PROGRAMA DE PÓS-GRADUAÇÃO *STRICTO SENSU* EM RECURSOS NATURAIS DO CERRADO

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JAMIRA DIAS ROCHA

Avaliação dos efeitos biológicos e tóxicos de plantas do Cerrado: um enfoque em *Vernonanthura polyanthes*

Anápolis
2022

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Tese apresentada ao Programa de Pós-Graduação Stricto Sensu em Recursos Naturais do Cerrado, da Universidade Estadual de Goiás para obtenção do título de Doutor (a) em Recursos Naturais do Cerrado. Orientador(a): Prof(a) Dr(a). Elisa Flávia Luiz Cardoso Bailão.

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ATA DE DEFESA PÚBLICA DE TESE Nº 126/2022

Aos 10 dias do mês de novembro do ano de 2022, às 08h30min, reuniu-se no auditório do bloco IV do Câmpus Central da UEG, a banca Examinadora composta pelos: Dra. Elisa Flávia Luiz Cardoso Bailão (Universidade Estadual de Goiás), Dra. Luciane Madureira de Almeida (Universidade Estadual de Goiás), Dra. Samantha Salomão Caramori (Universidade Estadual de Goiás), Dra. Cátia Lira do Amaral (Universidade Estadual de Goiás), Dr. Clever Gomes Cardoso (Universidade Federal de Goiás) para sob a presidência do primeiro, procederem à "defesa de doutorado" intitulada: Avaliação dos efeitos biológicos e tóxicos de plantas do Cerrado: um enfoque em *Vernonanthura polyanthes*, de Jamira Dias Rocha, discente do PPG Recursos Naturais do Cerrado, nível doutorado. Foi realizada a avaliação oral no sistema de apresentação e defesa de tese de autoria do(a) discente. Terminada a avaliação oral, a Banca Examinadora reuniu-se emitindo os seguintes pareceres mediante as justificativas e sugestões abaixo:

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Dra. Luciane Madureira de Almeida	X	
Dra. Samantha Salomão Caramori	X	
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Justificativas e sugestões: Adequar às sugestões da banca e à estrutura formal da tese.

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JAMIRA DIAS ROCHA

AVALIAÇÃO DOS EFEITOS BIOLÓGICOS E TÓXICOS DE PLANTAS DO CERRADO: UM ENFOQUE EM *Vernonanthura polyanthes*

Tese defendida no Programa de Pós-Graduação *Stricto Sensu* em Recursos Naturais do Cerrado da Universidade Estadual de Goiás, para a obtenção do grau de doutor(a), aprovada em 10 de novembro de 2022, pela Banca Examinadora constituída pelos seguintes professores:

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Dedicatória

A Deus
A minha mãe Leda, pelo carinho e apoio
A minha orientadora e amiga Elisa Flávia, por todo insentivo e inspiração
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"Sonhar é acordar-se para dentro [...]"

Mário Quintana

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Resumo

O Cerrado possui uma ampla diversidade de plantas medicinais que são utilizadas para o tratamento de diversas doenças. O primeiro objetivo deste trabalho foi realizar uma revisão sistemática sobre o potencial tóxico destas espécies. Nossa busca na literatura identificou 194 plantas do Cerrado com potencial tóxico, sendo que maior parte das espécies apresentaram compostos com alta citotoxicidade contra células tumorais e baixa toxicidade contra células normais. Em relação a interação com DNA, os compostos extraídos de plantas do Cerrado em tratamentos agudos e/ou crônicos mosntraram baixa genotoxicidade e mutagenicidade. Atividades antibactericida, antifúngica, antiviral, inseticida e antiparasita também foram identificadas nos diferentes extratos das plantas do Cerrado. Dentre as diferentes espécies identificadas na nossa revisão, esta tese tem interesse especial em *Vernonanthura polyanthes* (Spreng.) A.J. Vega & Dematt, conhecida popularmente como assa-peixe. Essa espécie é amplamente utilizada na medicina popular como expectorante. Nosso grupo de pesquisa anteriormente mostrou que o extrato aquoso de *V. polyanthes* (*Vp*LAE) e fração n-butanol (n-BF) foram citogenotoxicas contra linfócitos humanos. No entanto, quando co-tratados com doxorrubicina (DXR), *Vp*LAE e n-BF diminuíram a genotoxicidade de DXR. Desta forma, outro objetivo desta tese foi avaliar o perfil químico por espectrometria de massas e toxicológico de *Vp*LAE e n-BF e sua interação com DXR em modelo murino por meio das técnicas de micronúcleo (MN) e ensaio cometa. Nossa análise identificou a presença de 8 compostos fenólicos caracterizados como flavonóides e ácidos clorogênicos (5-O- feruloilquínico, quercetina 3-O-rutinosídeo, 3,4-ácido di-O-cafeoilquínico, ácido 3,5-di-O- cafeoilquínico, ácido 4,5-di-O-cafeoilquínico, 3-O-cafeoilquínico ácido, ácido 5-O- cafeoilquínico e ácido 4-O-cafeoilquínico). No có, pré e pós-tratamento com DXR, tanto *Vp*LAE e n-BF inibiu significativamente a toxicidade de DXR, protegendo as células da medulaóssea do camundongo contra efeitos citotóxicos, genotóxicos e mutagênicos. Outro objetivo desta pesquisa foi realizar predição computacional para prever suas atividades biológicas dos 8compostos identificados *Vp*LAE e n-BF por espectrometria de massas. Os resultados *in sílico* estão de acordo com nossos *in vivo* nos murinos, mostrando que os compostos identificados demonstraram ser quimiopreventivos e antioxidantes. Em especial a molécula quercetina-3-O- rutinosídeo (Rutina) identificadas em *Vp*LAE e n-BF apresentou potencial anticancerígeno, além de apresentar baixa penetração através da barreira hematoencefálica (BHE) e dose letal mediana (DL50) com valor de 5000 mg/kg, representando uma margem segura, uma vez que ocomposto foi classificado na classe 5. Estas propriedades levaram a escolha da rutina para análise de docking molecular e demonstrou uma interação promissora antineoplásica, antimutagênica e/ou preventiva de câncer, de acordo com a previsão do PASS online. Em conclusão, estes resultados reforçam o potencial quimiopreventivo e antioxidante de espécies *V. polyanthes*.

Palavras-chave: estresse oxidativo; assa-peixe; ensaio cometa; micronúcleo; rutina; produtos naturais; docking molecular; Pass online.

Abstract

The Cerrado has a wide variety of medicinal plants that are used for the treatment of various diseases. The first objective of this work was to perform a systematic review on the toxic potential of these species. Our search in the literature identified 194 Cerrado plants with toxic potential, and most of the species presented compounds with high cytotoxicity against tumor cells and low toxicity against normal cells. Regarding the interaction with DNA, compounds extracted from Cerrado plants in acute and/or chronic treatments showed low genotoxicity and mutagenicity. Antibactericidal, antifungal, antiviral, insecticidal and antiparasitic activities were also identified in different extracts from Cerrado plants. Among the different species identified in our review, this thesis is of special interest in *Vernonanthura polyanthes* (Spreng.) A.J. Vega & Dematt, popularly known as assa-peixe. This species is widely used in folk medicine as an expectorant. Our research group previously showed that *V. polyanthes* aqueous extract (*Vp*LAE) and n-butanol fraction (n-BF) were cytogenotoxic against human lymphocytes. However, when co-treated with doxorubicin (DXR), *Vp*LAE and n-BF decreased DXR genotoxicity. Thus, another objective of this thesis was to evaluate the chemical profile by mass spectrometry and toxicology of *Vp*LAE and n-BF and their interaction with DXR in a murine model using micronucleus (MN) and comet assay techniques. Our analysis identified the presence of 8 phenolic compounds characterized as flavonoids and chlorogenic acids (5-O-feruloylquinic acid, quercetin 3-O-rutinoside, 3,4-di-O-caffeoylquinic acid, 3,5-di-O-cafeoylquinic acid , 4,5-di-O-caffeoylquinic acid, 3-O-caffeoylquinic acid, 5-O-caffeoylquinic acid and 4-O-caffeoylquinic acid). At co, pre and post DXR treatment, both *Vp*LAE and n-BF significantly inhibited DXR toxicity, protecting mouse bone marrow cells against cytotoxic, genotoxic and mutagenic effects. Another objective of this research was to perform computational prediction to predict their biological activities of the 8 compounds identified *Vp*LAE and n-BF by mass spectrometry. The *in silico* results are in agreement with our *in vivo* in murines, showing that the identified compounds proved to be chemopreventive and antioxidant. In particular, the molecule quercetin-3-O-rutinoside (Rutin) identified in *Vp*LAE and n-BF showed anticancer potential, in addition to presenting low penetration through the blood-brain barrier (BBB) and median lethal dose (LD50) with a value of 5000 mg/ kg, representing a safe margin, since the compound was classified in class 5. These properties led to the choice of rutin for molecular docking analysis and demonstrated a promising antineoplastic, antimutagenic and/or cancer preventive interaction, according to the PASS online prediction. In conclusion, these results reinforce the chemopreventive and antioxidant potential of *V. polyanthes* species.

Keywords: oxidative stress; assa-peixe; comet assay; micronucleus; routine; products natural; molecular docking; PASS online.

Introdução

1. Introdução

As plantas medicinais são apontadas como um grande potencial para a produção de novos medicamentos (CALIXTO, 2019). Além de seu uso como matéria-prima para a produção de novos medicamentos, as plantas também são utilizadas nas práticas da medicina popular e tradicional, como remédios caseiros (BRASIL, 2010). No entanto, de acordo com a Anvisa, é preciso que os riscos e à eficácia das plantas medicinais ou de seus subprodutos sejam caracterizados por análise farmacológicos e comprovada por documentações técnico científicas em publicações através de ensaios pré-clínicos ou clínicos que sejam caracterizados pela estabilidade de sua qualidade (ANVISA, 2014; DUTRA et al., 2016).

O Brasil possui uma alta biodiversidade, com mais de 50.000 espécies de plantas já identificadas, o que corresponde a cerca de 20 a 22% do total da flora mundial (CALIXTO, 2019; DUTRA et al., 2016; SIBBR, 2019). Ou seja, além do vasto acervo genético (flora), o Brasil é detentor de uma rica diversidade cultural e étnica que resulta em um amplo conhecimento e tecnologias tradicionais, passados de geração a geração, entre os quais se destacam a compreensão sobre o manejo e o uso de plantas medicinais (BRASIL, 2016). Além do que, o país abriga um dos hotspots de biodiversidade mundiais, o bioma Cerrado.O Cerrado é o segundo maior bioma brasileiro, ocupa quase 23% do território nacional (Figura 1), com mais de 12.000 espécies de plantas, sendo que dentre estas estima-se que mais de 4000 mil são endêmicas (FORZZA et al., 2012; RATTER; RIBEIRO; BRIDGEWATER, 1997). Nos últimos anos, a maior parte deste bioma, cerca de 2 milhões de km^2 foram tomados pela agropecuária, contribuindo para perda de grande parte de sua biodiversidade incluindo principalmente sua vegetação (ESCOBAR et al., 2020; KLINK; MACHADO, 2005). O Cerrado é um bioma com uma ampla diversidade de plantas medicinais, que são utilizadas principalmente pelas comunidades tradicionais que ali vivem para o tratamento de diversas doenças (RIBEIRO NETO et al., 2020). Neste sentido, as plantas com potencial medicinal do Cerrado apresentam grande importância econômica, cultural e social contribuindo para o bem-estar da população, especialmente em comunidades com acesso remoto aos sistemas de saúde pública (BAILÃO et al., 2015; DOS SANTOS et al., 2020; TRINDADE et al., 2022). Esta biodiversidade de espécies vegetais ricas em compostos bioativos faz com que as plantas medicinais sejam utilizadas como um recurso medicinal alternativo para o tratamento de diversas doenças (BAILÃO et al., 2015).

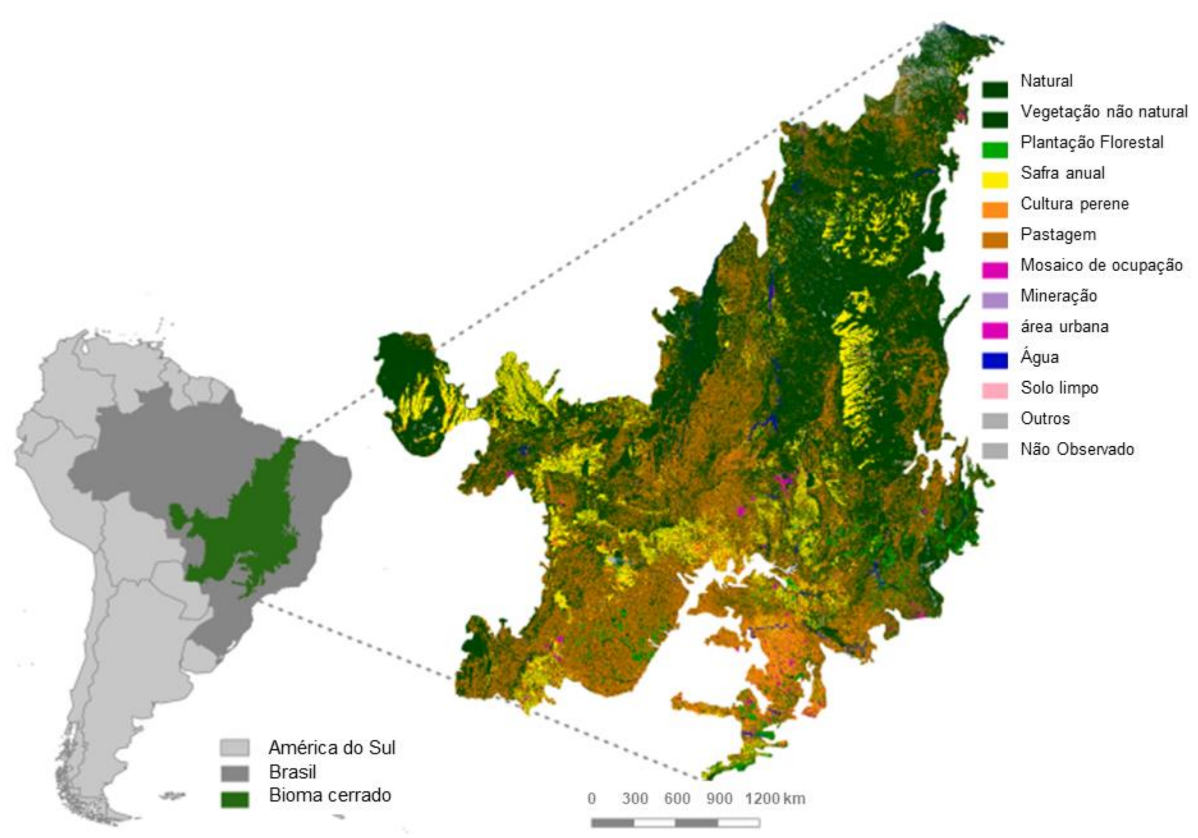


Figura 1.Cerrado brasileiro. Localização do Cerrado em relação ao Brasil e América do Sul e mapa de uso e cobertura da terra do Cerrado. Fonte: Santos et al., 2021.

Dentre as espécies medicinais do Cerrado, destaca-se *Vernonanthura polyanthes* (Spreng.) A.J. Vega & Dematt (Syn.: *Vernonia polyanthes Less) (Figura 2),* pertencente à família Asteracea (LORENZI; MATOS, 2008). *V. polyanthes* é uma planta medicinal amplamente distribuída no Cerrado brasileiro e é popularmente conhecida como assa-peixe. *V. polyanthes* é usada no tratamento de diversas afecções do trato respiratório, assim como doenças renais, infecções uterinas, úlceras, hipertensão, leishmaniose, febre, hemorragias e condições gástricas (BARBASTEFANO et al., 2007; BRAGA et al., 2007; LORENZI, H.; MATOS, 2002; OLIVEIRA et al., 2007; RODRIGUES et al., 2016; RODRIGUES; CARVALHO, 2001; SILVA et al., 2012; TEMPONI et al., 2012). Além de *V. polyanthes*, outras espécies do gênero também são conhecidas como assa-peixe, a exemplo de *Vernonia ferruginea* Less., *Vernonia cognata* Less., *Vernonia polysphaera* Baker., entre outras (BRASIL, 2011; DA SILVA OLIVEIRA et al., 2019; GALLON et al., 2018; TOYANG; VERPOORTE, 2013). No entanto, somente *V. polyanthes* é regulamentada para o uso fitoterápico, inscrita no Formulário de Fitoterápicos da Farmacopeia Brasileira (FFFB) como expectorante, na forma de chá obtido por infusão de folhas secas (BRASIL, 2011). O formulário fitoterápico é considerado o código oficial farmacêutico do país, onde são estabelecidos os

requisitos mínimos de qualidade para insumos farmacêuticos, medicamentos e produtos para a saúde, incluindo fitoterápicos e plantas medicinais (ANVISA, 2022).

Figura 2. Representante da espécie *Vernonanthura polyanthes* (Spreng.) A.J. Vega & Dematt. Arbusto ereto, bastante ramificado, constituído por folhas verdes e lanceoladas e capítulos florais em seu ápice. Fonte: Arquivo pessoal e https://farm6.static.flickr.com/5595/14614741956_646.

O potencial farmacológico de *V. polyanthes* vem sendo estudado devido à presença de compostos bioativos encontrados em extratos de folhas de *V. polyanthes* (Tabela1) (GALLON; JAIYESIMI; GOBBO-NETO, 2018; IGUAL et al., 2013; MARTUCCI et al., 2014; ROCHA et al., 2022a).

Estudos com intuito de avaliar o potencial citogenotóxico do extrato aquoso de folhas de *V. polyanthes* (*Vp*LAE) vêm sendo realizados em diferentes organismos. O *Vp*LAE não demonstrou toxicidade, genotoxicidade, ou antigenotoxicidade em *Drosophila melanogaster*. No entanto, este extrato foi capaz de potencializar a genotoxicidade da doxorrubicina (DXR) (GUERRA-SANTOS et al., 2016). Em contraste, *Vp*LAE foi citotóxico para *Allium cepa* e *Artemia salina* (ALMEIDA et al., 2020). Da mesma forma, extrato hidroalcoólico de folhas de *V. polyanthes* (2000 mg/kg) foi citogenotóxico quando administrado a camundongos (JORGETTO et al., 2011). *Vp*LAE e suas três frações (aquosa; n-butanol, n-BF; e acetato de

etila) não apresentaram citogenotoxicidade contra linfócitos humanos. No entanto, quando co-tratados com DXR, *V. polyanthes* diminuiu a genotoxicidade de DXR em ~15% (ROCHA et al., 2020). A DXR é um quimioterápico amplamente utilizado na terapia anticâncer; porém, seu uso é limitado pelos efeitos colaterais, como por exemplo aumento do estresse oxidativo e cardiotoxicidade (KORGA et al., 2017; VOLKOVA; RUSSELL, 2012; XU et al., 2001; ZHAO; ZHANG, 2017). Já se sabe que estes efeitos colaterais são provocados pelo distúrbio do equilíbrio redox causado pela DXR que ativa mecanismos que levam ao dano celular, causando um aumento na produção de radicais livres e uma diminuição de antioxidantes endógenos, induzindo toxicidade em vários órgãos e tecidos por meio do estresse oxidativo (GRANADOS-PRINCIPAL et al., 2010; KORGA et al., 2017; SINGAL et al., 2000; XU et al., 2001).

Tabela 1. Trabalhos realizados com extratos e frações de folhas de *Vernonanthura polyanthes*, utilizando diferentes ensaios e modelos experimentais para a averiguação das atividades biológicas.

Parte da planta	Tipo de extrato ou fração	Classes de compostos bioativos	Referência
Partes aéreas	_______	Lactonas sesquiterpênicas e triterpenos	(BOHLMANN et al., 1981)
Folhas	Metanólico e clorofórmico	Flavonoides, triterpenoides e lactonas sesquiterpênicas	(BARBASTEFANO et al., 2007)
Folhas	Aquoso	Fenois, taninos, chalconas, auronas, flavonoides, saponinas, ácidos fixos fortes, esteroides livres e quinonas	(SILVA et al., 2010)
Folhas	Metanólico	Alcaloides, triterpenoides, cumarinas e flavonoides	(BRAGA et al., 2007)
Folhas	Etanólico	Alcaloides, aminoácidos, antraquinonas, cumarinas, ácidos fixos, flavonoides, saponinas, esteroides, taninos e triterpenos	(TEMPONI et al., 2012)
Folhas	_______	Flavonas e lactonas sesquiterpênicas	(MARTUCCI et al., 2014)
Folhas	_______	Fenóis, flavonoides e ácidos fixos fortes	(SILVA et al., 2012)
Folhas	_______	Lactonas sesquiterpênicas flavonoides e ácidos clorogênico	(IGUAL et al., 2013)
Folhas	________	Lactonas sesquiterpênicas flavonoides e ácidos clorogênico	(GALLON; JAIYESIMI; GOBBO-NETO, 2018)
Folhas	Aquoso e frações n-butanólico e acetato de etila	Flavonoides, fenois e taninos	(ROCHA et al., 2020)
Folhas	Extrato etanólico	Flavonas, ácidos clorogênicos e flavonoide,	(FELETI et al., 2020)
Folhas	Extrato aquoso e fração n-butanol	Flavonóide e ácidos clorogênicos	(ROCHA et al., 2022a)

Fonte: Arquivo pessoal.

É importante destacar que o uso de plantas medicinais pode promover eventos adversos associados à sua composição química, pois as plantas medicinais possuem diversas substâncias que, além de apresentarem ação terapêutica, podem também ocasionar toxicidade e interação

medicamentosa com outros fármacos e/ou substâncias bioativas (CASANOVA; COSTA, 2017; DAI et al., 2015; FUJIKI; SUGANUMA, 2012; PATRA et al., 2021; ROCHA et al., 2022b, 2022a)**.** Essas interações entre plantas e fármacos e/ou compostos bioativos podem levar a alterações farmacológicas e ainda a toxicidade do medicamento. Ou seja, pode haver um aumento ou diminuição do efeito do fármaco, devido ao sinergismo ou antagonismo, podendo haver ainda, interações farmacocinéticas, que poderão provocar alterações na absorção e disposição do fármaco no organismo (DE OLIVEIRA; DALLA COSTA, 2004; SILVA; COLINO; PONTES NETO, 2021).

Desta forma, o presente trabalho teve por objetivo avaliar o perfil toxicológico de *V. polyanthes* (*Vp*LAE e n-BF) e sua interação com DXR em modelo murino por meio das técnicas de micronúcleo (MN), ensaio cometa e perfil bioquímico relacionado com o estresse oxidativo. Os perfis químicos de *Vp*LAE e n-BF foram determinados e os metabólitos identificados foram submetidos à análise de predição computacional para prever suas atividades biológicas.

Objetivos

Objetivos

1.1 Objetivo Geral

- Avaliar se o extrato aquoso de folhas de *V. polyanthes* ou sua fração n-butanol, associados ou não a doxorrubicina (DXR) causam alterações citogenotóxicas e/ou em modelo murino e identificar os compostos presentes no *Vp*LAE e na n-BF.

1.2 Objetivos específicos

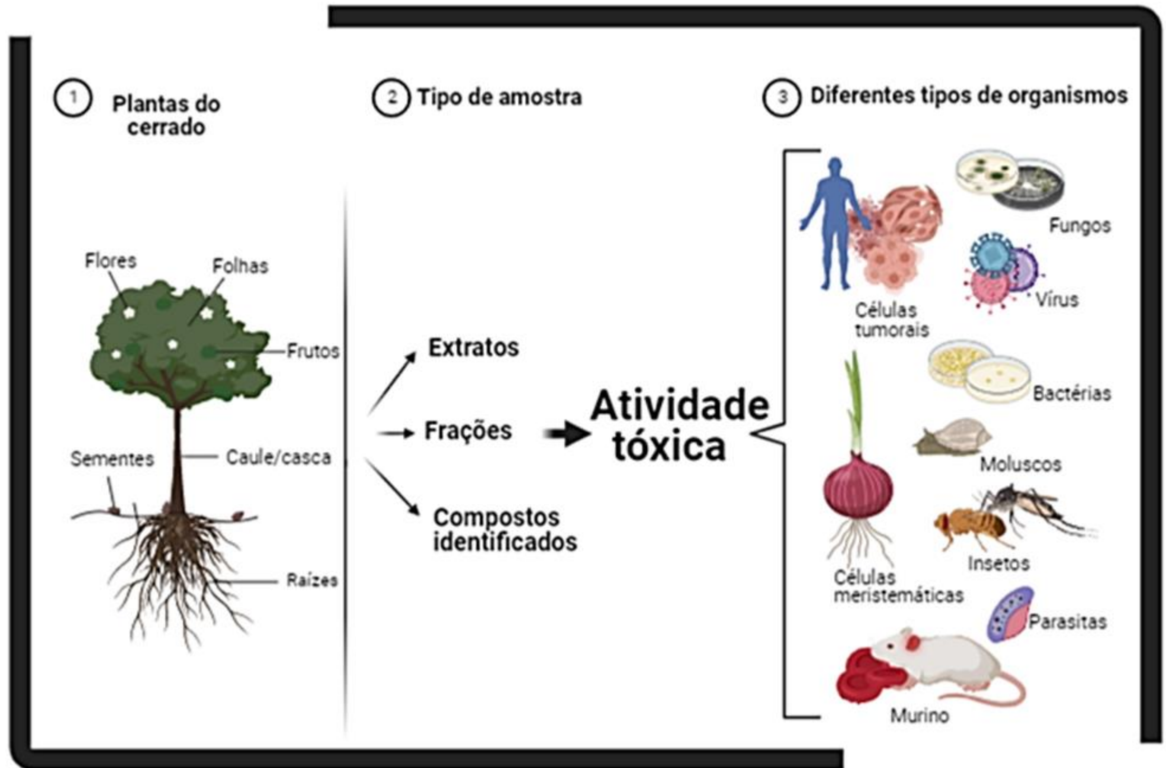
- Preparo da infusão e fracionamento do extrato aquoso de folhas de *Vernonanthura polyanthes*;
- Definir doses a serem administradas aos animais;
- Realizar a exposição e o manejo dos animais de acordo com os protocolos já estabelecidos;
- Avaliar o potencial citogenotóxico de *Vp*LAE e n-BF, associados ou não a DXR em eritroblastos da medula óssea de camundongos por meio do teste do MN;
- Avaliar o potencial genotóxico de *Vp*LAE e na n-BF, associados ou não a DXR em eritroblastos da medula óssea de camundongos por meio do ensaio cometa;
- Avaliar o perfil químico de *Vp*LAE e n-BF por cromatografia líquida acoplado à espectrometria de massas, com intuito de identificar os metabólitos presentes;
- Realizar análises *in silico* para avaliação da farmacocinética e farmacodinâmica dos compostos presentes no *Vp*LAE e na n-BF;
- Determinar *in silico* o perfil toxicológico dos compostos presentes no *Vp*LAE e na n-BF;
- Proceder a predição da atividade biológica dos compostos presentes no *Vp*LAE e na n-BF;
- Realizar uma ancoragem molecular para avaliação da interação entre ligante e receptor.

Resultados

3. Artigo 1

Potencial tóxico de plantas do cerrado em diferentes organismos

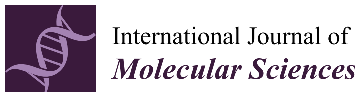
Resumo gráfico



Resumo

O Cerrado possui muitos compostos que têm sido utilizados como biopesticidas, herbicidas, medicamentos e outros devido ao seu alto potencial tóxico. Assim, esta revisão tem como objetivo apresentar informações sobre a toxicidade das plantas do Cerrado. Para tanto, foi realizada uma revisão nas bases de dados PubMed, Science Direct e Web Of Science. Após a aplicação dos critérios de exclusão, 187 artigos publicados nos últimos 20 anos foram selecionados e analisados. Informações detalhadas sobre a preparação do extrato, parte da planta utilizada, dose/concentração testada, sistema modelo e ensaio empregado foram fornecidas para diferentes atividades tóxicas descritas na literatura, a saber: citotóxica, genotóxica, mutagênica, antibacteriana, antifúngica, antiviral, inseticida, antiparasitária e atividades moluscicidas. Além disso, foram discutidos os passos para realizar pesquisas sobre toxicidade de plantas e os métodos mais comuns empregados. Esta revisão sintetizou e organizou as pesquisas disponíveis sobre os efeitos tóxicos das plantas do Cerrado, que poderiam contribuir para o futuro desenho de novos produtos ambientalmente seguros.

Palavras-chave: savana brasileira; compostos químicos; microrganismos; produtos naturais; extrato vegetal; células tumorais



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Review

Toxic Potential of Cerrado Plants on Different Organisms

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Abstract: Cerrado has many compounds that have been used as biopesticides, herbicides, medicines, and others due to their highly toxic potential. Thus, this review aims to present information about the toxicity of Cerrado plants. For this purpose, a review was performed using PubMed, Science Direct, and Web Of Science databases. After applying exclusion criteria, 187 articles published in the last 20 years were selected and analyzed. Detailed information about the extract preparation, part of the plant used, dose/concentration tested, model system, and employed assay was provided for different toxic activities described in the literature, namely cytotoxic, genotoxic, mutagenic, antibacterial, antifungal, antiviral, insecticidal, antiparasitic, and molluscicidal activities. In addition, the steps to execute research on plant toxicity and the more common methods employed were discussed. This review synthesized and organized the available research on the toxic effects of Cerrado plants, which could contribute to the future design of new environmentally safe products.

Keywords: Brazilian savanna; chemical compounds; microorganisms; natural products; plant extract; tumor cells

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1. Introduction

Among the natural products found in plants, secondary metabolites are particularly important for humans [1]. These compounds exhibit different biological activities and have a wide range of uses. Secondary metabolites have been used as biopesticides, herbicides, cosmetics, and food additives, and have been used to improve human health significantly [1]. Secondary metabolites have been used in pharmaceutical product development, with approximately 50% of all drugs currently in clinical trials being derived from plants [2].

Although secondary metabolites are mainly used for beneficial biological activities, some are highly toxic [3]. The toxicity of a substance concerns its ability to cause harmful effects, which can be observed in a single cell, a group of cells, an organ system, or the entire body. Secondary metabolites can act by different mechanisms to exert toxic effects, making these natural compounds very useful in the pharmaceutical, agricultural, and food industries.

Identifying new natural compounds with specific toxicities is essential to reduce the use of synthetic chemicals that lead to increased resistance in pests or pathogens in both the agricultural and medical sectors. Drug discovery has developed significantly in recent decades but an urgent need remains for less toxic drugs with greater efficacy and economic accessibility. Plant-derived bioactive phytochemicals are promising novel

compounds that could address some of these problems. Therefore, there is a continuous need to explore new active molecules with different mechanisms of action within the plant kingdom. Secondary metabolites in plants are defensive toxic compounds capable of inhibiting vital processes when touched and/or ingested. Phytochemical biomolecules can maximize the effectiveness and specificity of future drug design because they often have specific or multiple targets, and are both economically and ecologically sustainable [4,5].

The vast and unique biodiversity of the Cerrado biome contains many bioactive compounds [6], which enable Brazilian researchers to carry out sustainable research and to develop innovative products based on these compounds. The Brazilian Cerrado has 5% of the world's biodiversity and 44% of the Brazilian flora [7–9]. This biome comprises a mosaic of various types of vegetation consisting of plant formations ranging from grassland, savanna, and even forest physiognomies, such as dry forests and gallery forests [10]. This diversity of environments influences the abundance of herbaceous, shrub, arboreal, and vine plants, consisting of more than 12,000 species that occur spontaneously in the Cerrado domain, with a high degree of endemicity [9,11,12]. The Fabaceae, Myrtaceae, Melastomataceae, Lauraceae, and Rubiaceae families are the most prominent in this biome regarding species richness [13]. The Cerrado flora is used by traditional populations (quilombolas, riverside dwellers, healers, and indigenous people). Various Cerrado plants, such as *Caryocar brasiliense*, *Mauritia flexuosa*, *Hancornia speciosa*, *Dypteryx alata*, and *Eugenia dysenterica*, are used ancestrally by local people as food and for therapeutic purposes in the treatment of various diseases [14,15]. It is important to highlight that the knowledge of these traditional populations associated with the use and application of natural products from the Cerrado contributes to the institution of this biome as a national heritage of great importance.

Cerrado plants have many secondary metabolites that act alone or synergistically to produce beneficial or harmful bioactivities depending on the point of view. For example, a toxic activity of a Cerrado biomolecule against insects could be beneficial to humans because we could use this valuable information to develop products to control disease vectors or agricultural plagues. Thus, in this review, we aimed to synthesize the information available about the toxicity of Cerrado plants, especially the secondary metabolites, on different organisms. This information provides the basis for future studies to develop novel bioactive compounds based on these plants for the control of human diseases and agricultural pests, and highlights the importance and fragility of this biome. Ongoing conservation of the Cerrado biome is vital for sustaining local communities and preserving endemic plant biodiversity.

2. Results and Discussion

2.1. Toxic Activity of Cerrado Plants

Although Cerrado plants are used in traditional medicine (Table 1), their biological activity is often not scientifically determined and their toxicity is unknown. Based on the literature search, the most common toxic qualities of Cerrado plants are antibacterial, antiparasitic, cytotoxic, insecticide, antifungal, and antiviral activities (Figure 1a and Tables S1–S10). In total, 194 different plant species from the Cerrado biome with potential toxic activity were identified in this literature search (Tables S1–S10). The species *Cochlospermum regium* (Bixaceae) was mentioned in most studies ($n = 14$) and had the following bioactivities: antibacterial, antifungal, cytotoxic, and mutagenic (Figures 2 and 3). *C. regium* is a shrub widely distributed in Brazil and requires careful conservation based on the medicinal potential of its roots (Table 1). Since the harvesting of the roots kills the plant, it is in danger of being overexploited [16]. *E. dysenterica* (Myrtaceae) has the widest array of different bioactivities among plants included in the literature search, including antibacterial, antifungal, antiviral, cytotoxic, antiparasitic, molluscicide, and mutagenic activities (Figures 2 and 3). *E. dysenterica* is native to the Cerrado and is highly regarded by local populations for its medicinal uses [15]. Different parts of this plant are used in tradi-

tional medicine to treat various disorders (Table 1). The wide distribution and popularity of these species contributed to the high number of studies on their bioactive compounds.

Table 1. Ethnobotanical data for the Cerrado biome plant species included in the present review.

