UNIVERSIDADE FEDERAL DA GRANDE DOURADOS
FACULDADE DE CIÊNCIAS BIOLÓGICAS E AMBIENTAIS
PROGRAMA DE PÓS-GRADUAÇÃO EM BIOLOGIA GERAL/BIOPROSPECÇÃO

SIDNEY MARIANO DOS SANTOS

Plantas medicinais presentes em áreas de preservação no Mato Grosso do Sul: Composição química e atividade anti-inflamatória de *Allophylus edulis* e levantamento etnofarmacológico de espécies

DOURADOS – MS
2020

UNIVERSIDADE FEDERAL DA GRANDE DOURADOS
FACULDADE DE CIÊNCIAS BIOLÓGICAS E AMBIENTAIS
PROGRAMA DE PÓS-GRADUAÇÃO EM BIOLOGIA GERAL/BIOPROSPECÇÃO

SIDNEY MARIANO DOS SANTOS

Plantas medicinais presentes em áreas de preservação no Mato Grosso do Sul: Composição química e atividade anti-inflamatória de *Allophylus edulis* e levantamento etnofarmacológico de espécies

Defesa apresentada ao Programa de Pós-graduação em Biologia Geral/Bioprospecção da Universidade Federal da Grande Dourados (UFGD), para obtenção do título de Mestre em Biologia Geral.

Área de concentração: Bioprospecção

Orientadora: Profa. Dra. Anelise Samara Nazari Formagio

Coorientador: Profa. Dra. Candida Aparecida Leite Kassuya

DOURADOS – MS
2020

Dados Internacionais de Catalogação na Publicação (CIP).

S237p Santos, Sidney Mariano Dos

Plantas medicinais presentes em áreas de preservação no Mato Grosso do Sul: Composição química e atividade anti-inflamatória de Allophylus edulis e levantamento etnofarmacológico de espécies [recurso eletrônico] / Sidney Mariano Dos Santos. -- 2020.

Arquivo em formato pdf.

Orientadora: Anelise Samara Nazari Formagio.

Coorientadora: Candida Aparecida Leite Kassuya.

Dissertação (Mestrado em Biologia Geral/Bioprospecção)-Universidade Federal da Grande Dourados, 2020.

Disponível no Repositório Institucional da UFGD em: https://portal.ufgd.edu.br/setor/biblioteca/repositorio

1. Plantas medicinais. 2. Cerrado. 3. Allophylus edulis. 4. Terpenos. 5. Inflamação. I. Formagio, Anelise Samara Nazari. II. Kassuya, Candida Aparecida Leite. III. Título.

Ficha catalográfica elaborada automaticamente de acordo com os dados fornecidos pelo(a) autor(a).

UFGD

MINISTÉRIO DA EDUCAÇÃO
UNIVERSIDADE FEDERAL DA GRANDE DOURADOS
PROGRAMA DE PÓS-GRADUAÇÃO EM BIOLOGIA GERAL/BIOPROSPECÇÃO

ATA DA DEFESA DE **DISSERTAÇÃO DE MESTRADO** APRESENTADA PELO CANDIDATO SIDNEY MARIANO DOS SANTOS, ALUNO DO PROGRAMA DE PÓS-GRADUAÇÃO *STRICTO SENSU* EM BIOLOGIA GERAL, ÁREA DE CONCENTRAÇÃO "BIOPROSPECÇÃO".

Aos cinco dias do mês de março de dois mil e vinte (05/03/2020), às 9h00min, em sessão pública, realizou-se, no Anfiteatro 01 da Faculdade de Ciências Biológicas e Ambientais, da Universidade Federal da Grande Dourados, a Defesa de Dissertação de Mestrado intitulada "PLANTAS MEDICINAIS PRESENTES EM ÁREAS DE PRESERVAÇÃO NO MATO GROSSO DO SUL: COMPOSIÇÃO QUÍMICA E ATIVIDADE ANTI-INFLAMATÓRIA DE *Allophylus edulis* E LEVANTAMENTO ETNOFARMACOLÓGICO DE ESPÉCIES", apresentada pelo mestrando **Sidney Mariano dos Santos**, do Programa de Pós-Graduação em Biologia Geral/Bioprospecção, à Banca Examinadora constituída pelos professores: Dr.ª Anelise Samara Nazari Formagio / UFGD (presidente/orientadora), Dr. Caio Fernando Ramalho de Oliveira / UFGD (membro titular) e Dr.ª Claudia Andrea Lima Cardoso / UEMS (membro titular). Iniciados os trabalhos, a presidência deu a conhecer ao candidato e aos integrantes da Banca as normas a serem observadas na apresentação da Dissertação. Após o candidato ter apresentado a sua Dissertação, os componentes da Banca Examinadora fizeram suas arguições, que foram intercaladas pela defesa do candidato. Terminadas as arguições, a Banca Examinadora, em sessão secreta, passou aos trabalhos de julgamento, tendo sido o candidato considerado Aprovado, fazendo *jus* ao título de **MESTRE EM BIOLOGIA GERAL - ÁREA DE CONCENTRAÇÃO "BIOPROSPECÇÃO"**. Nada mais havendo a tratar, lavrou-se a presente ata, que vai assinada pelos membros da Banca Examinadora.

Dourados-MS, 05 de março de 2020.

Dr.ª Anelise Samara Nazari Formagio
Presidente

Dr. Caio Fernando Ramalho de Oliveira
Membro

Dr.ª Claudia Andrea Lima Cardoso
Membro

ATA HOMOLOGADA EM: ___/___/_____, PELA PRÓ-REITORIA DE ENSINO DE PÓS-GRADUAÇÃO E PESQUISA / UFGD.

Diante de um rio, eu sinto que posso tudo.

Diante do mar, sempre acho que não terei tempo.

Fabricio Carpinejar

Agradecimentos

Agradeço primeiro e especialmente aos meus pais, que pelo acaso do universo se encontraram e me tiveram. A eles dedico não só essa dissertação, como toda e qualquer vitória que já tive e ainda terei. Afinal, é tudo culpa deles.

Aos meus irmãos, que partilham da culpa dos meus pais, especialmente os mais velhos.

A minha orientadora, Anelise Formagio.

A Universidade Federal da Grande Dourados pela possibilidade.

A CAPES, por tornar a possibilidade praticável.

A Faculdade de Ciências Biológicas e Ambientais, especialmente o secretário Felipe D'Apolito em sua competência exemplar.

A Faculdade de Ciências da Saúde, na pessoa da Dra. Candida Aparecida Kassuya.

A Universidade Estadual de Mato Grosso do Sul, na pessoa da Dra. Claudia Andrea Lima.

A colega Cleide Bratchvogel, desbravadora das selvas.

Aos meus valiosos amigos, os que passaram, os que ficaram, os que sempre estarão no meu coração, mas especialmente aqueles que tenho um respeito grandioso.

Por ordem cronológica, agradeço ao Lucas Munaro, que sabe ser jovem e sábio. Gislaine Gonzaga, uma das mulheres mais fortes que conheço. Welber Sanches, que sempre sabe o que quer. Ao Guilherme Morales, por ser tão genuíno. Ao Antonio Stradiotto pelos incontáveis momentos de alegria e os também incontáveis momentos de sofrimento didático do nosso relacionamento.

Aos Anelídios, que tem papel fundamental nesta caminhada. Carla Volobuff, Kamila Nascimento, Milena Menezes, Rafael Claudino, Julyana Borges e Janaine Marangoni.

Ao Pedro Jr., que tanto me ensinou e atormentou. Que me apresentou o Rotaract e algumas das pessoas mais legais da região.

Aos Rotaractianos do distrito mais amado do Brasil (4470), mas especialmente ao meu clube.

Aproveito para dedicar o significado implícito desta dissertação a todas as vidas negras e LGBTs perdidas que nunca poderão viver o que eu vivi, pois tiveram suas vidas ceifadas pela injustiça do mundo. Que o futuro daqueles que ficaram seja mais digno e justo.

Agradeço a toda e qualquer pessoa ou instituição que contribuiu direta ou indiretamente para a produção deste trabalho.

LISTA DE ILUSTRAÇÕES

LISTA DE ABREVIATURAS E SIGLAS

CEUA	Comitê de Ética no Uso de Animais
CFA	Complete Freund's adjuvant
CONCEA	Conselho Nacional de Controle de Experimentação Animal
DDMS	Herbário da Universidade Federal da Grande Dourados
DEXA	Dexametasona
DPPH	2,2-diphenyl-1-picrylhydrazyl
EOAE	Essential oil of *Allophylus edulis*
EOAE-B	Essential oil of *A. edulis* collected in Bonito city
EOAE-D	Essential oil of *A. edulis* collected in Dourados city
GC/MS	Gas chromatography-mass spectrometry
ICD-11	Eleventh revision of the International Classification of Diseases for Mortality and Morbidity Statistics
MS	Estado do Mato Grosso do Sul
RENISUS	Relação Nacional de Plantas Medicinais de Interesse ao Sistema Único de Saúde
SUS	Sistema Único de Saúde
UFGD	Universidade Federal da Grande Dourados

RESUMO

O Cerrado brasileiro é considerado a savana mais biodiversa do mundo e o segundo maior bioma da América do Sul. Sendo responsável por abrigar uma ampla gama de espécies vegetais, incluindo diversas plantas medicinais. A documentação científica da diversidade presente no cerrado é crucial para a conservação e o uso sustentável dos recursos vegetais existentes neste bioma. Considerando ainda que as plantas medicinais vêm sendo utilizadas há milênios para o tratamento de uma pletora de sintomas e doenças, o estudo das espécies de forma a caracterizá-las quanto a sua importância medicinal também pode contribuir para a preservação e descoberta de potenciais fontes terapêuticas. Neste estudo foi feito o levantamento e a identificação das espécies vegetais presentes em uma área de Cerrado stricto sensu na reserva do assentamento 17 de Abril, no município de Nova Andradina, MS, Brasil. Foram identificadas 89 espécies, de 39 famílias diferentes, de espécies vegetais, sendo a Fabaceae (n=13), Myrtaceae (n=7), Rubiaceae (n=7) e Bignoniaceae (n=5), aquelas com a maior quantidade de espécies identificadas. Analisando os estudos químicos e farmacológicos descritos na literatura, apenas treze espécies não tiveram sua composição química investigada e quinze não possuem estudos farmacológicos publicados; e dentre as espécies estudadas, a classe predominante de metabólitos secundários identificadas nestas espécies foram os terpenos, seguidos de compostos fenólicos e alcaloides. Uma das espécies encontradas neste levantamento foi *Allophylus edulis* (Sapindaceae), já estudada por nosso grupo de pesquisa. No presente estudo, investigamos a composição química e atividade anti-inflamatória do óleo essencial das folhas de *A. edulis*. A coleta foi realizada em duas cidades do estado do MS no mês de julho de 2018; uma área nativa de Cerrado na cidade de Dourados/MS e no Parque Nacional da Serra da Bodoquena, no município de Bonito/MS, A análise da composição do óleo de *A. edulis* coletados em duas cidades distintas foi realizada com o propósito de investigar se as mudanças na composição do solo, temperatura e fatores ambientais seriam responsáveis por modular a composição dos óleos. Os resultados encontrados evidenciaram a predominância de sesquiterpenos nas amostras obtidas nos dois municípios, variando entre oxigenados (Dourados) e não oxigenados (Bonito). O potencial farmacológico avaliado, por meio da inflamação local induzida por carragenina e CFA (Adjuvante Completo de Freund), evidenciaram o efeito anti-inflamatório do óleo essencial de *A. edulis*.

Palavras-chave: Plantas medicinais, Cerrado, *Allophylus edulis*, terpenos, inflamação.

ABSTRACT

The Brazilian Cerrado is considered the most biodiverse savanna in the world and the second-largest biome in South America. It is responsible for housing a wide range of plant species, including several medicinal plants. The scientific documentation of the diversity present in the cerrado is crucial for the conservation and sustainable use of plant resources in this biome. Considering that medicinal plants have been used for millennia to treat a plethora of symptoms and diseases, the study of species to characterize them as to their medicinal importance can also contribute to the preservation and discovery of potential therapeutic sources. In this study, the survey and identification of plant species present in an area of Cerrado stricto sensu in the reserve of the 17 de Abril settlement, in the municipality of Nova Andradina, MS, Brazil, was carried out. All 89 species were identified, from 39 different families, of plant species, being Fabaceae (n = 13), Myrtaceae (n = 7), Rubiaceae (n = 7), and Bignoniaceae (n = 5), those with the highest amount of identified species. Analyzing the chemical and pharmacological studies described in the literature, only thirteen species have not had their chemical composition investigated and fifteen do not have published pharmacological studies; and among the species studied, the predominant class of secondary metabolites identified in these species was terpenes, followed by phenolic compounds and alkaloids. One of the species found in this survey was *Allophylus edulis* (Sapindaceae), already studied by our research group. In the present study, we investigated the chemical composition and anti-inflammatory activity of the essential oil of *A. edulis* leaves. The collection was carried out in two cities in the state of MS in July 2018; a native area of Cerrado in the of Dourados / MS city and the Serra da Bodoquena National Park, in the municipality of Bonito / MS. The analysis of the composition of *A. edulis* oil collected in two different cities implemented to investigate whether changes in soil composition, temperature, and environmental factors would be responsible for modulating the oil compositions. The results found showed the predominance of sesquiterpenes in the samples obtained in the two municipalities. Varying between oxygenated (Dourados) and non-oxygenated (Bonito). The pharmacological potential assessed, through local inflammation induced by carrageenan and CFA (Freund's Complete Adjuvant), showed the anti-inflammatory effect of the essential oil of *A. edulis*.

Keywords: Medicinal plants, Cerrado, *Allophylus edulis*, terpenes, inflammation.

SUMÁRIO

1 INTRODUÇÃO

O estado do Mato Grosso do Sul, localizado na região centro-oeste brasileira, possui uma área de 350,000 km^2, dos quais somente 47% é coberto por vegetação natural (SARTORI e POTT, 2018). Distribuído sob três diferentes biomas: Cerrado, Mata Atlântica e Pantanal, o Cerrado é o predominante, abrangendo cerca de 65% do território (SILVA et al., 2011). Considerado um hotspot de biodiversidade global, o Cerrado brasileiro é considerado a savana com a flora mais diversificada do mundo, mas que, no entanto, enfrenta desafios na sua conservação, pela substituição de áreas preservadas, principalmente como resultado da expansão da agricultura e pecuária (BONANOMI et al., 2019).

Considerando a rica biodiversidade dos ambientes preservados, incluindo diversas plantas medicinais, a documentação científica da diversidade, distribuição e usos tradicionais da flora medicinal pode ser crucial na conservação e no uso sustentável dos recursos vegetais existentes, no caso deste trabalho, em áreas preservadas do Cerrado sul-mato-grossense. As plantas medicinais vêm sendo utilizadas desde o início da civilização para o tratamento de uma pletora de sintomas e doenças, de forma que a preservação dos biomas e posteriormente da biodiversidade vegetal está intimamente relacionada com a preservação de potenciais fontes terapêuticas (HOAREAU e SILVA, 1999).

O conhecimento medicinal tradicional faz parte das práticas terapêuticas consolidadas nas culturas locais e que cada vez mais é utilizada para promoção ativa de pesquisa com plantas medicinais. Além do desenvolvimento de políticas que viabilizam ou estimulam a utilização destas como medida terapêutica principalmente em países em desenvolvimento, como o Brasil (LÓPEZ-RUBALCAVA e ESTRADA-CAMARENA, 2016; DUTRA et al, 2016; VAN WYK et al., 2020).

Com cerca de 21.000 espécies de plantas que podem ser potencialmente utilizadas com propósitos medicinais, estima-se que, ao redor do mundo, os medicamentos fitoterápicos ou extratos vegetais estão inseridos em práticas terapêuticas de aproximadamente 80% da população. E ainda, com o avanço das tecnologias relacionadas ao desenvolvimento de fármacos, estima-se de que entre as drogas sintéticas atualmente prescritas, 24% são derivados de espécies vegetais, 9% são produtos sintéticos modelados

a partir de produtos naturais e 6% são extraídos diretamente de espécies vegetais (BARREIRO e BOLZANI, 2009).

Na primeira parte deste estudo, foi feito um levantamento do uso tradicional das plantas, com o objetivo de coletar informações básicas sobre a diversidade, distribuição e usos tradicionais da flora medicinal presente um uma reserva na cidade de Nova Andradina, MS. Com a pretensão de fornecer informações relativas a biodiversidade e a riqueza de plantas que pode levar a descoberta, e o desenvolvimento de novas abordagens terapêuticas baseadas em plantas medicinais.

De forma complementar, a segunda parte deste estudo trata da análise química e avaliação do potencial anti-inflamatório do óleo essencial das folhas de *Allophylus edulis*. Esta espécie pertence à família Sapindaceae e está distribuída por diversos países da América do Sul (PIAGGIO e DELFINO, 2003). Popularmente conhecida como chal-chal, cocú e vacum, ela é utilizada empiricamente em quadros clínicos relacionados a distúrbios intestinais, diabetes, hipertensão, e ainda como anti-inflamatório (KÖRBES, 1995; FRANCO e FONTANA, 2001; ABREU et al., 2005). A capacidade anti-inflamatória do óleo essencial das folhas de *A. edulis* foi investigada anteriormente por nosso grupo de pesquisa (TREVIZAN et al., 2016). Dessa forma, considerando que o metabolismo secundário das plantas é responsável pela biossíntese das moléculas responsáveis pela ação farmacológica, e que elas podem divergir dependendo da exposição a fatores bióticos e abióticos, neste trabalho foi avaliada a ação anti-inflamatória do óleo essencial das folhas de *A. edulis* coletadas em duas localidades de Mato Grosso do Sul.

2 REVISÃO DE LITERATURA

2.1 Metabolismo secundário de espécies vegetais

As plantas possuem a capacidade de sintetizar uma pletora de compostos orgânicos, comumente classificados como metabólitos primários e secundários (VERPOORTE e ALFERMANN, 2000). De forma que os primários são aqueles com funções primárias para os organismos vegetais, como a fotossíntese, respiração, crescimento e desenvolvimento (SEIGLER, 1998). As moléculas oriundas do metabolismo primário incluem moléculas pequenas como carboidratos, aminoácidos e ácidos carboxílicos, ou seja, unidades elementares para formação de moléculas

complexas, como lipídios e ácidos nucléicos, responsáveis por funções vitais, como enzimática, estrutural, composição de material genético e substrato energético (O'CONNOR, 2015).

De forma complementar, os metabólitos secundários se apresentam em concentrações menores, mas compreendem uma gama muito maior de estruturas químicas dentro de classes como alcaloides, compostos fenólicos e terpenos (SHITAN, 2016; VIJAYAKUMAR & RAJA, 2018). Eles são responsáveis por funções como defesa contra herbivoria (sabor amargo dos alcaloides), auxílio na reprodução (pigmentos de cores vivas das antocianinas e carotenoides), por exemplo (WURTZEL & KUTCHAN, 2016). Os produtos dessa interação com o meio podem ter seus usos extrapolados para além da medicina, como aplicação na alimentação humana e animal, como aditivo alimentar, e no setor de bioenergia e agricultura (WURTZEL & KUTCHAN, 2016; KALLSCHEUER et al., 2019). E mesmo diante das descobertas relevantes feitas até o momento, as 200.000 estruturas químicas de produtos naturais conhecidas são resultado de estudo feito com apenas 15% das 350.000 espécies de plantas já descritas (CRAGG & NEWMAN, 2013). Deste modo, apesar do sucesso na descoberta de moléculas com propriedades farmacológicas, existe uma imensa quantidade delas a ser descoberta no reino vegetal (ATANASOV et al., 2015; BUYEL, 2018).

Influências ambientais de caráter biótico e abiótico tendem a influenciar na biossíntese dos metabólitos secundários, que culminarão na variação do acúmulo e biogênese dessas substâncias (KROYMANN, 2011). Esses fatores podem ser induzidos por meio de vários mecanismos, como temperatura (BROWN, 2010), altitude (GANZERA et al., 2008), latitude (JAAKOLA & HOHTOLA, 2010), composição atmosférica (STILING & CORNELISSEN, 2007), disponibilidade hídrica (LAVOIR et al., 2009), nutrientes do solo (SANTOS et al., 2011), exposição aos raios UV (JENKINS, 2009), e ainda fatores bióticos, como interação planta/microrganismo, planta/insetos, planta/planta, idade, estágio de desenvolvimento e ritmo circadiano (PAVARINI et al., 2012). Dessa forma, o aspecto dinâmico da síntese e acumulação de compostos bioativos permite que as plantas se comuniquem e reajam ao ambiente no qual estão inseridas.

2.2 Importância da conservação e uso de plantas medicinais

A pesquisa com produtos naturais vem sendo cada vez mais promovida no mundo, e as plantas medicinais são uma fonte notável de conhecimento agregado. Utilizadas desde as sociedades mais antigas até o presente momento, para o tratamento empírico de diversas patologias, a busca por opções de tratamento baseada em produtos naturais criam a oportunidade de descoberta de novas abordagens terapêuticas de maior eficácia e com efeitos colaterais mínimos em comparação às drogas sintéticas disponíveis (FINCH E DRUMMOND, 2015; SIQUEIRA-LIMA et al., 2017; BOY et al., 2018).

No Brasil, em 2006, foi implementado o Programa Nacional de Plantas Medicinais e Fitoterápicos, com objetivos como a introdução da fitoterapia no Sistema Único de Saúde (SUS), fomentar a pesquisa com plantas medicinais e promover o uso sustentável dos recursos naturais (BRASIL, 2006). Ainda neste contexto, foi publicada a Relação Nacional de Plantas Medicinais de interesse para o SUS (RENISUS), em 2009, contendo 71 espécies estabelecidas como prioritárias no desenvolvimento de estudos e pesquisas. Espera-se, dessa forma a identificação das necessidades da comunidade por medicamentos à base de plantas, elaboração e modificação de políticas públicas, estabelecimento de normas para produção e fomento de publicações técnico-científicas com plantas nativas brasileiras (BRASIL, 2009).

Dentre os resultados, o Ministério da Saúde destaca a instalação de Farmácias Vivas em alguns municípios brasileiros, e ainda o fato de que algumas Unidades Básicas de Saúde pelo país já disponibilizam plantas medicinais *in natura*, na forma de droga vegetal e fitoterápico manipulado ou industrializado (LOPES et al., 2015; BRASIL, 2017). No entanto, mesmo representando um aumento na fitoterapia no SUS, ainda existe a necessidade de melhor distribuição espacial e fomento de práticas regionais, visto sua concentração em regiões como o Sul e o Sudeste do país (RIBEIRO et al., 2019).

2.3 Processo inflamatório e controle farmacológico

A resposta inflamatória é filogeneticamente e ontogeneticamente um dos sistemas de defesa mais antigos do corpo. Pode se iniciar por irritações de origem física, química ou biológica, como infecções ou lesão tecidual e se caracteriza pela presença dos 5 sinais cardinais: calor, rubor, edema, dor e perda de função (SERHAN, 2010). O mecanismo da inflamação é controlado por uma gama de fatores, incluindo citocinas, enzimas pró-inflamatórias, mediadores lipídicos, mediadores vasoativos, leucócitos e plaquetas

(TODD et al., 2015). Esses mediadores inflamatórios representam uma cadeia de respostas dinâmicas e estruturadas, incluindo eventos celulares e vasculares que são essenciais para a sobrevida do organismo afetado. Em alguns casos, no entanto, pode haver resposta inflamatória exagerada gerando danos graves, de forma que esta pode ser conceituada em aguda e crônica, de acordo com a duração e evolução do processo (ABDULKHALEQ et al., 2018).

A fase aguda da inflamação é caracterizada por alterações vasculares que ocorrem logo após o dano tecidual ou infecção microbiana (com duração de horas ou dias). Como resultado há vasodilatação, ocasionada por mediadores como óxido nítrico e prostaglandinas, formação de edema pela exsudação plasmática e alteração da localização física de leucócitos (monócitos, basófilos, eosinófilos e neutrófilos) (ELGORASHI & MCGAW, 2019). A inflamação crônica, por sua vez, se estende por período maior de tempo (semanas a meses), na qual a resposta inflamatória persistente causa danos aos tecidos, devido à secreção contínua de mediadores químicos e espécies reativas de oxigênio, levando a uma má adaptação funcional e remodelação tecidual (MURAKAMI, 2012). Nesse ínterim, alguns mediadores liberados são responsáveis pela promoção de dor, ao ativar ou diminuir o limiar de ativação das fibras aferentes primárias, que culminam no recrutamento de outros mediadores, incluindo aminas vasoativas, peptídeos vasoativos, fragmentos de componentes do complemento, quimiocinas e enzimas proteolíticas e mais mediadores lipídicos e citocinas (ITO et al., 2001).

Há muito que existe o interesse nos mecanismos tanto da inflamação quanto da hiperalgesia a estímulos nocivos e dor tátil, com o intuito de aliviar a dor persistente, de forma que as abordagens farmacológicas culminaram no desenvolvimento de medicamentos como os anti-inflamatórios não-esteroidais e opioides para o tratamento clínico da dor (DALE & STACEY, 2016). Entretanto, o uso crônico destes acarreta efeitos colaterais graves, como ulceração gástrica ou intestinal, distúrbios renais, edema, retenção de sódio e consequente hipertensão arterial (HYLANDS-WHITE et al., 2017).

2.4 Gênero *Allophylus*

A família Sapindaceae é composta por 141 gêneros e 1900 espécies, distribuídas principalmente em regiões tropicais e subtropicais, composta em sua maioria por plantas lenhosas. (ZINI et al., 2012). No território brasileiro são catalogados 27 gêneros e 419

espécies, das quais 193 são endêmicas, com presença em todos os biomas que compõem o território nacional (COELHO, 2014).

Dentre os gêneros da família Sapindaceae, o *Allophylus* é considerado um dos maiores, com cerca de 100 espécies registradas, sendo algumas de grande relevância etnofarmacológica (JOLY, 2005; JUDD, 2008). Alguns exemplos englobam *Allophylus serratus*, espécie utilizada na medicina tradicional asiática em casos de fraturas ósseas, *Allophylus cobbe* para o tratamento de erupções cutâneas, cortes, úlcera e diarreia (CHAVAN E GAIKWAD, 2013) e *Allophylus africanus* no tratamento de malária, na África (OLADOSU et al., 2013). Algumas atividades biológicas são relatadas, tais como antibacteriana de *A. cobbe* e *A. serratus* (CHAVAN E GAIKWAD, 2013), antimalárica e antioxidante de *A. africanus* (OLADOSU et al., 2013; BALOGUN et al., 2014), anti-diabética de *Allophylus cominia* (SEMAAN et al., 2017), citotóxica de *Allophylus timoriensis* (BRADACS et al., 2010) e atividade protetiva contra úlcera gástrica de *A. serratus* (DHARMANI, et al., 2005). Para este gênero, os estudos químicos relatam a presença de saponinas, terpenos, flavonoides, cumarinas, e taninos e alcaloides (DAVID et al., 2004; OLADOSU et al., 2013; CHAVAN E GAIKWAD, 2013; OLADOSU et al., 2015; ZHANG et al., 2012).

2.4.1 *Allophylus edulis* **(A.St.-Hil., A.Juss. & Cambess.) Radlk.**

A *A. edulis* possui como sinonímias: *Allophylus cambessedei* Blume, *Allophylus edulis* var. *gracilis* Radlk., *Allophylus edulis* var. *rosae* F. A. Barkley e *Allophylus edulis* var. *subsessilis* Huber (THEPLANTLIST, 2019). Conhecida popularmente como chal-chal, três folhas, vacum e cocú, é descrita como uma árvore pequena, muito ramificada, de casca escura, descamante em lâminas irregulares rígidas e alongadas, e seus frutos são compostos por três drupas globosas vermelhas, de cerca de 5mm de diâmetro (DURIGAN et al., 2004; ABREU et al., 2005). Possui folhas alternas, longo-pecioladas, compostas ternadas, folíolos subsésseis, flores alvas, pequenas em tirsos ou panículas curtas, como mostrado na Figura 1. Ocorre no cerradão, floresta estacional semidecidual, mata de galeria (de vale) e mata seca (SANO et al., 2008). Em estudo que buscou identificar o potencial de espécies arbóreas para recuperação ambiental, foram descritos os usos não madeiráveis de *A. edulis*, como utilização ornamental, apícola, forragem, alimentício, ecológico e medicinal, além de ser descrita como planta pioneira e essencial para

reflorestamentos heterogêneos destinados à recomposição de áreas degradadas (MARQUES, 2007).

