-Mato Grosso	Bark resin	Burning the resin	Form of use was not mentioned	Airway cleaning (1) (R29)
Pereira et al., 2012	Dourados-Mato Grosso do Sul	Oil extracted from the bark	Mode of preparation was not mentioned	Form of use was not mentioned	Antiseptic (D19) and Inflammation in general (2) (A29)
Conceição et al., 2011	Teresina-Piauí	Leaf, Seed	Mode of preparation was not mentioned	Form of use was not mentioned	Ulcer (A29), wound (S18), sinusitis (R75) and rheumatism (4) (L88)
Pasa, 2011	Cuiabá-Mato Grosso	Stem resin	Mode of preparation was not mentioned	On-site application	Inflammation in general (A29) and healing (2) (S18)
Pasa et al., 2011	Cuiabá-Mato Grosso	Stem resin	Mode of preparation was not mentioned	On-site application	Inflammation in general (A29) and healing (2) (S18)
Silva et al., 2010	Caxias-Maranhão	Bark, oil extracted from the bark	Infusion, ointment	Form of use was not mentioned	Respiratory (R29) and urinary tract disorders (U29) and inflammation in general (3) (A29)
Souza et al., 2010	Cuiabá-Mato Grosso	Stem resin	Mode of preparation	On-site application	Inflammation in general (A29) and healing (2) (S18)

			was not mentioned		
Moreira and Guarim-Neto, 2009	Rosário Oeste-Mato Grosso	Bark, resin-oil	Tea, diluted in water	Form of use was not mentioned	Bronchitis (R78), spine (L29) and flu (3) (R80)
Maciel and Guarim Neto, 2006	Juruena-Mato Grosso		Syrup, tea	Washing	Wound (1) (S18)
Souza and Felfili, 2006	Alto Paraíso-Goiás	Resin-oil	Mode of preparation was not mentioned	Form of use was not mentioned	Healing (S18), tumors (S04) and bruises (3) (S29)
Pasa et al., 2005	Cuiabá-Mato Grosso		Mode of preparation was not mentioned	Form of use was not mentioned	Inflammation in general (A29), blood purification (B04) and healing (3) (S18)
Guarim Neto and Morais, 2003	Mato Grosso	Bark	Tea	Gargle	Inflammation in general (A29) and bronchitis (2) (R78)
Rodrigues and Carvalho, 2001	Lavras, Itumirim, Ingaí, Itutinga and Carrancas-Minas Gerais		Mode of preparation was not mentioned	Form of use was not mentioned	Respiratory tract disorders (R29), healing (S18), urinary tract disorders (U29) and inflammation in general (5) (A29)

limbs, injuries and internal infections (Southeast); prostate inflammation, intestinal inflammation, ovarian problems, skin wound healing, stomach wound healing, burns, insect repellent, antiseptic, body strengthening, immunity, tumors, bruises, and antidiabetes (Central-West); and bone fractures, angina, knee problems, heart murmur, indigestion, epilepsy, stomach problems, ulcer, sinusitis, cough, asthma, sexually transmitted infections (STIs), migraine, cancer, cold, depression, lung inflammation, stomach pain, fever, allergy, and swelling (Northeast).

This demonstrates the great variability in the use of *C. langsdorffii* and the peculiarities of each region. Given that factors such as cultural aspects, availability of the resource in the environment, accessibility, and efficacy have been reported to be important in the selection of medicinal plants and their uses in medical systems over time (ALBUQUERQUE; ALVES, 2018; PHILLIPS; GENTRY, 1993; STEPP; MOERMAN, 2001), the therapeutic indications of a species are considered to vary in different regions. Furthermore, the use of a species by communities in different environments to treat specific diseases in each location may likely be related to the chemical composition of the species (ENDARA; COLEY, 2011), as this can vary in the same species when analyzed in different environments.

Despite the lack of tests that prove its efficacy for many of its uses, most of the traditional uses find justification in the anti-inflammatory and healing properties of the plant. It is worth noting that most of the time in ethnopharmacological surveys, the natural development of the disease is not considered. Thus, there is no way to know whether the plant product is used to cure the disease or relieve some specific symptom. In this regard, some reported uses may be related to the relief of symptoms promoted by inflammatory conditions, and not necessarily to the cure of diseases.

Regarding the plant parts, resin-oil (33) and stem bark (18) are the most used structures, followed by leaf (10), inner stem bark (5), fruit (2), seed (2), root (1) and sap (1) (Table 1). There is variation regarding the use of the plant part of *C. langsdorffii* in different Brazilian regions in the Northeast (PENIDO et al., 2016; SANTOS et al., 2019a) and North (MESQUITA; TAVARES-MARTINS, 2018; SILVA; RORIZ; SCARELI-SANTOS, 2018) there is a preference for the use of the stem bark, while in the Central-West (MARIANO et al., 2015; PEREIRA et al., 2016; SOUZA; FELFILI, 2006) and Southeast (OLIVEIRA-SILVA et al., 2018; RONCHI et al., 2016) the use of the resin-oil stands out. This variation may be associated with the cultural aspects of each region, as well as the characteristics of the plant, because a given resource may be more available to individuals in certain regions, and scarce in others, causing communities to choose to use certain plant parts instead of others because they are more abundant there. Research validating such questions is necessary in order to justify this variation observed in different Brazilian regions.

The use of the barks and the resin-oil of *C. langsdorffii* is a frequent practice among different communities for the treatment of different therapies and the resin-oil is an important phytotherapeutic of great economic value, especially for the pharmaceutical industry (GAMA; NASCIMENTO JÚNIOR, 2019; NISGOSKI et al., 2012). It is worth noting that the predominant use of structures such as bark and resin-oil can probably make the species more vulnerable, possibly causing a reduction in its populations, as there is no control regarding their collection (SANTOS et al., 2019a). Lima et al. (2011) and Pinto et al. (2013) highlight that the use of resources that affect the survival of the plant can compromise the conservation of the species. Therefore, there is a need to know which compounds are developing the action to see the possibility of substituting the use of these structures by the use of the leaves for example, because these are plant parts that renew themselves quickly in the plant. Moreover, bioprospecting or breeding may be proposed to help to select or enhance specific plant properties that are desired, such as quick growth or the cultivation of a specific chemotype.

One of the uses most established by communities for the resin-oil of *C. langsdorffii* is as a wound-healing agent. However, there are few scientific reports that corroborate the efficacy of this species in relation to this activity. Despite the promising effects concerning the use of *C. langsdorffii* resin-oil as a wound-healing agent, the lack of a positive control makes it difficult to evaluate the real potential of this species as a natural wound-healing product (ARRUDA et al., 2019). In addition to the few research studies on healing activity for this species, and the lack of positive controls, the mode of action has not yet been elucidated, although some authors have reported increased vascularization and increased fibroblast production, which may contribute to this effect (SILVA et al., 2009).

Preparations such as teas (decoction and infusion) (17 studies), syrup (5), dilution of the resin-oil in water (4), immersion of the barks in water (2), resin-oil in natura, maceration, dripping on the spot, powder in food, in cachaça, burning the resin, mixing the oil-resin with coffee, and ointment were listed in the use of *C. langsdorffii* in the different Brazilian regions (Table 1). In the Northeast, North, and Central-West there is a preference for teas, while in the Southeast the in natura form was the most used (Table 1). For the Southern region, the studies did not address the forms of preparation. Among the articles analyzed, more than 50% did not mention forms of preparation. The preference for the use of teas by communities and the choice of this preparation are probably related to the availability of the part used and the characteristics of the plant, and because it is often seen by the population as an effective way (AMOROZO, 2002; OLIVEIRA; BARROS; MOITA NETO, 2010). Tea is considered the second most consumed beverage by the world population, which, besides its aromatic properties, may have several benefits for human health, such as antioxidant and antimutagenic activity, by acting in the prevention of cardiovascular diseases, as an aid in accelerating metabolism, besides having antibacterial and antifungal action, among others (ARAÚJO; LIMA, 2019; KUJAWSKA et al., 2016). Nevertheless, when plant structures are prepared by immersing them in water, there is less risk of losing important active ingredients (AMOROZO, 2002).

The forms of administration were researched in only 24% of the surveys, highlighting oral ingestion and local application present in a larger number of surveys (five each), followed by washing (2), bathing (1) and gargling (1) (Table 1). Oral intake was favored by the strong preference for using teas to treat internal body problems, while topical aplication is related to the strong use of resin-oil in communities for health problems on the outside of the body.

Due to its wide distribution, *C. langsdorffii* has medicinal importance recognized and spread throughout different Brazilian regions. The therapeutic potential of this species is justified by the various scientific publications that report both its ethnobiological use, indicating a high number of citations, and investigations related to the proof of medicinal effects in general

(MACÊDO et al., 2018; RIBEIRO et al., 2014; SANTOS et al., 2019a). Due to the diversity of ethnobiological properties reported, and the large number of indications for use as a cicatrizing and inflammatory agent, there is a growing interest and need to deepen more specific studies that favor its use.

3.2 Chemical Composition

A total of 277 compounds were identified in *C. langsdorffii* individuals, ranging from six to 58 in the different studies. These compounds were extracted from different plant parts of this species, through essential oil (leaf, resin, aril, branch, root, inner stem bark, fruit and fruit peel), crude resin and extract (leaf (methanolic,) seed (chloroform and fixed oil) and stem bark (aqueous, ethanolic, hydrochloric acid, acetic acid, hydrogen peroxide solution, hexanic and ethyl acetate)), with 162, 80 and 62 compounds, respectively (Tables 2, 3 and 4).

Table 2: Chemical components found in the crude resin oil of *Copaifera langsdorffii* Desf.

Collection site	**Chemical compounds**	**Major compounds (wt. %)**	**Authors**
Amazonas (North)	1-hexene, 4-methyl; Heptane, 2,4-dimethyl; β –Clavene; δ –Selinene; Longifolene- (V4); Alloaromadendrene; Caryophyleine- (I3); Cyperene; β –Guajene; τ –Selinene; τ –Mururene; Cuparene; Cadinene; β-silene; Elixene; Germacrene B; α –Himachalene; α –Gurjunene; β-Chamigrene; Cubenol; (-) - Caryophyllene - (I1); Isoaromadendene epoxide; β –Eudesmene; Eudesma-4 (14), 11-diene; τ –Eudesmol; Calarene epoxide; β-Humulene; Sclaral; Androst-5-en-4-one; Androstan-17-one, 3-ethyl-3-hydroxy -, (5a); Gibberellic acid; Isopimaco gone; Pentadecanoic acid, 13-methyl; Pimarinal; Abietic acid; 13-Isopimaradene; Kaur-16-ene; Sclarene; Bifena; Ent kaur-16-ene; Cembrene; 8,11-octadecadienic acid; Elaidic acid; Sclareol; labd-7-en-15-Oic acid; Copalic acid A isomer; Copalic acid; Valencene; Pyramic acid; Daniellic acid; Lambertinic acid; Kauran-19-oic acid; labd-8 (20) -ene-15,18-dioic acid, dimethyl ester. (53 compounds)	Copalic acid (22.2 %)	Gelmini et al., 2013
Minas Gerais, Belo Horizonte (Southeast)	α-copaene; β-elemene; β-Caryophyllene; bergamotene; aromadendrene; α-humulene; γ-muurolene; β-selinene; γ-cadinene; spathulenol; kaurenal; copalic acid; kaurenoic acid; 3β-acetoxycopalic acid. (14 compounds)	β-Caryophyllene (31.4 %), γ-muurolene (16.1 %) and bergamotene (10.2 %)	Zimmermam-Franco et al., 2013
Minas Gerais, Patos (Southeast)	α-cubebene; Ciclosavitene; α-copaene; β-Caryophyllene; γ-muurolene; γ-Patchoulene; *trans*-β-guaiene; α-cedrene epoxide; Zizanone; (Z) - α-	Methyl-9-octdecenoate (26,5 %), γ -	Estevão et al., 2013

Table 2: Chemical components found in the crude resin oil of *Copaifera langsdorffii* Desf.

Collection site	Chemical compounds	Major compounds (wt. %)	Authors
	santalol; Mustakone; curcumenol; eremophilone; Abieta-8,12-diene; Caurene; Methyl-9-octdecenoate (16 compounds)	muurolene (22,7 %)	

Mass basis (wt.%)

Table 3: Chemical components found in the essential oil of different plant parts of *Copaifera langsdorffii* Desf.

Part of the plant studied	Location	Chemical compounds	Major compounds (wt. %)	Authors
Leaf	Botucatu, SP (Southeast)	α-Copaene, β-Elemene, β – Caryophyllene, γ-Gurjunene, γ-Elemene, α –Humulene, γ-Muurolene, Germacrene D, Bicyclogermacrene, α –Mururolene, γ-Cadinene, δ-Cadinene, Germacrene B, Spathulenol, Caryophyllene oxide, Humulene epoxy II, α-cadinol Total: (17)	Germacrene D, β-Caryophyllene, bicyclogermacrene, spathulenol, Caryophyllene oxide and α-cadinol	Almeida et al., 2016
Leaf	Botucatu, SP (Southeast)	α-copaene (hs), β-elemene (hs), *trans*-Caryophyllene (hs), γ-gurjunene (hs), γ-elemene (hs), α-humulene (hs), γ-muurolene (hs), germacrene D (hs), bicyclogermacrene (hs), α-muurolene (hs), γ-cadinene (hs), δ-cadinene (hs), germacrene B (hs), spathulenol (os), Caryophyllene oxide (os), epoxide humulene II (os), α-cadinol (os) Total: (17)	Germacrene D (20.5 %), spathulenol (11.4 %), *trans*-Caryophyllene (9.8 %) and Caryophyllene oxide (7.4 %)	Portella et al., 2015
Leaf	Botucatu, SP (Southeast)	α-Thujene (m), o-cymene (m), (Z) - β-Ocimene (m), (E) - β-Ocimene (m), γ-Terpinene (m), terpinolene (m), δ- Elemene (s), α-Copaene (s), β-Elemene (s), *trans* – Caryophyllene (s), γ-Elemene (s), α-Humulene (s), Seychellene (s), γ-Muurolene (s)) Germacrene D, Bicyclogermacrene (s), α-Muurolene (s), γ-cadinene (s), δ-cadinene (s), Germacrene B (s), spathulenol (os), Caryophyllene oxide (os), Cubenol (os), α-Cadinol (os) Total: (24)	Germacrene D (26.5 %), *trans*-Caryophyllene (13.6 %), Spathulenol (12.5), Caryophyllene oxide (10.2 %)	Almeida et al., 2014
Leaf	Lavras – MG (Southeast)	Methyl geranate, δ -elemene, α-cubebene, α-cupene, β-cubebene, β -elemene, Cyperene, (E) – Caryophyllene, β-cupene, γ -elemene, Aromadendrene, Guaia-6,9-diene, α -humulene, allo-aromadendrene, γ -mururene, α -amorphene, Germacrene D, β -selinene, Viridiflorene, Bicyclogermacrene, α -muurolene, γ -	(E) – Caryophyllene (12.9 %), Caryophyllene oxide (11.2 %)	Nascimento et al., 2012

		cadinene, *trans*-calamenene, δ -cadinene, *trans*-cadina-1,4-diene, α-cadinene, α-copen-11-ol, α-calcacene, Elemol, Germacrene B, (E) -nerolidol, Palustrol, Spathulenol, Caryophyllene oxide, Viridiflorol, Humulene epoxide II, Junenol, 1-*epi*-cubenol, *epi*– α-muurolol, α-muurolol, α-cadinol, Mustakone, Eudesma-4 (15), 7-dien-1 β -ol, (2E, 6E) -methyl farnesoate, (E, E) -geranyl linalool, Kaurene Total: (47)		
Leaf	Crato-CE (Northeast)	p-cymene, camphor, δ-elemene, α-cubebene, α-cepene, β - elemene, β – Caryophyllene, β -gurjunene, *trans* -α - bergamotene, α -humulene, γ -mururolene, β -selinene, α - muurolene, γ-cadinene, *cis*-calamenene, δ-cadinene, cubebene, α-cadinene, elemol, germacrene B, Caryophyllene oxide, guaiol, α-muurolol, β –eudesmol Total: (24)	γ –muurolene (25.2 %), β – Caryophyllene (16.6 %)	Gramosa and Silveira, 2005
Aril	Botucatu, SP (Southeast)	δ-elemene (hs), α-copaene (hs), β-cubebene (hs), β-elemene (hs), *trans*-Caryophyllene (hs), α-humulene (hs), seychellene (hs), γ-muurolene (hs), germacrene D (hs), bicyclogermacrene (hs), α-muurolene (hs), germacrene A (hs), γ-cadinene (hs), δ-cadinene (hs), elemol (os), germacrene B (hs), spathulenol (os), Caryophyllene oxide (os), guaiol (os), cubenol (os), α-cadinol (os), bulnesol (os) Total: (22)	Germacrene D (35.0 %), bicyclogermacrene (7.6 %), cubenol (5.1 %) and α-cadinol (7.4 %)	Portella et al., 2015
Resin	Crato, CE (Northeast)	Aristolene, Cycloisativene, α-ialangene, α-cubebene, βelemene, γ-cadinene, β- Caryophyllene, α-copaene, γ-elemene, valencene, α-bergamontene, 3.7 (11) selinadiene, α-guaiene, α- humulene, α-selimene, α-amorphene, germacrene D, β-selinene, δ-guaiene, β-bisabolene, δ-cadinene, alloaromadendrene, germacrene B, Caryophyllene oxide, caur-16-ene, δ-elenene, junipene, γ - muurulene, α-muurulene, δ-muurulene, α-selina-4 (19) 11-diene, aromadendrene, humuladienone, α-calacorene, kuran-18-al, α-cadinol, spathulenol, iso spathulenol, aromadendrene oxide, patchulan, *cis* – Caryophyllene, aromadendrene epoxide, kurene-16-ene Total: (43)	β- Caryophyllene: anthropic December (72.2 %) and conserved July (61.0 %)	Oliveira et al., 2017
Resin	Piracicaba, SP (Southeast)	δ-elemene, (+) - cyclosativene, α-copaene, β-elemene, β-Caryophyllene, α-bergamotene, α-guaiene, β-farnesene, α-Caryophyllene, τ-muurolene, β-cubebene, β-selinene, α-selinene, τ-gurjenene, β-chamigrene, β-bisabolene, β-sesquipelellene, α-curcumene, α-cedrene, β-cedrene, α-himachalene, Kaurene Total: 22	β-bisabolene (23.7 %), β-Caryophyllene (21.7 %), α-bergamotene (20.5 %)	Alencar et al., 2015

Resin	Amazonas (North)	3-Octene, (Z); 3-octene, (E); Paraffin not identified; 4-octene, (Z); (+) - Ciclosativene; α –Copaene; τ - Gurjunene; α –Farnesene; β-Elemene; Di-*epi*- α-cirrrene; δ –Selinene; α-Longipinene; α-Santalene; β-Caryophyllene; α-bergamotene; Cedrene; Bergamotol, Z-α-*trans*; *epi*-Santalene; β –Farnesene; α –Humulene; Isolongifolene, 4,5-dehydro; β-Guaiene; Cuparene; Isocaryophyllene; β-silene; α –Selinene; α –Himachalene; Isolongifolene, 4,5,9,10-dehydro; β –Chamigrene; Karyophylline oxide; Diepicedrene-1-oxide; Aroomendene oxide- (2); α -Elemene; Longipinocarveol, *trans*; Ledeno (II); τ –Himachalene; Unidentified sesquiterpene; (-) - spathulenol; Methyl ester of dehydroabetic acid; Abietic acid, methyl ester. Total: (44)	α –Bergamotene (48.4 %), α –Himachalene (11.2 %).	Gelmini et al., 2013
Resin	Crato-CE (Northeast)	β -elemene, β-Caryophyllene, γ -elemene, α -guaiene, α -humulene, γ -muurolene, germacrene D, β -selinene, α - selinene, cadinene, cubebene, seline-3.7 (11) diene, germacrene B Total: (13)	β-Caryophyllene (53.3 %)	Gramosa and Silveira, 2005
Root	Crato-CE (Northeast)	β -elemene, β-Caryophyllene, α -humulene, γ -muurolene, β -selinene, α - selinene, β -guaiene *, seline-3.7 (11) diene, elemol, Caryophyllene oxide, 4-α-copaenol , carotol, γ-eudesmol, *epi*- α-cadinol, selin-3,11-dien-6 α -ol, kaurene Total: (16)	Caryophyllene oxide (40.5 %), 4-α-copaenol (17.6 %)	Gramosa and Silveira, 2005
Stem inner bark	Crato-CE (Northeast)	β- Caryophyllene, γ-muurolene, γ-kadinene, Caryophyllene oxide, carotol, *epi*- α-cadinol, α-muurolol, kauren, kaurenal Total: (9)	Caryophyllene oxide (31.0 %), Kaurene (30.2 %)	Gramosa and Silveira, 2005
Fruit (pericarp)	Botucatu, SP (Southeast)	δ-elemene (hs), α-copaene (hs), β-cubebene (hs), β-elemene (hs), *trans*- Caryophyllene (hs), α-humulene (hs), seychellene (hs), γ-muurolene (hs), germacrene D (hs), bicyclogermacrene (hs), α-muurolene (hs), germacrene A (hs), γ-cadinene (hs), δ-cadinene (hs), elemol (os), germacrene B (hs), spathulenol (os), Caryophyllene oxide (os), guaiol (os), bulnesol (os) Total: (20)	Germacrene D (51.1 %), bicyclogermacrene (12.2 %), *trans*-Caryophyllene (8.3 %) and δ -elemene (9.3 %)	Portella et al., 2015
Fruit (pericarp)	Lavras – MG (Southeast)	Methyl geranate, δ-elemene, α-cubebene, Cyclosativene, α -ylangene, α-cupene, β-cubebene, β -elemene, Cyperene, (E) -Caryophyllene, β -copaene, γ -elemene, *Trans*– α -bergamotene , Aromadendrene, Guayana-6,9-diene, α-humulene, allo-aromadendrene, γ-muurolene, Germacrene D, β -selinene, *cis*– β -guaiene, Bicyclogermacrene, α -muurolene, γ -cadinene, δ -cadinene, *trans*-cadina-1,4-diene, α-cadinene, α-copen-11-ol, α-calacorene, Elemol, Germacrene B, (E) -nerolidol, β-	iso-spathulenol (10.6 %), Spathulenol (10.2 %)	Nascimento et al., 2012

		calcacorene, Spathulenol, Caryophyllene oxide, Salvial-4 (14) -en-1-one, Ledol, Humulene epoxide II, iso-spathulenol, *epi*– α-muurolol, α-cadinol, *cis*-calamenen-10-ol, Mustakone, Eudesma-4 (15), 7-dien- 1 β -ol, nor-calamenen-10-one, Opoplanone, 14-hydroxy- α-muurolene, Kaurene, Kaurenal Total: (50)		
Fruit (pericarp)	Crato-CE (Northeast)	p-cymene, camphor, δ -elemene, α-cubebene, α-cepene, β -elemene, β – Caryophyllene, β -gurjunene, γ -elemene, *trans*-α-bergamotene, α -humulene, γ -muurolene, selinene, α-muurolene, *cis*-calamenene, γ-cadinene, cadinene, germacrene B, Caryophyllene oxide, guaiol, β-eudesmol, β-bisabolol Total: (22)	γ –muurolene (29.8 %), β – Caryophyllene (14.8 %)	Gramosa and Silveira, 2005
Fruit peel	Crato-CE (Northeast)	β- Caryophyllene, α -humulene, γ-muurolene, β -selinene γ-cadinene, Caryophyllene oxide Total: (6)	Caryophyllene oxide (47.3 %)	Gramosa and Silveira, 2005
Branch	Lavras – MG (Southeast)	Methyl geranate, δ -elemene, α -cubebene, α -ylangene, α -copaene, β -cubebene, β -elemene, Cyperene, (Z) - Caryophyllene, (E) – Caryophyllene, β -copaene, γ -elemene, *Trans* - α -bergamotene, Aromadendrene, Guayana-6,9-diene, α -humulene, allo-aromadendrene, *cis*-cadina-1 (6), 4-diene, γ -mururene, Germacrene D, *cis*– β -guaiene, Bicyclogermacrene , α-muurolene, δ -amorphene, γ-cadinene, *trans*-calamenene, δ-cadinene, *trans*-cadina-1,4-diene, α-cadadene, α-copopa-11-ol, Elemol, Germacrene B, (E) -nerolidol, Spathulenol, Caryophyllene oxide, Viridiflorol, Salvial-4 (14) -en-1-one, Guaiol, Ledol, Humulene epoxide II, Junenol, Dillapiole, 1-*epi*-cubenol, iso-spathulenol, Caryophylla-4 (12), 8 (13) -dien-5-ol, *epi*– α-muurolol, α-muurolol, α-cadinol, Mustakone, Eudesma-4 (15), 7-dien-1 β -ol, 14-hydroxy- α -muurolene, (2E, 6E) -methyl farnesoate, 14-hydroxy- δ -cadinene, Kaurene, Kaurenal, Kaurenol Total: (58)	β-Caryophyllene, Caryophyllene oxide, germacrene D	Nascimento et al., 2012

Mass basis (wt.%)

Table 4: Exclusive compounds from different parts of *Copaifera langsdorffii* Desf.