Family/Scientific Name	Popular Name	Popular Use	Reference
Anacardiaceae			
Anacardium occidentale L.	Caju	Treatment of malaria and yellow fever	[17]
Astronium urundeuva (M.Allemão) Engl.or *Myracrodruon urundeuva* Allemão	Aroeira	Antiseptic for external ulcers	[18]
Schinus terebinthifolius var. *radiannus* Engl.	Aroeira-de-brejo and aroeira-da-praia	Treatment of leprosy and tumors	[19]
Annonaceae			
Anaxagorea dolichocarpa Sprague & Sandwith	Bananinha	Treatment of grippe and cold	[20]
Annona coriacea Mart.	Aaraticum	Treatment of dermatitis, and used as a depurative agent	[21]
Annona crassiflora Mart.	Araticum or marolo	Treatment of chronic diarrhea	[19]
Annona mucosa Jacq.	Araticum, Graviola Brava, Condessa, Fruta de Conde, Biribá, Fruta de Condessa, Fructa da Komdessa	N/F	[22]
Cardiopetalum calophyllum Schltdl.	Imbirinha	N/F	[22]
Duguetia furfuracea (A. St. Hil.) Benth & Hook	Araticum do cerrado or ata brava	Treatment of rheumatism and renal colic, and used as antihyperlipidemic and anorexic agent	[23]
Duguetia lanceolata A.St.-Hil.	Pindaíba, Pindahiba, Pindaúba, Capreuva Vermelho	N/F	[22]
Xylopia aromatica (Lam.) Mart.	Pimenteira	Treatment of digestive problems and inflammation, and used as tonic and aphrodisiac	[24]
Xylopia emarginata Mart.	Pindaíba-do-brejo	N/F	[25]
Apocynaceae			
Aspidosperma macrocarpon Mart. & Zucc.	Peroba-gigantedo-cerrado	Antimalaric and anti-inflammatory	[26]
Aspidosperma tomentosum Mart.	Guatambu	Treatment of gastritis	[27]
Hancornia speciosa Gomes	Mangaba, Mangabeira	Treatment of gastrointestinal diseases, tuberculosis, diabetes, hypertension, dermatitis, diarrhea, ulcers, gastritis, acne, warts, and cancer, and used as anti-inflammatory	[28,29]
Himatanthus drasticus (Mart.) Plumel	Janaúba and Tiborna	Treatment of cancer	[30]
Himatanthus obovatus (Müll. Arg.) Woodson	Angelica	Treatment of anemia, wound healing, cholesterol, pain, nose bleeding, hypertension, uterine inflammation, labyrinthitis, pneumonia, worms, and vitiligo, and is a blood cleanser and muscular relaxant	[27]
Secondatia floribunda A.DC.	Catuaba-de-rama or Catuaba-decipó	Treatment of sexual impotence, nerve complications, depression, rheumatism, and inflammatory conditions	[31]
Arecaceae			
Attalea phalerata Mart. ex Spreng.	Bacuri	Pulmonary decongestant, anti-inflammatory for joints, and is antipyretic	[32]
Attalea speciosa	N/F	N/F	
Mauritia flexuosa L.f.	Buriti	Treatment of burns and used as a potent vermifuge	[22]
Aristolochiaceae			
Aristolochia cymbifera Mart. & Zucc	Caçaú, milhome, Crista-De-Galo	Treatment of oral diseases	[33,34]
Asteraceae			
Ageratum conyzoides L.	Mentrasto	Treatment of malaria, ulcers, dysentery, and yellow fever, and is a purgative, febrifuge, anti-microbial, and anti-lytic agent	[35]
Ageratum fastigiatum (Gardner) R.M.King & H.Rob.	Mata pasto	Cicatrizing and anti-inflammatory, and is an analgesic and antimicrobial agent	[36]
Aldama discolor (Baker) E.E.Schill. & Panero	N/F	N/F	[22]
Baccharis dracunculifolia DC.	Alecrim-do-campo and vassourinha	Anti-inflammatory agent mainly for the treatment of gastrointestinal diseases	[37]
Chromolaena squalida (DC.) R.M.King & H.Rob.	N/F	N/F	[22]
Cyrtocymura scorpioides (Lam.) H.Rob.	Piracá, Enxuga or Erva-de-São-Simão	Treatment of dermal diseases, including chronic wounds and ulcers	[38]
Eremanthus incanus (Less.) Less.	N/F	N/F	[22]
Lychnophora pinaster Mart.	Arnica	Treatment of inflammation, pain, rheumatism, contusions, bruises, and insect bites	[39]
Lychnophora trichocarpha Spreng.	Arnica	Treatment of inflammation and rheumatologic diseases, and is an insecticide agent	[39]
Mikania laevigata Sch.Bip. ex Baker	Guaco	Treatment of inflammatory disorders, such as bronchitis, chronic lung diseases, and bronchial asthma	[40]
Piptocarpha rotundifolia (Less.) Baker	N/F	N/F	[22]
Pseudogynoxys cabrerae H.Rob. & Cuatrec.	N/F	N/F	[22]
Vernonanthura polyanthes (Spreng.) A.J. Vega & Dematt.	Assa-peixe	Treatment of bronchitis, coughing, bruises, ocular inflammation, rheumatism, hemorrhoids, kidney disorders, and uterine infections	[41]
Bignoniaceae			
Adenocalymma nodosum (Silva Manso) L.G.Lohmann	N/F	N/F	[22]
Amphilophium elongatum (Vahl) L.G.Lohmann	N/F	N/F	[22]
Anemopaegma setilobum A.H. Gentry	N/F	N/F	[22]

Table 1. *Cont.*

Family/Scientific Name	Popular Name	Popular Use	Reference
Arrabidaea brachypoda (DC.) Bureau	Cipó-una, tintureiro or cervejinha do campo	Treatment of kidney diseases and painful joints (arthritis)	[42]
Callichlamys latifolia (Rich.) K. Schum.	Cipó-guachana amarelo	Treatment of intestinal colic and skin conditions	[43]
Cuspidaria sceptrum (Cham.) L.G.Lohmann	Lírio-do-campo	N/F	[22]
Cybistax antisyphilitica (Mart.) Mart.	Ipeˆ-branco, cincofolhas and pe′-de-anta	Depurative, antisyphilitic, and diuretic agents	[44]
Distictella elongata (Vahl) Urb.	N/F	N/F	[22]
Fridericia chica (Bonpl.) L.G.Lohmann	Carajuru or guajuru-piranga or Crajiru	Wound healing	[45]
Fridericia craterophora (DC.) L.G.Lohmann	Cipó-una, tintureiro or cervejinha do campo	Treatment of kidney diseases	[43]
Fridericia formosa (Bureau) L.G.Lohmann	N/F	N/F	[22]
Fridericia platyphylla (Cham.) L.G.Lohmann	Cipó-una, tintureiro or cervejinha do campo	Treatment of kidney diseases	[46]
Fridericia samydoides (Cham.) L.G.Lohmann	N/F	N/F	[22]
Jacaranda cuspidifolia Mart.	Jacarandá, caroba, caiuá, caroba-branca, pau-de-colher, dacarandá-de-minas	Treatment of syphilis and gonorrhea, and is an antimycobacterial activity	[47]
Pyrostegia venusta (Ker Gawl.) Miers	Cipó-de-são-joão	General tonic and used to treat diarrhea, vitiligo, and coughing	[48]
Zeyheria tuberculosa (Vell.) Bureau ex Verl.	Ipê Felpudo	Treatment of cancer and dermatosis	[49]
Bixaceae			
Cochlospermum regium (Mart. ex Schrank) Pilg.	Algodãozinho-do-campo, algodãozinho-do-cerrado, algodãobravo, periquiteira, algodão-do-mato, algodãozinho, algodãozinhocravo, algodoeiro-do-campo, butua-de-corvo, periquiteira-do-campo, pacote, ruibarbo-do-campo and sumaúma-do-igapó	Treatment of ulcers, arthritis, intestinal infections, gynecological infections, and skin diseases	[50]
Calophyllaceae			
Calophyllum brasiliense Cambess.	Guanandi, olandi, and jacareúba	Anti-inflammatory, used for treatment of rheumatism, vein-related problems, hemorrhoids, gastric ulcers, pain, inflammation, diabetes, hypertension, and herpes	[51]
Kielmeyera coriacea Mart. & Zucc.	Pau-Santo	Antiparasitic, antifungal, antibacterial, and antimalaria, used for treatment of schistosomiasis and leishmaniosis	[52]
Kielmeyera lathrophyton Saddi	Murici-pequeno	Treatment of schistosomiasis, leishmaniasis, malaria, and both fungal and bacterial infections	[53]
Caryocar brasiliense Cambess.	Pequi	Anti-inflammatory and used for treatment of high blood pressure	[54]
Caryocar coriaceum Wittm.	"pequi", "piqui", "pequá", "Thorn almond", "horse bean" or "Brazilian almond	Anti-inflammatory and used to promote healing	[55]
Celastraceae			
Cheiloclinium cognatum (Miers) A.C.Sm.	Bacupari, pitombinha	Treatment of fever and edema	[56]
Salacia crassifolia (Mart. ex Schult.) G. Don	Bacupari, cascudo, and saputá	Treatment of pediculosis, kidney disease, gastric ulcers, skin cancer, malaria, chronic coughs, and headaches	[57]
Clusiaceae			
Garcinia gardneriana (Planch. & Triana) Zappi	Bacupari	Treatment of inflammation, pain, urinary infections, and other infections	[58]
Combretaceae			
Terminalia argentea Mart. & Zucc.	Capitão, capitão-do-campo or pau-de-bicho	Treatment of gastric ulcers, bronchitis and hemorrhages, ulcers, flu with fever, diarrhea, inflammation, wounds, cramps, cancer, rheumatism, and body pains, and used as tranquilizer, diuretic, and anti-anxiety agent	[59]
Terminalia fagifolia Mart.	Mirindiba, capitão do mato, capitão, capitão-do-cerrado and cachaporra do gentio	Treatment of oral mucosa lesions by *Candida* strains, tumors (breast cancer), and diseases of the gastrointestinal tract (diarrhea and gastritis)	[60]
Connaraceae			
Connarus suberosus Planch	Tropeiro or bico de papagaio, galinha-choca	Treatment of diarrhea and heart problems	[61]
Costaceae			
Chamaecostus subsessilis (Nees & Mart.) C.D.Specht & D.W.Stev.	N/F	N/F	[22]
Costus spiralis (Jacq.) Roscoe	Cana-de-macaco or cana-do-brejo	Treatment of urinary infections and kidney stones	[62]
Dilleniaceae			
Curatella americana L.	Lixeira cajueiro-bravo	N/F	[63]
Davilla elliptica A.St.-Hil.	Lixinha	Astringent tonic and purgative, used for treatment of swellings, especially of the lymphatic nodes and testicles	[64]
Davilla nitida (Vahl) Kubitzki	Cipó-de-fogo, sambaibinha, lixeirinha de rama	Treatment of gastric problems	[64]
Davilla rugosa Poir	Sambaibinha, Cipó de Carijó, Cipó-caboclo,	Treatment of ulcers	[18]
Ebenaceae			
Diospyros hispida A. DC.	Olho-de-boi	Treatment of pain and leprosy	[27]
Diospyros lasiocalyx (Mart.) B.Walln.	Olho-de-boi	Treatment of pain and leprosy	[27]
Ericaceae			
Gaylussacia brasiliensis Meisn	Camarinha	Treatment of inflammation	[65]
Erythroxylaceae			
Erythroxylum daphnites Mart.	Chapadinho, fruta-de-tucano, mercúrio and pimenta	N/F	[22]
Erythroxylum subrotundum A.St.-Hil.	N/F	N/F	[22]
Erythroxylum suberosum St. Hil.	Cabelo de negro	Abortive and used for prevention of inflammatory processes	[66]

Table 1. *Cont.*

Family/Scientific Name	Popular Name	Popular Use	Reference
Euphorbiaceae			
Alchornea triplinervia (Spreng.) Müll.Arg.	Tapiá	Treatment of gastric disturbances	[67]
Croton heliotropiifolius Kunth	velame	Treatment of influenza, general pain, inflammation, dermatitis, gastrointestinal disturbances, malaise, poor digestion, boils, and back pain, and used as a depurative agent	[21]
Croton urucurana Baill.	Sangra-d'agua	Treatment of cancer, prostate cancer, diabetes, stomach pain, gastritis, uterine inflammation, kidneys, and ulcers	[27]
Croton velutinus Baill.	Pimentinha	Treatment of cancer	[68]
Fabaceae			
Anadenanthera colubrina (Vell.) Brenan	Angico	Treatment of inflammation, respiratory problems related to infection (cough, influenza, and bronchitis), diarrhea, and toothache	[69]
Bauhinia holophylla (Bong.) Steud.	Pata-de-vaca	Treatment of diabetes and infections, and used as an analgesic, antidiarrheal, anti-inflammatory, and diuretic agent	[70]
Bowdichia virgilioides Kunth	Sucupira preta	Treatment of spinal pain, rheumatism, sexual impotence, bone pain, inflammation of the skin, general inflammation, inflammation of the uterus, wounds, general pain, back pain, vaginal inflammation, and throat pain, and used as a purifying agent	[47]
Copaifera langsdorffii Desf.	Copaíba	Anti-rheumatic, anti-inflammatory, and emollient agent; used as a general tonic; and used for treatment of wounds and infections of the bladder, inflammation, stomach aches, and uterine inflammation	[71]
Copaifera multijuga Hayne	Copaiba	Anti-rheumatic, anti-inflammatory, and emollient agent; used as a general tonic; and used for treatment of wounds and infections of the bladder, inflammation, stomach aches, and uterine inflammation	[72]
Dimorphandra mollis Benth.	Faveiro-de-anta	Treatment of inflammation (swelling/pain)	[56]
Dipteryx alata Vogel	Cumbaru	Treatment of dysentery, pain, throat pain, flu, snakebites, and coughs	[27]
Enterolobium gummiferum (Mart.) J.F.Macbr.	N/F	N/F	[22]
Eriosema crinitum (Kunth) G. Don	Pustemeira	Treatment of inflammatory diseases, including inflammatory skin disorders such as psoriasis	[73]
Hymenaea courbaril L.	Jatobá ORFarinheira	Treatment of diarrhea, dysentery, intestinal colic, pulmonary weakness, and chronic cystitis	[63]
Hymenaea martiana Hayne	Jatoba-da-mata	Treatment of gastrointestinal, urinary, and respiratory tract infections, as well as for inflammatory disorders (rheumatoid arthritis), liver problems, respiratory disorders, inflammation, and stomach and chest aches	[74]
Hymenaea stigonocarpa Mart. ex Hayne	Jatobá-do-cerrado	Treatment of diarrhea, infections, prostate cancer, anemia, leukemia, anxiety (tranquilizer), weakness, cataracts, eye irritation, asthma, bronchitis, flu, pneumonia, gastritis, indigestion, ulcers, inflammation, rheumatism, uterine and ovary infections, prostate diseases, kidneys, wounds, bone fractures, body pain, throat infections, throat inflammation, coughing with catarrh, and vomiting, and used as a depurative, expectorant, female intimate-cleaning, and lung-strengthening agent, and general tonic	[59]
Inga laurina (Sw.) Willd.	Ingá Branco	Anti-inflammatory and antidiarrheal, nasal decongestant, used for treatment of skin conditions and earaches, and for cleaning teeth	[75]
Lachesiodendron viridiflorum (Kunth) P.G. Ribeiro, L.P. Queiroz & Luckow	Surucucu	N/F	[22]
Peltophorum dubium (Spreng.) Taub.	N/F	N/F	[22]
Plathymenia reticulata Benth.	Candeia, vinhático	Treatment of hemorrhaging, swelling of injuries, liver, kidneys, and wounds	[76]
Pterodon emarginatus Vogel	Sucupira and sucupira-branca	Anti-inflammatory and analgesic agent	[56]
Stryphnodendron adstringens (Mart.) Coville	Barbatimão, casca-da-virgindade	Treatment of gynecological problems, diarrhea, and decubitus ulcers	[63]
Stryphnodendron polyphyllum Mart.	Barbatimão	Treatment of inflammation and infection, and used to promote healing	[77]
Stryphnodendron rotundifolium Mart.	Barbatimao	Treatment of leucorrhea and diarrhea; as an anti-inflammatory and antiseptic agent; and used to promote blood clotting and wound healing	[77]
Tachigali aurea Tul.	N/F	Treatment of scabies and used as an antimalarial agent	[53]
Vatairea macrocarpa (Benth.) Ducke	Amargoso, maleiteira and Angelim-do-Cerrado	Treatment of diabetes	[78]
Zornia brasiliensis Vogel	Urinária, urinana, and carrapicho	Diuretic agent and used for treatment of venereal diseases	[76]

Table 1. *Cont.*

Family/Scientific Name	Popular Name	Popular Use	Reference
Lamiaceae			
Hyptis crenata Pohl ex Benth.	Hortelã-brava or hortelã do campo	Treatment of gastrointestinal disturbances, including gastric ulcers	[79]
Hyptis passerina Mart. ex Benth.	N/F	N/F	[22]
Hyptis radicans (Pohl) Harley & J.F.B. Pastore	N/F	N/F	[22]
Lauraceae			
Aiouea trinervis Meisn	N/F	N/F	[22]
Nectandra amazonum Ness	Jigua or Canelo or Louro	N/F	[80]
Nectandra gardneri Meisn.	N/F	N/F	[22]
Nectandra hihua (Ruiz & Pav.) Rohwer	N/F	N/F	[22]
Nectandra lanceolata Nees	N/F	N/F	[22]
Nectandra megapotamica (Spreng.) Mez	Canela-lora, canela-preta or canela-do-mato	Treatment of rheumatism and pain	[81]
Ocotea lancifolia (Schott) Mez	Canela pilosa and laurel né	N/F	[82]
Ocotea velloziana (Meisn.) Mez	N/F	N/F	[22]
Loganiaceae			
Strychnos pseudoquina St. Hil.	Quina-quina	Treatment of digestive problems, anemia, diabetes, coughs, and headaches, and used as a vermifuge, depurative, and appetite-stimulating agent	[83]
Lythraceae			
Lafoensia pacari A.St.-Hil.	Mangava-brava, pacari, dedaleiro, louro-da-serra	Treatment of inflammatory conditions, gastric ulcers, wounds, fevers, and various types of cancer	[84]
Malpighiaceae			
Banisteriopsis argyrophylla (A. Juss.) B. Gates	Cipo-prata or cipó-folha-de-prata	Treatment of renal problems and used as an anti-inflammatory agent	[85]
Byrsonima coccolobifolia Kunth	Murici de flor rósea, murici-do-cerrado	Treatment of diarrhea	[63]
Byrsonima crassa A.Juss.	Murici-cascudo or Murici-vermelho	Treatment of snake bites, febrile illnesses, skin infections, diarrhea, and gastric disorders	[86]
Byrsonima intermedia A. Juss.	Murici-pequeno	Treatment of fevers, skin infections, stomach pain, diarrhea, and dysentery, and used as a diuretic and anti-asthmatic agent	[87]
Byrsonima verbascifolia (L.) Richard	Murici de flor amarela, murici-cascudo	Treatment of fever and diarrhea, and used as an astringent and mild laxative agent	[63]
Malvaceae			
Guazuma ulmifolia Lam	Mutamba, Chicomagro	Treatment of skin diseases and gastric ulcers	[88]
Melastomataceae			
Miconia albicans (SW.) Triana	Canela-develho	Treatment of rheumatoid arthritis, pain, and inflammation	[89]
Mouriri elliptica Martius	Puçá-preto or jaboticaba-do-cerrado, coroa-de-frade or coroa	Treatment of gastric ulcers and gastritis	[90]
Mouriri pusa Gardner	Pucá-preto, jaboticaba-do-cerrado	Treatment of gastric ulcers	[91]
Pleroma stenocarpum (Schrank et Mart. Ex DC.) Triana	N/F	N/F	[22]
Meliaceae			
Cabralea canjerana (Vell.) Mart.	Canjarana	N/F	[92]
Guarea guidonia (L.) Sleumer	Açafroa	Astringent, purgative, febrifuge, abortive, emetic, and anti-inflammatory agent	[26]
Guarea kunthiana A.Juss.	Jatuaúba	Antimalaric agent and used for treatment of stomach aches	[26]
Metteniusaceae			
Emmotum nitens Miers	Unha-d'anta, unha-de-anta	Treatment of hemorrhoids	[93]
Moraceae			
Brosimum gaudichaudii Trécul.	Inharé, mamacachorro, mamacadela	Treatment of infections, venereal diseases, furuncles, "impingem" (superficial skin mycoses), cancer, anemia, pneumonia, prickly heat, vitiligo, joint pain, inflammation, rheumatism, kidney diseases, and wounds, and used as a depurative and heart tonic agent	[93]
Myristicaceae			
Virola sebifera L.	Ucuúba-do-cerrado or mucuíba or Ucuúba, ucuúba branca-de-folha grande	Treatment of wounds and rheumatism	[18]
Myrtaceae			
Blepharocalyx salicifolius (Kunth) O.Berg	Murta	Treatment of respiratory diseases, coughs, colds, hypotension, rheumatism, hypoglycemia, diarrhea, leukorrhea, urethritis, and bladder diseases	[94]
Campomanesia adamantium (Cambess.) O. Berg	Gabiroba or guabiroba-do-campo or guavira	Antirheumatic, antidiarrheal, hypocholesterolemic, and anti-inflammatory, and used for treatment of cystitis and urethritis	[95]
Campomanesia sessiliflora (O.Berg) Mattos	N/F	N/F	[22]
Campomanesia velutina (Cambess) O. Berg	Gabiroba, guavira, cambuci	Treatment of diarrhea and intestinal cramps	[93]
Eugenia dysenterica (Mart.) DC.	Cagaiteira, cagaita	Purgative agent for treatment of diarrhea	[63]
Eugenia involucrata DC.	Pitanga vermelha or cereja pitanga do cerrado	Hypotensive, diuretic, antimicrobial, hypoglycemiant, and anti-inflammatory agent	[96]
Eugenia klotzschiana O.Berg	Pêra-do-cerrado, Cabacinha	N/F	[97]
Eugenia uniflora L.	Pitanga or pitangueira	Treatment of intestinal disorders and hypertension	[98]
Myrcia bella Cambess	Mercurinho	Treatment of gastrointestinal disorders and both hemorrhagic and infectious diseases	[99]
Myrcia linearifolia Cambess	N/F	N/F	[99]

Table 1. *Cont.*

Family/Scientific Name	Popular Name	Popular Use	Reference
Myrcia splendens (Sw.) DC.	N/F	Treatment of gastrointestinal disorders and both hemorrhagic and infectious diseases	[99]
Myrcia variabilis Mart. ex DC.	N/F	N/F	[22]
Psidium brownianum Mart. ex DC	Araçá-de-veado, murtinha do mato	Treatment of influenza and fever	[100]
Psidium guineense Sw	Goiabinha-araçá, araçá-do-campo, araçá verdadeiro or goiabinha selvagem	Treatment of inflammation and gastrointestinal disorders, and used as a diuretic agent	[101]
Psidium laruotteanum Cambess.	Araçá-Cascudo	N/F	[22]
Psidium myrsinites DC	Araçá	Treatment of cicatrization and diarrhea	[22]
Psidium cattleyanum Sabine	araça-rosa, araça-vermelho, or araça do campo	Adstringent, hepatoprotective, antidiarrheal, and analgesic agent	[102]
Nyctaginaceae			
Neea theifera Oerst.	N/F	N/F	[22]
Ochnaceae			
Ouratea castaneifolia (DC.) Engl.	Farinha-seca or mangue-do-mato or Tuiohy	Tonic and astringent agent	[20]
Ouratea semiserrata (Mart. & Nees) Engl.	N/F	N/F	[22]
Ouratea spectabilis (Mart.) Engl.	Folha-de-serra or batiputá	Treatment of diseases of the liver and skin	[103]
Phytolaccaceae			
Gallesia integrifolia (Spreng.) Harms	Pau-d'alho or garlic plant	Treatment of microbial, respiratory, and skin infections	[104]
Piperaceae			
Piper aduncum L.	Matico	Anti-inflammatory and antiseptic agent for the promotion of wound healing and for treatment of rheumatic conditions and diarrhea	[105]
Polygonaceae			
Polygonum spectabile Mart.	Erva-de-bicho	Stimulant and anti-helminths agent, and for treatment of hemorrhoids, diarrhea, ulcers, and gingivitis	[46]
Primulaceae			
Myrsine guianensis (Aubl.) Kuntze	Caapororoca, capororoca and pororoca	Antiseptic, antiparasitic, and contraceptive agent	[106]
Proteaceae			
Roupala montana var. *brasiliensis* (Klotzsch) K.S.Edwards	Carne-de-vaca, Bosta-de-urubu	Treatment of intestinal and non-specific blood disorders	[66]
Rubiaceae			
Genipa americana L.	Jenipapo	Treatment of bronchitis, diabetes, and kidney disease	[27]
Psychotria deflexa DC.	N/F	N/F	[22]
Psychotria prunifolia (Kunth) Steyerm.	N/F	N/F	[22]
Palicourea rigida Kunth	Gritadeira, bate caixa and douradão	Antifungal, diuretic, hypotensive, antiulcerogenic, cicatrizing, and anti-inflammatory agent, and for treatment of coughs, stomach aches, and kidney pains	[107]
Psychotria capitata Ruiz & Pav.	N/F	N/F	[22]
Psychotria hoffmannseggiana (Willd. ex Schult.) Müll.Arg.	N/F	N/F	[22]
Rutaceae			
Spiranthera odoratissima A. St.-Hi	manacá	Blood purgative and appetite-stimulating agent, and for treatment of renal and hepatic diseases, stomach aches, headaches, sore muscles, hepatic dysfunction, and rheumatism	[108]
Zanthoxylum rhoifolium (Lam.)	Mamica de cadela, mamica de porca	Roots are used as a febrifuge, digestant, and tonic; stem bark is used to treat flatulence, colic, dyspepsia, earaches, toothaches, and snake bites	[109]
Zanthoxylum riedelianum (Engl.)	Laranjeira-Brava, Limãozinho Branco, Mamonilha-De-Porca, Mamicão, Mama-De-Porca, Tamanquaré, Limãozinho	Analgesic agent for treatment of toothaches, inflammation, rheumatism, and skin stains	[110]
Salicaceae			
Casearia sylvestris Sw. var. sylvestris	Guaçatonga	Anti-inflammatory and anti-spasmodic agent, and for treatment of diarrhea, leprosy, fever, syphilis, herpes, and snake bites	[111]
Sapindaceae			
Cupania cinerea Poepp. & Endl.	N/F	N/F	[22]
Cupania vernalis Cambess.	Arco-de-barril, rabo-de-bugio	Treatment of inflammation and used as a febrifugic agent and tonic	[112]
Matayba guianensis Aubl.	Camboatá	N/F	[25]
Serjania lethalis A.St.-Hil.	Cipó-timbó, timbó	Piscicidal, used topically to treat pain	[19]
Serjania marginata Casar.	Cipó-uva or cipó-timbó	Treatment of gastric pain	[113]
Sapotaceae			
Pouteria ramiflora (Mart.) Radlk.	Curriola (curiola), brasa-viva, figo-do-cerrado, grao-de-galo, fruta-do-veado, massaranduba or maçaranduba, pessegueiro-do-cerrado, abiu-cutite, and pitomba-de-leite	Antihyperlipidemic agent and for treatment of worms, dysentery, pain, and inflammation	[114]
Pouteria torta (Mart.) Radlk	Guapeva, curiola, acá ferro, abiu do cerrado, and grão de galo	Antidysenteric	[115]
Simaroubaceae			
Simarouba versicolor A. St.-Hil.	Mata-barata	Insecticide, vermifuge, febrifuge, and antisyphilitic agent	[26]
Siparunaceae			
Siparuna guianensis Aubl.	Folha-santa, Negramina, Mõe-Hanakë, Limão-Bravo, Caápitiú, Capitiú	Tarminative, aromatic, stimulant, antidispeptic, and diuretic agent, and for treatment of back pain, rheumatism, and arthritis	[116]

Table 1. *Cont.*

Family/Scientific Name	Popular Name	Popular Use	Reference
Smilax brasiliensis Sprengel	Salsaparrilha or japecanga	Diuretic, diaphoretic, stimulant, anti-hypertensive, and antisyphilitic agent, and for treatment of arthritis, rheumatism, and skin disorders	[117]
Solanaceae			
Solanum lycocarpum A. St.-Hil.	Lobeira or fruta-do-lobo	Treatment of diabetes, obesity, and hypercholesterolemia	[118]
Solanum palinacanthum Dunal	Joá	Treatment of skin diseases	[119]
Styracaceae			
Styrax camporum Pohl	Laranjeira-do-mato	N/F	[22]
Styrax ferrugineus Nees & Mart.	Laranjinha do campo	Treatment of gastrointestinal diseases and fevers	[120]
Verbenaceae			
Lippia lupulina Cham.	N/F	Treatment of oral and throat infections	[121]
Lippia origanoides Kunth.	Salva-deMarajo and alecrim d'Angola	General antiseptic agent for the mouth, throat, and wounds, and for treatment of infant colic, diarrhea, indigestion, flatulence, heartburn, nausea, vaginal discharges, menstrual complaints, and fever	[122]
Lippia salviaefolia Cham.	N/F	N/F	[22]
Vitaceae			
Cissus erosa Rich.	Cipó-fogo	Treatment of warts and external ulcers	[20]
Vochysiaceae			
Qualea grandiflora Mart.	Pau-terra	Treatment of diarrhea and pain	[27]
Qualea multiflora Mart.	N/F	Treatment of external ulcers, gastric diseases, and inflammation	[123]
Qualea parviflora Mart.	Pau-terra, pau-ferro, pau-de-tucano	Treatment of diarrhea, blood diseases, intestinal colic, amebiasis, skin diseases, and inflammation, specifically ulcers and gastritis	[124]

N/F: Not Found.

2.2. Toxic Cerrado Plant Families

Diverse plant families can cause toxicity on different cells or organisms (Tables S1–S9). In the present review, we found 53 different plant families with toxic properties, the most represented of which were the Fabaceae and Myrtaceae families (Figure 1b). Fabaceae and Myrtaceae are the most frequently studied plant families in the Brazilian Cerrado and are also present in more than 80% of the localities sampled [13]. The large number of studies on these plant families may be due to their widespread occurrence, which means that they are easy to collect and more likely to be used as traditional medicine.

Some botanical families were significantly associated with bioactive properties (Figure 4). The Myristicaceae, Ericaceae, Polygonaceae, Vitaceae, and Ochnaceae families are associated with antiviral activity. The Siparunaceae, Phytolaccaceae, Euphorbiaceae, Aristolochiaceae, and Arecaceae are related to antibacterial activity. Nyctaginaceae is associated with antifungal activity. Sapindaceae, Malvaceae, Ebenaceae, and Solanaceae are associated with antiparasitic activity, while the Metteniusaceae family is associated with a molluscicidal activity. Piperaceae and Meliaceae are associated with insecticidal activity. Sapotaceae, Erythroxylaceae, Costaceae, Clusiaceae, Lythraceae, and Celastraceae are associated with cytotoxicity, predominantly against tumor cells (Table S1).

Other than cytotoxicity against tumor cells, Cerrado plants had low genotoxicity, mutagenicity, and toxic effects in acute and chronic treatment regimens using murine models (Figure 4 and Tables S1–S3). This low toxicity against mammals suggests that medicinal plants originating from the Brazilian Cerrado are generally safe to handle and could be used to develop safe and effective drugs, such as insecticides, antimicrobials, and antiparasitic drugs.

2.3. Experimental Design for Evaluating Plant Toxicity

The toxicity of plants is often complex and requires a careful experimental design to evaluate and characterize this toxic potential (Figure 5). First, it is necessary to choose the target plant species and the more appropriate part of the plant. Various approaches have been proposed, including (i) random selection based on plant availability, (ii) chemotaxonomic or phylogenetic selection based on known chemical classes in a particular genus or species, and (iii) ethnopharmacological selection based on the prior use of a particular plant

in local or traditional medical practice [125]. In the present review, most studies focused on plants' leaves, roots, and stems rather than fruit or seeds (Figure 1c). Secondary metabolites vary depending on the part of the plant consumed, with different amounts of specific secondary metabolites accumulating in different plant parts [126]. From a conservation perspective, it should be noted that the collection of root specimens usually leads to the death of the plant.

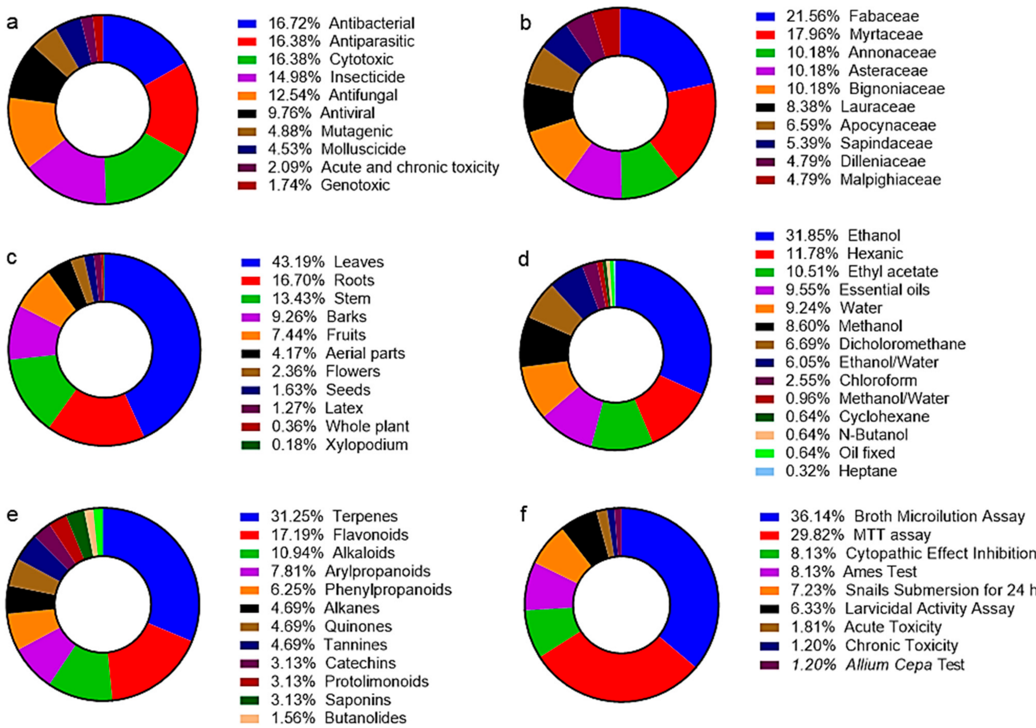

Figure 1. Summary of studies on the toxic activities of Cerrado plants included in the present review. The included manuscripts were screened to generate donut charts to visualize the proportions of (**a**) toxic activities studied, (**b**) plant families studied, (**c**) part of the plant studied, (**d**) type of extract or fraction studied, (**e**) classes of secondary metabolites studied, and (**f**) main techniques used to assess the toxicity of medicinal plants.

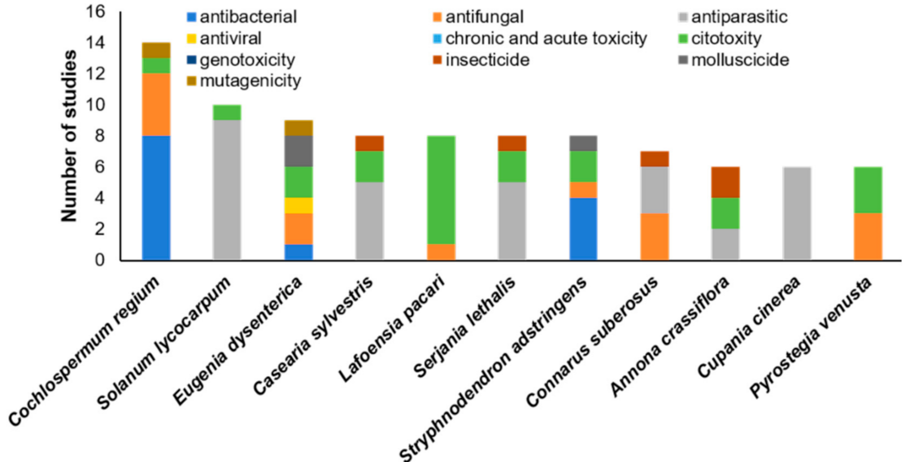

Figure 2. The bioactive properties of the Cerrado plant species that have been investigated in multiple studies. The most studied Cerrado species was *Cochlospermum regium*, while *Eugenia dysenterica* had the most diverse bioactive properties.

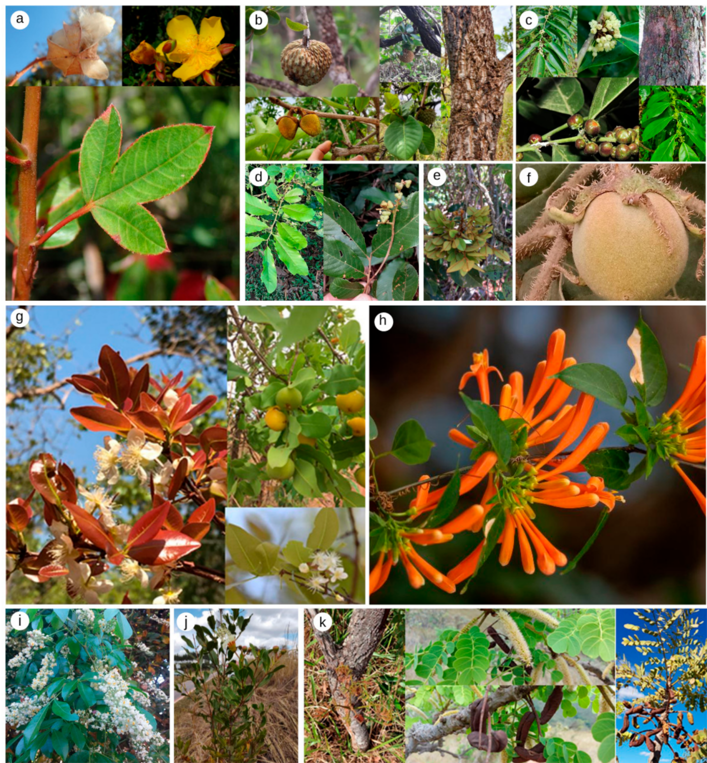

Figure 3. Most representative Cerrado species with toxic activity on different organisms according to this literature survey. (**a**) *Cochlospermum regium* (Mart. ex Schrank) Pilg. ("algodãozinho-do-campo"); (**b**) *Annona crassiflora* Mart ("araticum"); (**c**) *Cupania cinerea* Poepp. and Endl; (**d**) *Casearia sylvestris* Sw. var. sylvestris ("guaçatonga"); (**e**) *Connarus suberosus* Planch ("bico de papagaio"); (**f**) *Solanum lycocarpum* A.St.-Hil. ("lobeira"); (**g**) *Eugenia dysenterica* (Mart.) DC ("cagaita"); (**h**) *Pyrostegia venusta* (Ker Gawl.) Miers ("cipó-de-são-joão"); (**i**) *Serjania lethalis* A.St.-Hil. ("cipó-timbó"); (**j**) *Lafoensia pacari* A.St.-Hil. ("pacari"); and (**k**) *Stryphnodendron adstringens* (Mart.) Coville ("barbatimão"). All photographs were obtained from the Herbário da Universidade Estadual de Goiás (HUEG) and are available at https://www.gbif.org/pt/dataset/bbb1f181-3221-4a10-ad52-14f1da0dca26 (accessed on 23 October 2021).

After selecting the plant species, it is crucial to choose the collection site by considering the environmental factors that affect the production of secondary metabolites, such as season, circadian rhythm, temperature, altitude, atmospheric composition, soil fertility, humidity, solar radiation, wind, herbivory, air pollution, and soil pollution [126,127]. After collecting the plant samples, the correct identification of the species should preferably be carried out by a botanist and an exsiccate must be deposited into an herbarium [125].

Quality control and standardization of all processing stages are fundamental to the successful characterization of plant-derived bioactive compounds. These steps ensure the reproducibility and safety of plant-derived products [15]. Therefore, the collected material must be dried with air circulation and stored in low humidity and temperature. Grinding should only be performed when preparing the extracts. Extracts are usually prepared by percolation (cold extraction method is commonly used), by a Soxhlet extractor (hot extraction method), or by an acid base. A polar solvent (methanol or ethanol) is generally used for single extractions (cold or hot). For multiple extractions, three types of solvents are usually used: non-polar (hexane or petroleum ether), moderate polarity (chloroform or dichloromethane), and polar (methanol or ethanol) [125]. However, it is important to highlight that organic solvents are often toxic and reuse is not always possible. As a result, great efforts are being made to replace conventional organic solvents with less toxic solvents, such as supercritical fluids, ionic liquids at room temperature, perfluorinated hydrocarbons, and water, to decrease the release of toxic solvents into the water, air, and

soil, and thus to reduce the amount of environmental pollution [128]. In the present review, most studies (31.85%) used ethanol as the extraction solvent (Figure 1d). Ethanol is a suitable solvent for polyphenol extraction and is considered safe for both human and environmental health [129].

In general, the liquid extract obtained must be concentrated. Once the concentrated extract is obtained, several quality parameters are essential for standardization, such as pH, solid content, density, chemical marker content, and viscosity. After considering the chemical and physical stability of the chemical extract, drying is the most commonly used preservation method to obtain a stable plant product [15]. At this point, the investigation into the chemical constituents and/or toxic activities of the plant material can begin (Figure 5).

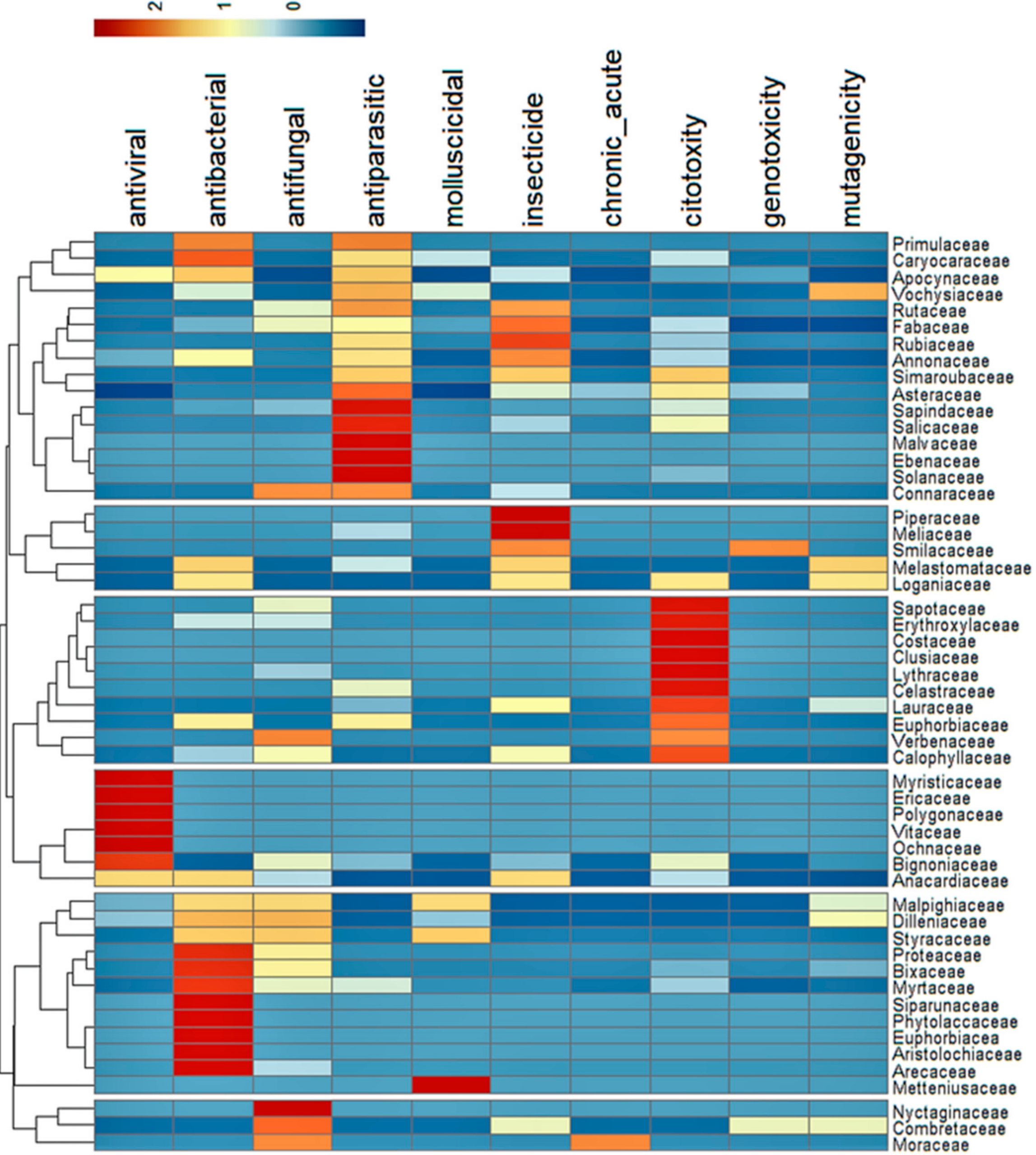

Figure 4. Heatmap of the plant families included in the present review grouped according to the frequency of the important bioactive properties associated with each family.