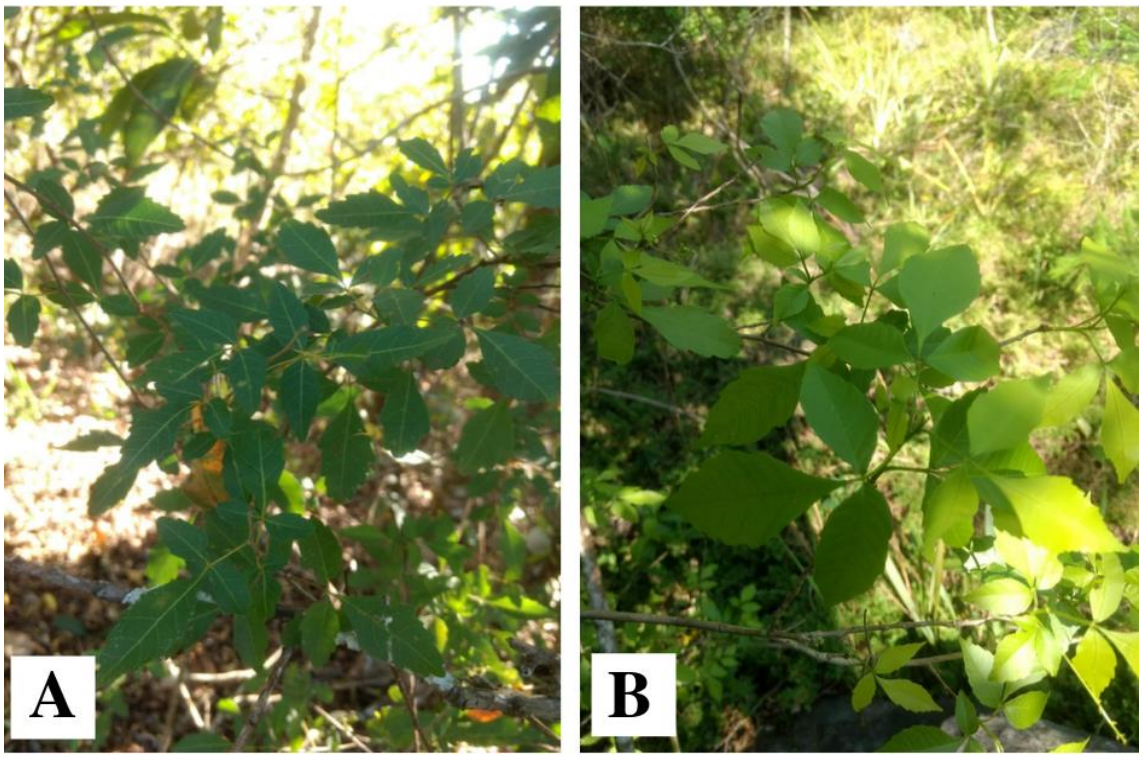


Figura 1. Folhas de *A. edulis* fotografadas em uma área nativa de Cerrado na cidade Dourados/MS (A) e no Parque Nacional da Serra da Bodoquena em Bonito (B). Fonte: Santos, 2018.

Na América do Sul, *A. edulis* está distribuída em formações de mata nativa em países como a Argentina, Uruguai, Paraguai, Bolívia e Guianas (PIAGGIO & DELFINO, 2003). Em relato feito por KUJAWSKA & PARDO-DE-SANTAYANA (2015), no qual foram inventariadas plantas medicinais encontradas nos jardins de imigrantes poloneses, na cidade de Misiones, na Argentina, local com abundância desta árvore, a espécie foi uma das mais encontradas nas residências, principalmente naquelas em que membros da família possuíam algum tipo de problema circulatório. Também há relato do uso desta espécie no preparado de *Ilex paraguaiensis* St. Hil. (Aquifoliaceae), conhecido como tereré, tanto na Argentina quanto no Paraguai (KUJAWSKA E PARDO-DE-SANTAYANA, 2015; KUJAWSKA, 2018).

Apesar do epiteto *edulis* (comestível, em latim), o uso desta planta na fruticultura não é relatado. KINUPP et al. (2007) cita que existe aceitabilidade na utilização dos frutos como fruta de mesa, no entanto, pela perecibilidade, seu uso para a fabricação de licores, sucos e polpa congelada são mais indicados. Os frutos quando submetidos a processo de

fermentação produzem uma bebida vinosa conhecida como “aloja de chachal”, *“*chicha*”* ou *“*aloja*”*, sendo preparado com milho e consumida por índios peruanos, argentinos e brasileiros (ABREU et al., 2005; CHEBEZ & MASARICHE, 2010).

Diversas aplicações medicinais são reportadas para esta espécie, tanto das folhas, quanto dos frutos, como o consumo do infuso destas partes para o tratamento de desinteria, febre e diabetes (FRANCO & FONTANA, 2001). Também é relatado o uso da infusão das folhas como agente anti-inflamatório da garganta, distúrbios intestinais (KÖRBES, 1995), para o tratamento de diabetes (DÍAZ et al., 2008), feridas, hipertensão e digestivo (ABREU et al., 2005).

Há estudos que relatam o extrato etanólico dos galhos de *A. edulis* como detentor de propriedades repelentes contra os insetos, como o Pulgão Verde do Pessegueiro (*Myzus persicae*), e joaninha (*Epilachna paenulata*) (CASTILLO et al., 2009). Ao utilizar o extrato etanólico e frações, também foi possível encontrar atividade contra o pulgão-da-aveia (*Rhopalosiphum padi*) e o verme de algodão egípcio (*Spodoptera littoralis*) (DÍAZ et al., 2014). Neste último estudo, observou-se que o extrato foi mais efetivo contra pulgões, enquanto que as frações foram mais efetivas contra insetos mastigadores, revelando um possível sinergismo dos compostos do extrato, na ação contra pulgões.

Em estudos que analisaram o perfil de ácidos graxos do óleo das sementes de *A. edulis* foram encontrados cianolipídios e triacilgliceróis (AICHHOLZ et al., 1997). A exemplo dos ácidos palmítico, palmitoléico, esteárico, oleico, linoleico, linolênico, araquídico e gadoleico, identificados em uma tentativa de produzir padrões para fins taxonômicos em espécies da família Sapindaceae (ABBURRA et al., 1992; COUTINHO, 2013).

Utilizando extrato etanólico das folhas, foram encontrados seis flavonoides, uma dihidrocumarina (ARISAWA et al., 1989), os sesquiterpenos 6,7-epoxicariofileno, espatulenol, o triterpeno lupeol, o diterpeno 2-oxo-13-hidroxi-neo-cleroda-3,14-dieno e os fitosteróis sitosterona e sitosterol (Figura 2**)** (DÍAZ et al., 2014), e o L-quebracitol, estudado por sua ação hipoglicemiante (DÍAZ et al., 2008).

Em estudos bromatológicos utilizando plantas alimentícias não-convencionais, o suco concentrado da polpa dos frutos de *A. edulis in natura* foram utilizados, no qual foram encontrados os seguintes valores proteicos e minerais: teor de proteínas (0,1190%), Cálcio (0,0068%), Magnésio (0,0039%), Manganês (0,000062%), Fósforo (0,0048%),

Ferro (0,0004%), Sódio (0,0004%), Potássio (0,0684%), Cobre (0,000016%), Zinco (0,00002%), Enxofre (0,0037%), Boro (0,00004%) (KINUPP & BARROS, 2008). Além de gorduras (216,0 g/kg $^{-1}$), fibras (180,0 g/kg $^{-1}$), teor de cinzas (28,0 g/kg $^{-1}$), parte do extrato livre de nitrogênio/carboidratos (466 g/kg $^{-1}$), do extrato metanólico dos frutos (SCHMEDA-HIRSCHMANN et al., 2005).

Muitas atividades biológicas tem sido reportadas utilizando extratos de *A. edulis*. Em um estudo feito por Tirloni et al. (2015), o extrato etanólico das folhas exibiu atividade antioxidante *in vitro* pela eliminação de radicais livres, inibiu hemólise de eritrócitos humanos e peroxidação lipídica. Também foi relatado alto percentual de inibição do radical DPPH utilizando extrato etanólico (UMEO et al., 2011) e metanólico dos frutos (SCHMEDA-HIRSCHMANN et al., 2005). Ao avaliar a atividade antimicrobiana dos extratos, não houve inibição do crescimento de *Escherichia coli* e *Candida albicans*, mas foram relatadas atividades anti-*Staphylococcus aureus* para o extrato etanólico, e atividade basteriostática para o extrato aquoso das folhas Tirloni et al. (2015). Arruda et al. (2018) por sua vez não relatou atividade antimicrobiana ao utilizar o extrato aquoso das folhas.

Em um trabalho realizado por nosso grupo de pesquisa utilizando o óleo essencial de *A. edulis*, cujas folhas foram coletadas no mês de março de 2015 na cidade de Dourados, MS, foi encontrada atividade antioxidante, antimicrobiana e anti-inflamatória. Neste estudo a composição química do óleo essencial evidenciou presença maior de hidrocarbonetos sesquiterpênicos, de forma que o composto majoritário, o viridiflorol (Figura 2**)** foi encontrado em 30,88% da amostra (TREVIZAN et al. 2016). A avaliação anti-inflamatória foi feita utilizando os modelos de pleurisia e edema de pata induzido por carragenina, e tanto as doses do óleo quanto do composto majoritário isolados foram efetivos nos modelos avaliados (TREVIZAN et al. 2016).

Quanto aos estudos de toxicidade, o extrato etanólico e aquoso das folhas produziu baixa toxicidade em modelos animais (TIRLONI et al., 2015, ARRUDA et al., 2018). Assim como em estudo utilizando o microcrustáceo *Artemia salina*, com extrato etanólico dos frutos (UMEO et al., 2011). Complementar a esses relatos, foi encontrada atividade anticolinesterásica moderada para o extrato etanólico (UMEO et al., 2011) e ainda atividade inibidora da enzima conversora de angiotensina (ARISAWA et al, 1989).

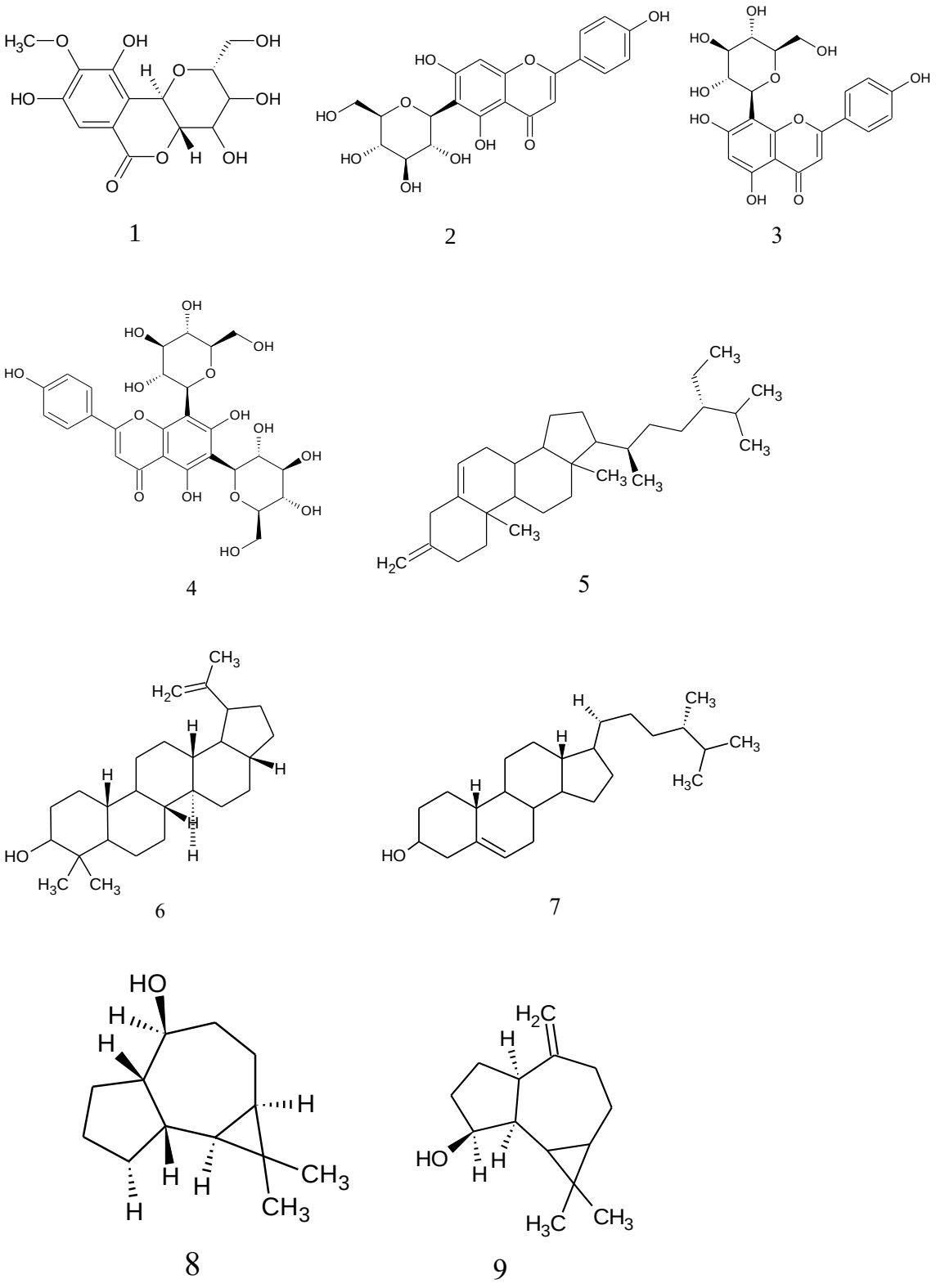


Figura 2. Compostos isolados de *A. edulis*: 1: bergenina, 2: isovitexina, 3: vitexina, 4: vicenina, 5: sisterona, 6: lupeol, 7: sitosterol, 8: viridiflorol e 9: espatulenol.

3 JUSTIFICATIVA

O estudo de plantas medicinais sempre foi uma das áreas mais promissoras na busca de novas alternativas terapêuticas, já que a natureza é responsável bela biossíntese de uma enorme quantidade de compostos com esse potencial. A avaliação da diversidade das plantas medicinais existente em parte do bioma Cerrado é uma forma de ampliar a visão sobre a distribuição dessas espécies e reafirmar sua importância tanto na pesquisa, quanto na utilização empírica. Além disso, para aquelas plantas com potencial medicinal, o conhecimento do melhor período de produção em termos de qualidade e quantidade são de extrema relevância para o monitoramento químico, visando seu uso seguro como um fitoterápico e ainda possibilitando a prospecção fitoquímica de protótipos de substâncias com aplicação farmacológica.

4 OBJETIVOS

GERAL

Avaliar a diversidade de plantas medicinais em uma área de Cerrado stricto sensu em Nova Andradina/MS, analisar as diferenças nos perfis químicos e na atividade anti-inflamatória do óleo essencial das folhas de *A. edulis* coletadas em Dourados/MS e Bonito/MS.

ESPECÍFICOS

Descrever as espécies vegetais presentes em parte de uma área de Cerrado stricto sensu da reserva 17 de Abril, no município de Nova Andradina/MS.

Levantar informações respectivas à indicação popular, além de estudo químico e farmacológico das espécies encontradas.

Caracterizar quimicamente o óleo essencial de *A. edulis* extraído em dois diferentes locais do Mato Grosso do Sul no mês de julho de 2018.

Executar ensaios *in vivo* para as atividades anti-inflamatória e antinociceptiva de doses do óleo essencial das duas localidades.

REFERÊNCIAS BIBLIOGRÁFICAS

ABBURRA, R. E.; ZYGADLO, J. A.; GUZMAN, C. A. Fatty acids variation in Sapindaceae. **Biochemical Systematics and Ecology,** v. 20, p. 469-471, 1992.

ABDULKHALEQ, L. A.; ASSI, M. A.; ABDULLAH, R.; ZAMRI-SAAD, M.; TAUFIQ-YAP, Y. H.; HEZMEE, M. N. M. The crucial roles of inflammatory mediators in inflammation: A review. **Vet World.** v. 11, n. 5, p. 627-635, 2018.

ABREU, D. C. A.; KUNIYOSHI, Y. S.; NOGUEIRA, A. C.; MEDEIROS, A. C. S. Caracterização morfológica de frutos, sementes e germinação de *Allophylus edulis* (St.-Hil.) Radlk. (Sapindaceae). **Revista Brasileira de Sementes,** v. 27, n. 2, p. 59-66, 2005.

AICHHOLZ, R.; SPITZER, V.; LORBEER, E. Analysis of cyanolipids and triacylglycerols from Sapindaceae seed oils with high-temperature gas chromatography and high-temperature gas chromatography-chemical ionization mass spectrometry. **Journal of Chromatography A**, v. 787, p. 181-194, 1997.

ARISAWA, M.; MORINAGA, Y.; NISHI, Y.; UENO, H.; SUZUKI, S.; HAYASHI, T.; YOSHIZAKI, M. S.; MORITA, N.; BERGANZA, L. H. Chemical and pharmaceutical studies on medicinal plants in Paraguay. Constituents of angiotensin converting enzyme inhibitory fraction from 'Cocu', *Allophylus edulis* Radlk**. Japanese Journal of Pharmacognosy.** v. 43, n. 1, p. 78-80, 1989.

ARRUDA, G.; PÉRICO, L. G. V.; PARPINELLI, R.; PERETTI, R. F.; SCUR, M. C.; FOLLADOR, F. A. C. Phytochemical Prospecting, Antimicrobial Activity, and Acute Toxicity of Aqueous Plant Extract of Two Plant Species *Allophylus edulis* (A. St. Hilaire, Cambessedes & A. Jussieu) RADLK ex WARM and *Matayba elaeagnoides* RADLK. **International Journal of New Technology and Research,** v. 5, n. 2, p. 10-13, 2018.

ATANASOV, A. G.; WALTENBERGER, B.; PFERSCHY-WENZIG, E.-M.; LINDER, T.; WAWROSCH, C.; UHRIN, P.; … STUPPNER, H. Discovery and resupply of pharmacologically active plant-derived natural products: A review. **Biotechnology Advances**, v. 33, n. 8, p. 1582–1614, 2015.

BALOGUN, S. O.; I.A. OLADOSU, I. A.; LIU, Z. Chemical compositions and antioxidant potential of essential oils from leaves and flowers of *Allophylus africanus*. **Journal of Essential Oil Bearing Plants**, v.17, n. 5, p. 769-775, 2014.

BARREIRO, E. J., BOLZANI, V. D. S. "Biodiversidade: fonte potencial para a descoberta de fármacos", Quimica Nova, v. 32, n. 3, p. 679–688, 2009. DOI: 10.1590/S0100-40422009000300012.

BONANOMI, J., TORTATO, F. R., GOMES, R. de S. R., et al. "Protecting forests at the expense of native grasslands: Land-use policy encourages open-habitat loss in the Brazilian cerrado biome", Perspectives in Ecology and Conservation, v. 17, n. 1, p. 26–31. DOI: 10.1016/j.pecon.2018.12.002.

BOY, H. I. A.; RUTILLA, A. J. H.; SANTOS, K. A.; TY, A. M. T.; YU, A. I.; MAHBOOB, T.; TANGPOONG, J.; NISSAPATORN, V. Recommended Medicinal Plants as Source of Natural Products: A Review. **Digital Chinese Medicine**, v. 1, n. 2, p. 131-142, 2018.

BRADACS, G.; MAES, L.; HEILMANN, J. In vitro cytotoxic, antiprotozoal and antimicrobial activities of medicinal plants from vanuatu. **Phytoterapy Research,** v. 24, p. 800-809, 2010.

BRASIL. Ministério da Saúde. Secretaria de Ciência, Tecnologia e Insumos Estratégicos, Departamento de Assistência Farmacêutica. Programa Nacional de Plantas Medicinais e Fitoterápicos, 2006. Disponível em: <http://bvsms.saude.gov.br/bvs/publicacoes/politica_nacional_fitoterapicos.pdf>. Acesso em: 12 fev. 2020.

BRASIL. Ministério da Saúde. Portal da Saúde: Plantas Medicinais de Interesse ao SUS – Renisus. 2009. Disponível em: <https://www.saude.gov.br/acoes-e-programas/programa-nacional-de-plantas-medicinais-e-fitoterapicos-ppnpmf/politica-e-programa-nacional-de-plantas-medicinais-e-fitoterapicos/plantas-medicinais-de-interesse-ao-sus-renisus>. Acesso em: 12 fev. 2020.

BRASIL. Ministério da Saúde. Programa de Fitoterápico e Plantas Medicinais. 2017. Disponível em:<https://www.saude.gov.br/noticias/agencia-saude/737-acoes-e-programas/programa-de-fitoterapico-e-plantas-medicinais>. Acesso em: 12 fev. 2020.

BROWN, G. D. The biosynthesis of artemisinin (Qinghaosu) and the phytochemistry of *Artemisia annua* L. (Qinghao). **Molecules,** v. 15, p. 7603-7698, 2010.

BUYEL, J. F. Plants as sources of natural and recombinant anti-cancer agents. **Biotechnology Advances,** v. 36, n. 2, p. 506–520, 2018.

CASTILLO, L.; GONZÁLEZ-COLOMA, A.; GONZÁLEZ, A.; DÍAZ, M.; SANTOS, E.; ALONSO-PAZ, E.; BASSAGODA, M. J.; ROSSINI, C. Screening of Uruguayan plants for deterrent activity against insects. **Industrial Crops and Products,** v. 29, n. 1, p. 235–240, 2009.

CHAVAN, R. B.; GAIKWAD, D. K. Antibacterial Activity of Medicinally Important Two Species of *Allophylus*- *Allophylus cobbe* (L.) Raeusch. and *Allophylus serratus* (Roxb.) Kurz. **Journal of Pharmacognosy and Phytochemistry,** v. 2, n. 1, p. 1-7, 2013.

CHEBEZ, J. C.; MASARICHE, M. **Nuestros árboles.** 1. ed. Buenos Aires: Albatros, 128 p., 2010.

COELHO, R. L. G. **Estudos sistemáticos das espécies neotropicais de *Allophylus L.* (Sapindaceae).** 479 f. Tese (Doutorado). Programa de Pós-Graduação em Biologia Vegetal da Universidade Estadual de Campinas. Campinas - SP, 2014.

COUTINHO, D. J. G. **Lipídios de sementes: potencial econômico e quimiossistemático.** 70 f. Dissertação (Mestrado). Pós-graduação em Biologia Vegetal da Universidade Federal de Pernambuco, 2013.

CRAGG, G. M.; NEWMAN, D. J. Natural products: A continuing source of novel drug leads. **Biochimica et Biophysica Acta (BBA)** - General Subjects, v. 1830, n. 6, p. 3670–3695, 2013.

DALE, R.; STACEY, B. Multimodal Treatment of Chronic Pain. **Medical Clinics of North America,** v. 100, n. 1, p. 55–64, 2016.

DAVID, J. P. et al. A new sesquiterpene from the fruits of *Allophylus laevigatus*. **Fitoterapia,** v. 75, 795– 798, 2004.

DHARMANI, P. et al. *Allophylus serratus*: A plant with potential anti-ulcerogenic activity. **Journal of Ethnopharmacology**, v. 99, p. 361–366, 2005.

DÍAZ, M; GONZÁLEZ, A.; CASTRO-GAMBOA, I.; GONZALEZ, D.; ROSSINI, C. First record of L-quebrachitol in *Allophylus edulis* (Sapindaceae). **Carbohydrate Research,** v. 343, n. 15, 2699-700 p., 2008.

DÍAZ, M.; CASTILLO, L.; DÍAZ, C. E.; ÁLVAREZ, R. G.; GONZÁLEZ-COLOMA, A.; ROSSINI, C. Differential Deterrent Activity of Natural Products Isolated from

Allophylus edulis (Sapindaceae). **Advances in Biological Chemistry**, v. 4, p. 168-179, 2014.

DURIGAN, G. et al. **Plantas do Cerrado:** imagens de uma paisagem ameaçada. São Paulo: Páginas & Letras Editora e Gráfica, 2004.

DUTRA, R. C., CAMPOS, M. M., SANTOS, A. R. S., et al. Medicinal plants in Brazil: Pharmacological studies, drug discovery, challenges and perspectives. Pharmacological Research. [S.l.], Academic Press. 1 out. 2016.

ELGORASHI, E. E.; MCGAW, L. J. African plants with in vitro anti-inflammatory activities: A review. **South African Journal of Botany,** 2019.

FINCH, P. M.; DRUMMOND, P. D. Topical treatment in pain medicine: from ancient remedies to modern usage. PAIN MANAGEMENT, v. 5, n. 5, p. 359–371, 2015.

FRANCO, L. J.; FONTANA, V. L**. Ervas & plantas:** a medicina dos simples, 6. ed. v. 1. Erexim: Edelbra, 183-184 p., 2001.

GANZERA, M; GUGGENBERGER, M.; STUPPNER, H.; ZIDORN, Z. Altitudinal variation of secondary metabolite profiles in flowering heads of *Matricaria chamomilla* cv BONA. **Planta Med.**, v. 74, p. 453-457, 2008.

HOAREAU, L., SILVA, E. J. Medicinal plants: A re-emerging health aid. Electronic Journal of Biotechnology. [S.l.], Electronic Journal of Biotechnology,15 ago. 1999.

HYLANDS-WHITE, N.; DUARTE, R. V.; RAPHAEL, J. H. An overview of treatment approaches for chronic pain management. **Rheumatol Int,** v. 37, n. 1, p. 29-42, 2017.

ITO, S.; OKUDA-ASHITAKA, E.; MINAMI, T. Central and peripheral roles of prostaglandins in pain and their interactions with novel neuropeptides nociceptin and nocistatin. **Neuroscience Research,** v. 41, n. 4, p. 299–332, 2001.

JAAKOLA, L.; HOHTOLA, A. Effect of latitude on flavonoid biosynthesis in plants. **Plant Cell Environ.,** v. 33, p. 1239-1247, 2010.

JENKINS, G. I. Signal transduction in responses to UV-B radiation. **Annu. Rev. Plant Biol., v.** 60, p. 407-413, 2009.

JOLY, A. B. **Botânica:** Introdução a taxonomia vegetal. 13. ed. São Paulo, SP: Nacional, 777 p. 2005.

JUDD, W. S. **Plant systematics: a phylogenetic approach.** 3. ed., Sinauer Associates, Inc, Sunderland, Mass, 611 p., 2008.

KALLSCHEUER, N., CLASSEN, T., DREPPER, T., et al. Production of plant metabolites with applications in the food industry using engineered microorganisms. Current Opinion in Biotechnology. [S.l.], Elsevier Ltd. , 1 abr. 2019.

KINUPP, V. F. **Plantas alimentícias não-convencionais da região metropolitana de Porto Alegre, RS**. 590 f. Tese (Doutorado). Programa de pós-graduação em fitotecnia da universidade do Rio Grande do Sul. Porto Alegre, 2007.

KINUPP, V. F.; BARROS, I. B. I. Teores de proteína e minerais de espécies nativas, potenciais hortaliças e frutas. **Ciênc. Tecnol. Aliment.**, Campinas, v. 28, n. 4, p. 846-857, 2008.

KÖRBES, V.C. **Plantas medicinais.** 51. ed. Francisco Beltrão: Associação de Estudos, Orientação e Assistência Rural (ASSESOAR), 188 p., 1995.

KROYMANN, J. Natural diversity and adaptation in plant secondary metabolism. **Current Opinion in Plant Biology**, v. 14, n. 3, p. 246–251, 2011.

KUJAWSKA, M. Yerba Mate (*Ilex paraguariensis*) Beverage: Nutraceutical Ingredient or Conveyor for the Intake of Medicinal Plants? Evidence from Paraguayan Folk Medicine. **Evidence-Based Complementary and Alternative Medicine**, 17 p., 2018.

KUJAWSKA, M; PARDO-DE-SANTAYANA, M. Management of medicinaly useful plants by European migrants in South America. **Journal of Ethnopharmacology**, v. 172, p. 347–355, 2015.

LAVOIR, A. V.; STAUDT, M.; SCHNITZLER, J. P.; LANDAIS, D.; MASSOL, F.; ROCHETEAU, A.; RODRIGUEZ, R.; ZIMMER, A.; RAMBAL, S. Drought reduced monoterpene emissions from *Quercus ilex* trees: results from a throughfall displacement experiment within a forest ecosystem. **Biogeosciences,** v. 6, p. 863-893, 2009.

LOPES, M. A., NOGUEIRA, I. S., OBICI, S. "Estudo das plantas medicinais, utilizadas pelos pacientes atendidos no programa “Estratégia saúde da família” em Maringá/PR/Brasil", Revista Brasileira de Plantas Medicinais, v. 17, n. 4, p. 702–706, 2015. DOI: 10.1590/1983-084X/12_173.

LÓPEZ-RUBALCAVA, C., ESTRADA-CAMARENA, E. "Mexican medicinal plants with anxiolytic or antidepressant activity: Focus on preclinical research", Journal of Ethnopharmacology, v. 186, p. 377–391, 20 jun. 2016. DOI: 10.1016/j.jep.2016.03.053.

MARQUES, T. P. **Subsídios à recuperação de formações florestais ripárias da Floresta Ombrófila Mista do Estado do Paraná, a partir do uso espécies fontes de produtos florestais não-madeiráveis.** 244 f. Dissertação (Mestrado em Produção Vegetal). Programa de Pós-graduação em Agronomia da Universidade Federal do Paraná. Curitiba, 2007.

MURAKAMI, M. **The Molecular Mechanisms of Chronic Inflammation Development.** Tokyo: Frontiers E-Books; 2012.

O'CONNOR, S. E. Engineering of Secondary Metabolism. **Annual Review of Genetics.** v. 49, p. 71-94, 2015.

OLADOSU, I. A.; BALOGUN, S. O.; ADEMOWO, G. O. Phytochemical screening, antimalarial and histopathological studies of *Allophylus africanus* and *Tragia benthamii*. **Chinese Journal of Natural Medicines**, v. 11, n. 4, p. 0371−0376, 2013.