Part of the plant studied	Amount of compounds	Chemical compounds
Resin	59	δ-selinene, cuparene, aristolene, cycloisativene, α-ialangene, valencene, α-bergamontene, 3.7 (11) selinadiene, α-guaiene, α-selimene, δ-guaiene, β-bisabolene, caur-16-eno, junipene, δ-muurulene, α-selina-4 (19) 11-diene, humuladienone, kuran-18-al, aromadendrene oxide,

		patchulan, *cis*- Caryophyllene, aromadendrene epoxide, kurene-16-ene, (+) - cyclosactene, β-farnesene, α- Caryophyllene, τ-muurolene, τ-gurjenene, β-chamigreno, β-sesquipelelleno, α-curcumene, α-cedrene, β-cedrene, α-hymachalene, 3-Octene (Z), 3-octene (E), 4-octene (Z), abietic acid, τ - Gurjunene, α-farnesene, Di-*epi*- α-cirrrene, α-longipinene, α-santalene, cedrene, Bergamotol Z-α-*trans*, *epi*- Santalene, isolongifolene, 4,5-dehydro, Isocaryophyllene, isolongifolene, 4,5,9,10-dehydro, diepicedrene-1-oxide, aromendene- (2) oxide, α-elemene, *trans* longipinocarveol, ledene acid (II), τ-himachalene, methyl ester of dehydroabetic acid, β-silene, and methyl ester
Leaf	10	γ-gurjunene, α-thujene (m), o-cymene (m), (Z) -β-ocimene (m), (E) -β-Ocimene (m), γ-terpinene (m), terpinolene (m), viridiflorene, palustrol and (E, E) -geranyl linalool
Fruit (pericarp)	9	β-calacorene, cyclosativene, *cis*-calamenene-10-ol, nor-calamenen-10-one, opoplanone, 14-hydroxy-kaurene, α-cepaene, selinene and β –bisabolol
Branch	8	(Z) – Caryophyllene, *cis*-cadina-1 (6), 4-diene, δ-amorphene, dillapiole, 8 (13) -dien-5-ol, 14-hydroxy-α-muurolene, 14-hydroxy-δ- cadinene, kaurenol and eudesma-4 (15), 7-dien-1 β –ol
Root	3	4-α-copaenol, γ-eudesmol and selin-3,11-dien-6 α-ol

3.2.1 Resin-oil

Out of 277 compounds already identified in *C. langsdorffii* individuals, 80 are present in its oil-resin, 58 of which are exclusive to this exudate (Table 2). A range of 14 to 53 constituents were recorded in the different studies developed with the crude resin of this species. Of the 277 compounds already registered for *C. langsdorffii*, 80 are present in its oil-resin, 58 of which are unique to this exudate (Table 2).

So far three works have been carried out with this exudate (ESTEVÃO et al., 2013; GELMINI et al., 2013; ZIMMERMAM-FRANCO et al., 2013), recording a total of 80 compounds. The Amazon (Northern region) had a richer composition, with 53 compounds (GELMINI et al., 2013). For the Southeast region, 14 compounds were registered in Belo Horizonte (Zimmermam-Franco et al., 2013) and 16 in Patos (Estevão et al., 2013), both in Minas Gerais. The compounds of *C. langsdorffii* may vary within the same region as well as between regions. Copalic acid was present for both regions (Table 2). And within the same region, the variation of compounds is notable; for example, only α-copene, β-caryophyllene and γ-muurolene were common in the two areas of the Southeast region. Thus, it is observed that there is great variation in the chemical composition both between different regions and within the same region for the crude resin of this species. The variability in chemical composition between regions can be explained by the need for plants to synthesize certain constituents in response to environmental factors and their need for survival (RIBEIRO et al., 2020). It is worth noting that the high biological diversity of the Amazon is directly proportional to the chemical diversity of this region, suggesting a greater possibility that this forest contains compounds with therapeutic activity (SUFFREDINI; DALY, 2001). In addition, the synthesis of secondary metabolites varies according to the age of the plants, reproductive status and performance of phytohormones, and these would be influenced by the circadian cycles of the plants, directly interfering in the quantity and quality of the compounds (CASTRO et al., 2010; CHAGAS et al., 2011; GOBBO-NETO; LOPES, 2007a; NASCIMENTO et al., 2007).

The main compounds found in the resin-oil of *C. langsdorffii* were the sesquiterpenes, β-caryophyllene (31.4 %) (ZIMMERMAM-FRANCO et al., 2013), methyl 9-octadecenoate (26,5 %) (ESTEVÃO et al., 2013), γ-muurolene (16.1 % a 22,7 %) (ESTEVÃO et al., 2013; ZIMMERMAM-FRANCO et al., 2013), bergamotene (10.2 %) (ZIMMERMAM-FRANCO et al., 2013), and the diterpene copalic acid (22.2 %) (GELMINI et al., 2013), considered as the majority (Table 3). Among these constituents, β-caryophyllene and copalic acid are used as chemical markers of the resin-oil of this species (LEANDRO et al., 2012; OLIVEIRA; LAMEIRA; ZOGHBI, 2006; VEIGA JUNIOR; PINTO, 2002). Caryophyllane sesquiterpenes are natural substances widely occurring in nature, especially in plants, although further structures have been highlighted in marine species and fungi (CHUANG et al., 2007; SOTTO et al., 2020). In plants, they occur usually as mixtures of different sesquiterpenes, mainly β-caryophyllene, β-caryophyllene oxide, α-humulene, and isocaryophyllene, with minor metabolites and are involved in biotic interactions and indirect defense against pathogens (SOTTO et al., 2020). Among these compounds, copalic acid presents proven antimicrobial (*Streptococcus salivarius, S. sobrinus, S. mutans, S. mitis, S. sanguinis, Lactobacillus casei* and *Porphyromonas gingivalis*) and antibacterial (*Porphyromonas gingivalis*) activity (SOUZA et al., 2011b). Caryophyllane sesquiterpenes from plants have attracted a great attention in the years for their biological activities, although β-caryophyllene represents the most studied compound in several preclinical models of diseases (SOTTO et al., 2020). Indeed, it has been characterized by a plethora of biological activities, among which analgesic, anti-inflammatory, antioxidant, neuroprotective, and antiproliferative were the most investigated moreover, it has been reported to affect phospholipid cooperativity and membrane permeability (SOTTO et al., 2020). These properties have provided benefits in several experimental models of disease, such as neurodegeneration, inflammation, pain, anxiety, depression, autoimmune diseases, metabolic ailments, osteoarthritis and some cancer models (SHARMA et al., 2016; SOTTO et al., 2020; WANG; MA; DU, 2018).

Despite the diversity of compounds identified in the oil-resin, there are few studies on the pharmacological capacity of this exudate and its isolated constituents, requiring the development of studies aimed at the isolation and biological testing of these substances.

3.2.2 Essential Oil

The chemical composition of the essential oil of *C. langsdorffii* showed a total of 162 compounds, ranging from six (GRAMOSA; SILVEIRA, 2005) to 58 (NASCIMENTO et al., 2012) in the analyzed studies (Table 3). The numbers vary for the different Brazilian regions: the Southeast region presents the highest amount, with 97, followed by the Northeast with 73, and the North with 39 constituents (Table 3). The Southeast and Northeast regions had a greater number of compounds identified this result can be explained by the greater amount of work carried out in these regions (nine and seven studies, respectively). Thus, it is important to develop research in other regions of Brazil. This variation in chemical composition in different regions may be related to the production of secondary metabolites in plants, which may occur as a function of variables related to the plant itself (physiology, genetics) and external factors such as climatic (temperature, incidence of solar radiation, relative humidity, rainfall, wind, time of year) and soil (micro and macronutrients). According to Chagas et al. (2011), Brazil, due to its large territorial extension, has climatic and edaphic characteristics peculiar to each region, which would interfere, positively or negatively, in the development of native or introduced species, even if the conditions are similar to the place of origin (GOBBO-NETO; LOPES, 2007a; TAVEIRA et al., 2003), which ends up directly influencing the quantity and quality of the compounds (GOBBO-NETO; LOPES, 2007a).

Among the plant parts investigated for the essential oil of *C. langsdorffii*, the branch had the highest number of constituents with 58 identified compounds, followed by the fruit (50), leaves (47), resin (44), arila (22), root (16), bark (9) and fruit peel (6 (Table 3). The variation in chemical composition between different parts of the plant can probably be related to plant genetics (different populations / chemotypes) as well as to characteristics of each environment, which may present differences in biotic and abiotic factors, requiring studies that assess the chemical composition with environmental factors.

Compounds such as α-copaene, α-selinene, α-humulene, β-elemene, β-caryophyllene and caryophyllene oxide were recorded in all the articles analyzed, covering the Northeast, Southeast and North regions (Table 3). β-guaiene is present only in the Northeast and North. Five compounds were common to the Southeast and North ((+)-cyclosativene, α-bergamotene, β-farnesene, β-chamigrenene and α-himachalene). On the other hand, for the Southeast and Northeast 24 were common in these two regions (γ-elemene, γ-muurolene, γ-cadinene, germacrene D, germacrene B, aromadendrene, α-guaiene, α-amorphene, α-muurolene, α-muurolol, α-cadinol, α-cadinene, α-cubebene, α -calacorene, elemol, δ-elemene (s), δ-cadinene, β-selinene, β-bisabolene, trans-α-bergamotene, guaiol, α-guaiene, spatulenol, and kaurenal) (Table 3). The larger number of common compounds for the Southeast and Northeast regions is related to the higher number of researches developed in these regions, nine and seven, respectively. Among them, β-caryophyllene is commonly found in species of the *Copaifera* genus, such as in *C. langsdorffii* (GRAMOSA; SILVEIRA, 2005; OLIVEIRA et al., 2017); *C. duckei* (LAMEIRA et al., 2009); *C. reticulata* (ZOGHBI et al., 2009; ZOGHBI; MARTINS-DA-SILVA; TRIGO, 2009); *C. pubiflora* (ZOGHBI et al., 2009; ZOGHBI; MARTINS-DA-SILVA; TRIGO, 2009) and *C. multijuga* (CASCON; GILBERT, 2000). Besides presenting biological properties β-caryophyllene is the chemical marker of the genus *Copaifera*, since it is part of the composition of all oils of this genus, even in variable concentrations (LEANDRO et al., 2012; LIMA et al., 2020; VEIGA et al., 2007). This compound has several applications in the perfume and cosmetics industries, besides contributing markedly to the woody aroma of the resin-oil, which influences the aroma of the volatile fraction (LIMA et al., 2020).

Caryophyllene oxide was present in all analyzed plant parts (8) of *C. langsdorffii* (leaf, resin, root, branch, fruit, aril, inner stem bark, fruit peel), as well as in all regions studied (Table 5). Among the 17 studies analyzed with the different plant parts, this compound was not recorded only in two works with the resin oil, developed by Alencar et al. (2015) in the Southeast, and by Gramosa and Silveira (2005) in the Northeast. Other compounds are also found in the vast majority of the studied plant parts of this species, not being recorded only in one and two parts, among them: γ-cadinene (was not present only in the root), γ-muurolene (branch), β-caryophyllene (branch and aril) and β-elemene (inner stem bark and fruit peel) (Table 5). Caryophyllene oxide was also present in all *C. multijuga* oils at relatively low concentrations (0.004 mg.mL-1 to 0.272 mg.mL-1), which is commonly expected in oils of this species (LIMA et al., 2020). Many authors relate the caryophyllene oxide concentration to the state of conservation of the oil, which is often subjected to photochemical reactions and excessive exposure to heat, but previous work suggests that the caryophyllene oxide is a result of the metabolism of the plant itself, as a defense mechanism (BARBOSA et al., 2013; CASCON; GILBERT, 2000; LIMA et al., 2020).

Table 5: Compounds present in different plant parts of the essential oil of *Copaifera langsdorffii* Desf.

Chemical compounds	**Number of plant parts**	**Part of the plant studied**
caryophyllene oxide	8	leaf, resin, root, branch, fruit, aril, inner stem bark, fruit peel
γ-cadinene	7	leaf, resin, fruit, branch, aril, fruit peel, inner stem bark
γ-muurolene	7	leaf, fruit, aril, resin, root, fruit peel, inner stem bark
β- Caryophyllene	6	leaf, resin, root, fruit, fruit peel, inner stem bark
β-elemene	6	leaf, fruit, branch, aril, resin, root
α-humulene	5	resin, root, fruit, aril, fruit peel

β-selinene	5	leaf, resin, root, fruit, fruit peel
β-cubebene; spathulenol; α-cadinol; δ-cadinene; germacrene D; germacrene B; δ-elemene; α-copaene	5	leaf, resin, fruit, branch, aril
Elemol	5	leaf, root, fruit, aril, branch
aromadendrene; allo-aromadendrene; α-cubebeno; γ-elemene	4	leaf, resin, fruit, branch
α-Muurolene	4	leaf, fruit, aril, resin
guaiol; bicyclogermacrene	4	leaf, fruit, branch, aril
trans-α-bergamotene; mustakone; (E) -nerolidol; *trans*-cadin-1,4-diene; guaia-6,9-diene; methyl geranate cyperene; humulene epoxy II; α-cadinene; *epi*-α-muurolol; (E) Caryophyllene; α-copaen-11-ol; β-copaene	3	leaf, fruit, branch
α-calacorene	3	leaf, resin, fruit
Kaurene	3	leaf, resin, branch
seychellene; *trans*-Caryophyllene (hs)	3	leaf, fruit, aril
iso-spathulenol	3	fruit, branch, resin
kaurenal; α-muurolol	3	fruit, branch, inner stem bark
α-selinene; β-guaiene	2	resin, root
α-amorphene; Cubebene	2	leaf, resin
(2E, 6E) -methyl farnesoate; Viridiflorol; Junenol; 1-*epi*-cubenol; *trans*-calamenene; α-humulene;	2	leaf, branch
cis-calamenene; β-eudesmol; p-cymene; camphor; β-gurjunene; eudesma-4 (15), 7-dien-1 β-ol	2	leaf, fruit
Cubenol	2	leaf, aril
selina-3.7 (11) diene	2	leaf, root
kaurene; carotol; *epi*-α-cadinol	2	Root and inner stem bark
bulnesol; germacrene A	2	Fruit and aril
ledol; salvial-4 (14) -en-1-one; α-ylangene; *cis*-β-guaiene	2	Fruit and branch
Cadinene	2	Resin, fruit

Some compounds were found to be exclusive to different parts of *C. langsdorffii*, among which 59 are present in the essential oil extracted from the resin, 10 from the leaves, nine from the fruits, eight from the branch and three from the roots (Table 4). The higher concentration of compounds in the essential oil extracted from the resin can be due to the large number of studies carried out with this part extracted from the plant, as it is widely used in local medicine, which leads to an increase in scientific research (LEANDRO et al., 2012; LEMOS et al., 2015; PIERI; MUSSI; MOREIRA, 2009). The presence or absence of the chemical compounds of a species in its different plant parts is likely related to the genetics of the plant, as well as the characteristics of each environment, which may present differences in biotic and abiotic factors, thus requiring studies that evaluate the chemical composition with environmental factors.

The major compounds identified varied for the different parts of the plant, with the following being observed in the leaf, germacrene D (20.5 % a 26.5 %), β-caryophyllene (12.9 % a 16.6 %), bicyclogermacrene (1.5 % a 5.8 %), spatulenol (11.4 % a 12.5), caryophyllene oxide (7.4 % a 11.2 %), α-cadinol (3.2 % a 7.9 %), γ-muurolene (25.2 %), and trans-caryophyllene (9.8 % a 13.6 %); in the resin, β-caryophyllene (21.7 % a 72.2 %), β-bisabolene (23.7 %), α-bergamotene (20.5 % a 48.4 %), and α-himachalene (11.2 %); in the aril, germacrene D (35.0 %), bicyclogermacrene (7.6 %), cubenol (5.1 %), and α-cadinol (7.4 %); in the fruit, germacrene D (51.1 %), bicyclogermacrene (12.2 %), trans-caryophyllene (8.3 %), δ-elemene (9.3 %), γ-muurolene (29.8 %), β-caryophyllene (14.8 %), iso-spathulenol (10.6 %), and Spathulenol (10.2 %); in the fruit peel, caryophyllene oxide (47.3 %); in the branch, β-caryophyllene (2.4 % a 13.9 %), caryophyllene oxide (4.9 % a 13.3 %), and germacrene D (9.4 % a 19.1 %); in the root, caryophyllene oxide (40.5 %) and 4-α-copaenol (17.6 %); and in the stem bark, caryophyllene oxide (31.0 %) and kaurene (30.2 %) (Table 3).

The sesquiterpenes germacrene D, β-caryophyllene, bicyclogermacrene, spatulenol and caryophyllene oxide are considered major compounds for different plant parts of *C. langsdorffii*. β-caryophyllene is the major compound also in other species of the genus *Copaifera*: in *C. duckei* (13.0 % a 61.8 %) (LAMEIRA et al., 2009); *C. reticulata* (1.4 % a 68.0 %) (SANTOS et al., 2008; ZOGHBI et al., 2009); *C. pubiflora* (65.9 %) (ZOGHBI; MARTINS-DA-SILVA; TRIGO, 2009); and *C. multijuga* (8.8 % a 19.1 %) (CASCON; GILBERT, 2000).

3.2.2.1 Essential oil yield

A range of 0.008 % o 7.3 % was recorded for the yield of several parts of an individual (resin, leaves, root bark, fruit peel, stem bark, trunk wood, root wood, and fruit) *of C. langsdorffii* (GRAMOSA; SILVEIRA, 2005); as well as a range of 0.05 % to 2.33 % for the average yield of parts (leaves, branches, pericarp, and seeds) of five individuals (NASCIMENTO et al., 2012). Thus, we can note that both different parts of the same individual and different individuals have variation in yield.

In addition, seasonality also influences the yield of the essential oils of this species. It was observed that both the resin-oil and the leaves present a higher yield in the rainy season (28.8 % and 28.3 % in Oliveira et al., 2017; 0.4 % and 0.6 % in Almeida et al., 2014) compared to the dry (5.1 % and 2.1 % in Oliveira et al., 2017; 0.3 % and 0.5 % in Almeida et al., 2014). The reduced yield of essential oils during the dry season may occur due to the natural source-drainage mechanism, which is the degradation of secondary metabolites for the maintenance of primary metabolism (DURSUN et al., 2009).

The location and forest type can also have an influence on yield. The Semidecidual Seasonal Forest presents a variation of 0.4 % to 0.3 %, while for the Cerrado *sensu stricto* it ranges from 0.6 % to 0.5 % (ALMEIDA et al., 2014). The study of the essential oil characteristics of *C. langsdorffii* leaves has ecological and physiological significance, as the volatile compounds of secondary metabolism can present allelopathic potentials and can help us to understand the dynamics of *C. langsdorffii* in different forest formations (ALMEIDA et al., 2014). Different environmental conditions seem to be another determining factor for changing the nature and content of the chemical compounds of *C. langsdorffii* essential oils (OLIVEIRA et al., 2017). Not only in the case of volatile secondary metabolites, but the metabolism is generally associated with the adaptation of the plant to the environment (VALENTINI et al., 2010b).

3.2.3 Extract

The chemical composition of the extract of *C. langsdorffii* presented a total of 62 constituents, ranging from three to 22 in the analyzed works, extracted with 10 different solvents, being the methanolic extract from leaves (COSTA et al., 2015), chloroform and fixed oil from seeds (LIMA NETO; GRAMOSA; SILVEIRA, 2008; STUPP et al., 2008) and aqueous, ethanolic, hydrochloric acid, acetic acid, hydrogen peroxide solution, hexanic and ethyl acetate from stem bark (CARMO et al., 2016; LISBOA et al., 2018; VEIGA JUNIOR; PINTO, 2006) (Table 6). The numbers varied according to the different Brazilian regions, with the Southeast region presenting the greatest amount, with 28 compounds, followed by the Central-West with 25, and the Northeast with 11 (Table 6). Considering the lack of research (6 to this date) with *C. langsdorffii* extract, as well as the limited number of compounds registered so far, studies with the extract of different plant parts, involving different environments and biotic and abiotic variables, are necessary in order to comprehend the real chemical composition of this species.

For the *C. langsdorffii* extract, a higher amount of compounds was recorded in the stem bark, with a variation of three to 22 compounds for the three studies analyzed, followed by the leaf with 13, recorded in only one research, and seed in two studies with eight and 11 constituents (Table 6). Except for the studies developed with the seeds, in which there was a compatibility of seven of the compounds registered, in the other plant parts, the compounds were all different, even in those developed with the same part of the plant, as in the case of the stem bark, in which the compounds were not repeated in the three studies developed with this structure. The genetics of the different populations of the plant, as well as soil and climatic factors, are probably influencing this variation.

Table 6: Chemical composition of the extract of different parts of the species *Copaifera langsdorffii* Desf.

Part of the plant studied	**Location**	**Type of extrat**	**Chemical compounds**	**Major compounds (wt. %)**	**Authors**
Leaf	Ribeirão Preto-SP (Southeast)	Methanolic	Quinic Acid, Methyl Gallate, Gallic Acid, Galoylquinic Acid with 1 Methyl, Galoylquinic Acid with 1 Methylhydrate, Di Galloylquinic Acid with 2 Methyl Groups, Quercetin, Kaempferol, Eupatorin, Quinoleyl Quinic Acid, Dimethyl Quercetine, 4-Gallic Acid , Kaurenoic acid Total: (13)	-	Costa et al., 2015
Seed	Crato-CE (Northeast)	Chloroform	octanoic (caprylic C8: 0), decanoic (capric C10: 0), hexadecanoic (palmitic C16: 0), 9,12-octadecadienic (linoleic C18: 2), 9-octadecenoic (oleic C18: 1), octadecanoic (stearic C18: 0), *cis*-11-eicosenoic (gondic C20: 1), eicosanoic (arachidic C20: 0), docosanoic (behenic C22: 0), tetracosanoic (lignoceric C24: 0), hexacosanoic (cerotic C26: 0) Total: (11)	9-Octadecenoic (C18: 1 oleic) (33.1 %), hexadecanoic (palmitic C16: 0) (22.2 %)	Lima Neto et al., 2008
Seed		Fixed oil	Palmitic acid, stearic acid, oleic acid, linoleic acid, arachidic acid, *cis*-11-eicoseneic acid, behenic acid, lignoceric acid Total: (8)	Palmitic acid (12.7 %), oleic acid (30.9 %), linoleic acid (45.3 %)	Stupp et al., 2008
Stem bark	Valparaíso-Goiás (Midwest)	Aqueous, ethanolic and hydrochloric acid	Tannins, alkaloids and flavonoids Total: (3)		Lisboa et al., 2018
Stem bark	Itauba-Mato Grosso (Midwest)	Acetic acid and hydrogen peroxide solution (1:1)	Ash (4.2 %), Total extractives (21.3 %), Dichloromethane (2.1), Ethanol (17.4 %), Water (1.8 %), Suberine (0.8 %), Total lignin (36.6 %), Klason lignin (35.3 %) Soluble Lignin (1.3 %), Glucose (66.4 %), Xylose (23.5 %), Galactose (3.3 %), Arabinose (6.0 %), Mannose (0.8 %), Calcium (1.0930 %), Potassium (0.1918 %), Sodium (0.0139 %), Magnesium (0.0451		Carmo et al., 2016

			%), Iron (0, 0023 %), Copper (0.0003 %), Zinc (0.0013 %) Manganese (0.0312 %) Total: (22)		
Stem bark	Campinas-SP (Southeast)	Hexanic and ethyl acetate	Sesquiterpenes: α-cubebene, α-copaene, β-cubebene, spathulenol and Caryophyllene oxide; sterols: campesterol, stigmasterol and β-sitosterol; triterpene: lupeol; diterpenic acids: ent-kaurenoic, copalic and collavenic; triterpene: betulinic acid Total: (15)	diterpenic acids *ent*-kaurenoic, copalic and collavenic. Triterpene betulinic acid	Veiga Junior and Pinto, 2006

The chemical composition varied for different regions of Brazil, with 28 compounds having been recorded for the Southeast region, 13 from the leaves (Costa et al., 2015) and 15 from the stem bark (Veiga Jr and Pinto, 2006), followed by the Central-West region, with 25 constituents, of which three were present in the study by Lisboa et al. (2018), and 22 in Carmo et al. (2016) developed with the stem bark, while the Northeast region had 11 compounds in a study developed with the seeds (LIMA NETO; GRAMOSA; SILVEIRA, 2008) (Table 6). An article developed by Stupp et al. (2008) with the seed did not inform the study location, and consequently was not calculated by region, which presented eight compounds. Among these, only the cis-11-eicosenoic acid did not match the compounds present in Lima Neto et al. (2008), who also worked with the seed in the Northeast region.

The major compounds identified in *C. langsdorffii* extracts were palmitic, oleic, and linoleic acids for the seeds, and ent-caurenoic, copalic, colavenic, and betulinic diterpenic acids for the the stem bark (Table 6). Among these compounds, only copalic acid is also the major compound in the crude resin-oil from this species. Diterpene acids, similar to kaurenoic acid, are considered an important part of the chemical compounds of *C. langsdorffii* (COSTA et al., 2015). Kaurenoic acid shows antimicrobial, antifungal (PADLA; SOLIS; RAGASA, 2012), anti-inflammatory (CHOI et al., 2011), vasodilatory (TIRAPELLI et al., 2004), wound healing (BALEKAR et al., 2012), anti-psoriasis (GELMINI et al., 2013), trypanocidal, cytotoxic, potent uterine contraction stimulators (BATISTA et al., 2007, 2013), and antitumor activity (CAVALCANTI et al., 2009; SOUZA; FELFILI, 2006). Moreover, karenoic acid has been used as a semi-synthesis, as well as a precursor to obtain more selective and/or more bioactive derivatives, for instance, to increase trypanomicidal activity (BATISTA et al., 2007), and even to obtain compounds with increased antiplasmodial activity (BATISTA et al., 2013).