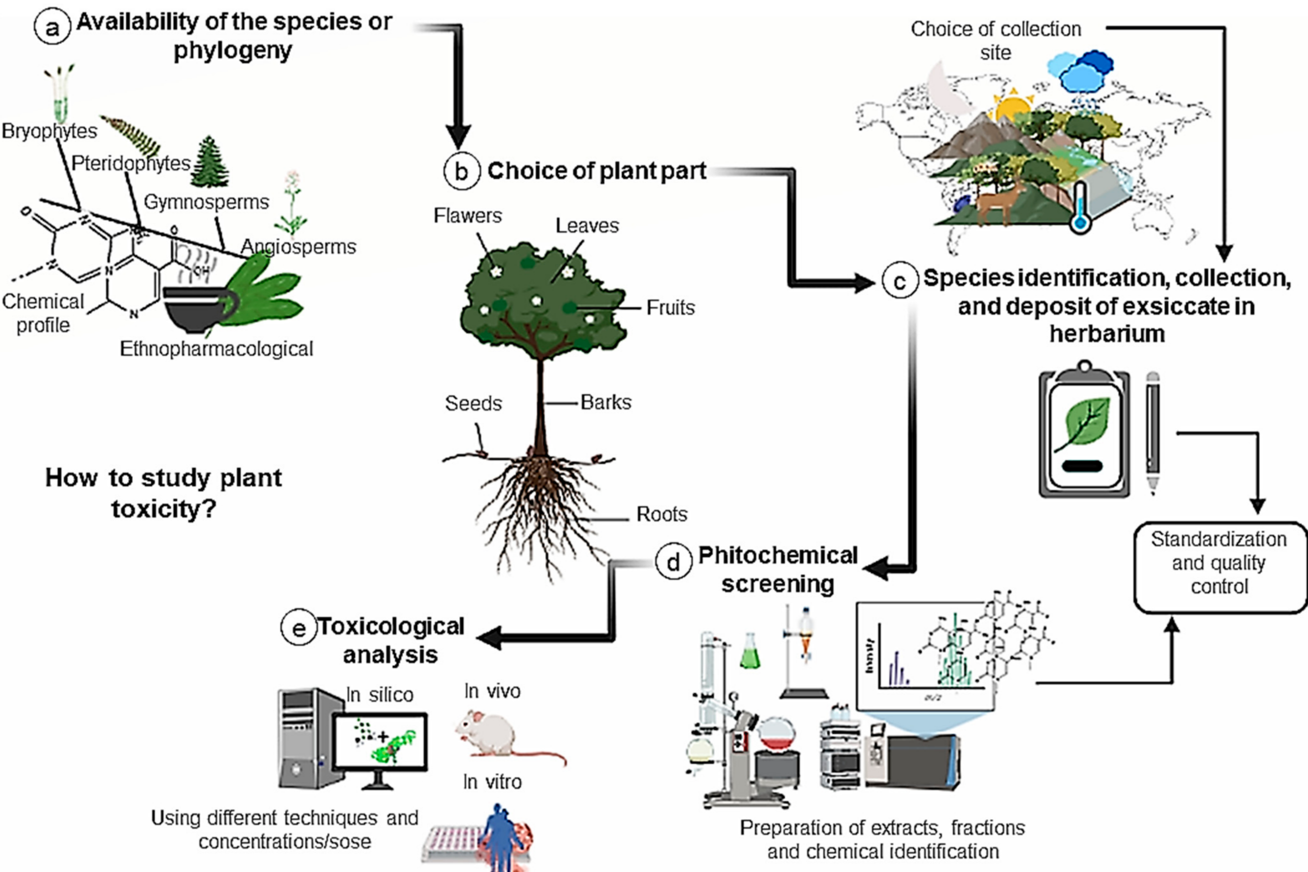

Figure 5. Proposed workflow for the effective study of plant toxicity. The study of plant toxicity should be carefully designed with the following steps carefully considered: (**a**) Selection of species according to plant availability, chemotaxonomy/phylogenetics, or ethnopharmacology. (**b**) Selection of the part of the plant to be used. It is important to understand that environmental factors also affect the production of secondary metabolites in different parts of the plant. (**c**) Identification of species, collection, and deposition of the exsiccate into an herbarium. (**d**) Obtainment of extracts by percolation, Soxhlet extractor, or acid-base strategies. Various quality parameters are used to standardize the preparation of samples (pH, solids content, density, content of chemical markers, and viscosity). At this stage, it is common to investigate the chemical constituents of the extract. (**e**) Toxicological analysis of the plant material using different experimental methods (in silico, in vitro, and/or in vivo).

The regulatory compliance of toxicity assessments is mainly handled globally by the Organization for Economic Cooperation and Development (OECD). Until recently, toxicological analyses were primarily performed using animal models. However, in vitro and in silico analyses are becoming more acceptable in regulatory settings as an alternative to animal testing [3,130], which can reduce the cost and duration of these tests, as well as reduce the number of experimental animals used [130]. Different toxic prediction tools have become more accurate and effective [130,131]. The "-omics era" (concerning genomic, transcriptomic, proteomic, and metabolomic data) has enabled researchers to derive hypotheses on the mechanisms of action and target identification of chemical compounds using high-throughput specialized instrumentation. These techniques offer whole-organism data rather than specific information on a particular pathway or target [132]. However, bioactive promiscuity, lack of complete genome sequence data, poor gene annotation, high costs, expensive and specific equipment, and the need for qualified, trained personnel remain as limiting factors in the use of omics technology in this field.

Different testing systems exist to determine if a substance is toxic and many different toxic endpoints may be considered such as cytogenotoxicity, carcinogenesis, hepatotoxicity,

renal toxicity, neurotoxicity, reproductive toxicity, endocrine toxicity, and immunotoxicity [133]. Toxicity assessments are essential for developing drugs, agrochemicals, cosmetics, food additives, and other important products.

The cytotoxic activity of plant extracts or isolated compounds can be determined using methods that evaluate (i) cell morphology variations using fresh cell preparations; (ii) cell membrane integrity using dye exclusion assays such as trypan blue and Congo red; and (iii) the inhibition of cellular metabolism using MTT and resazurin reduction assays, which evaluate the mitochondrial function of cells by measuring the activity of mitochondrial enzymes [125,134]. In the present review, the most commonly used method for determining the cytotoxic potential of Cerrado plants was the MTT assay (Figure 1f). This method to determine cytotoxicity and cell viability is easy to use, safe, and has high reproducibility [134].

A variety of laboratory methods can be used to evaluate or screen the in vitro antimicrobial activity of an extract or pure compound. The most well-known and simple methods to detect antibacterial and antifungal compounds are disk diffusion and broth or agar dilution methods. More sophisticated techniques, such as flow cytofluorometric and bioluminescent methods, can be employed but they are not widely used because they require specific and expensive equipment [135]. In the present review, the broth microdilution assay was the most commonly used method to determine the antibacterial and antifungal properties of Cerrado plants (Figure 1f). Dilution methods are appropriate for determining the minimum inhibitory concentration (MIC) of a compound or extract, which is the lowest concentration of an antimicrobial that inhibits visible growth [135]. The methods commonly used for in vitro evaluation of antiviral activity are based on the ability of viruses to replicate in cultured cells because they are obligate intracellular symbiotes. Some viruses cause cytopathic effects or form plaques. Others can produce specialized functions or cell transformations. Viral replication can also be monitored by detecting viral products, such as viral DNA, RNA, or polypeptides [136]. The cytopathic effect inhibition assay is one of the most reliable and robust assays for screening natural antiviral compounds [137]; is a rapid and sensitive method; and has been extensively used to detect the antiviral potential of Cerrado plants (Figure 1f).

Unlike assays used to determine the antibacterial, antifungal, and antiviral activity of plant products, bioassays for parasites tend to be highly species-specific [136]. To improve the performance of antiparasitic assays, the following should be carefully considered: (i) the use of a well-characterized, drug-sensitive parasite strain, with validated model availability, which is safe for the researcher, and (ii) the use of sensitive endpoint-reading techniques [136]. The cytotoxic potential of natural products on *Leishmania* spp. and *Trypanosoma* spp. was evaluated by the MTT assay, which was widely used in the articles included in the present review (Figure 1f).

Similar to antiparasitic assays, bioassays for substances that control insects are highly variable due to the abundance and variety of insects and their life cycle stages [138]. Notably, the insects used in the assay should have been standardized concerning species, age, and physiological state [138]. In general, topical application is used to study the insecticide potential of natural products because it has a faster response than ingestion and is independent of insect activity. The disadvantages of topical application are that the compound may not overcome penetration barriers, the application process is tedious, and the process requires manual dexterity [139,140]. Tests on larvae are preferred because insecticides that are effective on larval stages can prevent the development of the next generation of insects [140]. Bioassays performed under conditions that simulate management applications are also required; however, formulated products should be used to ensure standardization. On-host applications or field tests should be considered but present a particular challenge because of the possible interactions with the host [139]. The larvicidal activity assay is one of the most commonly used assays when studying natural compounds with insecticide potential (Figure 1f). However, topical tests are scarce in Cerrado plants.

2.4. Toxicity of Secondary Metabolites

Secondary metabolites are organic molecules that are not involved in the normal growth and development of an organism. The absence of secondary metabolites does not result in immediate death but rather in a long-term impairment of the organism's survivability, as they often play an essential role in plant defense. Toxicity is, therefore, an excellent strategy to inhibit the action of predators. Secondary metabolites act on the predators through multiple mechanisms (Figure 6). They can interact specifically or not specifically with proteins (enzymes, receptors, ion channels, and structural proteins), nucleic acids, biomembranes, and other cellular components [141,142]. The interaction with these different targets can disturb the vital components of the cellular-signaling system, resulting in dysregulated essential signaling in the nervous system (e.g., concerning neurotransmitter synthesis, storage, release, binding, re-uptake, receptor activation and function, and enzymes involved in signal transduction) or in interference with vital enzymes and blocking of metabolic pathways [143]. When interacting with nucleic acids, some secondary metabolites can have both mutagenic and antimutagenic roles, and act as a mutagen by directly binding to DNA, generating ROS, or inhibiting topoisomerase enzymes [144].

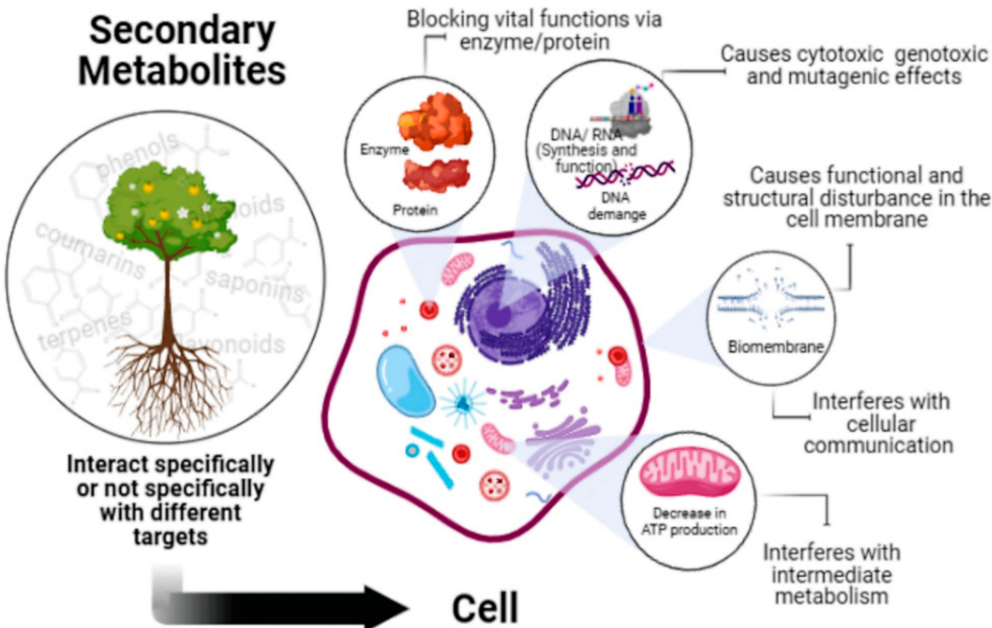

Figure 6. Mechanisms of action of secondary metabolites with cytotoxic effects. Secondary metabolites can interact specifically or not specifically with biomolecules, biomembranes, and other cellular components, disturbing the vital components of the cell.

Secondary metabolites can be simply classified into three main groups: (i) terpenes (such as plant volatiles, cardiac glycosides, carotenoids, and sterols); (ii) phenolics (such as phenolic acids, coumarins, lignans, stilbenes, flavonoids, tannins, and lignin); and (iii) nitrogen-containing compounds (such as alkaloids and glucosinolates) [145]. In the present review, 60 compounds with toxic activity were detected among the studied plants (Table S10 and Supplementary Material Figure S1). The most representative secondary metabolites isolated from Cerrado plants with toxic activities were terpenes, flavonoids, and alkaloids (Figure 1e). Many alkaloids are toxic and can cause death, even in small quantities. It seems that alkaloid function in plants and animals is linked to defense mechanisms, including antibiotic activities [145]. The beneficial antibiotic effects of plant secondary metabolites could therefore be similarly useful in human medical interventions, although care should be taken to establish safety profiles for plant-derived extracts.

3. Materials and Methods

The review was performed using the PubMed (*n* = 314), Science Direct (*n* = 2184), and Web of Science (*n* = 378) databases. In total, 2876 abstracts were selected using the following search terms: "Cerrado" AND "cytotoxic*" OR "genotoxic*" OR "insecticide*" OR "antiparasitic*" OR "antibacterial*" OR "antifungal*" OR "molluscicide*" OR "antiviral*" OR "chronic toxicity*" OR "acute toxicity*" OR "mutagenic*". The asterisk (*) was used as a wildcard and enabled the search of any letters in its place. The inclusion criteria were species (i) native to the Cerrado biome and (ii) presenting toxic activity. Gray literature and review articles were excluded (PubMed (*n* = 93), Science Direct (*n* = 1963), and Web of Science (*n* = 157)). Studies that overlapped were also excluded (*n* = 34). Thus, 2665 articles were considered to be outside the scope of this review and were excluded. A total of 187 articles published between 2000 (first record within the inclusion and exclusion criteria) and December 2020 were selected and analyzed (Figure 7).

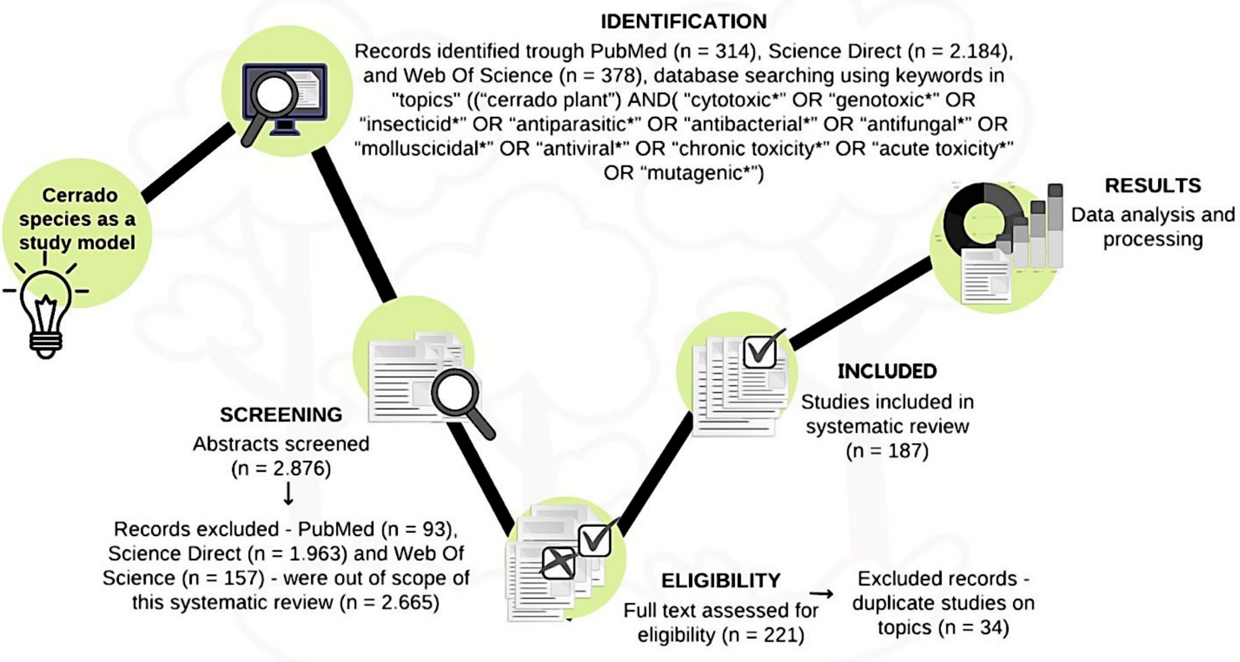

Figure 7. The experimental workflow used in the present review to identify articles containing information about Cerrado plants with toxic bioactivities. The workflow involved the identification, screening, eligibility assessment, and inclusion of available manuscripts from several online databases. During the search for the terms in the databases, the asterisk (*) was used as a wildcard and enabled the search of any letters in its place.

We extracted the species, part of the plant, type of extract, dose/concentration, activity, and extraction method used from each manuscript in our analysis. The plant species were then classified into their respective families according to the Flora do Brasil website [22]. The frequency of each type of toxic activity reported was associated with plant families by generating a heatmap in R [146] using the "pheatmap" package [147].

4. Conclusions

The present review summarizes the literature from the last two decades related to the toxicity of plant species from the Cerrado biome and the secondary metabolites that have been both identified and evaluated for their toxicity. The species and compounds reported in the present review have high cytotoxicity against tumor cells and low toxicity against non-tumor cells, indicating that Cerrado plants could be used to develop new anti-

cancer drugs. Plants from the Cerrado biome presented low genotoxicity, mutagenicity, and toxic effects on murine models in acute and chronic treatments. Moreover, Cerrado plants are effective against bacteria, fungi, viruses, insects, and parasites. In combination, these data suggest that Cerrado plants can be used to develop products that can be safely handled and administered (because of the low toxicity on mammals), including insecticides against urban and agricultural pests, antimicrobials, and antiparasitic products. The notable limitations of this review are the relatively low number of studies investigating the molluscicidal activity and the scarcity of associated omics data. We hope that this review supports the conservation of the Cerrado biome against anthropogenic activities, ensuring the preservation of the vast biodiversity and natural wealth provided by this unique biome.

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Author Contributions: J.D.R.: conceptualization, formal analysis, investigation, and writing—original draft preparation. F.M.C.: conceptualization and formal analysis. A.S.F.: investigation and formal analysis. J.M.M.: investigation. L.L.B.: writing—review and editing. L.C.-C.: writing—review and editing. L.M.d.A.: writing—review and editing. E.F.L.C.B.: conceptualization, formal analysis, investigation, writing, and supervision. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: Not applicable.” for studies not involving humans or animals. You might also choose to exclude this statement if the study did not involve humans or animals.

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Review

Toxic potential of Cerrado plants on different organisms

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Abstract: Cerrado has plenty of compounds that have been used as biopesticides, herbicides, cosmetics, medicines, and others due to their highly toxic potential. So, this review aims to bring information about the toxicity of Cerrado plants. For this, a review was performed using PubMed, Science Direct, and Web Of Science databases. After applying exclusion criteria, 187 articles published in the last 20 years were selected and analyzed. Detailed information about extract preparation, part of the plant used, dose/ concentration tested, model system, and assay employed was provided for different toxic activities described in the literature, namely cytotoxic, genotoxic, mutagenic, antibacterial, antifungal, antiviral, insecticidal, antiparasitic, and molluscicidal. In addition, the steps to execute research about plant toxicity and the more common methods employed were discussed. This review synthesized and organized the available research on the toxic effects of Cerrado plants, which could contribute to the future design of new environmental-safe products

Keywords: Brazilian savanna; chemical compounds; microorganisms; natural products; plant extract; tumor cells.

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(1) (2) (3)

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(8)

d-tocotrienol

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(25) (26) (27)

(28) (29) (30) (31)

Figure S1. Molecular structure of secondary metabolites isolated from Cerrado plant species. For names refers to Table S10. -R1=glucose; -R2=glucopyranosyl.

Table S1 Cytotoxic activity from different species of Cerrado. Information about part from plant and extract preparation, dose tested, model and method analyzed.

Family/Species	Part[1]	Extract[2]	Dose/Concentration	Activity against	Technique	Model[3]	Reference
Annonaceae							
Annona crassiflora Mart.	RB, RW or F	A, Eth or MA	5.36-230.12 and 6.0-24.9 μg/mL	Tumor cells	SRB and MTT assay	HCT-8, MDA-MB-435, SF-295, U251, MCF-7NCIADR/RES, NCI-H460, PC-3, OVCAR-03, HT-29, K562, and HaCaT	[1,2]
Asteraceae							
Baccharis dracunculifolia DC.	L	EA	200.0 and 400.0 μg/mL^{-1}	Murine cells	Trypan Blue Assay	V79 cells	[3]
Anacardiaceae							
Schinus terebinthifolius var. raddianus Engl.	L	HE or DM	1.1-41.8 μg/mL	Tumor cells	MTT assay	HCT-8, MDA-MB-435, and SF-295	[1]
Annonaceae							
Xylopia aromatica (Lam.) Mart.	RW	DM	5.9-19.1 μg/mL	Tumor cells	MTT assay	HCT-8, MDA-MB-435, SF-295, and HL60	[1]
Apocynaceae							
Himatanthus drasticus (Mart.) Plumel	La	Aq	50 and 100 μg/mL	Tumor cells	MTT assay	S-180 cells	[4]
Asteraceae							
Vernonanthura polyanthes (Sprengel) Vega & Dematteis	L	Aq, n-BF or EA	20-40 and 0.25, 0.5, and 1 mg/mL	Crustacean, onion and human cells	*Artemia salina, Allium cepa* and, Trypan Blue assay	*Artemia salina*, Meristematic cells and Human lymphocytes	[5,6]
Eremanthus incanus (Less.) Less.	AE	EA or Eth	50 μg/mL	Tumor cells	MTT assay	HCT 116, OVCAR 8 and, SF-295	[7]

Bignoniaceae							
Distictella elongata (Vahl) Urb.	RO	HE	100 µg/mL^{-1}	Tumor cells	Neutral Red	SK-ME and SK-OV-3	[8]
Pyrostegia venusta (Ker Gawl.) Miers	FL	Hep	28.96 mg/mL or 41.08 µg/mL	Tumor cells	MTT assay	B16F10-Nex2	[9]
Bixaceae							
Cochlospermum regium (Mart. ex Schrank) Pilg.	R	Aq	19, 38, 76 and 114 mg/kg	Murine cells	Micronucleus test	Erythrocytes	[10]
Calophyllaceae							
Kielmeyera coriacea Mart. & Zucc.	L, SB, SW or R	Chl or HE	5-40 µg/mL	Tumor and murine cells	MTT and Trypan Blue assay	SKMel 28 or A2058 cells and B16F10-Nex2, HCT-8, MDA-MB-435, SF-295, HL-60, and SF-295 cells lines	[1,11,12]
Calophyllum brasiliense Cambess.	R	DM	3.0- 17.6 µg/mL	Tumor cells	MTT assay	Cell lines: HCT-8, MDA-MB-435, and SF-295	[1]
Caryocaraceae							
Caryocar brasiliense Cambess.	F	EO	173.7 – 442.7 µg/mL	Tumor cells	MTT assay	4T1 and NIH/3T3	[13]
Celastraceae							
Salacia crassifolia (Mart. ex Schult.) G.Don	RW or B	HE	0.3-8.7 µM and 50-150 mg/kg	Tumor and murine cells	Formazan Endpoint assay and Micronucleus test	KM12, A498, HCT-15, UO-31, T-47D, A549, 786-O, NCI-60 and murine erythrocytes	[14,15]
Cheiloclinium cognatum (Miers) A.C.Sm.	Bra		9.92- 55.65 µmol/L-1	Tumor and non-tumor cells	MTT assay	ATCC TIB-202 (THP-1), ATCC CRL-3343 (K562) and PBMCs	[16]

Clusiaceae							
Garcinia gardneriana (Planch. & Triana) Zappi	L or F	Eth, HE, Chl, HM or AE	0.25, 2.5, 25 and 250 μg/mL	Tumor and non-tumor cells	SRB assay	B16-F10, MCF-7, 786-0, HT-29 and NIH-3T3	[17]
Costaceae							
Costus spiralis (Jacq.) Roscoe	L or S	Aq	18 and 9 mg/mL	Onion cells	*Allium cepa* test	Meristematic cells	[18]
Chamaecostus subsessilis (Nees & Mart.) C.D.Specht & D.W.Stev.	Rh	Chl or Eth	4.6 and 15.1 μg/mL	Tumor cells	MTT assay	HL60	[19]
Erythroxylaceae							
Erythroxylum daphnites Mart.	L	Aq, Eth or HE	448.9 and 500 μg/mL	Tumor cells	MTT assay	SCC-9, HaCat and FaDu	[20,21]
Erythroxylum suberosum A.St.-Hil.	L	Aq, Eth or HE	500 μg/mL	Tumor cells	MTT assay	SCC-25, SCC-9, FaDu and, HaCat	
Erythroxylum subrotundum A.St.-Hil.	L	Aq, Eth or HE	500 μg/mL	Tumor cells	MTT assay	SCC-SCC-9	[20]
Euphorbiaceae							
Croton velutinus Baill.	R	HE	6.8-19.4 μM/mL	Tumor cells	Alamar Blue assay	MCF7 and HepG2	[22]
Croton urucurana Baill.	La	EA	3.93-5.42 μg/mL^{-1} and 50-200 μg/mL	Tumor cells	SRB assay and WST-1 assay	786-0, NCI-ADR/RES and Huh-7	[23,24]
Fabaceae							
Eriosema crinitum (Kunth) G.Don	R	DM or Eth	100 μg/mL	Human cells	Trypan blue assay	T cells	[25]
Stryphnodendron adstringens (Mart.) Coville	B	Aq or Eth	65-100 μg/mL and 0.5 mg/plate	Tumor and Bacterial cells	MTT assay and Ames test	PBMC, B16F10-Nex2 and *Salmonella typhimurium* (TA100, TA98, TA97a and, TA102)	[26,27]
Dipteryx alata Vogel	N	C or HD	0.781 and 50 mg/mL	Tumor cells	MTT assay and PrestoBlue assay	HT29	[28]

Hymenaea stigonocarpa Mart. ex Hayne	B	Aq or HD	0.5-1.5 mg/mL and 0.082-0.328g/mL	Onion cells	*Allium cepa* test	Meristematic cells	[29,30]
Lauraceae							
Nectandra amazonum Nees	L	EO	58.0 and 29.40 µg/mL	Murine cells	SRB assay	J774.A1 and NIH/3T3	[31]
Nectandra gardneri Meisn.	SB	EO	51.60 and 29.90 µg/mL	Murine cells	SRB assay	J774.A1 and NIH/3T3	[31]
Nectandra hihua (Ruiz & Pav.) Rohwer	L	EO	54.90 and 29.80 µg/mL	Murine cells	SRB assay	J774.A1 and NIH/3T3	[31]
Nectandra lanceolata Nees	L or B	EO	14.6, 67.5, 72.4, 107.0 and 195.2 µg/mL $^{-1}$	Tumor cells	SRB assay	786-0, HT-29 and K562	[32]
Nectandra megapotamica (Spreng.) Mez	L or SB	EO	71- 415.60 µg/mL	Tumor and murine cells	MTT and SRB assays	Human erythrocytes,Vero cells, J774.A1) and NIH/3T3	[31,33]
Loganiaceae							
Strychnos pseudoquina A.St.-Hil.	L	M	26.60 mg/plate	Bacterial cells	Ames test	*Salmonella typhimurium* (TA98)	[34]
Lythraceae							
Lafoensia pacari A.St.-Hil.	B	M, Mac, or Dec	18.32- 21.08 µg/mL and 0.1-1000 mg/mL	Tumor cells	MTT, Clonogenic and Trypan blue assays	HRT-18, SH-SY5Y, HeLa, HRT-18, U-937, Daudi, T-cell and, Jurkat	[35,36]
Myrtaceae							
Eugenia dysenterica (Mart.) DC.	L	Aq or Eth	15.6 µg/mL and 100, 150 and 200 mg/kg	Tumor and murine cells	XTT assay and Micronucleus test	SH-SY5Y and Murine erythrocytes	[37,38]
Eugenia uniflora L.	L	EO	76.5-102,2 µg/mL	Tumor and non-tumor cells	XTT assay	MO59 J, HeLa, MCF-7 and GM07492 A	[39]
Myrcia bella Cambess.	L	HA	200- 500 mg/mL	Human cells	MTT assay	ACP02	[40]
Psidium brownianum Mart. ex DC.	L	Aq	1000 µg/mL	Murine cells	Resazurin Assay	NCTC-929	[41]

Salicaceae							
Casearia sylvestris Sw.	L, SB, RB, RD, F or SW	Eth or HE	0.1- 33.7 and 111.3-149.3 μg/mL	Tumor and murine cells	MTT assay	HCT-8, MDA-MB-435, SF-295 and J774	[1,42]
Sapindaceae							
Cupania vernalis Cambess.	L, S, B, SB or RB	Eth or HE	4.0- 4.2 and 66.5-160. 0 μg/mL	Tumor and murine cells	MTT assay	HCT-8, MDA-MB-435, SF-295 and J774	[1,42]
Serjania lethalis A.St.-Hil.	L, S, B, SB or RB	Eth or HE	8.0- 205.1 μg/mL	Tumor and Murine cells	MTT assay	J774, HCT-8, MDA-MB-435, and SF-295	[1,42]
Sapotaceae							
Pouteria torta (Mart.) Radlk.	L	Aq, Eth or HE	125 and 500 μg/mL	Tumor cells	MTT assay and Violet crystal test	FaDu, OSCC-3 or MCF-7	[20,43]
Pouteria ramiflora (Mart.) Radlk.	L	Aq, Eth or HE	500 μg/mL	Tumor cells	MTT assay	FaDu and HaCat	[20]
Simaroubaceae							
Simarouba versicolor A.St.-Hil.	RB or F	Eth or HE	0.2- 16.6 μg/mL	Tumor cells	MTT assay	HCT-8, MDA-MB-435 and, SF-295	[1]
Solanaceae							
Solanum lycocarpum A.St.-Hil.	F	Eth	5, 10, 25, 50 and 80 mg/kg	Murine cells	Micronucleus test	Murine erythrocytes	[38]
Verbenaceae							
Lippia salviaefolia Cham.	L or S	Eth	20-40 μM	Tumor cells	MTT assay	HEK-293 and M14	[44]

Part used[1](AP= aerial parts, Bra= Branches, F= Fruits, FL= Flowers, La= Latex, N= Nuts, L= Leaves, RB=root bark; R= Root; Root Wood= RW; Rh=Rhizome, and S= Stem; Stem Bark= SB; Bark= B). Type of extract[2] (Aqueous= Aq; Dichloromethane= DM; Ethanolic= Eth; Ethyl-acetate= EA; Methanol-acetate= MA; Hexane= HE; n-butanol= n-BF; Heptane= Hep; Chloroform= Chl; Essential oils= EO; Hydromethanolic=HM; Crude= C; Hydrolyzed= HD; Methanol= M; Macerated= Mac, Decoction= Dec; Hydroalcoholic= HÁ; Hydroethanolic= HEth).

Cells lines[3]: MDA-MB-435 (melanoma), HCT-8 (colon), SF-295 (glioblastoma), NCI-ADR/RES (multidrug resistant ovary adenocarcinoma), U251 (glioma), MCF-7 (breast), NCI-H460 (non-small cell lung cancer), PC-3 (prostate) , OVCAR-03 (ovary), HT-29 (colon), K562 (leukemia), HaCaT (spontaneously transformed kerati- nocytes from histologically normal skin), V79 cells (Chinese hamster lung fi broblasts), S-180 (Sarcoma-180), HCT-116 and OVCAR-8 (human cancer cell lines), SK-MEL (melanoma), SK-OV-3 (ovary adenocarcinoma), B16F10-Nex2 (murine melanoma), 471 (breast), NIH/3T3 (non-tumoral), Colo205 and KM12 (colon cancer), A498 and U031 (renal cancer), HEP3B and SKHEP (liver cancer) MG63 and MG63.3 (osteosarcoma), K562 and THP-1 (leukemia), B16-F10 (Murine melanoma), 786-0 (kidney adenocarcinoma), SCC-25 and SCC-9 (Oral cavity squamous cell carcinoma), FaDu (carcinoma) HaCat (keratinocyte), Huh-7 (human hepatocarcinoma), PBMC (Peripheral blood mononuclear cells), Murine macrophage (J774.A1), K562 (leukemia), Jurkat, and Daudi (leukemic cell lines), SH-SY5Y (neuroblastoma), MO59J (human glioblastoma), GM07492 A (lung fibroblasts), HeLa (human cervical adenocarcinoma), HL-60 (leukemia), HepG2 (hepatocyte carcinoma), M14 (melanoma) and, NCI-60 (Mammalian Cell Lines),

Table S2 Mutagenic and genotoxic activities from different species of Cerrado. Information about part of plant and extract preparation, dose tested, model and method analyzed.

Family/Species	Part[1]	Extract[2]	Dose/Concentration	Activity against	Technique	Model	Reference
Apocynaceae							
Himatanthus drasticus (Mart.) Plumel	L	Aq	2000 mg/kg	Murine cells	Assay comet	Erythrocytes	[4]
Asteraceae							
Baccharis dracunculifolia DC.	L	EA	50 and 100 μg/mL	Murine and Mammalian cells	Assay comet and Chromosomal aberration assay	V79 and CHO9 cells	[3,45]
Vernonanthura polyanthes (Sprengel) Vega & Dematteis	L	Aq, n-BF or EA	0.25- 1 mg/mL	Human cells	CometChip	Human lymphocytes	[6]
Bignoniaceae							
Arrabidaea brachypoda (DC.) Bureau	L, S or R	Aq or HA	12-24 mg/plate	Bacterial cells	Ames test	*Salmonella typhimurium* (TA98)	[46]
Bixaceae							
Cochlospermum regium (Mart. ex Schrank) Pilg.	R	Aq	19- 114 mg.kg	Murine cells	Micronucleus test	Erythrocytes	[10]
Combretaceae							
Terminalia argentea Mart. & Zucc.	L	HEth	10-100 μg/mL	Tumor cells	Assay comet and Micronucleus test	CHO-K1 cells	[47]
Dilleniaceae							
Davilla elliptica A.St.-Hil.	L	Aq, M, HA or EA	0-84 mg/plate	Bacterial cells	Ames test	*Salmonella typhimurium* (TA98 and TA97a)	[48]
Dilleniaceae							
Davilla nitida (Vahl) Kubitzki	L	Aq, M, HA or EA	0-84 mg/plate	Bacterial cells	Ames test	*Salmonella typhimurium* (TA98 and TA97a)	[49]
Loganiaceae							

Strychnos pseudoquina A.St.-Hil.	L	M	3.33-26.60 mg/plate and 1800 mg/kg	Bacterial and human cells	Ames and Micronucleus test	*Salmonella typhimurium* (TA98 and TA100) human reticulocytes	[34]
Malpighiaceae							
Byrsonima crassa Nied.	L	M or EA	0-35.5 mg/plate	Bacterial cells	Ames test	*Salmonella typhimurium* (TA98 and TA100)	[50]
Melastomataceae							
Mouriri elliptica Mart.	L	M	2.3 – 18.6 mg/plate	Bacterial and Murine cells	Ames and Micronucleus test	*Salmonella typhimurium* (TA98, TA100 and TA97a)	[51]
Mouriri pusa Gardner	L	M	2.84-22.70 mg/plate	Bacterial and Murine cells	Ames and Micronucleus test	*Salmonella typhimurium* (TA98, TA100 and TA97a)	[51]
Myrtaceae							
Eugenia dysenterica (Mart.) DC.	L	Eth	150 and 200 mg/kg	Murine cells	Micronucleus test	Erythrocytes	[38]
Smilacaceae							
Smilax brasiliensis Spreng.	L	M, DM or EA	250-1000 μg/mL	Onion cells	*Allium cepa* test	Meristematic cells	[52]
Vochysiaceae							
Qualea grandiflora Mart.	B	Aq, M or Chl	1.92-15.40 mg/plate	Bacterial and Murine cells	Ames and Micronucleus test	*Salmonella typhimurium* (TA98, TA100, TA97a and TA102)	[48]
Qualea multiflora Mart.	B	Aq, M or Chl	2.07-16.60 mg/plate	Bacterial and Murine cells	Ames and Micronucleus test	*Salmonella typhimurium* (TA98, TA100, TA97a and TA102)	[48]

Part used[1] (AP= aerial parts, Bra= Branches, F= Fruits, FL= Flowers, La= Latex, N= Nuts, L= Leaves, RB=root bark; R= Root; Root Wood= RW; Rh=Rhizome, and S= Stem ; Stem Bark= SB; Bark= B). Type of extract[2] (Aqueous= Aq; Dichloromethane= DM; Ethanolic= Eth; Ethyl-acetate= EA; Methanol-acetate= MA; Hexane= HE; n-butanol= n-BF; Heptane= Hep; Chloroform= Chl; Essential oils=EO; Hydromethanolic=HM; Crude= C; Hydrolyzed= HD; Methanol= M; Macerated= Mac, Decoction= Dec; Hydroalcoholic= HÁ; Hydroethanolic= HEth; Exsudate=EX).

Table S3 Acute and chronic toxicity on murine model. Information about part of plant and extract preparation, dose tested, model and method analyzed.