OLADOSU, I. A.; BALOGUN, S. O.; LIU ZHI-QIANG. Chemical constituents of Allophylus africanus. **Chinese Journal of Natural Medicines,** v. 13, n. 2, p. 0133-0141, 2015.

PAVARINI, D. P. et al. Exogenous influences on plant secondary metabolite levels. **Animal Feed Science and Technology**, v. 176, p. 5– 16, 2012.

PIAGGIO, M.; DELFINO, L. Plantas nativas del Uruguay. 2003. Disponível em: <http://micol.fcien.edu.uy/flora/Allphyllus-edulis.html>. Acesso em 11 ago. 2019.

RIBEIRO, L. H. L. "Análise dos programas de plantas medicinais e fitoterápicos no Sistema Único de Saúde (SUS) sob a perspectiva territorial", Ciencia & saude coletiva, v. 24, n. 5, p. 1733–1742, 2019. DOI: 10.1590/1413-81232018245.15842017.

SANO, S. M.; ALMEIDA, S. P.; RIBEIRO, J. F. **Cerrado: ecologia e flora.** Brasília: Embrapa Informação Tecnológica, v. 2, 279 p., 2008.

SANTOS, R.M.; FORTES, G.A.C.; FERRI, P. H.; SANTOS, S. C. Influence of foliar nutrients on phenol levels in leaves of *Eugenia uniflora*. **Rev. Bras. Farmacogn.,** v. 21, p. 581-586, 2011.

SARTORI, A. L. B., POTT, A. "Floristic-taxonomic knowledge of the Flora of Mato Grosso do Sul, Brazil: Yesterday and Today", Iheringia - Serie Botanica, v. 73, p. 18–21, 2018. DOI: 10.21826/2446-8231201873s18.

SCHMEDA-HIRSCHMANN, G.; FERESIN, G.; TAPIA, A.; HILGERT, N.; THEODULOZ, C. Proximate composition and free radical scavenging activity of edible fruits from the Argentinian Yungas. **Journal of the Science of Food and Agriculture.** v. 85, p. 1357–1364, 2005.

SEIGLER, D. S. Plant secondary metabolism. **Springer Science+Business Media.** New York, 1998.

SEMAAN, D.G. et al. In vitro anti-diabetic activity of flavonoids and pheophytins from *Allophylus cominia* Sw. on PTP1B, DPPIV, alpha-glucosidase and alpha-amylase enzymes. **Journal of Ethnopharmacology**. v. 203, p. 39-46, 2017.

SERHAN, C. N.; WARD, P. A.; GILROY, D. W. **Fundamentals of inflammation.** Everbest, 2010.

SHITAN, N. Secondary metabolites in plants: transport and self-tolerance mechanisms. **Bioscience, Biotechnology, and Biochemistry**, v. 80, n. 7, p. 1283–1293, 2016.

SILVA, J. S. V., SPERANZA, E. A., VENDRUSCULO, L. G., ESQUERDO, J. C. D. M., MAURO, R. A., BIANCHINI, S. L., FLORENCE, R. O. Projeto GeoMS: melhorando o sistema de licenciamento ambiental do Estado de Mato Grosso do Sul. Campinas: Embrapa Informática Agropecuária, 64 p., 2011.

SIQUEIRA-LIMA, P. S., SILVA, J. C., QUINTANS, J. S. S., ANTONIOLLI, A. R., SHANMUGAM, S., BARRETO, R. S. S., … QUINTANS-JÚNIOR, L. J. Natural products assessed in animal models for orofacial pain – a systematic review. **Revista Brasileira de Farmacognosia,** v. 27, n. 1, 124–134, 2017.

STILING, P.; CORNELISSEN, T. How does elevated carbon dioxide (CO2) affect plant–herbivore interactions? A field experiment and meta-analysis of CO2-mediated changes on plant chemistry and herbivore performance. **Glob. Change Biol.,** v. 13, p. 1823-1842, 2007.

THEPLANTLIST. *Allophylus edulis* **(A.St.-Hil., A.Juss. & Cambess.) Radlk**. Disponível em: <http://www.theplantlist.org/tpl1.1/record/kew-2629327>. Acesso em: 10 ago. 2019.

TIRLONI, C. A. S.; MACORINI, L. F. B.; SANTOS, U. P.; ROCHA, P. S.; BARROS, S. V.; MELO, A. M. F.; VIEIRA, M. C.; SOUZA, K. P.; SANTOS, E. L. Evaluation of the antioxidant activity, antimicrobial effect and acute toxicity from leaves of *Allophylus edulis* (A. St.-Hil., A. Juss. Cambess.) Hieron. ex Niederl. **African Journal of Pharmacy and Pharmacology**. v. 9, p. 353-362, 2015.

TODD, I.; SPICKETT, G.; FAIRCLOUGH, L. **Lecture Notes:** Immunology. New York: John Wiley & Sons; 2015.

TREVIZAN, L. N. F., NASCIMENTO, K. F. DO, SANTOS, J. A., KASSUYA, C. A. L., CARDOSO, C. A. L., VIEIRA, M. DO C., … FORMAGIO, A. S. N. Anti-inflammatory, antioxidant and anti- Mycobacterium tuberculosis activity of viridiflorol: The major constituent of *Allophylus edulis* (A. St.-Hil., A. Juss. & Cambess.) Radlk. Journal of Ethnopharmacology, v. 192, p. 510–515, 2016.

UMEO, S. H.; ITO, T. M.; YOKOTA, M. E.; ROMAGNOLO, M. B.; LAVERDE-JUNIOR, A. Avaliação das propriedades antioxidantes, anticolinesterásicas e citotóxicas dos frutos de *Allophylus edulis* (A.St.-Hil., Cambess. & A. Juss.) Radlk. (Sapindaceae). **Arq. Ciênc. Saúde** UNIPAR, Umuarama, v. 15, n. 2, p. 167-171, 2011.

VAN WYK, B. E. A family-level floristic inventory and analysis of medicinal plants used in Traditional African Medicine. Journal of Ethnopharmacology., Elsevier Ireland Ltd., 1 mar. 2020. DOI: 10.1016/j.jep.2019.112351.

VERPOORTE, R.; ALFERMANN, A. W. Metabolic Engineering of Plant Secondary. **Metabolism. Springer Netherlands**, 286 p., 2000.

VIJAYAKUMAR, R.; RAJA, S. S. S. **Secondary Metabolites:** Sources and Applications. Croatia: IntechOpen, 2018.

WURTZEL, E. T.; KUTCHAN, T. M. Plant metabolism, the diverse chemistry set of the future. **Science,** v. 353, n. 6305, 1232–1236, 2016.

ZHANG, X. Y.; CAI, X. H.; LUO, X. D. Chemical constituents of *Allophylus longipes*. **Chinese Journal of Natural Medicines,** v. 10, n. 1, p. 0036-0039, 2012.

ZINI, L. M.; GALATI, G. B.; SOLÍS, S. M.; FERRUCCI, M. S. Anther structure and pollen development in *Melicoccus lepidopetalus* (Sapindaceae): An evolutionary approach to dioecy in the family. **Flora - Morphology, Distribution, Functional Ecology of Plants,** v. 207, n. 10, p. 712-720, 2012.

ARTIGO 1

Escolha para submissão: Journal of Ethnopharmacology, Fator de Impacto: 3,115,

Qualis A2

The ethnopharmacological literature: An analysis of the scientific landscape in Cerrado in the central-western Brazil

Sidney Mariano dos Santos[b], Kamilla Felipe do Nascimento[a], Zefa Valdevina Pereira[b], Josimo Diego Bazanella Line[b], Pedro Cruz de Oliveira Junior[b], , Anelise Samara Nazari Formagio[a,b,*]

[a]Faculty of Biological and Environmental Sciences, Federal University of Grande Dourados UFGD, MS, Brazil.

[b]Faculty of Health Sciences, Federal University of Grande Dourados UFGD, MS, Brazil.

***Corresponding author address:** aneliseformagio@ufgd.edu.br; aneliseformagio@gmail.com

ABSTRACT

Ethnopharmacological relevance: The research into pharmacological and phytochemistry originating from medicinal plants has accumulating diverse publications, highlighting Cerrado in the Brazilian central-western with a remarkable diversity of plant species. However, no ethnopharmacological review exists focusing on the plants that occur in reserve area of the settlement "April 17", MS, even though the consumption of medicinal plants is a widespread practice.

Aim of the study: The aims of this study were: 1) we documented a survey of the medicinal plants presents in reserve area of the settlement "April 17", MS; 2) to provide an overview of recent studies ethnopharmacological, phytochemical and pharmacological review of these plants, and 3) provide insight for future studies.

Materials and methods: Reserve area selected for the study is the Cerrado *stricto sensu* settlement "17 April", MS, Brazil. The literature search and relevant information were collected through authentic resources using data bases such as Science Direct, PubMed, Google Scholar, Web of Science and Scopus, peer reviewed articles, books and thesis.

Results and discussion: This study showed a large number of medicinal plants present in the study area. A variety of 89 plants were found, belonging to 39 different families, the most abundant of which were Bignoniaceae (n = 5), Fabaceae (n = 13), Myrtaceae (n = 7) and Rubiaceae (n = 7). In the search for each plant, in terms of empirical use, the most used parts are leaves (41%), barks (22%) and roots (15%). Popular use is focused on the treatment of intestinal disorders, infections or parasitic diseases and endocrine and metabolic diseases. Studies already carried out with some of the species have shown the evidence of medicinal use, especially for those indicated for disorders of the digestive system and infections. Chemical studies report the greater presence of compounds from the classes of terpenes, phenolic compounds, and alkaloids.

Conclusion: This study showed the large amount of medicinal plants in an area of Cerrado in the state of Mato Grosso do Sul, Brazil. Noting the importance of biodiversity for the development of new pharmacological approaches, since many studies prove the empirical use of medicinal plants.

Keywords: Medicinal plants, ethnobotanical, Cerrado.

1. INTRODUCTION

The Brazil is characterizing as the country with one of the largest biodiversities on the planet, due to the presence of different biomes, such as Amazon (tropical forest), Caatinga (thorn forest), Pantanal (flooded pasture), Pampas (subtropical pastures or pastures), Atlantic Forest (deciduous forest) and Cerrado (savanna) (Guerra et al., 2020). The Cerrado is the second largest biome in South America, occupying an area around 22% of the Brazilian territory, being the second largest biome rich in biodiversity (Sano et al., 2010). The state of Mato Grosso do Sul is located in the Midwest of Brazil so that most of its territory is occupied by the Cerrado (Amaral et al., 2017). Nevertheless, 46% of the original Cerrado area has already been converted to pasture and crops, mainly, and is continually threatened by the indiscriminate use of fire (Durigan and Ratter, 2015; Strassburg et al., 2017).

The study of ethnopharmacology is closely related to sustainable development, as it is an effective way to develop medicines using the perspective of traditional plant use (Mukherjee, 2019). In this sense, the importance of studies in this area is clear as they contribute to the improvement of the traditional application of natural products, and they emphasize the importance of biodiversity for the sustainability of local populations (Di Stasi, et al. 2002). In this context, the Brazilian government encouraged the use of herbal

remedies and medicinal plants as a strategy to improve the use of Brazilian biodiversity and public access to herbal medicines (Brasil, 2006).

In this study, we documented a survey of the medicinal plants presents in reserve area of the settlement “April 17”, MS, Brazil, in Cerrado biome. An exhaustive research evaluated the current status of scientific knowledge related to the popular use, phytochemical and pharmacological data of these plants is also presented. We also discuss the species found in the study area that are listed for research to herbal medicines. The population residing this area is concentrated in agriculture, and characterized mainly by its means of subsistence, depending on the natural resources for different purposes. Considering the abundant vegetation and the scarcity of financial resources, the local population often uses natural resources as a source of treatment for diseases, but without any scientific knowledge of scientific evidence. After identification of all species found in this area, survey of scientific studies involving these species becomes absolutely relevant and necessary, aiming to contribute to the safety and well-being of those who commonly make use of these plants. Both in the target region of this study, as in the others.

2. MATERIAL AND METHODS

2.1 Sites of study

In the framework of this study, the selected area, Cerrado *stricto sensu* (21°46'54.6"S and 53°13'23.6"W) was the reserve area of the settlement “17 April”, located in Casa Verde district, Nova Andradina city, MS (**Fig. 1**).

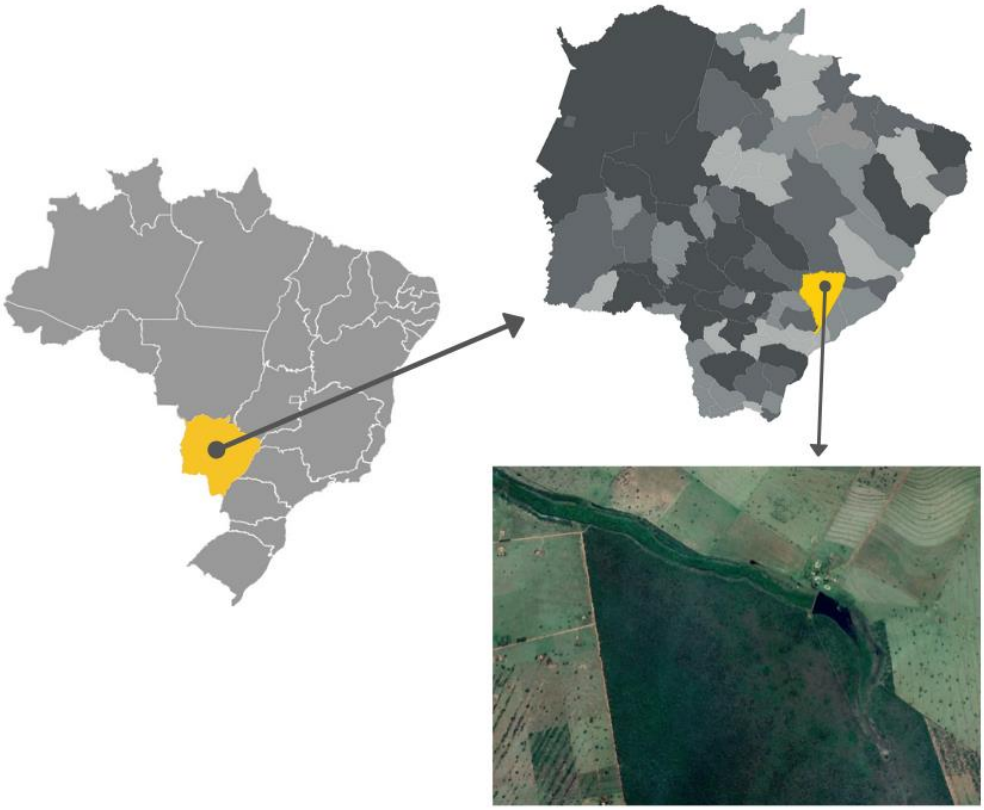


Fig. 1. Geographical location of the study area (reserve area of the settlement “17 April”).

2.2. Collection and identification of species

The collections of the species present in this area were carried out between the months of 09/2017 to 01/2018 and botanical material identified by Dr. Zefa Valdevina Pereira (Faculty of Biological and Environmental Sciences) and later deposited in the herbarium of the Federal University of Grande Dourados-UFGD. Each exsicata generated an identification protocol number (DDMS) (**Table 2**).

2.3 Bibliographical survey

A review of the the popular use, phytochemical and pharmacological data species found in the reserve region of the settlement “April 17” was performed using online

journals and books that are published in English, Portuguese and Spanish. The information related to this article was collected from the scientific literature databases including Science Direct, PubMed, Scopus and Google Scholar. Articles were selected according to the family, gender, and species (including synonymous species).

2.5 Traditional applications

The popular indications described for the plants found at the analysed site were categorized according to the International Classification of Diseases and Related Health Problems (ICD-11) (**Table 1**), as described in the reference guide published by the World Health Organization (WHO, 2019).

Table 1. Eleventh revision of the Internation Classification of Diseases for Mortality and Morbidity Statistics (ICD-11).

Abbreviation	**Title**
IPD	Infectious and parasitic diseases
NEO	Neoplasms
BHD	Blood and hematopoietic organ diseases and some immune disorders
ENM	Endocrine, nutritional and metabolic diseases
CNS	Nervous system diseases
EAD	Eye and eye attachment diseases
CSD	Circulatory system diseases
RSD	Respiratory system diseases

DSD	Digestive system diseases
SSD	Skin and subcutaneous tissue diseases
MCD	Musculoskeletal system and connective tissue diseases
GSD	Genitourinary system diseases
PBP	Pregnancy, childbirth and postpartum
SSA	Symptoms, signs and abnormal clinical and laboratory findings, not classified in other part
IPC	Injury, poisoning and some other consequences of external causes
ECM	External causes of morbidity and mortality
FIS	Factors that influence health status and contact with health services

3. RESULTS AND DISCUSSION

For the first time 89 medicinal plants belonging to 39 families were documented from the study area, reported as trees (*n*=60), bush (*n*=19), and shrub (*n*=1), mainly (**Table 2**). The families Bignoniaceae (*n*=5), Fabaceae (*n*=13), Myrtaceae (*n*=7) and Rubiaceae (*n*=7), were the most species-rich (**Table 2**). The leaves (41%), barks (22%) and roots (15%) were the most reported parts for popular use (**Table 2**). **Table 2** presents information of a scientific research, describing the forms of use of the plants, as well as the part used of the plants and their use.

The more widespread traditional use of these plants involves the treatment of diarrhea to *Anacardium humile*, *Astronium fraxinifolium*, *Annona coriacea*, *A. crassiflora*, *A. dioica*, *Jacaranda decurrens*, *Tabebuia aurea*, *Connarus suberosus*, *Davilla elliptica*, *Erythroxylum suberosum*, *Dimorphandra mollis*, *Stryphnodendron adstringens*,

Lafoensia pacari, *Byrsonima basiloba*, *Byrsonima coccolobifolia*, *Byrsonima intermedia*, *Campomanesia adamantium*, *Eugenia punicifolia*, *Myrcia bella*, *Guettarda viburnoides*, *Casearia sylvestris*, *Qualea grandiflora*, *Q. multiflora*, and *Q. parviflora* (**Table 2**). According to the World Health Organization, diarrheal diseases are the main cause of death in children under five years old, so that there are almost 1.7 billion cases of childhood diarrhea every year, with about 525,000 deaths (WHO, 2017).

Table 2. Identification of the species found and recorded literature (name, popular use and utilized part) in reserve area of the settlement "April 17", located in Casa Verde district, Nova Andradina city, MS, Brazil.

Family	**Botanical taxon (DDMS)/Habit**	**Popular name**	**Reported popular uses (Used parts and application)**
Amaranthaceae	*Gomphrena officinalis* Mart.(4629)/Bush	Para-tudinho, para-tudo	Roots: Tonic, counteracts weakness, debility in general and panacea for all ills (Almeida et al., 1998; Alzugaray and Alzugaray, 1983; Balbach, n.d.; Lorenzi and Matos, 2002)
Anacardiaceae	*Anacardium humile* A. St. Hil (5418)/Bush	Cajuzinho-do-cerrado, ca*ju do campo,*	Purgative, diarrhea, anti-inflammatory, adstringente and external ulcers (Pott and Pott, 1994; Thomas and Filho, 1985, 1985; Vila Verde et al., 2003; Agra et al., 2007)
	Astronium fraxinifolium Schott (5107)/Tree	Gonçalo-alves	Leaves: Allergies, inflammation, diarrhea and ulcers (Viana et al., 1997, Silva et al., 2011; Resende et al., 2015)
	Tapirira guianensis Aubl. (6035)/Tree	Tapirira, pau-pombo, cupiúva, tatapiririca, jobo, cedroí, fresmo	Leaves: Antibacterial, treatment of malária, leshmaniosis and syphilis (David et al., 1998; Roumy et al., 2009) Barks: Anti-leishmanial, anti-plasmodial, anti-bacterial and anti-fungal, snake bites, oral thrush and sore throat (Deharo et al., 2001; Roumy et al., 2009; Zoghbi et al., 2014; Vásquez et al., 2015)
Annonaceae	*Annona coriacea* (5818)/Tree	Araticum, marolo, araticum-liso	Leaves: Stomach diseases, stomatitis, neuralgia, headache, antirheumatic and anthelmintic (Morais Cardoso et al., 2013); chronic diarrhea (Rodrigues and Carvalho, 2001)
	Annona crassiflora Mart.(61640)/Tree	Araticum-do-cerrado, araticum-do-campo, pinha-do-cerrado, marolo	Leaves: Tumors and analgesic (Roesler et al., 2007) Seeds: Skin infection and antidiarrheal (Luzia et al., 2013; Roesler et al., 2006)

	Annona dioica A.St.-Hil.(6037)/Bush	Ceraticum, arixicum e ariticum	Leaves: Rheumatism, antidiarrheal, sedative and anti-catarrhal (Pott and Pott, 1994)
	Xylopia aromatica (Lam.) Mart.(5937)/Tree	Pimenta de macaco	Roots: Antimalarial (de Mesquita et al., 2007) Fruits: Carminative and aphrodisiac (Oliveira et al., 2014)
	Aspidosperma macrocarpa Mart.(4835)/Tree	Are not reports	Are not reports
Apocynaceae	*Aspidosperma tomentosum* Mart.(3528)/Tree	Guatambu	Bark: Hypercholesterolemia, anorexic, diuretic (Silva et al., 2010; de Almeida et al., 2019)
	Hancornia speciosa Gomes (5822)/Tree	Mangabeira, mangaba	Leaves: Diabetes, anti-hypertensive and anti-obesity (Hirschmann & Arias, 1990; Rodrigues & Carvalho, 2001; Macedo & Ferreira, 2004; Pereira et al., 2015)
	Himatanthus obovatus (Müll. Arg.) Woodson	Tiborna, pau-de-leite, janaguba	Leaves: Cancer, herpes and verminoses (Mesquita et al., 2005)
Araliaceae	*Schefflera macrocarpa* (Cham. & Schltdl.) Frodin/Tree	Mandiocão, mandiocão-do-campo, caixeta, caixeiteiro	Are not reports
Arecaceae	*Allagoptera campestris* (Mart.) Kuntze (4793)/Tree	Buri-do-campo, pissandó, paissandu, pissandu e coqueiro-pissandó	Are not reports
	Syagrus flexuosa (Mart.) Becc./Tree	Coquinho-babão, Acumã, Coco do campo	Are not reports
	Anemopaegma arvense (Vell.) Stellfeld & J.F. Souza(5247)/Shrub	Vergateza, vergateso, catuaba-do-cerrado, catuaba, pau-de-	Roots and leaves: Aphrodisiac, nervous system stimulator, inflammation of the ovaries and varicose veins, stimulant, insomnia, neurasthenia, nervousness, hypochondria. poor memory, in recovery from serious illness, asthenia, anxiety, chronic bronchitis, bronchial

		resposta and alecrim-do-campo	asthma and sexual impotence (Barros, 1982; Guarim Neto, 1987; Brandão, 1991; Lorenzi and Matos, 2002; Longhini et al., 2017)
	Cybistax antisyphilitica (Mart.)/(4763)Tree	Carobinha verde, caroba de flor verde, Ipê-mandioca, Ipê-de-flor-verde, pé-de-anta, cinco-em-folhas, ipê, jangua, ipê mirim, ipê-amarelo	Young branches, roots and leaves: Antisyphilitic, dysuria, hydrops, water retention, poultice, syphilitic ulcers, fever, headache and invigorating baths (Siqueira, 1982; Guarim Neto, 1987; Sanz-Biset et al., 2009; Breitbach et al., 2013) Stem bark: Antirheumatic, antiarthritic, anticancer, antimalarial and healing of ulcers (Llorente et al., 2016)
Bignoniaceae	*Handroanthus ochraceus* (Cham.) Mattos	Mangabeira, mangaba	Leaves: Diabetes, anti-hypertensive and anti-obesity (Hirschmann & Arias, 1990; Rodrigues & Carvalho, 2001; Macedo & Ferreira, 2004; Pereira et al., 2015)
	Jacaranda decurrens Cham./(5565)Bush	Carobinha, carobinha-do-campo, caroba	Leaves and roots: Inflammatory diseases, infections, syphilis, rheumatism, dermatological diseases, treatment of diarrhea and dysentery, blood cleanser, wound healing in the uterus and ovary, prostate inflammation, allergies, diabetes, hyperlipidemia and rheumatic problems (Nunes et al., 2003; Tresvenzol et al., 2006; Gachet and Schühly, 2009; Bieski et al., 2012; Neiva et al., 2014)
	Tabebuia aurea (Silva Manso) Benth. & Hook.f. ex S.Moore/(5348)Tree	Paratudo, craibeira, caraiberia, caroba-do-campo, cinco-em-rama, cinco-folhas-do-campo, ipê-amarelo-craibeira, ipê-amarelo-do-cerrado, pau-d'arco	Stem bark: Cancer, wounds, snakebite, colds, bronchitis, rheumatism, malaria, abdominal disorders, kidney disorders, cancer, antidiarrheal and dysentery (Nunes et al., 2003; Agra et al., 2007; Hajdu and Hohmann, 2012; Reis et al., 2014)

Bixaceae	*Cochlospermum regium* (Mart. ex Schrank) Pilg.(5941)/Bush	Algodão-do-campo; Algodãozinho	Shell: Cholesterol, blood depurative, inflammation of the uterus and ovary, inflammation of the skin (Nunes et al., 2003) Roots: Treatment of uterine and intestinal infections, gastritis, ulcers and arthritis (Camillo et al., 2009)
Burseracea	*Protium heptaphyllum* (Aubl.)Marchand (6142)/Tree	Almécega, breu branco, amescla, breu, almíscar	Resin: Skin diseases, healing of ulcers, scirrhus, anti-inflammatory, analgesic, expectorant, insect repellant, antioxidant, respiratory disorders (Pernet, 1972; Guarim Neto, 1987; Susunaga et al., 2001; Aragão et al., 2006; Marques et al., 2010)
Calophyllaceae	*Kielmeyera coriacea* Mart. & Zucc.(5443)/Tree	Pau-santo	Leaves: Schistosomiasis, leishmaniasis, malaria. fungal and bacterial infections (Alves et al., 2000; Albernaz et al., 2010)
Caryocaraceae	*Caryocar brasiliense* Cambess(5937)/Tree	Pequi; piqui, pequiá, amêndoa de espinho, grão de cavalo ou amêndoa do Brasil	Chestnut oil and lumps: Asthma, bronchitis, pertussis, colds, aphrodisiac and tonic (Rodrigues and Carvalho, 2001; Lima et al., 2007)
Celastraceae	*Plenckia populnea* Reissek (6189)/Tree	Marmelinho, marmeleiro-do-campo	Leaves and branches: Allergy and wound healing (Rodrigues and Carvalho, 2001)
Combretaceae	*Terminalia argentea* Mart. (6063)/Tree	Capitão, pau-garrote, caxaporra-do-gentio	Purgative (Pott and Pott, 1986; Ricardo et al., 2017)
Connaraceae	*Connarus suberosus* Planch.(6038)/Tree	Are not report	Shell: Antidiarrheal (da Costa et al., 2014)
	Rourea induta Planch. (5345)/Bush, tree	Chapeudinha, pau de porco, campeira	Leaves: Chagas disease and antirheumatic (Kalegari et al., 2014)
Cucurbitaceae	*Cayaponia espelina* (Silva Manso) Cogn./Vine (6033)/	Taiuia-de-Pimenta, Abobrinha-do-Mato, Espelina, Espelina-Verdadeira, Tomba, Purga-de-Carijó, Aspirina, Purga-de-	Whole plants: Tonic, stomachic, purgative, emetic, liver disorders, strikes, injuries, depurative, rheumatism, arthritic, bronchopulmonary diseases and secondary syphilitic manifestations (Cardoso Júnior, 2017; Ricardo et al., 2017; Sangalli et al., 2002)

		Carijó, Tomba, Espelina, Purga-de-Carijo e Pirima; cerejeira de purga, espelina, tomba	
	Curatella americana L. (6184)/Bush	Cajueiro-bravo, Lixa, lixeira, Sambaíba	Aerial parts: Hypertension (García, 1975, Correa and Bernal, 1992) Barks: Cuts, cancer, anaemia, inflammations, cold, healing wounds, ulcers, diabetes, hypertension, anti-inflammatory, skin diseases (Corrêa, 1984; Vila Verde et al., 2003; Luz, 2001; Pinto and Maduro, 2004; Franco and Barros, 2006; de Medeiros et al., 2013; Guerrero et al., 2002; Souza and Felfili et al., 2006; Costa et al., 2008). Flowers: against cough, bronchitis and flu (Silva et al., 2001)
Dilleniaceae	*Davilla elliptica* A.St.-Hil.(5951)/Tree	Lixeirinha, lixeira, lixeira-rasteira, bugre, sambaibinha, muricizinho, pau-de-bugre, cipó-caboclo	Leaves and stems: Arthritis, diabetes and high blood pressure, antiseptic and astringent (Macedo and Ferreira, 2004; de Medeiros et al., 2013) Leaves: treatment of hemorrhoids, hernia and diarrhea, and in topical applications as an antiseptic in wound cleaning (Soares et al., 2005) Roots: Astringent, tonic and laxative (Rodrigues and Carvalho, 2001)
Ebenaceae	*Diospyros hispida* Warm.(5754)/Tree	Caqui do Cerrado, olho de boi	Leprosy, skin eruptions, eye infections and other infectious diseases (Mallavadhani et al., 1998; Albernaz et al., 2010)
Erythroxylacea	*Erythroxylum campestre* A.St.-Hil.(5933)/Tree	Cabeça-de-negro	Barks and stalk: Laxative, astringent in case of bleeding (Rodrigues and Carvalho, 2001; Paula, 2012)
	Erythroxylum suberosum A.St.-Hil.(5944)/Tree	Galinha-choca, mercúrio-do-campo, sessenta-e-dois, azougue-do-campo, cabelo-de-negro	Leaves: Astringent, infectious diseases, antidiarrheal, anesthetics, antirheumatic and indigestion (Violante et al., 2012; Fuzer Grae et al., 2015; Rodrigues et al., 2015)
	Erythroxylum tortuosum Mart.(6194)/Bush	Cabelo-de-negro	Anti-inflammatory, bronchitis and asthma (Cano and Volpato, 2004; Gonzales-Guevara et al., 2006)