The extract from *C. langsdorffii* seeds is composed of 43.5 % linoleic acid, 31.0 % oleic acid, and 12.7 % palmitic acid, 32.3 % monounsaturated, 45.3 % polyunsaturated, and 22.4 % saturated (Table 6). The average levels of saturated acids can be considered comparable to other vegetable oils, such as cotton, corn, soybean and sunflower, with 25.5 %, 15.8 %, 16.4 % and 10.8 % respectively (STUPP et al., 2008). Maia et al. (1978) recorded higher percentages in the composition of fatty acids in oil from *Copaifera multijuga* seeds: palmitic acid (24.9 %), oleic acid (35.3 %), linoleic acid (35.7 %), arachidic acid (1.1 %) and behenic acid (3.0 %) and 0.15 % coumarin.

Flavonoids are considered the main phenolic group in *C. langsdorffii* bark extract, with 442 mg EC/g extract, while tannins account for only 55 mg EC / g extract (Table 6). The content of phenolic compounds for *C. langsdorffi* is higher when compared to other species, although different extraction and reporting procedures make comparisons difficult (LUÍS et al., 2014; SANTOS et al., 2012; SHARMIN et al., 2014; SULTANA; ANWAR; PRZYBYLSKI, 2007; TAMOKOU et al., 2012; VÁZQUEZ et al., 2008).

3.3 Biological Activity

A total of 28 proven biological activities were recorded for *C. langsdorffii*, with the most tested being antioxidant (6), cytotoxic, anti-inflammatory and antibacterial (4 tests each) (Table 7). Different plant parts were used through extract of (leaf, seed, stem bark, fruit and flower) essential oil (resin) and crude resin to test the different properties of this species, as well as through isolated compounds (leaf: galoylquinic acid, kaurenoic acid, quercitrin, afeleline, α-humulene, β-caryophyllene and caryophyllene oxide; seed: native xyloglucan and polyphenols; resin-oil: copalic acid, kaurenoic acid, caryophyllene oxide, acetoxy-copalic acid, agactic acid, agaric acid, hydroxy-copalic acid, 3-hydroxy-copalic acid, 3-acetoxy-copalic acid, hardwickiic acid, 15-methyl kolavic ester).

Table 7: Biological activities of *Copaifera langsdorffii* Desf.

Part Used	Activities	Effect	Ref.
Leaf			
Galoylquinic acid	Gastroprotective	30 mg/kg	Motta et al., 2017
Kaurenoic acid, quercitrin, afelelin, α-humulene, β-Caryophyllene and Caryophyllene oxide	Gastroprotective	30 mg/ kg	Lemos et al., 2015
Kaurenoic acid and quercitrin	Antioxidant	EC_{50}=7,581µg/mL	Costa et al., 2015
Hydroalcoholic extract	Antioxidant	10, 20, 40 and 80 mg kg^{-1}	Alves et al., 2013
Hydroalcoholic extracts	Gastroprotective	500 mg/ kg	Lemos et al., 2015

Hydroalcoholic extract	Antimalarial	IC_{50}: 3,4 µg / mL	Sousa et al., 2012
Hydroalcoholic extract	Nephrolithiasis	0,7 and 1,0 mg / mL	Oliveira et al., 2013
Hydroalcoholic extract	Urolithiasis	20 mg / kg	Brancalion et al., 2012
Hydroalcoholic extract	Antiedematogenic	100 and 200 mg / kg	Furtado et al., 2015
Hydroalcoholic extract	Insecticide and residual	Dilution: 5 %	Barbosa et al., 2011
Methanolic extract	Antibacterial	MIC: 5 g/mL; MBC: >5 g/mL	Oliveira et al., 2007
Hydroalcoholic extract	Protective effect against colon carcinogenesis	40 and 80 mg / kg	Senedese et al., 2013
Resin			
Copalic acid and kaurenoic acid	Moderate intestinal permeability	237,4 and 154,0 µM	Mauro et al., 2019
Kaurenoic acid	Anti-inflammatory	100 mg / kg	Paiva et al., 2003
Copalic acid	Antimicrobial	7,0 mg / mL MIC: 2,0 to 6,0 mg / mL	Souza et al., 2011
Copalic acid	Antimicrobial	MIC:3,1 µg mL^{-1}	Souza et al., 2011b
Copalic acid, acetoxycopalic acid, hydroxycopalic acid and agaric acid	Antibacterial (periodontitis)	MIC: 3,1 to 400,0 µg mL^{-1}	Souza et al., 2011b
Karyophylline oxide, copalic acid, kaurenoic acid, acetoxycopalic acid, agatic acid and hydroxycopic acid	Antimicrobial	IC_{50} = 0,5 to 200,00 µg mL^{-1}	Abrão et al., 2015
Copalic acid	Antibiofilm	IC_{50} = 62,5 to 2000 µg mL^{-1}	Abrão et al., 2015
Copalic acid	Antiproliferative	IC_{50} = 44,03 µg mL^{-1}	Abrão et al., 2015
Copalic acid, 3-hydroxy-copalic, 3-acetoxy-copalic, hardwickiic, 15-methyl kolavic ester and kaurenoic acid	Cytotoxicity	IC_{50} =100 µM	Vargas et al., 2015
Kaurenoic acid	Cytotoxic	IC_{50}: 78 Mm CEM: 95,3 %; MFC-7: 47,5 %; HCT-8: 47,5 %.	Costa-Lotufo et al., 2002
Kaurenoic acid	Embryotoxic	Cleavage: IC_{50}: 84,2 mM; Blastula: IC_{50}: 44,7 mM;	Costa-Lotufo et al., 2002

		Larvae: IC_{50}: 10 mM.	
Kaurenoic acid	Uterine relaxer	IC_{50}: 0.1 mm to 1.2 mm	Cunha et al., 2003
Essential oil	Larvicide (*Aedes aegypti*)	CL_{50}: 41 Ag / l	Mendonça et al., 2005
Essential oil	Antifungal	MIC e MFC = 170 µg mL $^{-1}$; MIC = 1,360 µg mL $^{-1}$ and MFC = 2,720 µg mL $^{-1}$.	Zimmermam-Franco et al., 2013
Essential oil	Antifungal	MIC: 0,1083 and 34,7 mg / mL	Alencar et al., 2015
Essential oil	Antibacterial	MIC: 55,4 and 221,7 mg / mL	Alencar et al., 2015
Essential oil	Antiparasitic	IC_{50}:20,0 µg / mL	Albuquerque et al., 2017
Essential oil	Anti-psoriatic	IC_{50}: 8,71 mg / mL	Gelmini et al., 2013
Essential oil	Anti-inflammatory	IC_{50}: 8,71 mg / mL	Gelmini et al., 2013
Essential oil	Antioxidant	IC_{50}: 8,71 mg / mL	Gelmini et al., 2013
Crude resin-oil	Healing	MIC: 10 %	Masson-Meyers et al., 2013
Crude resin-oil	Healing	MIC: 4 %	Paiva et al., 2002
Crude resin-oil	Endometriosis	0,63 mg/ day	Nogueira Neto et al., 2011
Crude resin-oil	Antimicrobial	Concentração: 10 %.	Pieri et al., 2011
Crude resin-oil	Myeloperoxidase	200 and 400 mg / kg	Paiva et al., 2004b
Crude resin-oil	Anti-inflammatory	400mg	Silva et al., 2009
Crude resin-oil	Anti-inflammatory	200 and 400 mg / kg	Paiva et al., 2004b
Crude resin-oil	Anti-inflammatory	IC_{50}: 2,30 mg / mL	Gelmini et al., 2013
Crude resin-oil	Anti-psoriatic	IC_{50}: 2,30 mg / mL	Gelmini et al., 2013
Crude resin-oil	Antioxidant	IC_{50}: 2,30 mg / mL	Gelmini et al., 2013
Crude resin-oil	Antioxidant	400mg	Silva et al., 2009
Crude resin-oil	Antilipoperoxidation	400mg	Silva et al., 2009
Crude resin-oil	Antileishmanial	IC_{50}: 20,0 µg/mL	Santos et al., 2008
Crude resin-oil	Intestinal damage associated with mesenteric ischemia / reperfusion in rats	200 mg / kg	Paiva et al., 2004
Xyloglucan resin	Anti-psoriatic	IC_{50}: 9.23 mg / mL	Gelmini et al., 2013
Xyloglucan resin	Anti-inflammatory	IC_{50}: 9.23 mg / mL	Gelmini et al., 2013

Resin-oil ointment	Favors angiogenesis and accelerates the viability of random skin flaps in rats	Concentration: 10 %	Estevão et al., 2013
Seed			
Native xyloglucan	Cytotoxic	5 μg/ mL	Farias et al., 2019
Lyophilized cotyledons		300 μg / mL	
Polyphenols	Antioxidant	IC_{50}: 0,3–1 g l^{-1}	Batista et al., 2016
Ethanol and methanol extract		60 %: $0,5^{-3}$ gl^{-1}	
		80 %: $0,2^{-1}$ g l^{-1}	
Stem bark			
Extract	Antioxidant	IC_{50}: 3,95 μg / mL	Carmo et al., 2016
Fruit (pericarp)			
Hydroalcoholic extract	Antileishmanial	IC_{50}: 40 μg / mL	Sousa et al., 2012
Flower			
Hydroalcoholic extract	Antimalarial	IC_{50}: 6,2 μg / mL	Sousa et al., 2012
Stem bark	Toxicity	DL_{50}: > 2000 mg / kg	Lemos et al., 2015

Among the isolated compounds, the compounds with the most proven pharmacological properties were kaurenoic acid (antioxidant, gastroprotective, antibacterial, antibiofilm, antiproliferative, cytotoxic, embryotoxic, anti-inflammatory, and uterine relaxant), and copalic acid (antibacterial, antibiofilm, antiproliferative, antimicrobial, and cytotoxic) (Table 7).

Research on the pharmacological properties of *C. langsdorffii* is concentrated in the Southeast region (17), however, it is also observed, in a smaller frequency, in the Northeast (8), North (4) and Central-West (1) (Table 7). Some studies (8) have made use of commercial samples, and it was not possible to detect their origins.

The antioxidant activity is the most studied; it presents pharmacological confirmation through the extract of the leaves and stem bark, the crude resin and its essential oil, and through compounds isolated from the seed extract, such as Polyphenols (Table 7). The resin-oil (IC_{50} 2.30 mg/ml) exhibits better results for this activity compared to its essential oil (IC_{50} 8.71 mg/ml) in *in vitro* assays (GELMINI et al., 2013) (Table 7). As for the fruits, the ethanolic extract was found to be more efficient compared to the methanolic extract in *in vivo* assays (Table 7) (BATISTA et al., 2016). The antioxidant activity, conferred to both the fruit and the stem barks of this species, is probably related to the presence of polyphenols high levels (gallic acid), and this effect may also be related to the presence of flavonoids (isoquercitrin) and tannins (epicatechin gallate, procyanidins, catechin, and epicatechin), present in smaller amounts in these plant parts (Table 7) (BATISTA et al., 2016; CARMO et al., 2016). For the hydroalcoholic extract of the leaves, the antioxidant effect tested *in vivo* is related to the presence of quercitrin and afzelin, present as the main representatives in its composition (Table 7) (ALVES et al., 2013b).

Quercitrin and afzelin belong to the flavonols group (HERTOG; HOLLMAN; PUTTE, 1993), and they have been recognized as the most effective antioxidants among the flavonoids (MELLO; GUERRA, 2002). The antioxidant activity of flavonoids derives from their ability to capture free radicals by acting as a hydrogen donor, which reduces potential occurrences of chronic degenerative diseases (ALONSO; GONZALO, 2002; RICE-EVANS; MILLER; PAGANGA, 1996). Gallic acid, on the other hand, besides the antioxidant activity, is also related to neuroprotective (MANSOURI et al., 2013), anticarcinogenic, antimutagenic, and anti-inflammatory activities (VERMA; SINGH; MISHRA, 2013). Catechins have been associated with anticancer, anti-inflammatory, anti-diabetic, anti-obesity, and neuroprotective effects (BRAICU et al., 2013; WILLIAMS; SPENCER, 2012; ZAVERI, 2006). Isoquercitrin is related to functional effects, such as antioxidant, antitumor, anti-inflammatory, and it is used against diabetes and cardiovascular disorders as well (VALENTOVÁ et al., 2014).

The antimicrobial activity is an important property attributed to the *C. langsdorffii* species, which has been proven by studies with different bacterial and fungal strains through the hydroalcoholic extract of the leaves, crude resin-oil, essential oil (resin), and compounds isolated from the resin (caryophyllene oxide, copalic acid, kaurenoic acid, acetoxycopalic acid, agactic acid, and hydroxycopalic acid) (Table 7). The resin-oil of *C. langsdorffii* at 10% in *in vitro* tests inhibited the growth of eight *Escherichia coli* strains obtained from mastitic milk (Table 7) (PIERI et al., 2011). In contrast, the essential oil from the resin of this species shows, *in vitro*, an effect against bacterial and fungal strains of the genera *Staphylococcus, Pseudomonas, Candida* and *Trichophyton* (Table 7) (ALENCAR et al., 2015; ZIMMERMAM-FRANCO et al., 2013). Isolated compounds from the resin, such as caryophyllene oxide, copalic acid, kaurenoic acid, acetoxycalic acid, agacic acid, and hydroxycalic acid, exhibited antibacterial effect *in vitro*, with copalic acid also showing antibiofilm, and antiproliferative activity (Table 7) (ABRÃO et al., 2015; SOUZA et al., 2011b). For the hydroalcoholic extract of *C. langsdorffii* leaves, *in vitro*, significant antimicrobial action was observed against *Aeromonas hydrophila*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* with MIC values ranging from 0.625 to 5.000 mg / ml (Table 7) (OLIVEIRA et al., 2007).

The antibacterial and antifungal activity conferred to *C. langsdorffii* essential oil may be related to the presence of high concentrations of sesquiterpenes, such as β-caryophyllene and α-hialchalene (ALENCAR et al., 2015). On the other hand, copalic acid is an important compound for the development of new selective antimicrobial agents to treat infections caused by microorganisms (ABRÃO et al., 2015). The elucidation of the compounds that have antimicrobial activity is a fundamental step in the progress of the studies, emphasizing the possibility of performing tests that can demonstrate the ability of these compounds to enhance the therapeutic effect of established drugs, and acting as adjuvants against multidrug-resistant strains or even being used as active agents for new formulations based on natural products.

The anti-inflammatory activity of *C. langsdorffii* has been confirmed using the crude resin-oil (GELMINI et al., 2013; PAIVA et al., 2004a; SILVA et al., 2009), and the kaurenoic acid (PAIVA et al., 2003) isolated from this exudate (Table 7). The resin-oil has been observed to have a protective action in *in vivo* tests against induced injury, both in intestinal tissue and colon tissues. Thereby, it reduces levels of myeloperoxidase and malonaldehyde (Table 7) (PAIVA et al., 2004a). Furthermore, this resin employed on human THP-1 monocytes reduced the release of pro-inflammatory cytokines (IL-1β, IL-6, TNFα) over a dose range of 0.1 to 10 μM in *in vivo* tests (Table 7) (GELMINI et al., 2013). The diterpene caurenoic acid, isolated from the resin-oil of this species, in *in vivo* tests, reduced the inflammatory process induced by acetic acid, showing a remarkable reduction in the gross damage score (52 % and 42 %) and in the wet weight of the damaged colon tissue (39 % and 32 %), respectively, by oral and rectal routes (Table 7) (PAIVA et al., 2003). The anti-inflammatory action of *C. langsdorffii* resin-oil is probably due to the presence of sesquiterpenes and diterpenes in its composition.

The cytotoxicity of *C. langsdorffii* was tested using the leaf extract, the xyloglucans from the seeds, and the kaurenoic acid isolated from the resin (Table 7). It was found that kaurenoic acid at 78 μM in *in vitro* tests produced 95 % growth inhibition of leukemic CEM cells and 4 5% inhibition of MCF-7 (human breast) and HCT-8 (human colon) cancer cells (Table 7) (COSTA-LOTUFO et al., 2002). This diterpene also inhibited approximately 28 % of tumor cells of the AGP01 (gastric) lineage and viability of SF295 (human glioblastoma) after 72 h of exposure to 20 µmol / L in *in vitro* tests (Table 7) (VARGAS et al., 2015). For Xyloglucan extracted from the cotyledons of the seeds, tested against murine melanoma cells (B16F10), it was found that after 24 h of treatment the lowest concentration (5 µg / mL) promoted a reduction of approximately 20% in cell viability, while at the highest concentration (300 µg / mL) the reduction was about 48% in *in vitro* tests (Table 7) (FARIAS et al., 2019). However, in *in vivo* tests, the hydroalcoholic extract of *C. langsdorffii* combined with 1,2-dimethylhydrazine (DMH), a colon carcinogen, shows protective effect against colon carcinogenesis; possibly this effect is related to the presence of the flavonols quercetin-3-O-α-L-rhamnopyranoside 1 and kaempferol-3-O-α-L-rhamnopyranoside 2 present as major compounds in this extract (Table 7) (SENEDESE et al., 2013).

One of the most traditional uses for the resin-oil of *C. langsdorffii* is as a wound-healing agent (Table 1). However, there are few scientific reports that corroborate the efficacy of this species regarding this activity. The crude resin-oil at 4% (PAIVA et al., 2002), and the cream-based resin-oil at 10% (MASSON-MEYERS et al., 2013), were found to significantly accelerate the wound healing process in rats (wistar) and rabbits, respectively, in *in vivo* treatment (Table 7). Despite the promising effects regarding the use of *C. langsdorffii* resin-oil as a healing agent, the lack of a positive control makes it difficult to evaluate the real potential of this species as a natural wound-healing product (ARRUDA et al., 2019).

Besides the few research studies on the healing activity for this species, and the lack of positive controls, the mode of action has not yet been elucidated, although some authors have reported increased vascularization, and increased fibroblast production, which may contribute to this effect (SILVA et al., 2009). Therefore, only after further studies approaching these and other pharmacological information will the traditional use of *C. langsdorffii* as a healing agent be validated. In this sense, studies that can complement the explored mechanisms and corroborate the already established studies are necessary, using comparative quality controls, as well as trials that can demonstrate possible side effects and / or pharmacological interactions for the development of the investigations with the resin-oil.

The alcoholic leaf extract of *C. langsdorffii*, in *in vivo* tests, exhibits insecticidal effect towards *Bemisia tabaci* and *E. kuehniella* (BARBOSA et al., 2011), while its resin-oil shows both insecticidal and larvicidal effect against *Aedes aegypti* L. (MENDONÇA et al., 2005) (Table 7). The insecticidal effect of the leaf extract of this species is probably related to the presence of coumarin in its composition (VEIGA JUNIOR; PINTO, 2002).

The antimalarial activity of *C. langsdorffii* was verified in *in vitro* tests through the resin-oil and extract of the leaves, flowers and fruits (Table 7). For the extract of its leaves and flowers, it exhibited activity with IC_{50} of 3.4 and 6.2 µg / mL, respectively, for different *Plasmodium falciparum* clones (Table 7) (SOUSA et al., 2012). The fruit extract shows antileishmanial activity against *Leishmania donovani*, with IC50 of 40 µg / mL (SOUSA et al., 2012), while the oil-resin shows activity against *Leishmania amazonenses*, with IC_{50} of 20.0 ± 0.8 µg / mL (Table 7) (SANTOS et al., 2008). Compounds such as kaurenoic acid and β-caryophyllene, which are found in the leaves, flowers, fruits and resin-oil, are probably responsible for observed antiparasitic activities (SANTOS et al., 2008; SOUSA et al., 2012). Considering that the resin-oil is a natural product, and has a biological effect similar to a reference drug on the market, it may be a future new herbal medicine for the treatment of leishmaniasis after further drug development studies (ARRUDA et al., 2019).

The gastroprotective activity of *C. langsdorffii* was proven in *in vivo* tests using the crude hydroalcoholic extract and compounds isolated from the leaves (Table 7). Both the crude extract (LEMOS et al., 2015) and isolated compounds such as kaurenoic acid, quercitrin, afeleline, α-humulene, β-caryophyllene, caryophyllene oxide (LEMOS et al., 2015) and galloilquinic acid (MOTTA et al., 2017) isolated from the leaf extract were efficient in ethanol / HCl induced ulcer model (Table 7). The results obtained suggest that the observed action is due to the decrease of gastric acidity, probably by promoting the secretion of gastric mucus and bicarbonate (PAIVA et al., 1998). Literature data show that the compounds quercitrin, caryophyllene oxide and α-humulene are present in the chemical composition of extracts and essential oils with gastroprotective activity (ESTEVES et al., 2005; LIMA et al., 2012; ZAKARIA et al., 2014). Terpenes and flavonoids show protective effects on gastric ulcer, and their activities are associated with cytoprotective mechanisms (HIRUMA-LIMA et al., 2006; KLEIN-JÚNIOR et al., 2012; SANTIN et al., 2014; SIQUEIRA et al., 2012).

The extract of *C. langsdorffii* leaves, in *in vivo* tests, shows significant effect for urolithiasis, since it decreases the number of stones formed, and reduces the pressure required to break the stones, with an increase in Mg and P levels and decrease in uric acid levels being verified (BRANCALION et al., 2012); moreover, also in *in vivo* trials, it has a prophylactic potential in preventing the formation of kidney stones, with 100% inhibition of crystal formation for all doses tested, as well as for crystal dissolution with doses of 0.7 (79.7 % dissolution) and 1.0 mg / mL (100 % dissolution) (Table 7) (OLIVEIRA et al., 2013). The increase in Mg concentration plays an important role in stone formation and hardness, while the decrease in uric acid may indicate a potential for this extract in the treatment of uric acid-formed stones (BRANCALION et al., 2012).

The resin-oil was tested to treat endometriosis *in vivo*, and it was found that at daily doses of 0.63 mg, 55 % of the rats had a well-preserved epithelial layer, and 45 % had slightly preserved epithelium, showing a strong reduction in endometrial growth, from 47.00 mm^3 to 23.38 mm^3 ($p=0.016$) (Table 7) (NOGUEIRA NETO et al., 2011). On the other hand, the caurenoic acid, isolated from this resin, was tested *in vitro* in the uterus of rats to verify if it presents a relaxing effect on smooth muscle, revealing that this diterpene in the concentration of 160 µM inhibits the contraction induced by CaCl2, while in concentrations ranging from 0, 1 mm to 1.2 mm significantly inhibits tonic contraction induced by oxytocin and acetylcholine (83 % and 91 % respectively), acting mainly through calcium blockade and partly by opening ATP-sensitive potassium channels (Table 7) (CUNHA et al., 2003).

Thus, considering the properties reported by communities, as well as the diverse chemical composition of *C. langsdorffii*, the isolation of compounds from its different plant parts for pharmacological tests is needed in order to prove its therapeutic properties.

4. Conclusion

The growing interest in the species *Copaifera langsdorffii* Desf. by communities for medicinal use is possibly associated with its wide distribution and its pharmacological potential for numerous phytotherapeutic activities, especially as a wound healing and anti-inflammatory agent. *C. langsdorffii* is often indicated in communities to treat rheumatism, bone fracture, epilepsy, and depression; however, so far no pharmacological studies have been developed to confirm its efficacy**,** thus needing to test this action *in vivo* and *in vitro* to detect which compounds are contributing to this effect.

The chemical composition of *C. langsdorffii* is quite varied, observing that there is great variation both between the essential oil, extract, and crude resin, and between the different plant parts and the same part analyzed in different environments. Compounds such as α-cubebene, α-copaene, and spathulenol can be found in the essential oil, extract, and crude resin of this plant. Therefore, the isolation of these compounds, with *in vitro* and *in vivo* tests, is necessary to determine their pharmacological potential, since they are constituents with great relevance for being present in different plant structures of *C. langsdorffii*.

There is a lack of research on the chemical composition of the *C. langsdorffii* extract, as well as a reduced number of compounds registered so far for this exudate, hence studies with different plant parts are necessary as a way to register the chemical composition of these extracts.

Some biological activities have been proven for this species, with the most studied being antioxidant, cytotoxic, anti-inflammatory, and antibacterial, and where its action is related mainly to the presence of the kaurenoic and copalic acids in its composition.

A more extensive biological investigation, besides the characterization and isolation of compounds, is necessary in view of the promising biological activities already presented by *C. langsdorffii*, which can determine the role of each compound regarding the pharmacological potential, subsidize the development of new drugs, as well as validate the traditional medicinal use of this species.