Family/Species	Part[1]	Extract[2]	Dose/Concentration	Activity against	Technique	Model	Reference
Asteraceae							
Lychnophora pinaster Mart.	AP	Eth	125-500 mg/kg	Mice	One single dose by oral route	Swiss	[53]
Lychnophora trichocarpha (Spreng.) Spreng.	AP	Eth	0.5 - 1.5 g/kg	Mice	one single dose by intraperitoneal route	Albino Swiss	[54]
Fabaceae							
Dimorphandra mollis Benth	F	HA	2000 mg/kg	Rats	Oral administration for 180 days	Male Wistar	[55]
Moraceae							
Brosimum gaudichaudii Trécul	RB	EX	LD50 3517 and 2871.76 mg/kg	Mice	One single dose by oral or intraperitoneal routes	Albino male mice	[56]
Myrtaceae							
Campomanesia velutina (Cambess) O. Berg	L or Bra	Aq	300-1200 mg/kg	Mice	One single dose or 14 consecutive days by oral route	Albino Swiss	[57]
Sapindaceae							
Serjania marginata Casar.	L	Aq	30-750 mg/kg	Rats	28 consecutive days by oral route	Wistar	[58]

Part used[1] (AP= aerial parts; Bra= Branches; F= Fruits; RB=root bark; R= root; root wood= RW).
Type of extract[2] (Aqueous= Aq; Ethanolic= Eth; Hydroalcoholic= HA; Exsudate=EX).

Table S4. Antibacterial activity from different species of Cerrado. Information about part from plant and extract preparation, dose tested, model and method analyzed

Family/Species	Part[1]	Extract[2]	Dose /Concentration	Activity against	Technique	Experimental model	Reference
Anacardiaceae							
Myracrodruon urundeuva M. Allemão	L	HEth	MIC = 2.5 mg/mL	*Streptococcus mutans*	Broth Microdilution Assay	*S. mutans* (ATCC 21175)	[59]
Schinopsis brasiliensis Engl.	L	Eth	MIC = 0.17 mg/mL	*Escherichia coli*	Broth Microdilution Assay	*E. coli* isolates (E2 and E3)	[60]
Annonaceae							
Annona coriacea Mart.	L	AC and C	MIC = 3.12--6.25-50 and 100-200 μg/mL	*Streptococcus mutans*, *Streptococcus mitis* , *Streptococcus sanguinis* and *Streptococcus salivarius*	Broth Microdilution Assay	*S. mutans* (*ATCC* 25175), *S. mitis* (ATCC 49456), *S. sanguinis* (ATCC 10556) and *S. salivarius* (ATCC 25975)	[61]
Cardiopetalum calophyllum Schltdl.	L	EO	MIC = 100 and 400 μg/mL	*Streptococcus mutans*, *Streptococcus sanguinis*, *Streptococcus sobrinus*, *Bacteroides fragilis* and *Streptococcus mitis*	Microdilution Assay	*S. mutans*, *S. sanguinis*, *S. sobrinus*, *B. fragilis* and *S.mitis*	[62]
Apocynaceae							
Hancornia speciosa Gomes	B	Eth	MIC = 50 and 125 μg/mL	*Helicobacter pylori* and *Staphylococcus aureus*	Broth Microdilution Assay	*H. pylori* (ATCC 43504), and *S. aureus* (ATCC 25923)	[63]
Secondatia floribunda A.DC.	SIB	Eth	MIC = 64 and 128 μg/mL	*Staphylococcus aureus and Escherichia coli*	Broth Microdilution Assay	*S. aureus* (ATCC 12692) and *E. coli* (ATCC 25922)	[64]
Arecaceae							

Attalea speciosa Mart. ex Spreng.	F or L	FO or EO	MIC = 32-400 µg/mL	*Escherichia coli, Staphylococcus aureus, Streptococcus sanguinis* and *Streptococcus mitis , Streptococcus mutans Agregatibacter actinomycetemcomitans , Actinomyces naeslundii , Porphyromonas gingivalis and Fusobacterium nucleatum.*	Broth Microdilution Assay	*E. coli* Ec 27 (multiresistant); *S. aureus* 358 (multiresistant); *S. sanguinis* (ATCC 10556); *S. mitis* (ATCC 49456), *S. mutans* (ATCC 25175), *A. actinomycetemcomitans* (ATCC 43717), *A. naeslundii* (ATCC 19039), *P. gingivalis* (ATCC 33277) and *F. nucleatum* (ATCC 25586)	[65,66]
Mauritia flexuosa L.f.	S	DM	MIC = 31.3 µg/mL	*Methicillin-susceptible Staphylococcus aureus* and *methicillin-resistant Staphylococcus aureus*	Broth Microdilution Assay	methicillin-susceptible *S. aureus* (MSSA- ATCC 29213) and methicillin-resistant *S. aureus* (MRSA - clinical sample 155)	[67]
Aristolochiaceae							
Aristolochia cymbifera Mart. & Zucc.	S, W and R	Eth and HE	MIC = 0.5-4.0 and 125-500 µg/mL	*P. intermedia, P. gingivalis , F.nucleatum, S.mutans, L. casei and S. aureus, S. epidermidis , S. haemolyticus, P. aeruginosa*	Broth Microdilution Assay	*P. intermedia (*ATCC 25611), *P. gingivalis* (ATCC 49417), *F. nucleatum* (ATCC 25586), *S. mutans* (ATCC 25175), *L. casei* (ATCC 4646), *S. aureus*, *S. epidermidis* (10 multi-resistant strains), *S. haemolyticus* (12 multi-resistant), *P. aeruginosa* (21 multi-resistant strains)	[68,69]
Asteraceae							
Chromolaena squalida (DC.) R.M.King & H.Rob.	L	EO	MIC = 7.80 µg/mL	*multi–resistant Staphylococcus sp. 841*	Broth Microdilution Assay	*multi–resistant Staphylococcus sp. 841*	[70]
Bixaceae							
Cochlospermum regium (Mart. ex Schrank) Pilg.	X, R and L	HEth, EA, Aq and Eth	MIC = 31-500 µg/mL and 1 mg/mL	*Helicobacter pylori, Pseudomonas aeruginosa, Acinetobacter baumannii, Staphylococcus epidermidis, Staphylococcus aureus, Streptococcus agalactiae; Escherichia coli, Klebsiella pneumoniae,* and *Acinetobacter baumannii*	Broth Microdilution Assay	*H. pylori* (ATCC 43504*), P. aeruginosa* (25619), *A. baumannii* (19606), *S. epidermidis* (12228), *S. aureus* (29213), *E. coli* (25922), *S. agalactiae* (13813), *K. pneumoniae* (43816), *P. aeruginosa* (25619), *A. baumannii* (19606)	[71–74]
Calophyllaceae							

Kielmeyera lathrophyton Saddi	B	BC	MIC = 250-500 µg/mL	*Staphylococcus aureus* and *Bacillus subtilis*	Microdilution Assay	*S. aureus* (ATCC 25923), *B. subtilis* (ATCC 6623),	[75]
Caryocar brasiliense Cambess.	L	Eth and HEth	MIC = 0.27, 22.50 and 11.25 mg/mL	*Staphylococcus aureus* and *Staphylococcus haemolyticus; Escherichia coli* and *Pseudomonas aeruginosa*	Broth Microdilution and agar diluition Assay	*Staphylococcus* isolates (S178, S135 and S182)	[76,77]
Dilleniaceae							
Curatella americana L.	B	BC	MIC = 500 µg/mL	Staphylococcus aureus	Microdilution Assay	*S. aureus* (ATCC 25923)	[75]
Davilla nitida (Vahl) Kubitzki	L	M	MIC = 125 µg/mL	*Helicobacter pylori*	Broth Microdilution Assay	*H. pylori* (ATCC 43504)	[78]
Davilla elliptica A.St.-Hil.	L	M	MIC = 250 µg/mL	*Helicobacter pylori*	Broth Microdilution Assay	*H. pylori*(ATCC 43504)	[78]
Erythroxylaceae							
Erythroxylum suberosum A.St.-Hil.	SB	Eth	MIC = 250 µg/mL	*Staphylococcus aureus*	Broth Microdilution Assay	*S. aureus* (ATCC 25923)	[79]
Euphorbiaceae							
Alchornea triplinervia (Spreng.) Müll.Arg.	L	M	MIC= 0.25 mg/mL	*Helicobacter pylori*	Broth Microdilution Assay	*H. pylori* (ATCC 43504)	[80]
Croton heliotropiifolius Kunth	L and S	EO	MIC = 62.5 and 500 µg/mL	*Staphylococcus aureus* and *Bacillus subtilis*	Broth Microdilution Assay	*S. aureus* and *B. subtilis*	[81]
Fabaceae							
Plathymenia reticulata Benth.	L	M	MIC = 5 mg	*Escherichia coli* and *Pseudomonas aeruginosa*	Agar Diffusion assays	*E. coli* and *P. aeruginosa*	[82]
Stryphnodendron adstringens (Mart.) Coville	L and B	D, M and W	MIC = 0.19-12.5 µg/mL and 5 mg	*Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella pneumoniae,* and *Escherichia coli*	Broth Microdilution and Agar Diffusion Assay	*S. aureus* (ATCC 25923), *P. aeruginosa* (ATCC 27853), *K. pneumoniae* (ATCC 4352) and *E. coli* (ATCC 25922)	[82,83]
Lamiaceae							

Hyptis crenata Pohl ex Benth.	WP	DM	MIC = 62.5 µg/mL	*Staphylococcus aureus* and *Enterococcus faecalis*	Broth Microdilution Assay	*S. aureus* (ATCC 25923) and *E. faecalis* (ATCC 29218)	[79]
Hyptis multibracteata Benth.	AP	HE, EA and HE	MIC = 37.55 and 12.13-23.6 µg/mL	*Pseudomonas aeruginosa* and *Bacillus subtilis*	Broth Microdilution Assay	*P. aeruginosa* (ATCC 10.145) and *B. subtilis* (PY79)	[84]
Hyptis passerina Mart. ex Benth.	L	EO	MIC = 62.5-125 µg/mL	*Staphylococcus aureus* and *Pseudomonas aeruginosa*	Broth Microdilution Assay	*S. aureus* (ATCC 25923) and *P. aeruginosa* (ATCC 15422)	[85]
Hyptis radicans (Pohl) Harley & J.F.B.Pastore	AP	EA	MIC = 140.91 and 195.32 µg/mL	*Bacillus subtilis* and *Pseudomonas aeruginosa*	Broth Microdilution Assay	*B. subtilis* (PY79) and *P. aeruginosa* (ATCC 10.145)	[84]
Loganiaceae							
Strychnos pseudoquina A.St.-Hil.	L	EAF	MIC = 75 µg/mL	*Helicobacter pylori*	Broth Microdilution Assay	*H. pylori* (ATCC 43504)	[86]
Malpighiaceae							
Byrsonima intermedia A.Juss.	L	M	MIC= 0.125-0.500 mg/mL	*Helicobacter pylori; Staphylococcus aureus and Escherichia coli*	Microdilution Assay	*H. pylori* (ATCC 43504), *S. aureus* (ATCC 25923) and *E. coli* (ATCC 25922)	[87]
Melastomataceae							
Miconia albicans (SW.) Triana	L	M	MIC = 5 mg	*Escherichia coli* and *Pseudomonas aeruginosa*	Agar Diffusion Assay	*E. coli* and *P. aeruginosa*	[82]
Mouriri elliptica Mart.	L	M	MIC = 0.025 mg/mL	*Helicobacter pylori*	Broth Microdilution Assay	*H. pylori* (ATCC 43504)	[88]
Myrtaceae							
Eugenia dysenterica (Mart.) DC.	P	Pw	MIC = 0.16 mg/mL	*Staphylococcus aureus* and *Listeria monocytogenes*	Broth Microdilution Assay	*S. aureus and L. monocytogenes*	[89]
Eugenia involucrata DC.	L	OE or DM	MIC = 50, 100 and 200 µg/mL	*Prevotella nigrescens, Porphyromonas gingivalis, Streptococcus mutans, Streptococcus mitis, Streptococcus sanguinis, Streptococcus sobrinus* and *Bacteroides fragilis*	Broth Microdilution Assay	*P. nigrescens* (ATCC 33563) and *P. gingivalis* (ATCC 33277), *S. mutans* (ATCC 25175), *S. mitis* (ATCC 49456), *S. sanguinis* (ATCC 10556), *S. sobrinus* (ATCC 33478) and *B. fragilis* (ATCC 25285)	[90]

Eugenia klotzschiana O.Berg	L and FL	EO	MIC = 50 µg/mL	*Streptococcus mutans* and *Prevotella nigrescens*	Broth Microdilution Assay	*S. mutans* (ATCC 25175) and *P. nigrescens* (ATCC 33563)	[91]
Eugenia uniflora L	L	EO	MIC = 100, 200 and 400 µg/mL	*Streptococcus mutans, Stre ptococcus sobrinus, Prevotella nigrescens, Porphyromonas gingivalis, Streptococcus sanguinis* and *Streptococcus mitis*	Broth Microdilution Assay	*S. mutans, S. sobrinus, P. nigrescens, P. gingivalis; S.* and *sanguinis; S. mitis*	[92]
Myrcia bella Cambess	L	HEth	MIC = 300 µg/mL	*Escherichia coli*	Broth Microdilution Assay	*E. coli* (ATCC 11775)	[93]
Myrcia splendens (Sw.) DC.	L	HEth	MIC = 250 µg/mL	*Escherichia coli*	Broth Microdilution Assay	*E. coli* (ATCC 11775)	[93]
Psidium cattleyanum Sabine	L	PL	MIC = 1.56-3.13 mg/mL	*Staphylococcus aureus, Listeria monocytogenes, Pseudomonas aeruginosa* and *Enterococcus faecalis*	Agar Diffusion Assay	*S. aureus* (ATCC 25923), *L. monocytogenes Scott A, P. aeruginosa* (ATCC 9027) and *E. faecalis* FAIR (E77)	[94]
Psidium guineense Sw.	L	EO	MIC = 126.4 and 231.9 µg/mL	*Mycobacterium tuberculosis*	REMA method	*M. tuberculosis virulent type (H37Rv)*	[95]
Psidium myrsinites DC.	L	C	MIC = 62.5 and 125 µg/mL	*Staphylococcus epidermidis and Staphylococcus aureus*	Broth Microdilution Assay	*S. epidermidis* (ATCC 12228) and *S. aureus* (ATCC 25923)	[96]
Campomanesia adamantium (Cambess.) O.Berg	F and L	EA and Eth	MIC = 62.5 µg/mL	*Mycobacterium tuberculosis, Staphylococcus aureus, Staphylococcus epidermidis* and *Enterobacter cloacae*	Microplate Alamar Blue and Broth Microdilution Assay	*M. tuberculosis H37Rv* (ATCC 27294), *S. aureus* (ATCC 25923), *S. epidermidis* (ATCC 12229) *and E. cloacae*	[97,98]
Campomanesia sessiliflora (O.Berg) Mattos	L	EO	MIC = 31.25 µg/mL	*multi−resistant Staphylococcus sp. 841*	Broth Microdilution Assay	multi−resistant *Staphylococcus sp. 841*	[70]
Phytolaccaceae							
Gallesia integrifolia (Spreng.) Harms	B	HEth	MIC = 25-400 µg/mL and 10-250 mg/kg p.o	*Shigella flexneri, Streptococcus pyogenes, Escherichia coli, Salmonella typhimurium, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Staphylococcus aureus*	Broth Microdilution Assay	*S. flexneri, S. pyogenes, E. coli, S. typhimurium, K. pneumonia, P.aeruginosa and S. aureus strains, S. aureus* strain inoculated in female albino Wistar rats	[99]

Primulaceae							
Myrsine guianensis (Aubl.) Kuntze	L	EO	MIC = 31.25 µg/mL	*multi−resistant Staphylococcus sp. 841*	Broth Microdilution Assay	multi−resistant *Staphylococcus sp. 841*	[70]
Proteaceae							
Roupala montana var. brasiliensis (Klotzsch) K.S.Edwards	SB and L	Eth and W	MIC = 5 and 125 µg/mL	*Staphylococcus aureus* and *Escherichia coli*	Broth Microdilution and Agar Diffusion Assay	*S. aureus* (ATCC 25923) and *E. coli*	[79,82]
Sapindaceae							
Serjania marginata Casar.	L	HA	MIC= 75-250 µg/mL	*Helicobacter pylori*	Broth Microdilution Assay	*H. pylori* (ATCC 43504)	[100]
Siparunaceae							
Siparuna guianensis Aubl.	L	EO	MIC = 50-500 µg/mL	*Streptococcus mutans, Streptococcus mitis, Streptococcus sobrinus, Streptococcus salivarius, Mycobacterium tuberculosis, Mycobacterium kansasii,* and *Mycobacterium avium*	Broth Microdilution Assay	*S. mutans* (ATCC 25175); *S. mitis* (ATCC 49456); *S. salivarius* (ATCC 25975) and *S. sobrinus* (ATCC 33478); *M. tuberculosis H37Rv* (ATCC 27294) and *M. kansasii* (ATCC 12478) and *M. avium* (ATCC 25291)	[101]
Vochysiaceae							
Qualea parviflora Mart.	B	M	MIC = 75 µg/mL	*Helicobacter pylori*	Broth Microdilution Assay	*H. pylori* (ATCC 43504)	[102]

Part of plant[1] (AP= aerial parts; F= Fruits; FL= Flowers; L= Leaves; S= Stem; Stem Bark= SB; Bark= B; Whole plant= WP; Pulp= P; Xylopodium= X).
Type of extract[2] (Acetogenin-rich fraction= AC; Aqueous= Aq; Dichloromethane= DM; Ethanolic= Eth; Ethyl-acetate= EA; Hexane= HE; Essential oils= EO; Fixed oil= FO; Crude= C; Methanol= M; Hydroalcoholic= HA; Stalk's inner bark= SIB; Hydroethanolic= HEth; Brazilian cachaça was used as the extractor liquid = BC; Dry extract = D; Water extracts = W; Powder extract = Pw; Pressurized liquid extraction with water= PL).

Table S5 Antifungal activity from different species of Cerrado. Information about part from plant and extract preparation, dose tested, model and method analyzed.

Family/Species	Part[1]	Extract[2]	Dose/Concentration	Activity against	Technique	Model	Reference
Anacardiaceae							
Myracrodruon urundeuva M. Allemão	IB	Aq	MIC = 31.25 µg/mL	*Candida albicans*	Broth Microdilution Assay	*C. albicans* isolated from the oral mucosa of individuals with HIV/AIDS	[103]
Annonaceae							

Cardiopetalum calophyllum Schltdl.	L	EO	300 µl/mL	*Sclerotinia sclerotiorum*	Disk Diffusion Test	*S. sclerotiorum*	[62]
Arecaceae							
Asteraceae							
Mikania glomerata Spreng	L	EO	MIC = 0.25 mg/mL	*Candida albicans*	Minimal Inhibitory Concentration (MIC) Test	*C. albican*s CBMAI 0475 (ATCC 10231)	[104]
Bignoniaceae							
Pyrostegia venusta (Ker Gawl.) Miers	FL	n-BF	MIC= 0.7-6.0 µg/mL	*Candida albicans* and *clinical*, *Candida krusei* ,*Candida tropicalis, Candida parapsilosis* and *Candida guilhermondii*	Broth Microdilution Assay	*C. albicans* (ATCC 10231), C. *albicans* (USP 1), *C. albicans* (USP-1565), *C. albicans* (OF M3-20), *C. albicans* (OF M7-19), *C. krusei* (ATCC 6258), *C. krusei* (USP-2223), *C. tropicalis* (USP-B3), *C. tropicalis* (USP-1658), *C.parapsilosis* (USP-1933), and *C. guilhermondii* (USP)	[105]
Bixaceae							
Cochlospermum regium (Mart. ex Schrank) Pilg.	R and L	EA and Eth	MIC= 31.25-250 µg/mL and 0.5 mg/mL	*Candida albicans*, *Candida krusei*, *Candida glabrata, Candida tropicalis* and *Candida*	Broth Microdilution Assay	*C. albicans* (10231 250), *C. krusei* (34135), *C. glabrata* (13813), *C. tropicalis* (ATCC 750) and *C. tropicalis* clinical isolated yeasts	[71,106]
Calophyllaceae							
Calophyllum brasiliense Cambess.	RW	DM	MIC= 1.95 and 1.95 µg/mL	*Cryptococcus gattii, Candida albicans* and *Candida krusei*	Broth Microdilution Assay	*C. gattii* (LMGO 01), *C. albicans* (ATCC 10231) and *C. krusei* (LMGO 174)	[107]
Combretaceae							
Terminalia fagifolia Mart.	SB	Aq	MIC = 0.4-25 µg/mL	*Candida albicans*, *Candida tropicalis,*	Broth Microdilution Assay	*C. albicans* (SC 5314/ATCC MYA-	[108]

				Candida parapsilosis and Candida albicans		2876), *C. tropicalis* (ATCC 750), *C. parapsilosis* (ATCC 22901) and *C. albicans* (ATCC 96901 fluconazole-resistant strain)	
Connaraceae							
Connarus suberosus Planch.	RB	Eth	MIC= 15.62-250 μg/mL	*Candida albicans*, *Candida parapsilosis* and *Candida glabrata*	Broth Microdilution Assay	*C. albicans* (ATCC 10231), *C. parapsilosis* (ATCC 22019) and *C. glabrata* (LMGO 44)	[109]
Dilleniaceae							
Curatella americana L.	SB and B	C, BC	MIC= 7.8-125 μg/mL	*Candida albicans*, *Candida tropicalis*, *Candida parapsilosis*, *Candida albicans*	Broth Microdilution Assay	*C. albicans* (LC352), *C. tropicalis* (LC299), *C. parapsilosis* (LC144), *C. parapsilosis, C. tropicalis (*four strains that were resistant to fluconazole, *C. albican*s 32res, 32Bres, 48res, and 103res), (*C. albicans* 48sen), *C. albicans* (ATCC 10231) and *C. parapsilosis* (ATCC 22019)	[75,110]
Erythroxylaceae							
Erythroxylum suberosum A.St.-Hil.	SB	EA	MIC= 62.5-500 μg/mL	*Candida krusei* and *Cryptococcus neoformans*	Broth Microdilution Assay and Disk Diffusion Test	*C. krusei* (ATCC 6258) and *C. neoformans* (ATCC 32045)	[79]
Fabaceae							
Tachigali aurea Tul.	RW and B	EA and BC	MIC= 0.12-125 μg/mL	*Candida albicans, Candida parapsilosis, Candida glabrata, Trichophyton*	Broth Microdilution Assay	*C. albicans* (ATCC 10231), *C. parapsilosis*(ATCC 22019), *C. glabrata* (LMGO 44), *T.*	[75,111]

				mentagrophytes and *Trichophyton rubrum*		*mentagrophytes* (LMGO 09) and *T. rubrum* (LMGO 06)	
Hymenaea martiana Hayne	T and B	C	MIC= 4-64 μg/mL	*Cryptococcus neoformans, Cryptococcus gattii, Trichopyton rubrum, Trichopyton mentagrophytes* and *Microsporum canis*	Broth Microdilution Assay	*C. neoformans, C. gattii T. rubrum, T. mentagrophytes* and *M. canis*	[112]
Plathymenia reticulata Benth.	B	BC	MIC= 62.5 μg/mL	*Candida albicans* and *Candida parapsilosis*	Broth Microdilution Assay	*C. albicans* (ATCC 10231) and *C. parapsilosis* (ATCC 22019)	[75]
Vatairea macrocarpa (Benth.) Ducke	RB	EA	MIC= 0.98- 125 μg/mL	*Candida albicans, Candida parapsilosis, Candida, glabrata, Trichophyton mentagrophytes* and *Trichophyton rubrum*	Broth Microdilution Assay	*C. albicans* (ATCC 10231), *C. parapsilosis* (ATCC 22019), *C. glabrata* (LMGO 44), *T. mentagrophytes* (LMGO 09) and *T. rubrum* (LMGO 06)	[111]
Copaifera langsdorffii Desf.	S	OR	MIC= 62.5 μg/mL	*Paracoccidioides lutzii, Paracoccidioides brasiliensis, Paracoccidioides americana* and *Paracoccidioides restrepiensis*	Broth Microdilution Assay	*P. lutzii* (Pb01), *P. brasiliensis* (Pb18), *P. americana* (Pb03), and *P. restrepiensis* (EPM83)	[113]
Inga laurina (Sw.) Willd.	L	Eth	MIC= 11.7-93.8 μg/mL	*Candida albicans, Candida glabrata* and *Candida tropicalis*	Broth Microdilution Assay	*C. albicans* (ATCC 28366), *C. glabrata* (ATCC 15126) and *C. tropicalis* (ATCC 13803)	[114]
Stryphnodendron adstringens (Mart.) Coville	L	D	MIC= 12.5 μg/mL	*Candida albicans, Candida tropicalis* and *Candida parapsilosis*	Broth Microdilution Assay	*C. albicans* (ATCC 18804), *C. tropicalis* (ATCC 13803) and *C. parapsilosis* (ATCC 22009)	[83]

Lamiaceae							
Hyptis crenata Pohl ex Benth.	WP	Eth	MIC= 125 µg/mL	*Candida krusei* and *Cryptococcus neoformans*	Broth Microdilution Assay	*C. krusei* (ATCC 6258) and *C. neoformans* (ATCC 32045)	[79]
Lythraceae							
Lafoensia pacari A.St.-Hil.	SB	EA and Eth	MIC= 100-1000 µg/mL	*Candida krusei,Candida parapsilosis, Saccharomyces cerevisiae and Cryptococcus neoformans*	Broth Microdilution Assay	*C. krusei* (ATCC 6258), *C. parapsilosis* (ATCC 22019), *S. cerevisiae* (ATCC 9763) and *C. neoformans* (ATCC 32264)	[115]
Malpighiaceae							
Banisteriopsis argyrophylla (A.Juss.) B.Gates	L	Eth	MIC =31.25-93.75 µg/mL	*Candida albicans, Candida tropicalis* and *Candida glabrata*	Broth Microdilution Assay	*C. albicans* (ATCC 28366), *C. tropicalis* (ATCC 13803) and *C. glabrata* (ATCC 15126)	[116]
Banisteriopsis laevifolia (A.Juss.) B.Gates	L	Eth	MIC= 31 and 63 µg/mL	*Candida albicans, Candida tropicalis and Candida glabrata*	Broth Microdilution Assay	*C. albicans* (ATCC28366), *C. tropicalis* (ATCC13803) and *C. glabrata* (ATCC15126)	[117]
Moraceae							
Brosimum gaudichaudii Trécul	R	DM	1 mg	*Cladosporium sphaerospermum*	Bioautographic Assay	Spore suspension of the fungus *C. sphaerospermum*	[82]
Myrtaceae							
Campomanesia adamantium (Cambess.) O.Berg	L	Eth	MIC = 7.81 and 31.25 µg/mL	*Candida krusei, Candida tropicalis, Cryptococcus neoformans var. neoformans* and *Cryptococcus neoformans var. gatti*	Broth Microdilution Assay	*C. krusei* (ATCC 34135), *C. tropicalis* (ATCC 28707), *C. neoformans* var. *neoformans* (L2) and *C.*	[97]

						neoformans var. *gatti* (L1)	
Eugenia dysenterica (Mart.) DC.	L	Aq and EO	MIC= 125-500 µg/disc and 15.6-250 µg/mL	*Candida guilliermondii* , *Candida tropicalis* , *Candida parapsilosis* , *Candida famata, Candida krusei, Cryptococcus neoformans var.*		*C. guilliermondii* (ATCC 6260), *C. tropicalis* (ATCC 28707), *C.parapsilosis* (ATCC 22019), *C. famata* (ATCC 62894),*C. krusei* (ATCC 34135), *C. neoformans* var. *gattii* and *C. neoformans* var.	[118,119]
Eugenia involucrata DC.	L	HE	MIC= 31.2-62.5 µg/mL	*Cryptococcus sp. D, Cryptococcus gatti* and *Cryptococcus neoformans*	Broth Microdilution Assay	*Cryptococcus* sp. D, *C.gatt*i (L48), and *C.neoformans* (L3)	[120]
Myrcia linearifolia Cambess	R	EA	MIC= 31.15-125 µg/mL	*Candida albicans, Candida parapsilosis* and *Candida glabrata*	Broth Microdilution Assay	*C. albicans* (ATCC 10231), *C. parapsilosis* (ATCC 22019) and *C. glabra*ta (LMGO 44),	[121]
Psidium brownianum Mart. ex DC.	L	Aq	MIC = 2.05-8.192 µg/mL µg/mL	*Candida albicans* and *Candida tropicalis*	Broth Microdilution Assay	clinical isolates of *C. albicans* and *C. tropicalis* namely (CA INCQS 40006, CA LM 77, CT INCQS 40042 and CT LM 23)	[122]
Nyctaginaceae							
Neea theifera Oerst.	SW	HE	MIC = 0.122-62.5 µg/mL	*Candida albicans, Candida parapsilosis* and *Candida glabrata*	Broth Microdilution Assay	*C. albicans* (ATCC 10231), *C. parapsilosis* (ATCC 22019) and *C. glabra*ta (LMGO 44)	[121]
Proteaceae							
Roupala montana var. brasiliensis (Klotzsch) K.S.Edwards	SB	Eth	MIC =15.6-500 µg/mL	*Candida albicans, Candida glabrata, Candida krusei, Candida parapsilosis, Candida*	Broth Microdilution Assay	*C. albicans* (ATCC 90028), *C. glabrata* (ATCC 9030), *C. krusei* (ATCC 6258), *C.*	[79]

				tropicalis and *Cryptococcus neoformans*		*parapsilosis* (ATCC 22019), *C. tropicalis* (ATCC 760) and *C. neoformans* (ATCC 32045)	
Rutaceae							
Spiranthera odoratissima A.St.-Hil.	L	EA	MIC= 31.25 µg/mL	*Cryptococcus gattii*	Broth Microdilution Assay	*C.gattii* (LMGO 01)	[107]
Sapindaceae							
Matayba guianensis Aubl.	RB	Eth	MIC= 0.97-31.25 µg/mL	*Candida albicans*, *Candida parapsilosis*, *Trichophyton mentagrophytes* and *Trichophyton rubrum*	Broth Microdilution Assay	*C. albicans* (ATCC 10231), *C. parapsilosis* (ATCC 22019), *T. mentagrophytes* (LMGO 09) and *T. rubrum* (LMGO 06)	[123]
Sapotaceae							
Pouteria ramiflora (Mart.) Radlk.	L	Aq	MIC = 500 µg/disc	*Candida tropicalis*	Disk Diffusion Test	*C. tropicalis* (ATCC 28707)	[118]

Part of plant[1] (FL= Flowers, L= Leaves; Stem Bark= SB; Whole plant= WP; Inner bark = IB; Stem= S; Stem wood = SW; Root Wood= RW; RB=root bark; R= Root).
Type of extract[2] (Aqueous= Aq; Dichloromethane= DM; Ethanolic= Eth; Ethyl-acetate= EA; Essential oils= EO; Brazilian cachaça was used as the extractor liquid = BC; Dry extract = D; Inner bark = IB; Resin oil = OR; Dry extract = D; n-butanol= n-BF; Hexane= HE).

Table S6 Antiviral activity from different species of Cerrado. Information about part from plant and extract preparation, dose tested, model and method analyzed.

Family/Species	Part[1]	Extract[2]	Dose/Concentration	Activity against	Technique	Model	Reference
Anacardiaceae							
Myracrodruon urundeuva M. Allemão	L	Eth	50 and 500 μg/mL	Simian rotavirus SA11	Rotavirus cytopathic effect inhibition and confirmation by RT-PCR	MA-104 cells	[124]
Annonaceae							
Anaxagorea dolichocarpa Sprague & Sandwith	S	Eth	EC50 = 90.5 μg/mL	EMCV	Cytopathic effect inhibition	Vero cells	[125]
Annona dolabripetala Raddi	L	Eth	EC50 = 13.3 μg/mL	VACV	Cytopathic effect inhibition	Vero cells	[125]
Apocynaceae							
Aspidosperma tomentosum Mart. & Zucc.	L	DM	IC50 = 45.86 μg/mL	Avian metapneumovirus	Cytopathic effect inhibition	Chicken embryo related cell	[126]
Hancornia speciosa Gomes	S	Eth	> EC50 > 81.9 μg/mL	HSV-1, VACV, and EMCV	Cytopathic effect inhibition	Vero cells	[125]
Himatanthus phagedaenicus (Mart.) Woodson	S	Eth	EC50= 48.2 μg mL	HSV-1	Cytopathic effect inhibition	Vero cells	[125]
Bignoniaceae							
Amphilophium elongatum (Vahl) L.G.Lohmann	L or S	Eth	EC50 > 24.3 μg/ mL	VACV	Cytopathic effect inhibition	Vero cells	[127]
Cuspidaria sceptrum (Cham.) L.G.Lohmann	S	Eth	EC50= 40.6 μg/ mL	VACV	Cytopathic effect inhibition	Vero cells	[128]
Fridericia formosa (Bureau) L.G.Lohmann	L or S or F	Eth	EC50 > 148.5 μg/mL	HSV-1	Cytopathic effect inhibition	Vero cells	[128]
Fridericia samydoides (Cham.) L.G.Lohmann	L or S	Eth	EC50 > 377.2 μg/mL	HSV-1, VACV, and EMCV	Cytopathic effect inhibition	Vero cells	[127]
Zeyheria tuberculosa (Vell.) Bureau ex Verl.	L	Eth	EC50 > 81.8 μg/mL	HSV-1 and VACV	Cytopathic effect inhibition	Vero cells	[128]
Anemopaegma setilobum A.H.Gentry	S	Eth	EC50 = 95.2 μg/mL	EMCV	Cytopathic effect inhibition	Vero cells	[128]
Callichlamys latifolia (Rich.) K.Schum.	L or S	Eth	EC50 > 312.3 μg/mL	HSV-1, VACV, and EMCV	Cytopathic effect inhibition	Vero cells	[127]

Fridericia chica (Bonpl.) L.G.Lohmann	L	M	IC50 = 412.7 µg/mL	Avian metapneumovirus	Cytopathic effect inhibition	chicken embryo related cell	[126]
Fridericia craterophora (DC.) L.G.Lohmann	L	Eth	EC50 = 68.2 µg/mL	EMCV	Cytopathic effect inhibition	Vero cells	[128]
Dilleniaceae							
Curatella americana L.	B	BC	EC50 = 49 µg/mL	Poliovirus	Cytopathic effect inhibition	Vero cells	[75]
Ericaceae							
Gaylussacia brasiliensis (Spreng.) Meisn. var. brasiliensis	L	DM	IC50 = 22.33 µg/mL	Avian metapneumovirus	Cytopathic effect inhibition	Chicken embryo related cell	[126]
Fabaceae							
Hymenaea courbaril L.	L	Eth	500 µg/mL	Simian rotavirus SA11	Rotavirus cytopathic effect inhibition and confirmation by RT-PCR	MA-104 cells	[129]
Bauhinia holophylla (Bong.) Steud.	L	HEth	IC50= 3.2 µg/mL	DENV-2	Cytopathic effect inhibition	Vero cells	[130]
Lamiaceae							
Hyptis radicans (Pohl) Harley & J.F.B.Pastore	AP	Eth, HE, and HM	MIC50= 159 and 180 µg/mL	HIV-1	Reverse transcriptase (RT) inhibitory assay	*in vitro*	[84]
Malpighiaceae							
Byrsonima verbascifolia (L.) DC.	L	Eth	500 µg/mL	Simian rotavirus SA11	Rotavirus cytopathic effect inhibition and confirmation by RT-PCR	MA-104 cells	[129]
Myristicaceae							
Virola sebifera Aubl.	L	DM	IC50 = 202 µg/mL	Avian metapneumovirus	Cytopathic effect inhibition	Chicken embryo related cell	[126]
Myrtaceae							
Eugenia dysenterica (Mart.) DC.	L	Eth	500 µg/mL	Simian rotavirus SA11	Rotavirus cytopathic effect inhibition and confirmation by RT-PCR	MA-104 cells	[129]

Ochnaceae							
Ouratea spectabilis (Mart.) Engl.	L	Eth	EC50 > 11.4 µg/mL	HSV-1 and VACV	Cytopathic effect inhibition	Vero cells	[125]
Ouratea castaneifolia (DC.) Engl.	L	Eth	EC50 > 465.7 µg/mL	HSV-1, VACV, and EMCV	Cytopathic effect inhibition	Vero cells	[125]
Ouratea semiserrata (Mart. & Nees) Engl.	L or S	Eth	EC50 > 254.4 µg/mL	HSV-1, VACV, and EMCV	Cytopathic effect inhibition	Vero cells	[125]
Polygonaceae							
Polygonum spectabile Mart.	AP	Eth	EC50 > 30.5 µg/mL	HSV-VACV	Cytopathic effect inhibition	Vero cells	[125]
Vitaceae							
Cissus erosa Rich.	S	Eth	EC50 = 27.9 µg/mL	VACV	Cytopathic effect inhibition	Vero cells	[125]

Part of plant[1] (L= Leaves; S= Stem; F= Fruits; Bark= B; AP= aerial parts).
Type of extract[2] (Dichloromethane= DM; Ethanolic= Eth; Ethyl-acetate= EA; Hexane= HE; Methanol= M; Ethanolic= Eth; Hydromethanolic=HM).

Table S7 Antiparasitic activity from different species of Cerrado. Information about part from plant and extract preparation, dose tested, model and method analyzed.