Euphorbiaceae	*Mabea fistulifera* Mart./Tree	Canudo-de-pito, canudeiro, mamoninha do mato e leiteira preta	Are not reports
	Sapium obovatum Klotzsch ex Müll.Arg.	Sarã-do-campo	Omach pain, headache (Ribeiro et al., 2017)
	Acosmium subelegans (Mohlenbr.) Yakovlev (5068)/Tree	Genciana, perobinha-do-campo, leptolobio	Roots and stem: soothing, tranquilizing and sedative nervous system (Oliveira et al., 1994)
	Anadenanthera peregrina (L.) Speg. (5848)/Tree	Angico	Are not reports
	Andira humilis Mart. ex Benth.(5926)/Tree	Angelim rasteiro, Angelim-do-campo ou Mata-barata	Roots: Diabetes and anthelmintic (Periotto et al., 2004; Conceição et al., 2011)
	Bauhinia rufa (Bong.) Steud.(6029)/Tree	Pata-de-boi; patevaca, patebuey; Pata de vaca	Fruits: Renal disorders, diuretic and diabetes (Bieski et al., 2015) Leaves: Antihyperlipidemic (Silva et al., 2010)
	Bowdichia virgilioides Kunth/Tree	Sucupira, Sucupira-preta	Barks: Wound healing, anti-ulcer and anti-diabetic (Macedo and Ferreira, 2004) Seeds: Rheumatism, arthritis and skin diseases (Cruz, 1965)
	Copaifera langsdorffii Desf.(5939)/Tree	Copaifera langsdorffii var. langsdorffii, Copaiba langsdorfii (Desf.) Kuntze, Copaifera nitida Hayne, Copaifera sellowii	Trunk resin oil: Sore throat, urinary and pulmonary infections, hasten ulcer and wound healing (Cardoso et al., 2017)

		Hayne. (Theplantlist.org)	
Fabaceae	*Dalbergia miscolobium* Benth.	Caviúna do campo	Aphrodisiac, abortifacient, expectorant, anthelmintic, antipyretic, appetizer, allays thirst, vomiting, burning sensation, skin diseases, ulcers, blood diseases, reduces obesity, leucoderma, dyspepsia, dysentery, eye and nose diseases, syphilis, stomach troubles, leprosy, leucoderma, scabies and ringworm (Nadkarni, 1954; Gregson et al., 1978; Kirtikar and Basu, 1991)
	Dimorphandra mollis Benth.(4906)/Tree	Falso barbatimão, farinha-seca, enche-cangalha, barbatimão de folha miúda	Stem bark: Antidiarrheal, gynecological problems and for wound healing (Lorenzi, 1991; Macedo et al., 2000; Santos et al., 2002; Feres et al., 2006; Petacci et al., 2010; Mendes et al., 2013)
	Dipteryx alata Vogel(5995)/Tree	Baru	Bark: Fever (Puebla et al., 2010) Seed oil: Snake bites antirheumatic and menstrual regulator (Lorenzi, 1992; Santo et al., 2004; Puebla et al., 2010; Ferraz et al., 2012)
	Diptychandra aurantiaca Tul.(6149)/Tree	Balsaminho	Are not reports
	Pterodon pubescens (Benth.)(5947)/Tree	Sucupira-branca, faveira	Fruit (oil) and seed: Rheumatic diseases (analgesia and anti-inflammation) (Nucci-Martins et al., 2015)
	Stryphnodendron adstringens (Mart.) Coville/Tree	Barbatimão, barba-de-timão, casca-da-virgindade, faveira, barbatimão-branco, barbatimão-verdadeiro	Bark: Uterine and vaginal conditions, infections urinary tract infections, skin lesions, ulcer wounds, antidiarrheal, inflammation of the throat, bleeding, scurvy, pulmonary complications and respiratory infections (Herzog-Soares et al., 2002; Brasil, 2014; de Freitas et al., 2018)
	Vatairea macrocarpa (Benth.)Ducke(6193)/Tree	Amargoso, maleiteira, angelim-do-cerrado	Stem bark: Diabetes and mycoses (Oliveira et al., 2008)

	Aiouea trinervis Meisn.(5924)/Tree	Brinco-de-princesa, Louro-de-Goiás; uridol, urinosa, vergateza	Leaves: Aphrodisiac (Moraes, 2005; Maier, 2016)
Lauraceae Juss.	*Ocotea minarum* (Nees & Mart.) Mez/Tree	Canelinha, canela vassoura	Candidiasis (Rodrigues et al., 2014)
Loganiaceae	*Strychnos pseudoquina* A.St.-Hil.(5405)/Tree	Guararoba, quina do cerrado, quina branca, quina-quina	Shell: Tonic, antipyretic, antimalarial, liver, spleen and stomach diseases, fever and malaria (Andrade-Neto et al., 2003; Honório-França et al., 2008; Bonamim et al., 2011)
Lycopodiaceae Mirb.	*Lycopodium clavatum* L.(5934)/Herb	Licopódio, Pé de Lobo, Clavatum e Musgo Terrestre	Liver abnormalities, flatulent dyspepsia, abdominal distention, headaches related to digestive disorders (Silva et al., 2015; Farmacopéia Brasileira, 2017)
Lythraceae J.St.-Hil.	*Lafoensia pacari* A.St.-Hil.(6049)/Tree	Mangava-brava, pacari, dedaleiro, louro-da-serra	Leaves, roots, bark and sap: Gastritis, ulcers, bloody diarrhea, venereal diseases, fever, boil, syphilis, worms, cancer; depurative, diabetes, obesity, hemorrhoids, swelling, labyrinthitis, pneumonia, tuberculosis, heartburn, liver, indigestion, gallstones, back pain, uterine inflammation, diuretic and burn (Ribeiro et al., 2017; Pereira et al., 2018)
Magnoliaceae Juss.	*Magnolia ovata* (A.St.-Hil.) Spreng.(5954)/Tree	Pinha-do-brejo, baguaçu	Trunk bar: Fever and diabetes (Kassuya et al., 2009; Mori et al., 2011)
	Byrsonima basiloba A. Juss.(6030)/Tree	Murici	Leaves: Diarrhea and gastric ulcer (Figueiredo et al., 2005; Lira et al., 2008)
	Byrsonima coccolobifolia Kunth (6169)/Bush	Murici, Murici de flor rósea, murici-do-cerrado	Antidiarrheal (Lorenzi, 2002 and Brandão et al., 1992)
Malpighiaceae	*Byrsonima intermedia* A. Juss. (5735)/Bush	Murici pequeno	Laeves: Fever, ulcers, diuretic, antiasthmatics and skin infections (de Cássia Santos et al., 2019) Stem bark: Diarrhea, dysentery, antifungal and anti-inflammatory activity (Rodrigues and Carvalho, 2011)

	Diplopterys pubipetala (A.Juss.) W.R.Anderson & C.C.Davis (5932)/Bush	Cipó-preto	Are not reports
Malvaceae Juss.	*Eriotheca gracilipes* (K.Schum.) A.Robyns (6185)/Tree	Paineira, paineira-da-mata.	Are not reports
	Luehea divaricata Mart. & Zucc.(6046)/Tree	Açoita cavalo, caiboti	Leaves: Uric acid, kidney disease, throat inflammation, influenza, hemorrhoids, pneumonia, muscle aches, cough and tumors (Tirloni et al., 2018)
Melastomataceae	*Miconia albicans* (Sw.) Triana (5492)/Bush	Canela de velho	Leaves: Anti-inflammatory and antidiabetic (De Cássia Lemos Lima et al., 2018)
Moraceae	*Brosimum gaudichaudii* trécul (5406)/Bush, tree	Mama-de-cadela, Mama-cadela, mamica-de-cadela, algodãozinho, inharé, mama-cachorro (Pozetti 2005; Rodrigues, 2007; Agra et al., 2008; Monteiro et al., 2014)	Stem-bark, leaves, roots and latex: Vitiligo, skin diseases, infections, venereal disease, furuncle, “impingem” (superficial skin mycoses), cancer, anemia, heart tonic, pneumonia, prickly heat, tonic, inflammation, rheumatism, kidneys, wound healing, flu, bronchitis, depurative, improvement of blood circulation, pain in general, mosquito bite allergy (Rodrigues and Carvalho, 2001; Amorozo, 2002; Agra et al., 2008; Monteiro et al., 2014; Ribeiro et al., 2017)
	Campomanesia adamantium (Cambess.) O.Berg.(5856)/Tree	Guavira	Leaves and fruits: Anti-inflammatory, antidiarrheal, urinary infection, anti-inflammatory, antidepressant, antihyperalgesic, antidiarrheal, rheumatism, hypocholesterolemic, treatment of cystitis and urethritis, urinary, antiseptic and stomach disorders (Lorenzi, 2000; Piva, 2002; Ramos et al., 2007; Coutinho et al., 2008; Lorenzi et al., 2008; Vieira et al., 2011; Pascoal et al., 2014; Lescano et al., 2016; Souza et al., 2017) Roots: Diabetes (Alice et al., 1995)

Myrtaceae	*Eugenia aurata* O.Berg	Murtinha, Pitangobí, Pitangobí Azul do Cerrado	Are not reports
	Eugenia dysenterica (Mart.) DC.(6425)/Tree	Cagaita, cagaiteira (Fidelis-de-Oliveira et al., 2020)	Leaves: Diarrhoea, diabetes, jaundice, kidney, bladder infections, laxative and cardiovascular diseases (Almeida et al., 1998; Martinotto et al., 2008; Silva et al., 2010; Lima et al., 2010)
	Eugenia pitanga (O. Berg) Kiaersk. (6111)/	Are not reports	Are not reports
	Eugenia punicifolia (Kunth) DC.(5925)/Bush	Pitanga do campo, murta vermelha; pedra-ume caá (Indigenous term applied to plants indicated for diabetes, pitanga do cerrado, muta	Leaves and fruits: Antidiabetic, cough, diarrhea, stomach disorders, pain, inflammation, fever, influenza, sores and infections (Brunetti et al., 2006; Leite et al., 2010; Rocha et al., 2011; Pascu'al et al., 2012; Sales et al., 2014; Basting et al., 2014; Costa et al., 2016; Costa et al., 2016)
	Myrcia bella Cambess./Bush	Pedra-ume caá, mercurinho	Leaves: Astringent, against diabetes, diarrhea, diuretic, to stop bleeding, against hypertension and ulcers (Saldanha et al., 2013; Vareda et al., 2014; Serpeloni et al., 2015)
	Myrcia guianensis (Aubl.) DC.	Pitanga-miúda, pedra-ume-caá	Are not reports
Ochnaceae	*Ouratea spectabilis* (Mart.) Engl.	Folha de serra	Gastric and rheumatic disorders (Paulo et al., 1986)
Primulaceae	*Myrsine umbellata* Mart./Tree	Capororoca, Pororoca	Snake bites, tumors and wounds (Rodrigues and Carvalho, 2001)
Proteaceae Juss.	*Roupala montana* Aubl.(6049)/Tree	Carvalho brasileiro, carne de vaca, congonha, caxuá ou farinha-seca	Leaves: Pain in the kidneys, legs and spine, malaise, soothing, pain (Souza et al., 2014) Barks: Fever and pain in the stomach (Júnior and Júnior, 2009)

	Alibertia edulis (Rich.) A.Rich.	Marmelada-bola, marmelo-do-cerrado	Hypertension (de Santana Aquino et al., 2017)
	Cordiera sessilis (Vell.) Kuntze(6145)/Bush	Marmelinho, marmelada-de-cachorro	Leaves: Skin diseases (Rodrigues and Carvalho, 2001; Flora do Brasil, 2018)
	Guettarda viburnoides Cham. & Schltdl. (6416)/Bush, tree	Veludo branco	Stalk: Anti-inflammatory, diarrhea, respiratory diseases, rheumatism, fever, diabetes and hepatitis (Capasso, et al., 1998; Coelho-Ferreira, 2009; Magalhães et al., 2019)
	Palicourea coriacea (Cham.) K.Schum.(5928)/Bush	Douradinha do campo, congonha do campo, douradinha	Roots and leaves: Liver diseases, diuretic, renal calculi, kidney and bladder infection and pain (Laureano 2001; Nunes et al., 2003; Freitas et al., 2011)
Rubiaceae Juss.	*Psychotria poeppigiana* Müll. Arg.(5292)/Bush	Arbusto da boca dolorida, lábios de fogo, beijo, beijo de negra, chapéu do diabo	Leaves: Gastrointestinal disorders, pain, stomach pain, dyspnoea, anti-inflammatory in bites and stings (snakes, insects and scorpions), fever, infection, diabetes, abortifacient orally, wounds and rashes, cuts and bleeding (Coe and Anderson, 1996; Taylor et al., 2006; Pino-Benítez, 2006; Guerrero et al., 2010)
	Tocoyena brasiliensis Mart.(6174)/Tree	Jenipapinho	Burn and rheumatism (Souza et al., 2013)
	Tocoyena formosa (Cham. & Schltdl.) K.Schum.(6202)/Tree	Jenipapo do bravo	Coughs, torsions, cystitis, rheumatism, renal and cardiac problems (de Albuquerque et al., 2007)
Salicaceae	*Casearia sylvestris* Sw.(6411)/Tree	Guaçatonga, guafatonga, erva-de-lagarto, lingua-de-tiu, cafezinho-do-mato, corta-lengua, bugre herb e café selvagem	Leaves: Diarrhea, fever, depurative, rheumatism, skin conditions and snake bites (Ferreira et al., 2011) Stem bark: Inflammation (Ferreira et al., 2016)

Sapindaceae	*Allophylus edulis* (A.St.-Hil. et al.) Hieron.(3508)/Tree	Chal-chal, vacum, fruto-de-pombo, vacunzeiro, murta vermelha, pau-de-pedreira, baga-de-morcego	Leaves: Diabetes, throat inflammation, intestinal and digestive problems, high blood pressure, washing wounds, liver and digestive troubles, cholecystitis and jaundice (Arisawa et al., 1989; Körbes, 1995; Franco and Fontana, 2001; Díaz et al., 2008)
Sapotaceae	*Pouteria torta* (Mart.) Radlk. (6414)/Tree	Guapeva, curiola, acá ferro, abiu do cerrado e grão de galo	Bark: Dysentery (Costa et al., 2014)
Solanaceae A.Juss.	*Solanum lycocarpum* A.St.-Hil.(5955)/Tree	Fruta do lobo, lobeira, jurubebão, beringela-do-cerrado	Roots and green fruits: Sedative, anti epilepsy, spasms, abdominal and renal pains, hemorrhoids, influenza, hepatitis, diabetes, obesity, snakebite, tissue atrophy (Munari et al., 2019) Fruits: Hypoglycemic and cholesterol lowering (Schwarz et al., 2013) Leaves: Cough and malaria (Ribeiro et al., 2017)
Vochysiaceae A.St.-Hil.	*Qualea grandiflora* Mart.(6171)/Tree	Cinzeiro, boizinho, pau-terrinha	Leaves and bark: Diarrhea with blood, intestinal colic, amoebiasis, skin diseases, inflammation, ulcers and gastritis (de Mesquita et al., 2015)
	Qualea multiflora Mart.(6178)/Tree	Cinzeiro, pau-tucano, uva-puva-do-campo, pau-terra-do-campo, pau-terra-liso	Bark: Antidiarrheal, ulcers, gastric diseases and inflammation (Santos et al., 2011)
	Qualea parviflora Mart.(6026)/Tree	Pau-terra, pau-ferro, pau-de-tucano	Leaves and bark: Diarrhea with blood, intestinal colic, amebiasis, skin diseases, ulcers and gastritis (de Mesquita et al., 2015)
	Vochysia tucanorum Mart./Tree	Pau-de-tucano, tucaneiro, vinheiro.	Are not reports

Due to the widespread use of the terms transcribed in the review, the species were grouped in **Fig. 2,** into categories according to traditional use, with reference to the ICD-11 shown in **Table 1**. It was found that most species are indicated for the treatment of diseases of the digestive system (15%), endocrine, nutritional and metabolic disorders (12%), infectious and parasitic diseases (10%), followed by skin, musculoskeletal diseases, clinical signs and symptoms, diseases of the respiratory system, and diseases of the genitourinary system, ranging from 9 to 5% (**Fig. 2**). The other indications represented <5% each (**Fig. 2**).

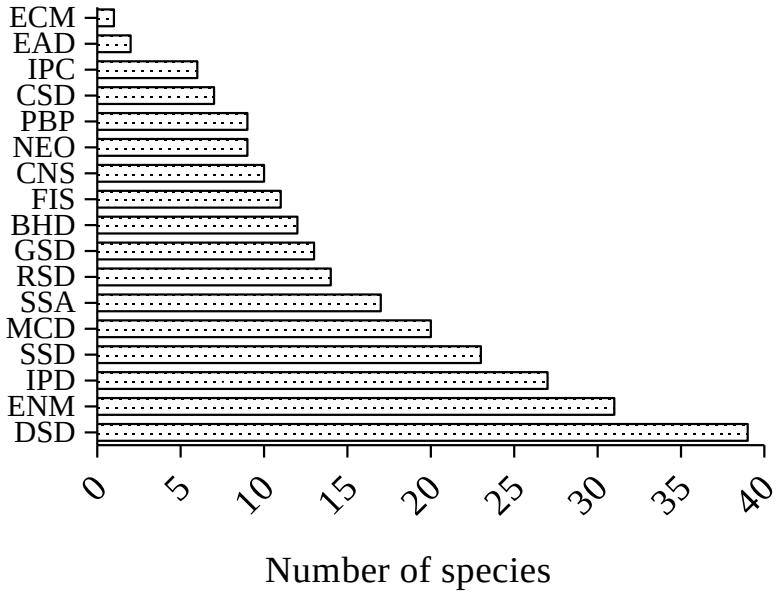


Fig. 2. Popular indications of plants found in the study areas, according to International Classification of Diseases and Related Health Problems (ICD-11) (WHO, 2019).

3.3 Pharmacological and phytochemistry studies

Many of the species listed in the study area have already been chemically and biologically evaluated, possibly in an attempt to prove the popular indication. **Table 3** is a scientific survey reporting the chemical and pharmacological studies already done with the species in question. Regarding pharmacological studies, only *Gomphrena officinalis,*

Schefflera macrocarpa, *Allagoptera campestris*, *Syagrus flexuosa*, *Cayaponia espelina*, *Sapium obovatum*, *Diptychandra aurantiaca*, *Diplopterys pubipetala*, *Eugenia pitanga*, *Myrsine umbellate*, *Anadenanthera peregrina*, *Andira humilis*, *Dalbergia miscolobium*, *Eriotheca gracilipes* and *Tocoyena brasiliensis* have not been studied (**Table 3**).

Scientific evidence has shown that most studies are related to the main popular uses, highlighting *Anacardium humile*, *Astronium fraxinifolium*, *Cochlospermum regium*, *Protium heptaphyllum*, *Curatella americana*, *Davilla elliptica*, *Lafoensia pacari*, *Byrsonima basiloba*, *Byrsonima intermedia*, *Eugenia dysenterica*, *E. punicifolia*, *Qualea grandiflora* and *Q. parviflora* grouped into the DSD category that have scientific studies that validate the effect on some classes of intestinal disorders, mainly diarrhea and gastroprotective effect (**Table 2, 3**).

Another prominent category is IPD, in which some species presented have popular indication and studies that prove the effect, such as *Tapirira guianensis*, *Annona coriacea*, *A. crassiflora*, *Xylopia aromatica*, *Himatanthus obovatus*, *Jacaranda decurrens*, *Cochlospermum regium*, *Kielmeyera coriacea*, *Diospyros hispida*, *Erythroxylum suberosum*, *Stryphnodendron adstringens*, *Ocotea minarum*, *Strychnos pseudoquina*, *Byrsonima intermedia*, *Brosimum gaudichaudii*, *Campomanesia adamantium* and *Eugenia dysenterica* (**Table 2, 3**). These data show high herbal diversity of medicinal plants in reserve area of the settlement “April 17”, located in Casa Verde district, Nova Andradina city, MS, Brazil, as well as great potential for further more studies on the therapeutic activities. Another factor is the conservation of biodiversity ensures the sustainability of natural resources and allows the maintenance of various services essential to human well-being.

In the review only twelve species were not studied chemically, and fourteen do not report pharmacological studies. For the studied species the predominant class of

substances was terpenes, followed by phenolic compounds and alkaloids related to isolation or contents (**Table 3**).

Table 3. Pharmacological and chemical studies of the species found in the reserve area of the settlement "April 17", located in Casa Verde district, Nova Andradina city, MS, Brazil.

Species	Pharmacological studies	Chemical studies
Gomphrena officinalis Mart.	Are not reports	Are not reports
Anacardium humile A. St. Hil.	Larvicidal (Porto et al., 2008), gastric lesion reducer (Luiz-Ferreira et al., 2008; Luiz-Ferreira et al., 2010), anthelmintic (Nery et al., 2010), antimicrobial (Pereira et al., 2010; Perim et al., 2018) and hypoglycemic (Urzêda et al., 2013)	Tannins, flavonoids, terpenes, coumarins, saponins (Agra et al., 2007), tannins, flavonoids, and alkaloids (Nery et al., 2010), flavonoids (Luiz-Ferreira et al., 2010), phenolic compounds, catechins and terpenes (Cecílio et al., 2012)
Astronium fraxinifolium Schott.	Antiviral (Cecílio et al., 2012), antibacterial (Montanari et al., 2012), gastroprotective and antioxidant (Martins et al., 2018)	Terpenes (Montanari et al., 2012)
Tapirira guianensis Aubl.	Cytotoxic (David, 1998; Taylor et al., 2013), anti-protozoal, anti-bacterial and anti-fungical (Roumy et al., 2009), antiproliferative (Silva-Oliveira et al., 2016), vasodilatory and antioxidant (Rodrigues et al., 2017)	Terpenoids (Correia et al., 2003, 2008; Zoghbi et al., 2014; Silva-Oliveira et al., 2016), flavonoids (Silva-Oliveira et al., 2016; Rodrigues et al., 2017), norisoprenoids (Silva-Oliveira et al., 2016), tannins (Rodrigues et al., 2017), flavonoids and phenolic acids (Martins et al., 2018)

Annona coriacea Mart.	Insecticide (Coelho et al., 2007; Costa et al., 2012; Freitas et al., 2014), phytotoxic (Formagio et al., 2010; Novaes et al., 2016), cytotoxic (Brandão et al., 2011), antiprotozoal (De Toledo et al., 2011; Siqueira et al., 2011), antioxidant (Benites et al. 2015; Novaes et al., 2019), antiproliferative and enzymatic inhibitor effect (Formagio et al., 2015), cytoprotector (Júnior et al., 2016), potential antitumor agents (Tundis et al., 2017; Gomes et al., 2019), antifungal (Almeida-Apolonio et al., 2019), anxiolytic and antidepressant (Monteiro et al., 2020)	Terpenes (Mussini et al., 1973; Siqueira et al., 2011), acetogenins (Yu et al., 1994; Silva et al, 1996; Silva et al., 1997; Silva et al., 1998), alkaloids (Machado et al., 2013), phenolic compounds (Freitas et al., 2014; Júnior et al., 2016; Novaes et al., 2018; Novaes et al., 2019; Monteiro et al., 2020) and tannins (Benites et al. 2015)
Annona crassiflora Mart.	Antioxidant (Santos et al., 1996; Roesler et al., 2006, 2011; de Souza et al., 2012; Justino et al., 2016), cytotoxic (Santos et al., 1996), larvicidal (Santos et al., 2003), antifungal, antiparasitic, anti-inflammatory, antinociceptive and anti-arthritic (Santos et al., 2003), antiplasmodic (de Mesquita et al., 2007), antibacterial (Silva et al., 2014), antiglycant (Justino et al., 2016) and pancreatic lipase inhibitory activity (Pereira et al., 2017)	Phytosterols, tocopherols and unsaturated fatty acids (de Mesquita et al., 2007), flavonoids, isoflavones and carotenoids (Justino et al., 2016) and alkaloids (Pereira et al., 2017)
Annona dioica A.St.-Hil.	Anti-inflammatory, hypoglycemic, antiproliferative and antioxidant (Formagio et al., 2013)	Flavonoids (De Souza et al., 2012; Formagio et al., 2013) and alkaloids (Justino et al., 2016)
Xylopia aromatica (Lam.) Mart.	Antimalarial (Garavito et al., 2006), larvicidal (Rodrigues et al., 2006), antiplasmodic (de Mesquita et al., 2007), cytotoxic (Suffredini et al., 2007; Taylor et al., 2014), antitumor and antiprotease (Peter et al., 2008) cytostatic (Taylor et al., 2014), and anti- inflammatory (Oliveira et al., 2017)	Terpenes (Martins et al., 1998), phenolic acids (de Souza et al., 2012) and flavonoids (Oliveira et al., 2017; Oliveira et al., 2018)
Aspidosperma macrocarpa Mart.	Antioxidant (Silva et al., 2009)	Indole alkaloid (Bolzani et al., 1987)

Aspidosperma tomentosum Mart.	Antinociceptive and anti-inflammatory (de Aquino et al., 2013)	Indole alkaloids (Pereira et al., 2007; Dolabela et al., 2012)
Hancornia speciosa Gomes	Antihypertensive (Ferreira et al., 2007a; Ferreira et al., 2007b), chemopreventive (Endringer et al., 2009b), antioxidant and anti-inflammatory (Endringer et al., 2009a; Silva et al., 2011)	Terpenoids, steroids and tannins (Honda et al., 1990; Brandão et al., 2010)
Himatanthus obovatus (Müll. Arg.) Woodson	Activity in cancer cell lines and antimicrobial (Mesquita et al., 2009; De Toledo et al., 2011)	Iridoides (Lima, 2005)
Schefflera macrocarpa (Cham. & Schltdl.) Frodin	Are not reports	Are not reports
Allagoptera campestris (Mart.) Kuntze	Are not reports	Are not reports
Syagrus flexuosa (Mart.) Becc.	Are not reports	Are not reports
Anemopaegma arvense (Vell.) Stellfeld & J.F. Souza	Antioxidant (Tabanca et al., 2007), antiplasmodial (De Mesquita et al., 2007) and antifungal (Costanzo et al., 2013)	Flavanolignans (Tabanca et al., 2007) and flavonoids (Costanzo et al., 2013)
Cybistax antisyphilitica. (Mart.) Mart.	Activity against *A. aegypti* larvae (Rodrigues et al., 2005)	Iridoids (Felicio et al., 1994), quinones (Rodrigues et al., 2005)
Handroanthus ochraceus (Cham.) Mattos	Citotoxic (Correia et al., 2016)	Glycerides, carboxylic acids, phytosteroid and terpenoids (Salatino et al., 2020)
Jacaranda decurrens Cham.	Cytotoxic (Subbaramaiah et al., 2000; Casagrande et al., 2014), antioxidant (Carvalho et al., 2009), antimicrobials and chemopreventive properties (Zatta et al., 2009), effects on development of the reproductive system in male rats (Arena et al., 2011), anti-inflammatory (Santos et al., 2012a) and antiobesity effects (Antunes et al., 2016)	Triterpenes (Varanda et al., 1992; Subbaramaiah et al., 2000; Carvalho et al., 2009) and flavonoids (Blatt et al., 1998; Antunes et al., 2016)
Tabebuia aurea (Silva Manso) Benth. & Hook.f. ex S. Moore	Antimicrobial (Barbosa et al., 2004; Santos et al., 2015), anti-inflammatory, myotoxic and anti-hemorrhagic (Reis et al., 2014), and antidematogenic (Santos et al., 2015)	Phenolic acids and terpenes (Barbosa et al., 2004)