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4. CAPÍTULO 3: Artigo II

Título: Consensus of the medicinal use of *Copaifera langsdorfflii* Desf. in different phytophysiognomies

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Consensus of the medicinal use of *Copaifera langsdorfflii* Desf. in different phytophysiognomies

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ABSTRACT

This study had as its objective to carry out an ethnobotanical survey of *C. langsdorffii* in Cerradão, Carrasco, Humid Forest and Caatinga phytophysiognomies in the Chapada do Araripe, Northeast Brazil, with a standardized form. Semi-structured interviews and the snowball technique were used. Usage diversity, plant part consensus and level of fidelity were analyzed to verify the consensus of the usage categories, plant part and indicated diseases. 61 therapeutic indications were cited for Cerradão (38), Caatinga (33), Humid Forest (20) and Carrasco (15), with cicatrizing, rheumatic arthritis, bone pain, back problems and throat inflammation being the most cited. Despite Cerradão and Caatinga registering a greater number of therapeutic indications, their general level of fidelity was low, ranging from 3.57 to 25 and 4.35 to 26.09, respectively. Of the 13 registered categories, musculoskeletal and skin were the categories with the highest usage diversity values among the studied phytophysiognomies. The data obtained for *C. langsdorffii* emphasize its therapeutic potential and the need for studies that evaluate medicinal species as a source of biologically active natural products, contributing to the search and development of new drugs.

Keywords: *Copaifera langsdorffii*, Different phytophysiognomies, Informant consensus, Therapeutic indications, Chapada do Araripe

1 INTRODUCTION

The systematic search for substances with medicinal potential has been performed using several approaches, allowing the selection of plants that represent an effective alternative for obtaining new bioactive compounds and consequently new medicines (Nascimento *et al*. 2014; Verma & Shukla 2015). Traditional knowledge as a strategy for selecting plants and their therapeutic treatments opens up several options for data analysis by ordering species and prioritizing a set of plants for further study (Araújo *et al*. 2008; Brito *et al*. 2015).

It should be taken into account that over time the knowledge and use of medicinal plants by traditional communities can be lost, as can be seen in Reyes-García et al. (2013) in an analysis of a subsample of people interviewed twice, which indicated that under rapidly changing socioeconomic, political, and environmental conditions, cultural loss can occur within a single generation, and not only during the transmission process (Reyes-Garcia *et al*. 2013), since one generation forgets to pass on knowledge to the next generation (Aunger 2000; Casagrande 2002; Gomez-Baggethun *et al*. 2010; Reyes-García *et al*. 2009). Reyes-Garcia *et al*. (2013) suggests that contemporary indigenous societies may be abandoning their traditional knowledge because they perceive that this form of knowledge does not prepare them well to deal with the new socioeconomic and cultural conditions they currently face.

On the other hand, investigations on medicinal plants and their uses have been the subject of studies in different geographical regions. Ethnobiological studies carried out in different plant formations in Brazil are promising instruments for the discovery of new drugs, since Brazil has high biodiversity and endemism associated with a considerable wealth of knowledge regarding its flora (Kong *et al*. 2009; Alves & Nascimento 2010).

Several medicinal plant studies have been carried out in different Brazilian ecosystems, with 10 to 142 species for the Cerrado vegetation (Ustulin *et al*. 2009; Moreira & Guarim-Neto 2009), 51 to 98 for the Atlantic Forest (Pinto *et al*. 2006; Ranchi *et al*. 2016), 18 to 62 for Caatinga (Gomes *et al*. 2008; Roque *et al*. 2010), and 31 to 35 for Carrasco (Souza *et al*. 2014; Chaves 2005) being registered so far, demonstrating that local communities know and use a great variety of plants, as well as their different forms of preparation and administration.

Some species have a wide distribution, meaning that they can be found in different regions and vegetation types. Knowing that factors such as cultural, chemosensory aspects, environmental resource availability, accessibility and effectiveness have been reported as important in the selection of medicinal plants and their uses in medical systems over time (Phillips & Gentry 1993; Stepp & Moerman 2001; Geck *et al*. 2017; Albuquerque & Alves 2018; Ferreira Júnior & Albuquerque 2018), the therapeutic indications of a species can be expected to vary in different ecosystems. Moreover, the use of a given species by communities from different phytophysiognomies to treat specific diseases is associated with their chemical composition (Endara & Coley 2011), which can vary for the same species when analyzed in different ecosystems. This qualitative and quantitative variation in plant secondary metabolism can be influenced by ecogeographical variations (for example, variations between ecosystems) such as light intensity, water and carbon-nitrogen availability (Herms & Mattson 1992; Barone & Coley 2002).

Copaifera langsdorffii Desf., which can be found from Northeast Argentina to Venezuela (Almeida *et al*. 1998; Lorenzi 2000), shows a wide distribution and can, for example, be highlighted. In Brazil *C. langsdorffii* Desf. naturally extends to the Northeast, North, Midwest, Southeast and South regions, and can be found in different phytophysiognomies, such as Campo Rupestre, Cerrado (*lato sensu*), Ciliary or Gallery Forest, Terra Firme Forest, Semideciduous Seasonal Forest and Rainforest, as well as in anthropized areas (Costa 2018).

In the Chapada do Araripe region, *C. langsdorffii* can be found in Cerradão, Carrasco and Humid Forest phytophysiognomies (Santos *et al*. 2019; Saraiva *et al*. 2015; Ribeiro *et al*. 2014; Cartaxo *et al*. 2010). This species has great medicinal potential and importance for communities and is indicated for the treatment of several diseases (Veiga Junior & Pinto 2002; Pasa *et al*. 2005; Saraiva *et al*. 2015; Ribeiro *et al*. 2014; Macêdo *et al*. 2018). Differences in chemical composition as a function of geographic location have been reported for different species, including *C. langsdorffii* (Almeida *et al*. 2014; Oliveira *et al*. 2017). In a review of *C. langsdorffii* Santos *et al*. (2022) found that there is variation between different Brazilian regions, both in relation to diseases, body systems, parts used, preparation and form of administration, as well as in relation to chemical composition. This shows the great variability in the use of *C. langsdorffii* and the specificities of each region.

Given that each region and vegetation formation has its specific characteristics and, consequently, culture, different behaviors may influence the type of therapeutic indications, as well as the used parts, forms of preparation, etc. Thus, the present study was carried out to verify the number of therapeutic indications in different phytophysiognomies (Cerradão, Carrasco, Humid Forest and Caatinga) and to evaluate the usage agreement/informant's knowledge on therapeutic indications in communities from the different environments. This information is of paramount importance as it indicates which pathology the species has the greatest treatment consensus among the informants, thus guiding targeted and more in-depth studies for *C. langsdorffii*.

2 MATERIALS AND METHODS

2.1 Study Area

The research was carried out in the Chapada do Araripe, in rural communities inserted in different vegetation types, such as Cerradão (A: Barreiro Grande 39W 33' 38''; 7S 27' 14'', B: Manoel Coco 39W 33' 32''; 7S 12' 02'', C: Zabelê 39W 35' 09''; 7S 10' 24''), Carrasco (D: Minguiriba 39W 33' 47''; 7S 15' 35''), Humid Forest (E: Guaribas 39W 30' 06''; 7S 17' 29'') and Caatinga (F: Baixio das Palmeiras 39W 23' 02''; 7S 16' 48'', G: Baixio do Muquén 39W 23' 10''; 7S 16' 26'', H: Baixio da Chapada 39W 23' 27''; 7S 16' 36''), located in the municipality of Crato, Ceará, Brazil (Fig. 1).

[insert fig 1]

All families residing in the different phytophysiognomies of the Chapada do Araripe, municipality of Crato, Ceará, were approached, making a total of 429 families, being 103 families in Humid Forest, 107 in Carrasco, 109 in Cerradão and 110 in Caatinga (Table 1).

The places studied have electricity, the water is from rain accumulated in cisterns or from artisanal wells and there is a Catholic chapel and primary schools. Regarding the educational level, most of them did not finish elementary school and people over 60 years old are mostly illiterate (Table 1). The main activity of the residents is subsistence agriculture, mainly of corn, beans and cassava, followed by other practices, such as handling and selling the faveira legume (*Dimorphandra gardneriana* Tul.) to the pharmaceutical industry, pequi fruit (*Caryocar coriaceum* Wittm) for trade and poultry farming.

Located within the Caatinga domain in Northeast Brazil, the Chapada do Araripe has a tabular surface with an altitude ranging from 800 m to 900m , and encompasses the states of Ceará, Pernambuco and Piauí (Moro *et al*. 2015). The vegetation in this area is composed of phytophysiognomies from Cerrado, Cerradão, Carrasco, Rainforest and Hypoxerophillic Caatinga (Souza & Oliveira 2006; Moro *et al*. 2015). Red-yellow latosols, litolic neossols and red-yellow argisols are the predominant soils, which due to this mosaic, present varied phytophysiognomies and characterize different environmental gradients throughout the Chapada area (Souza & Oliveira 2006; IPECE 2016; MMA 2011). Latosols are present at the top of the Chapada, these being deep soils with low fertility and Cerrado, Cerradão and Carrasco vegetation covers. Neossols cover the slope and declive areas, being very shallow and stony soils with low fertility, presenting transitions from a rainforest vegetation to a hypoxerophillic caatinga. Finally, argisols are located in middle to low parts of the Chapada, where these are shallow soils that have high fertility and vegetation constituted by subperennial vegetation and hypoxerophillic caatinga (Souza & Oliveira 2006). The typology of the superior part of the Chapada do Araripe reflects a rainwater permeability that acts as an infiltration and supply zone for underground aquifers, which reappear as several springs, streams and rivers in the middle and lower parts of this plateau (Silva & Linhares 2011). The Chapada do Araripe is protected by an Environmental Protection Area (APA da Chapada do Araripe) and part of its territory is also protected by the Araripe National Forest and the Araripe Geological Park (Costa *et al*. 2004).

The climate is Hot Tropical Humid, presenting little thermal variation, with an average annual temperature between 24ºC and 26ºC (Cavalcanti & Lopes 1994; Costa *et al*. 2004). The region has two distinct seasons; a rainy season concentrated between the months of January and April and a long dry season lasting about seven months, with critical scarcity between July and September. Despite this, the region does not present accentuated characteristics of water deficit, due to the resurgence of infiltrated water throughout the area of the top (Loiola et al., 2015). The Chapada do Araripe, depending on atmospheric and sea conditions, receives an average of 1,043 millimeters (mm) of rain per year, resulting in an average of 700-1000 mm/year. Its topography directly influences climatic conditions, interacting with air masses and providing a mild climate in relation to the other surrounding semi-arid regions, causing direct interference to the local flora (Costa *et al*. 2004).

2.2 Data Collection

2.2.1 Ethnobotanical survey

The ethnobotanical study was carried out from January 2019 to February 2020, through semi-structured interviews (Albuquerque *et al*. 2010), using a standardized form (Table S1), with residents of different phytophysiognomies (Cerradão, Carrasco, Humid Forest and Caatinga) of the Chapada do Araripe, Ceará, Brazil. 74 people were interviewed (28 Cerradão, 23 Caatinga, 15 Humid Forest and eight Carrasco), being 47 female and 27 male, with ages ranging from 21 to 97 years (Table 1). All the families in the communities were approached, making a complete census, with the heads of the families being interviewed (Table 1). To reach each residence, the *snowball* technique was used (Bailey, 1994), in order to visit all the families of the different phytophysiognomies. It is worth mentioning that some families did not know or never used *C. langsdorffii*. At the beginning of the interviews the research objectives were explained, at which point the interviewees were presented with an Informed Consent Form (ICF). After this step, people were then free to voluntarily accept (or refuse) to participate in the research. The free list technique (Silva *et al*. 2014) was used to ask participants to name or list the diseases, part used, preparation, administration, collection time, storage type, storage conditions (temperature), storage time and dosage/route of administration of the species *C. langsdorffii*.

For the recognition of the species by the interviewees, visual stimuli were used, such as photographs (Garcia 2006) of leaves, flowers, fruits, resin and trunk of *C. langsdorffii* and exsiccates with reproductive branches (Blanckaert *et al*. 2007) were taken by the author himself, in the field in the Chapada do Araripe with the help of a forester who knows the region, and used in the interviews. The quality of the images was guaranteed using a professional camera with 24.1 megapixels and an EF-S 18-55mm IS II compact zoom lens and 4x optical zoom for different subjects. *C. langsdorffii* is known in the Chapada do Araripe region by more than one common name (copaíba, podoia and pau d'oleo) as reported by the forester thus, these names were also reported in the interviews, as a way for the interviewees to recognize the species.

The research was submitted to the Ethics Committee of the Regional University of Cariri, approved with opinion number 3.183.176, and to the National System for the Management of Genetic Heritage and Associated Traditional Knowledge (Sistema Nacional de Gestão do Patrimônio Genético e do Conhecimento Tradicional Associado; SISGEN), under registration number AF4C8BB.

2.2.2 Botanical material collection and identification

C. langsdorffii reproductive branches (flower or fruit) were collected from the four study areas (Cerradão, Carrasco, Humid Forest and Caatinga) and taken to the Plant Ecology Laboratory of the Regional University of Cariri. The collected material was packaged in plastic bags and treated according to standard herborization techniques (Mori *et al*. 1989), being subsequently identified and incorporated into the Herbarium Caririense Dárdano de Andrade-Lima collection from the Regional University of Cariri (HCDAL/URCA) registered as N° 14.312 (Cerradão), N° 14.313 (Carrasco), N° 14.314 (Humid Forest) and N° 14.315 (Caatinga). Identification occurred through specialized bibliography and comparison with herbarium exsiccates. The Angiosperm Phylogeny Group IV (APG 2017) was adopted as the classification system. The list of Brazilian flora species was consulted to review the scientific name of the species (FLORA E FUNGA DO BRASIL 2020). Authorization for botanical material collection was provided by the Biodiversity Authorization and Information System (Sistema de Autorização e Informação em Biodiversidade; SISBIO) of the Brazilian Institute for the Environment and Renewable Resources (Instituto Brasileiro do Meio Ambiente e dos Recursos Renováveis; IBAMA), registered under number 67422-1.

2.3 Classification of therapeutic indications

Therapeutic indications for *C. langsdorfii*, were grouped into 13 body systems categories based on the International Classification of Primary Care (ICPC-2) proposed by the International Classifications Committee (Wonca 2000): Circulatory System (K); Digestive System (D); Endocrine, Metabolic and Nutritional System (T); Female Genital System (X); Male Genital System (Y); General and Unspecified System (A); Muscle - Skeletal (L); Neurological System (N); Ear System (H); Skin System (S); Psychological System (P); Respiratory System (R); and Urology System (U).

2.4 Data analysis

2.4.1 Usage Diversity Value (UD)

The usage diversity index value measures the importance of the usage categories and how they contribute to the total usage values:

$$UD = Ucx/Uct$$

Calculated through the number of citations for each usage category (Ucx), divided by the number of citations for all usage categories (Uct) (Oliveira *et al*. 2014).

2.4.2 Level of Fidelity (FL)

Determines the informant's consensus on each therapeutic indication mentioned for the species under study:

$$FL (\%) = (Np/N) \times 100$$

This index is calculated by dividing Np which corresponds to the number of reported uses for a given species for a particular disease, by N which is the total number of respondents who cited the given species (Oliveira *et al*. 2014).

2.4.3 Plant part consensus value (PPC)

This index measures the degree of agreement between the informants regarding the plant part used:

$$PPC = Px/Pt$$

Where: Px is the number of times a particular plant part was mentioned; Pt corresponds to the total number of parts (Oliveira *et al*. 2014).

3 RESULTS AND DISCUSSION

3.1 Medicinal indications for *Copaifera langsdorffii* Desf.

Different *C. langsdorffii* structures (oil-resin, leaf, seed and bark and stem bast) were indicated to treat 61 health problems in Cerradão (38 therapeutic indications), Caatinga (33), Humid Forest (20) and Carrasco (15) phytophysiognomies, with cicatrizing (21) being the most commonly mentioned, followed by rheumatic arthritis (17), bone pain (15), back problems (15) and throat inflammation (13) (Table 2). These health problems are among the most recurrent in ethnobiological studies that address this species (Macêdo *et al*. 2018; Fagundes *et al*. 2017; Ribeiro *et al*. 2014). The accentuated medicinal use of this species may be associated with its wide distribution, where its numerous phytotherapeutic activities are determinants for its intensified use (Bruneton 2001; Saraiva *et al*. 2015). The abundance of its individuals, as well as its distribution in the environment, increase the probability of use by human populations that use resources from their flora (Guarim Neto & Morais 2003; Pinto *et al*. 2013).

The set of medicinal plants that make up the medical arsenal of a given culture is the result of a long process of cultural validation, which is always dynamic (Stepp & Moerman 2001; Palmer 2004). These investigations have thus contributed to the understanding of the factors that modulate the selection of medicinal plants in medical systems over time, such as resource availability in the environment and its effectiveness, which have been reported as important in the selection of medicinal plants (Stepp & Moerman 2001). Regarding the variation in the number of uses of *Copaifera langsdorffii* in different phytophysiognomies, it is probably related to the availability of the resource in the environment, causing communities to prefer to use other plants that are available close to these communities and that can alleviate the same symptoms as the species under study. In addition, different ecosystems seem to have different vocations from a pharmacological point of view (Albuquerque *et al*. 2012).

Furthermore, we cannot ignore the role of culture in human perception of environmental resources. In particular, we assume that culture acts by attributing meanings to what we perceive through our senses, so that something mentioned as unpleasant by one culture may be pleasant and desired by another (Albuquerque & Alves 2018). Thus, culture generally provides the meaning and context for the expression of innate behaviors in the contact of humans with different tastes and smells (Shepard 2004), acting as a filter for innate responses. For example, plants with a strongly bitter taste are mainly indicated for the treatment of gastrointestinal diseases by the Tzeltal Mayans of Mexico, due to their wide cultural acceptance (Brett 1998). Furthermore, there are certain foods that are extremely tasty for certain cultural groups, while for others they can be disgusting (Albuquerque & Alves 2018).

Health problems such as rheumatoid arthritis, bone pain, throat inflammation, bumps and back problems were cited in all studied physiognomies. Whereas, other diseases were restricted to a certain phytophysiognomy, with 15 therapeutic indications being cited only in the Cerradão (asthma, bronchitis, throat cancer, uterine cancer, prostate, sprains, insomnia, mycosis, anxiety, sunburn, sinusitis, worms, hypertension, earache and loss of appetite), 10 being indicated only in the Caatinga (stroke, muscle pain, herniated disc, poor circulation, osteoporosis, xiphoid process dislocation, insect bite, tendonitis, tumor and skin burn), 4 in the Carrasco (painful veins, pregnancy stretch marks, vaginal inflammation and diarrhea) and 4 in the Humid Forest (diabetes, laxative, gastric ulcer and general infection) (Table 4). This variation observed between the phytophysiognomies may be related to the number of informants who know *Copaifera langsdorffii* to treat their health problems, having been recorded that in the Cerradão and Caatinga a greater number of people know and use this species as medicinal and, consequently, a greater number of diseases in general was registered in these areas and also a greater number of exclusive diseases, compared to the areas of Carrasco and Humid Forest. Real perceptions of reality are difficult to access, as they are abstract and influenced by several factors, such as age, gender, income and biological and evolutionary aspects (Albuquerque & Alves 2018). And such factors may be related to variations in the uses of *Copaifera langsdorffii* in the different phytophysiognomies of the Chapada do Araripe.

Almeida *et al*. (2011) found that medicinal plants harvested from the Caatinga exhibited greater antimicrobial activity than plants from the same species that were harvested in the Atlantic Forest. Moreover, plants harvested from the Caatinga generally have greater versatility and greater inhibition of sensitive microorganisms (Albuquerque *et al*. 2012). Thus, the Caatinga can be a promising environment for bioprospecting research of antimicrobial compounds (Albuquerque *et al*. 2012). Evidence suggests that medicinal plants from the dry forest are a rich source of drugs in which phenolic compounds, especially tannins, are directly responsible for their therapeutic activity and may be good candidates for bioprospecting efforts (Albuquerque *et al*. 2012).

Ten different preparation methods were reported in the studied vegetation types (Cerradão, Carrasco, Humid Forest and Caatinga) (Table 2). The Cerradão recorded eight preparation methods, with the preparation by mixing the oil with water, coffee or tea standing out with 33 citations, followed by decoction (25), soaking (three), cooking (two), warm oil (two) and leaving the oil in the sun to amend (one). In the Carrasco, seven preparation methods were recorded, where decoction received the highest number of citations (11), followed by preparing the seed (four), mixing the oil with water, coffee or tea (three), warm oil (two) and cooking (one). In the Humid Forest, six preparation methods were cited, where the preparation by mixing the oil with water, coffee, tea or honey was the most commonly cited (seven), followed by soaking (five) and seed preparation (one). In the Caatinga, six preparation methods were recorded, where the mixture of oil with water, coffee or tea was the most commonly cited (10), followed by warm oil (nine), soaking (two) and decoction (one). From the preparation methods indicated, mixing the oil with water, coffee or tea was mentioned in all phytophysiognomies. The leaves and trunk bark were indicated for preparations such as decoction, soaking and cooking, while the oil-resin was dissolved with water, coffee, tea and honey, or warmed up before use. To use the seed, its oil needs to be extracted, through a process where it is first roasted and then cooked. There is a preference for the use of teas in communities in different Brazilian regions (Macedo *et al*. 2016; Ribeiro *et al*. 2017; Fagundes *et al*. 2017; Silva *et al*. 2018), where the choice for this preparation may be associated with the availability of the used part, the plant characteristics and in many cases for being seen by the population as an effective method (Amorozo 2002; Oliveira *et al*. 2010).

In terms of administration, oral intake, massage and poultices were indicated for *C. langsdorffii* use in Cerradão (55; 32; 12), Caatinga (19; 37; 12), Humid Forest (30; 14; eight) and Carrasco (13; eight; six) phytophysiognomies and encompassed the largest number of citations (Table 2). Nasal inhalation was recommended only in the Cerrado (one) and Caatinga (one), sit down baths (two) only in the Carrasco, putting the oil on the skin only in the Cerrado (one) and gargling only in the Caatinga (one) (Table 2). The large indication for oral intake is associated with the preference of the communities to use teas and the crude resin to cure their illnesses, while massage and poultices are associated with using the oil-resin to treat rheumatoid arthritis, spine, bones and cicatrizing, which are administered to the external body.

Evidence exists for some of the *C. langsdorffii* therapeutic indications, acquired through bioprospecting, chemical and pharmacological studies, showing important anti-inflammatory activities (Paiva *et al*. 2003; Paiva *et al*. 2004; Silva *et al*. 2009; Gelmini *et al*. 2013), gastroprotective (Lemos *et al*. 2015; Motta *et al*. 2017), antimicrobial (Pieri *et al*. 2011; Souza *et al*. 2011), antineoplastic (Senedese *et al*. 2013), antitumor (Oshakiet *et al*. 1994), diuretic (Paiva *et al*. 2003; Brancalion *et al*. 2012), antioxidant (Costa *et al*. 2015; Carmo *et al*. 2016; Batista *et al*. 2016), cicatrizing (Masson Meyers *et al*. 2013; Paiva *et al*. 2002), antinociceptive (Gomes *et al*. 2007) and cytotoxic (Vargas *et al*. 2015; Lemos *et al*. 2015; Farias *et al*. 2019).

3.3 Usage Diversity Value (UD)

Sixty-one health problems grouped into 13 body system categories, with a usage diversity value (UD) ranging from 0.01 to 0.37 (Table 3), were reported in the Cerradão, Carrasco, Humid Forest and Caatinga phytophysiognomies. From these categories, the Musculoskeletal, Skin, Digestive and Respiratory systems encompassed the largest number of diseases (12; nine; nine; eight) and usage citations (73; 40; 27; 31), respectively, with rheumatic arthritis (17), cicatrizing (21), gastritis and stomachache (six each) and throat inflammation (13) (Table 3) as the most indicated diseases, respectively.

In the Cerradão, 94 citations were recorded for 38 health problems, belonging to 13 body system categories, with a usage diversity value ranging from 0.01 to 0.33 (Table 3). The most cited categories were: Musculoskeletal (UD: 0.33), with seven diseases and 30 usage citations, where the most commonly indicated diseases were bone pain (seven), rheumatoid arthritis (six), back problems (six), leg pain (four), and joint pain (four), which were treated by massaging the oil-resin; Skin (UD: 0.13), with 12 citations for five diseases, where cicatrizing (six) and cracked feet (three) received the highest number of citations, with the oil-resin being administered through poultices; and, General and Unspecific (UD: 0.10), with nine citations for four diseases, where general pain (five) was the most commonly cited, and was treated using different plant parts, such as the oil-resin, leaf and stem bast, administered through oral intake of the decoction or through massaging. The 10 remaining categories obtained usage diversity values ≤ 0.09. The categories, female genital (uterine cancer) and male genital (prostate) were those with the lowest usage diversity value (0.01 each), with one disease and one citation each.

For the Caatinga, 68 citations were cataloged for 33 diseases, distributed across eight body systems, with a usage diversity value ranging from 0.01 to 0.37 (Table 3). Four categories obtained UD values ≤ 0.06 and four UD values ≥ 0.12. The most cited body system categories in this phytophysiognomy were Musculoskeletal (UD: 0.37) and Skin (UD: 0.21). The Musculoskeletal system encompassed 25 citations for 11 health problems, of which, rheumatoid arthritis was the most cited with six citations, with an oil-resin massage being indicated. The Skin category received 14 citations for six health problems, with cicatrizing (five) obtaining the most citations and being treated by the oil-resin poultice.