Family/Species	Part[1]	Extract[2]	Dose /Concentration	Activity against	Technique	Experimental model	Reference
Annonaceae							
Annona coriacea Mart.	L	BC	IC50 = 175 µg/mL	*Leishmania amazonensis*	N/S	Promastigotes	[75]
Annona crassiflora Mart.	RB	Eth	IC50= 3.7 and 5.9 µg/mL	*Leishmania donovani* and *Trypanosoma cruzi*	MTT assay and Growth inhibition	Promastigotes	[131]
Duguetia furfuracea (A.St.-Hil.) Saff.	RB	HE	IC50 = 6.6 µg/mL	*Trypanosoma cruzi*	Growth inhibition	Amastigotes	[131]
Xylopia aromatica (Lam.) Mart.	RW	HE	IC50 = 4.7 µg/mL	*Plasmodium falciparum*	Tritiated hypoxanthine incorporation assay	Chloroquine-resistant strain	[132]
Xylopia emarginata Mart.	RB	HE	IC50 = 4.9 µg/mL	*Plasmodium falciparum*	Tritiated hypoxanthine incorporation assay	Chloroquine-resistant strain	[132]
Apocynaceae							
Aspidosperma tomentosum Mart. & Zucc.	S	Eth	IC50 = 9.70 and 15.88 µg/mL	*Leishmania infantum*	Resazurin and infection of macrophage cultures method	Promastigotes and amastigotes	[133]
Himatanthus obovatus (Müll. Arg.) Woodson	B	Eth	IC50 = 7.5 µg/mL	*Leishmania donovani*	MTT assay	Promastigotes	
Aspidosperma							
Aspidosperma macrocarpon Mart. & Zucc.	RB	Eth	IC50 = 4.9 µg/mL	*Plasmodium falciparum*	Tritiated hypoxanthine incorporation assay	Chloroquine-resistant strain	[132]
Asteraceae							
Cyrtocymura scorpioides (Lam.) H.Rob.	AP	EA	IC50 = 16.0 µg/mL	*Leishmania amazonensis*	Infection of macrophage cultures	Amastigotes	[134]
Eremanthus incanus (Less.) Less.	AP	EA	IC50 = 6.0 µg/mL	*Leishmania amazonensis*	Infection of macrophage cultures	Promastigotes	[134]
Pseudogynoxys cabrerae H.Rob. & Cuatrec.	AP	EA	IC50 = 5.0 µg/mL	*Leishmania amazonensis*	Infection of macrophage cultures	Tmastigotes	[134]
Bignoniaceae							
Jacaranda caroba (Vell.) DC.	L	Eth	IC50 = 13.22 µg/mL	*Leishmania amazonensis*	MTT assay	promastigotes	[135]
Jacaranda cuspidifolia Mart.	L	Eth	IC50 = 10.96 µg/mL	*Leishmania amazonensis*	MTT assay	Promastigotes	[135]
Caryocaraceae							

Caryocar coriaceum Wittm.	F or L	Eth and EA	IC50 < 38 µg/mL	*Leishmania amazonensis*	Antipromastigote assay	Promastigotes	[136,137]
Celastraceae							
Connaraceae							
Connarus suberosus Planch.	RB or RW	HE	IC50 = 1.8 27.57 µg/mL	*Leishmania amazonensis, Trypanosoma brucei gambiense* and *Plasmodium falciparum*	MTT assay	Promastigotes	[135,138]
Ebenaceae							
Diospyros hispida A.DC.	R	EA	IC50 = 1 and 18.9 µg/mL	*Leishmania chagasi* and *Plasmodium falciparum*	MTT and Tritiated hypoxanthine incorporation assay	Promastigotes and chloroquine-resistant strain	[107]
Diospyros lasiocalyx (Mart.) B.Walln.	L	Eth	IC50 = 55.48 and 80.63 µg/mL	*Leishmania infantum*	Resazurin method and Infection of macrophage cultures	Promastigotes and amastigotes	[133]
Euphorbiaceae							
Croton urucurana Baill.	SW	HE	IC50 = 3.5 µg/mL	*Plasmodium falciparum*	Tritiated hypoxanthine incorporation assay	Chloroquine-resistant strain	[107]
Fabaceae							
Dipteryx alata Vogel	L	HE	IC50 = 0.08 µg/mL	*Leishmania amazonensis*	MTT assay	Promastigotes	[135]
Enterolobium gummiferum (Mart.) J.F.Macbr.	SB	EA	IC50 = 9.23 µg/mL	*Leishmania amazonensis*	MTT assay	Promastigotes	[139]
Hymenaea courbaril L.	L	Eth and HE	IC50 < 44.10 µg/mL	*Leishmania amazonensis*	MTT assay	Promastigotes	[135]
Hymenaea stigonocarpa Mart. ex Hayne	L	Eth	IC50 = 4.69 µg/mL	*Leishmania amazonensis*	MTT assay	Promastigotes	[135]
Lachesiodendron viridiflorum (Kunth) P.G. Ribeiro, L.P. Queiroz & Luckow	L	Aq and Eth	IC90 = 2.1 and 2.4 µg/mL and 283 mg/kg bw	*Haemonchus contortus*	Egg hatching and fecal egg count inhibition test	Fresh nematode eggs and lambs infected with H. contortus L3	[140]
Stryphnodendron rotundifolium Mart.	SB	Or	IC50 = 1.7- 24.5 µg/mL	*Leishmania amazonensis*	MTT assay	Promastigotes	[141]
Vatairea macrocarpa (Benth.) Ducke	RB	EA	IC50 = 71.47 µg/mL	*Leishmania amazonensis*	MTT assay	Promastigotes	[139]
Lauraceae							

Nectandra megapotamica (Spreng.) Mez	L	EO	IC50 = 98.7 μg/mL	*Trichomonas vaginalis*	Trypan blue assay	Trophozoites	[142]
Malvaceae							
Guazuma ulmifolia Lam	L	Eth	EC50 = 282.63-454.68 μg/mL	*Leishmania brasiliensis, Leishmania infantum* and *Trypanosoma cruzi*	Chlorophenol red-b-Dgalactopyranoside assay	Promastigotes and epimastigotes	[143]
Melastomataceae							
Pleroma stenocarpum (Schrank et Mart. ex DC.) Triana	AP	HE	IC50 = 23.6 μg/mL	*Trypanosoma cruzi*	N/S	Trypomastigotes	[144]
Meliaceae							
Guarea kunthiana A.Juss.	R	HE	IC50 = 7.9 μg/mL	*Leishmania donovani*	MTT assay	Promastigotes	[131]
Myrtaceae							
Blepharocalyx salicifolius (Kunth) O.Berg	L or SB	He, Eth and EA	IC50 < 7 9.3 μg/mL	*Trypanosoma brucei gambiense* and *Plasmodium falciparum*	N/S	Bloodstream forms and chloroquine-resistant strain	[145]
Eugenia uniflora L.	L	EO	IC50 = 0.99 μg/mL	*Leishmania amazonensis*	flagellar motility avaliation	Promastigotes	[39]
Myrcia variabilis DC.	AP	Eth	IC50 = 30.5 μg/mL	*Trypanosoma cruzi*	N/S	Trypomastigotes	[144]
Psidium brownianum Mart. ex DC	L	HEth or Aq	1000 μg/mL	*Trypanosoma cruzi*	Chlorophenol red-b-Dgalactopyranoside assay	Tpimastigotes	[41]
Psidium laruotteanum Cambess.	L	HE or EA	IC50 < 6.8 μg/mL	*Trypanosoma brucei gambiense*	N/S	Bloodstream forms	[145]
Primulaceae							
Myrsine guianensis (Aubl.) Kuntze	SW	HE	IC50 = 5.0 μg/mL	*Plasmodium falciparum*	N/S	Chloroquine-resistant strain	[138]
Rubiaceae							
Genipa americana L.	L	M	IC50 = 470 and 710 μg/mL	*Trypanosoma cruzi*	Cell infection and mobility avaliation	Amastigotes, epimastigotes and trypomastigotes	[92]
Spiranthera odoratissima A.St.-Hil.	R and L	HE and EA	IC50 = 22.3 and 56.3 μg/mL	*Leishmania chagasi* and *Trypanosoma cruzi*	MTT assay	Epimastigotes and promastigotes	[107]

Salicaceae							
Casearia sylvestris Sw. var. sylvestris	L, RB, SW, SB or RW	Eth or HE	IC50 < 9.48 µg/mL	*Leishmania donovani*, *Plasmodium falciparum*, *Leishmania infantum* and *Trypanosoma cruzi*	Growth inhibition, tritiated hypoxanthine incorporation and MTT assay	Amastigotes, chloroquine-resistant strain promastigotes andtrypomastigotes	[131,132,146]
Sapindaceae							
Serjania lethalis A.St.-Hil.	RB, L and S	HE and DM	IC50 < 28.33 µg/mL	*Leishmania donovani* and *Leishmania amazonensis*	MTT, XTT assay and infection of macrophage cultures	Promastigotes and amastigotes	[131,147]
Cupania vernalis Cambess.	L	HE	IC50 = 0.9 and 7.1 µg/mL	*Leishmania donovani* and *Plasmodium falciparum*	MTT and tritiated hypoxanthine incorporation assay	Promastigotes and chloroquine-resistant strain	[131,132]
Simarouba versicolor A.St.-Hil.	L	DM	IC50 = 3.1 µg/mL	*Plasmodium falciparum*	Tritiated hypoxanthine incorporation assay	chloroquine-resistant strain	[107]
Solanaceae							
Solanum palinacanthum Dunal	F	Eth	IC50 = 15.3 and 175.9 µg/mL	*Trypanosoma cruzi*	MTT assay	Epimastigotes	[148]
Solanum lycocarpum A.St.-Hil.	F	Eth or HA	IC50 = 3.0-194.7 µg/mL	*Leishmania infantum* and *Trypanosoma cruzi*	flagellar motility avaliation, infection of macrophage cultures and MTT assay	Promastigotes, amastigotes, epimastigotes and trypomastigotes	[144,148,149]
Vochysiaceae							
Qualea grandiflora Mart.	L and F	Eth and EA	IC50 < 15 µg/mL	*Trypanosoma brucei gambiense* and *Plasmodium falciparum*	Resazurin method and SYBR Green I method	Bloodstream forms and sensitive and resistant strains	[150,151]

Part of plant[1] (AP= aerial parts; F= Fruits; L= Leaves; RB=root bark; R= Root; Root Wood= RW; S= Stem; Stem Bark= SB; Bark= B).
Type of extract[2] (Aqueous= Aq; Dichloromethane= DM; Ethanolic= Eth; Ethyl-acetate= EA; Hexane= HE; Essential oils= EO; Hydroalcoholic= HÁ; Hydroethanolic= HEth; Organic fraction=Or; Methanol= M).
NOT SPECIFIED=NS

Table S8 Insecticidal activity from different species of Cerrado. Information about part from plant and extract preparation, dose tested, model and method analyzed.

Family/Species	Part[1]	Extract[2]	Dose /Concentration	Activity against	Technique	Model	Reference
Anacardiaceae							
Anacardium occidentale L.	N	EO	LC50 = 14.5 µg/L	*Aedes aegypti*	Mortality determination	4th-stage larvae	[152]
Annonaceae							
Annona crassiflora Mart.	R and S	Eth and Chl	LC50 = 23.06 µg/mL	*Aedes aegypti* and *Chrysodeixis includens*	Mortality determination and topical application	3rd-stage larvae and larvae	[28, 229]
Annona mucosa Jacq.	S	Eth	411.55 mg/kg	*Helicoverpa armigera*	Greenhouse trial	neonate larvae	[155]
Duguetia furfuracea (A. St. Hil.) Benth & Hook	R	HE	LC50 = 56.6 µg/mL	*Aedes aegypti*	Mortality determination	3rd-stage larvae	[153]
Duguetia lanceolata A.St.-Hil.	L	EO	LC50 = 442 and 457 µg/mL	*Zabrotes subfasciatus* and *Sitophilus zeamais*	Residual contact	0 to 24 h aged insects and nonsexed 10 to 20-day-old adults	[156]
Xylopia aromatica (Lam.) Mart.	L or F	Eth and EO	LC50 = 384.37 µg/mL	*Aedes aegypti* and *Bemisia tabaci*	Mortality determination and no-choice and free-choice bioassay	3rd-stage larvae and adults whiteflies	[153,157]
Apocynaceae							
Aspidosperma macrocarpon Mart. & Zucc.	RW	HE	IC50 > 1000 µg/mL	*Zabrotes subfasciatus*	*In vitro* inhibition assay	Larvae digestive enzymes	[158]
Asteraceae							
Ageratum conyzoides L.	L	EO	LC50 = 148 µg/L	*Aedes aegypti*	Mortality determination	4th-stage larvae	[152]
Ageratum fastigiatum (Gardner) R.M.King & H.Rob.	L and FL	Eth	Mortality = 6.67%	Coccinellidae predators	Residual contact	4-day-old adult	[159]
Piptocarpha rotundifolia (Less.) Baker	R	HE	LC50 = 162.31 µg/mL	*Aedes aegypti*	Mortality determination	3rd-stage larvae	[153]
Bignoniaceae							

Adenocalymma nodosum (Silva Manso) L.G.Lohmann	L	MA	80% mortality at 0.01%	Tenebrio molitor	Topical application	2-day-old pupae	[160]
Cybistax antisyphilitica (Mart.) Mart.	S	HE	LC50 = 27.61 µg/mL	*Aedes aegypti*	Mortality determination	3rd-stage larvae	[153]
Calophyllaceae							
Kielmeyera coriacea Mart. & Zucc.	SB	Heth	IC50 = 110 and 272.12 µg/mL	*Zabrotes subfasciatus* and *Acanthoscelides obtectus*	*In vitro* inhibition assay	Larvae digestive enzymes	[158]
Combretaceae							
Terminalia fagifolia Mart.	S	Eth	LC50 = 373.14 µg/mL	*Aedes aegypti*	Mortality determination	Larvae	[161]
Fabaceae							
Anadenanthera colubrina (Vell.) Brenan	W	CHE	LC50 = 11.9 µg/mL	*Nasutitermes corniger*	No-choice feeding termiticidal assay	active termites	[162]
Bowdichia virgilioides Kunt	HW	CHE	LC50 = 7.2 or 21.95 µg/mL	*Nasutitermes corniger* and *Aedes aegypti*	Mortality determination and No-choice feeding termiticidal assay	4th-stage larvae and active termites	[162,163]
Copaifera multijuga Hayne	OR and B	EO, Eth	LC50 = 0.7, 0.9, 3 and 18 ppm	*Aedes aegypti* and *Anopheles darlingi*	Mortality determination	larvae	[164]
Hymenaea stigonocarpa Mart. ex Hayne	HW	EA	LC50 = 17.3 µg/mL	*Nasutitermes corniger*	No-choice feeding termiticidal assay	Active termites	[162]
Copaifera langsdorffii Desf.	S, L and F	EO and M	LC50 = 13.7-41 µg/mL	*Aedes aegypti* and *Spodoptera frugiperda*	Mortality determination and artificial diet	4th-stage larvae and 1st and 2nd-instar caterpillars	[152,165]
Peltophorum dubium (Spreng.) Taub.	S	TI	Survival = 44.3% at 1.6%	*Anagasta kuehniella*	Artificial diet	4th-stage larvae	[166]
Pterodon emarginatus Vogel	F	EO	LC50 = 371.6 µg/mL	*Aedes aegypti*	Mortality determination	4th-stage larvae	[167]
Lamiaceae							
Hyptis crenata Pohl ex Benth.	AP	EO	PE = 94.4% at 2.5% concentration	*Rhipicephalus microplus*	Adult immersion test	Engorged females	[79]
Lauraceae							

Ocotea lancifolia (Schott) Mez	L	Eth	PE = 34.50% at 0.2 % concentration	*Rhipicephalus microplus*	Adult immersion test	Engorged females	[168]
Ocotea velloziana (Meisn.) Mez	SW	Eth	LC50 = 30.2 and 213.70 µg/mL	*Aedes aegypti*	Mortality determination and bioassay-directed fractionation	larvae	[161]
Loganiaceae							
Strychnos pseudoquina A. St.-Hil.	S	Eth	PE = 48.03% at 0.2 % concentration	*Rhipicephalus microplus*	Adult immersion test	Engorged females	[168]
Melastomataceae							
Mouriri elliptica Mart.	L	EA and M	12.43- 20 µg/mL	Generic α-amylase and generic acetylcholinesterase	*In vitro* inhibition assay	Purified enzyme	[169]
Meliaceae							
Cabralea canjerana (Vell.) Mart.	SE	EA	330 mg/kg	*Spodoptera frugiperda*	Artificial diet	3rd instar larvae	[170]
Guarea guidonia (L.) Sleumer	R	HE	50 µg	*Rhodnius milesi*	Topical test	4th-instar nymphs	[171]
Guarea kunthiana A. Juss.	S and F	Eth	LC50 = 14.44 and 169.93 µg/mL	*Aedes aegypti* and *Rhipicephalus microplus*	Mortality determination and adult immersion test	3rd-stage larvae andengorged females	[168,172,173]
Myrtaceae							
Eugenia involucrata DC.	L	EO	LC50 = 199.3 µg/mL	*Aedes aegypti*	Mortality determination	3rd-stage larvae	[169]
Psidium laruotteanum Cambess.	L	Eth	2% concentration	*Diabrotica speciosa*	soil treatment	3-day old larvae	[174]
Piperaceae							
Piper aduncum L.	L	EO	LC50 = 289.9 ppm	*Aedes aegypti*	Mortality determination	Larvae	[175]
Rubiaceae							
Psychotria capitata Ruiz & Pav.	S	Eth	Efficacy = 71.05%	Sitophilus zeamais	Artificial diet	nonsexed 10-day-old adults	[176]
Psychotria deflexa DC. subsp. deflexa	S	Eth	Efficacy = 95.83%	*Spodoptera frugiperda*	Artificial diet	1-day-old caterpillar	[176]
Psychotria hoffmannseggiana	S	Eth	Efficacy = 56.00%	Sitophilus zeamais	Artificial diet	nonsexed 10-day-old adults	[176]

(Willd. ex Schult.) Müll.Arg.							
Psychotria prunifolia (Kunth) Steyerm.	L	Eth	LT50 = 89.73 h and Efficacy = 60.21%	*Sitophilus zeamais* and *Sitotroga cerealella*	Artificial diet and residual contact	90-day-old unsexed adults and larvae	[177,178]
Rutaceae							
Zanthoxylum rhoifolium Lam.	F	EO	Efficiency = 98.3% at 2%	*Bemisia tabaci*	No-choice and free-choice bioassay	adults whiteflies	[179]
Zanthoxylum riedelianum Engl.	F	EO	Efficiency = 94.2% at 1.5%	*Bemisia tabaci*	No-choice and free-choice bioassay	adults whiteflies	[179]
Salicaceae							
Casearia sylvestris Sw. var. sylvestris	S	HE	LC50 = 232.4 μg/mL	*Aedes aegypti*	Mortality determination	3rd-stage larvae	[153]
Sapindaceae							
Serjania lethalis A.St.-Hil.	R	Eth	LC50 = 285.76 μg/mL	*Aedes aegypti*	Mortality determination	3rd-stage larvae	[153]
Simaroubaceae							
Simarouba versicolor A.St.-Hil.	RB	Eth	50 μg	*Rhodnius milesi*	Topical test	4th-instar nymphs	[171]
Smilacaceae							
Smilax brasiliensis Spreng.	L	CHE	LC50 = 469.78 μg/mL	*Culex quinquefasciatus*	Mortality determination	Larvae	[180]

Part of plant[1] (Aerial parts=AP; Fruits= F; Flowers= F; Nuts=N; Leaves= L; Root bark= RB; Root= R; Root Wood= RW; Stem= S; Stem Bark= SB; Bark= B; Send= SE; Heartwood=HW).
Type of extract[2] (Ethanolic= Eth; Ethyl-acetate= EA; Methanol-acetate= MA; Hexane= HE; Chloroform= Chl; Essential oils= EO;Methanol= M; Hydroethanolic= HEth; Cyclohexane= CHE; Trypsin inhibitor=TI).

Table S9 Molluscicidal activity from different species of Cerrado. Information about part from plant and extract preparation, dose tested, model and method analyzed.

Family/Species	Part[1]	Extract[2]	Dose /Concentration	Activity against	Technique	Experimental model	Reference
Caryocaraceae							
Caryocar brasiliense Cambess.	L or B	Eth	100 ppm = 90% mortality in 48 h	*Biomphalaria glabrata*	Snails submersion for 24 h	*Biomphalaria glabrata*	[181]
Dilleniaceae							
Davilla rugosa Poir.	L	DM	LC100/72 h = 100 ppm	*Biomphalaria glabrata*	Snails submersion for 24 h	*Biomphalaria glabrata*	[82]
Fabaceae							
Stryphnodendron adstringens (Mart.) Coville	L or B	Eth	50 ppm = 60-90% mortality in 48 h	*Biomphalaria glabrata*	Snails submersion for 24 h	*Biomphalaria glabrata*	[181]
Stryphnodendron polyphyllum Mart.	L or B	Eth	50 ppm = 70% mortality in 48 h	*Biomphalaria glabrata*	Snails submersion for 24 h	*Biomphalaria glabrata*	[181]
Hymenaea stigonocarpa Mart. ex Hayne	B or L	DM or M	40 < LC100/72 h > 100 ppm	*Biomphalaria glabrata*	Snails submersion for 24 h	*Biomphalaria glabrata*	[82]
Plathymenia reticulata Benth.	L	M	LC100/72 h = 100 ppm	*Biomphalaria glabrata*	Snails submersion for 24 h	*Biomphalaria glabrata*	[82]
Malpighiaceae							
Byrsonima coccolobifolia Kunth	L	DM	LC100/72 h = 100 ppm	*Biomphalaria glabrata*	Snails submersion for 24 h	*Biomphalaria glabrata*	[82]
Byrsonima intermedia A.Juss.	L	M	LC100/72 h = 20 ppm	*Biomphalaria glabrata*	Snails submersion for 24 h	*Biomphalaria glabrata*	[82]
Byrsonima verbascifolia (L.) DC.	L or B	DM or M or Aq	40 < LC100/72 h > 60 ppm	*Biomphalaria glabrata*	Snails submersion for 24 h	*Biomphalaria glabrata*	[82]
Metteniusaceae							
Emmotum nitens (Benth.) Miers	S	M	LC100/72 h = 100 ppm	*Biomphalaria glabrata*	Snails submersion for 24 h	*Biomphalaria glabrata*	[82]
Myrtaceae							
Eugenia dysenterica (Mart.) DC.	L	DM and Eth	LC100/72 h = 100 ppm and 100 ppm = 100% mortality in 48 h	*Biomphalaria glabrata*	Snails submersion for 24 h	*Biomphalaria glabrata*	[82,181]
Styracaceae							
Styrax camporum Pohl	L	DM	LC100/72 h = 100 ppm	*Biomphalaria glabrata*	Snails submersion for 24 h	*Biomphalaria glabrata*	[82]

Vochysiaceae							
Qualea parviflora Mart.	B	Aq	LC100/72 h = 100 ppm	*Biomphalaria glabrata*	Snails submersion for 24 h	*Biomphalaria glabrata*	[82]

Part of plant[1] (Leaves= L; Stem= S; Bark= B).
Type of extract[2] (Aqueous= Aq; Dichloromethane= DM; Ethanolic= Eth; Methanol= M).

Table S10 Secondary metabolites isolated from Cerrado plants that present toxic activity. Information on chemical class, tested dose, model and analyzed method.

Identified compound	Species	Class	Concentration	Technique	Experimental model	Reference
Cytotoxic						
Octacosane **(1)**	*Pyrostegia venusta* (Ker Gawl.) Miers	Alkanes	41.08 µg/mL	MTT assay	B16F10-Nex2 cells	[9]
Triacontane **(2)**	*Pyrostegia venusta* (Ker Gawl.) Miers	Alkanes	20.9 µg/mL	MTT assay	B16F10-Nex2 cells	[9]
Sellovicine B **(3)**	*Croton velutinus* Baill.	Phenylpropanoids	6.8-18.3 µM/mL	Alamar Blue assay	HepG2 and MCF-7 cells	[182]
(E)-1-(7,8-epoxypropen) phenyl benzoate **(4)**	*Croton velutinus* Baill.	Phenylpropanoids	11.1-19.4 µm/mL	Alamar Blue assay	HepG2 and MCF-7 cells	[182]
Phloretin **(5)**	*Lippia salviaefolia* Cham.	Flavonoids	20-40 µM	MTT assay	HEK-293 and M14 cells	[44]
[1-9-NαC]-crourorb A1 (6)	*Croton urucurana* Baill.	Corbitides	50- 200 µg/mL	WST-1 assay	Huh-7 cells	[23]
d-tocotrienol **(7)**	*Kielmeyera coriácea* Mart. & Zucc.	Terpenes	5 and 10 µg/mL	Trypan blue assay	MDA-MB-435, HCT-8, HL-60 and SF-295 cells	[12]
d-tocotrienol peroxy-dimer **(8)**	*Kielmeyera coriacea* Mart. & Zucc.	Terpenes	5 and 10 µg/mL	Trypan blue assay	MDA-MB-435, HCT-8, HL-60 and SF-295 cells	[12]
11β-hydroxypristimerin **(9)**	*Salacia crassifólia* (Mart. ex Schult.) G.Don	Terpenes	8.7 µM	Formazan Endpoint assay	NCI-60 and 786-0 cells	[183]
Pristimerin **(10)**	*Salacia crassifolia* (Mart. ex Schult.) G.Don	Terpenes	0.3-1.2 µM	Formazan Endpoint assay	NCI-60, UO-31, T-47D and A549 cells	[183]
Zornioside (C-glycosylated dihydrochalcone) **(11)**	*Zornia brasiliensis* Vogel	Flavonoids	37.26 µM	MTT assay	HL60 cells	[184]
Vallesiachotamine **(12)**	*Palicourea rigida* Kunth	Alkaloids	50 µM	MTT assay	SK-MEL-37 cells	[185]
β-friedelinol **(13)**	*Cheiloclinium cognatum* (Miers) A.C.Sm.	Terpenes	15.75-55.20 µmol/L-1	MTT assay	THP-1, K562 and PMBC cells	[16]
α-amyrin **(14)**	*Cheiloclinium cognatum* (Miers) A.C.Sm.	Terpenes	9.92-55.65 µmol/L-1	MTT assay	THP-1, K562 and PMBC cells	[16]
Dioscin **(15)**	*Chamaecostus subsessilis* (Nees & Mart.) C.D.Specht & D.W.Stev.	Saponins	4.6 and 15.1 µg/mL	MTT assay	HL60 cells	[19]
Gracillin **(16)**	*Chamaecostus subsessilis* (Nees & Mart.) C.D.Specht & D.W.Stev.	Saponins	4.6 and 15.1 µg/mL	MTT assay	HL60 cells	[19]
Mutagenic						
Isoobtusilactone A **(17)**	*Aiouea trinervis* Meisn.	Butanolides	0.1- 0.3 mg/mL	SMART test	*Drosophila melanogaster*	[186]
Obtusilactone A **(17)**	*Aiouea trinervis* Meisn.	Butanolides	0.1- 0.3 mg/mL	SMART test	*Drosophila melanogaster*	[186]

Amentoflavone **(18)**	*Byrsonima crassa* Nied.	Flavonoids	0.1- 0.3 mg/mL	Ames test	*Salmonella typhimurium*	[50]
Antibacterial						
Gallic acid **(19)**	*Cochlospermum regium* (Mart. ex Schrank) Pilg.	Tannines	MIC = 50.8 - 101.6 µg/mL	Broth Microdilution Assay	*Staphylococcus aureus*, *Staphylococcus epidermidis*, *Escherichia coli*, *Pseudomonas aeruginosa* and E*nterococcus faecalis*	[187]
Tannic acid **(20)**	*Cochlospermum regium* (Mart. ex Schrank) Pilg.	Tannines	MIC = 250-500 µg/mL	Broth Microdilution Assay	*Staphylococcus aureus* (29213)and *Escherichia coli* (25922) strains	[71]
Spathulenol **(21)**	*Psidium guineense* Sw.	Terpenes	MIC = 31.25-125 µg/mL	Broth Microdilution Assay	*Klebsiella pneumoniae*, P*seudomonas aeruginosa* and *Acinetobacter baumannii*	[95]
Mauritic acid **(22)**	*Mauritia flexuosa* L.f.	Terpenes	MIC = 231.9 µg/mL	REMA method	*Mycobacterium tuberculosis*	[187]
5-(3''-hydroxypropyl)- 7- methoxy-2-(3',4' -dimethoxyphenyl) benzofuran **(23)**	*Styrax ferrugineus* Nees & Mart.	Arylpropanoids	MIC= 10-20 µg/mL	Broth Microdilution Assay	*Staphylococcus aureus*	[188]
5-(3''-hydroxypropyl)-7-methoxy-2-(3',4'-methylenedioxyphenyl) benzofuran **(24)**	*Styrax ferrugineus* Nees & Mart.	Arylpropanoids	MIC= 10-20 µg/mL	Broth Microdilution Assay	*Staphylococcus aureus*	[188]
5- [3''-(b-d-glucopyranosyloxy)propyl]-7-methoxy-2-(3' ,4' - methylenedioxyphenyl) benzofuran **(25)**	*Styrax ferrugineus* Nees & Mart.	Arylpropanoids	MIC= 10-20 µg/mL	Broth Microdilution Assay	*Staphylococcus aureus*	[188]
5-[3''-(b-d-glucopyranosyloxy)propyl]-7-methoxy-2-(3' ,4' - dimethoxyphenyl) benzofuran **(26)**	*Styrax ferrugineus* Nees & Mart.	Arylpropanoids	MIC= 10-20 µg/mL	Broth Microdilution Assay	*Staphylococcus aureus*	[188]
Dihydrodehydrodiconiferyl alcohol **(27)**	*Styrax ferrugineus* Nees & Mart.	Arylpropanoids	MIC= 10-20 µg/mL	Broth Microdilution Assay	*Staphylococcus aureus*	[188]
Antifungal						
Gallic acid **(19)**	*Cochlospermum regium* (Mart. ex Schrank) Pilg.	Tannines	MIC = 31.25 µg/mL	Broth Microdilution Assay	*Candida albicans*	[71]

Tannic acid **(20)**	*Cochlospermum regium* (Mart. ex Schrank) Pilg.	Tannines	MIC = 125-250 μg/mL	Broth Microdilution Assay	*Candida albicans*, *Candida krusei* and *Candida glabrata*	[71]
Mauritic acid **(22)**	*Mauritia flexuosa* L.f.	Terpenes	MIC = 203.5 μg/mL	Broth Microdilution Assay	*Candida albicans*	[187]
5-(3''-hydroxypropyl)- 7- methoxy-2-(3',4' -dimethoxyphenyl) benzofuran (23)	*Styrax ferrugineus* Nees & Mart.	Arylpropanoids	MIC= 10-20 μg/mL	Broth Microdilution Assay	*Staphylococcus aureus*	[188]
5-(3''-hydroxypropyl)-7-methoxy-2-(3',4'-methylenedioxyphenyl) benzofuran (24)	*Styrax ferrugineus* Nees & Mart.	Arylpropanoids	MIC= 10-20 μg/mL	Broth Microdilution Assay	*Candida sphaerospermum* and *Candida albicans*	[188]
5- [3''-(b-d-glucopyranosyloxy)propyl]-7-methoxy-2-(3' ,4' - methylenedioxyphenyl) benzofuran (25)	*Styrax ferrugineus* Nees & Mart. Nees & Mart.	Arylpropanoids	MIC= 10-20 μg/mL	Broth Microdilution Assay	*Candida sphaerospermum* and *Candida albicans*	[188]
5-[3''-(b-d-glucopyranosyloxy)propyl]-7-methoxy-2-(3' ,4' - dimethoxyphenyl) benzofuran (26)	*Styrax ferrugineus* Nees & Mart.	Arylpropanoids	MIC= 10-20 μg/mL	Broth Microdilution Assay	*Candida sphaerospermum* and *Candida albicans*	[188]
Dihydrodehydrodiconiferyl alcohol **(27)**	*Styrax ferrugineus* Nees & Mart.	Arylpropanoids	MIC= 10-20 μg/mL	Broth Microdilution Assay	*Candida sphaerospermum* and *Candida albicans*	[188]
Vatacarpan **(28)**	*Vatairea macrocarpa* (Benth.) Ducke	Flavonoids	MIC = 0.98 μg/mL	Broth Microdilution Assay	*Candida albicans*	[111]
Brachydin B (BR-B) **(29)**	*Arrabidaea brachypoda* (DC.) Bureau	Flavonoids	MIC = 161 μg/mL	Broth Microdilution Assay	*Candida albicans*	[189]
4'-O-Methyl-catechin **(30)**	*Curatella americana* L.	Catechins	MIC = 31.3 -125 μg/mL	Broth Microdilution Assay	*Candida albicans*, *Candida tropicalis* and *Candida parapsilosis*	[110]
Epicatechin-3-O-gallate **(31)**	*Curatella americana* L.	Catechins	MIC = 31.3 -125 μg/mL	Broth Microdilution Assay	*Candida albicans*, *Candida tropicalis* and *Candida parapsilosis*	[110]
Isoverbascoside **(32)**	*Pyrostegia venusta* (Ker Gawl.) Miers	Phenylpropanoids	MIC = 0.7-6.0 μg/mL	Broth Microdilution Assay	*Candida albicans*, *Candida krusei*, *Candida tropicalis*, *Candida parapsilosis* and *Candida guilhermondii*	[190]

Verbascoside **(33)**	*Pyrostegia venusta* (Ker Gawl.) Miers *Pyrostegia venusta* (Ker Gawl.) Miers	Phenylpropanoids	MIC = 0.7-1.5 μg/mL	Broth Microdilution Assay	*Candida albicans, Candida krusei, Candida tropicalis, Candida parapsilosis and Candida guilhermondii*	[190]
Rapanone **(34)**	*Connarus suberosus* Planch.	Quinones	MIC = 15.62 μg/mL	Broth Microdilution Assay	*Candida albicans*	[121]
Suberonone **(35)**	*Connarus suberosus* Planch.	Quinones	MIC = 125-250 μg/mL	Broth Microdilution Assay	*Candida parapsilosis* and *Candida glabrata*	[121]
(2S)- and (2R)-30 ,40,5,6-Tetrahydroxyflavanone-7-O-b-glucopyranoside **(36)**	*Lippia origanoides* Kunth	Flavonoids	MIC = 5-12 μg/mL	Broth Microdilution Assay	*Candida albicans* and *Cladosporium cladosporioides*	[188]
(2S)- and (2R)-30 ,40 ,5,8-tetrahydroxyflavanone-7-O-b-glucopyranoside **(37)**	*Lippia origanoides* Kunth	Flavonoids	MIC = 31.2- 62.5 μg/mL	Broth Microdilution Assay	*Candida krusei*, *Candida parapsilosis* and *Cryptococcus neoformans*	[191]
Biochanin A **(38)**	*Lippia lupulina* Cham.	Flavonoids	MIC = 62.5 μg/mL	Broth Microdilution Assay	*Candida krusei* and *Cryptococcus neoformans*	[191]
Antiparasitic						
Sellovicin B **(3)**	*Croton velutinus* Baill.	Phenylpropanoids	EC50 = 9 μM	Parasite Integrity and Motility	Trypomastigotes	[182]
(E)-1-(7,8-epoxypropen) phenyl benzoate **(4)**	*Croton velutinus* Baill.	Phenylpropanoids	EC50 = 9.58 μM	Parasite Integrity and Motility	Trypomastigotes	[182]
gallic acid **(19)**	*Stryphnodendron obovatum* Benth.	Tannines	IC50 = 1.7 μg/mL^{-1}	MTT assay	Promastigotes	[141]
Cupacinoside **(39)**	*Cupania cinérea* Poepp. & Endl.	Terpenes	IC50 = 1.3 μM	Tritiated Hypoxanthine Incorporation assay	K1 strain	[192]
6′-de-O-acetylcupacinoside **(40)**	*Cupania cinérea* Poepp. & Endl.	Terpenes	IC50 = 1.8 μM	Tritiated Hypoxanthine Incorporation assay	K1 strain	[192]
Cupacinoxepin **(41)**	*Cupania cinerea* Poepp. & Endl.	Terpenes	IC50 = 8.7 μM	Tritiated Hypoxanthine	K1 strain	[192]

				Incorporation assay		
Casearin A **(42)**	*Casearia sylvestris* Sw.	Terpenes	4.45-9.48 μg/mL^{-1}	MTT assay	Promastigotes	[146]
Casearin B **(43)**	*Casearia sylvestris* Sw.	Terpenes	0.53- 2.77 μg/mL^{-1}	MTT assay	Trypomastigotes	[146]
Casearin J **(44)**	*Casearia sylvestris* Sw.	Terpenes	4.45 -9.48 μg/mL^{-1}	MTT assay	Promastigotes	[146]
Casearin G **(45)**	*Casearia sylvestris* Sw.	Terpenes	0.53- 2.77 μg/mL^{-1}	MTT assay	Trypomastigotes	[146]
Tingenone **(46)**	*Cheiloclinium cognatum* (Miers) A.C.Sm.	Terpenes	IC50 = 486.6 μM	N/S	Trypomastigotes	[193]
Tingenol **(47)**	*Cheiloclinium cognatum* (Miers) A.C.Sm.	Terpenes	IC50 = 306.9 μM	N/S	Trypomastigotes	[193]
Solamargine **(48)**	*Solanum lycocarpum* A.St.-Hil.	Alkaloids	IC50 = 3.0 and 8.1 μg/mL^{-1}	Flagellar Motility Avaliation	Promastigotes	[194]
Solamargine **(48)**	*Solanum palinacanthum* Dunal	Alkaloids	IC50 = 15.3 μg/mL^{-1}	MTT assay	Epimastigotes	[148]
ent-kaurane **(49)**	*Aldama discolor* (Baker) E.E.Schill. & Panero	Terpenes	IC50 = 2.5 μM	Tritiated Hypoxanthine Incorporation assay	K1 strain	[195]
ent-pimarane **(50)**	*Aldama discolor* (Baker) E.E.Schill. & Panero	Terpenes	IC50 = 3.8 μM	Tritiated Hypoxanthine Incorporation assay	K1 strain (resistant to chloroquine and pyrimethamine)	[195]
Epigallocatechin gallate **(51)**	*Stryphnodendron obovatum* Benth.	Flavonoids	IC50 = 16.3 μg/mL^{-1}	MTT assay	Promastigotes	[141]
Solasodine **(52)**	*Solanum lycocarpum* Benth.	Alkaloids	IC50 = 4.7 and 10.8 μg/mL^{-1}	Flagellar Motility Avaliation	Promastigotes	[194]
Solasonine **(53)**	*Solanum lycocarpum* Benth.	Alkaloids	IC50 = 4.7 and 22.7 μg/mL^{-1}	Flagellar Motility Avaliation	Promastigotes	[194]
Insecticidal						
(+)-dicentrine **(54)**	*Ocotea velloziana* (Meisn.) Mez	Alkaloids	LC50 = 30.2 μg/mL^{-1}	Bioassay-Directed Fractionation	larvae	[161]
Alepterolic acid **(55)**	*Copaifera multijuga* Hayne	Terpenes	LC50 = 0.7 ppm	Mortality Determination	larvae	[164]
Maackiain **(56)**	*Bowdichia virgilioides* Kunth	Flavonoids	LC50 = 21.95 μg/mL^{-1}	Mortality Determination	4th-stage larvae	[163]
Melianodiol **(57)**	*Guarea kunthiana* A.Juss.	Protolimonoids	LC50 = 14.44 μg/mL^{-1}	Mortality Determination	3rd-stage larvae	[196]

3β-O-tigloylmelianol **(58)**	*Guarea kunthiana A.Juss.*	Protolimonoids	1%	Adult Immersion test	engorged females	[173]
Astilbin **(59)**	*Dimorphandra mollis* Benth.	Flavonoids	10- 20 mg/mL^{-1}	Topical Application and Artificial Diet	eggs neonate larvae	[197–199]
Tectoquinone **(60)**	*Connarus suberosus* Planch.	Quinones	LC50 1.1 μg/mL	Mortality Determination	larvae	[200]
Lectin (N/S)	*Myracrodruon urundeuva* M. Allemão	(N/A)	LC50 = 202 $\mu g/mL^{-1}$	Mortality Determination	4th-stage larvae	[201]

Not Specificid=N/S

Cells lines: MDA-MB-435 (melanoma), HCT-8 (colon), HL-60 (leukemia), SF-295 (glioblastoma), B16F10-Nex2 (murine melanoma), 786-0 (kidney adenocarcinoma),Huh-7 (human hepatocarcinoma), HepG2 (hepatocyte carcinoma), HEK-293 (Human embryonic kidney), M14 (melanoma), NCI-60 (Mammalian Cell Lines), UO31 (Human Kidney Renal Cell Carcinoma), A549 (adenocarcinomic human), SK-MEL-37 (Human Melanoma), THP-1 (acute monocytic leukemia ATCCTIB-202), K562 (chronic myeloid leukemia ATCC CRL-3343) and PBMCs (Peripheral Blood Mononuclear).