Cochlospermum regium (Mart. ex Schrank) Pilg.	Cytotoxic activity (Ceschini and Campos, 2006; Taylor et al., 2013), antioxidant, antidiabetic, antiglycation and anticholinesterase (Agra et al., 2007), gastroprotective (Hajdu and Hohmann, 2012), antibacterial and antifungical (Carvalho et al., 2018)	Phenolic acids, flavonoids and condensed tanins (Miranda Pedroso et al., 2019)
Protium heptaphyllum (Aubl.) Marchand	Cercaricidal activity (Frischkorn et al., 1978), non-opioid analgesia (Susunaga, 1996), anti-inflammatory-related activity (Siani et al., 1999), gastroprotective (Oliveira et al., 2004a; Araujo et al., 2011), possible antipruritic effect (Oliveira et al., 2004b), hepatoprotective (Oliveira et al., 2005), antinociceptive (Lima-Júnior et al., 2006), antimicrobial and antioxidant (Bandeira et al., 2006; Violante et al., 2012), anti-inflammatory (Holanda Pinto et al., 2008; Melo et al., 2011), antihyperglycemic and hypolipidemic (Santos et al., 2012b), antimutagenic (de Lima et al., 2016), fat reducer (Carvalho et al., 2017; de Melo et al., 2019) and vasorelaxant (Mobin et al., 2017)	Terpenes (Zoghbi et al., 1995; Susunaga, 1996; Maia et al., 2000; Susunaga et al., 2001; Oliveira et al., 2004a; Oliveira et al., 2005; Vieira Júnior et al., 2005; Bandeira et al., 2006; Marques et al., 2010; Santos et al., 2012; de Lima et al., 2016; Mobin et al., 2017)
Kielmeyera coriacea Mart. & Zucc.	Anti-ulcerogenic and antiprotozoal (Garcia Cortez et al., 1998), antifungical (Garcia Cortez et al., 1998), antibacterial (Cortez et al., 2002), anxiolytic (Martins et al., 2004; Biesdorf, et al., 2012), stimulation of oxygen consumption, inhibition of gluconeogenesis and stimulation of glycogenolysis and glycolysis (Zagoto et al., 2006), schistosomicide (Zagoto et al., 2006), antidepressant (Sela et al., 2010; de Mesquita et al., 2011), cytotoxicity (de Mesquita et al., 2011), and panicolytic effects (Biesdorf, et al., 2012)	Xanthones (Mesquita et al.,1987; Garcia Cortez et al., 1998; Cortez et al., 2002; Zagoto et al., 2006; Martins et al., 2006) and triterpenes (Biesdorf, et al., 2012)
Caryocar brasiliense Cambess.	Antifungical (Passos et al., 2002), antioxidant (Roesler et al., 2008; Rocha et al., 2015; Torres et al., 2018), reduction of exercise-induced inflammatory markers and blood pressure (Miranda Vilela et al., 2009), cytotoxic (Braga et al., 2017), peritoneal toxicity in mice (Fonseca et al., 2018), vasorelaxation endothelial (Oliveira et al., 2018), and antimicrobial activity (Moreira et al., 2019)	Phenolic acids (Miranda Vilela et al., 2009; Rocha et al., 2015), fatty acids, and carotenoids (Moreira et al., 2019)
Plenckia populnea Reissek	Antimicrobial (Gonçalves de Lima et al., 1972)	Triterpenes (De Souza et al., 1990; Espindola et al., 2018)

Terminalia argentea Mart.	Non-cytotoxic and antigenotoxic (Beserra et al., 2018)	Triterpenoids, lignan and flavonoids (Garcez et al., 2003), flavonoids, saponins, and phytosterols (Beserra et al., 2018)
Connarus suberosus Planch.	Leishmanicide and antifungal (da Costa et al., 2014) and antiprotozoal (Charneau et al., 2016)	Benzoquinones (da Costa et al., 2014)
Rourea induta Planch.	Hemolytical (Kalegari et al., 2011), antibacterial, antioxidant and allelopathic (Kalegari et al., 2012), antioxidant and hepatoprotective potential (Kalegari et al., 2014a) and antinociceptive (Kalegari et al., 2014b)	Flavonoids (Kalegari et al., 2011; Kalegari et al., 2014)
Cayaponia espelina (Silva Manso) Cogn.	Are not reports	Are not reports
Curatella americana L.	Anti-inflammatory and peripheral analgesic (Alexandre-Moreira et al., 1999; Guevara et al., 2011), gastroprotective effect and healing action (Hiruma-Lima et al., 2009), genotoxic potential (Vilar et al., 2009), synergistic antifungal activity (Toledo et al., 2015), antioxidant and hypolipidemic (Lopes et al., 2016) and antioxidant (Fujishima et al., 2018; Nunes et al., 2018)	Phenolic compounds (El-Azizi et al., 1980; Lopes et al., 2016), flavonoids, saponins, terpenes and tannins (Costa et al., 2008) and proanthocyanidins (Hiruma-Lima et al., 2009)

Davilla elliptica A.St.-Hil.	Modulatory (Carlos et al., 2005), antimicrobial (Michelin et al., 2005), antimycobacterial (Lopes et al., 2007), antinociceptive (Azevedo et al., 2007; Campos et al., 2013), antidematogenic (Azevedo et al., 2007), gastroprotective and anti-inflammatory (Azevedo et al., 2007; Kushima et al., 2009), immunomodulatory and anti-*Helicobacter pylori* action (Kushima et al., 2009), antitumor (Carli et al., 2009) and mutagenic potential (Biso et al., 2010)	Flavonic and saponin heteroside compounds, steroids, coumarins (Soares et al., 2005), tannins (Soares et al., 2005; Biso et al., 2010), flavonoids (Carlos et al., 2005; Michelin et al., 2005; Biso et al., 2010), steroids and triterpenes (Soares et al., 2005; Soares et al., 2005; Michelin et al., 2005) and derivatives of phenolic acids (Biso et al., 2010)
Diospyros hispida Warm.	Antimicrobial and antifungal (Gu et al., 2004; Albernaz et al., 2010)	Terpenes (Ganapaty et al., 2005) and alkaloids (Aynilian et al., 1974; Pereira et al., 2015)
Erythroxylum campestre A.St.-Hil.	Antitumor (Pereira et al., 2015)	Flavonoids (Bohm et al., 1988)
Erythroxylum suberosum A.St.-Hil.	Lethality against *Artemia salina* (do Nascimento et al., 2012), antimicrobial, antioxidants and cytotoxic (Violante et al., 2012), antirheumatic and anti-inflammatory (Fuzer Grae et al., 2015)	Phenolic compounds and alkaloids (Bohm et al., 1988), diterpenes and flavonoids (Rodrigues et al., 2015), flavonoids, tannins, coumarins, saponins and resins (Rodrigues et al., 2015), triterpenes, alkaloids, anthocyanins, coumarins, flavonoids and condensed tannins (Fuzer Grae et al., 2015)
Erythroxylum tortuosum Mart.	Anti-inflammatory, bronchitis and asthma (Cano and Volpato, 2004; Gonzales-Guevara et al., 2006)	Tannin (Ishino et al., 2012)

Mabea fistulifera Mart.	Antioxidant and anti-inflammatory (Coqueiro, 2006)	Flavonoids (Kinghorn, 2001) and flavanone glycosides (Coqueiro et al., 2007)
Sapium obovatum Klotzsch ex Müll.Arg.	Are not reports	Are not reports
Acosmium subelegans (Mohlenbr.) Yakovlev	Anticonvulsant (Vieira et al., 2002)	Alkaloids (Oliveira et al., 1994)
Anadenanthera peregrina (L.) Speg.	Are not reports	Tanins (Carneiro et al., 2012; Sartori et al., 2014) and fenolic compounds (Mota et al., 2017)
Andira humilis Mart. ex Benth.	Are not reports	Phenolic compounds (Garcez et al., 2010)
Bauhinia rufa (Bong.) Steud.	Proteinase inhibitor (Nakahata et al., 2006; Ferreira et al., 2013), antifungal (Duarte-Almeida et al., 2004; Correia et al., 2016), and thrombolytic (Silveira et al., 2006)	Terpenes (Duarte-Almeida et al., 2004)
Bowdichia virgilioides Kunth	Cytotoxic activity (Torrenegra et al., 1989), antimalarial (Deharo et al., 2001), antimicrobial (Almeida et al., 2006; Agra et al., 2013), antinociceptive e anti-inflammatory (Barros et al., 2010; Thomazzi et al., 2010; Silva et al., 2010), antibacterial activity (Leite et al., 2014), protective effect on muscular damage and oxidative stress (Dos Santos et al., 2014), larvicidal (Bezerra-Silva et al., 2015) and antihyperglycemic effect (Silva et al., 2015)	Terpenes (Arriaga et al., 1996; Cordero et al., 2004), tannins and flavonoids (Arriaga et al., 2000; Leite et al., 2014) and alkaloids (Torrenegra et al., 1989; Barbosa-Filho et al., 2004)

Copaifera langsdorffii Desf.	Gastroprotective (Paiva et al., 2004, Motta et al., 2018), protective effect for ischemia / reperfusion of intestinal tissue (Paiva et al., 2004), antifungal (Amorim et al., 2004; Zimmermam-Franco et al., 2013), larvicidal (Mendonça et al., 2005), immunomodulatory (Rosario et al., 2008), antibacterial (Souza et al., 2011), anti-inflammatory (Gelmini et al., 2013), chemopreventive effect (Senedese et al., 2013), potential antipsychotic effect (Gelmini et al., 2013), antioxidant (Gelmini et al., 2013; Batista et al., 2016), antibacterial activity (Bonan et al., 2015), apoptotic (Cardoso et al., 2017), and protective effect against carcinogenesis of the colon (Cardoso et al., 2017; Tobouti et al., 2017)	Terpenes, xyloglucans and phenolic compounds (Rosario et al., 2008; Do Nascimento et al., 2012; Gelmini et al., 2013; Senedese et al., 2013; Baldissera et al., 2014; Nogueira et al., 2015)
Dalbergia miscolobium Benth.	Are not report	Phenolic compounds (Gregson et al., 1978; Vasudeva et al., 2009; Kite et al., 2010) and triterpenoids (Salatino et al., 2020)
Dimorphandra mollis Benth.	Oedematogenic (Mello et al., 2006), non-toxic (Feres et al., 2006), antioxidant (Petacci et al., 2010) and anti-triptic (Mendes et al., 2013)	Flavonoids (Feres et al., 2006) and tanins (Mendes et al., 2013)
Dipteryx alata Vogel	Antifungal (Nazato et al., 2010; Puebla et al., 2010; Ferraz et al., 2012; Yoshida et al., 2015), non-mutagenic (Esteves-Pedro et al., 2012; Yoshida et al., 2015), antioxidant and hypolipidemic (Bento et al., 2014; Fernandes et al., 2015), leshmanicidal (Ribeiro et al., 2014), and reduction of abdominal adiposity and increase of HDL (de Souza et al., 2018)	Phenolic compounds and terpenoids (Puebla et al., 2010; Marques et al., 2015)
Diptychandra aurantiaca Tul.	Are not report	Are not report
Pterodon pubescens (Benth.)	Did not induce any toxicity in mice (Pinto Coelho et al., 2001), non-cytotoxic, non-toxic, non-mutagenic and antiproliferative (Vieira et al., 2008),	Terpenes (Hoscheid et al., 2012; Nucci-Martins et al., 2015)

	antinociceptive (Nucci et al., 2012; Nucci-Martins et al., 2015), and potential anti-inflammatory (da Silva Santos et al., 2016; Hoscheid et al., 2017)	
Stryphnodendron adstringens (Mart.) Coville	Anti-inflammatory (Lima et al., 1998), antioxidant (Lima et al., 1998; Souza-Moreira et al., 2006; Santos Filho et al., 2011), antibacterial (Lima et al., 1998; Souza-Moreira et al., 2006; Hasenack et al., 2008; Soares et al., 2008), antiulcerogenic (Audi et al., 1999), trypanocidal (Herzog-Soares et al., 2002, 2006), antimutagenic (Costa et al., 2010), antigenic (Santos Filho et al., 2011) and antifungal (Freitas et al., 2018),	Proanthocyanidins (Palazzo de Mello et al., 1999; de Mello et al., 1996; Costa et al., 2010), flavan-3-oys (de Mello et al., 1996), prorobinetinidines (Palazzo de Mello et al., 1996) and tannins (Santos et al., 2002)
Vatairea macrocarpa (Benth.) Ducke	Edematogenic (Alencar et al., 2003) and antihyperglycemic (Oliveira et al., 2008)	Are not reports
Aiouea trinervis Meisn.	Antiproliferative (Garcez et al., 2005) and trypanocidal activity (Maier, 2016)	Lignin (De Carvalho et al., 1986), lignans (Garcez et al., 2005) and butanolide (Tsai et al., 2002)
Ocotea minarum (Nees & Mart.) Mez	Antioxidant and antimicrobial (Rodrigues et al., 2019) and antifungal (Rodrigues et al., 2014)	Indole alkaloids (Vecchietti et al., 1979), phenolic compound and terpenes (Garcez et al., 2005)
Strychnos pseudoquina A.St.-Hil.	Antiulcer (Silva et al., 2005), mutagenicity (Santos et al., 2006), hypoglycemic and cicatrization (Honório-França et al., 2008), antibacterial (Bonamin et al., 2011), antileishmanial (Lage et al., 2013), anti-HSV and anti-inflammatory (Boff et al., 2016), healing (Sarandy et al., 2018), antihyperglicemic and antihyperlipidemic (Cosenza et al., 2019),	Alkaloid (Monache et al., 1969; Andrade-Neto et al., 2003; Silva et al., 2005; Bonamin et al., 2011), flavonoids (Lage et al., 2013), alkaloids, flavonoids, polyphenols and tannins (Cosenza et al., 2019)

Lycopodium clavatum L.	Inhibition of acetylcholinesterase (Orhan et al., 2003; Rollinger et al., 2005), anti-inflammatory (Orhan et al., 2007), antibacterial and antifungal (Orhan et al., 2007), hepatoprotective (Pathak et al., 2009), inhibition of growth of HeLa cells (Mandal et al., 2010), protective effect in human keratinocytes and skin tissues (Das et al., 2013), and reduction of the pathogenic progression of Chagas disease (Brustolin Aleixo et al., 2017)	Alkaloids (Orhan et al., 2003, 2007), terpenoids (Rollinger et al., 2005) and flavonoids (Das et al., 2013)
Lafoensia pacari A.St.-Hil.	Cytotoxic and apoptogenic (da Silva Marcondes et al., 2014), anti-inflammatory, anti-allergic, analgesic, antidepressant, microbicide, antiviral, antioxidant, sedative and antidepressant-like effects, chemopreventive, angiogenic and antidiabetic (Carneiro et al., 2016), antibacterial, antiviral, anti-inflammatory, analgesic, antiulcerogenic and antidepressive (Pereira et al., 2018)	Polyphenols (Pereira et al., 2018)
Magnolia ovata (A.St.-Hil.) Spreng.	Antipyretic (Kassuya et al., 2009), anti-inflammatory (Kassuya et al., 2009; Mori et al., 2011) and analgesic (Mori et al., (2011)	Neolignans, terpenes, alkaloids, steroids, tannins and saponins (Kassuya et al., 2009)
Byrsonima basiloba A. Juss.	Antidiarrheal (Figueiredo et al., 2005), antimutagenic (Lira et al., 2008), antibacterial and antifungal (Michelin et al., 2008) and antioxidant activity (Bonacorsi et al., 2013)	Flavonoids (Figueiredo et al., 2005; Lira et al., 2008;)
Byrsonima coccolobifolia Kunth	Mutagenic activity (Espanha et al., 2014), leishmanicidal (Souza et al., 2014) and antioxidant (Pereira et al., 2015)	Flavonoids (Pereira et al., 2015)
Byrsonima intermedia A. Juss.	Antimicrobial, anti-hemorrhagic, anti-diarrheal and anti-inflammatory (Corrêa, 1984, Pinto and Bertolucci, 2002), antimicrobial (Michelin et al., 2008), anti-inflammatory and antinociceptive (Orlandi et al., 2011), anti-inflammatory (Moreira et al., 2011), mutagenic (Sannomiya et al., 2014), anti-ulcer, antimicrobial and antidiarrheal (Santos et al., 2012), antioxidant and anti-inflammatory and against peptic ulcers (de Cássia dos Santos et al., 2019)	Phenolic compounds (Santos et al., 2012; Sannomiya et al., 2014), tannins (Orlandi et al., 2011)

Diplopterys pubipetala (A.Juss.) W.R.Anderson & C.C.Davis	Are not reports	Are not reports
Eriotheca gracilipes (K.Schum.) A.Robyns	Are not reports	Fatty acids (Mayworm and Salatino, 1996)
Luehea divaricata Mart. & Zucc.	Diuretic, hypotensive, antifungal, antioxidant, neuroprotective, anti-inflammatory, analgesic, immunostimulatory and anti-cholinesterase (Tirloni et al., 2018)	Phenolic compounds, triterpenoids and phytosterols (Tirloni et al., 2018)
Miconia albicans (Sw.) Triana	Antimicrobial (Alves et al., 2000), analgesic (Vasconcelos et al., 2003), anti-inflamatory, (Vasconcelos et al., 2006), DNA protective effect (Serpeloni et al., 2010), antioxidant (Pieroni et al., 2011), antidiabetic (Ortiz et al., 2016; Lima et al., 2018), antimicrobial (Tomé et al., 2019) and antioxidant (Pasta et al., 2019)	Terpenes (Macari et al., 1990; Crevelin et al., 2006), Phenolic compounds (Pieroni et al., 2011; Lima et al., 2018; Pasta et al., 2019), coumarins, triterpenes, tannins, flavonoids and saponins (Tomé et al., 2019)
Brosimum gaudichaudii Trécul	Potential mutagenic effect (Varanda et al., 2002; Thiago et al., 2015), antimicrobial activity (Borges et al., 2017), stimulation of migration and pigmentation of melanocytes (Quintão et al., 2019) and antioxidant activity (Ferreira et al., 2019)	Coumarins (Gottlieb et al., 1972; Morais et al., 2018; Quintão et al., 2019), condensed tannins (Monteiro et al., 2014), flavonoids (Thiago et al., 2015)
Campomanesia adamantium (Cambess.) O. Berg	Antioxidant and antihyperlipidemic (Ramos et al., 2007; Espindola et al., 2016), antioxidant (Vallilo et al, 2006; Coutinho et al., 2009; Coutinho et al., 2010; Pascoal et al., 2011), antimicrobial (Coutinho et al., 2009; Pavan et al., 2009; Cardoso et al., 2010; Moura-Costa et al., 2012, Breda et al., 2016), antinociceptive (Ferreira et al., 2013) , antiproliferative (Pascoal et al., 2014; Campos et al., 2017; Ferreira et al., 2013; Fernandes et al., 2014; Lima e	Phenolic compounds (Pavan et al., 2009; Coutinho et al., 2010; Pascoal et al., 2011, 2014; Espindola et al., 2016)

	Silva et al., 2018), anti-inflammatory (Viscardi et al., 2017), antidepressant (Souza et al., 2014)	
Eugenia aurata O. Berg	Anti-inflammatory (Costa et al., 2016)	Are not reports
Eugenia dysenterica (Mart.) DC.	Antifungal (Costa et al., 2000), molluscicidal activity (Bezerra et al., 2002), laxative potential (Lima et al., 2010), diarrhoea inhibition (Lima et al., 2011; Galheigo et al., 2016), antiviral (Cecílio et al., 2012), tyrosinase inhibitory activity (Souza et al., 2012), gastroprotective (Prado et al., 2014), prevention of obesity (Donado-Pestana, 2015), antiproliferative and moderate acetylcholinesterase inhibitory activity (Gasca et al., 2017), antioxidante (Daniel Daza et al., 2017; Ferreira-Nunes et al., 2018), neuroprotective (Thomaz et al., 2018), wound healing (Silva et al., 2018), hypotensive (Fidelis-de-Oliveira et al., 2020), angiogenic and antibacterial (Silva et al., 2020)	Terpenes (Costa et al., 2000; Duarte et al., 2009; Galheigo et al., 2016; Silva et al., 2018), saponins (Cecílio et al., 2012), tannins (Prado et al., 2014) and flavonoids (Donado-Pestana, 2015; Silva et al., 2020)
Eugenia pitanga (O. Berg) Kiaersk.	Are not reports	Are not reports

Eugenia punicifolia (Kunth) DC.	Antidiabetic (Brunetti et al., 2006; Sales et al., 2014), positive effect in oral glucose tolerance test in mice (Brunetti et al., 2006), recovery of the action of competitive nicotinic antagonists at the neuromuscular junction of the diaphragm of rats (Grangeiro et al., 2006), anti-inflammatory (Leite et al., 2010; Basting et al., 2014; Leite et al., 2014; Costa et al., 2016), antinociceptive and gastroprotective (Basting et al., 2014), increases the exocytotic release of catecholamines from bovine adrenal chromaffin cells stimulated with ACh or K + (Pascual et al., 2012), cytostatic effect and activation of skeletal muscle remodeling (Leite et al., 2014), antioxidant and inhibition of enzymes related to the metabolic syndrome (Lopes et al., 2014)	Flavonoids (Basting et al., 2014; Sales et al., 2014), phenolic compounds and tannins (Brunetti et al., 2006; Costa et al., 2016)
Myrcia bella Cambess.	Antimutagenic, antioxidant and hypoglycemic (Saldanha et al., 2013; Vareda et al., 2014)	Phenolic compounds (Saldanha et al., 2013; Santos et al., 2018)
Myrcia guianensis (Aubl.) DC.	Antiproliferative, moderate antimicrobial and antioxidant (dos Santos et al., 2018)	Polyphenolic compounds (dos Santos et al., 2018)

Ouratea spectabilis (Mart.) Engl.	Antioxidant (Felício et al., 1995; Patel et al., 2012)	Phenolic compounds (Felício et al., 1995; Patel et al., 2012; Mecina et al., 2014)
Myrsine umbellata Mart.	Are not reports	Are not reports
Roupala montana Aubl.	Schistosomicidal (Cunha et al., 2012) and antigenotoxic (Cunha et al., 2012)	Terpenes (Cunha et al., 2012), flavonoids, carotenoids and saponins (Francielli et al., 2014; Kuster and Vale, 2016)
Alibertia edulis (Rich.) A.Rich.	Antimicrobial (Da Silva et al., 2008), diuretic, hypotensive and antihypertensive (De Santana Aquino et al., 2017)	Flavonoids, terpenoids and saponin (Brochini et al., 1994), tannins, alkaloids and carotenoids (Soto-Sobenis et al., 2001; Cândida da Silva et al., 2008; Menegati et al., 2016)
Cordiera sessilis (Vell.) Kuntze	Antioxidant and antimicrobial (Aquino et al., 2013)	Terpenes, phenolic compounds and saponins (Aquino et al., 2013)
Guettarda viburnoides Cham. & Schltdl.	Anti-inflammatory and antioxidant (Naressi, et al. 2015)	Iridoids (Naressi, et al. 2015)
Palicourea coriacea (Cham.) K.Schum.	Anti-genotoxic (Nunes et al., 2003) and diuretic (Freitas et al., 2011)	Triterpenes (Somova et al., 2003), alkaloids (do Nascimento et al., 2007; do Nascimento et al., 2008), saponins, tannins and cumarins (Silva et al., 2008)

Psychotria poeppigiana Müll. Arg.	Vasoactive (Coe and Anderson, 1996)	Flavonoids, alkaloids, steroids, triterpenes and coumarins (Pino-Benítez, 2006; Villasmil et al., 2006; Silva et al., 2013)
Tocoyena brasiliensis Mart.	Are not reports	Terpenoids, saponins and flavonoids (Hamerski et al., 2005)
Tocoyena formosa (Cham. & Schltdl.) K.Schum.	Antifungal (Bolzani et al., 1996), antioxidant (David et al., 2007), anti-nociceptive (Cesário et al., 2018), anti-inflammatory (Cesário et al., 2019)	Iridoids, ethyl esters (Bolzani et al., 1996; Bolzani et al., 1997, Hamerski et al., 2005), polyphenolic flavonoids (Cesário et al., 2018); phenolic compounds, terpenoids and saponins (Cesário et al., 2019)

Casearia sylvestris Sw.	Antiulcerogenic (Basile et al., 1990; Sertié et al., 2000; de Mattos et al., 2007; Ferreira et al., 2011), antitumor (Itokawa et al., 1990; Silva et al., 2008; dos Santos et al., 2010; Felipe et al., 2014; Ferreira et al., 2016), antihemorrhagic and anticoagulant (Borges et al., 2001), antiparasitic (Oberlies et al., 2002; Espindola et al., 2004; Antinarelli et al., 2015), genotoxic (Maistro et al., 2004), anti-inflammatory (Esteves et al., 2005; Ferreira et al., 2016; Pierre et al., 2017), antimicrobial (Schneider and Fernandes, 2006), antinociceptive (de Mattos et al., 2007), cytotoxic and antihyperlipidemic (Schoenfelder et al., 2008), allelopathic (Capobiango et al., 2009), inhibitory activity of phospholipase A2 (Ferreira et al., 2011), antioxidant (Albano et al., 2013), antinociceptive and lipid-lowering (Frediani et al., 2014)	Flavonoids (Bueno et al., 2016; Vieira Júnior et al., 2017) and terpenes (Basile et al., 1990; Oberlies et al., 2002; Espindola et al., 2004; Santos et al., 2007)

Allophylus edulis (A.St.-Hil. et al.) Hieron.	Inhibition of angiotensin converting enzyme (ACE), β-glucuronidase and cytotoxicity to KB cells (Arisawa et al., 1989), antihepatotoxic (Hoffmann-Bohm et al., 1992), negative ionotropic effects (Matsunaga et al., 1997), antioxidante, antimicrobial and low toxicity (Tirloni et al., 2015), antioxidant, antimicrobial and anti-inflammatory (Trevizan et al., 2016)	Triterpenoids, alkaloids and anthocyanidins (Bandoni et al., 1972), Cyanolipid and triacylglycerol (Aichholz et al, 1997), phenolic compounds (Arisawa et al., 1989; Hoffmann-Bohm et al., 1992), L-quebrachitol (Díaz et al., 2008) and terpenes (Trevizan et al., 2016)

Pouteria torta (Mart.) Radlk.	Antimutagenic (Costa et al., 2014)	Flavonoids (Costa et al., 2014)
Solanum lycocarpum A.St.-Hil.	Anti-inflammatory (Vieira et al., 2003), antidiabetogenic (Yoshikawa et al., 2007), antihelminthic (Costa et al., 2008), cytotoxic, genotoxic and antigenotoxic (Munari et al., 2012), antioxidante (Schwarz et al., 2013) and immunomodulating effect (Miranda et al., 2013)	Phenols, tannins, flavonoids, steroids, terpenes, saponins and alkaloids (Araújo et al., 2003), alkaloids (Munari et al., 2012; Torralbo et al., 2012;) and pectin (Torralbo et al., 2012)
Qualea grandiflora Mart.	Anti-inflammatory, antiulcerogenic, gastric mucosal protection, analgesic, anticonvulsant, antiseptic and antibacterial, CNS depressant (Gaspi et al., 2006), mutagenic (Santos et al., 2011), antioxidant (Bonacorsi et al., 2013) and antimicrobial (Pires et al., 2018)	Are not reports
Qualea multiflora Mart.	Molluscicidal (de Souza et al., 1984), cytotoxic (Nasser et al., 2008), mutagenic (Santos et al., 2011)	Terpenes and steroids (Santos et al., 2011) and ellagic acid derivatives (Nasser et al., 2008; Carnevale Neto et al., 2011)

Qualea parviflora Mart.	Antioxidant (Bonacorsi et al., 2013), *in vitro* mutagen (Santos et al., 2011), gastroprotective, antidiarrheal, antihemorrhagic and mutagenic (Mazzolin et al., 2010)	Are not reports
Vochysia tucanorum Mart.	Gastroprotective (Gomes et al., 2009)	Polyphenols, flavonoids and condensed tannins (Franco et al., 2019)

3.2 Brazilian Government – Public Access to Herbal Medicines

In Brazil, the Unified Health System (SUS) is in place, which consists of a public health system that covers everything from primary care to organ transplantation, guaranteeing full, universal and free access to all the country's population (Bevilacqua et al., 2013). Among the existing projects in the SUS, there is the RENISUS (National List of Medicinal Plants of Interest to the SUS), which contains medicinal plants that have the potential to generate products of interest to the SUS. Among the listed species are 71 plants used by popular wisdom and scientifically confirmed. The purpose of the list is to guide studies and research that can support the elaboration of the list of herbal medicines available for use by the population, safely and effectively to treat a certain disease (Ferreira et al., 2019).

Considering the relevance of the plant species found in the RENISUS list, we researched which ones are present in the studied area (Settlement 17 de Abril) and related to their popular uses and scientific studies. Of the 89 species found in April 17, only three are listed in the RENISUS: *Casearia sylvestris*, *Copaifera* spp * (*Copaifera langsdorffii*) and *Stryphnodendron adstringens*.

Casearia sylvestris popularly known as guaçatonga is used in folk medicine, to treat diarrhea, fever, purification, rheumatism, skin disorders and snake bites (Ferreira et al., 2011). Scientific studies report of antiulcerogenic, anti-inflammatory, antitumor, antihyperlipidemic, anticoagulant, trypanocidal, leshmanicidal, antimicrobial, genotoxic, allelopathic, antihyperalgesic, antioxidant, phospholipase A2 inhibitory and antiparasitic activity (Ferreira et al., 2011; Basile et al., 1990; Esteves et al., 2005; Sertié et al., 2000; Ferreira et al., 2016; Pierri et al., 2017; dos Santos et al., 2010; Silva et al., 2008; Felipe et al., 2014; Schoenfelder et al., 2008; de Mattos et al., 2007; Borges et al., 2001; Espindola et al., 2004; Antinarelli et al., 2015; Schneider and Fernandes 2006; Maistro et

al., 2004; Capobiango et al., 2009; Frediani et al., 2014; Albano et al., 2013; Bou et al., 2014) by leaves. Already the barks demonstrated antitumor activity (Itokawa et al., 1990). Phytochemical studies report the presence of flavonoids in leaves and aerial parts and terpenes in leaves of this species (Basile et al., 1990; Espindola et al., 2004; Oberlies et al., 2002; Santos et al., 2007; Bueno et al., 2016; Vieira Júnior et al., 2017) (**Table 3**).