The Humid Forest obtained 49 citations for 20 therapeutic indications, grouped across 6 body systems, with a usage diversity value varying from 0.02 to 0.22 (Table 3). From the six registered categories, only the Endocrine, Metabolic and Nutritional category presented a low usage diversity value (UD: 0.02), with one disease (diabetes) and one citation, with the oil-resin being administered through oral ingestion. UD values ≥ 0.14 were observed in the remaining five categories. Of these, the most cited were: Skin (UD: 0.22), with 11 citations for two therapeutic indications, where cicatrizing (10) was the most indicated, treated mainly with an oil-resin poultice; respiratory (UD: 0.22), with 11 citations for four diseases, where throat inflammation (five) was the most cited, with the oil-resin being administered through oral intake and massaging; and, Musculoskeletal (UD: 0.20), encompassing 10 citations for four health problems, with bone pain (four) presenting the highest number of citations, treated through an oil-resin massage.

For the Carrasco, 29 citations for 15 diseases were recorded, across 8 body system categories, with usage diversity values ranging from 0.03 to 0.28 (Table 3). From the registered categories, five obtained UD values ≥ 0.10, while three presented UD values ≤ 0.07. The Musculoskeletal (UD: 0.28) and Digestive (UD: 0.24) systems were the most representative systems, with 3 diseases each and 8 and 7 citations, respectively. The most commonly cited therapeutic indications within these systems were stomachache (four), rheumatoid arthritis (three) and bone pain (three), which were treated by ingesting the leaf decoction or by massaging the oil-resin. The Circulatory system was the body system category with the lowest UD value in this phytophysiognomy with one disease (pain in the veins) and one usage citation.

The most representative category in the Caatinga, Cerrado, Carrasco and Humid Forest phytophysiognomies was the Musculoskeletal system, with a usage diversity value equal to 0.37, 0.33, 0.28 and 0.20, respectively, with rheumatic arthritis (17), back problems (15) and bone pain (15), as the most commonly indicated diseases in this system (Table 3). Rheumatism and bone problems are among the diseases for which *C. lansgsdorffii* is used, as reported by Macêdo *et al*. (2018), Fagundes *et al*. (2017) and Ribeiro *et al*. (2014), which affirms these uses in different communities. The vast indication of diseases in this system within the communities may be associated with a limited access to modern medicine and the high cost of pharmaceutical drugs used to treat these health problems, causing populations to select and test plants, as is the case of *C. langsdorffii*, where the oil-resin is widely indicated for such diseases.

The Skin category obtained the second highest usage diversity value, with values equal to 0.22 (Humid Forest), 0.21 (Caatinga), 0.13 (Cerradão) and 0.10 (Carrasco) in the different areas. Cicatrizing (21) received the highest number of citations (Table 3). *C. langsdorffii* has been reported to have cicatrizing properties in other studies (Macêdo *et al*. 2018; Macêdo *et al*. 2016; Macêdo *et al*. 2015), conferring cicatrizing (Paiva *et al*. 2002; Masson Meyers *et al*. 2013) and anti-inflammatory properties (Paiva *et al*. 2004; Gelmini *et al*. 2013; Paiva *et al*. 2003; Silva *et al*. 2009) that have been proven through pharmacological studies.

The Digestive system presented divergences between the phytophysiognomies, in terms of usage diversity (UD), where the Cerradão and Caatinga presented low UD values, 0.08 and 0.06, respectively, for this system, while this category was well represented in the Carrasco and Humid Forest, with UD values equal to 0.24 and 0.18, respectively (Table 3). Stomachache (six) and gastritis (six) obtained the greatest number of indications. *C. langsdorffii* is highly indicated in ethnobotanical surveys, carried out in Northeast Brazil, for different digestive symptoms (Macêdo *et al*. 2015; Saraiva *et al*. 2015; Silva *et al*. 2015; Souza *et al*. 2014), where this plant has previously demonstrated a gastroprotective activity (Lemos *et al*. 2015; Motta *et al*. 2017), where the compounds responsible for this activity are likely to be kaurenoic acid, quercitrin, afelelin, α-humulene, β-caryophyllene, caryophyllene oxide (Lemos *et al*. 2015) and galloylquinic acid (Motta *et al*. 2017), present in different parts of that species.

The Respiratory category was another body system category which showed variation when analyzed in different phytophysiognomies (Table 3). In the Cerrado and Carrasco, its usage diversity value was ≤ 0.10, while in the Humid Forest and Caatinga, its values were 0.22 and 0.15, respectively. Throat inflammation was the most commonly cited disease (13) (Table 3). *Copifera langsdorffii* is often indicated for this system (throat problems) in different Brazilian regions (Pinto *et al*. 2013b – Midwest; Pereira *et al*. 2016 – Midwest; Ribeiro *et al*. 2017 – Midwest; Franco & Souza 2016 – North; Santos *et al*. 2019 – Northeast; Baptistel *et al*. 2014 – Northeast), bronchitis (Guarim Neto & Morais 2003– Midwest; Moreira & Guarim Neto 2009 – Midwest; Bitu *et al*. 2015 – Northeast; Fagundes *et al*. 2017 – Southeast), colds (Moreira & Guarim Neto 2009 – Midwest; Santos *et al*. 2014 – North; Silva *et al*. 2018 – North; Macêdo *et al*. 2018 – Northeast) and coughs (Baptistel *et al*. 2014 – Northeast; Macêdo *et al*. 2015 – Northeast; Macêdo *et al*. 2018 – Northeast), also being used less frequently for sinusitis (Conceição *et al*. 2011 – Northeast) and asthma (Baptistel *et al*. 2014 – Northeast). Its medicinal properties are likely associated with the presence of sesquiterpenes in its essential oil, such as β-caryophyllene and h-hyalchalene, which confer antimicrobial activity (Alencar *et al*. 2015).

The categories with the lowest representation in the different phytophysiognomies studied were Circulatory (K), Endocrine, Metabolic and Nutritional (T), Female Genital (X), Male Genital (Y), Neurological (N), Ear (H), Psychological (P) and Urology (U) system, with usage diversity values ≤ 0.10 (Table 3).

3.2 Level of Fidelity (FL)

The level of fidelity determines the informant's consensus on each therapeutic indication mentioned for the species under study and was calculated for all health problems reported in the Cerradão, Carrasco, Humid Forest and Caatinga phytophysiognomies (Table 4).

Although the Cerradão and Caatinga phytophysiognomies registered the highest number of therapeutic indications (38 and 33, respectively), their general level of fidelity was lower, varying from 3.57 to 25 and 4.35 to 26.09, respectively. While a fewer number of diseases were indicated in the Humid Forest and Carrasco (15 and eight, respectively), their level of fidelity was more expressive, ranging from 6.67 to 66.67 and 13 to 50, respectively (Table 4). This difference may be due to the dissemination of knowledge in communities, where a lower number of diseases treated by a given plant in a community is more easily dispersed, reaching a larger number of people, thus having a greater consensus among members from the area. Whereas, in a community where a plant is known to treat various illnesses, this total knowledge will be restricted to a few people, with only the most common uses being passed on to other members from the community, thus a high probability of reducing knowledge consensus among informants in an area exists.

The most cited therapeutic indications in the Cerradão, Carrasco, Humid Forest and Caatinga areas were bone pain, stomachache, cicatrizing and rheumatic arthritis/throat inflammation, respectively, with a level of fidelity equal to 25%, 50%, 66.67% and 26.09%, respectively (Table 4). In general, fidelity levels for the diseases reported were high, showing consensus among the informants. The *C. langsdorffii* effectiveness in treating these health problems may be related to the presence of compounds such as α-humulene, β-caryophyllene, galoylquinic acid, quercitrin, afelelin, kaurenoic acid, caryophyllene oxide, acetoxicopalic acid, agatic acid, hydroxycopic acid and copalic acid, which have proven anti-inflammatory, antibacterial and gastroprotective actions (Motta *et al*. 2017, Lemos *et al*. 2015, Abraão *et al*. 2015, Souza *et al*. 2011, Paiva *et al*. 2003).

Health problems such as rheumatic arthritis and back problems showed a high consensus among all the studied phytophysiognomies, with a fidelity level of 38% and 25% in Carrasco, 26.09% and 17.39% in Caatinga, 21.43% in Cerradão and 13.33% and 20% in Humid Forest areas (Table 4), respectively, these being considered a good and reliable indicator of potential *C. langsdorffii* therapeutic properties.

The lowest level of fidelity value (3.57%) was recorded in the Cerradão area for the following therapeutic indications: swelling, bumps, sinusitis, headache, asthma, cancer, throat cancer, cervical cancer, migraine, throat inflammation, sprains, sunburn, bronchitis, insomnia, mycosis and prostate (Table 4). However, some of these diseases were well represented in the other vegetation types, such as throat inflammation, which despite having a low consensus in the Cerradão, presented robust values in the Humid Forest (33.33%), Caatinga (26.09%) and Carrasco (13.00%) areas (Table 4).

3.3 Plant part consensus value (PPC)

Different *C. langsdorffii* plant parts were reported by community informants to treat their illnesses, such as the resin oil, leaf, stem bast, stem bark and seed (Table 5). The resin oil stands out with greater consensus from all the studied phytophysiognomies, with 0.96, 0.88, 0.71 and 0.45 for the Caatinga, Humid Forest, Cerrado and Carrasco areas, respectively (Table 5). The stem bast was cited in all the environments, however, it presented a low consensus, with a PPC value ≤ 0.10. The leaf was cited by informants in the Carrasco (PPC: 0.34), Cerradão (PPC: 0.18) and Caatinga (PPC: 0.01) areas, however, it was not indicated in the Humid Forest. The seed was not cited in the Caatinga, however, it presented a PPC value equal to 0.14 for

Carrasco and 0.02 for Cerradão and Humid Forest areas. The stem bark is used only by Cerradão communities and obtained a low consensus (0.03) (Table 5).

The diversified use of plant structures from the same species is associated with the fact that many symptoms can be treated by any plant part, given they contain similar bioactive properties that are useful to treat the symptoms (Ashraf *et al*. 2016). It should be noted that in Northeast (Santos *et al*. 2019; Penido *et al*. 2016; Silva *et al*. 2015) and Northern regions (Mesquita & Tavares-Martins 2018; Santos *et al*. 2014; Silva *et al*. 2018), a preference for using the stem bark exists, while in the Midwest (Pereira *et al*. 2016; Mariano *et al*. 2015; Souza & Felfile 2006) and Southeast (Oliveira-Silva *et al*. 2018; Ronchi *et al*. 2016; Ferrão *et al*. 2014) the use of the resin oil stands out. The intensified use of structures such as barks and resin oil, may make the species more vulnerable and cause a reduction in their populations (Santos *et al*. 2019), thus their collection requires control so as to not harm the conservation of the species.

Human perceptions associated with the use of natural resources need to be thoroughly investigated, as the results from these works can help to understand the selection criteria of certain natural resources by different cultural groups (Albuquerque & Alves 2018). In addition, such factors, in general, do not act in isolation, and it is necessary to understand the forces that act together in the various forms of interaction between people and the biota (Albuquerque & Alves 2018).

4 CONCLUSION

The research carried out with *Copaifera langsdorffii* Desf. in the Cerradão, Carrasco, Humid Forest and Caatinga phytophysiognomies in the Chapada do Araripe, Northeast Brazil, showed a considerable amount of therapeutic indications, indicating that the informants know and use *C. langsdorffii* to treat diseases that affect different body systems.

C. langsdorffii is indicated to treat rheumatoid arthritis, bone pain, throat inflammation, bumps and back problems in all the studied phytophysiognomies, demonstrating a wide transmission of knowledge between areas for its uses. However, certain disease indications are unique to each ecosystem and may be associated with both a cultural factor from each community, as well as resource availability in the environment and a variation in chemical composition of the species given their different environments.

Therapeutic indications such as rheumatic arthritis and back problems presented a high consensus in Cerradão, Carrasco, Humid Forest and Caatinga phytophysiognomies, this being considered a good and reliable indicator of potential *C. langsdorffii* therapeutic properties.

The consensus values among the informants showed a high knowledge/usage transmission, regarding *C. langsdorffii*, within the different phytophysiognomies, especially in the Musculoskeletal, Skin, Digestive and Respiratory systems.

The *C. langsdorffii* data obtained in this study highlight its therapeutic potential and the need for studies to evaluate plant species that are used by local communities as a source of biologically active natural products, paving the way for a contribution to the search and development of new drugs.

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AUTHOR CONTRIBUTIONS

Todos os autores contribuíram para a concepção e desenho do estudo. Maria de Oliveira Santos, Bianca Vilar de Almeida, Flávia Geane Torres de Mendonça e Márcia Jordana Ferreira Macêdo: Conceptualização e Metodologia. Maria de Oliveira Santos: Redação - Elaboração do projeto original e investigação. Maria de Oliveira Santos, Bianca Vilar de Almeida, Flávia Geane Torres de Mendonça, Márcia Jordana Ferreira Macêdo, Daiany Alves Ribeiro, Irwin Rose Alencar de Menezes, José Galberto Martins da Costa e Marta Maria de Almeida Souza: Prévia. José Galberto Martins da Costa e Marta Maria de Almeida Souza: Supervisão. Maria de Oliveira Santos, José Galberto Martins da Costa e Marta Maria de Almeida Souza: Redação-Resenha e Edição. Todos os autores leram e aprovaram o manuscrito final.

CONFLICTS OF INTEREST

The author declares no conflict of interest associated with this publication.

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TABLES AND FIGURE LEGENDS

Table 1: Socio-cultural data of respondents, including the number of respondents in each community studied.

Table 2. Ethnobotanical Survey of *Copaifera langsdorffii* Desf. Fabaceae in Chapada do Araripe, Northeast, Brazil.

Table 3: Usage Diversity Value for *Copaifera langsdorffii* Desf. in Chapada do Araripe Nordeste communities, Brazil.

Table 4: Comparison of the Level of Fidelity (FL) in relation to the medicinal indications of *Copaifera langsdorffii* Desf. in Chapada do Araripe communities, Northeast, Brazil.

Table 5: Plant part consensus value (PPC) *Copaifera langsdorffii* Desf. in Chapada do Araripe communities, Northeast, Brazil.

Fig. 1. Geographic location of the study areas in Chapada do Araripe, Ceará, Brazil.

Table 1: Socio-cultural data of respondents, including the number of respondents in each community studied.

	Total residences per community	Number of people who responded by community
Communities		
A: Barreiro Grande	13	04
B: Manoel Coco	52	10
C: Zabelê	44	14
D: Minguiriba	107	08
E: Guaribas	103	15
F: Baixio das Palmeiras	13	06
G: Baixio do Muquén	42	07
H: Baixio da Chapada	55	10
Sex		
Women	-	47
Men	-	27
Age		
20 to 33 years	-	04
40 to 56	-	31
> 60 years	-	39
Education		
Illiterate	-	20
Incomplete Elementary School	-	37
Complete primary education	-	02
Incomplete high school	-	03
Complete high school	-	09
Complete Higher Education	-	03

SUBTITLE: A a C: Cerradão; D: Carrasco; E: Humid Forest; F a H: Caatinga

Table 2. Ethnobotanical Survey of *Copaifera langsdorffii* Desf. Fabaceae in Chapada do Araripe, Northeast, Brazil.

Therapeutic Indications / Communities	Part Used	Preparation	Administration	Collection Time	Storage type	Storage conditions (temperature)	Storage time	Dosage / Route of administration
Rheumatoid arthritis (17) / A (2); B (3); C (1); D (3); E (2); F (3); G; H (3)	Oil-resin (16), leaf (1), Stalk stem (1)	Mix with water (2), mix with coffee (1), heat the oil (2), soak (1), decoction (1)	Massage (15), oral intake (5)	Half day (1), any time (5), afternoon (1)	Glass container (8), plastic (9)	Environment (13), refrigeration (1)	Undefined (5), 1 month (1), 2 years (1), more than 4 years (1)	Topic (14), oral (11) 1 time a day (3); 2 times a day; 2 times a day, until it heals (2); 3 times a day, until it heals; 2 times a day, for 5 days, until it heals; 2 times a day, for 8 days (2); 1 teaspoon, 2 or 3 times a day, until cured; 2 or 3 times a day, until it heals; 6 drops, 2 times a day, for 3 to 4 days
Arthrosis (5) / B (2); F (2); G (1); H (1)	Oil-resin (4), leaf (1)	Warms up the oil (1), decoction (1)	Massage (4), oral intake (1)	Any Time (2)	Plastic container (3), glass (2)	Environment (4)	2 years (1)	Topic (3), oral (3) 1 time a day (3); 2 times a day, for 8 days (2); 3 times a day (1)
Asthma (1) / B (1)	Oil-resin (1)	Mix with tea (1) or coffee (1)	Oral ingestion (1)	Morning (1), any time (1)	Glass container (1), plastic (1)	Environment (1)	Undetermined (1)	Oral (1) 1 time a day (1)
Stroke (1) / F (1)	Oil-resin (1)	Mix with coffee (1)	Oral ingestion (1)	-	Plastic container (1)	Environment (1)	Undetermined (1)	Oral (1) 3 drops (1). 1 time a day (1)
Bronchitis (1) / C (1)	Oil-resin (1)	Mix with water (1)	Oral ingestion (1)	Morning (1)	Plastic container (1)	Refrigeration (1)	1 year (1)	Oral (1)

Therapeutic Indications / Communities	Part Used	Preparation	Administration	Collection Time	Storage type	Storage conditions (temperature)	Storage time	Dosage / Route of administration
								10 drops (1). 3 times a day (1). For 8 days (1)
Cancer (6) / B(1); E(2); F (2); H (1)	Oil-resin (5), Stalk stem (1)	Soak (1), mix the oil with water (3), coffee or tea (1)	Oral ingestion (6)	Any time (3), morning (1)	Plastic container (3), glass (2)	Environment (3), refrigeration (1)	-	Oral (6) Oil: 5 ml, 2 times a day, for 15 to 45 days; Stalk stem: 3 drops, 3 times a day, for 6 months
Throat cancer (1) / B(1)	Oil-resin (1)	Drinking pure (1)	Oral ingestion (1)	Morning (1)	Glass container (1), plastic (1)	Environment (1)	Undetermined (1)	Oral (1) Once a day (1). 3 to 4 days (1)
Uterine cancer (1) / B(1)	Oil-resin (1)	Drinking pure (1)	Oral ingestion (1)	Morning (1)	Glass container (1), plastic (1)	Environment (1)	Undetermined (1)	Oral (1) Once a day (1). 3 to 4 days (1)
Healing (wound and cut) (21) / B (2); C (4); E (10); F (3); G(1); H(1)	Oil-resin (19), Stalk stem (1), seed oil (1)	Soak (1), toast and cook the seed and remove the oil (1), mix with some tea (1)	Poultice (18), massage (1), oral intake (2)	Any time (2), morning (4)	Plastic container (9), glass (12)	Environment (18), refrigeration (3)	2 months (1), more than 1 year (3), more than 6 months (2), undetermined (4), 3 to 4 years (1), more than 4 years (1)	Topic (19), oral (2) 1 time (2); 1 time a day, for 3 days; 3 drops, 2 to 3 times a day; 2 times a day (5); 2 times a day, until it heals (5); 2 to 3 times a day, for 8 days; 2 to 3 times a day; 3 times a day (2)
Diabetes (1) / E(1)	Oil-resin (1)	-	Oral ingestion (1)	-	Glass container (1)	Environment (1)	-	Oral (1) 5 to 6 drops, 2 to 3 times a day
Diarrhea (2) / D (2)	Leaf (2)	Decoction (2)	Oral ingestion (2)	Any Time (2)	-	-	-	Oral (2) 2 times a day, for 3 days; Several times a day, until it heals.

Therapeutic Indications / Communities	Part Used	Preparation	Administration	Collection Time	Storage type	Storage conditions (temperature)	Storage time	Dosage / Route of administration
Bellyache (6) / D (4); E(2)	Leaf (4), Stalk stem (1), Oil-resin (1)	Decoction (4), sauce (1), mix with water (1)	Oral ingestion (6)	Any Time (6)	Plastic container (2)	Environment (1)	-	Oral (6) 1 time; 2 times a day, for 3 days; several times a day, until it heals (2); 3 drops, 2 times a day, for 5 days; 2 times a day for 5 days
Headache (4) / A (1); D (2); F(1)	Leaf (1), Oil-resin (3)	Decoction (1), mix the oil with water (1), tea (1) or coffee (1)	Oral ingestion (3), massage (1)	Any time (3)	Plastic container (2), glass (2)	Environment (3)	2 years	Topic (1); Oral (3) 1 time a day; 4 drops, 1 time a day; 3 times a day, until it heals; 3 drops, twice a day, until cured
Toothache (3) / B (2); H(1)	Oil-resin (3)	Mixing with water (1), Mixing with coffee (1)	Massage outside the tooth (1), poultice (2), Oral water intake (2)	Any time (1)	Plastic container (2), glass (1)	Environment (2)	Undetermined (2), cannot save (1)	Topic (2), oral (2) 9 drops, 3 times a day; 1 time
Earache (3) / A (1); B (2)	Oil-resin (3)	Dissolves the resin with water and coa (1)	Poultice (3)	Any time (2)	Glass container (2), plastic (1)	Environment (2)	Undetermined (2), cannot save (1)	Topic (3) 2 drops, 1 time; Drip 2 drops in the ear, 2 times a day, until it heals; 4 drops in the ear, 3 times a day, until it heals
General pain (7) / B(1); C (4); F(1); H (1)	Oil-resin (5), Stalk stem (1), leaf (1)	Soak (1), decoction (2), warm the oil (1)	Oral ingestion (3), massage (4)	Any time (1)	Plastic container (2), glass (2)	Environment (2)	Cannot save (1)	Oral (3), topical (4) 3 times a day, indefinitely; 2 times a day; 3 times a day, until it heals
Pain in the legs (5) /A (3); C (1); F(1)	Oil-resin (4),	Warm oil (1), cooking (1)	Massage (4), Oral ingestion (2)	Any time (2)	Glass container (3), plastic (1), plastic bag (1)	Environment (1)	Undetermined (2), 1 year (1)	Topic (4), oral (2)

Therapeutic Indications / Communities	Part Used	Preparation	Administration	Collection Time	Storage type	Storage conditions (temperature)	Storage time	Dosage / Route of administration
	Stalk stem (1)							2 or 3 times a day, until it heals; 3 times a day for 1 month
Urinary pain (3) / A (1); C(1); H (1)	Leaf (2), Oil-resin (1)	Decoction (2), mix the oil with water (1)	Oral ingestion (3)	Any time (1)	Plastic container (1)	Environment (1)	Undetermined (1)	Oral (3) Half an American glass, 3 times a day, until it heals; 3 times a day; 3 drops, 1 time
Muscular pain (1) / H(1)	Oil-resin (1)	-	Massage (1)	-	Plastic container (1)	Environment (1)	-	Topic (1) 3 times a day (1)
Joint pain (10) / A (1); B (1); C (3); E (1); G (1); H (3)	Oil-resin (10)	Mix with water (2), coffee (2), warm the oil (8)	Oral ingestion (2), poultice (1), massage (5)	Any time (1)	Glass container (5), plastic (4)	Environment (7)	Undetermined (1), 1 year (1)	Oral (1), topic (7) 2 or 3 (3) times a day, until it heals (3); 3 drops; 2 times a day, until it heals; 2 times a day; Once a day
Pain in the veins (1) / D (1)	Oil-resin (1)	-	Massage (1)	-	Glass container (1)	Environment (1)	Undetermined (1)	Topic (1)
Body ache (1) / E(1)	Oil-resin (1)	Mix oil with water (1)	Oral ingestion (1)	Morning (1)	Plastic container (1), glass (1)	-	3 to 4 years (1)	Oral (1) Child: 3 drops; Adult: 4 or 5 drops, once a day
Stomach ache (4) / E (3); G (1)	Stalk stem (1), Oil-resin (3)	Soak (1), mix the oil with water (1)	Oral ingestion (4)	Any time (2)	Plastic container (3), glass (1)	Environment (4)	More than 6 months (1)	Oral (4) 3 drops, 2 times a day, for 5 days; 2 times a day, for 5 days; 20 to 25 drops, 2 times a day, until cured; 3 drops, 2 times a day
Bone pain (15) / A (1); B (5);	Oil-resin (13), leaf	Dissolves the resin in the coffee (1), heats the resin	Oral ingestion (3), massage (13)	Half day (1), any time (5),	Glass container (8), plastic (5), yard (1)	Environment (7), refrigeration (1)	Undetermined (2), more than 1 (1), 2 (1) years, 1 month	Oral (3), topical (13) 3 times a day, indefinitely; 2 times a