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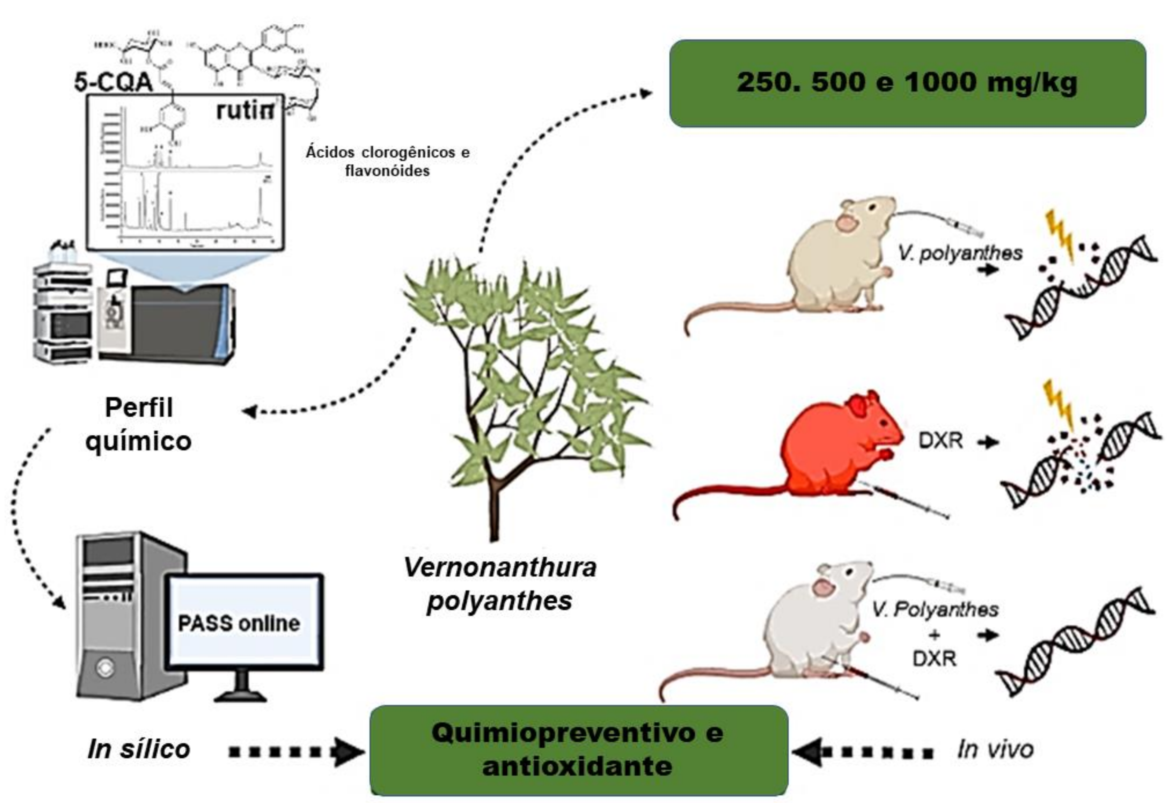
4. Artigo 2

Composição fitoquímica e efeito protetor das folhas de *Vernonanthura polyanthes* contra a toxicidade mediada por doxorrubicina *in vivo*

Resumo gráfico



Resumo

Vernonanthura polyanthes (Spreng.) A.J. Vega & Dematt. (sin.: *Vernonia polyanthes* Less) é popularmente conhecida como "assa peixe" e suas folhas são utilizadas na medicina popular principalmente no tratamento de doenças respiratórias. Neste estudo, avaliamos o potencial citogenotóxico e anticitogenotóxico do extrato aquoso da folha de *V. polyanthes* (*Vp*LAE) e sua fração n-butanol (n-BF) na presença ou ausência de doxorrubicina (DXR) (pré-, co-, e pós-tratamentos) em um modelo murino por 24 h ou 120 h. O teste do micronúcleo (MN) e o ensaio do cometa foram utilizados para avaliar o potencial citogenotóxico e anticitogenotóxico de *Vp*LAE e n-BF (250, 500 e 1000 mg/kg) administrados por gavagem a camundongos Swiss Webster. Os perfis químicos de *Vp*LAE e n-BF foram avaliados por cromatografia líquida acoplada à espectrometria de massa, e seus metabólitos foram supostamente identificados. Por fim, as possíveis atividades biológicas relacionadas à (anti)citogenotoxicidade dos compostos foram previstas usando o servidor online PASS. Os resultados *in vivo* mostraram que diferentes doses de *Vp*LAE e n-BF não apresentaram atividade citotóxica; no entanto, o teste de MN revelou uma leve atividade mutagênica para os tratamentos de 24 h. Efeitos genotóxicos moderados foram

demonstrados para todos os tratamentos no ensaio do cometa. Em relação à anticitotoxicidade e antimutagenicidade, *Vp*LAE e n-BF apresentaram alto potencial citoprotetor contra efeitos tóxicos de DXR. No co-tratamento, o *Vp*LAE reduziu a genotoxicidade do DXR em ~27% e o n-BF não demonstrou potencial antigenotóxico. Em contraste, um efeito antigenotóxico foi observado para *Vp*LAE e n-BF nos pré e pós-tratamentos, reduzindo a genotoxicidade do DXR em ~41% e ~47%, respectivamente. A análise química de *Vp*LAE e n-BF mostrou a presença de oito compostos fenólicos, incluindo sete ácidos clorogênicos e um flavonóide. A ferramenta online PASS previu atividades antimutagênica, anticancerígena, antineoplásica, quimioprotetora, antioxidante e de eliminação de radicais para todos os constituintes identificados em *Vp*LAE e n-BF. As folhas de *V. polyanthes* apresentaram efeito protetor contra a citogenotoxicidade do DXR. Em geral, *Vp*LAE e n-BF apresentaram maior potencial antigenotóxico nos pré e pós-tratamentos. Os metabólitos supostamente identificados em *Vp*LAE e n-BF apresentaram potencial antioxidante e quimioprotetor de acordo com a análise de predição computacional. Ao todo, nossos resultados destacam a potencial aplicação de *V. polyanthes* para proteção contra manifestações tóxicas induzidas por DXR.

Palavras-Chave: Cerrado; ensaio cometa; teste do micronúcleo; modelo murino; produtos naturais.

Article

Phytochemical Composition and Protective Effect of *Vernonanthura polyanthes* Leaf against In Vivo Doxorubicin-Mediated Toxicity

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Abstract: *Vernonanthura polyanthes* (Spreng.) A.J. Vega & Dematt. (syn.: *Vernonia polyanthes* Less) is popularly known as "assa-peixe" and its leaves are used in folk medicine mainly to treat respiratory diseases. In this study, we evaluated the cytogenotoxic and anticytogenotoxic potential of the *V. polyanthes* leaf aqueous extract (*Vp*LAE) and its *n*-butanol fraction (*n*-BF) in the presence or absence of doxorubicin (DXR) (pre-, co-, and post-treatments) on a murine model for 24 h or 120 h. The micronucleus test (MN) and the comet assay were used to assess the cytogenotoxic and anticytogenotoxic potential of *Vp*LAE and *n*-BF (250, 500, and 1000 mg/kg) administered via gavage to Swiss Webster mice. The chemical profiles of *Vp*LAE and *n*-BF were assessed by liquid chromatography coupled to mass spectrometry, and their metabolites were putatively identified. Lastly, the possible biological activities related to the (anti) cytogenotoxicity of the compounds were predicted using the PASS online webserver. The in vivo results showed that different doses of *Vp*LAE and *n*-BF did not present cytotoxic activity; however, the MN test revealed a slight mutagenic activity for the 24 h treatments. Moderate genotoxic effects were demonstrated for all treatments in the comet assay. Regarding anticytotoxicity and antimutagenicity, *Vp*LAE and *n*-BF presented a high cytoprotective potential against DXR toxic effects. In the co-treatment, *Vp*LAE reduced the DXR genotoxicity by ~27%, and *n*-BF did not demonstrate antigenotoxic potential. In contrast, an antigenotoxic effect was observed for both *Vp*LAE and *n*-BF in the pre- and post-treatments, reducing DXR genotoxicity by ~41% and ~47%, respectively. Chemical analysis of *Vp*LAE and *n*-BF showed the presence of eight phenolic compounds, including seven chlorogenic acids and a flavonoid. The PASS online tool predicted antimutagenic, anticancer, antineoplastic, chemoprotective, antioxidant, and radical scavenging activities for all constituents identified in *Vp*LAE and *n*-BF. *V. polyanthes* leaves presented a protective effect against DXR cytogenotoxicity. In general, *Vp*LAE and *n*-BF showed a greater antigenotoxic potential in the pre- and post-treatments. The metabolites putatively identified in *Vp*LAE and *n*-BF exhibited antioxidant and chemoprotective potential according to computational prediction analysis. Altogether, our results highlight the potential application of *V. polyanthes* to protect against toxic manifestations induced by DXR.

Keywords: Cerrado; comet assay; micronucleus test; murine model; natural products

1. Introduction

The search for plant metabolites is constantly increasing because they are more eco-friendly and usually less toxic to normal cells. According to the Food and Drug Administration agency, 40% of the approved molecules are natural compounds or inspired by them [1]. Moreover, many plant species are considered a good source of natural antioxidants and could be used as a functional food [2–4].

Vernonanthura polyanthes (Spreng.) A.J. Vega & Dematt. (syn.: *Vernonia polyanthes* Less), popularly known as "assa-peixe", is an Asteraceae family species [5]. *V. polyanthes* leaves are used in folk medicine to treat respiratory disorders, pneumonia, bronchitis, coughs, flu, and colds, as well as kidney diseases, uterine infections, ulcers, hypertension, leishmaniasis, fever, hemorrhages, and gastric conditions [6–12]. Although there are other species popularly called "assa-peixe", such as *Vernonia brasiliana*, *Vernonia cognata* Less., and *Vernonia ferruginea* Less., only *V. polyanthes* is regulated for phytotherapeutic use, registered in the Brazilian Pharmacopoeia of Herbal Medicines as an expectorant, in the form of tea obtained by infusion of the dry leaves [13]. The presence of flavonoids, saponins, tannins, coumarins, triterpenes, sesquiterpene lactones, chlorogenic acids, and phenolic acids was demonstrated in extracts from *V. polyanthes* leaves [14–18].

The *V. polyanthes* leaf aqueous extract (*Vp*LAE) did not demonstrate toxicity, genotoxicity, or antigenotoxicity on *Drosophila melanogaster*. However, this extract potentiated the genotoxicity of doxorubicin (DXR) [19]. In contrast, *Vp*LAE was cytotoxic to *Allium cepa* cells and *Artemia salina* [14]. Similarly, *V. polyanthes* leaf hydroalcoholic extract (2000 mg/kg) was cytogenotoxic when administrated to mice [20]. *Vp*LAE and its three fractions (aqueous; *n*-butanol, n-BF; and ethyl acetate) showed cytogenotoxicity against human lymphocytes in vitro using a cell viability test and CometChip assay. However, when co-treated with DXR, *V. polyanthes* decreased DXR genotoxicity by ~15% [21].

DXR is a chemotherapeutic drug widely used in anticancer therapy; however, its use is limited by the increased oxidative stress caused by the drug [22,23]. It is already known that the redox balance disorder caused by DXR activates mechanisms that lead to cell damage, causing an increase in the production of free radicals and a decrease in endogenous antioxidants, inducing toxicity in various organs and tissues [22–25].

In this sense, it is important to study the effects of *V. polyanthes* and its interaction with DXR on a murine model. Initially, a micronucleus test (MN) and comet assay were performed, associated (pre-, co-, and post-treatments) or not with DXR on Swiss Webster mice, aiming to evaluate the cytogenotoxic and anticytogenotoxic potentials of *Vp*LAE and *n*-BF. Then, the chemical profiles of both were determined, and the putatively identified metabolites were submitted to computational prediction analysis to predict their biological activities.

2. Methodology

2.1. Botanical Material

V. polyanthes leaves were collected at the Central Campus, in Anápolis, Goiás, Brazil (S 16°23′0.16″/W 48°56′37.8″, 1073 m) in November 2018. The botanical identification of this specimen was carried out by Dr. Aristônio Magalhães Teles from the Federal University of Goiás and an exsiccate (N° 10512) was deposited in the Herbarium of the State University of Goiás.

2.2. Infusion Preparation and Fractionation

The botanical material was subjected to drying at room temperature and pulverized in a knife mill E-625 (Tecnal Ltda, Piracicaba, SP, Brazil). Powdered material was stored sheltered from light and moisture for subsequent use. Initially, the powder from *V. polyanthes* leaves was subjected to quality parameters. The aqueous extract was prepared, according to Brazilian Pharmacopoeia (1st edition), by infusion of *V. polyanthes* (syn.: *Vernonia polyanthes* Less) leaves in the proportion of 0.02 g of dried and powdered plant material for each mL of water [13]. Samples were frozen at −18 °C and lyophilized. The solvent partitioning was

obtained by percolation as previously described [21], resulting in three fractions (aqueous; *n*-BF; and ethyl acetate). The *n*-BF was evaporated under reduced pressure, and the dry extract and fraction were lyophilized and stored at −20 °C for further biological assays. The *n*-BF was selected to continue the experiments because it presented the highest total phenolic, flavonoids, and tannins contents, and the highest antioxidant activity, according to previous work [21].

2.3. Animals

Male *Mus musculus* (Swiss Webster) outbred mice, weighing between 20 to 30 g and aged from 7 to 12 weeks, were obtained from the Central Animal Facility of the Federal University of Goiás. This study was approved by the Animal Research Ethics Committee of the Federal University of Goiás (CEUA/UFG), protocol number 069/18 (Supplementary Materials).

2.4. In Vivo Experimental Procedures

This study used 140 mice (28 groups with 5 animals). Before the experiments were carried out, the animals remained acclimated for 7 days in the Laboratory of Radiobiology and Mutagenesis of the Federal University of Goiás. On these days, the animals were kept in polypropylene cages (Length: 40 cm, Width: 30 cm, and Height: 16 cm) with 5 animals in each cage lined with shavings changed every two days, and fed commercial feed and filtered water, both offered ad libitum. The animals were kept at room temperature, humidity 50% ± 20%, and a 12 h light/dark-light cycle. Doses of 250, 500, and 1000 mg/kg of *Vp*LAE and *n*-BF were selected for the micronucleus test in mouse bone marrow based on previous work [20]. The animals in Group 1 (negative control) received mineral water orally in the same volume used to administer the aqueous extract of *V. polyanthes*. The animals in Group 2 (positive control) received DXR administered intraperitoneally (ip) at 50 mg/kg p.c. Animals from Groups 3 to 28 received different treatments with *Vp*LAE or *n*-BF (Table 1). After 24 or120 h of treatment, the animals were euthanized by cervical dislocation. Bone marrow cells were obtained from the femurs of mice using 1 mL of fetal bovine serum and centrifuged at 300× *g* for 5 min to make slides for the MN test and the comet assay.

2.5. Micronucleus Test (MN)

Mouse bone marrow cells were used to make cell smears on glass slides. After drying, the smears were fixed in absolute methanol (CH_4O) for 5 min, then stained in buffered Giemsa dye (dibasic sodium phosphate and monobasic sodium phosphate, pH 6.8). For each animal, four slides were prepared. As recommended [26], 4000 polychromatic erythrocytes (PCEs) were analyzed for each animal to determine the frequency of micronucleated polychromatic erythrocytes (MNPCE). Cytotoxicity and anticytotoxicity were evaluated by the ratio of PCE and normochromatic erythrocytes (NCE). Whereas genotoxicity and antigenotoxicity were assessed by the frequency of MNPCE concerning the total number of cells analyzed. The analysis of the slides was performed under an optical light microscope (Olympus BH-2, Tokyo, Japan, objective 100×).

2.6. Comet Assay

Microscope slides were previously coated with 1.5% agarose of normal melting point (1.5%). Subsequently, a solution containing 10 µL of bone marrow cells previously diluted in fetal bovine serum, and 120 µL of low melting point agarose at 0.5% and 37 °C, was placed on the agarose-precoated slides. The slides were then kept in the refrigerator, inside a foil-lined slide holder, containing lysis solution (2.5 M NaCl, 100 mM EDTA, 10 mM TRIS, 10% DMSO, 1% Triton X-100, and 1000 mL H_2O, pH 10 at 4 °C overnight). After this period, the slides were transferred to a horizontal electrophoresis vat, containing electrophoresis buffer (30 mM NaOH, 1 mM EDTA, pH 13) at 5 ± 2 °C, where they remained for 30 min for DNA unwinding. Then, they were subjected to 300 mA and 1 V/cm for 30 min. After

electrophoresis, the slides were immersed in a neutralizing buffer solution (0.4 M, Tris-HCl, pH 7.5) for 5 min. The slides were stained with 20 µL of Nucleic Acid Dye (Diamond™, 10%) and covered with a coverslip. The capture of comet images was performed in a fluorescence microscope (Axio Imager® A2 and Zen 2.3 software Carl Zeiss AG, Germany, with 510–560 nm excitation filter and 590 nm barrier filter, in a 20× objective). The software TriTek CometScore™ (version 1.5) was used to assess DNA damage. In this software, pixel intensity in nucleoid images provides values corresponding to the estimation of genomic damage, which is expressed as arbitrary units (AU). Nucleoids with fragmented heads (hedgehogs) were not included in the analyses. The parameter adopted for quantifying DNA damage was the percentage of DNA in the tail.

Table 1. Experimental design of the micronucleus test and comet assay.

Animal Groups	Dose	Number of Animals (n)	Exposure Time
	Controls		
G1	NC (H_2O)	5	24 h
G2	PC (DXR 50 mg/kg ip)	5	24 h
Genotoxicity			
	***Vp*LAE**		
G3	250 mg/kg	5	24 h
G4	500 mg/kg	5	24 h
G5	1000 mg/kg	5	24 h
G6	1000 mg/kg	5	120 h
	***n*-BF**		
G7	250 mg/kg	5	24 h
G8	500 mg/kg	5	24 h
G9	1000 mg/kg	5	24 h
G10	1000 mg/kg	5	120 h
Co-treatment			
	***Vp*LAE**		
G11	DXR + 250 mg/kg	5	24 h
G12	DXR + 500 mg/kg	5	24 h
G13	DXR +1000 mg/kg	5	24 h
	***n*-BF**		
G14	DXR + 250 mg/kg	5	24 h
G15	DXR + 500 mg/kg	5	24 h
G16	DXR + 1000 mg/kg	5	24 h
Pre-treatment			
	***Vp*LAE**		
G17	250 mg/kg + DXR	5	120 h
G18	500 mg/kg + DXR	5	120 h
G19	1000 mg/kg + DXR	5	120 h
	***n*-BF**		
G20	250 mg/kg + DXR	5	120 h
G21	500 mg/kg + DXR	5	120 h
G22	250 mg/kg + DXR	5	120 h
Post-treatment			
	***Vp*LAE**		
G23	DXR + 250 mg/kg	5	24 h
G24	DXR + 500 mg/kg	5	24 h
G25	DXR + 1000 mg/kg	5	24 h
	***n*-BF**		
G26	DXR + 250 mg/kg	5	24 h
G27	DXR + 500 mg/kg	5	24 h
G28	DXR + 1000 mg/kg	5	24 h

NC: Negative control; PC: positive control; DXR: doxorubicin; *Vp*LAE: *Vernonanthura polyanthes* leaf aqueous extract; *n*-BF: *n*-butanol fraction of *V. polyanthes* leaf aqueous extract.

2.7. Statistical Analysis

For the parameters PCE/NCE and MNPCE, the mean ± standard deviations were calculated for each group. Data distribution was checked for normality using the Shapiro-Wilk test. The different groups were compared using the parametric (one-way ANOVA) or nonparametric Kruskal-Wallis test followed by the Dunn's multiple comparison test. The comet assay results are presented as the mean ± standard deviations, and the analysis of variance (one-way ANOVA) was performed, followed by Tukey's multiple comparison test. Analyzes were performed using the GraphPad Prism software version 8.0.1. $p < 0.05$ was considered significant.

2.8. Chemical Profiles

For the LC-MS analyses, extracts of *Vp*LAE and *n*-BF were prepared using 10 mg of the dry powder of each extract or fraction and 1 mL of a MeOH:H_2O (7:3, *v:v*) solution with hydrocortisone (10 mg/mL) as an internal standard. Extraction was performed in an ultrasonic bath for 10 min at room temperature. The extracts were filtered through a 0.20 mm PTFE membrane before analysis. Chemical profiles were obtained on an Accela UHPLC instrument (Thermo Scientific™, Waltham, MA, USA) with a diode array ultraviolet light detector (UV-DAD) coupled to an ExactiveTM Plus mass spectrometer (Thermo Scientific™, Waltham, MA, USA) with electrospray ionization source and orbitrap analyzer. Chromatograms were acquired in positive and negative ionization modes using a C18 Kinetex column (1.7 µm, XB-C18, 150 mm × 2.1 mm, Phenomenex) and an elution gradient of water and acetonitrile both with 0.1% of formic acid. All other chromatographic and spectroscopic parameters followed the methodology employed by Gallon et al. (2018b). Metabolites detected in *Vp*LAE and *n*-BF were putatively identified by comparing the spectroscopic data of each chromatographic signal with the data available in the *in-house* database of secondary metabolites reported for Vernonieae species.

2.9. Prediction of Activity Spectra for Substances

The bioactivity of the metabolites identified in the *Vp*LAE and *n*-BF were predicted using the PASS online webserver (http://www.pharmaexpert.ru/passonline/, accessed on 20 May 2020). Pa and Pi estimate the probability of the substance to be active or inactive, respectively, for each type of activity from the database [27,28]. Therefore, the results presenting Pa > 0.7 and Pi < 0.05 were selected for the analysis.

3. Results

3.1. Cytogenotoxic Evaluation

*Vp*LAE and *n*-BF did not present cytotoxicity against mice bone marrow cells (Figure 1) and presented genotoxicity after acute (24 h) exposition to all concentrations tested in this work (250, 500, and 1000 mg/kg) (Figure 2). The genotoxicity observed at the highest concentration of *Vp*LAE (1000 mg/kg, G5) was similar to that observed for the positive control (DXR) (Figure 2a). Although *Vp*LAE and *n*-BF presented a genotoxic potential on mice bone marrow cells, these materials did not present or presented a mild mutagenicity potential (Figure 3). As expected, animals treated with DXR (positive control) showed cytogenotoxic effects compared to the negative control (Figures 1–6).

3.2. Anticytogenotoxic Evaluation

The evaluation of *Vp*LAE and *n*-BF anti-cytogenotoxicity in the presence of the DXR positive control (co-, pre-, and post-treatments) was also performed. *Vp*LAE and *n*-BF were anti-cytotoxic in all doses (250, 500, and 1000 mg/kg) and in different treatment schemes used in this work (Figure 4). The PCE/NCE ratios in treatments of DXR + *Vp*LAE or *n*-BF were restored to the ratio obtained in the negative control (Figure 4). Regarding antigenotoxicity, *Vp*LAE reduced the DXR genotoxicity by ~27% during co-treatment (Figure 5a). In contrast, *n*-BF did not demonstrate anti-genotoxic potential in the co-treatment with DXR (Figure 5b). Regarding pre-treatment, *Vp*LAE and *n*-BF reduced the

genotoxicity of DXR by ~41% (Figure 5). In the post-treatment, *Vp*LAE and *n*-BF also reduced the genotoxicity of DXR by ~47% (Figure 5). Moreover, the association of *Vp*LAE or *n*-BF with DXR in the co-, pre-, and post-treatments showed a significant reduction in the frequency of MN/PCE when compared to the positive control (Figure 6), revealing a relevant anti-genotoxic effect of *V. polyanthes*.

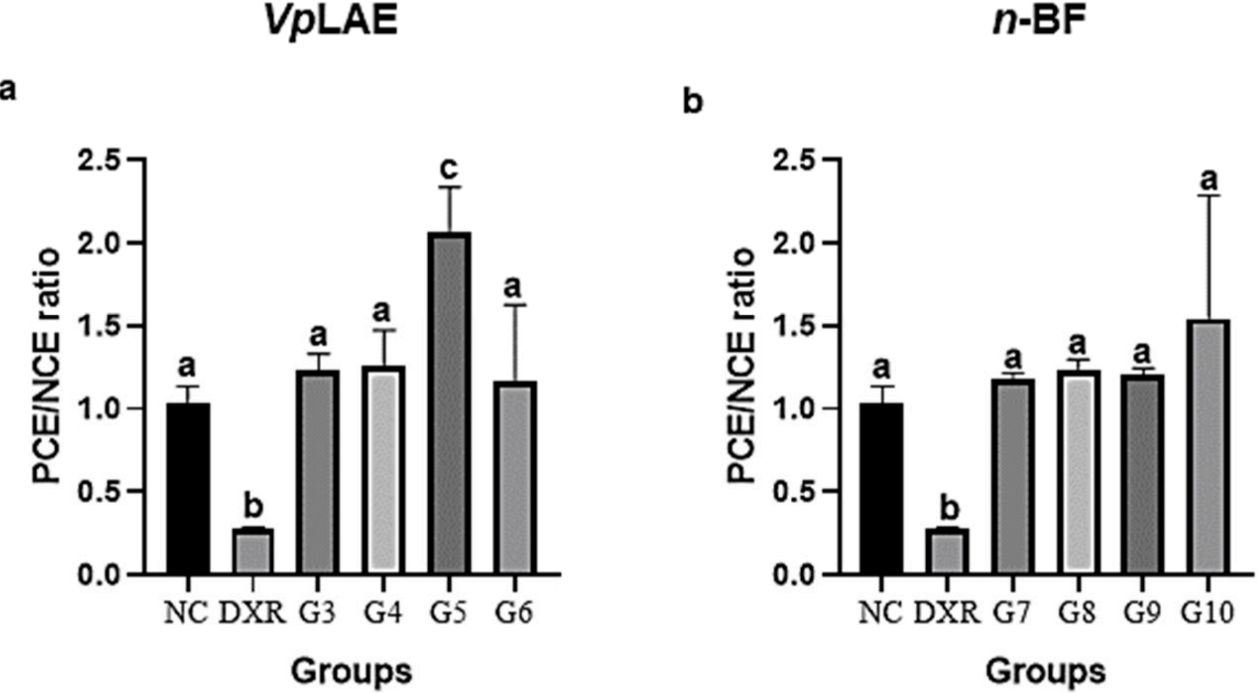

Figure 1. Evaluation of the cytotoxic potential of *Vernonanthura polyanthes* leaves aqueous extract (*Vp*LAE) and its *n*-butanol fraction (*n*-BF) on mouse bone marrow cells using the micronucleus test. The animals were treated with different concentrations of *Vp*LAE or its *n*-BF fraction. (**a**) Polychromatic erythrocytes (PCE)/normochromatic erythrocytes (NCE) ratio of animals treated with *Vp*LAE (G3: 250 mg/kg, G4: 500 mg/kg, G5: 1000 mg/kg for 24 h, and G6: 1000 mg/kg for 120 h). (**b**) PCE/NCE ratio of animals treated with *n*-BF (G7: 250 mg/kg, G8: 500 mg/kg, G9: 1000 mg/kg for 24 h, and G10: 1000 mg/kg for 120 h). NC: negative control (mineral water); DXR: positive control (doxorubicin: 50 mg/kg ip). Results are expressed as the mean ± standard deviation. The groups were compared by ANOVA (*Vp*lae) or Kruskal–Wallis (*n*-BF) followed by the respective Tukey or Dunn's tests. Different letters indicate statistically significant differences between groups ($p < 0.05$).

3.3. Chemical Profiles of VpLAE and n-BF

LC-MS analyses of *Vp*LAE and *n*-BF confirmed the presence of phenolic compounds (flavonoids and chlorogenic acids) typically reported in *V. polyanthes* (Table 2 and Supplementary Table S1). The compounds 5-*O*-feruloylquinic acid, quercetin 3-*O*-rutinoside, 3,4-di-*O*-caffeoylquinic acid, 3,5-di-*O*-caffeoylquinic acid, and 4,5-di-*O*-caffeoylquinic acid were putatively identified in both the *Vp*LAE and *n*-BF samples. Whereas 3-*O*-caffeoylquinic acid, 5-*O*-caffeoylquinic acid, and 4-*O*-caffeoylquinic acid were detected in higher relative abundance in the *n*-BF. Accordingly, all the detected *O*-caffeoylquinic acids and di-*O*-caffeoylquinic acids exhibited greater relative abundances in *n*-BF (Figures 7 and 8).

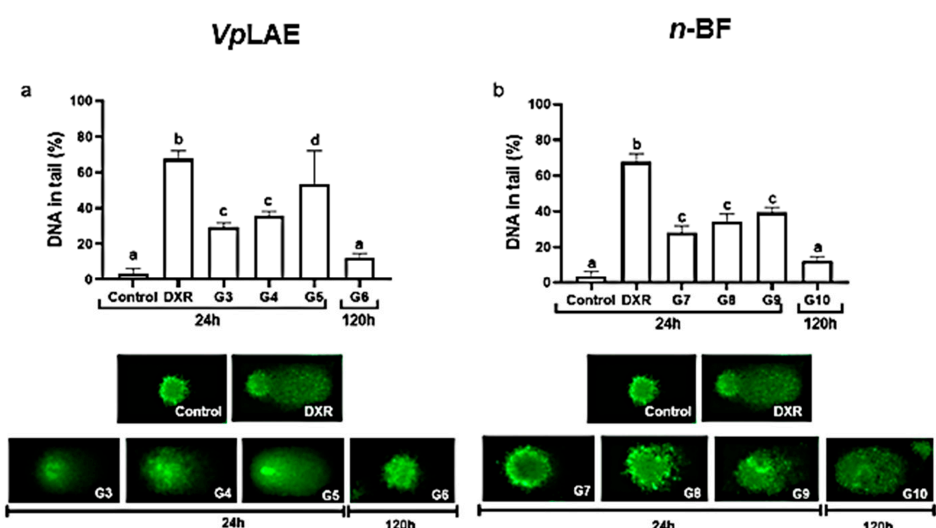

Figure 2. Evaluation of the genotoxic potential of *Vernonanthura polyanthes* leaves aqueous extract (*Vp*LAE) and its *n*-butanol fraction (*n*-BF) on mouse bone marrow cells using the comet assay. The animals were treated with different concentrations of *Vp*LAE or its *n*-BF fraction. The parameter used to assess genetic damage was % DNA in the tail. (**a**) *Vp*LAE (G3: 250 mg/kg, G4: 500 mg/kg, G5: 1000 mg/kg for 24 h, and G6: 1000 mg/kg for 120 h). (**b**) *n*-BF (G7: 250 mg/kg, G8: 500 mg/kg, G9: 1000 mg/kg for 24 h, and G10: 1000 mg/kg for 120 h). NC: negative control (mineral water); DXR: positive control (doxorubicin: 50 mg/kg ip). Results are expressed as the mean ± standard deviation. The groups were compared by ANOVA followed by the Tukey test. Different letters indicate statistically significant differences between groups ($p < 0.05$). Images below graphs are representative photomicrographs of nucleoids stained with Diamond^{TM} Nucleic Acid Dye. The images were captured using a fluorescence microscope (Axioplan-ImagingVR) and the Lucia software, with an excitation filter of 510–560 nm and a barrier filter of 590 nm (10× objective).

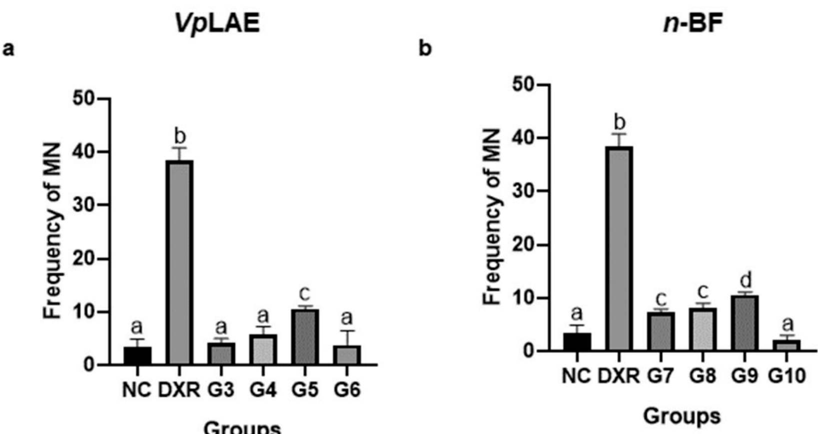

Figure 3. Evaluation of the mutagenic potential of *Vernonanthura polyanthes* leaves aqueous extract (*Vp*LAE) and its *n*-butanol fraction (*n*-BF) on mouse bone marrow cells using the micronucleus test. The animals were treated with different concentrations of *Vp*LAE or its *n*-BF fraction. (**a**) Micronucleated polychromatic erythrocyte frequency in animals treated with *Vp*LAE (G3: 250 mg/kg, G4: 500 mg/kg, G5: 1000 mg/kg for 24 h, and G6: 1000 mg/kg for 120 h). (**b**) Micronucleated polychromatic erythrocyte frequency in animals treated with *n*-BF (G7: 250 mg/kg, G8: 500 mg/kg, G9: 1000 mg/kg for 24 h, and G10: 1000 mg/kg for 120 h). NC: negative control (mineral water); DXR: positive control (doxorubicin: 50 mg/kg ip). Results are expressed as the mean ± standard deviation. The groups were compared by ANOVA followed by the Tukey test. Different letters indicate statistically significant differences between groups ($p < 0.05$).

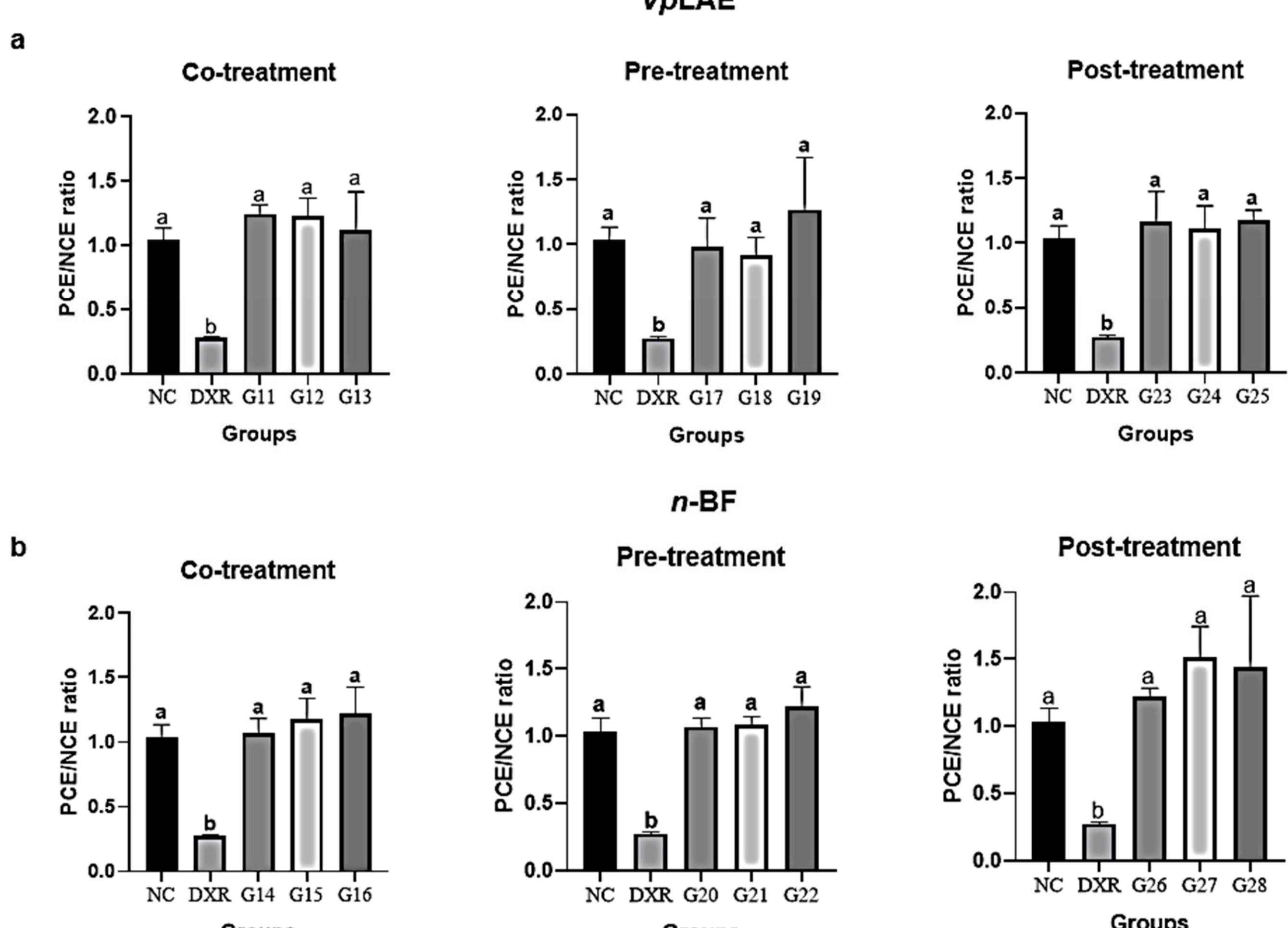

Figure 4. Evaluation of the anticytotoxic potential of *Vernonanthura polyanthes* leaves aqueous extract (*Vp*LAE) and its *n*-butanol fraction (*n*-BF) on mouse bone marrow cells using the micronucleus test. The animals were treated with different concentrations of *Vp*LAE or its *n*-BF fraction associated with the positive control doxorubicin (DXR; 50 mg/kg ip). (**a**) Polychromatic erythrocytes (PCE)/normochromatic erythrocytes (NCE) ratio of animals treated with *Vp*LAE (G3: 250 mg/kg, G4: 500 mg/kg, G5: 1000 mg/kg for 24 h, and G6: 1000 mg/kg for 120 h). (**b**) PCE/NCE ratio of animals treated with *n*-BF (G7: 250 mg/kg, G8: 500 mg/kg, G9: 1000 mg/kg for 24 h, and G10: 1000 mg/kg for 120 h). NC: negative control (mineral water). Results are expressed as the mean ± standard deviation. The groups were compared by ANOVA followed by the Tukey test. Different letters indicate statistically significant differences between groups ($p < 0.05$).