Copaifera langsdorffii is popularly known as Copaíba, Resin-extracted oil from its trunk is used by the population to treat inflammation, sore throat, urinary and pulmonary infections, and accelerate wound and ulcer healing (Cardoso et al., 2017; Rodrigues and Carvalho 2001). Studies conducted with the leaves of this species report gastroprotective potential, anti-inflammatory, antifungal activity and significant genotoxicity (Amorim et al., 2004; do Nascimento et al., 2012; Motta et al., 2018; Senedese et al., 2013). Still on the leaves, phytochemical studies reported the presence of galloquinquinic acids. Oil extracted from the trunk, popularly used in folk medicine, in biological studies has been shown to induce cell cycle arrest and apoptosis, a protective effect against colon carcinogenesis, cytotoxic, embryotoxic and antibacterial activity (Baldissera et al., 2014; Cardoso et al., 2017). Already the seeds present immunomodulatory activity, presence of xyloglucans and galloquinquinic acids (do Nascimento et al., 2012; Rosario et al., 2008). Another part also studied of this species were the fruits, which presented antioxidant activity (Batista et al., 2016) (**Table 3**).

The barbed bark from *Stryphnodendron adstringen*s (barbatimão) is widely used in two different ways. External use: treatment of uterine conditions, vaginal conditions, urinary tract infections, skin lesions, ulcers, inflammation, infections and skin infections, internal use: diarrhea, throat inflammation, bleeding, scurvy, pulmonary complications, and respiratory infections. And also for internal use to treat diarrhea, sore throat, bleeding, scurvy, pulmonary complications, and respiratory infections (Brasil, 2014; Herzog-

Soares et al., 2002). Scientific studies validate the popular indications, highlighting some biological activities in the stem barks of this species. Studies report trypanocidal, antifungal, antibacterial, antioxidant, antiulcerogenic, antigenic, anti-inflammatory and antimutagenic activity, as well as the presence of proanthocyanidins, flavonoids, prorobinetinidines and tannins (Costa et al., 2010; de Mello et al., 1996; de Freitas et al., 2018; Herzog-Soares et al., 2002; Herzog-Soares et al., 2006; Lima et al., 1998; Palazzo de Mello et al., 1999; Santos et al., 2002) (**Table 3**).

The presence of these species demonstrates the importance of further scientific studies to prove their ethnopharmacological action against diseases, as well as ensuring secure access and rational use of medicinal and herbal medicines, the development of technologies and innovations, as well as the strengthening of chains and productive arrangements, the sustainable use of Brazilian biodiversity and the development of the Health Productive Complex (Brasil, 2006).

4. CONCLUSION

This study provides by first time 89 medicinal plants belonging to 39 families documented from the study area. Most species have popular use, with evidenced pharmacological and chemical studies, which justifies the conservation of biodiversity. Also noting that three species are listed in the National Program for Medicinal and Phytotherapeutic Plants.

ACKNOWLEDGEMENTS

The authors are grateful to FUNDECT (Fundação de Apoio ao Desenvolvimento do Ensino, Ciência e Tecnologia do Estado de Mato Grosso do Sul, Brazil), CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, Brazil, 2764/2011),

CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico, Brazil), and UFGD (Universidade Federal da Grande Dourados, Brazil) for financial support and fellowships.

Conflicts of interest

No competing financial interests exist.

REFERENCES

Albano, M.N., da Silveira, M.R., Danielski, L.G., Florentino, D., Petronilho, F., Piovezan, A.P., 2013. Anti-inflammatory and antioxidant properties of hydroalcoholic crude extract from Casearia sylvestris Sw. (Salicaceae). J. Ethnopharmacol. 147, 612-617. https://doi.org/10.1016/j.jep.2013.03.049.

Amaral, A., Munhoz, C., Walter, B., Aguirre-Gutiérrez, J. and Raes, N., 2017. Richness pattern and phytogeography of the Cerrado herb-shrub flora and implications for conservation. J. Veg. Sci., 28, 848-858. https://doi.org/10.1111/jvs.12541.

Amorim, A., Cardoso, M., Pinto, J.E., Souza, P., Delú, N., 2004. Fungitoxic activity avaliation of the hexane and methanol extracts of copaiba plant leaves Copaifera langsdorffi Desfon. Ciênc. Agrotec. 28, 314-322. http://dx.doi.org/10.1590/S1413-70542004000200010.

Antinarelli, L.M., Pinto, N.C., Scio, E., Coimbra, E.S., 2015. Antileishmanial activity of some Brazilian plants, with particular reference to Casearia sylvestris. Anais da An. Acad. Bras. Ciênc. 87, 733-742. http://dx.doi.org/10.1590/0001-3765201520140288.

Basile, A.C., Sertié, J.A.A., Panizza, S., Oshiro, T.T., Azzolini, C.A., 1990. Pharmacological assay of Casearia sylvestris. I: Preventive anti-ulcer activity and toxicity of the leaf crude extract. J. Ethnopharmacol. 30, 185-197. https://doi.org/10.1016/0378-8741(90)90007-G.

Batista, A.G., Ferrari, A.S., da Cunha, D.C., da Silva, J.K., Cazarin, C.B., Correa, L.C., Prado, M.A., Carvalho-Silva, L.B., Esteves, E.A., Marostica Junior, M.R., 2016. Polyphenols, antioxidants, and antimutagenic effects of Copaifera langsdorffii fruit. Food Chem. 197, 1153-1159. https://doi.org/10.1016/j.foodchem.2015.11.093.

Bevilacqua, M., Filho, O., Castiquini, E., de Freitas Zambonatto, T., Morettin, M., Moret, A. and Amantini, R. 2013. Hearing aid fitting at SUS (Brazilian Public Health Care System) compared with a compact fitting model. Braz. J. Otorhinolaryngol., 79, 276-284. https://doi.org/10.5935/1808-8694.20130051.

Borges, M.H., Soares, A.M., Rodrigues, V.M., Oliveira, F., Fransheschi, A.M., Rucavado, A., Giglio, J.R., Homsi-Brandeburgo, M.I., 2001. Neutralization of proteases from Bothrops snake venoms by the aqueous extract from Casearia sylvestris (Flacourtiaceae). Toxicon. 39, 1863-1869. https://doi.org/10.1016/S0041-0101(01)00169-6.

Bou, D.D., Tempone, A.G., Pinto, E.G., Lago, J.H., Sartorelli, P., 2014. Antiparasitic activity and effect of casearins isolated from Casearia sylvestris on Leishmania and Trypanosoma cruzi plasma membrane. Phytomedicine. 21, 676-681. https://doi.org/10.1016/j.phymed.2014.01.004.

Brasil, Ministério da Saúde. Secretaria de Ciência, Tecnologia e Insumos Estratégicos, Departamento de Assistência Farmacêutica. Política Nacional de Plantas Medicinais e Fitoterápicos. Brasília: Ministério da Saúde, 2006. (accessed in 11 December 2019). https://doi.org/10.1590/S0103-73312014000200004.

Brasil. Política Nacional de Plantas Medicinais e Fitoterápicos, 2006. http://portalsaude.saude.gov.br (accessed 18 December 2019).

Brasil, Monografia da espécie Stryphnodendron adstringens (MART.) Coville (barbatimão). Ministério da Saúde. Brasília, Distrito Federal, Brasil, 2014. (acessed in 08/08/2019).

Bueno, P., Passareli, F., Anhesine, N., Torres, R., Cavalheiro, A., 2016. Flavonoids from Casearia sylvestris Swartz variety lingua (Salicaceae). Biochem. System. Ecol. 68, 23-26. https://doi.org/10.1016/j.bse.2016.06.002.

Capobiango, R., Vestena, S., Bittencourt, A., 2009. Alelopatia de Joanesia princeps Vell. e Casearia sylvestris Sw. sobre espécies cultivadas. Rev. Bras. Farmacogn. 19. http://dx.doi.org/10.1590/S0102-695X2009000600023.

Cardoso Junior, I. M. 2017. Cayaponia silva manso (cucurbitaceae juss.), no estado de goiás: uma abordagem morfológica e anatômica. 145 f. Dissertação (Mestrado em Biodiversidade Vegetal). Universidade Federal de Goiás.

Cardoso, P., Rocha, C., Leal, M.F., Bahia, M.O., Alcantara, D., Santos, R.A.D., Goncalves, N.D.S., Ambrosio, S.R., Cavalcanti, B.C., Moreira-Nunes, C.A., Pessoa, C.D.O., Burbano, R.M.R., 2017. Effect of diterpenoid kaurenoic acid on genotoxicity and cell cycle progression in gastric cancer cell lines. Biomed. Pharmacother. 89, 772-780. https://doi.org/10.1016/j.biopha.2017.02.085.

Costa, M.A., Ishida, K., Kaplum, V., Koslyk, E.D., de Mello, J.C., Ueda-Nakamura, T., Dias Filho, B.P., Nakamura, C.V., 2010. Safety evaluation of proanthocyanidin polymer-rich fraction obtained from stem bark of Stryphnodendron adstringens (BARBATIMAO) for use as a pharmacological agent. Regul. Toxicol. Pharmacol. 58, 330-335. https://doi.org/10.1016/j.yrtph.2010.07.006Get.

de Freitas, A.L.D., Kaplum, V., Rossi, D.C.P., da Silva, L.B.R., Melhem, M.S.C., Taborda, C.P., de Mello, J.C.P., Nakamura, C.V., Ishida, K., 2018. Proanthocyanidin polymeric tannins from Stryphnodendron adstringens are effective against Candida spp. isolates and for vaginal candidiasis treatment. J. Ethnopharmacol. 216, 184-190. https://doi.org/10.1016/j.jep.2018.01.008.

de Mattos, E.S., Frederico, M.J., Colle, T.D., de Pieri, D.V., Peters, R.R., Piovezan, A.P., 2007. Evaluation of antinociceptive activity of Casearia sylvestris and possible

mechanism of action. J. Ethnopharmacol. 112, 1-6. https://doi.org/10.1016/j.jep.2007.01.034.

de Mello, J.P., Petereit, F., Nahrstedt, A., 1996. Flavan-3-ols and prodelphinidins from Stryphnodendron adstringens. Phytochemistry. 41, 807-813. https://doi.org/10.1016/0031-9422(95)00686-9.

Di Stasi, L.C., Oliveira, G.P., Carvalhaes, M.A., Queiroz, M., Jr., Tien, O.S., Kakinami, S.H., Reis, M.S., 2002. Medicinal plants popularly used in the Brazilian Tropical Atlantic Forest. Fitoterapia 73, 69-91. https://doi.org/10.1016/S0367-326X(01)00362-8.

Durigan, G., Ratter, J., 2015. The need for a consistent fire policy for Cerrado conservation. J. Appl. Ecol. 53, 11-15. https://doi.org/10.1111/1365-2664.12559.

dos Santos, A.G., Ferreira, P.M., Vieira Junior, G.M., Perez, C.C., Gomes Tininis, A., Silva, G.H., Bolzani V., S., Costa-Lotufo, L.V., Pessoa C., O., Cavalheiro, A.J., 2010. Casearin X, its degradation product and other clerodane diterpenes from leaves of Casearia sylvestris: evaluation of cytotoxicity against normal and tumor human cells. Chem. Biodivers. 7, 205-215. https://doi.org/10.1002/cbdv.200800342.

Espindola, L.S., Vasconcelos Junior, J.R., de Mesquita, M.L., Marquie, P., de Paula, J.E., Mambu, L., Santana, J.M., 2004. Trypanocidal activity of a new diterpene from Casearia sylvestris var. lingua. Planta Med. 70, 1093-1095. https://doi.org/10.1055/s-2004-832655.

Esteves, I., Souza, I.R., Rodrigues, M., Cardoso, L.G., Santos, L.S., Sertie, J.A., Perazzo, F.F., Lima, L.M., Schneedorf, J.M., Bastos, J.K., Carvalho, J.C., 2005. Gastric antiulcer and anti-inflammatory activities of the essential oil from Casearia sylvestris Sw. J. Ethnopharmacol. 101, 191-196. https://doi.org/10.1016/j.jep.2005.04.020.

Felipe, K.B., Kviecinski, M.R., Silva, F.O., Bucker, N.F., Farias, M.S., Castro, L.S., de Souza Grinevicius, V.M., Motta, N.S., Correia, J.F., Rossi, M.H., Pedrosa, R.C., 2014. Inhibition of tumor proliferation associated with cell cycle arrest caused by extract and

fraction from Casearia sylvestris (Salicaceae). J. Ethnopharmacol. 155, 1492-1499. https://doi.org/10.1016/j.jep.2014.07.040.

Ferreira, P., Santos, D., Silva, J., Goudinho, A., Ramos, C., Souza, P., Almeida, R., Moura, D., Oliveira, R., Grisolia, C., Cavalheiro, A., Carvalho Melo-Cavalcante, A., Ferreira, J., Moraes Filho, M. and Pessoa, C. 2019. Toxicological findings about an anticancer fraction with casearins described by traditional and alternative techniques as support to the Brazilian Unified Health System (SUS). J. Ethnopharmacol., 241, 112004. https://doi.org/doi:10.1016/j.jep.2019.112004.

Ferreira, P.M., Costa-Lotufo, L.V., Moraes, M.O., Barros, F.W., Martins, A.M., Cavalheiro, A.J., Bolzani, V.S., Santos, A.G., Pessoa, C., 2011. Folk uses and pharmacological properties of Casearia sylvestris: a medicinal review. An. Acad. Bras. Cienc. 83, 1373-1384. http://dx.doi.org/10.1590/S0001-37652011005000040.

Ferreira, P.M.P., Bezerra, D.P., Silva, J.d.N., Costa, M.P., Ferreira, J.R.O., Alencar, N.M.N., Figueiredo, I.S.T., Cavalheiro, A.J., Machado, C.M.L., Chammas, R., Alves, A.P.N.N., Moraes, M.O., Pessoa, C., 2016. Preclinical anticancer effectiveness of a fraction from Casearia sylvestris and its component Casearin X: in vivo and ex vivo methods and microscopy examinations. J. Ethnopharmacol. 186, 270-279. https://doi.org/10.1016/j.jep.2016.04.011.

Frediani Brant, N.M., Mourão Gasparotto, F., Oliveira Araújo, V., Christian Maraschin, J., Lima Ribeiro, R.C., Botelho Lourenço, E.L., Cardozo Junior, E.L., Gasparotto Junior, A., 2014. Cardiovascular protective effects of Casearia sylvestris Swartz in Swiss and C57BL/6 LDLr-null mice undergoing high fat diet. J. Ethnopharmacol. 154, 419-427. https://doi.org/10.1016/j.jep.2014.04.019.

Guerra, A., Reis, L., Borges, F., Ojeda, P., Pineda, D., Miranda, C., Maidana, D., Santos, T., Shibuya, P., Marques, M., Laurance, S., Garcia, L., 2020. Ecological restoration in Brazilian biomes: Identifying advances and gaps. Forest. Ecol. Manag. 458, 117802. https://doi.org/10.1016/j.foreco.2019.117802.

Herzog-Soares, J.D.A., Alves, R.K., Isac, E., Bezerra, J.C.B., Gomes, M.H., Santos, S.C., Ferri, P.H., 2002. Atividade tripanocida in vivo de Stryphnodendron adstringens (barbatimão verdadeiro) e Caryocar brasiliensis (pequi). Revista Brasileira de Farmacognosia 12, 1-2. http://dx.doi.org/10.1590/S0102-695X2002000300001.

Herzog-Soares, J.D.A., Alves, R.K., Isac, E., Castro, A.M. Bezerra, J.C.B., 2006. Bioactivity of Stryphnodendron adstringens, S. Polyphyllum, Caryocar brasiliense, plants from brazilian's savannah on the Trypanosoma cruzi in vivo. Biosci. J. 22, 113-118.

Lima, J., Martins, D., Jr, P., 1998. Experimental evaluation of stem bark of Stryphnodendron adstringens (Mart.) Coville for antiinflammatory activity. Phytother. Res. 12, 218-220. https://doi.org/10.1002/(SICI)1099-1573(199805)12:3<218::AID-PTR220>3.0.CO;2-4.

Maistro, E.L., Carvalho, J.C.T., Mantovani, M.S., 2004. Evaluation of the genotoxic potential of the Casearia sylvestris extract on HTC and V79 cells by the comet assay. Toxicol. In Vitro. 18, 337-342. https://doi.org/10.1016/j.tiv.2003.10.002.

Motta, E.V., Lemos, M., Costa, J.C., Bandero-Filho, V.C., Sasse, A., Sheridan, H., Bastos, J.K., 2018. Galloylquinic acid derivatives from Copaifera langsdorffii leaves display gastroprotective activity. Chem. Biol. Interact. 261, 145-155. https://doi.org/10.1016/j.cbi.2016.11.028.

Mukherjee, P. 2019. Ethnopharmacology and Ethnomedicine-Inspired Drug Development. Quality Control and Evaluation of Herbal Drugs, 29-51. https://doi.org/10.1016/B978-0-12-813374-3.00002-8.

Nascimento, M.E., Zoghbi, M.G.B., Brasil Pereira Pinto, J.E., Vilela Bertolucci, S.K., 2012. Chemical variability of the volatiles of Copaifera langsdorffii growing wild in the Southeastern part of Brazil. Biochem. Syst. Ecol. 43, 1-6 https://doi.org/10.1016/j.bse.2012.02.003.

Oberlies, N.H., Burgess, J.P., Navarro, H.A., Pinos, R.E., Fairchild, C.R., Peterson, R.W., Soejarto, D.D., Farnsworth, N.R., Kinghorn, A.D., Wani, M.C., Wall, M.E., 2002. Novel bioactive clerodane diterpenoids from the leaves and twigs of Casearia sylvestris. J. Nat. Prod. 65, 95-99. https://doi.org/10.1021/np010459m.

Palazzo de Mello, J.C., Petereit, F., Nahrstedt, A., 1999. A dimeric proanthocyanidin from Stryphnodendron adstringens. Phytochemistry. 51, 1105-1107 https://doi.org/10.1016/S0031-9422(98)00715-8.

Pierri, E.G., Castro, R.C., Vizioli, E.O., Ferreira, C.M.R., Cavalheiro, A.J., Tininis, A.G., Chin, C.M., Santos, A.G., 2017. Anti-inflammatory action of ethanolic extract and clerodane diterpenes from Casearia sylvestris. Rev. Bras. Farmacog. 27, 495-501. http://dx.doi.org/10.1016/j.bjp.2016.12.008.

Rodrigues, V.E.G., Carvalho, D.A., 2001. Levantamento etnobotânico de plantas medicinais no domínio do cerrado na região do Alto Rio Grande - Minas Gerais. Ciênc. Agrotec. 25, 102-123.

Rosario, M.M., Noleto, G.R., Bento, J.F., Reicher, F., Oliveira, M.B., Petkowicz, C.L., 2008. Effect of storage xyloglucans on peritoneal macrophages. Phytochemistry. 69, 464-472. https://doi.org/10.1016/j.phytochem.2007.08.011.

Sano, E.E., Rosa, R., Brito, J.L., Ferreira, L.G., 2010. Land cover mapping of the tropical savanna region in Brazil. Environ. Monit. Assess. 166, 113-124. https://doi 10.1007/s10661-009-0988-4.

Schneider, N., Fernandes de Moura, N., 2006. The volatile oil composition and antimicrobial activity of Casearia sylvestris Swart. Rev. Bras. Farm. 87, 112-114.

Schoenfelder, T., Pich, C.T., Geremias, R., Avila, S., Daminelli, E.N., Pedrosa, R.C., Bettiol, J., 2008. Antihyperlipidemic effect of Casearia sylvestris methanolic extract. Fitoterapia. 79, 465-467. https://doi.org/10.1016/j.fitote.2008.03.008.

Santos, A.G., Perez, C.C., Tininis, A.G., Bolzani, V.S., Cavalheiro, A.J., 2007. Clerodane diterpenes from leaves of Casearia sylvestris Swartz. Quim. Nova. 30, 1100-1103. http://dx.doi.org/10.1590/S0100-40422007000500009.

Santos, S.C., Costa, W.F., Ribeiro, J.P., Guimaraes, D.O., Ferri, P.H., Ferreira, H.D., Seraphin, J.C., 2002. Tannin composition of barbatimao species. Fitoterapia. 73, 292-299. https://doi.org/10.1016/s0367-326x(02)00081-3.

Senedese, J., Alves, J., Lima, I., Andrade, E., Andrade, R., Bastos, J., Tavares, D., 2013. Chemopreventive effect of Copaifera langsdorffii leaves hydroalcoholic extract on 1,2-dimethylhydrazine-induced DNA damage and preneoplastic lesions in rat colon. BMC Complem. Altern. Med. 13, 3. https://doi.org/10.1186/1472-6882-13-3.

Sertié, J.A., Carvalho, J.C., Panizza, S., 2000. Antiulcer activity of the crude extract from the leaves of Sasearia sylvestris. Pharm. Biol. 38, 112-119. https://doi.org/10.1076/1388-0209(200004)3821-1FT112.

Silva, S.L.d., Chaar, J.d.S., Figueiredo, P.d.M.S., Yano, T., 2008. Cytotoxic evaluation of essential oil from Casearia sylvestris Sw on human cancer cells and erythrocytes. Acta Amaz. 38, 107-112. http://dx.doi.org/10.1590/S0044-59672008000100012.

Strassburg, B., Brooks, T., Feltran-Barbieri, R., Iribarrem, A., Crouzeilles, R., Loyola, R., Latawiec, A., Oliveira Filho, F.J., De Mattos Scaramuzza, C., Scarano, F., Filho, B., Balmford, A., 2017. Moment of truth for the Cerrado hotspot. Nat. Ecol. Evol. 1, 1-3. https://www.nature.com/articles/s41559-017-0099.

Vieira Júnior, G.M., Dutra, L.A., Torres, R.B., Boralle, N., Bolzani, V.d.S., Silva, D.H.S., Chaves, M.H., Cavalheiro, A.J., 2017. Chemical constituents from Casearia spp. (Flacourtiaceae/Salicaceae sensu lato). Rev. Bras. Farmacogn. 27, 785-787. http://dx.doi.org/10.1016/j.bjp.2017.10.003.

WHO, 2017. Diarrhoeal disease. https://www.who.int/en/news-room/fact-sheets/detail/diarrhoeal-disease. Accessed in 07 feb. 2020.

WHO, 2019. International Classification of Diseases for. Mortality and Morbidity Statistics (ICD-11). Eleventh Revision. https://icd.who.int/browse11/Help/en (accessed 18 December 2019).

ARTIGO 2

Journal of Ethnopharmacology, Fator de Impacto: 3,115,

Qualis A2

Variation in essential oil components and anti-inflammatory activity of *Allophylus edulis* leaves collected in central-western Brazil

S.M. Santos[a], P.C. Oliveira Junior[a], N. M. Balsalobre[b], C.A.L. Kassuya[b], C.A.L. Cardoso[c], Z. V. Pereira[a], A.S.N. Formagio[a,b*]

[a]*Faculty of Biological and Environmental Sciences, Federal University of Grande Dourados, Dourados, Mato Grosso do Sul, Brazil*

[b]*Faculty of Health Sciences, Federal University of Grande Dourados, Dourados, Mato Grosso do Sul, Brazil*

[c]*State University of Mato Grosso do Sul, Dourados, Mato Grosso do Sul, Brazil*

*Correspondence: Anelise Samara Nazari Formagio. Laboratório de Manejo de Plantas Medicinais. Federal University of Grande Dourados. Dourados-Itahum Highway, Zip Code: 79804-970, Dourados, Brazil. E-mail: aneliseformagio@gmail.com.br; aneliseformagio@ufgd.edu.br

E-mail address: sidneysmariano@gmail.com (S.M. Santos); pedrojuniorbiologo@gmail.com (P.C. Oliveira Junior); nataliabalsalobre@hotmail.com (N. M. Balsalobre); candida2005@gmail.com (C.A.L. Kassuya); claudia@uems.br (C.A.L. Cardoso), zefapereira@ufgd.edu.br (Z. V. Pereira), aneliseformagio@gmail.com (A.S.N. Formagio).

Abbreviations

CEUA	Committee of Ethics on the Use of Animals
CFA	Complete Freund's adjuvant
CONCEA	National Council for Control of Animal Experimentation
DEXA	Dexamethasone
EOAE	Essential oil of *Allophylus edulis*
EOAE-B	Essential oil of *Allophylus edulis* collected in Bonito city
EOAE-D	Essential oil of *Allophylus edulis* collected in Dourados city
GC/MS	Gas chromatography-mass spectrometry
MS	Mato Grosso do Sul State
UFGD	Federal University of Grande Dourados

ABSTRACT

Ethnopharmacology relevance. An infusion obtained from the leaves of "chal-chal" (*Allophylus edulis* Radlk.) is used for popular treatment of intestinal disorders and as an anti-inflammatory throat treatment. Because of the anti-inflammatory medicinal folk use, a previous work reported scientific research confirming the anti-inflammatory activity of *Allophylus edulis* essential oil collected in Dourados, MS, Brazil, in March 2015.

Aim of the study. The aim of this study was to evaluate the variation of the chemical profiles of the essential oil of *A. edulis* plants collected in Dourados (EOAE-D) and Bonito (EOAE-B), two cities from Mato Grosso do Sul State, Brazil. Additionally, to correlate environmental differences, the substances with the anti-inflammatory properties were identified in both essential oils.

Materials and methods. Leaves were collected from plants at both sites in July 2018. The composition of the essential oil was determined by GC/MS. Both samples were evaluated

for their anti-inflammatory capacities using two classical models of inflammatory models, carrageenan- and CFA-induced paw inflammation.

Results. Both EOAE-D and EOAE-B showed sesquiterpenes as a major constituent, namely, caryophyllene oxide (29.5%) and α-zingiberene (45.0%), respectively. In all tests, EOAE-induced antiedematogenic and antihyperalgesic effects were found in the different utilized models.

Conclusions. The results indicate that samples from the two cities differed in chemical composition but not in their anti-inflammatory and antihyperalgesic effects. This finding corroborates the use of *A. edulis* as a medicinal plant and indicates its potential in the therapy of inflammatory conditions.

Keywords: Sapindaceae; chal-chal; essential oil; sesquiterpenes; carrageenan; CFA.

1. INTRODUCTION

The Brazilian Cerrado (savanna-like landscape) is characterized by diversity in native plant species with an enormous number of bioactive molecules resulting from several biotic and abiotic stress factors (Sano et al., 2019; Fang et al., 2019). It is a strategic biome that enables a relationship with the Pantanal, the Amazonia and the Caatinga due to their direct link, as well as ensuring the ecological balance and biological diversity of these biomes (Silva Junior et al., 2019).

In the Brazilian Cerrado, a popularly small native tree known as “chal-chal” or “cocu”, *Allophylus edulis* (A. St.-Hil., Cambess. & A. Juss.) Radlk. (syn. *A. cambessedei* Blume and *A. edulis* var. *gracilis* Radlk.) (Sapindaceae), is used in folk medicine as an anti-inflammatory agent (Arisawa et al., 1989; Körbes, 1995).

Studies conducted by our research group showed that the essential oil obtained from *A. edulis* exhibits anti-inflammatory activity in mice models (Trevizan et al., 2016). Relevantly, bark, roots and leaves of species of the genus are used for the treatment of arthritic conditions and anti-inflammatory agents (Iwu and Anyanwu, 1982; Ferreres et al., 2018). However, there are few studies available in the literature regarding the chemical and anti-inflammatory effects of the essential oil of *A. edulis.*

An infusion obtained from the leaves of *A. edulis* is typically prepared for the treatment of intestinal disorders and as an anti-inflammatory throat treatment. Leaves and young stems of *A. edulis* are used in popular phytotherapy in Missiones Province (Argentina) in the form of infusions and concoctions, either alone or combined with *Ilex paraguariensis* St. Hil. (Yerba Mate) as refresher, digestant and in the treatment of hepatitis (Lewis and Elvin-Lewis, 2003; Chavan and Gaikwad, 2016).

Compounds found in plants could be affected by genetic and environmental conditions, such as climatic factors, phase of growth and different geographical distributions (Howard et al., 2003). These alterations in chemical composition in parts of plants could affect popular usage (Khan et al., 2019; Abd-ElGawad et al., 2019). However, there are few studies available in the literature regarding the chemical habitat variation and anti-inflammatory effects of the essential oil of *A. edulis*.

The inflammation model using carrageenan as an inflammatory agent produces an inflammatory reaction characterized by cell infiltration and production of proinflammatory mediators, such as prostaglandins, leukotrienes, cytokines, and molecules resulting from the response to oxidative stress (Morris, 2003).

In Trevizan et al. (2016), the decision to show scientific data on the anti-inflammatory activity of *A. edulis* essential oil was based on its anti-inflammatory medicinal folk use, and the material was collected in Dourados, MS, Brazil, in March

2015. The chemical analysis of the essential oil showed that the major constituent of the oil was viridiflorol (30.88%), and all tests of the anti-inflammatory activity *A. edulis* essential oil and viridiflorol were based on the yield of this compound.

The aims of the present study were (1) to determine the essential oil composition of *A. edulis* leaves collected from the cities of Dourados and Bonito, (2) to assess the anti-inflammatory activity of the essential oil according to an in vivo model and (3) to evaluate the correlation of environmental factors (soil and climatic parameters) with essential oil constituents.