Therapeutic Indications / Communities	Part Used	Preparation	Administration	Collection Time	Storage type	Storage conditions (temperature)	Storage time	Dosage / Route of administration
C(1); D (3); E (4); H(1)	(1), Stem bark (1)	and passes it on the spot (1), decoction (2), with sauce (1)		afternoon (1)			(1), if you spend too much time curdling (1), you cannot save (1)	day, for 8 days (2); 2 small pieces of the peel in half a glass of water, 1 time, until cured; 2 times a day, for a week (2); 2 times a day, until it heals; 2 times a day; 1 time a day, indefinitely; 3 times a day, until it heals (2)
Sprains (1) / A(1)	Oil-resin (1)	Heat resin on fire and strain (1)	Massage (1)	-	Plastic container (1)	-	-	Topic (1) 2 times a day (1), for 1 week (1)
Migraine (2) / B(1); D (1)	Leaf (1), Oil-resin (1)	Decoction (1)	Oral ingestion (1), Massage (1)	Any time (2)	Glass container (1), plastic (1)	Environment (1)	2 years (1)	Oral (1), topic (1) 1 time a day; 3 times a day, until it heals
Stretch mark of pregnant woman (1) / D(1)	Seed oil (1)	Roast the seed and extract the oil (1)	Massage (1)	Any time (1)	Plastic container (1), aluminum (1), pot (1)	Environment (1)	Undetermined (1)	Topic (1) Several times a day (1)
Gastritis (6) / C (2); E(2); F(1); H(1)	Oil-resin (4), Stalk stem (1), leaf (1)	Soak (1), decoction (1), mix the oil with water (3)	Oral ingestion (6)	Any time (3)	Glass container (3), plastic bag (1), plastic container (3)	Environment (4)	1 year (1), undetermined (1)	Oral (6) 1 time a day; 1 time; 3 drops, 2 times a day, for 5 days; 2 times a day, for 5 days; 5 ml, 2 times a day, for 3 days; 1 drop, once a day
Flu (5) / D (1); E (3); H(1)	Oil-resin (5)	With honey (1), with coffee (1)	Oral ingestion (4), inhalation (1)	-	Plastic container (3), glass (3)	Environment (4)	Undetermined (1)	Oral (4), Inhalation (1) 4 drops, 1 time a day; 10 drops, 2 to 3 (2) times a day, until cured; 1 to 2 drops, 2 (2) times a day

Therapeutic Indications / Communities	Part Used	Preparation	Administration	Collection Time	Storage type	Storage conditions (temperature)	Storage time	Dosage / Route of administration
Hemorrhoid (6) / B (4); F (2)	Oil-resin (6)	Put it in the sun to find out (1)	Poultice (5), Oral ingestion (2)	Morning (1)	Glass container (4), plastic (2)	Environment (5)	Undetermined (3)	Topic (5), oral (2) 2 to 3 times a day; 1 tablespoon; 1 time a day (2)
Herniated disc (1) / G (1)	Oil-resin (1)	-	Massagem (1)	-	Plastic container (1)	Environment (1)	-	Topic (1) 3 times a day (1)
Tonsils hypertrophy (2) / E(1); H(1)	Oil-resin (2)	Warm the oil (1)	Oral ingestion (1), Massage (1)	-	Glass container (2), plastic (1)	Environment (2)	Undetermined (1)	Oral (1), topic (1) 1 to 2 drops, 2 times a day; 3 times a day
Swelling (7) / A(1); D(3); F(1); H (2)	Oil-resin (6), Seed (1)	Heat the resin on the fire (2), Roast the seed and cook to extract an oil (1)	Massage (5), Poultice (2)	Any time (2)	Plastic container (4), glass (5), pot (2), aluminum (2), can (2)	Environment (4), refrigeration (1)	Undetermined (3)	Topic (7) 2 times a day, for a week; 3 times a day, until it heals (2); 2 times a day, for 1 month; 2 times a day
Infection in general (2) / E (2)	Oil-resin (2)	-	Oral ingestion (2)	-	Plastic container (2), glass (2)	Environment (2)	Undetermined (1)	Oral (2) 10 drops, 2 to 3 times a day, until cured; 1 to 2 drops, 2 times a day
Inflamed throat (13) / B(1); D(1); E (5); F (2); G (2); H(2)	Leaf (1), Oil-resin (11), Stalk stem (1)	Decoction (1), mix the oil with water (3), soak (1), warm the oil (1)	Oral ingestion (10), massage (4), gargle (1)	Any time (2)	Glass container (6), plastic (4)	Environment (10)	More than 6 months (oil) (1), undetermined (1), more than 4 years (1), Cannot save (1)	Oral (11), topic (4) 1 spoon, 2 times a day, for 3 days; 1 American cup, 1 time a day, until cured; 10 drops, 2 to 3 times a day, until cured; 2 times a day, until it heals; 10 to 15 drops, 2 times a day, until cured; 3 times a day; 1 to 2 drops, 2 times a day; 2 drops, 1 time a day, for 2 days; 2 drops, 2 times a day,

Therapeutic Indications / Communities	Part Used	Preparation	Administration	Collection Time	Storage type	Storage conditions (temperature)	Storage time	Dosage / Route of administration
								for 3 days; 3 drops, 3 times a day (4)
Inflammation in general (4) / B(2); E (2)	Oil-resin (3), Stem bark (1)	Mixing with honey (1), decoction (1)	Oral ingestion (3), massage (2)	-	Plastic container (2), glass (1)	Environment (2)	More than 6 months (1), undetermined (1)	Oral (3), topical (2) 2 times a day (2); 2 times a day, until it heals; 1 to 2 drops, 2 times a day
Vaginal inflammation (2) / D (2)	Stalk stem (2)	Cooking (1), decoction (1)	Bathe (2)	Any time (1)	-	-	-	Topic (2) 1 time a day (night) (2)
Insomnia (1) / C (1)	Leaf (1)	Decoction (1)	Oral ingestion (1)	-	-	-	-	Oral (1)
Laxative / Constipation (1) / E(1)	Oil-resin (1)	-	Oral ingestion (1)		Glass container (1), plastic (1)	Environment (1)	Undetermined (1)	Oral (1) 10 to 15 drops, 2 times a day
Bad circulation (1) / F(1)	Oil-resin (1)	Warm the oil (1)	Massage (1)	-	Glass container (1), plastic (1)	Environment (1)	-	Topic (1) 3 times a day (1). For 1 month (1)
Indigestion (3) / B (2); D(1)	Leaf (1), Oil-resin (2)	Decoction (1), mix with water (2), coffee (1) or tea (1)	Oral ingestion (3)	Any time (1)	Plastic (2), Glass (2)	Refrigeration (1), environment (1)	1 month (1), undetermined (1)	Oral (3) 15 drops; 5 drops; 2 times a day for 3 days
Ringworm (1) / C(1)	Oil-resin (1)	Mix with some tea (1)	Oral ingestion (1)	-	Backyard (1)	-	-	Oral (1) 5 (1) to 9 (1) drops. Once a day (1). Until cure (1)
Nervousness (2) / B(1); C(1)	Leaf (1), Stem bark (1)	Decoction (2), sauce (1)	Oral ingestion (2)	Morning (1), any time (1)	Backyard (1)	-	-	Oral (2) 2 small pieces of the peel in half a glass of water (1). Until cure (1)
Osteoporosis (1) / H(1)	Oil-resin (1)	-	Massage (1)	-	Glass container (1), plastic (1)	Environment (1)	Undetermined (1)	Topic (1) Once a day

Therapeutic Indications / Communities	Part Used	Preparation	Administration	Collection Time	Storage type	Storage conditions (temperature)	Storage time	Dosage / Route of administration
Beat (6) / A(1); D(2); E(1); F(1); H(1)	Oil-resin (5), seed oil (1)	Dissolve the resin with coffee (1), roast the cooking seed and add the oil (1)	Oral ingestion (1), Massage (3), poultice (2)	Any time (2)	Plastic container (4), glass (2), aluminum (2), pot or can (2)	Environment (4)	Undetermined (3)	Oral (1), topic (5) 2 times a day, for 1 week; 3 times a day, until it heals (2); 2 times a day, until it heals; Once a day
Open chest (1) / F(1)	Oil-resin (1)	Mix the oil with water (1)	Oral ingestion (1)	-	Plastic container (1)	Environment (1)	Undetermined (1)	Oral (1) 1 time a day (1)
Loss of appetite (6) / C (6)	Seed (2), leaf (3), Stalk stem (1)	Decoction (6)	Oral ingestion (6)	Any time (1)	Glass container (2), yard (1)	Environment (2)	1 year (2)	Oral (6) 1 handful of leaves in half a glass of water (1). 1 time a day (1)
Bug bite (1) / H(1)	Oil-resin (1)		Poultice (1)	-	Glass container (1), plastic (1)	Environment (1)	Undetermined (1)	Topic (1) 1 time a day (1)
High pressure (2) / B (2)	Leaf (2)	Decoction (2)	Oral ingestion (2)	-	-	-	-	Oral (2) 2 to 3 times a day; 1 to 2 times a day
Spine problems (15) / B(1); C (5); D(2); E (3); G(1); H (3)	Seed (1), Oil-resin (13), leaf (1)	Mix with water (3), decoction (1), Roast the seed and cook to extract an oil (1)	Massage (11), poultice (2), Oral ingestion (3)	Any time (3), late afternoon (1)	Plastic container (8), glass (6), aluminum (2), pot or can (2)	Environment (10)	Undetermined (4), if you keep too much curd (1), more than 1 year (1)	Topic (12), oral (4) 2 to 3 times a day; 2 drops, 1 time a day; 3 times a day, until it heals (5); 2 times a day; 1 time a day, indefinitely (2); 1 time
Kidney problem (3) / A (1); C (1); G (1)	Leaf (2), Oil-resin (1)	Decoction (2)	Oral ingestion (3)	Any time (2)	Glass container (1), bag (1)	Cooling (1), environment (1)	-	Oral (3) Half an American glass, 3 times a day, until it heals; 1 time a

Therapeutic Indications / Communities	Part Used	Preparation	Administration	Collection Time	Storage type	Storage conditions (temperature)	Storage time	Dosage / Route of administration
								day, until it heals; 3 drops, 2 times a day
Prostate (1) /C(1)	Oil-resin (1)	Mix with some tea (1)	Oral ingestion (1)	-	Plastic container (1), glass (1)	Environment (1)	-	Oral (1) 3 drops, 2 times a day
Skin burn (3) / G(1); H (2)	Oil-resin (2)	-	Poultice (2), massage (1)	-	Plastic container (2), glass (1)	Environment (3)	-	Topic (3) 2 times a day (2); 1 time
Sun burn (1) / C(1)	Oil-resin (1)	Passes on the skin (1)	-	-	-	-	-	Topic (1)
Cracked feet (4) / C (3); H(1)	Oil-resin (4)	-	Massage (4)	-	Glass container (3)	Environment (1)	1 year (2)	Topic (4) 1 time (2); 3 times a day (1)
Sinusitis (1) / A(1)	Stalk stem (1)	Decoction (1)	Inhalation through the nose (1)	-	Plastic bag (1)	Environment (1)	1 year (1)	Inhalation (1)
Tendonitis (1) / H(1)	Oil-resin (1)	-	Massage (1)	-	Plastic container (1), glass (1)	Environment (1)	-	Topic (1) 2 times a day (1)
Cough (7) / A (2); B (1); E (2); H (2)	Oil-resin (5), Stalk stem (1), leaf (1)	Dissolve the resin in coffee (2) or tea (1), cooking (1), mix with oil-resin honey (1), leaf decoction (1)	Oral ingestion (7)	Any time (3), morning (1)	Plastic container (1), glass (3)	Environment (4)	Undetermined (2), if too much curd is spent (1)	Oral (7) 3 drops in 1 cup of coffee, 2 times a day; 3 times a day, until it heals (3); 1 time a day, until it heals; 2 times a day, until it heals
Tumor (2) / F(2)	Oil-resin (2)	-	Poultice (1), oral ingestion (1)	-	Plastic container (1)	Environment (1), refrigeration (1)	-	Topic (1), oral (1) 3 times a day; 3 drops, 3 times a day, for 6 months
Gastric ulcer (1) / E(1)	Oil-resin (1)	Mix with tea (1)	Oral ingestion (1)	-	-	Environment (1)		Oral (1) 2 times (1). Until cure (1)

Therapeutic Indications / Communities	Part Used	Preparation	Administration	Collection Time	Storage type	Storage conditions (temperature)	Storage time	Dosage / Route of administration
Worm (1) / B(1)	Oil-resin (1)	Mixing with water (1), coffee (1) or tea (1)	Oral ingestion (1)	-	Glass container (1), plastic (1)	Environment (1)	Undetermined (1)	Oral (1) 5 drops (1)

SUBTITLE: A: Barreiro Grande; B: Manoel Coco; C: Zabelê; D: Minguiriba; E: Guaribas; F: Baixio das Palmeiras; G: Baixio do Muquén; H: Baixio da Chapada; AVC: Stroke.

Table 3: Usage Diversity Value for *Copaifera langsdorffii* Desf. in Chapada do Araripe Nordeste communities, Brazil.

Category Body systems / Initials (ICPC-2)	Cerradão Therapeutic indication and code / number of citations for use	UD	Carrasco Therapeutic indication and code / number of citations for use	UD	Humid Forest Therapeutic indication and code / number of citations for use	UD	Caatinga Therapeutic indication and code / number of citations for use	UD
Circulatory (K)	(K96) Hemorrhoid (4), (K85) High pressure (2)	0.07	(K95) Pain in the veins (1)	0.03			(K96) Hemorrhoid (2), (K90) Stroke (1), (K99) Bad circulation (1)	0.06
Digestive (D)	(D82) Toothache (2), (D07) Indigestion (2), (D96) Worm (1), (D99) Gastritis (2)	0.08	(D07) Indigestion (1), (D29) Bellyache (4), (D11) Diarrhea (2)	0.24	(D99) Gastritis (2), (D02) Stomach ache (3), (D29) Bellyache (2), (D12) Laxative / Constipation (1), (D86) Gastric ulcer (1)	0.18	(D82) Toothache (1), (D99) Gastritis (2), (D02) Stomach ache (1)	0.06
Endocrine / Metabolic and Nutritional (T)	(T03) Loss of appetite (6)	0.07			(T89/T90) Diabetes (1)	0.02		
Female Genital (X)	(X75) Uterine cancer (1)	0.01	(X15) Vaginal inflammation (2)	0.07				
Male Genital (Y)	(Y06) Prostate (1)	0.01						
General and Nonspecific (A)	(A08) Swelling (1), (A79) Cancer (1), (A01) General pain (5), (A29) Inflammation in general (2)	0.10	(A08) Swelling (3)	0.10	(A79) Cancer (2), (A29) Inflammation in general (2), (A29) Body ache (1), (A78) Infection in general (2)	0.14	(A08) Swelling (3), (A79) Cancer (3), (A01) General pain (2)	0.12
Muscle - Skeletal (L)	(L88) Rheumatoid arthritis (6), (L14) Pain in the legs (4), Bone pain (7), (L79) Sprains (1), (L91) Arthrosis (2), (L20) Joint pain (4), (L29) Spine problems (6)	0.33	(L88) Rheumatoid arthritis (3), Bone pain (3), (L29) Spine problems (2)	0.28	(L88) Rheumatoid arthritis (2), Bone pain (4), (L29) Spine problems (3), (L20) Joint pain (1)	0.20	(L88) Rheumatoid arthritis (6), (L14) Pain in the legs (1), Bone pain (1), (L91) Arthrosis (4), (L20) Joint pain (4), (L29) Spine problems (4), (L99) Herniated disc (1), (L18) Muscular	0.37

Category Body systems / Initials (ICPC-2)	Cerradão Therapeutic indication and code / number of citations for use	UD	Carrasco Therapeutic indication and code / number of citations for use	UD	Humid Forest Therapeutic indication and code / number of citations for use	UD	Caatinga Therapeutic indication and code / number of citations for use	UD
							pain (1), (L91) Osteoporosis (1), (L87) Tendonitis (1), (L04) Open chest (1)	
Neurological (N)	(N89) Migraine (1), (N01) Headache (1)	0.02	(N89) Migraine (1), (N01) Headache (2)	0.10			(N01) Headache (1)	0.01
Ear (H)	(H01) Earache (3)	0.03	-		-		-	
Skin (S)	(S19) Beat (1), (S18) Healing (6), (S76) Ringworm (1), (S21) Cracked feet (3), (S80) Sun burn (1)	0.13	(S19) Beat (2), (S19) Stretch mark of pregnant woman (1)	0.10	(S19) Beat (1), (S18) Healing (10)	0.22	(S19) Beat (2), (S18) Healing (5), (S21) Cracked feet (1), (S14) Skin burn (3), (S12) Bug bite (marimbondo) (1), (S04) Tumor (2)	0.21
Psychological (P)	(P01) Nervousness (2), (P06) Insomnia (1)	0.03						
Respiratory (R)	(R75) Sinusitis (1), (R05) Cough (3), (R96) Asthma (1), (R92) Throat cancer (1), (R21) Inflamed throat (1), (R78) Bronchitis (1)	0.09	(R21) Inflamed throat (1), (R80) Flu (1)	0.07	(R05) Cough (2), (R21) Inflamed throat (5), (R80) Flu (3), (R90) Tonsils hypertrophy (1)	0.22	(R05) Cough (2), (R21) Inflamed throat (6), (R80) Flu (1), (R90) Tonsils hypertrophy (1)	0.15
Urinary (U)	(U29) Urinary pain (2), (U14) Kidney problem (2)	0.04	-		-		(U29) Urinary pain (1), (U14) Kidney problem (1)	0.03

Table 4: Comparison of the Level of Fidelity (FL) in relation to the medicinal indications of *Copaifera langsdorffii* Desf. in Chapada do Araripe communities, Northeast, Brazil.

Cerradão		**Carrasco**		**Humid Forest**		**Caatinga**	
Therapeutic indications	**FL%**	**Therapeutic indications**	**FL%**	**Therapeutic indications**	**FL%**	**Therapeutic indications**	**FL%**
Bone pain	25.00	Bellyache	50.00	Healing	66.67	Artrite reumática	26.09
Healing	21.43	Swelling	38.00	Inflamed throat	33.33	Inflamed throat	26.09
Artrite reumática	21.43	Artrite reumática	38.00	Bone pain	26.67	Healing	21.74
Loss of appetite	21.43	Bone pain	38.00	Spine problems	20.00	Arthrosis	17.39
Spine problems	21.43	Diarrhea	25.00	Flu	20.00	Spine problems	17.39
General pain	17.86	Headache	25.00	Stomach ache	20.00	Joint pain	17.39
Pain in the legs	14.29	Beat	25.00	Artrite reumática	13.33	Cancer	13.04
Joint pain	14.29	Vaginal inflammation	25.00	Inflammation in general	13.33	Swelling	13.04
Hemorrhoid	14.29	Spine problems	25.00	Cancer	13.33	Skin burn	13.04
Earache	10.71	Migraine	13.00	Cough	13.33	General pain	8.70
Cracked feet	10.71	Indigestion	13.00	Infection in general	13.33	Gastritis	8.70
Cough	10.71	Pain in the veins	13.00	Gastritis	13.33	Hemorrhoid	8.70
Inflammation in general	7.14	Stretch mark of pregnant woman	13.00	Bellyache	13.33	Beat	8.70
Urinary pain	7.14	Flu	13.00	Joint pain	6.67	Tumor	8.70
Nervousness	7.14	Inflamed throat	13.00	Beat	6.67	Cough	8.70
High pressure	7.14			Diabetes	6.67	Stroke	4.35
Gastritis	7.14			Body ache	6.67	Headache	4.35
Kidney problem	7.14			Tonsils hypertrophy	6.67	Pain in the legs	4.35
Toothache	7.14			Laxative / Constipation	6.67	Tendonitis	4.35
Indigestion	7.14			Gastric ulcer	6.67	Bad circulation	4.35
Arthrosis	7.14					Open chest	4.35
Swelling	3.57					Stomach ache	4.35
Beat	3.57					Herniated disc	4.35
Sinusitis	3.57					Kidney problem	4.35
Headache	3.57					Cracked feet	4.35
Asthma	3.57					Toothache	4.35
Cancer	3.57					Urinary pain	4.35
Throat cancer	3.57					Muscular pain	4.35
Uterine cancer	3.57					Bone pain	4.35
Migraine	3.57					Flu	4.35
Inflamed throat	3.57					Tonsils hypertrophy	4.35
Sprains	3.57					Osteoporosis	4.35
Sun burn	3.57					Bug bite	4.35

Bronchitis	3.57
Insomnia	3.57
Ringworm	3.57
Prostate	3.57

Table 5: Plant part consensus value (PPC) *Copaifera langsdorffii* Desf. in Chapada do Araripe communities, Northeast, Brazil.

Part Used	PPC: Cerradão	PPC: Carrasco	PPC: Humid Forest	PPC: Caatinga
Oil-resin	0.71	0.45	0.88	0.96
Leaf	0.18	0.34	-	0.01
Stalk stem	0.05	0.07	0.10	0.03
Stem bark	0.03	-	-	-
Seed	0.02	0.14	0.02	-

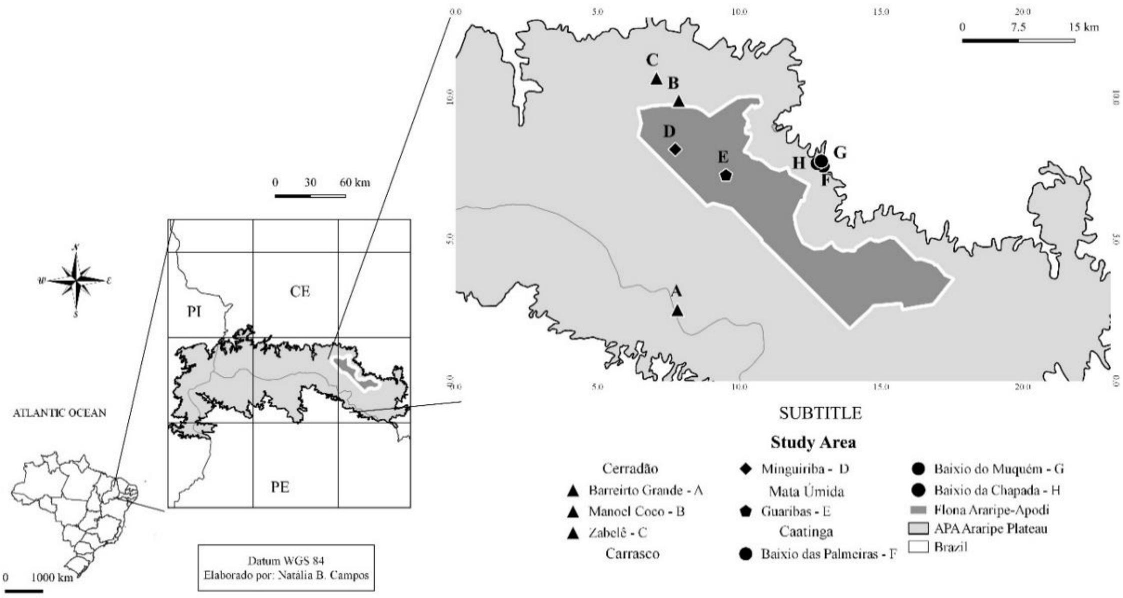

Fig. 1. Geographic location of the study areas in Chapada do Araripe, Ceará, Brazil.

Supplementary material

Table S1: Semi-structured roadmap for ethnobotanical data collection

Name: ____
Age: ________; Sex: ( ) W ( ) M ; Level of Education ________________________
Specie: *Copaifera langsdorffii* Desf.

Doença	Qual área é coletada (Cerrado, Carrasco ou Mata Úmida)	Parte da planta armazenada	Como é coletada	Hora da coleta	Como é armazenada	Tipo de armazenamento	Condições de armazenamento (temperatura)	Tempo de armazena mento	Como se prepara?	Como se usa?	Via de administração	Posologia
		Folha ( ) Fruto( ) Flor( ) Raiz( ) Entrecasca( ) Leite( ) Óleo ( ) Resina( )	Seca ( ) Verde ( )	Manhã () Tarde () Noite () Qualquer horário () Outros: se tem uma hora específica______	Seca ( ) Verde ( )	Embalagem de: Papel ( ) Plástico ( ) Papel alumínio ( ) Lata ( ) Pote ( ) No álcool( ) Na cachaça( ) Quintal () Outros:_________	Ambiente ( ) Refrigeração ( ) Outros:_______		Infusão ( ) Decocção( ) De molho( ) Lambedor( ) Sumo ( )	Banho ( ) Lavagem( ) Cataplasma( ) Maceração( ) Outros: __________	Tópico ( ) Oral ( ) Inalação ( ) Outros: ________	Quantidade utilizada: Vezes ao dia: Quanto tempo: Contraindicação: Toxicidade:
		Folha ( ) Fruto( ) flor( ) Raiz( ) Entrecasca( ) leite( ) óleo ( ) resina( )	Seca ( ) Verde ( )	Manhã () Tarde () Noite () Qualquer horário () Outros: se tem uma hora específica______	Seca ( ) Verde ( )	Embalagem de: Papel ( ) Plástico ( ) Papel alumínio ( ) Lata ( ) Pote ( ) No álcool( ) Na cachaça( ) Quintal () Outros:_________	Ambiente ( ) Refrigeração ( ) Outros:_______		infusão ( ) decocção( ) de molho( ) lambedor( ) sumo ( ) no álcool( ) cachaça( )	banho ( ) lavagem( ) cataplasma( ) maceração( ) Outros: __________	Tópico ( ) Oral ( ) Inalação ( ) Outros: ________	Quantidade utilizada: Vezes ao dia: Quanto tempo: Contraindicação: Toxicidade:
		Folha ( ) Fruto( ) flor( ) Raiz( ) Entrecasca( ) leite( ) óleo ( ) resina( )	Seca ( ) Verde ( )	Manhã () Tarde () Noite () Qualquer horário () Outros: se tem uma hora específica______	Seca ( ) Verde ( )	Embalagem de: Papel ( ) Plástico ( ) Papel alumínio ( ) Lata ( ) Pote ( ) No álcool( ) Na cachaça( ) Quintal () Outros:_________	Ambiente ( ) Refrigeração ( ) Outros:_______		infusão ( ) decocção( ) de molho( ) lambedor( ) sumo ( ) no álcool( ) cachaça( )	banho ( ) lavagem( ) cataplasma( ) maceração( ) Outros: __________	Tópico ( ) Oral ( ) Inalação ( ) Outros: ________	Quantidade utilizada: Vezes ao dia: Quanto tempo: Contraindicação: Toxicidade:

5. CAPÍTULO 4: Artigo III

Título: Chemical composition variation of essential oils of *Copaifera langsdorffii* Desf. from different vegetational formations

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Chemical composition variation of essential oils of *Copaifera langsdorffii* Desf. from different vegetational formations

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Abstract

This study aims to provide information about the chemical profile of the essential oil from *C. langsdorffii* resin in areas of *Cerradão*, *Carrasco*, and Humid Forest. In order to obtain the essential oils, oil-resin was submitted to hydrodistillation process, and the chemical components were analyzed by gas chromatography coupled to mass spectrometry (GC/MS). Twenty-six constituents were identified in the essential oil of *C. langsdorffii* resin, of which 12 were present in *Cerradão*, 15 in *Carrasco* and 18 in Humid Forest, with β-bisabolene, caryophyllene oxide, γ-muurolene, α-caryophyllene and β-caryophyllene common to the three phytophysiognomies. Among the studied areas, the resin collection varied from 2.652 g to 20.263 g, while the essential oil yield varied from 2.216% to 11.764%. A concentration range of 0.60% to 84.57% was recorded among the compounds in the three study areas. There was variation in chemical composition both among phytophysiognomies and among individuals from the same location, where β-caryophyllene showed to be the majority for all areas studied, being present in all individuals from *Cerradão*, *Carrasco* and Humid Forest.