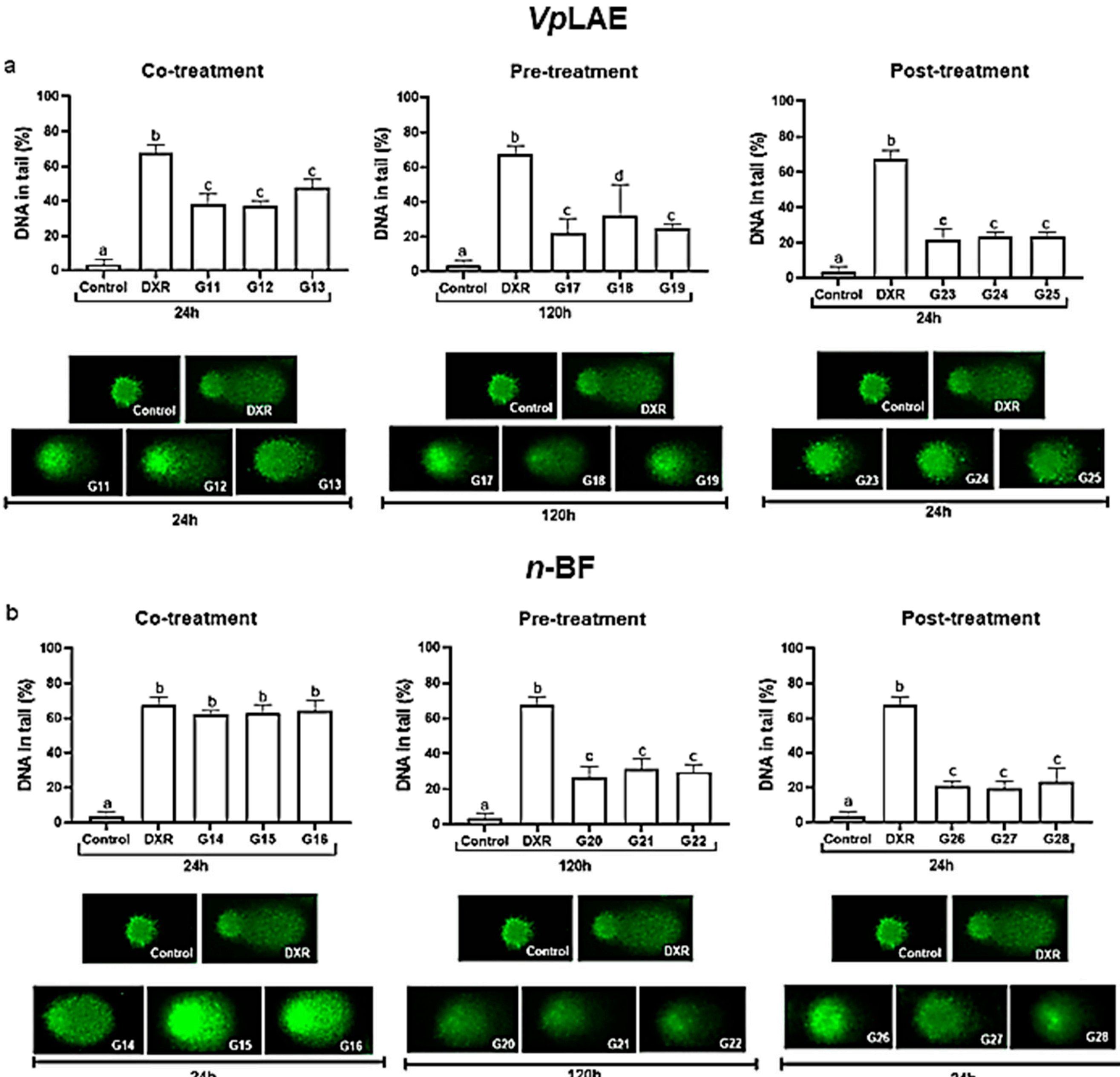

Figure 5. Evaluation of the antigenotoxic potential of *Vernonanthura polyanthes* leaves aqueous extract (*Vp*LAE) and its *n*-butanol fraction (*n*-BF) on mouse bone marrow cells using the comet assay. The animals were treated with different concentrations of *Vp*LAE or its *n*-BF fraction associated with the positive control doxorubicin (DXR; 50 mg/kg ip). The parameter used to assess genetic damage was % DNA in the tail. (**a**) *Vp*LAE (G3: 250 mg/kg, G4: 500 mg/kg, G5: 1000 mg/kg for 24 h, and G6: 1000 mg/kg for 120 h). (**b**) *n*-BF (G7: 250 mg/kg, G8: 500 mg/kg, G9: 1000 mg/kg for 24 h, and G10: 1000 mg/kg for 120 h). NC: negative control (mineral water). Results are expressed as the mean ± standard deviation. The groups were compared by ANOVA followed by the Tukey test. Different letters indicate statistically significant differences between groups ($p < 0.05$). Images below graphs are representative photomicrographs of nucleoids stained with Diamond™ Nucleic Acid Dye. The images were captured using a fluorescence microscope (Axioplan-ImagingVR) and Lucia software, with an excitation filter of 510–560 nm and a barrier filter of 590 nm (10× objective).

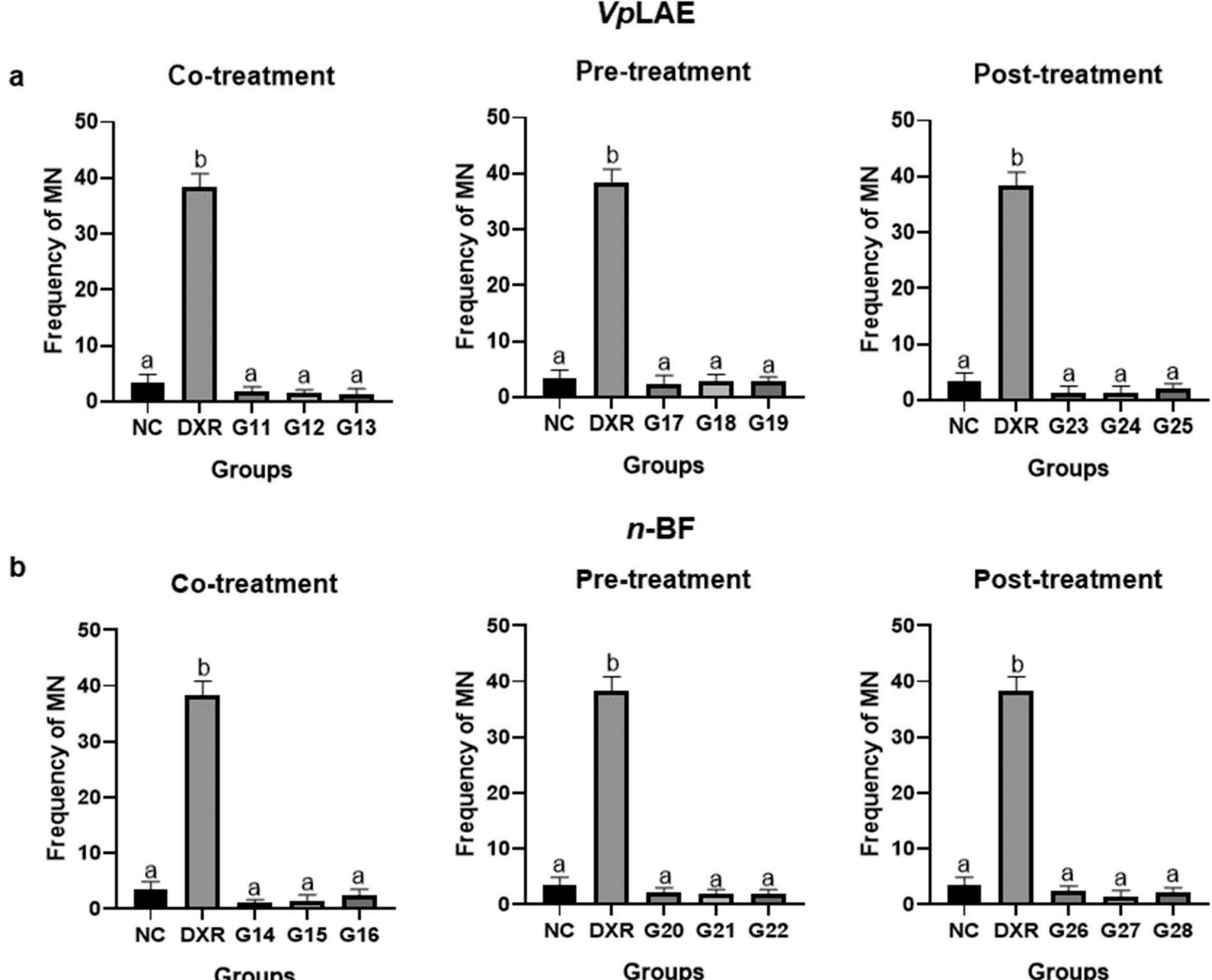

Figure 6. Evaluation of the antimutagenic potential of *Vernonanthura polyanthes* leaves aqueous extract (*Vp*LAE) and its *n*-butanol fraction (*n*-BF) on mouse bone marrow cells using the micronucleus test. The animals were treated with different concentrations of *Vp*LAE or its *n*-BF fraction associated with the positive control doxorubicin (DXR; 50 mg/kg ip). (**a**) Micronucleated polychromatic erythrocyte frequency in animals treated with *Vp*LAE (G3: 250 mg/kg, G4: 500 mg/kg, G5: 1000 mg/kg for 24 h, and G6: 1000 mg/kg for 120 h). (**b**) Micronucleated polychromatic erythrocyte frequency in of animals treated with *n*-BF (G7: 250 mg/kg, G8: 500 mg/kg, G9: 1000 mg/kg for 24 h, and G10: 1000 mg/kg for 120 h). NC: negative control (mineral water). Results are expressed as the mean ± standard deviation. The groups were compared by ANOVA followed by the Tukey test. Different letters indicate statistically significant differences between groups ($p < 0.05$).

Table 2. Secondary metabolites putatively identified in *Vernonanthura polyanthes* leaf aqueous extract (*Vp*LAE) and its n-butanol fraction (*n*-BF).

Metabolites	*Vp*LAE	*n*-BF
***O*-caffeoylquinic acids**		
3-CQA, **4-CQA**, **5-CQA**		X
***O*-feruloylquinic acid**		
5-FQA	X	X
di-*O*-caffeoylquinic acids		
3,4-di-CQA, **3,5-di-CQA**, **4,5-di-CQA**	X	X
Flavonoid		
rutin	X	X

The X symbol indicates the presence of the metabolite on *Vp*LAE or *n*-BF. 3-CQA, 3-*O-caffeoylquinic* acid; 4-CQA, 4-*O-caffeoylquinic* acid; 5-CQA, *O-caffeoylquinic* acid; 5FQA, 5-*O*-feruloylquinic acid; 3,4-di-CQA, 3,4-di-*O*-caffeoylquinic acid; 3,5-di-CQA, 3,5- di-*O*-caffeoylquinic acid; 4,5-di-CQA, 4,5-di-*O*-caffeoylquinic acid.

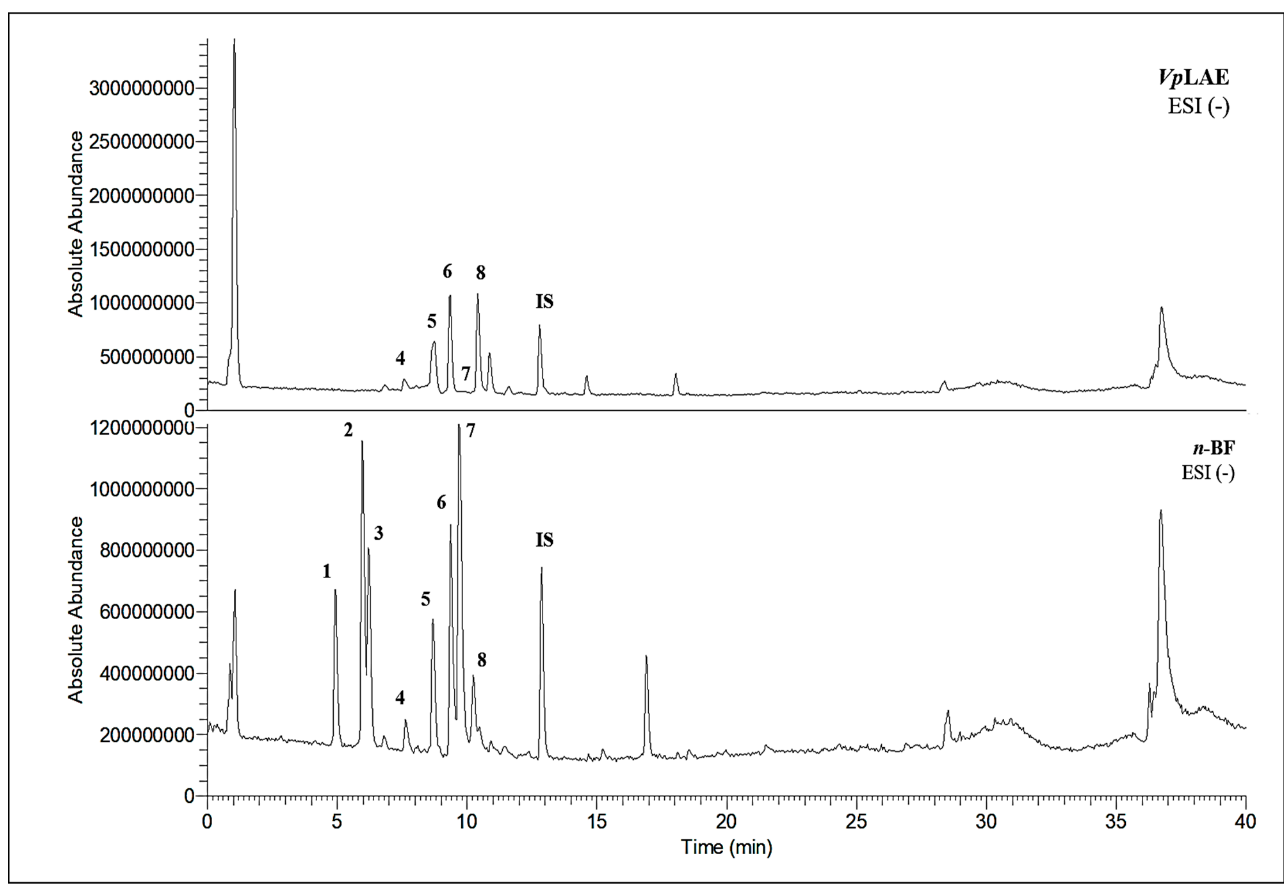

Figure 7. Total ion chromatograms (TIC) of *Vernonanthura polyanthes* leaf aqueous extract (*Vp*LAE) and its *n*-butanol fraction (*n*-BF) analyzed by UHPLC-UV-MS (Orbitrap) in the negative ionization mode. **1**, 3-*O*-caffeoylquinic acid; **2**, 5-*O*-caffeoylquinic acid; **3**, 4-*O*-caffeoylquinic acid; **4**, 5-*O*-feruloylquinic acid; **5**, rutin; **6**, 3,4-di-*O*-caffeoylquinic acid; **7**, 3,5-di-*O*-caffeoylquinic acid; **8**, 4,5-di-*O*-caffeoylquinic acid; **IS**, internal standard (hydrocortisone 10 mg/mL).

3.4. Biological Activity Prediction of Identified Secondary Metabolites

Potential antimutagenic, anticancer, antineoplastic, chemoprotective, antioxidant, and radical scavenging effects were attributed to all metabolites putatively identified in *Vp*LAE and *n*-BF by computational prediction analysis using the PASS online tool (Table 3). Moreover, the identified molecules are predicted modulators of enzymes involved in antioxidant processes such as HMOX1, lipid peroxidase inhibitors, aryl sulfotransferase, β-glucuronidase, α-glucosidase, UDP-glucuronosyl transferase, glutathione-disulfide reductase, and different P450 isoforms (CYP1A, CYP1A1, CYP3A4, CYP2C9, CYP3A) (Table 4). Among the metabolites detected in *Vp*LAE and *n*-BF, quercetin-3-*O*-rutinoside (rutin) seems to be the most active considering the analyzed antioxidant and chemopreventive parameters provided by the PASS online tool (Tables 3 and 4).

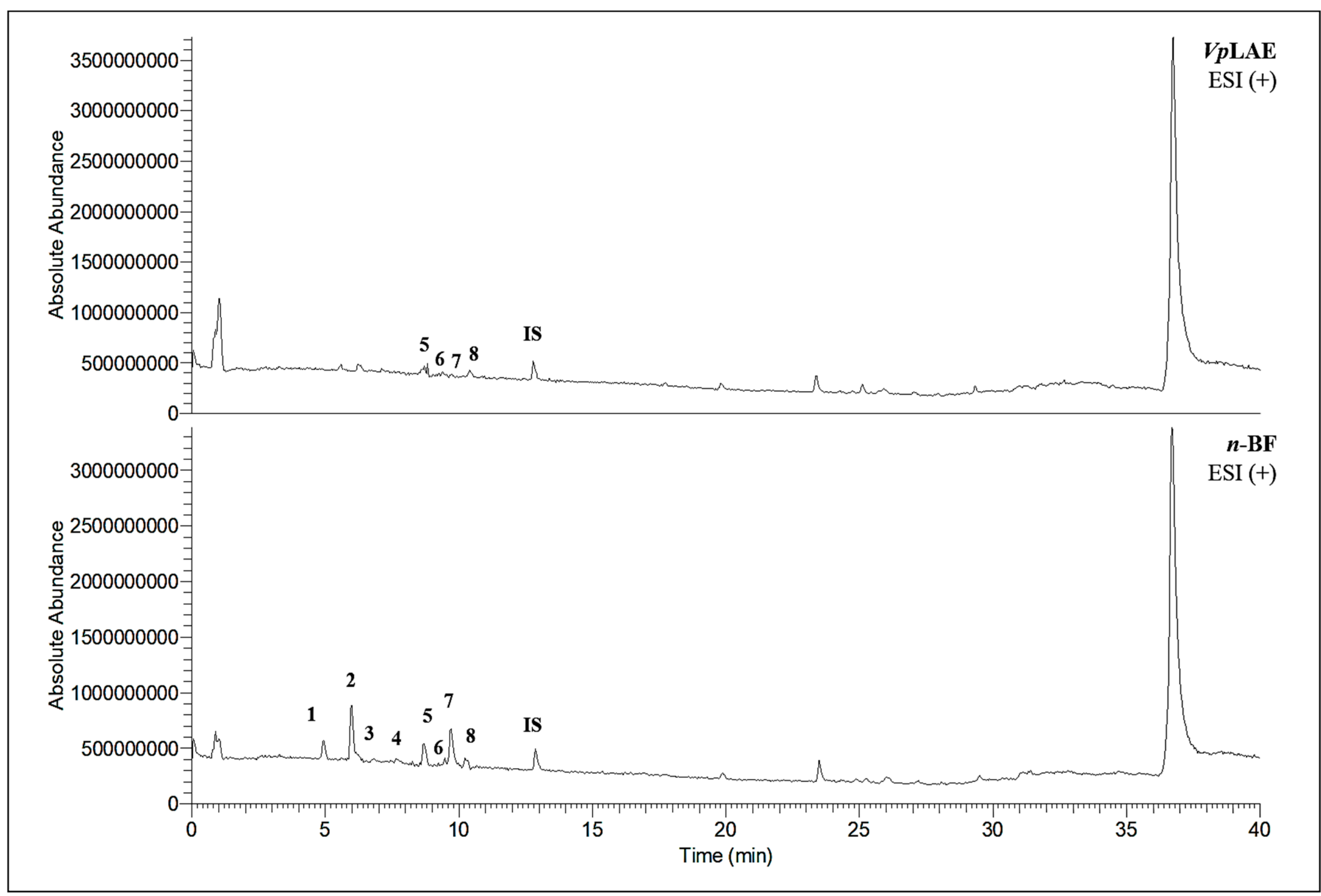

Figure 8. Total ion chromatograms (TIC) of *V. polyanthes* leaf aqueous extract (*Vp*LAE) and its *n*-butanol fraction (*n*-BF) analyzed by UHPLC-UV-MS (Orbitrap) in the positive ionization mode. **1**, 3-*O*-caffeoylquinic acid; **2**, 5-*O*-caffeoylquinic acid; **3**, 4-*O*-caffeoylquinic acid; **4**, 5-*O*-feruloylquinic acid; **5**, rutin; **6**, 3,4-di-*O*-caffeoylquinic acid; **7**, 3,5-di-*O*-caffeoylquinic acid; **8**, 4,5-di-*O*-caffeoylquinic acid; **IS**, internal standard (hydrocortisone 10 mg/mL).

Table 3. Biological activity prediction of putatively identified metabolites in *Vernonanthura polyanthes* leaf aqueous extract (*Vp*LAE) and its *n*-butanol fraction (*n*-BF) by the PASS online webserver.

Biological Activity	3-CQA		5-CQA		4-CQA		5-FQA		RUTIN		3,4-di-CQA		3,5-di-CQA		4,5-di-CQA	
	Pa	*Pi*	*Pa*	*Pi*	*Pa*	*Pi*	*Pa*	*Pi*	*Pa*	*Pi*	*Pa*	*Pi*	*Pa*	*Pi*	*Pa*	*Pi*
Antimutagenic	N/A	N/A	N/A	N/A	0.946	0.001	0.966	0.001	N/A	N/A	0.955	0.001	0.961	0.001	0.955	0.001
Anticarcinogenic	0.846	0.004	0.846	0.004	0.824	0.004	0.863	0.003	0.983	0.001	0.850	0.004	0.837	0.004	0.850	0.004
Antineoplastic	0.778	0.014	0.778	0.014	0.756	0.018	0.792	0.013	0.849	0.007	0.790	0.013	0.777	0.015	0.790	0.013
Chemopreventive	0.833	0.003	0.833	0.003	0.812	0.004	0.875	0.003	0.968	0.001	0.830	0.003	0.827	0.003	0.830	0.003
Antioxidant	0.785	0.004	0.833	0.003	0.771	0.004	0.727	0.004	0.923	0.003	0.806	0.003	0.780	0.004	0.806	0.003
Free radical scavenger	0.856	0.002	0.856	0.002	0.830	0.002	0.913	0.002	0.988	0.001	0.848	0.002	0.841	0.002	0.848	0.002

Pa: probability to be active (Pa > 0.7); Pi: probability to be inactive (Pi > 0.3); 3-CQA: 3-*O*-Caffeoylquinic acid; 4-CQA: 4-*O*-Caffeoylquinic acid; 5-CQA: 5-*O*-Caffeoylquinic acid; 5-FQA: 5-*O*-feruloylquinic; RUTIN: quercetin-3-*O*-rutinoside; 3,4-di-CQA: 3,4-di-*O*-caffeoylquinic acid; 3,5-di-CQA: 3,5-di-*O*-caffeoylquinic acid; 4,5-di-CQA: 4,5-di-*O*-caffeoylquinic acid. N/A: not active.

Table 4. Prediction of enzyme modulation by bioactive compounds putatively identified in *Vernonanthura polyanthes* leaf aqueous extract (*Vp*LAE) and its *n*-butanol fraction (*n*-BF).

Enzymatic Activity	3-CQA	5-CQA	4-CQA	5-FQA	RUTIN	3,4-di-CQA	3,5-di-CQA	4,5-di-CQA
CYP1A inducer	N/A	N/A	N/A	N/A	0.980	N/A	N/A	N/A
CYP1A1 inducer	N/A	N/A	N/A	N/A	0.970	N/A	N/A	N/A
CYP3A4 inducer	N/A	N/A	N/A	N/A	0.850	N/A	N/A	N/A
CYP2C9 inducer	N/A	N/A	N/A	N/A	0.830	N/A	N/A	N/A
CYP3A inducer	N/A	N/A	N/A	N/A	0.820	N/A	N/A	N/A
CYP2H substrate	N/A	N/A	N/A	N/A	0.820	N/A	N/A	N/A
UDP-glucuronosyltransferase substrate	0.710	0.710	0.820	0.850	0.970	0.830	0.840	0.830
Aryl sulfotransferase inhibitor	N/A	N/A	0.940	0.997	N/A	0.950	0.950	0.950
Glutathione-disulfide reductase inhibitor	N/A	N/A	N/A	N/A	0.740	N/A	N/A	N/A
Lipid peroxidase inhibitor	0.850	0.850	0.830	0.880	0.999	0.850	0.840	0.850
HMOX1 expression enhancer	N/A	N/A	N/A	N/A	0.750	N/A	N/A	N/A
NADPH oxidase inhibitor	N/A	N/A	N/A	N/A	0.850	N/A	N/A	N/A
β-glucuronidase inhibitor	N/A	N/A	N/A	N/A	0.760	N/A	N/A	N/A
α-glucosidase inhibitor	N/A	N/A	N/A	N/A	0.860	N/A	N/A	N/A

3-CQA:3-*O*-Caffeoilquinic acid; 4-CQA: 4-*O*-Caffeoilquinic acid; 5-CQA: 5-*O*-Caffeoilquinic acid; 5-FQA: 5-*O*-feruloylquinic; RUTIN: quercetin 3-*O*-rutinoside; 3,4-di-CQA: 3,4-di-*O*-caffeoylquinic acid; 3,5-di-CQA: 3,5-di-*O*-caffeoylquinic acid; 4,5-di-CQA: 4,5-di-*O*-caffeoylquinic acid; CYP: cytochrome P450. N/A: not active.

4. Discussion

In this study, the MN test and the comet assay in mouse bone marrow were performed to assess the cytotoxic, genotoxic, and mutagenic potential of *Vp*LAE and *n*-BF. Moreover, the anticytogenotoxic potential of *Vp*LAE and *n*-BF was evaluated in the presence of DXR, a widely used chemotherapy agent. The micronucleus test in mammals assesses the cytotoxic and mutagenic effects of chemical or physical agents, providing a system to detect cytogenetic damage resulting from clastogenic or aneugenic activity [29,30]. The comet assay (single-cell gel electrophoresis) is a methodology used to measure deoxyribonucleic acid (DNA) strand breaks in cells [31–34]. Both approaches can determine the antigenotoxic potential of a plant extract or isolated compound [35–37].

The animals treated with *Vp*LAE and *n*-BF (250, 500, and 1000 mg/kg) did not promote a PCE/NCE ratio reduction compared to the negative control group, revealing the cytotoxic activity absence of *V. polyanthes* leaves. These results are consistent with our previous study using the wing recombination and somatic mutation test (SMART/wing), which revealed the absence of cytotoxic activity of the aqueous extract of *V. polyanthes* leaves (0.25–1 mg/mL) on *Drosophila melanogaster* [19]. In contrast, when the *V. polyanthes* leaf hydroalcoholic extract (1000, 1500, and 2000 mg/kg) was administrated to mice, the relationship between PCE and NCE was significantly reduced in all treatments, regardless the exposition time (24 and 48 h) or gender, indicating cytotoxicity of the *V. polyanthes* leaf hydroalcoholic extract [20]. *V. polyanthes* leaves were also cytotoxic to human lymphocytes, sarcoma-180 cells, *Allium cepa* cells, and *Artemia salina* [14,16,21]. The mode of action of plant extracts may vary depending on different model systems and chemical compositions [38–40]. So, these contrasting results could be explained by the model used to study cytotoxicity (if it is a metabolizing system or not), the type of solvent used to prepare the extracts, and the part of the plant used [38,40].

The comet assay has several applications in testing new chemicals, particularly genotoxicity or DNA repair damage evaluation [32,33]. *Vp*LAE and *n*-BF showed genotoxicity for all concentrations used (250, 500, and 1000 mg/kg) after 24 h exposition. Likewise, *Vp*LAE and its fractions (aqueous, *n*-butanol, and ethyl acetate) demonstrated genotoxic activity on human lymphocytes [21]. In contrast, when the hydroalcoholic extract of *V. polyanthes* leaves (1000, 1500, and 2000 mg/kg) was administrated to mice, just the highest dose tested was demonstrated to be genotoxic [20]. Similarly, the absence of genotoxic

activity of *V. polyanthes* was verified on *D. melanogaster* and *A. cepa* at the studied conditions [14,19]. These discrepant results highlight the importance of using different models to study plant derivatives.

Slight mutagenicity was observed for some groups treated with *Vp*LAE (G5) and *n*-BF (G7–G9). On the other hand, the aqueous extract of *V. polyanthes* did not show mutagenicity at the concentrations used (0.25–1 mg/mL) on *D. melanogaster* using the wing somatic mutation and recombination test (SMART-wing) [19]. *V. polyanthes* aqueous extract did not also show a mutagenic effect on *A. cepa* meristematic cells [14]. The hydroalcoholic extract of *V. polyanthes* leaves (ethanol/water, 70/30 *v*/*v*) was mutagenic for mice only at the highest dose used (2000 mg/kg). The low and intermediate doses (1000 and 1500 mg/kg) were not mutagenic [20]. This discrepancy between the results may be associated with different models tested and the different solvents used to prepare the *V. polyanthes* extract (water or ethanol). The polarity-dependent increase in antioxidant activity may indicate that polar solvents are more likely to extract antioxidant compounds [41]. One of the most suitable solvents for aqueous mixtures is ethanol because it maximizes polyphenols extraction and is safe for human consumption [21,42].

This study also evaluated the anticytotoxic and antigenotoxic potential of *Vp*LAE and *n*-BF against DXR, a widely used chemotherapeutic, capable of performing single and double breaks in DNA. This drug is part of one of the most effective groups of antineoplastics used in current clinical practice. However, its use is limited by chronic and acute toxic side effects and susceptibility to numerous drug interactions [25,43–45]. The antitumor and toxic effects of DXR contribute to the production of free radicals and to the occurrence of oxidative stress, which can occur in four different ways: (i) semiquinone production; (ii) activation of NAD (P) H oxidases (NOXs); (iii) a non-enzymatic mechanism; and (iv) the generation of DXR metabolism products [24,46]. The generated oxidative stress confers non-specific cytotoxicity, leading to undesirable effects of chemotherapy with DXR [47]. DXR-mediated generation of excessive free radicals caused by increased free radical production and decreased endogenous antioxidants plays an important role in the pathogenesis of induced toxicity in various organs and tissues. DXR can also induce apoptosis and hyperlipidemia [24,25]. One of the oxidative stress reduction strategies has been the combination of the drug together with an antioxidant agent [25,44]. In this context, phytochemical compounds have been described as an alternative to mitigate the harmful effects caused by DXR since metabolites from natural products have shown to be promising in overcoming the limitations of DXR in pre-clinical models such as chemosensitizers, chemoresistance inhibitors, and protectors chemotherapeutics in different types of cancer [48].

The association of DXR with *Vp*LAE or *n*-BF in the co-, pre-, and post-treatments demonstrated an anticytotoxic potential of *V. polyanthes*. In contrast, the cytotoxicity of DXR was potentiated by *Vp*LAE and its aqueous, *n*-butanol, and ethyl acetate fractions (0.25–1 mg/mL) on human lymphocytes during co-treatment [21]. In vivo toxicity assessment involves important factors related to the dynamics of the accumulation of substances in cells that can occur through electron transport, absorption and diffusion, apoptosis process, production of reactive oxygen molecules, and biotransformation of molecules by intracellular/extracellular via activation of specific enzymes. The cell's communication with its environment is a key factor in differentiating between in vivo and in vitro models [49].

The antigenotoxic potential of *Vp*LAE and *n*-BF (in the presence of DXR) was also evaluated in co-, pre-, and post-treatment schemes by comet assay. The results revealed that *Vp*LAE and *n*-BF reduced DXR genotoxicity by ~38%. The exception is *n*-BF co-treated with DXR, which could not protect the DNA. Similar results were observed for *Vp*LAE and its fractions (aqueous, ethyl acetate, and *n*-butanol) co-treated with DXR in human lymphocytes. *V. polyanthes* decreased DXR genotoxicity by ~15% [21]. However, previous results with *D. melanogaster* showed that *Vp*LAE potentiated DXR genotoxicity when both were administered in a co-treatment regimen [19].

The association of *Vp*LAE and *n*-BF with DXR in co-, pre-, and post-treatments showed a significant reduction in the frequency of MN in erythrocytes from the bone marrow of mice, showing a protective effect against damage caused by DXR. Unlike this result, tests conducted to evaluate the genotoxic effects using the wing recombination and somatic mutation test (SMART-wing) showed that the association of the aqueous extract of *V. polyanthes* with DXR potentiated its mutagenic effect, increasing the number of mutations in *D. melanogaster* somatic cells [19]. The observed differences may be associated with the model used to conduct the studies (murine x insect), highlighting the importance of using different study models during the pre-clinical phase of drug development.

This study also investigated secondary metabolites in *Vp*LAE and *n*-BF to infer their association with the anti-cytogenotoxic activity against the redox effect generated by DXR. Our LC-MS results of *Vp*LAE and *n*-BF confirmed the presence of phenolic compounds abundantly found in plants [50–53]. We putatively identified eight phenolic compounds, including seven phenols identified as chlorogenic acids and a flavonoid identified as quercetin 3-*O*-rutinoside (rutin). The presence of these metabolites was observed for other species of the genus *Vernonia* [54,55]. Flavonoids are known for their antioxidant potential aiding in the capture and scavenging of radicals, as well as being one of the most widely found secondary metabolites in medicinal plants [23,50,51,53]. In this sense, due to their radical scavenging properties, flavonoids may act in the redox effect mediated by DXR in the generation of cellular oxidative stress. The phenolic compounds noted here, more specifically the chlorogenic acids, have been widely studied in recent years regarding their effects and redox effects in various cell types [45].

Recently, the antioxidant potential of *V. polyanthes* leaves aqueous extract and its fractions (aqueous, *n*-butanol, and ethyl acetate) was investigated by the DPPH method showing great antioxidant potential for the extract and the *n*-butanol fraction [21]. In this sense, the metabolites detected in *Vp*LAE and *n*-BF may contribute to the prevention of DXR-induced overproduction of free radicals, protecting the bone marrow cells of mice. Phenolic compounds have hydroxyl groups, which can help in the process of scavenging free radicals by direct proton transfer. ROS elimination occurs in proportion to the number of functional hydroxyl groups present within each molecule [56,57]. There is growing evidence that compounds with antioxidant properties can remove ROS before these species react with DNA resulting in a mutation [56,58]. In this way, metabolites in plant extracts can increase the maintenance of DNA structure and modulation of DNA metabolism and repair, minimizing the redox effect of toxic compounds [59].

A high degree of correlation was found between the in vivo and in silico results. Among the metabolites detected in *Vp*LAE and *n*-BF, rutin stands out as a potential antioxidant and chemopreventive molecule against DXR-mediated cytogenotoxicity. The result of the PASS online prediction tool showed that rutin might be able to enhance *hmox1* expression. Hmox1 is an antioxidant enzyme produced to respond to oxidative stress [60,61]. Hmox1 activation inhibits lipid peroxidation, preventing cell damage caused by DXR [60,62]. It had been demonstrated that rutin attenuated the toxic effects caused by DXR in cardiac and renal tissues via improvement of the antioxidant state of cells [63]. Rutin administration also decreased DXR-induced heart failure, inhibiting excessive autophagy and apoptosis [64]. This suggests that using antioxidant agents, such as flavonoids, in combination with DXR may reduce or inhibit DXR-induced side effects.

Moreover, rutin is a predicted CYP inducer. The cytochrome P450 enzymes metabolize xenobiotics, participating mainly in the conversion of toxic substances into more polar and water-soluble metabolites to be rapidly excreted, preventing cytotoxic and genotoxic effects [65]. However, during the biotransformation process, various unstable and reactive intermediates that react with DNA can be formed, causing genotoxicity and cell damage [65–67]. In this sense, it can be suggested that the moderate genotoxicity presented for the *Vp*LAE (G3, G4, G5, and G6) and the *n*-BF (G7, G8, G9, and G10), as well as the mild mutagenicity demonstrated for the G5 group (*Vp*LAE) and the groups G7, G8 and G9 (*n*-BF), could be a result of the CYP family induction. In addition, since the cytochrome

P450 enzymes catalyze many metabolic reactions involving xenobiotics [66], these enzymes may also have acted in the potent antigenotoxic and antimutagenic activity observed for *Vp*LAE and *n*-BF.

5. Conclusions

*Vp*LAE and *n*-BF in co-, pre-, and post-treatments significantly inhibited DXR toxicity, protecting the mouse bone marrow cells against the cytotoxic, genotoxic, and mutagenic effects of DXR. This cytoprotective activity may be correlated with the antioxidant potential of phenolic compounds present in *Vp*LAE and *n*-BF. Furthermore, both *Vp*LAE and *n*-BF did not demonstrate to be cytotoxic at the concentrations used. Thus, studies about the association of DXR with natural antioxidants are encouraged to reduce the level of oxidative stress generated by the drug; that is, its side effects.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/molecules27082553/s1, Table S1: Spectroscopic data of the putatively identified metabolites in *V. polyanthes* leaf aqueous extract (*Vp*LAE) and its *n*-butanol fraction (*n*-BF), Figure S1: Letter of the Animal Research Ethics Committee of the Federal University of Goiás (CEUA/UFG), protocol number 069/18.

Author Contributions: Conceptualization, J.D.R. and E.F.L.C.B.; analysis, J.D.R., M.E.G., A.V.d.M.B. and V.C.S.A.; data curation, L.L.B., L.C.-C., L.G.-N., and E.F.L.C.B.; formal analysis, J.D.R., L.M.d.A., L.L.B., L.C.-C. and E.F.L.C.B.; Comet assay and MN test, J.D.R., A.V.d.M.B., V.C.S.A., L.M.d.A., L.C.-C. and E.F.L.C.B.; HPLC analysis, J.D.R., M.E.G. and L.G.-N.; in silico analysis, J.D.R., L.L.B. and E.F.L.C.B.; supervision, L.L.B., L.C.-C., L.G.-N., E.F.L.C.B.; writing—original draft, J.D.R., M.E.G. and E.F.L.C.B.; writing—review and editing, J.D.R., M.E.G., A.V.d.M.B., V.C.S.A., L.M.d.A., L.L.B., L.C.-C., L.G.-N. and E.F.L.C.B. All authors have read and agreed to the published version of the manuscript.

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Supplementary Material

Phytochemical Composition and Protective Effect of *Vernonanthura polyanthes* leaf against in vivo doxorubicin-mediated toxicity

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Table S1. Spectroscopic data of the putatively identified metabolites in *V. polyanthes* leaf aqueous extract (*Vp*LAE) and its *n*-butanol fraction (*n*-BF).