2. MATERIALS AND METHODS

2.1. Ethical clearance

The protocol for animal experiments was approved by the Committee of Ethics on the Use of Animals – CEUA of the Federal University of Grande Dourados (UFGD), Brazil (Protocol No. 34/2018). International guidelines and recommendations of the National Council for the Control of Animal Experimentation - CONCEA were followed for the handling of animals. Assays were carried out at the Laboratory of the Study of Pain and Inflammation of UFGD.

2.2. Animals

Male Swiss and C57BL/6 mice (20-25 g, 8 weeks old) used in this study were housed in conventional installations in polypropylene cages under standard conditions with natural 12 h light/12 h dark cycles, and temperatures between 22 and 25 °C and were fed *ad libitum* with a pelleted commercial diet and clean fresh water. The animals were acclimatized for at least 1 week before the commencement of the experiments.

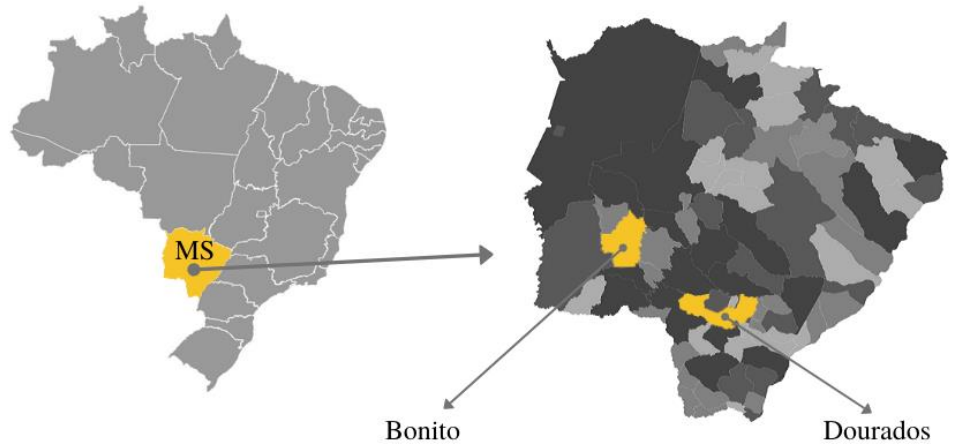
2.3. Chemicals

The chemicals used in this study were λ-carrageenan and dexamethasone (DEXA) and were purchased from Sigma-Aldrich (St. Louis, MO, USA). Additional materials used included analytical-grade acetone (Synth, Diadema, SP, Brazil) and anhydrous sodium sulfate (Dinâmica, Jaraguá do Sul, SC, Brazil).

2.4. Plant material

Allophylus edulis was collected at the flowering stage (July 2018) from two different regions, Serra da Bodoquena National Park, Bonito (MS), and Dourados (MS) (**Fig. 1**). The flowering stage of this plant is different in natural habitats and varies from July to November; however, sampling was performed from plants at similar developmental stages.

A plant from of each site was authenticated by Dr. Zefa Valdivina Pereira and deposited in the herbarium of the UFGD. Authorization for accessing and studying samples from the Brazilian genetic heritage site was obtained from the Sistema Nacional de Gestão do Patrimônio Genético e do Conhecimento Tradicional Associado (SisGen - A51F665).



Geographical coordinates	21°15'56" S and 56°42'10" W	22°08'23" S and 55°08'16" W
Accession number	DDMS 6342	DDMS 6343
Soil	Chernosol Rendzico (EMBRAPA, 1999)	Red Latosol (Amaral et al., 2000)
Temperature/ precipitation	19.86 °C/ 0.2 mm	20.19 °C/ 0.4 mm

Fig. 1. Detailed information on the *A. edulis* collection sites.

2.5. Extraction of essential oil of A. edulis

In this process, 385 g of fresh leaves of *A. edulis* was used. Hydrodistillation was carried out with a Clevenger-type apparatus for 4 h, and the essential oil was dried over anhydrous sodium sulfate, filtered, and stored at 4 °C until subsequent analyses. The yields were expressed as weight of oil/weight of plant material. The essential oil obtained from the samples from Dourados/MS was named EOAE-D, and that from Bonito/MS, EOAE-B.

2.6. Gas chromatography-mass spectrometry (GC/MS)

Analysis was performed using a gas chromatograph equipped with a mass spectrometer (GC/MS-QP2010 Ultra, Shimadzu, Kyoto, Japan). A DB-5 column (30 m length, 0.25 mm internal diameter, 0.25 μm film thickness) was used, with helium (99.999% purity) as the carrier gas at a flow rate of 1.0 $mL.min^{-1}$ and an injection volume of 1 μL (in split mode, 1:10). The initial oven temperature was 50 °C, with heating to 280 °C at 3 °C min^{-1}. The injector temperature was 220 °C, and the temperature of the transfer line and the quadrupole detector was 280 °C. The MS scan parameters included an electron impact ionization voltage at 70 V, a mass range from 50 to 600 Daltons and a scan interval of 0.3 s. The retention index was calculated using a mixture of linear alkanes (C_8-C_{40}) as an external reference. Compound identification was achieved by comparing the mass spectra of the samples with spectra available in the NIST21 and WILEY229 libraries, as well as with data reported in the literature (Adams, 2007).

2.7. Carrageenan-induced inflammatory reaction in mice

Carrageenan-induced paw inflammation was evaluated in accordance with Henriques et al., 1990. In a preventive mode of treatment, *Swiss* male mice were treated orally with EOAE-D (30, 100 and 300 mg/kg), EOAE-B (30, 100 and 300 mg/kg) (both mixed in 0.9% saline), or the vehicle (0.9% saline solution). Another group was treated with the commercial positive control dexamethasone (DEXA 0.5 mg/kg) orally. A solution of carrageenan was injected into the right paw (300 μg/paw, 50 μL of 0.9% saline solution) subcutaneously 1 h after administration of the preventive treatments, while, at the same time, the left paw received saline without carrageenan. Paw volume was measured after ½, 1, 2 and 4 h using a plethysmometer (PANLAB Harvard). Anti-inflammatory activity was expressed as the percentage of reduction in edema in treated mice compared to that in the control mice. Inhibition calculated using the following

equation: inhibition (%) = 100 (Vc-Vt)/Vc, where Vc is the mean change in paw size of the control mice and Vt is the mean change in paw size of the treated mice. The same animals were used for analysis of cold sensitivity and mechanical sensitivity, which were measured 3 and 4 h after carrageenan injection. Cold sensitivity was assessed by the acetone drop test as described by Decosterd and Woolf (2000), Möller et al. (1998) and Choi et al. (1994). S 30 µl drop of acetone was placed on the paw, and the duration (in seconds) before paw withdrawal was recorded, and minimal and maximal cutoffs were assigned at 0.5 and 20 s, respectively. Mechanical sensitivity of the hind paw was measured by determination of nociceptive thresholds (g) that were estimated using an electronic version of the von Frey test. This indicated the level of mechanical sensitivity induced by the sensitization. An analgesimeter was applied perpendicularly to the plantar surface of the paw with an upward force just sufficient to bend the apparatus. A scheme of the carrageenan experimental procedure is shown in **Fig. 2.**

2.8 CFA-induced inflammatory reaction in mice

Thirty C57BL/6 mice (male, 20 - 25 g each) were randomly distributed into groups (n=6/group): EOAE-D (30 mg/kg, p.o.), EOAE-B (30 mg/kg, p.o.), dexamethasone (DEXA, 1 mg/kg, s.c.), control and naive (saline, p.o.). The treatments were performed once every day. As described by Larson et al. (1986), at time zero, 20 µl of CFA (a suspension of killed *Mycobacterium tuberculosis* in oil) was injected into the right hind paw (intraplantar), and 20 µl of saline was injected into the left hind paw, while mice in the naive group had 20 µl of saline injected into both paws. The edema, mechanical hyperalgesia and cold allodynia were estimated at 1, 2, 4, and 8 h and 3, 6, 9, and 12 days after injection. The paw edema evaluation and cold and mechanical sensitivities were

measured according to the description in Section 2.7. A scheme of the CFA experimental procedure is shown in **Fig. 2.**

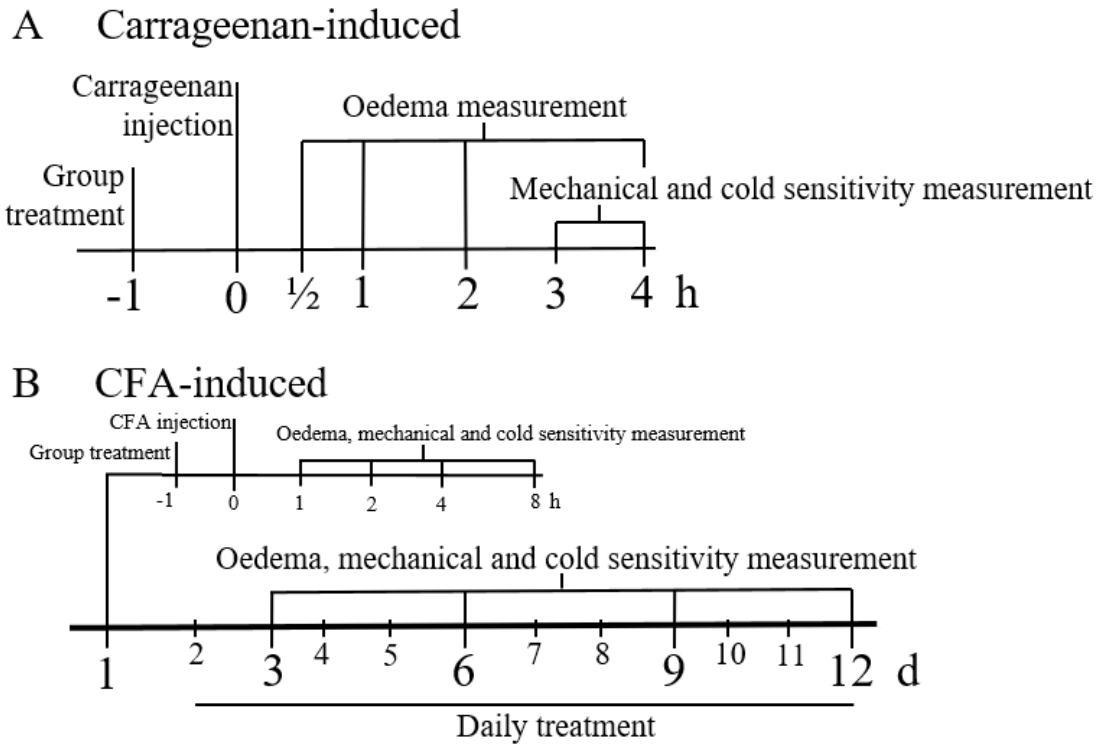


Fig. 2. Experimental procedure of the anti-inflammatory activity of an *A. edulis* leaf extract: A) carrageenan-induced and B) persistent CFA-induced paw edema in mice.

2.9. Statistical analysis

Statistical analysis of the results was performed using one-way analysis of variance (ANOVA) followed by the Student-Newman-Keuls test, and the differences were considered statistically significant when $P<0.05$ (GraphPad Software, San Diego, CA, USA). Determinations were carried out in triplicate, and the experimental results are expressed as the means ± standard deviations.

3. RESULTS AND DISCUSSION

3.1. Essential oil yield and composition

The essential oil yield of the studied populations was 0.1% for samples from both sites. Serra da Bodoquena National Park (Bonito city) was one of the collection sites, and its biome consists mainly of deciduous forest and semideciduous seasonal forest so that the territory comprises features such as the Caatinga, Cerrado, Chaco and Atlantic Forests (Cáceres et al., 2007; Uetanabaro et al., 2007). The climate in this area is characterized as Aw (tropical climate with a dry season in winter), according to the Köppen classification (Chagas et al., 2009). Because it is the season with the least amount of rainfall, only 0.2 mm of rain accumulated in July 2018, and an average temperature of 19.86 °C was recorded (CEMTEC, 2019). The soil of the park is characterized as Chernosol Rendzico (EMBRAPA, 1999). For the city of Dourados, the climate is considered a transition between tropical and subtropical, and Köppen's classification is Cwa (humid temperate climate with dry winter and hot summer) (Souza et al., 2017). In July 2018, an average of 20.19 °C and 0.4 mm of accumulated precipitation was recorded (CEMTEC, 2019). The soil at this location is classified as a Dystroferric Red Latosol, characterized by low natural fertility, acidic conditions and a clayey texture (Amaral et al., 2000; Araujo-Junior et al., 2015). These changes did not directly influence the yield of essential oil extracted from the leaves in July (flowering) of 2018.

The GC/MS chromatograms showed 70 (EOAE-D) and 37 (EOAE-B) substances present in the essential oil of leaves from *A. edulis*, which are identified in **Fig. 3** and **Table 1,** with a predominance of oxygenated sesquiterpenes (64.4%) and sesquiterpenes (78.4%), respectively, as determined in three replicates. In EOAE-D, the major compound was caryophyllene oxide, contributing to 29.5% of the total contents; other compounds, such α-pinene, trans-verbenol, (E)-caryophyllene, cis-eudesma-6,11-diene, bicyclogermacrene, α-zingiberene, cameroonan-7-α-ol, δ-cadinene, germacrene B,

viridiflorol, ledol, humulene epoxide II, caryophylla-4(12),8(13)-dien-5α-ol, agarospirol, 4-α-hydroxy-dihydro agarofuran, α-cadinol, occidenol, mustakone and acorenone, were present at relative concentrations ranging from 1.2% to 5.7% (**Table 1**). This result was different from that previously reported in our first study of *A. edulis*, which demonstrated that viridiflorol (30.8%) was a major constituent (Trevizan et al., 2016). In this reinvestigation of EOAE, viridiflorol was present at a concentration of 2.9% (**Table 1**), possibly due to the stage of development of the plant. In OEAE-B, the sesquiterpene α-zingiberene (45.0%) was the dominant constituent. Other constituents, including β-elemene, (E)-caryophyllene, α-trans-bergamotene, (E, E)-α-farnesene, β-sesquiphellandrene, α-muurolol, α-cadinol, and 11-αH-himachal-4-en-1-β-ol, were present at relative concentrations ranging from 1.9% to 12.7% (**Table 1**).

The chemical composition of both OEAE-D and OEAE-B showed similarities of 17 compounds, of which only (E)-caryophyllene (3.5-2.9%), α-zingiberene (1.8-45.0%), and α-cadinol (5.7-3.4%) were found in the samples at values greater than 1% (**Table 1**). Both Dystroferric Red Latosol (Dourados) and Chernosol Rendzico (Bonito) soils are appropriate for increasing sesquiterpene constituents of EOAE; however, they can vary significantly depending on the environmental conditions to which the plant is exposed, such as mineral and water supply and sunlight. The comparison of the chemical composition of the EOAE of different cultivation sites of MS is described herein for the first time.

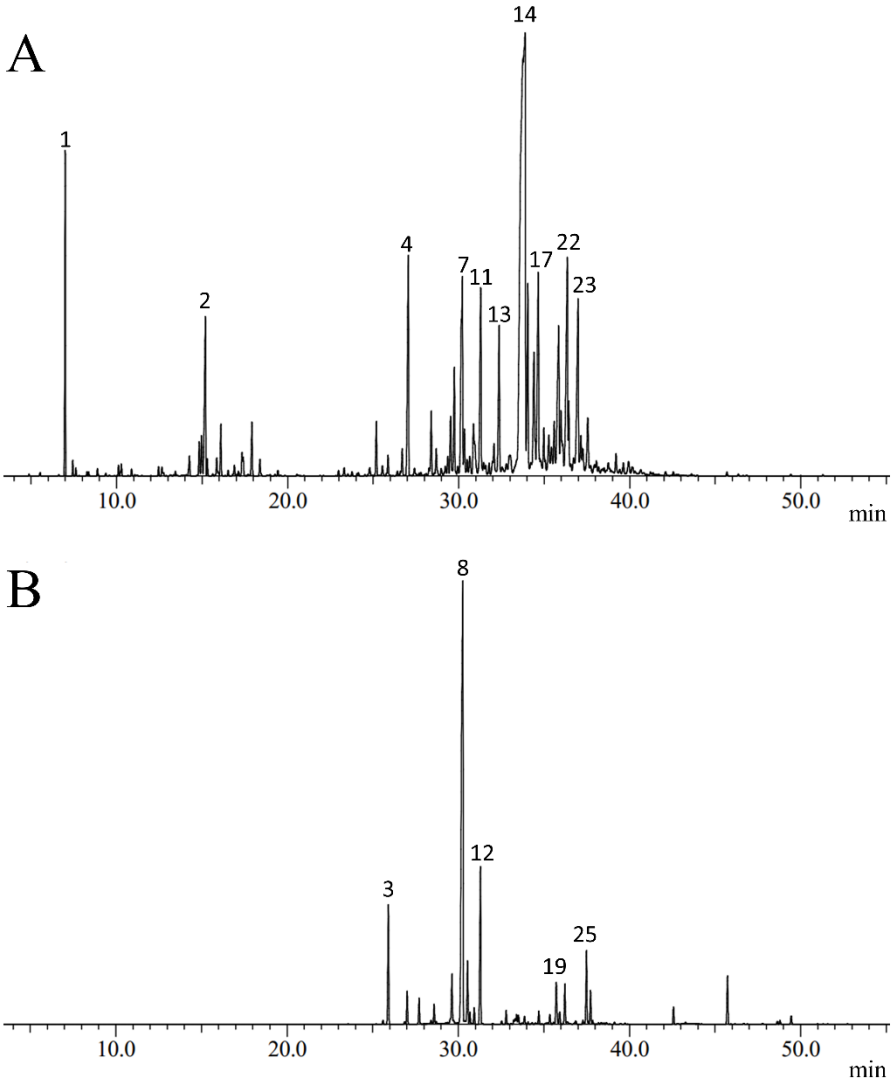


Fig. 3. GC/MS chromatogram of the essential oil of *A. edulis* collected in A) Dourados OEAE-D) and B) Bonito (OEAE-B).

Table 1. Identification of constituents of the essential oil obtained from the fresh leaves of *A. edulis* collected in the cities of Dourados (OEAE-D) and Bonito (OEAE-B).

No.	Identity	Retention indexes		Retention time	Content (%)	
		Determined	Literature		OEAE-D	OEAE-B
1	α-Pinene	938	932	7.001	3.0	0.2
2	Trans-verbenol	1143	1140	15.194	2.6	-
3	β-Elemene	1389	1389	25.571	0.2	8.2
4	(E)-Caryophyllene	1419	1417	27.056	3.5	2.9

5	α-Trans-bergamotene	1437	1432	27.713	-	1.9
6	Cis-eudesma-6,11-diene	1488	1489	29.747	1.5	0.1
7	Bicyclogermacrene	1498	1500	30.218	2.4	-
8	α-Zingiberene	1499	1493	30.267	1.8	45.0
9	(E,E)-α-Farnesene	1507	1505	30.545	-	5.9
10	Cameroonan-7-α-ol	1509	1510	30.651	1.7	-
11	δ-Cadinene	1522	1522	31.292	3.3	-
12	β-Sesquiphellandrene	1522	1521	31.296	-	12.7
13	Germacrene B	1558	1559	32.536	2.7	0.1
14	Caryophyllene oxide	1591	1582	33.882	29.5	0.5
15	Viridiflorol	1599	1592	34.047	2.9	-
16	Ledol	1607	1602	34.408	2.8	-
17	Humulene epoxide II	1613	1608	34.661	4.2	-
18	Caryophylla-4(12),8(13)-dien-5α-ol	1639	1639	35.597	1.5	0.1
19	α-Muurolol	1643	1644	35.724	-	3.9
20	Agarospirol	1646	1646	35.847	3.5	-
21	4-α-Hydroxy-dihydro agarofuran	1650	1651	35.990	1.6	-
22	α-Cadinol	1656	1652	36.356	5.7	3.4
23	Occidenol	1676	1676	36.975	4.2	-
24	Mustakone	1681	1676	37.156	1.2	-
25	11-αH-Himachal-4-en-1-β-ol	1692	1699	37.490	-	6.5
26	Acorenone	1692	1692	37.558	1.4	-
Total identified					**99.8**	**99.8**
Monoterpenes					3.8	0.3
Oxygenated monoterpenes					6.6	0.1
Sesquiterpenes					25.0	78.4
Oxygenated sesquiterpenes					64.4	21.0

(-) not determined; remaining constituents observed at concentrations of less than 1% in both samples: camphene, thuja-2,4(10)-diene, β-pinene, trans-meta-mentha-2,8-diene, σ-cymene, limonene, (E)-β-ocimene, fenchone, α-campholenal, trans-pinocarveol, cis-verbenol, p-mentha-1,5-dien-8-ol, pinocarvone, terpinen-4-ol, p-cymen-8-ol, myrtenal, myrtenol, verbenone, trans-carveol, carvone, silphiperfol-5-ene, presilphiperfol-7-ene, 7-epi-silphiperfol-5-ene, cyclosativene, β-longipinene, aromadendrene, cis-muurola-3,5-diene, α-humulene, 9-epi-(E)-caryophyllene, β-acoradiene, dauca-5,8-diene, γ-muurolene, germacrene D, trans-muurola-4(14),5-diene, α-muurolene, (Z)-γ-bisabolene, trans-cadina-1,4-diene, α-cadinene, α-agarofuran, palustrol, 10-epi-γ-eudesmol, α-acorenol, camphor, δ-elemene, α-copaene, α-gurjunene, longipinanol, spathulenol, ar-turmerol, cis-muurol-5-en-4-β-ol, helifolen-12-al A, 1,3,5 bisabolatrien-7-ol, 5-epi-7-epi-α-eudesmol, β-himachalene oxide, 1-epi-cubenol, cubenol, α-

bisabolol, (2E,6Z)-farnesol, cis-thujopsenal, oplopanone, γ-costol, xanthorrhizol, cyclocolorenone and β-costol.

3.2. Anti-inflammatory assay

In carrageenan paw inflammation, three analyzed parameters, edema, mechanical hyperalgesia, and cold allodynia, were inhibited by EOAE-D and EOAE-B (**Fig. 4, 5, 6**).

The EOAE-D and EOAE-B mice groups were subjected to carrageenan-induced paw edema, and an increase in paw volume (edema) in all groups was observed for 4 h (**Fig. 4**). This is a model used to evaluate nonsteroidal anti-inflammatory drugs. Oral treatment with EOAE-D and EOAE-B at the doses tested significantly inhibited edema formation compared to that in the control group 0.5, 1, 2 and 4 h after induction but did not occur in a dose-dependent manner (**Fig. 4**), as revealed by the time course analysis. The DEXA-treated group also displayed reduced paw inflammation (89%) over time after the injection of carrageenan in the paw (**Fig. 4**). The efficacies of the EOAE collected in different regions were similar to that of the DEXA-treated group in this test (**Fig. 4**). In the present study, the essential oil showed anti-inflammatory properties, corroborating the study by Trevizan et al. (2016). In an attempt to describe the observed effect, the reduced inflammation may be to the synergistic effect of the present compounds, among them, sesquiterpenes, which are reported in the literature to have anti-inflammatory activity (Recio et al., 2000; Feltenstein et al., 2004; Valério et al., 2007; Fonseca et al., 2010; McKinnon et al., 2014; Butturini et al., 2014; Turk et al., 2019).

Although the compounds were not tested in this study, caryophyllene oxide isolated from a petroleum ether extract of *Annona squamosa* bark showed analogous anti-inflammatory activity (Chavan et al., 2010). Similarly, ginger essential oil showed anti-inflammatory activity, the major compound of which is α-zingiberene (Jeena et al., 2013).

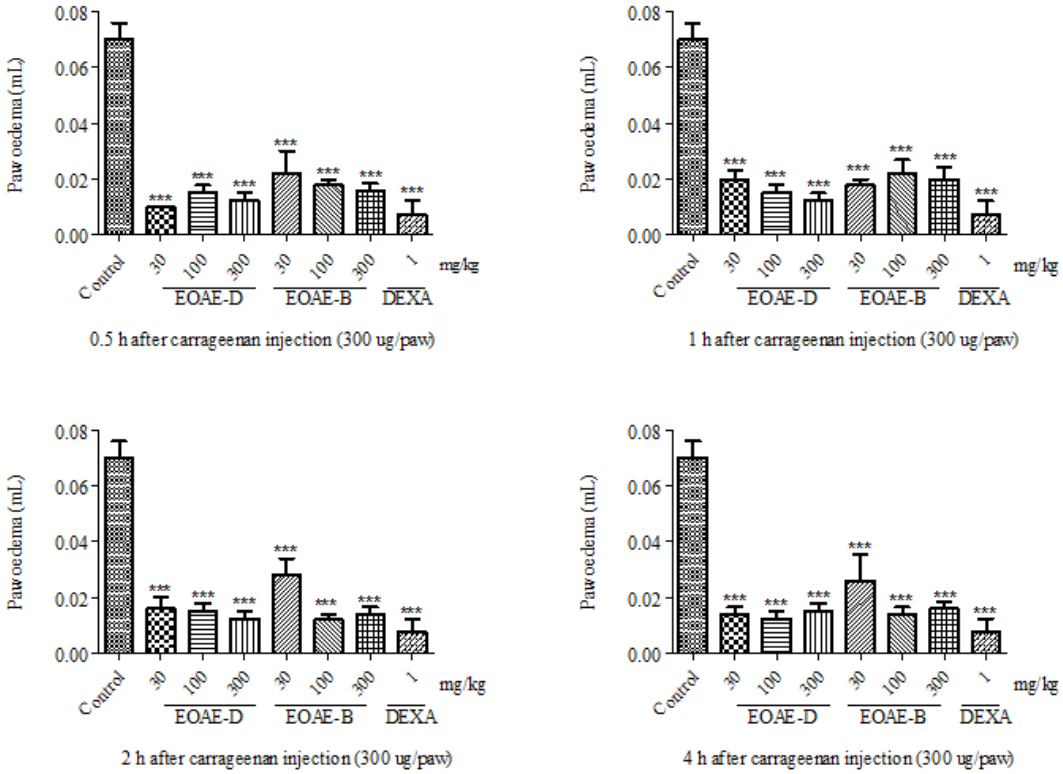


Fig. 4. Effect of oral EOAE administration on carrageenan-induced paw edema in mice. Animals received either EOAE-D (30, 100 or 300 mg/kg, p.o.), EOAE-B (30, 100 or 300 mg/kg, p.o.), dexamethasone (DEXA, 1 mg/kg, s.c.) or the vehicle (Control). Each bar represents the mean ± SEM of 6 animals. *** P<0.001 compared with the control treated group. Differences between groups were analyzed by one-way ANOVA followed by the Newman-Keuls test.

Administration of EOAE-D (30, 100 and 300 mg/kg) and EOAE-B (30, 100 and 300 mg/kg) significantly attenuated the duration of cold hypersensitivity; after 3 and 4 h, almost no paws were moved and were raised only a few times with acetone application. Furthermore, the hypersensitive response to cold in the treated group was < 2 s. There was a significant decrease in movements when compared with the those of the control

group (**Fig. 5**). Sensitivity to a cold stimulus was significantly reduced, with inhibition ranging widely in for all groups. (**Fig. 5**).

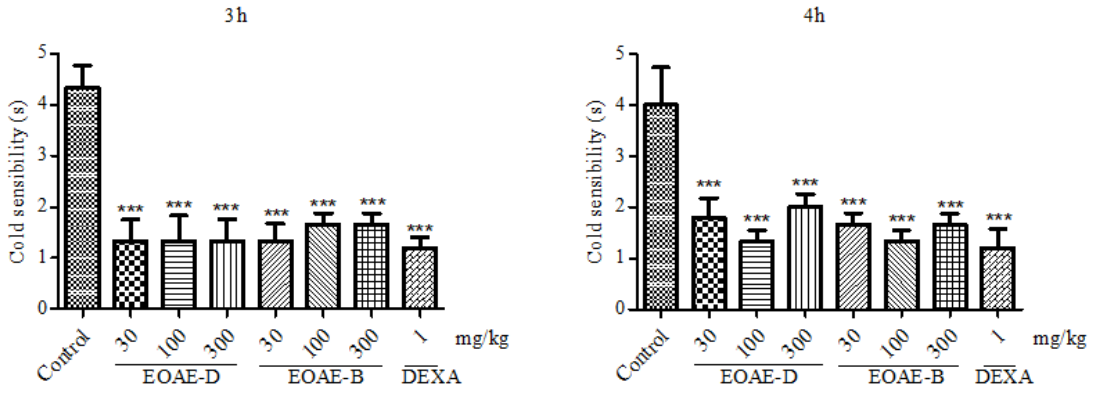


Fig. 5. Effect of oral EOAE-D (30, 100 or 300 mg/kg, p.o.) or EOAE-B (30, 100 or 300 mg/kg, p.o.) administration on acetone-induced cold allodynia. Measurements were made three and four h after gavage. Each column represents the mean of 6 animals. The asterisks denote the significance levels compared with the control group data. *** $P<0.001$ compared with the vehicle-treated group data (Control). Differences between groups were analyzed by one-way ANOVA followed by the Newman-Keuls test.

Oral administration of EOAE-B (30, 100 and 300 mg/kg) reduced the sensitivity induced by mechanical stimulus after 3 h and 4 h compared with that of the control group (**Fig. 6**). The DEXA group (1 mg/kg) also showed inhibition of 76.97 ± 1% and 85.11 ± 1% when evaluated after 3 h and 4 h, respectively (**Fig. 6**).