Keywords: *Copaifera langsdorffii*; Chemical profile; Chemical variability; Different phytophysiognomies; β-caryophyllene

1. Introduction

Copaifera langsdorffii Desf. is frequently used in folk medicine and the pharmaceutical industry, notable mainly for being a producer of oil-resin, a secondary metabolite extracted from the stem with phytotherapeutic effects of great economic value (Veiga Junior & Pinto 2002; Stupp et al. 2008; Nisgoski et al. 2012; Gama & Nascimento Júnior 2019), arousing interest in scientific research that proves the citations of uses by communities.

This species has a wide distribution, being found in Brazil, Paraguay, Argentina and Bolivia (GBIF 2021). In Brazil it is found throughout the territory (Costa 2020), in phytophysiognomies such as Campo Rupestre, Cerrado (lato sensu), Riparian Forest or Gallery, Terra Firme Forest, Semideciduous Seasonal Forest and Ombrophilous Forest (Rainforest), and in anthropized areas (Costa 2020).

In the Chapada do Araripe region, *C. langsdorffii* can be found in the phytophysiognomies of *Cerradão*, *Carrasco* and Humid Forest (Cartaxo et al. 2010; Ribeiro et al. 2014; Saraiva et al. 2015; Santos et al. 2019). This species has great medicinal potential, being of large importance for communities, and is indicated for the treatment of various health problems such as flu, coughs, expectorant, colds, bone problems, healing, inflammation, diuretic and allergies (Veiga Junior & Pinto 2002; Pasa et al. 2005; Ribeiro et al. 2014; Saraiva et al. 2015; Macêdo et al. 2018).

The numerous therapeutic indications of *C. langsdorffii* are linked to the presence of an active ingredient. Understanding the variability of chemical composition in different phytophysiognomies can help in expanding knowledge about ecological interactions of the plant with its environment (Gobbo-Neto & Lopes 2007), also indicating the best environment for collection in order to obtain desirable concentrations of chemical compounds that suit the needs of the market and communities (Figueiredo et al. 2009).

Differences in chemical composition as a function of the collection environment were reported for different species, including *C. langsdorffii* (Almeida et al. 2014; Oliveira et al. 2017). In a review of *C. langsdorffii* Santos et al. (2022) found that there was variation in the chemical composition of the essential oil both for the same region and between different Brazilian regions. This shows the great variability of the chemical composition of this species caused by the specificities of each environment.

Therefore, considering the medicinal and economic importance of *C. langsdorffii* for communities coupled with the lack of scientific information related to chemical data in different vegetational types, this study aims to analyze the chemical profile of the essential oils extracted from the stem resin of *C. langsdorffii* in areas of *Cerradão*, *Carrasco*, and Humid Forest in the

Northeast of Brazil in order to investigate the chemical variation of the species in different areas, and indicate in which environment the species produces highest chemical content.

2. Results and Discussion

2.1. Chemical profile and essential oil yield of *Copaifera langsdorffii* Desf. in different phytophysiognomies

Twenty-six different chemical constituents (Fig. S1) were identified in the essential oil extracted from *C. langsdorffii* trunk resin, of which 12 were present in *Cerradão*, 15 in *Carrasco*, and 18 in Humid Forest (Table S1). The common compounds in the *Cerradão*, *Carrasco* and Humid Forest phytophysiognomies were β-bisabolene, caryophyllene oxide, γ-muurolene, α-caryophyllene and β-caryophyllene. The concentration of each constituent varied between areas and individuals (Table S1). Similar concentrations are recorded for these compounds present in the essential oil of *Copaifera langdorffii* resin in studies developed in Brazil by Alencar et al. (2015), Gramosa & Silveira (2005) and Oliveira et al. (2017).

Among the compounds in the analyzed oil samples, a variation of 0.60% to 84.57% in the concentration of the essential oils was recorded (Table S1). These concentrations were both observed in the Humid Forest, the lowest being for β-elemene and (1R)-2,6,6-trimethylbicyclo[3.1.1]hept-2-ene, and the highest for β-caryophyllene (Table S1). Volatile extractions from the leaves (Almeida et al. 2014), and the resin (Oliveira et al. 2017) of the stem of *C. langsdorffii* were reported in the chemical composition of this species. This change in the chemical composition of the species in different phytophysiognomies may be related to ecophysiological events such as seasonality and temperature, as well as factors such as soil constitution, genetics, adaptive and evolutionary events, geographic area, and different developmental stages among individuals and populations (Wink 2003; Figueiredo et al. 2008; Teles et al. 2013).

Some compounds were exclusive to certain phytophysiognomies, three constituents (cedrene, (Z)-α-bisabolene and germacrene D) were recorded to be present only in *Cerradão*, five (α-copaene, α-guaiene, ylangene, cycloisosativene, and (1R)-2,6,6-trimethylbicyclo[3. 1.1]hept-2-ene) appeared only in the Humid Forest, and six (azulene, β-selinene, naphthalene, isoeremophilene, (E)-α-bergamotene and δ-cadinene) only in *Carrasco* (Table S1). Among them, germacrene D, α-copaene, β-selinene, (E)-α-bergamotene, and δ-cadinene have been recorded in the literature on Brazilian *Cerrado*, found in different plant parts of *Copaifera langsdorffii*, such as leaf, resin and fruit (Almeida et al. 2014; Portella et al. 2015; Almeida et al. 2016; Oliveira et al. 2017). In contrast, cedrene (Oliveira et al. 2017) and α-guaiene (Gelmini et al. 2013) appear only in the resin of this species. For the other compounds no record was found.

β-caryophyllene proved to be the dominant substance for all areas and individuals studied, with concentrations ranging from 22.83% to 84.57% (Table S1). β-caryophyllene together with β-bisabolene, (Z)-α-bergamotene, and α-himachalene are recorded in the literature as majorities (Gramosa & Silveira 2005; Gelmini et al. 2013; Alencar et al. 2015; Oliveira et al. 2017).

Among the areas, the collected resin varied from 2.652 g to 20.263 g, while the essential oil yield varied from 2.216% to 11.764% (Table S2). The variation in resin and essential oil yield are in accordance with that found by Oliveira et al. (2017) and Gelmini et al. (2013) for *C. langsdorffii*. The authors observed values for the resin between 1.10 g and 34.70 g, and for the yield of essential oil between 2.15% and 28.80%.

In the Humid Forest, the amount of resin collected was 15.672 g, 20.263 g and 12.784 g, giving 4.217%, 2.270% and 7.227% of essential oil for the three individuals analyzed, respectively. *Carrasco*, on the other hand, had 8.792 g, 14.341 g and 10.042 g of resin, giving 5.937 %, 5.376 % and 6.293 %, respectively. In *Cerradão* the resin collection was 4.081 g, 5.594 g and 2.652 g, giving 7.865%, 2.216% and 11.764% essential oil, respectively (Table S2). In areas of Conserved and Anthropized *Cerrado*, Oliveira et al. (2017) obtained, for the same month of collection (February), 10.6 g and 3.1 g of resin, yielding 23.2% and 11.6% essential oil, respectively. Almeida et al. (2014), on the other hand, using the leaves of this species, obtained a variation for the semideciduous seasonal forest of 0.11% to 0.38%, while in the *Cerrado strictu sensu*, a variation of 0.45% to 0.60% was observed. Almeida et al. (2016), also working with the leaves in *Cerrado* vegetation, obtained an essential oil yield ranging from 0.03% to 0.05%.

The yield of essential oil for the *Cerradão*, *Carrasco*, and Humid Forest areas is not related to the amount of oil-resin used in the extraction of this mixture. For the *Cerradão*, in a resin variation of 2.652 g to 5.594 g, 12 constituents were detected; in the *Carrasco*, between 8.792 g to 14.341 g of resin presented 15 compounds; as for Humid Forest, the resin collection varied between 12.784 g to 20.263 g, and its essential oil presented 18 compounds (Table S2).

Statistically, there were no significant differences between the yields of essential oils obtained and collected in the different phytophysiognomies ($p=0.397$). On average, the samples show only small differences, higher oil yields were verified in the *Cerradão*, where the lowest mass of oil resin was obtained, but the yields were the most considerable, different from the collections carried out in the Humid Forest, where the highest mass of oil resin was obtained and the yield showed the lowest average. In a comparative analysis between Humid Forest and *Cerradão*, although there was no significant difference in oil yield ($p>0.05$) when compared to each other, the lowest value of $p=0.329$ was verified. Between *Cerradão* and *Carrasco* a value of $p=0.850$ was verified and between *Carrasco* and Humid Forest $p=0.602$, showing that there is not a significant difference between the evaluated data.

Therefore, qualitative and quantitative variation is observed in the chemical composition of *C. langsdorffii* in the *Cerradão*, *Carrasco*, and Humid Forest phytophysiognomies, with differences in the number of compounds recorded in each environment, as well as in the concentration of these compounds, although statistically not considered relevant. Further studies are needed in order to determine which factors influence these variations.

3. Conclusion

The distinct phytochemical profiles presented in the essential oil of *Copaifera langsdorffii* Desf. resin, in vegetation formations of *Cerradão*, *Carrasco* and Humid Forest, show a variation among phytophysiognomies, as well as among individuals from the same site. This diversity in chemical composition is responsible for the biological activities conferred to this species. The compound β-caryophyllene proved to be the majority for all areas studied and it was present in all individuals from *Cerradão*, *Carrasco*, and Humid Forest. Among the phytophysiognomies analyzed, *Cerradão* is considered the most promising, both for further studies with *C. langsdorffii*, as well as for the elaboration of medicines, since it offers a higher yield in its essential oil.

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Conflicts of interest

The author declares no conflict of interest associated with this publication.

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Supplementary material

Experimental

Study field

The research was performed in Araripe National Forest (Portuguese FLONA), in Cerradão (39W 35' 08" 7S 20' 36"), Carrasco (39W 33' 47" 7S 15' 35") and humid forest (39W 31' 46" 7S 18' 42") phytophysiognomies located in the municipality of Crato, south of Ceará State, Northeast Brazil (Fig.S2).

The *Chapada do Araripe* covers a total area of 9,000 km², with altitudes ranging from 700 to 1000 mm, presenting a tabular relief (Velloso et al. 2001). The climate is hot and semi-arid with the annually average precipitation ranging from 698 to 934 mm, with the presence of orographic rains, which can increase this amount to more than 1000 mm per year, with rainy season occurring from December to May (Velloso et al. 2001). The soils are predominantly yellowish-red latosols, litholic neosols, and yellowish-red acrisols which, due to this mosaic, show a variety of phytophysiognomies, and characterize different environmental gradients throughout the entire area of the plateau (Souza & Oliveira 2006). The latosols, found at the top of the plateau, are deep, low-fertile, and characterized by *Cerrado* and *Cerradão* vegetation coverage. Neosols cover the slopes and downhill areas; they are very shallow and low-fertile stony soils, presenting a transition belt from the Subperenifolia Forest (Ombrophilous Forest) to the Hypoxerophilous Caatinga. Lastly, the acrisols are located from the middle to lower parts; they are shallow and high-fertile soils with a vegetation consisting of Subperennial Forest and Hypoxerophilic Caatinga (Souza & Oliveira 2006). The main water bodies in the headwaters of this plateau drain areas of high altitude Humid Forest, and are inserted within the Caatinga Middle-Northeast (CMN) hydrographic ecoregion (Albert & Reis 2011). This Ecoregion is limited by small coastal hydrographic basins, represented by the rivers *Coreaú*, *Choró* and *Apodi,* and medium-sized ones represented by the rivers *Piranha-Açu* and *Jaguaribe*. The latter are responsible for the drainage of the *Ibiapaba* Mountains and a large portion of the *Araripe* plateau (Rosa 2003).

Material collection and botanical identification

Copaifera langsdorffii was collected in the three study areas and taken to the *Laboratório de Ecologia Vegetal* (LEV) of the *Universidade Regional do Cariri - URCA.* The vegetal sample material was conditioned and treated according to the usual herborization techniques (Mori et al. 1989). Subsequently, it was identified and deposited in the *Carirense Dárdano de Andrade Lima Herbarium* of the *Universidade Regional do Cariri* (URCA) with registers No. 14.312 (*Cerradão*), No. 14.313 (*Carrasco*), and No. 14.314 (Humid Forest). Authorization for collecting botanical material was provided by the *Sistema de Autorização e Informação em Biodiversidade* (SISBIO) of the *Instituto Brasileiro do Meio Ambiente e dos Recursos Naturais Renováveis* (IBAMA), registered under number 67422-1.

Data collection

Oil-resin collection

Resin oil from trunks of *Copaifera langsdorffii* was collected in February 2019 in *Cerradão, Carrasco,* and Humid Forest areas. The methodology used by Oliveira et al. (2017) was adopted, in which three adult trees in each area were selected for collection. Individuals were selected with a visually healthy appearance, with similar characteristics regarding length, diameter, and with homogeneous environmental conditions. The extraction was performed by drilling the trunk of the trees with a 2 cm diameter auger at a height of 1.30 m from the ground. A piece of PVC pipe (¾) was inserted into the hole to drain the oil-resin off . The pipe was connected to a collecting container with a capacity of approximately 250 ml through a plastic hose (¾). After the oil-resin are collected, the pipes were removed and the holes sealed with a wooden plug. All the extracted oil-resin are packed in plastic jars and covered with aluminum foil for a safer transportation to the laboratory. The permission for collecting the oil-resin was provided by the *Sistema de Autorização e Informação em Biodiversidade* (SISBIO) of the *Instituto Brasileiro do Meio Ambiente e dos Recursos Naturais Renováveis* (IBAMA), registered under number 67422-1.

Obtaining the essential oils

Nine samples of resin oils were collected from the three study areas (*Cerradão*, *Carrasco* and Humid Forest), and submitted to hydrodistillation for 2 hours in a modified Clevenger apparatus in the *Laboratório de Pesquisa de Produtos Naturais* (LPPN) of the *Universidade Regional do Cariri-URCA*. The water-oils essential mixture was collected, treated with anhydrous sodium sulfate (Na_2SO_4), and the essential oils were separated and kept under refrigeration at less than 4 °C until further analysis.

Data analysis

Chemical composition analysis

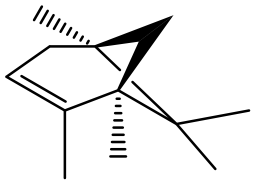
The identifications of the essential oil components from *Copaifera langsdorffii* oil-resin were performed by gas chromatography coupled to mass spectrometry (GC/MS) in a Shimadzu QP 2010 spectrometer operating at an ionization energy of 70 eV. DB-5 fused silica capillary column(30 m x 0.25 mm i.d., 0.25 µm film thickness), and helium gas carrier with 1mL/min split flow rate were used.

Injector and detector temperatures were preset 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, and these parameters have been previously analyzed (Oliveira et al. 2017). Individual components were identified by computational search using digital libraries of mass spectral data (NIST 08) and by comparing their authentic mass spectra. The Kovats retention index was obtained by injecting a mixture of C8-C40 linear hydrocarbons under the same conditions as the samples, as described by Van Den Dool & Kratz (1963). The identity of the compounds was confirmed by comparing their retention indices and mass spectra with those taken from the literature (Adams 2017).

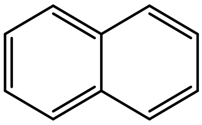
Statistical analysis of yield of essential oils

To assess the existence of significant differences between the oil yields obtained in different phytophysiognomies, the data was submitted to statistical evaluation using one-way analysis of variance (ANOVA), followed by Tukey's multiple comparison test. Differences were considered significant at $P < 0.05$, using the Prisma Graph-Pad software (version 5.0).

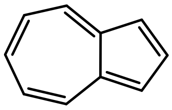
Figure S1: Compounds of the oil-resin of *Copaifera langsdorffii* Desf. of *Cerradão*, *Carrasco* and Humid Forest areas of Chapada do Araripe Nordeste, Brazil.



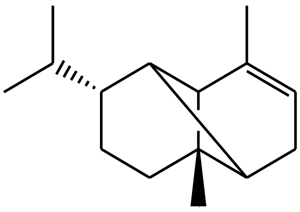
(1R)-2,6,6-trimethylbicyclo[3.1.1]hept-2-ene



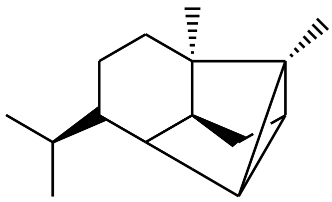
naphthalene



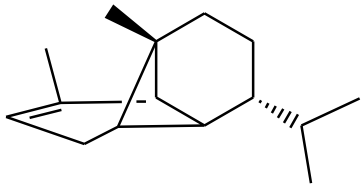
azulene



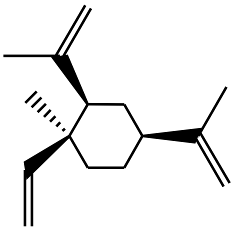
ylangene



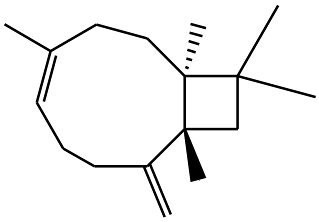
cycloisosativene



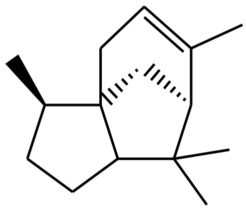
α-copaene



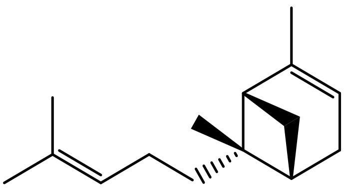
β-elemene



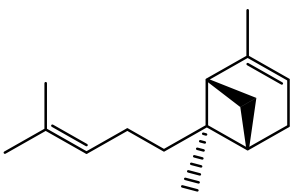
β-caryophyllene



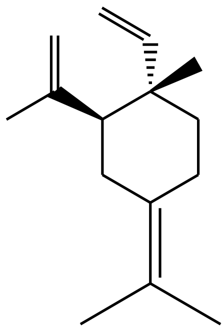
cedrene



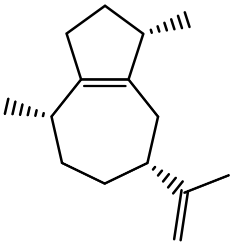
(Z)-α-bergamotene



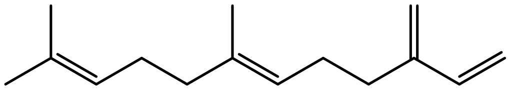
(E)-α-bergamotene



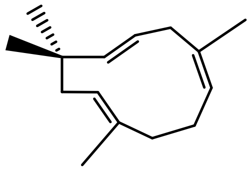
γ-elemene



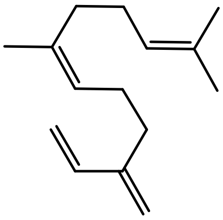
α-guaiene



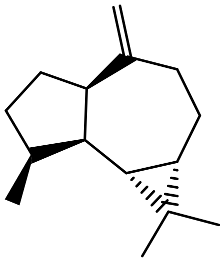
(E)-β-farnesene



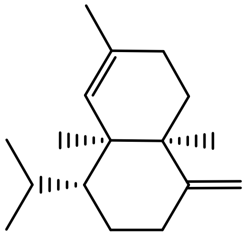
α-caryophyllene



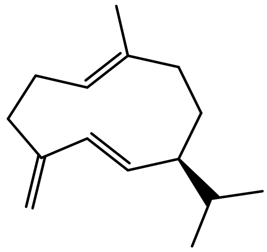
(Z)-β-farnesene



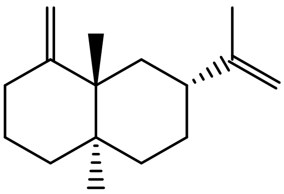
alloaromadendrene



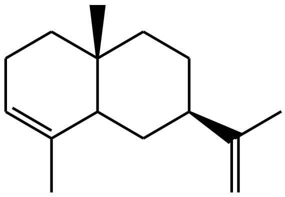
γ-muurolene



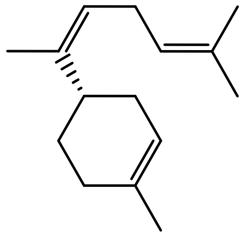
germacrene D



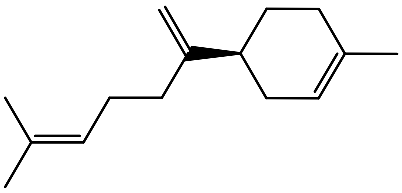
β-selinene



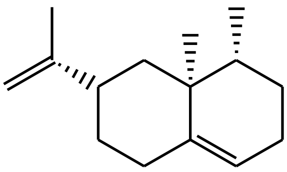
α-selinene



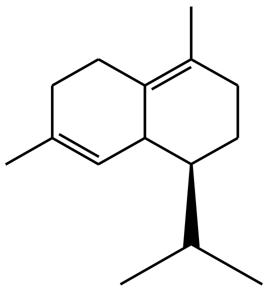
(Z)-α-bisabolene



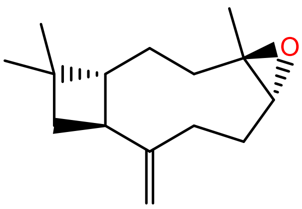
β-bisabolene



isoeremophilene



δ-cadinene



caryophyllene oxide

Figure S2. Geographic location of the study areas in Chapada do Araripe, Ceará, Brazil.

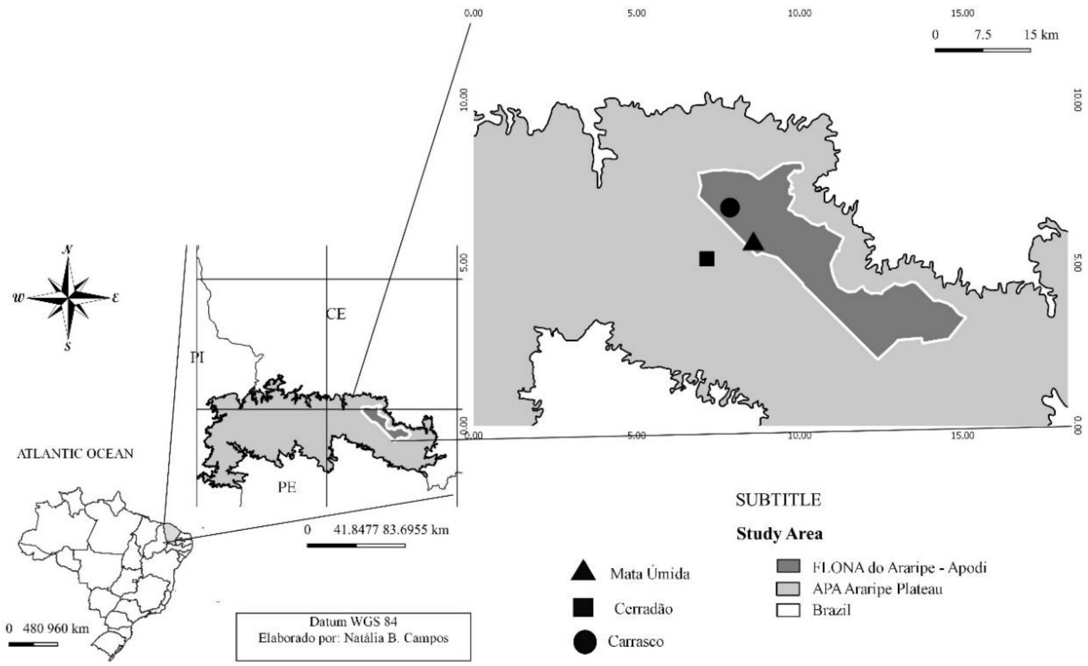


Table S1: Volatiles (%) identified from the phytophysiognomic resin of *Cerradão*, *Carrasco* and Humid Forest essential oils of *Copaifera langsdorffii* Desf.

Compounds	RI[1]	RI[2]	*Cerradão* Individual (%)			*Carrasco* Individual (%)			Humid Forest Individual (%)		
			1	2	3	1	2	3	1	2	3
(1R)-2,6,6-trimethylbicyclo[3.1.1]hept-2-ene	934	937	-	-	-	-	-	-	-	0.60	-
Naphthalene	1180	1176	2.24	1.18	-	3.94	-	-	1.41	-	-
Azulene	1291	1298	-	-	-	3.09	-	-	-	-	-
Ylangene	1348	1350	-	-	-	-	-	-	0.85	-	-
Cycloisosativene	1363	1369	-	-	-	-	-	-	-	1.50	-
α-copaene	1372	1372	-	-	-	-	-	-	0.74	1.39	-
β-elemene	1387	1389	-	-	-	-	3.36	1.75	-	0.60	6.33
β-caryophyllene	1404	1407	64.21	49.75	22.83	61.64	65.49	64.19	72.35	84.57	71.71
Cedrene	1408	1410	1.56	-	1.00	-	-	-	-	-	-
(Z)-α-bergamotene	1410	1411	-	4.98	43.68	-	-	-	9.08	-	2.35
(E)-α-bergamotene	1429	1432	-	-	-	-	9.88	6.07	-	-	-
γ-elemene	1434	1434	-	-	-	10.37	4.75	1.66	-	-	4.05
α-guaiene	1438	1437	-	-	-	-	-	-	-	0.98	5.47
(E)-β-farnesene	1441	1440	0.84	1.51	2.54	-	-	-	0.72	-	-
α-caryophyllene	1442	1444	8.54	6.18	5.05	5.46	5.15	5.90	5.90	6.32	5.13
(Z)-β-farnesene	1453	1454	-	-	4.39	-	-	-	0.68	-	-
Alloaromadendrene	1460	1461	-	-	-	3.21	-	-	-	0.61	-
γ-muurolene	1478	1477	2.33	6.60	1.24	5.12	4.30	4.03	-	1.31	-
germacrene D	1481	1484	1.68	1.98	-	-	-	-	-	-	-
β-selinene	1487	1489	-	-	-	-	2.63	1.62	-	-	-

α-selinene	1499	1498	-	-	-	7.17	-	-	-	-	4.97
(Z)-α-bisabolene	1503	1504	1.40	-	2.93	-	-	-	-	-	-
β-bisabolene	1510	1509	17.20	20.75	16.33	-	-	11.35	3.34	-	-
Isoeremophilene	1514	1516	-	-	-	-	2.08	-	-	-	-
δ-cadinene	1520	1522	-	-	-	-	2.35	1.63	-	-	-
caryophyllene oxide	1583	1582	-	7.07	-	-	-	1.81	4.94	2.11	-

Subtitle: RI^1: Experimental retention index; RI^2: Literature retention index (Adams, 2017); (-) Absent.

Table S2: Yield of essential oils from *Copaifera langsdorffii* Desf.

Individual	Collected oil-resin mass (g)			Yield (%)		
	Cerradão	*Carrasco*	Humid Forest	*Cerradão*	*Carrasco*	Humid Forest
1	4.081	8.792	15.672	7.865	5.937	4.217
2	5.594	14.341	20.263	2.216	5.376	2.270
3	2.652	10.042	12.784	11.764	6.293	7.227

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6. CAPÍTULO 5: CONSIDERAÇÕES FINAIS

6.1. PRINCIPAIS CONCLUSÕES

O crescente interesse por *Copaifera langsdorffii* Desf. no meio cientifico está relacionado à procura desta espécie pelas comunidades tradicionais e locais para uso medicinal. A sua ampla distribuição e o seu potencial para inúmeras atividades fitoterápicas, atribui a esta espécie grande versatilidade sendo frequentemente indicada para tratar processos inflamatórios, de cicatrização e traumas nos sistemas Musculo-Esquelético, Pele, Digestório, Neurológico e Respiratório. Grande parte das propriedades terapêuticas da *C. langsdorffii* está ligada a utilização da resina presente no caule, até mesmo para tratar determinadas doenças que são exclusivas de cada região.

O uso extenso da resina demonstra a transmissão do conhecimento entre comunidades, entretanto, outras partes da planta são utilizadas para o mesmo objetivo em algumas outras regiões, o que ressalta a influência de fatores culturais, disponibilidade do recurso no ambiente e até mesmo a acessibilidade na escolha da parte utilizada. A retirada incorreta e excessiva da resina do caule pode comprometer a sobrevivência da espécie em áreas conservadas, o que reforça mais ainda a necessidade de estudos que avaliem não apenas a resina, como também outras partes da planta, para elucidar a composição química da espécie como um todo, mesmo com a influência de variáveis externas.

A variabilidade existente entre o óleo essencial, extrato e resina bruta, de *C. langsdorffii* e entre as diferentes partes da planta e a mesma parte analisada em diferentes ambientes, demonstram as características peculiares de cada região que influenciam na sua utilização medicinal. A interação da espécie com diferentes condições ambientais e fitofisionomias frequentemente afetam a síntese de seus compostos químicos refletindo para a planta, em especial sua resina, uma variação qualitativa e quantitativa dos constituintes químicos responsáveis pelas atividades biológicas.

Pesquisa em diferentes fitofisionomias como Cerradão, Carrasco e Mata Úmida mostram consenso no uso da *C. langsdorffii*, porém, até o momento, poucos estudos químicos e farmacológicos foram desenvolvidos para confirmar a eficácia da espécie para estas enfermidades, principalmente para doenças relacionadas ao sistema Musculo-Esquelético sendo necessária a realização de análises *in vivo* e *in vitro* para detectar quais compostos estão contribuindo para esse efeito. Além disso, o conhecimento dos fatores que determinam a variabilidade química se torna importante, principalmente, para colaborar com a escolha de ambientes propícios com melhores condições de coleta e aperfeiçoamento para a obtenção de produtos com concentrações desejáveis de compostos químicos que favoreçam o isolamento e consequentemente mais estudos que podem determinar o papel de cada composto quanto ao potencial farmacológico.

Ao avaliar os óleos essenciais obtidos da resina da *C. langsdorffii* nas formações vegetais do Cerradão, Carrasco e Mata Úmida, seus distintos perfis fitoquímicos apresentam riqueza na composição química, variabilidade entre as fitofisionomias e entre indivíduos de um mesmo local. Dentre as fitofisionomias analisadas, mesmo com as alterações qualitativas e quantitativas verificadas na composição química dos óleos essenciais provindos dos diferentes ambientes, o Cerradão é considerado o mais promissor, tanto para estudos futuros com a espécie, quanto para elaboração de novos medicamentos, uma vez que oferece um maior rendimento em seu óleo essencial.

β-bisaboleno, óxido de cariofileno, γ-muurolene, α-cariofileno e β-cariofileno foram detectados nas três fitofisionomias estudadas, no entanto apresentaram variação das suas concentrações entre áreas e indivíduos. β-cariofileno mostrou-se majoritário para todas as áreas e esteve presente em todos os indivíduos avaliados. Este composto é encontrado em altas concentrações na resina retirado diretamente da planta, assim como, é presente em outras estruturas dessa espécie, reforçando a rica composição química registrada para diferentes partes vegetais, β-cariofileno, provavelmente é responsável por importantes atividades biológicas.

Investigações biológicas mais amplas tornam-se necessárias, além da caracterização e isolamento de compostos, tendo em vista as promissoras atividades biológicas já apresentadas por *C. langsdorffii*, que podem determinar o papel de cada composto quanto ao potencial farmacológico, subsidiando como fonte de produtos naturais biologicamente ativos, abrindo caminho para uma contribuição na busca e desenvolvimento de novas drogas, bem como, validar o uso na medicina tradicional.

Como os resultados mostraram elevada variabilidade na composição e concentração dos compostos químicos dos óleos essenciais extraídos nas diferentes fitofisionomias, ressalta-se além da investigação associando etnobotânica médica, composição química e atividades biológicas, a ecologia química desta espécie, uma vez que sabendo-se dos inúmeros fatores que podem levar a variação qualitativa e quantitativa de compostos químicos, fica clara a necessidade de estudos visando detectar, outras partes da planta, ambientes e as condições para cultivo e/ou coleta que conduzam a uma matéria-prima vegetal com concentrações desejáveis de princípios ativos.

6.2 CONTRIBUIÇÕES TEÓRICAS E/OU METODOLÓGICAS DA TESE

Os resultados apresentados em cada um dos capítulos são pertinentes, ao tempo em que propiciam um melhor entendimento das características químicas em diferentes fitofisionomias para *C. langsdorffii*, preenchendo lacunas de conhecimento ainda pouco abordadas. Essa pesquisa demonstrou o conhecimento etnobotânico, a composição química e atividades biológicas da *C. langsdorffii* em um contexto nacional. Vinculado a isso, essa tese trouxe os usos medicinais e o comportamento químico ecológico dessa espécie em diferentes fitofisionomias pertencentes à Chapada do Araripe.

A pesquisa desenvolvida com *C. langsdorffii* mostrou haver variação tanto dos usos medicinais nas comunidades, quanto na sua composição química dentro das diferentes fitofisionomias da Chapada do Araripe. Das indicações terapêuticas relatadas, reumatismo foi frequentemente indicada no estudo de revisão por diferentes comunidades da Chapada do Araripe. No entanto, tornam-se necessários testes farmacológicos *in vivo* para comprovar sua eficácia para esse uso. Em relação à química da espécie nas áreas de Cerradão, Carrasco e Mata Úmida, os resultados mostraram que o Cerradão foi considerado o melhor ambiente para coleta da resina dessa espécie, uma vez que oferece um maior rendimento em seu óleo essencial.

No campo metodológico, a tese traz um arranjo de revisão delineada de uma maneira clara e passível de ser replicada em investigações que busquem compreender características etnobotânicas, químicas e biológicas de uma espécie. Além disso, para o estudo local da espécie, utilizou-se uma metodologia acessível em relação a outras existentes para a elucidação dos constituintes químicos nas áreas de Cerradão, Carrasco e Mata Úmida e para a coleta dos dados etnobotânicos para uma espécie vegetal.

6.3 PRINCIPAIS LIMITAÇÕES DO ESTUDO

Dos desafios logísticos, as idas ao campo para a coleta da resina da espécie para o estudo químico, foram as mais complexas pela necessidade de não desperdiçar a resina no momento da extração, tendo em vista a utilização do método de extração racional através de uma pequena abertura no tronco da árvore utilizando-se um trado onde é inserido um cano que conduz a resina para o exterior, facilitando futuras extrações, podendo ser realizada de modo sustentável, assim como a realização do levantamento etnobotânico e, a dificuldade de contato com o mateiro por conta dos meios de comunicação e pandemia.

Devido a pandemia do coronavírus SARS-CoV-2 causador da COVID-19 que atingiu todo o mundo, levando os países a decretarem *lockdown* e dessa maneira, o fechamento e confinamento, os laboratórios ficaram impossibilitados de funcionar e dessa forma houve dificuldade para extração do óleo essencial e análise das amostras por Cromatografia Gasosa.

6.4 PROPOSTAS DE INVESTIGAÇÕES FUTURAS

Copaifera langsdorffii é indicada com frequência nas comunidades para tratar reumatismo, fratura óssea, epilepsia e depressão, mas até o momento nenhum estudo farmacológico foi desenvolvido para confirmar sua eficácia, necessitando assim testar essa ação *in vivo* e *in vitro* e detectar quais compostos estão contribuindo para esse efeito.

Levando em consideração que a resina é um fitoterápico bastante utilizado pelas populações, é importante conhecer sua composição química e quais compostos estão desenvolvendo a ação. Estudos químicos desenvolvidos com esse exudato e com outras partes vegetais dessa espécie mostram que alguns compostos que são encontrados na resina, também foram encontrados no óleo essencial e extrato de diferentes partes vegetais, assim como no extrato da casca do tronco dessa espécie, sendo eles: δ-Selinene, Cyperene, Cupareno, Cadineno, β-sileno, Germacrene B, α-Gurjunene, Cubenol, Ácido abiético, α-copaeno, β-elemeno, β-cariofileno, aromadendreno, α-humuleno, γ-muuroleno, β-selineno, γ-cadineno, espatulenol, kaurenal, α-cubebene, Mustakone e Caurene.

Com isso torna-se necessário o isolamento desses compostos e testes *in vitro* e *in vivo* como forma de conhecer o seu potencial farmacológico, levando em consideração que são constituintes com grande relevância por estarem presentes em diferentes estruturas vegetais da *C. langsdorffii*. No entanto, antes de se tornar um candidato à fitoterapia, vários outros aspectos devem ser considerados: a padronização da composição química da resina, a identificação dos compostos responsáveis pelo efeito e os métodos analíticos para a sua qualidade, que está diretamente relacionada à atividade farmacológica.

Um dos usos mais estabelecidos pelas comunidades para resina de *C. langsdorffii* é como agente cicatrizante de feridas. No entanto, existem poucos relatos científicos que corroboram a eficácia dessa espécie em relação a esta atividade. Apesar dos efeitos promissores sobre o uso da resina de *C. langsdorffii* como agente cicatrizante, a falta de um controle positivo dificulta a avaliação do real potencial desta espécie como produto natural de cicatrização de feridas. Além dos poucos estudos de pesquisa sobre a atividade cicatrizante para essa espécie e a falta de controles positivos, o modo de ação ainda não foi elucidado.

A atividade antioxidante é mais testada até o momento para *C. langsdorffii*, através de compostos isolados das folhas, como ácido caurenóico e quercitrina, e do seu extrato hidroalcoólico, da resina bruta e do óleo essencial extraído da resina, além de polifenóis e extrato da semente. No entanto, estudos farmacológicos com as diferentes partes vegetais dessa espécie, assim como, com compostos isolados, tornam-se necessários para promover um maior conhecimento do potencial desta espécie como produto natural antioxidante.

Como as atividades biológicas descritas para *C. langsdorffii* estão diretamente relacionadas à sua composição química, seu controle de qualidade é obrigatório. No desenvolvimento de medicamentos fitoterápicos, é necessário padronizar o produto, qualitativa e quantitativamente, para que seja aprovado pelas Agências de Vigilância, devido à correlação entre eficácia e segurança e composição química. Além disso, a adulteração da resina é frequentemente realizada pela adição de outros tipos de óleos para aumentar o volume do material e, consequentemente, propiciar um lucro maior com a venda da resina. Portanto, a adulteração deste produto frequentemente acontece e o controle de qualidade é importante para assegurar sua identidade e pureza. Dessa forma, como este produto ainda não foi padronizado, existem dificuldades na replicação dos ensaios biológicos, bem como a garantia de segurança do mesmo. Além disso, relatórios fitoquímicos e biológicos de outras partes da planta são escassos.

6.5 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. 88887.204213/2018-00) a aluna Maria de Oliveira Santos. 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$ 2.700,00 em 18 dias a campo, representando uma média de R$ 150 por dia. Com esse investimento diário foi possível coletar a resina de *C. langsdorffii* para a extração de óleo essencial em fitofisionomias de Cerradão, Carrasco e Mata Úmida da Chapada do Araripe. Foram gastos ainda cerca de R$ 4.000,00, em 40 dias de campo, com uma média de aproximadamente R$100 por dia, para um levantamento etnobotânico de uso medicinal da espécie em oito localidades da Chapada do Araripe, Município de Crato-CE. Essa pesquisa também recebeu auxílio concedido pelo programa de Pós-Graduação em Etnobiologia e Conservação da Natureza, dos recursos do PROAP no valor de R$ 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 Autorização para atividades com finalidade científica

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: 67422-1	Data da Emissão: 03/01/2019 14:18:56	Data da Revalidação*: 03/01/2020
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: Maria de Oliveira Santos	CPF: 048.435.523-64
Nome da Instituição: UNIVERSIDADE FEDERAL RURAL DE PERNAMBUCO	CNPJ: 00.394.445/0107-51

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: 67422-2	Data da Emissão: 08/01/2020 14:47:48	Data da Revalidação*: 01/12/2020
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: Maria de Oliveira Santos	CPF: 048.435.523-64
Título do Projeto: ANÁLISE DA VARIABILIDADE DOS COMPOSTOS QUÍMICOS DE ÓLEOS ESSENCIAIS DE Copaifera langsdorffii Desf. EM DIFERENTES PERÍODOS E AMBIENTES	
Nome da Instituição: UNIVERSIDADE FEDERAL RURAL DE PERNAMBUCO	CNPJ: 00.394.445/0107-51

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

Comprovante de registro para coleta de material botânico, fúngico e microbiológico

Número: 66098-1	Data da Emissão: 16/10/2018 14:19:44

Dados do titular

Nome: Maria de Oliveira Santos	CPF: 048.435.523-64

ANEXO B - Parecer do Comitê de Ética e Pesquisa

UNIVERSIDADE REGIONAL DO CARIRI - URCA

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: ANÁLISE DA VARIABILIDADE DOS COMPOSTOS QUÍMICOS DE ÓLEOS ESSENCIAIS DE Copaifera langsdorffii Desf. EM DIFERENTES PERÍODOS E

Pesquisador: Maria de Oliveira Santos

Área Temática:

Versão: 1

CAAE: 06442818.3.0000.5055

Instituição Proponente: Universidade Regional do Cariri - URCA

Patrocinador Principal: FUND COORD DE APERFEICOAMENTO DE PESSOAL DE NIVEL SUP

DADOS DO PARECER

Número do Parecer: 3.183.176

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

CRATO, 06 de Março de 2019

Assinado por:
Edilma Gomes Rocha Cavalcante
(Coordenador(a))

ANEXO C - Comprovante de cadastro do projeto de 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 AF4C8BB

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

Número do cadastro:	**AF4C8BB**
Usuário:	**MARIA DE OLIVEIRA SANTOS**
CPF/CNPJ:	**048.436.523-64**
Objeto do Acesso:	**Conhecimento Tradicional Associado**
Finalidade do Acesso:	**Pesquisa**

Espécie

Não será coletado material genético, portanto não se aplica.

Fonte do CTA

CTA de origem não identificável

Título da Atividade:	**VARIAÇÃO DOS COMPOSTOS QUÍMICOS DE ÓLEOS ESSENCIAIS DE Copaifera langsdorffii Desf. EM DIFERENTES TIPOS VEGETACIONAIS**

Equipe

MARIA DE OLIVEIRA SANTOS	**URCA**
Marta Maria de Almeida Souza	**Universidade Regional do Cariri**

Data do Cadastro:	**16/10/2018 16:43:08**
Situação do Cadastro:	**Concluído**

Conselho de Gestão do Patrimônio Genético
Situação cadastral conforme consulta ao SisGen em 16:43 de 16/10/2018.

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

ANEXO D - Comprovante de publicação no periódico *Biocatalysis and Agricultural Biotechnology*

Biocatalysis and Agricultural Biotechnology

Volume 39, January 2022, 102262

Copaifera langsdorffii Desf.: A chemical and pharmacological review

Maria de Oliveira Santos [a], Cicera Janaine Camilo [b], Julimery Gonçalves Ferreira Macedo [a], Maria Natália Soares de Lacerda [a], Cristiane Marinho Uchôa Lopes [c], Antonio Yony Felipe Rodrigues [d], José Galberto Martins da Costa [b], Marta Maria de Almeida Souza [a]

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https://doi.org/10.1016/j.bcab.2021.102262

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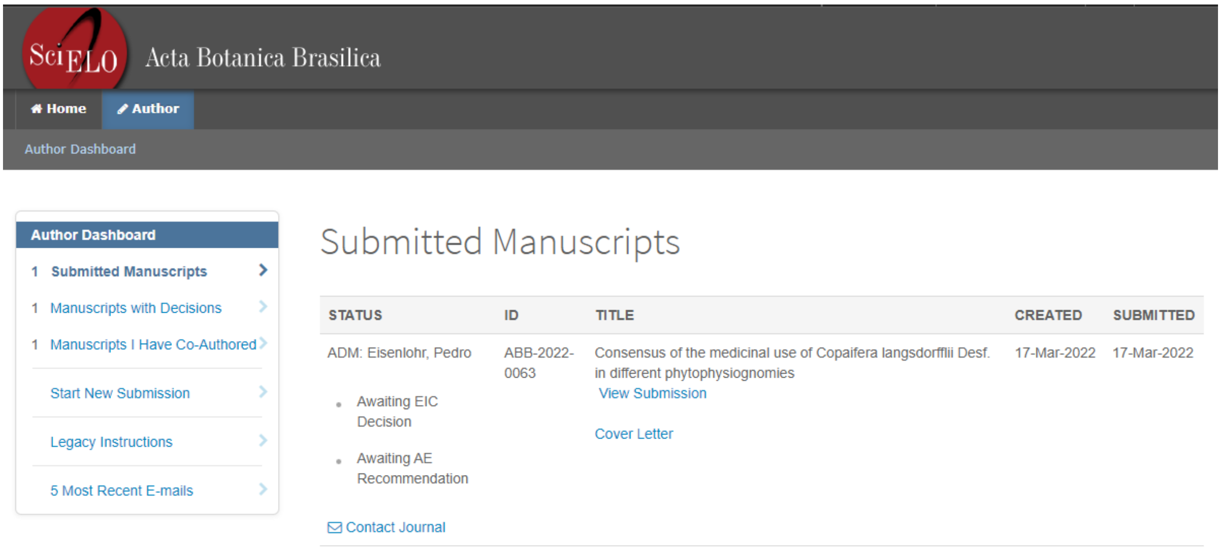
ANEXO E - Comprovante de submissão no periódico *Acta Botanica Brasilica*



SciELO Acta Botanica Brasilica

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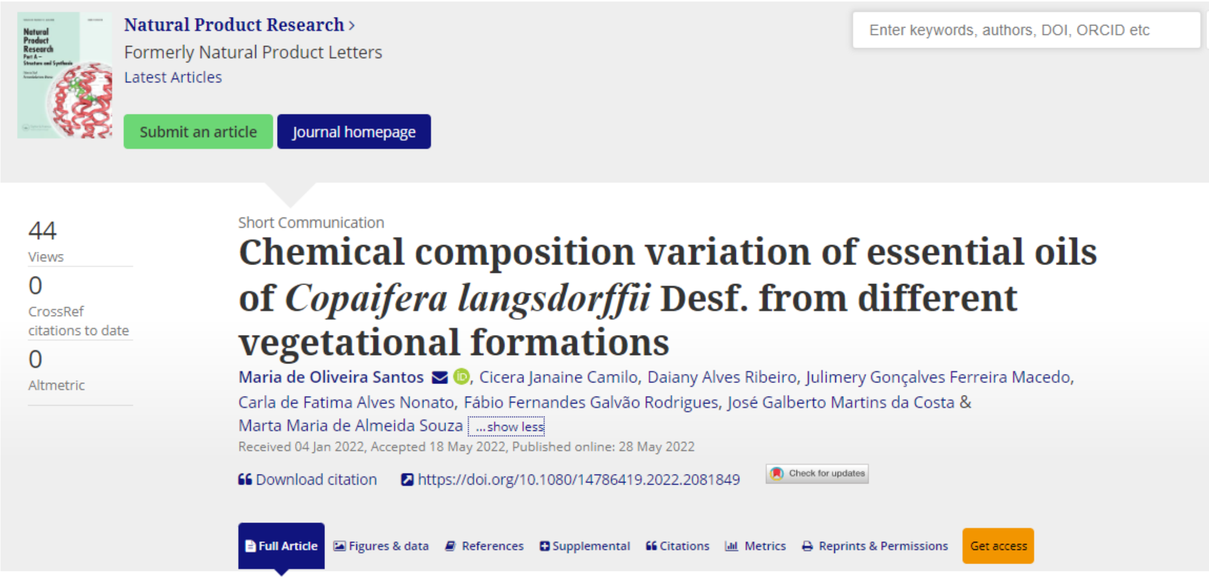
- 1 Manuscripts with Decisions
- 1 Manuscripts I Have Co-Authored
- Start New Submission
- Legacy Instructions
- 5 Most Recent E-mails

Submitted Manuscripts

STATUS	ID	TITLE	CREATED	SUBMITTED
ADM: Eisenlohr, Pedro • Awaiting EIC Decision • Awaiting AE Recommendation Contact Journal	ABB-2022-0063	Consensus of the medicinal use of Copaifera langsdorfflii Desf. in different phytophysiognomies View Submission Cover Letter	17-Mar-2022	17-Mar-2022

ANEXO F - Comprovante de publicação no periódico *Natural Product Research*



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Short Communication

Chemical composition variation of essential oils of *Copaifera langsdorffii* Desf. from different vegetational formations

Maria de Oliveira Santos, Cicera Janaine Camilo, Daiany Alves Ribeiro, Julimery Gonçalves Ferreira Macedo, Carla de Fatima Alves Nonato, Fábio Fernandes Galvão Rodrigues, José Galberto Martins da Costa & Marta Maria de Almeida Souza ...show less

Received 04 Jan 2022, Accepted 18 May 2022, Published online: 28 May 2022

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