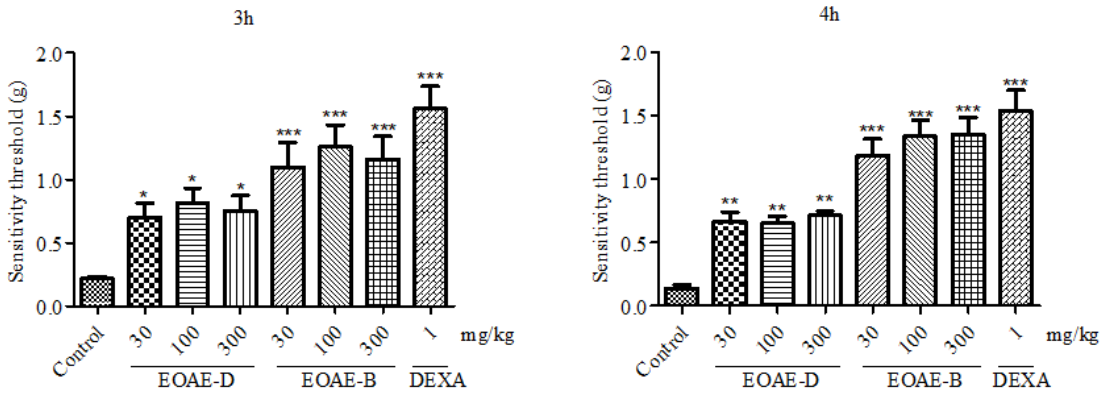


Fig. 6. Effect of oral EOAE-D (30, 100 or 300 mg/kg, p.o.) or EOAE-B (30, 100 or 300 mg/kg, p.o.) administration on mechanical hyperalgesia. Measurements were made three and four h after gavage. Each column represents the mean measurement of 6 animals. The asterisks denote the significance levels compared with the control group data. * P<0.05, ** P<0.01, *** P<0.001 compared with the vehicle-treated group data (Control). Differences between groups were analyzed by one-way ANOVA followed by the Newman-Keuls test.

The inflammatory process is a beneficial physiological mechanism used by the body to self-defend, normally, pain or increased sensitivity. Immediately after tissue injury, inflammatory transmitters and mediators are released, which progress with the onset and maintenance of pain. Additionally, somatosensory changes increase the response and sensitivity to stimuli in different ways, such as chemical, physical and mechanical stimuli, so that pain is felt by low-intensity stimuli (Simões et al., 2015).

EOAE-D and EOAE-B were assayed against the CFA-induced mechanical hyperalgesia, cold sensitivity, and paw edema induced by CFA (**Fig. 7**). Complete Freud's adjuvant (CFA) is a product widely used in biological research (Stein et al., 1988,

Wang et al., 2019) to induce intense immunological and inflammatory responses and central and peripheral sensitization (for example, mechanical and thermal hyperalgesia) in rodents. The oral acute treatment with EOAE-D and EOAE-B at 30 mg/kg significantly inhibited mechanical hyperalgesia (**Fig. 7A**) and edema formation (**Fig. 7C**) compared to those of the control group at all observed time points. It was possible to verify the ability of both products to inhibit inflammatory pain in response to cold only 4 h after CFA administration (**Fig. 7B**). Dexamethasone exhibited the same pattern of inhibition as that of the essential oils (**Fig. 7**). These results corroborated those of Trevizan et al. (2016), and we showed that the essential oils inhibited the inflammatory process induced by carrageenan.

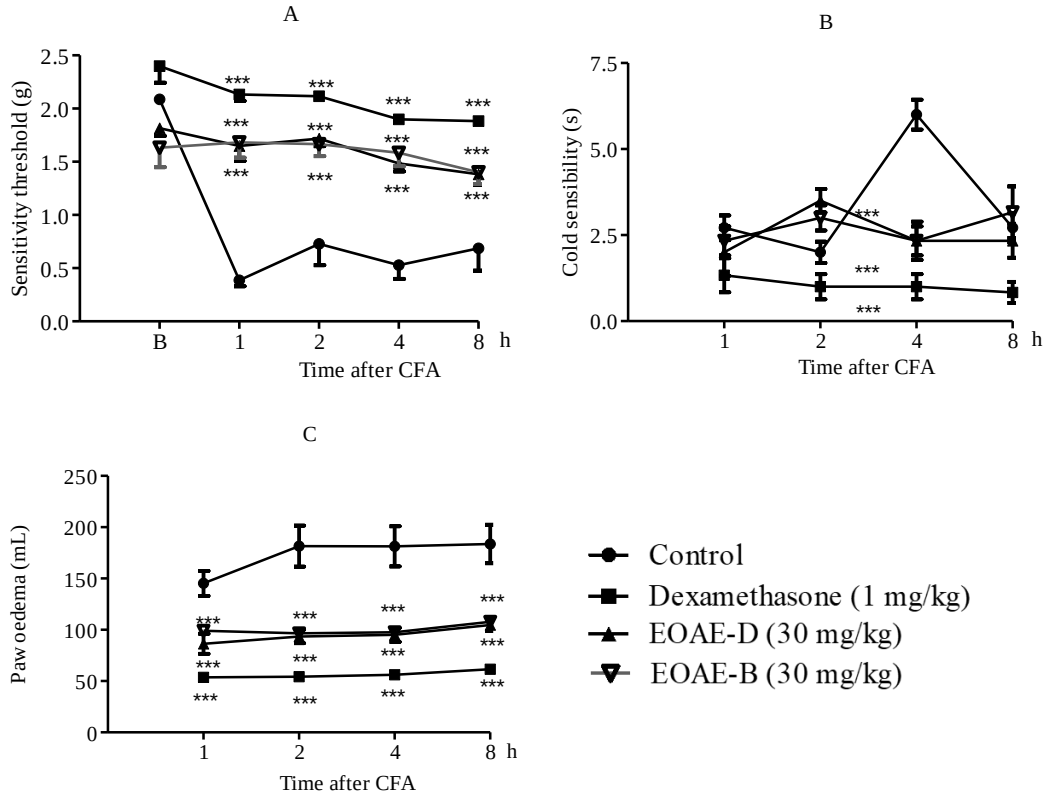


Fig. 7. Effect of acute oral EOAE-D (30 mg/kg) and EOAE-B (30 mg/kg) treatments on mechanical (A) and cold (B) hyperalgesia and oedema (C) 1, 2, 4, and 8 h after CFA

injection. Each group represents the mean measurement of 6 animals. The asterisks denote significance levels compared with the control group data (*** P<0.001). Differences between groups were analyzed by one-way ANOVA followed by the Newman-Keuls test.

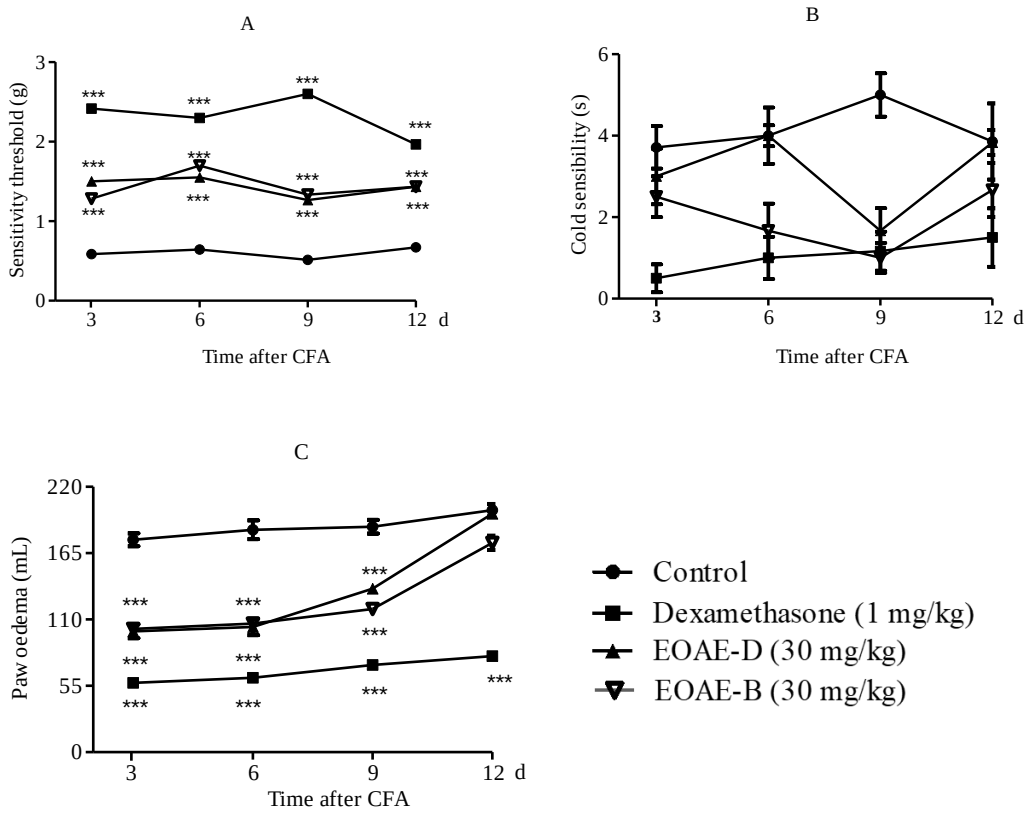


Fig. 8. Effect of persistent oral treatments with EOAE-D (30 mg/kg) and EOAE-B (30 mg/kg) on mechanical (A) and cold (B) hyperalgesia and oedema (C) 3, 6, 9, and 12 days after CFA injection. Each group represents the mean of 6 animals. The asterisks denote significance levels compared with the control group data (*** P<0.001). Differences between groups were analyzed by one-way ANOVA followed by the Newman-Keuls test.

Persistent oral treatment with EOAE-D and EOAE-B at 30 mg/kg significantly inhibited CFA-induced, sustained mechanical hyperalgesia (**Fig. 8A**) on all days observed, showing that for this inflammatory response, no signs of tolerance were

observed. Tolerance to opioids (for example) is a phenomenon common to morphine that required increased doses to induce the same analgesic effects on inflammatory pain (Kandasamy et al., 2017). The persistent and intense edema formation induced by CFA (**Fig. 8C**) was significantly inhibited by EOAE-D (30 mg/kg) and EOAE-B (30 mg/kg) after 3, 6, and 9 days but not 12 days after CFA injection. However, the response to cold (**Fig. 8B**) was not altered by essential oil or by dexamethasone administration.

4. CONCLUSION

Our study demonstrated that secondary metabolism involving *A. edulis* essential oil production changes according to the combination of the influence of biotic and abiotic factors. In turn, the environmental conditions produced different chemical profiles, but the results of the different inflammation models suggest that there was no significant difference between the two oils, which is in accordance the empirical use of the plant. Therefore, we concluded that this plant presents itself as a promising source of secondary metabolites with potential use in the treatment of pain and inflammation.

Author contributions

SMS, PCOJ, ASNF, designed the study, phytochemical analysis as extraction, characterization of the chemical constituent and anti-inflammatory assays; CALC analyzed by GC/MS; CALK and NMB performed the anti-inflammatory assays; ZVP material botanical and information of the collection sites. All authors participated in the design, interpretation, and analysis of the data and approved the final manuscript.

DISCLOUSURE STATEMENT

The authors declare that they have no competing interests.

ACKNOWLEDGEMENT

The authors express their gratitude to the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brazil (CAPES) - Finance Code 001, Fundação de Apoio ao Desenvolvimento do Ensino, Ciência e Tecnologia do Estado de Mato Grosso do Sul (FUNDECT), Financiadora de Inovação e Pesquisas (FINEP) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) (311975/2018-6 CALC)

REFERENCES

Abd-ElGawad, A.M., Elshamy, A.I., Al-Rowaily, S.L., El-Amier, Y.A., 2019. Habitat Affects the Chemical Profile, Allelopathy, and Antioxidant Properties of Essential Oils and Phenolic Enriched Extracts of the Invasive Plant *Heliotropium Curassavicum*. Plants. (Basel). 8. https://doi.org/10.3390/plants8110482.

Adams, R.P., 2007. Identification of essential oil components by gas chromatography/mass spectrometry, fourth ed. Allured Publishing Corporation, Illinois.

Amaral, J.A.M., Mothci, E.P., Oliveira, H., Carvalho Filho, A., Naime, U.J., Santos, R.D., 2000. Levantamento semidetalhado dos solos do Campo Experimental de Dourados, da Embrapa Agropecuária Oeste, município de Dourados. Embrapa Agropecuária Oeste, Rio de Janeiro.

Araujo-Junior, C.F., Martins, B.H., Higashi, V.Y., Hamanaka, C.A., 2015. The role of weed and cover crops on soil and water conservation in a tropical region, in: Pilipavicius, V. (Ed.), Weed Biology and Control. IntechOpen, Croatia. http://dx.doi.org/10.5772/59952.

Arisawa, M., Morinaga, Y., Nishi, Y., Ueno, H., Suzuki, S., Hayashi, T., Shimizu Yoshizaki, M., Morita, N., Berganza, L.H., 1989. Chemical and pharmaceutical studies

on medicinal plants in paraguay. Constituents of angiotensin converting enzime inhibitory fraction from “cocu” *Allophylus edulis*. Jpn. J. Pharmacog., 43, 78-80. http://ci.nii.ac.jp/naid/110009570582.

Butturini, E., Di Paola, R., Suzuki, H., Paterniti, I., Ahmad, A., Mariotto, S., Cuzzocrea, S., 2014. Costunolide and Dehydrocostuslactone, two natural sesquiterpene lactones, ameliorate the inflammatory process associated to experimental pleurisy in mice. Eur. J. Pharmacol. 730, 107–115. https://doi.org/10.1016/j.ejphar.2015.03.050.

Cáceres, N.C., Bornschein, M.R., Lopes, W.H., Percequillo, A.R., 2007. Mammals of the Bodoquena Mountains, southwestern Brazil: an ecological and conservation analysis. Rev. Bras. Zool. 24, 426-435. http://dx.doi.org/10.1590/S0101-81752007000200021.

CEMTEC, 2019. Centro de Monitoramento do Tempo e do Clima de MS. http://www.cemtec.ms.gov.br/boletins-meteorologicos/ (accessed 08 October 2019).

Chagas, C.S., Carvalho Junior, W., Bhering, S.B., Amaral, F.C.S., Pereira, N.R., Silva, E.F., Zaroni, M.J., Goncalves, A.O., Aglio, M.L.D., Daniel Filho, A.C.B., Lopes, C.H.L., Earp, C.G.S., Vargas, S.P., Frevrier, P.V.R., Pinheiro, T.D., Fernandes, T.G., Rodrigues, R.S., 2009. Zoneamento Agroecológico do Município de Bonito – MS. Embrapa Agropecuária Oeste, Rio de Janeiro.

Chavan, M.J., Wakte, P.S., Shinde, D.B., 2010. Analgesic and anti-inflammatory activity of Caryophyllene oxide from *Annona squamosa* L. bark. Phytomedicine, 17, 149–151. https://doi.org/10.1016/j.phymed.2009.05.016.

Chavan R.B., Gaikwad D.K., 2016. The ethnobotany, phytochemistry and biological properties of A*llophylus* species used in traditional medicine: a review. J. Pharm. Pharm. Sci. 6, 664-682. https://doi.org/10.20959/wjpps201611-8039.

Choi Y., Yoon Y.W., Na H.S., Kom S.H., 1994. Behavioral signs of ongoing pain and cold allodynia in a rat model of neuropathic pain. Pain. 59, 369-76. https:// 10.1016/0304-3959(94)90023-x.

Decosterd, I.; Woolf, C.J., 2000. Spared nerve injury: an animal model of persistent peripheral neuropathic pain. Pain. 87, 149-58. http://dx.doi.org/10.1016/S0304-3959(00)00276-1.

EMBRAPA, 1999. Centro Nacional de Pesquisa de Solos. Sistema Brasileiro de Classificação de Solos. Rio de Janeiro, 412.

Fang, C., Fernie, A., Luo, J., 2019. Exploring the Diversity of Plant Metabolism. Trends Plant Sci. 24, 83-98. https://doi.org/10.1016/j.tplants.2018.09.006.

Feltenstein, M.W., Schühly, W., Warnick, J.E., Fischer, N.H., Sufka, K.J., 2004. Anti-inflammatory and anti-hyperalgesic effects of sesquiterpene lactones from Magnolia and Bear's foot. Pharmacol. Biochem. Behav. 79, 299–302. https://doi.org/10.1016/j.pbb.2004.08.008.

Ferreres, F., Gomes, N.G.M., Valentão, P., Pereira, D.M., Gil-Izquierdo, A., Araújo, L., Silva, T.C., Andrade, P.B., 2018. Leaves and stem bark from *Allophylus africanus* P. Beauv.: An approach to anti-inflammatory properties and characterization of their flavonoid profile. Food Chem. Toxicol. 118, 430-438. https://doi.org/10.1016/j.fct.2018.05.045.

Fonseca, L.C., Dadarkar, S.S., Lobo, A.S., Suthar, A.C., Chauhan, V. S., Chandrababu, S., Sharma, S.D., Dagia, N.M., Padigaru, M., 2010. 7-hydroxyfrullanolide, a sesquiterpene lactone, inhibits pro-inflammatory cytokine production from immune cells and is orally efficacious in animal models of inflammation. Eur. J. Pharmacol. 644, 220–229. https://doi.org/10.1016/j.ejphar.2010.06.052.

Henriques, M.G., Weg, V.B., Martins, M.A., Silva, P.M., Fernandes, P.D., Cordeiro, R.S., Vargaftig, B.B., 1990. Differential inhibition by two hetrazepine PAF antagonists of acute inflammation in the mouse. Br. J. Pharm. 99, 164–168. https://doi.org/10.1111/j.1476-5381.1990.tb14671.x.

Howard, L.R., Clark, J.R.; Brownmiller, C., 2003. Antioxidant capacity and phenolic content in blueberries as affected by genotype and growing season. J. Sci. Food Agric. 83. https://doi.org/10.1002/jsfa.1532.

Iwu, M.M., Anyanwu, B.N., 1982. Phytotherapeutic profile of Nigerian herbs. I: anti-inflammatory and anti-arthritic agents. J. Ethnopharmacol. 6, 263-274. https://doi.org/10.1016/0378-8741(82)90049-6.

Jeena, K., Liju, V.B., Kuttan R., 2013. Antioxidant, anti-inflammatory and antinociceptive activities of essential oil from ginger. Indian J. Physiol. Pharmacol. 57, 51-62.

Kandasamy, R., Lee, A.T., Morgan, M.M., 2017. Depression of home cage wheel running is an objective measure of spontaneous morphine withdrawal in rats with and without persistent pain. Pharmacol. Biochem. Behav. 156, 10–15. https://doi.org/10.1016/j.pbb.2017.03.007.

Khan, M., Khan, S.T., Khan, M., Mousa, A.A., Mahmood, A., Alkhathlan, H.Z., 2019. Chemical diversity in leaf and stem essential oils of *Origanum vulgare* L. and their effects on microbicidal activities. AMB Express. 9, 176. https://doi.org/10.1186/s13568-019-0893-3.

Körbes, V.C., 1995. Plantas Medicinais. fifty-fifth ed. Grafit Grafica e Editora, Francisco Beltrão.

Larson A.A., Brow D.R., El-Atrash S., Walser M.M., 1986. Pain threshold changes in adjuvant-induced inflammation: a possible model of chronic pain in the mouse. Pharmacol. Biochem. Behav. 24, 49-53. https://10.1016/0091-3057(86)90043-2.

Lewis, W.H., Elvin-Lewis, P.F., 2003. Medical Botany: Plants affecting man's health. second ed. Publ. John Willey and Sons, New Jersey.

McKinnon, R., Binder, M., Zupkó, I., Afonyushkin, T., Lajter, I., Vasas, A., De Martin, R., Unger, C., Dolznig, H., Diaz, R., Frisch, R., Passreiter, C.M., Krupitza, G., Hohmann, J., Kopp, B., Bochkov, V. N., 2014. Pharmacological insight into the anti-inflammatory activity of sesquiterpene lactones from *Neurolaena lobata* (L.) R.Br. ex Cass. Phytomedicine. 21, 1695–1701. https://doi.org/10.1016/j.phymed.2014.07.019.

Möller, K.A., Johansson, B., Berge, O.G., 1998. Assessing mechanical allodynia in the rat paw with a new electronic algometer. J Neurosci Methods. 84, 41-47. https://10.1016/s0165-0270(98)00083-1.

Morris C. J., 2003. Carrageenan-Induced Paw Edema in the Rat and Mouse, in: Winyard P.G., Willoughby D.A. (Eds). Inflammation Protocols. Humana Press. 115-121. https://doi.org/10.1385/1-59259-374-7:115.

Recio, M.C., Giner, R.M., Uriburu, L., Máñez, S., Cerdá, M., De La Fuente, J.R., Ríos, J. L., 2000. In vivo activity of pseudoguaianolide sesquiterpene lactones in acute and chronic inflammation. Life Sci. 66, 2509–2518. https://doi.org/10.1016/S0024-3205(00)00585-3.

Sano, E.E., Rodrigues, A.A., Martins, E.S., Bettiol, G.M., Bustamante, M.M.C., Bezerra, A.S., Couto Junior., A.F., Vasconcelos, V., Schüler, J., Bolfe, E.L., 2019. Cerrado ecoregions: A spatial framework to assess and prioritize Brazilian savanna environmental diversity for conservation. J. Environ. Manage. 232, 818-828. https://doi.org/10.1016/j.jenvman.2018.11.108.

Silva Junior, C.A., Costa, G.M., Rossi, F.S., Vale, J.C.E., Lima, R.B., Lima, M., Oliveira-Junior, J.F., Teodoro, P.E., Santos, R.C., 2019. Remote sensing for updating the boundaries between the brazilian Cerrado-Amazonia biomes. Environ. Sci. Policy. 101, 383-392. https://doi.org/10.1016/j.envsci.2019.04.006.

Simões, R.R., Coelho, I.S., Junqueira, S.C., Maldaner, G., Morel, A.F., Venzke, D., Ruani, A.P., Pizzolatti, M.G., Zanchet, E.M., Santos, A.R.S., 2015. Pharmacological evidence favouring the traditional use of the root bark of *Condalia buxifolia* Reissek in

the relief of pain and inflammation in mice. J. Ethnopharmacol. 175, 370–377. https://doi.org/10.1016/j.jep.2015.09.028.

Souza, E.F.; Morassuti, C.Y.; Soares, E.; Duarte, G.S.V.; Soares, J.S.; Jorge, M.B.; Silva, C.A.A., 2017. Classificação de solos e análise da vegetação em relação às características locais nos municípios de Dourados e Jateí/MS. Engevista, 19, 293-305. https://doi.org/10.22409/engevista.v19i2.824.

Stein, C., Millan, M.J., Herz, A., 1988. Unilateral inflammation of the hindpaw in rats as a model of prolonged noxious stimulation: Alterations in behavior and nociceptive thresholds. Pharmacol. Biochem. Behav. 31, 445–451. https://doi.org/10.1016/0091-3057(88)90372-3.

Trevizan, L.N.F., Nascimento, K.F., Santos, J.A., Kassuya, C.A.L, Cardoso, C.A.L., Vieira, M.C., Moreira, F.M.F., Croda, J., Formagio, A.S.N., 2016. Anti-inflammatory, antioxidant and anti-*Mycobacterium tuberculosis* activity of viridiflorol: The major constituent of *Allophylus edulis* (A. St.-Hil., A. Juss. & Cambess.) Radlk. J. Ethnopharmacol. 192, 510–515. https://doi.org/10.1016/j.jep.2016.08.053.

Turk, A., Ahn, J.H., Jo, Y.H., Song, J.Y., Khalife, H.K., Gali-Muhtasib, H., Kim, Y., Hwang, B.Y., Lee, M.K., 2019. NF-κB inhibitory sesquiterpene lactones from *Lebanese Laurus nobilis*. Phytochem. 30, 120–123. https://doi.org/10.1016/j.phytol.2019.02.003.

Uetanabaro, M; Souza, F.L, Landgref Filho, P., Beda, A.F., Brandão, R.A., 2007. Amphibians and reptiles of the Serra da Bodoquena National Park, Mato Grosso do Sul, central Brazil. Biota Neotrop. 7, 279-289. http://dx.doi.org/10.1590/S1676-06032007000300030.

Valério, D.A.R., Cunha, T.M., Arakawa, N.S., Lemos, H.P., Da Costa, F.B., Parada, C. A., Ferreira, S.H, Verri, W.A., 2007. Anti-inflammatory and analgesic effects of the sesquiterpene lactone budlein A in mice: Inhibition of cytokine production-dependent mechanism. Eur. J. Pharmacol. 562, 155–163. https://doi.org/10.1016/j.ejphar.2007.01.029.

Wang, C., Wu, Q., Wang, Z., Hu, L., Marshall, C., Xiao, M., 2020. Aquaporin 4 knockout increases complete freund's adjuvant-induced spinal central sensitization. Brain Res. Bull. 156, 58–66. https://doi.org/10.1016/j.brainresbull.2020.01.004.

CONCLUSÃO FINAL

Pelos trabalhos realizados é possível inferir que o Cerrado brasileiro, aqui representado pelas áreas estudadas, apresenta rica diversidade de plantas medicinais. Estas espécies, por sua vez, são amplamente difundidas no saber da comunidade e por isso, são utilizadas para o tratamento de diversos quadros clínicos. Pela pesquisa realizada foi possível constatar que grande parte delas já foram estudadas quanto ao potencial farmacológico, e algumas indicações populares foram comprovadas, ou ainda apresentaram efeitos mesmo além da utilização empírica. Com a avaliação do potencial anti-inflamatório de *A. edulis* foi possível descrever a capacidade desta espécie de apresentar o efeito anti-inflamatório, mesmo com certa discrepância na composição química. Por tudo isso, pode-se concluir que o cerrado brasileiro é uma fonte potencialmente promissora na busca por moléculas com aplicação farmacológica, em razão da biodiversidade presente no bioma.

ANEXOS

Anexo 1. Documento que aprova o uso dos animais para experimentação citados no Artigo 2.

MINISTÉRIO DA EDUCAÇÃO
FUNDAÇÃO UNIVERSIDADE FEDERAL DA GRANDE DOURADOS
PRÓ-REITORIA DE ENSINO DE PÓS-GRADUAÇÃO E PESQUISA

COMISSÃO DE ÉTICA NO USO DE ANIMAIS - CEUA

Dourados-MS, 8 de fevereiro de 2019.

CERTIFICADO

Certificamos que a proposta intitulada "***Influência de fatores ambientais em propriedades de Allophylus edulis (A.St.-Hil., A.Juss. & Cambess.) Radlk.***", registrada sob o protocolo de nº 34/2018, sob a responsabilidade de *Anelise Samara Nazari Formagio* – que envolve a produção, manutenção e/ou utilização de animais pertencentes ao filo *Chordata, subfilo Vertebrata* (exceto o homem), para fins de pesquisa científica (ou ensino), encontra-se de acordo com os preceitos da Lei nº 11.794, de 08 de outubro de 2008, do Decreto nº 6.899, de 15 de julho de 2009, e com as normas editadas pelo Conselho Nacional de Controle da Experimentação Animal (CONCEA), e foi aprovada pela Comissão de Ética no Uso de Animais (CEUA/UFGD) da Universidade Federal da Grande Dourados, em reunião de 09/11/2018.

Finalidade	*( ) Ensino (X) Pesquisa Científica*
Vigência da autorização	*20/02/2019 a 28/02/2020*
Espécie/linhagem/raça	*Rattus norvegicus – Wistar / Mus musculus – Swiss*
Nº de animais	*353 / 76 Wistar – 277 Swiss*
Peso/idade	45-50 dias
Sexo	76 machos Wistar / 187 machos e 90 fêmeas - Swiss
Origem	Biotério Central UFGD

Melissa Negrão Sepulvida

Melissa Negrão Sepulvida
Coordenadora CEUA

Comissão de Ética no Uso de Animais – CEUA/UFGD – Rua João Rosa Góes, 1761 – Vila Progresso.
Dourados/MS. E-mail: ceua@ufgd.edu.br

Anexo 2. Carta de submissão do Artigo 2.

SERVIÇO PÚBLICO FEDERAL
MINISTÉRIO DA EDUCAÇÃO
UNIVERSIDADE FEDERAL DA GRANDE DOURADOS

FACULDADE DE CIÊNCIAS DA SAÚDE

To: A.M. Viljoen
Editor-in-Chief of Journal of Ethnopharmacology

February, 2020

Dear Editor

We're submitting the manuscript: **Variation in essential oil components and anti-inflammatory activity of *Allophylus edulis* leaves collected in the central-western of Brazil.** The referred manuscript has not been published or is under active consideration by another journal.

The emphasis of this work has relationship with scope of Journal, showing for the first time the evaluated the anti-inflammatory and its variation of the chemical components present in the essential oil of the leaves collected in different accessions in the central west region of Brazil. The study was conducted in part to provide evidence supporting the ethnobotanical use (anti-inflammatory) of the leaves of this species different access locations.

Thank you for your attention.
Sincerely yours,

Anelise Samara Nazari Formagio
Universidade Federal da Grande Dourados, UFGD
79825-070 Dourados, MS, Brasil