ID	Rt	Usual name (CAS number)	MF (Monoisot. Mass)	Positive Ionization Mode		Negative Ionization Mode		UV_{max}
				TIC (*m/z*)	AIF	TIC (*m/z*)	AIF	
1	4.9	3-*O*-caffeoylquinic acid (327-97-9)	$C_{16}H_{18}O_9$ (354.0951)	$[M+H]^+$ 355.1026 bp; $[(M+H) – QA]^+$ 163.0392	163.04	$[M-H]^-$ 353.0891 bp; $[2M-H]^-$ 707.1855	353.09; 191.06 bp; 179.03; 135.04	218; 244 sh; 296 sh; 324
2	6.0	5-*O*-caffeoylquinic acid (906-33-2)	$C_{16}H_{18}O_9$ (354.0951)	$[M+H]^+$ 355.1027 bp; $[(M+H) – QA]^+$ 163.0391	163.04	$[M-H]^-$ 353.0891 bp; $[2M-H]^-$ 707.1863; $[(M-H) – CAF]^-$ 191.0559	353.09; 191.06 bp; 135.04	218; 244 sh; 295 sh; 326
3	6.2	4-*O*-caffeoylquinic acid (87099-73-8)	$C_{16}H_{18}O_9$ (354.0951)	$[M+H]^+$ 355.1027 bp; $[(M+H) – QA]^+$ 163.0392	163.04	$[M-H]^-$ 353.0880	191.06; 179.03; 173.04 bp; 135.04	219; 246 sh; 298 sh; 325
4	7.6	5-*O*-feruloylquinic acid (62929-69-5)	$C_{17}H_{20}O_9$ (368.1107)	$[M+H]^+$ 369.1178	177.05; 163.04 bp	$[M-H]^-$ 367.1046	191.05	297; 326
5	8.6	quercetin 3-*O*-rutinoside (153-18-4)	$C_{27}H_{30}O_{16}$ (610.1534)	$[M+H]^+$ 611.1609 bp; $[(M+H) – rhamnosil]^+$ 465.1030; $[(M+H) – rhamnosil-glicose]^+$ 303.0498	303.05	$[M-H]^-$ 609.1466 bp	609.15 bp; 301.03	256; 266 sh; 355
6	9.4	3,4-di-*O*-caffeoylquinic acid	$C_{25}H_{24}O_{12}$ (516.1268)	$[M+H]^+$ 517.1353 bp; $[(M+H) – H_2O]^+$	163.04	$[M-H]^-$ 515.1213	515.12; 353.09; 191.06; 179.03;	219; 243 sh; 297 sh; 321

ID	Rt	Usual name (CAS number)	MF (Monoisot. Mass)	Positive Ionization Mode		Negative Ionization Mode		UV$_{max}$
				TIC (*m/z*)	AIF	TIC (*m/z*)	AIF	
		(89886-30-6)		499.1244; $[(M+H) – CAF]^+$ 355.1027; $[(M+H) – QA-CAF]^+$ 163.0387			173.04 bp	
7	9.7	3,5-di-*O*-caffeoylquinic acid (89919-62-0)	$C_{25}H_{24}O_{12}$ (516.1268)	$[M+H]^+$ 517.1382 bp. $[(M+H) – H_2O]^+$ 499.1227; $[(M+H) – QA-CAF]^+$ 163.0394	163.04	$[M-H]^-$ 515.1216	353.09; 191.06 bp; 179.03	221; 244 sh; 296 sh; 325
8	10.2	4,5-di-*O*-caffeoylquinic acid (89886-31-7)	$C_{25}H_{24}O_{12}$ (516.1268)	$[M+H]^+$ 517.1346 bp; $[(M+H) – H_2O]^+$ 499.1228; $[(M+H) – CAF]^+$ 355.1027; $[(M+H) -QA]^+$ 163.0392	163.04	$[M-H]^-$ 515.1213	515.12; 353.09; 191.06; 179.03; 173.04 bp	219; 244 sh; 299 sh; 327

ID, peak identification; Rt, retention time in minutes; MF, molecular formular; Monoisot. Mass, monoisotopic mass; TIC, Total Ion Chromatogram; AIF, All Ion Fragmentation; UV$_{max}$, wavelength of maximum absorption in the ultraviolet spectral region; sh, shoulder; QA, quinic acid; CAF, caffeoyl unit; bp, base peak.

MINISTÉRIO DA EDUCAÇÃO
UNIVERSIDADE FEDERAL DE GOIÁS
PRÓ-REITORIA DE PESQUISA E INOVAÇÃO
COMISSÃO DE ÉTICA NO USO DE ANIMAIS/CEUA

C E R T I F I C A D O

Certificamos que a proposta intitulada **ANÁLISE DAS FRAÇÕES DO EXTRATO AQUOSO DE FOLHAS DE Vernonanthura polyanthes QUE POTENCIALIZAM A GENOTOXICIDADE DA DOXORRUBICINA**, registrada com o protocolo **nº 069/18**, sob a responsabilidade de **JAMIRA DIAS ROCHA** que envolve a produção, manutenção ou utilização de animais pertencentes ao filo Chordata, subfilo Vertebrata (exceto humanos), para fins de pesquisa científica (ou ensino) - encontra-se de acordo com os preceitos da Lei nº 11.794, de 8 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 de Experimentação Animal (CONCEA), e foi aprovada pela COMISSÃO DE ÉTICA NO USO DE ANIMAIS (CEUA) da Universidade Federal de Goiás (UFG), em reunião de **17/09/2018**

- Finalidade: ( ) Ensino (X) Pesquisa Científica
- Vigência da autorização: 09/2018 a 03/2020
- Espécie/linhagem/raça: *Mus musculus*/Swiss Webster
- Nº de animais autorizados: 140
- Peso/Idade: 20 a 30 gramas, 7 a 12 semanas de idade
- Sexo: machos
- Origem (fornecedor): Biotério Central da Universidade Federal de Goiás

Dra. Liliana Borges de Menezes Leite
Vice-Coordenadora da CEUA/PRPI/UFG

Comissão de Ética no Uso de Animais/CEUA
Pró-Reitoria de Pesquisa e Inovação/PRPI-UFG, Alameda Flamboyant, Qd. K, Edifício K2, 1° andar, Prédio da Agência de Inovação, Parque Tecnológico, sala da CEUA, Campus Samambaia – Goiânia-GO, Fone: (55-62) 3521-1876.
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Figure S1. Letter of the Animal Research Ethics Committee of the Federal University of Goiás (CEUA/UFG), protocol number 069/18.

Chemopreventive and antineoplastic potentials of molecules present in *Morinda lucida, Momordica charantia,* and *Vernonanthura polyanthes*

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Abstract

Cancer is one of the leading causes of death worldwide and one of the top four causes of premature death in most countries. Several studies have shown that secondary metabolites found in medicinal plants have anticancer, antimutagenic, anti-genotoxic, and chemopreventive effects. Ethnobotany knowledge point to *Morinda lucida*, *Momordica charantia*, and *Vernonanthura polyanthes* as anticancer plants, turning them into promising candidates for cancer treatment. This study aimed to analyze *M. lucida*, *M. charantia*, and *V. polyanthes* isolated compounds to identify natural anticancer agents through *in silico* analysis. We performed pharmacokinetics, biological activities, and toxicological predictions using the softwares SwissADME and SwissTargetPrediction, PASSonline, and Protox II, respectively, and molecular docking using the Gold software. The molecules damnacanthal, momordicin 1, and quercetin-3-O-rutinoside identified in *M. lucida*, *M. charantia*, and *V. polyanthes* presented the best anticancer potential and were chosen for the molecular docking study. According to Lipinski's criteria, damnacanthal, momordicin 1, and quercetin-3-O-rutinoside were classified as potential drugs, especially for the pharmacokinetics criteria. Damnacanthal and momordicin 1 had high absorption in the gastrointestinal treatment, while quercetin-3-O-rutinoside had low absorption. These molecules also showed low penetration through the hematoencephalic barrier (BHE). Regarding the median lethal dose (LD_{50}) prediction, damnacanthal and quercetin-3-O-rutinoside had a value of 5000 mg/kg, while momordicin 1 had a value of 186 mg/kg, representing a safe margin given that the compounds were classified in classes 3 and 5. These compounds also demonstrated antineoplastic, antimutagenic, and/or cancer-preventive activity, according to the PASSonline prediction. In this sense, damnacanthal, momordicin 1, and quercetin-3-O-rutinoside were chosen to test their potential interactions with the beta estrogen receptor, receptor 2 of endothelial vascular growth factor, and xanthine dehydrogenase, respectively, using molecular docking. These results demonstrated a promising interaction between the studied compounds with the chosen targets. In conclusion, this computational study revealed that damnacanthal, momordicin 1, and quercetin-3-O-rutinoside are promising anticancer molecules with favorable pharmacokinetics and toxicological properties.

Keywords: Cerrado; damnacanthal; *in silico* predictions; quercetin-3-O-rutinoside; molecular docking; momordicin 1.

Introduction

Cancer is considered one of the most harmful diseases today (AKBAR et al., 2021). Conventional cancer treatments are expensive and cause many side effects, such as vomiting, alopecia, diarrhea, constipation, and myelosuppression, as well as neurological, cardiac, pulmonary, and renal toxicity (MANS; ROCHA; SCHWARTSMANN, 2000). In this sense, there is a growing need to discover new anticancer drugs that are more potent, selective, and less toxic (ALONSO-CASTRO et al., 2011).

In recent years, preclinical tests used to evaluate extracts of medicinal plants, as well as their bioactive compounds, have demonstrated remarkable anticancer (ALAMI MERROUNI; ELACHOURI, 2021). Drugs derived from natural products are considered less toxic than synthetic drugs, which drives research into medicinal plants' phytochemical composition (ALQETHAMI; ALDHEBIANI, 2021). Secondary metabolites have been used in the development of pharmaceuticals. Currently, approximately 50% of all drugs in clinical trials are derived from plants (SHAKYA et al., 2019). Recently, a study showed that Cerrado plant species used in folk medicine and their compounds demonstrate high cytotoxicity against tumor cells and low toxicity against non-tumor cells, indicating that Cerrado plants have a good potential for developing new anticancer drugs (ROCHA et al., 2022a). These findings reinforce that ethnobotanical knowledge can be a classic basis for advanced anticancer research and new drug discovery (ALAMI MERROUNI; ELACHOURI, 2021). There are several strategies for developing new anticancer drugs from natural compounds (MANS; ROCHA; SCHWARTSMANN, 2000).

In the last few decades, several computer models have been developed to predict the toxicity of a given compound, following a cross-reading approach and relying on the assumption that substances with similar structures share similar physicochemical and toxicological properties (GLÜCK et al., 2018). The *in silico* strategy assists in exploring pharmacology and therapeutic potential using computer-simulated models (MOHAMMED et al., 2022). Using computational tools, such as molecular docking and Lipinski filtering methods, is crucial and essential for the first screening assessment in drug discovery research (ZULKIPLI et al., 2020).

The species *Morinda lucida* Benth (Rubiaceae), *Momordica charantia* L. (Cucurbitaceae), and *Vernonanthura polyanthes* (Spreng.) A.J. Vega & Dematt. (syn.: *Vernonia polyanthes* Less) (Asteraceae), popularly known as mulberry, melão-de-São-Caetano, and assa-peixe, respectively, are widely used in folk medicine (ABU et al., 2016; DANDAWATE; SUBRAMANIAM; SUBHASH B. PADHYE, 2017; LORENZI; MATOS,

2008). Studies show that *M. lucida*, *M. charantia*, and *V. polyanthes* are rich in secondary metabolites with antioxidant potential and demonstrate anticancer activity (ADEWOLE, 2020; ALMEIDA et al., 2020; OHTA, 2018; RAINA; KUMAR; AGARWAL, 2016; ROCHA et al., 2020). The main phytochemical components with medicinal properties are tannins, saponins, glycosides, phenols, flavonoids, alkaloids, steroids, and resins (ALQETHAMI; ALDHEBIANI, 2021). These classes of compounds were identified in *M. lucida*, *M. charantia*, and *V. polyanthes* (OHTA, 2018; RAINA; KUMAR; AGARWAL, 2016; ROCHA et al., 2022b). These phytochemical compounds are called natural antioxidants and are necessary for the human body to have a positive response against oxidative stress caused by different types of infirmities (ALQETHAMI; ALDHEBIANI, 2021; ALZANDI et al., 2021).

Since *M. lucida*, *M. charantia*, and *V. polyanthes* present antioxidant properties and may be promising candidates for cancer treatment, we analyzed compounds identified in these species to identify natural anticancer agents via *in silico* analysis according to their pharmacokinetic and structural properties, including physicochemical, absorption, distribution, metabolism, excretion and toxicity (ADMET), and molecular docking.

2. Materials and methods

2.1 Molecules selection

Compounds identified in *M. lucidaM. charantia*, and *V. polyanthes* were selected for this study.

2.2 In silico bioactivity screening

2.2.1 ADMET prediction

The 2D structures (chemical canonical SMILES) were obtained from PubChem database (https://pubchem.ncbi.nlm.nih.gov/). After selecting the molecules present in *M. lucida*, *M. charantia*, and *V. polyanthes*, SwissADME online tool (http://www.swissadme.ch) was used to determine the absorption, delivery, metabolism, and excretion (ADME), and drug-likeness prediction of the selected compounds. The drug-likeness was predicted based on the Lipinski rule of 5

The toxicity prediction was carried out using the ProTox-II online tool (https://tox-new.charite.de/protox_II/).

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2.2.2 Biological activities prediction

Biological activities prediction was performed using the PassOnline server (http://.pharmaexpert.ru/passonline/). This server uses comparative analyzes between the

investigated structures and its database. Two parameters are generated: Pa (probability of the molecule being active) and Pi (probability of the molecule being inactive). Values of Pa > 0.7 and Pi < 0.05 were considered.

2.2.3 Toxicity prediction

2.3 Target prediction

SwissTargetPrediction (http://www.swistargetprediction.ch) is a web tool that aims to predict the most likely active site of a protein regarding the molecules present in *M.lucida*, *M. charantia,* and *V. polyanthes*. The program calculates the similarity between the users query compound and those compiled collection of known actives in well-defined experimental binding assays. The similarity quantification is two folds and it gives the active site bind to the molecule. .

2.4 Molecular Docking

For predicting the binding affinities of a selected ligands,molecular docking protocols was used. Then, using GOLD Suite 5.7.0 software, ligands are docked with the targets proteins (RODRIGUES; BORGES, 2022).

The grid box size was set for receptor, and the was set to 10 A. . Biovia Discovery Studio 3.5 was employed to obtain the 2D interaction figures, and PyMOL Molecular Graphics System 2.0 was used to obtain the 3D interaction images. Redocking with the co-crystallized ligand was performed to validate the models produced. The CHEMPLP score function was used.

2.5 Pharmacophoric Modeling

From a literature search, 5 water-soluble, ascorbic acid and flavonoids (luteolin, catechin, silybin, curcumin) were identified as antioxidant molecules, which may act by reducing the side effect of DXR (QUILES et al., 2002). PharmaGist webserver (https://bioinfo3d.cs.tau.ac.il/PharmaGist/) was the program employed to obtain 3D models and selects the highest-scoring ones. Thus, it was possible to predict that these 5 antioxidant molecules are polar and resemble the pharmacological mechanism of action of the molecules identified in *V. polyanthes* by the UHPLC -UV-HRMS methodology (ROCHA et al., 2022b). For the molecules selected for the species *V. polyanthes*, pharmacophoric analyses were performed based on identifying their possible targets using SwissTargetPrediction.. A minimum of 3 chemical characteristics and a maximum of 6 between hydrogen bond acceptors, hydrogen bond donors, hydrophobic groups, and aromatic rings were considered to generate the pharmacophoric data. Mapping figures were produced and visualized using Discovery Studio 3.5 software.

3. Results

3.1 In silico bioactive screening of M. lucida, M. charantia, and V. polyanthes

We identified 38 compounds for *M. lucida* species, 10 for *M. charantia*, and 8 compounds present in the extract of *V. polyanthes* leaves. Information on the pharmacokinetics and toxicities of these molecules are presented in the Table 1. The molecules were also classified as drug-likeness or non-drug-likeness according to Lipinski's rules ("rule of five"), which portray their respective abilities to behave similarly to drugs used orally. The possible antineoplastic, anticancer, antimutagenic, and chemoprotective biological activities and their respective targets were represented in Table 1.

Damnacanthal, momordicin 1, and quercetin-3-O-rutinoside (Figure 1) had the highest scores on the webservers (Table 1). Therefore, they were the chosen compounds e for evaluating the possible interactions with targets related to antineoplastic activity.

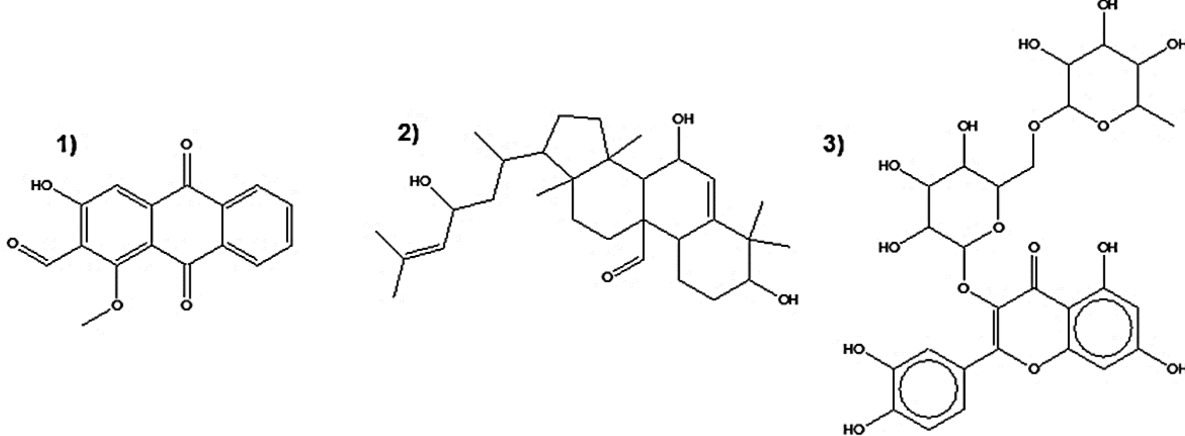

Figure 1. Selected molecules from *Morinda lucida*, *Momordica charantia*, and *Vernonanthura polyanthes* for molecular interaction analysis. **1**) damnacanthal, **2)** momordicina 1, and **3)** quercetin-3-*O*-rutinoside.

Damacanthal, momordicin 1, and quercetin-3-O-rutinoside were classified as drug-like according to Lipinski's criteria, being substances that could behave as potential drugs, particularly in the pharmacokinetic field. The pharmacokinetic predictions showed that damnacanthal and momordicin 1 molecules showed high absorption from the gastrointestinal tract. In contrast, quercetin-3-O-rutinoside showed low absorption (Table 1). These molecules also showed low penetration through the blood-brain barrier (BBB) (Table 1). Regarding the mean lethal dose (LD_{50}), damnacanthal and quercetin-3-O-rutinoside presented a value of 5000 mg/kg, and momordicin 1 showed the lowest LD_{50} value (186 mg/kg), representing a safe parameter since the compounds were classified as class 5 and 3. The classes vary from 1 to 6; the closer to 6, the less toxic the substance would be (Table 1). These molecules present

potential antineoplastic, antimutagenic, and chemopreventive activities. The pharmacokinetic profile of the possible candidate molecules was analyzed to detect whether they would be well absorbed, distributed, metabolized, and excreted without demonstrating high toxicity (Table 1).

Table 1. *In silico* predictions of the pharmacokinetic potential using SwissADME, biological potential using PASS online, and toxicological potential using ProTox II of molecules identified in *Morinda lucida*, *Momordica charantia*, and *Vernonanthura polyanthes.*

Plant species/ Compounds	Druglikeness	GI Abs.	PBH	IP-gp	DL_{50} mg/kg	Class	Toxicity	Antineoplastic activity	Antimutagenic activity	Chemopreventive activity
Morinda lucida										
1-Formylpyrrolidine	Yes	Low	No	No	1650	4	E	Yes	No	Yes
1-Hydroxy-2-methylanthraquinone	Yes	High	Yes	No	7000	5	C F G H I	Yes	Yes	No
2-methylanthraquinone	Yes	High	Yes	No	2795	5	B D F G L M	Yes	No	No
3-hydroxyanthraquinone-2-carbaldehyde	Yes	High	Yes	No	2795	5	B D F G L M	Yes	No	No
5,15-O-dimethylmorindole	Yes	High	No	No	5000	5	B C D	Yes	No	No
alpha terpinilline acetate	Yes	High	Yes	No	4800	5	J	Yes	No	No
Asperulosidic Acid	No	Low	No	No	200	4	A	Yes	No	No
hexacosanoic acid	Yes	Low	No	No	130	3	A	Yes	No	No
Oleanoic Acid	Yes	-	-		2000	4	B E J K N	Yes	No	Yes
palmitic acid	Yes	High	Yes	No	130	3	A	Yes	Yes	No
Ursolic Acid	Yes	Low	No	No	2000	4	B E J K N	Yes	No	No
alpha terpinene	Yes	Low	Yes	No	1680	4	A	Yes	No	No
anthraquinone-2-aldehyde	Yes	High	Yes	No	2795	5	B D F L M	Yes	No	No
asperulosidic	Yes	Low	No	No	2000	4	A	Yes	No	No
beta-bisabolene	Yes	Low	No	No	4400	5	B G	Yes	No	No
beta-sitosterol	Yes	Low	No	No	890	4	B	Yes	No	Yes
campesterol	Yes	Low	No	No	890	4	B	Yes	No	Yes
guanidine carbonate	Yes	Low	No	Yes	1750	4	A	Yes	No	No

Cycloartenol	Yes				5000	5	B	Yes	No	No
Damnacanthal*	Yes	High	No	No	5000	5	B D F G H	Yes	No	No
Damnacanthol	Yes	High	No	No	5000	5	B C D G	Yes	Yes	No
Digitolutein	Yes	High	Yes	No	7000	5	B C D F	Yes	Yes	No
stigmasterol	Yes	Low	No	No	890	4	B	Yes	No	Yes
Alizarin 1-Methyl Ether	Yes	High	Yes	No	7000	5	B D F H	Yes	Yes	No
Rubiadin 1-Methyl Ether	Yes	High	Yes	No	7000	5	B C D F G H	Yes	Yes	No
Morindone-5-Methyl Ether	Yes	High	No	No	7000	5	B C D F H	Yes	Yes	No
phenylthiourea	Yes	High	No	No	3	1	B	Yes	No	No
Phyto	Yes	High	Yes	Yes	5000	5	A	Yes	No	No
Munjistin	Yes	High	No	No	5000	5	B D F G	Yes	Yes	No
N-methyl mercapto acetamide	Yes	High	No	No	4300	5	B	Yes	No	No
Nordamnacanthal	Yes	High	No	No	5000	5	D F G H	Yes	No	No
Oruwacin	Yes	High	No	No	5530	6	B E	Yes	No	No
oruwal	Yes	High	Yes	No	2000	4	B	Yes	No	No
purporoxanthin	Yes	High	Yes	No	7000	5	C D F G H	Yes	Yes	No
rubiadine	Yes	High	Yes	No	7000	5	B C D F G H O	Yes Yes	Yes	No
Sabinene	Yes	Low	Yes	No	5000	5	A	Yes	No	No
Soranjidiol	Yes	High	Yes	No	7000	5	B C D F G H	Yes	Yes	No
subspinosin	Yes	High	Yes	No	5000	5	B C	Yes	No	No
Momordica charantia										
momordicine 1*	Yes	High	No	Yes	186	3	B E	Yes	No	Yes
Momordenol	Yes	Low	No	No	8800	6	B	Yes	No	Yes
Charina	Yes	Low	No	No	1000	4	A	Yes	No	No
momordina	No	Low	No	Yes	1750	4	B	Yes	No	No
Momordicoside G	Yes	Low	No	Yes	2000	4	B	Yes	No	Yes

cryptoxanthin	No	Low	No	Yes	10	2	A	Yes	No	Yes
cucurbitacin B	Yes	Low	No	Yes	14	2	B C M P	Yes	No	Yes
routine	No	Low	No	Yes	5000	5	B	Yes	No	No
Kuguacina J	No	High	No	No	186	3	B E	Yes	No	Yes
Kuguacina N	Yes	High	No	Yes	50	2	B	Yes	No	Yes
Vernonanthura polyanthes								No	No	No
3-O-Caffeoylquinic acid	Yes	Low	No	No	5000	5	B	Yes	No	Yes
4-O-Caffeoilquinic acid	Yes	Low	No	No	5000	5	B	Yes	Yes	Yes
5-O-Caffeoilquinic acid	Yes	Low	No	No	5000	5	B	Yes		Yes
5-O-feruloylquinic	Yes	Low	No	No	5000	5	B	Yes	Yes	Yes
Quercetin-3-O-rutinoside*	No	Low	No	Yes	5000	5	B	Yes		Yes
3,4-di-O-caffeoylquinic acid	No	Low	No	Yes	5000	5	B	Yes	Yes	Yes
3,5-di-O-caffeoylquinic acid	No	Low	No	Yes	5000	5	B	Yes	Yes	Yes
4,5-di-O-caffeoylquinic acid	No	Low	No	Yes	5000	5	B	Yes	Yes	Yes

A=No activity; B=Immunotoxicity, C=Mutagenicity, D=Mitochondrial Membrane Potential (MMP), E=Carcinogenicity, F=Aryl Hydrocarbon Receptor (AhR), G=Estrogen Receptor Alpha (ER), H= Ligand Binding Domain Receptor (ER – LBD), I= Cytotoxicity, J= Hepatoxicity, K= Nuclear factor (derived from erythroid 2), type 2/antioxidant responsive element (nrf2/ARE), L = Protein 5 that contains the ATPase family AAA (ATAD5), M = Androgen Receptor (AR), N = Heat Shock Factor Response Element (HSE), O = Phosphoprotein (Suppressor), P = Androgen Receptor Ligand Binding Domain (AR-LBD) .

Main active metabolites present in the species *M. lucida*, *M. charantia* and *V. polyanthes*, identified through literature review.

*Structures considered most promising for the investigation of the pharmacokinetic and toxicological potential of the species *M. lucida*, *M. charantia* and *V. polyanthes*

3.2 TargetPrediction

To select possible receptors involving anticancer activity to perform molecular docking, the 15 main targets of each compound were analyzed (Table 2). The selected compounds damnacanthal, momordicin 1, and quercetin-3-O-rutinoside are predicted to interact with estrogen receptor beta, vascular endothelial growth factor receptor 2, and xanthine dehydrogenase, respectively. The crystallographic structures of the targets were obtained from the PDB (Figure 2).

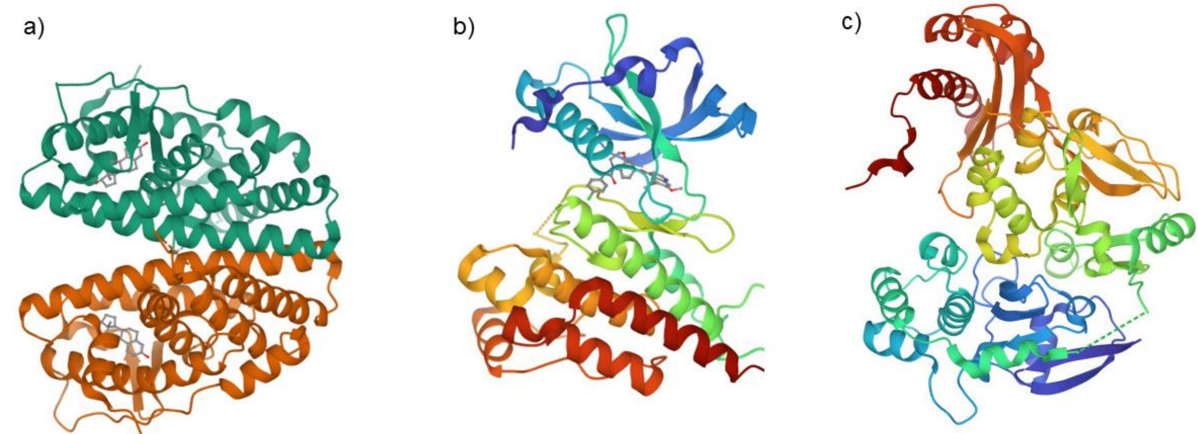

Figure 2. Crystallographic structures of selected targets for molecular docking. a) Estrogen receptor beta (5TOA) https://www.rcsb.org/structure/5TOA; b) Vascular endothelial growth factor receptor 2 (2RL5) https://www.rcsb.org/structure/2RL5; and c) Xanthine dehydrogenase (1JRP) https://www.rcsb.org/structure/1JRP.

3.3 Molecular Docking

3.3.1 Damnacanthal

Molecular docking revealed potential interactions of damnacanthal with the estrogen receptor beta complexed with estradiol (Figure 3a). The green represents the hydrogen bonds dashed color, being more intense interactions where hydroxyl makes a hydrogen bond with glycine (GLY472), oxygen makes a hydrogen bond interaction with histidine (HIS475). Another bond represented by the intense pink color is the π-π bond, the bond between the π- π electrons of the aromatic ring and phenylalanine (PHE396) in a T-shape. While the hydrogen bonds are the most intense and responsible for the anchoring mechanism, the other interactions are more fragile but define the pose, that is, the positioning of the molecule in the active cavity. This analysis suggests that damnacanthal is a compound that putatively binds to the estrogen receptor beta, which could represent an antineoplastic effect against breast cancer (Figures 3a-b).

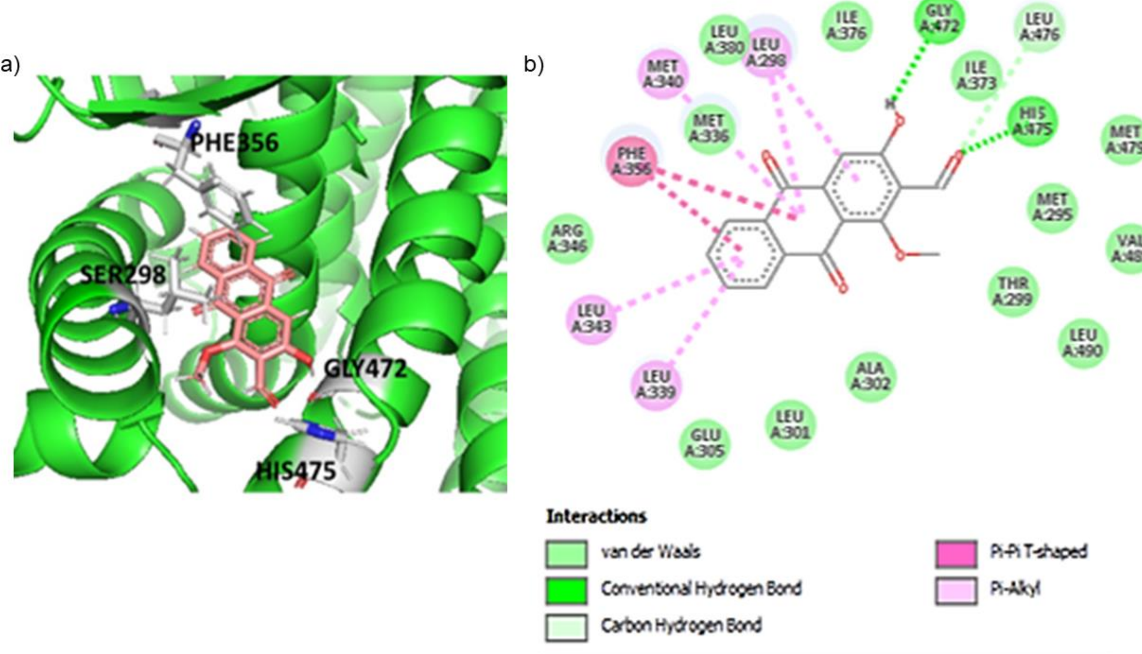

Figure 3. Molecular docking. **a)** Types of damnacanthal interaction at the 3D estrogen receptor beta active site. Image generated by Pymol 1.1r1 software; **b)** Diagram of 2D interaction of damnacanthal with the estrogen receptor beta.

Table 2. Main targets selected for damnacanthal, momordicin I, and quercetin-3-O-rutinoside compounds using SwissTargetPrediction.

Damnacanthal	**Momordicin I**	**Quercetin-3-O-rutinoside**
Receptors	***Receptors***	***Receptors***
Tyrosine-protein kinase LCK	Prostanoid FP receptor	Neuromedin-U receptor 2
LIM domain kinase 1	Prostanoid IP receptor	Alpha-2a adrenergic receptor
Leukocyte elastase	Solute carrier family 22 member 6 (by homology)	Adrenergic receptor alpha-2
Serine/threonine-protein kinase PIM1	Cytochrome P450 19A1	Acetylcholinesterase
Casein kinase II alpha	Prostanoid EP1 receptor	Aldose reductase
Protein-tyrosine phosphatase 4A3	Prostanoid EP2 receptor	Carbonic anhydrase VII
Estrogen receptor beta	Glucocorticoid receptor	Carbonic anhydrase XII
Protein farnesyltransferase	Prostanoid EP4 receptor	Carbonic anhydrase IV
Apoptosis regulator Bcl-2	Prostanoid EP3 receptor	NADPH oxidase 4
Epidermal growth factor receptor erbB1	Estrogen receptor beta	Carbonic anhydrase II
Caspase-3	LXR-alpha	Quinone reductase 2
Cytochrome P450 2C19	Protein-tyrosine phosphatase 1B	Ribosomal protein S6 kinase alpha 3
Solute carrier family 22 member 6 (by homology)	Niemann-Pick C1-like protein 1	**Xanthine dehydrogenase**
Adenosine A2a receptor	Peroxisome proliferator-activated receptor gamma	Lymphocyte differentiation antigen CD38
Inhibitor of nuclear factor kappa B kinase epsilon subunit	**Vascular endothelial growth factor receptor** 2	Cyclooxygenase-2

3.3.1 Momordicin I

The molecular docking of momordicin I with VEGFR-2 was performed (Figure 4). The main observed chemical bonds were electrostatic interactions with arginine (ARG1066) by hydrogen bonding and with phenylalanine (PHE1047) through a pi-sigma bond, which contribute to the stabilization of the molecule with the receiver. Other important pi-alkyl bonds were observed with arginine (ARG1032), leucine (LEU1049 and LEU1035), phenylalanine (PHE918), and cysteine (CYS919). The latter is an important amino acid in the interaction of the crystallized molecule found as a ligand in the structure obtained in the PDB (ID: 2RL).

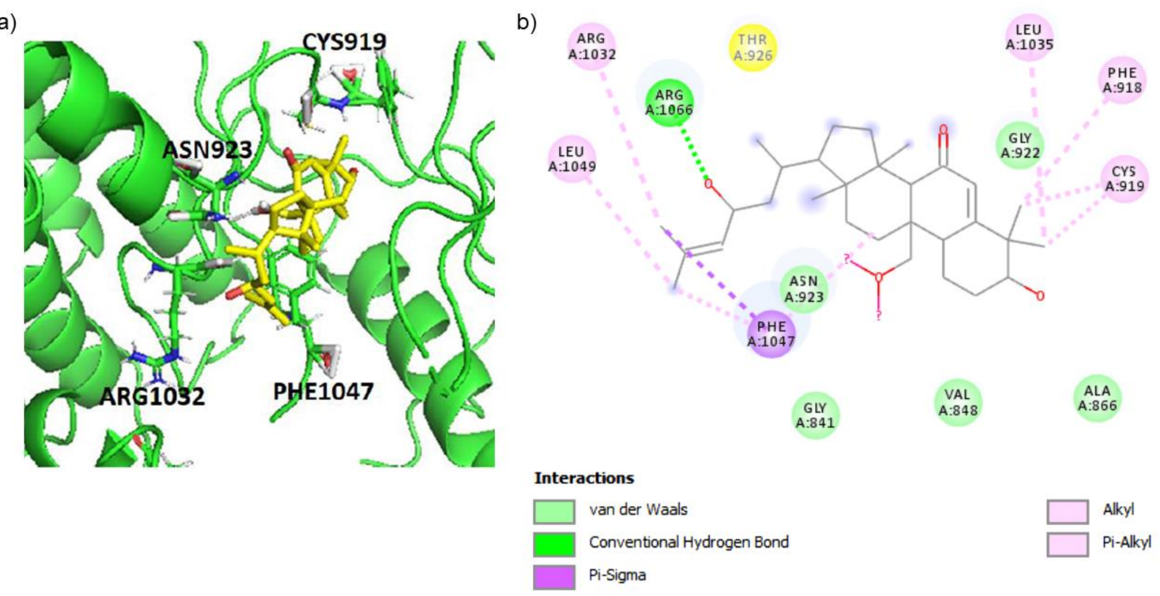

Figure 4. Molecular docking of momordicin I and the vascular endothelial growth factor receptor 2 (2RL5). **a)** Momordicin I 3D interaction with the vascular endothelial growth factor receptor 2; **b)** 2D interaction diagram of momordicin I with VEGFR-2.

3.3.1 Xanthine dehydrogenase

Molecular docking was performed with quercetin-3-O-rutinoside, illustrating the binding mode of the molecule with xanthine dehydrogenase (Figure 5). The main interactions involved between rutin and xanthine dehydrogenase are hydrogen bonds with leucine (LEU150), serine (SER78), aspartic acid (ASP), and glutamic acid (GLU197). Other important

Pi-anion bonds were shown for glutamic acid (GLU197) and alkyl for leucine (LEU150).

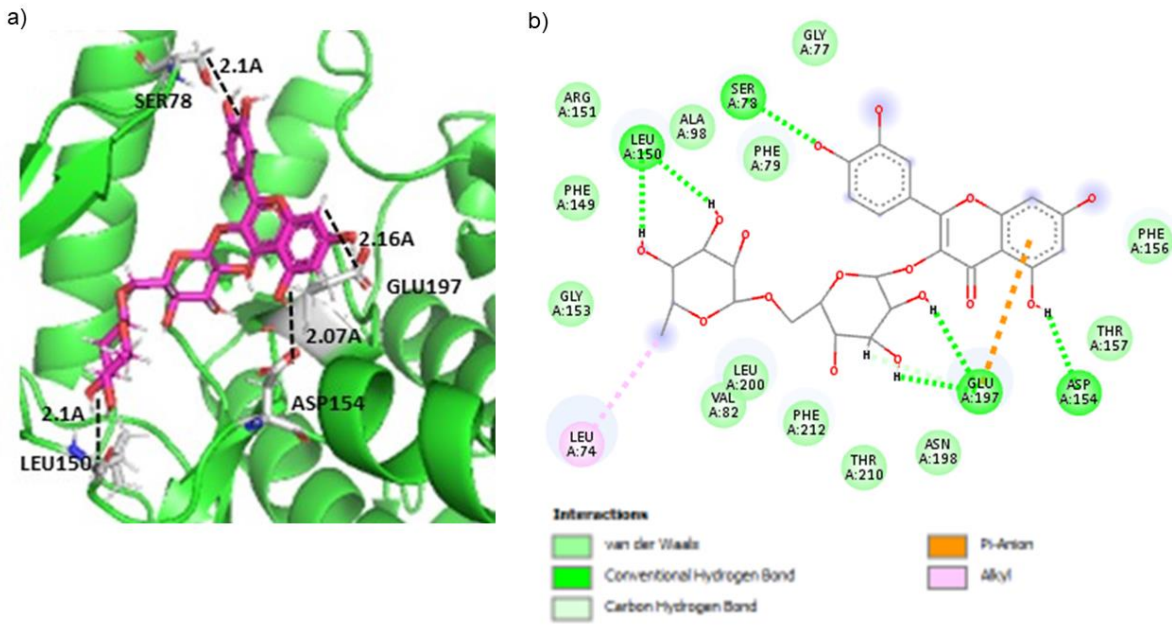

Figure 5. Molecular docking of quercetin-3-O-rutinoside and xanthine dehydrogenase **a)** quercetin-3-O-rutinoside 3D interaction with xanthine dehydrogenase; **b)** 2D interaction diagram of quercetin-3-O-rutinoside with xanthine dehydrogenase.

3.4 Pharmacophoric analysis of identified molecules of Vernonanthura polyanthes

From the pharmacophoric analysis,it is possible to observe in Figure 6 the chemical similarity between *Vernonanthura polyanthes* molecules and molecules previously identified as able to reduce DXR side effects.

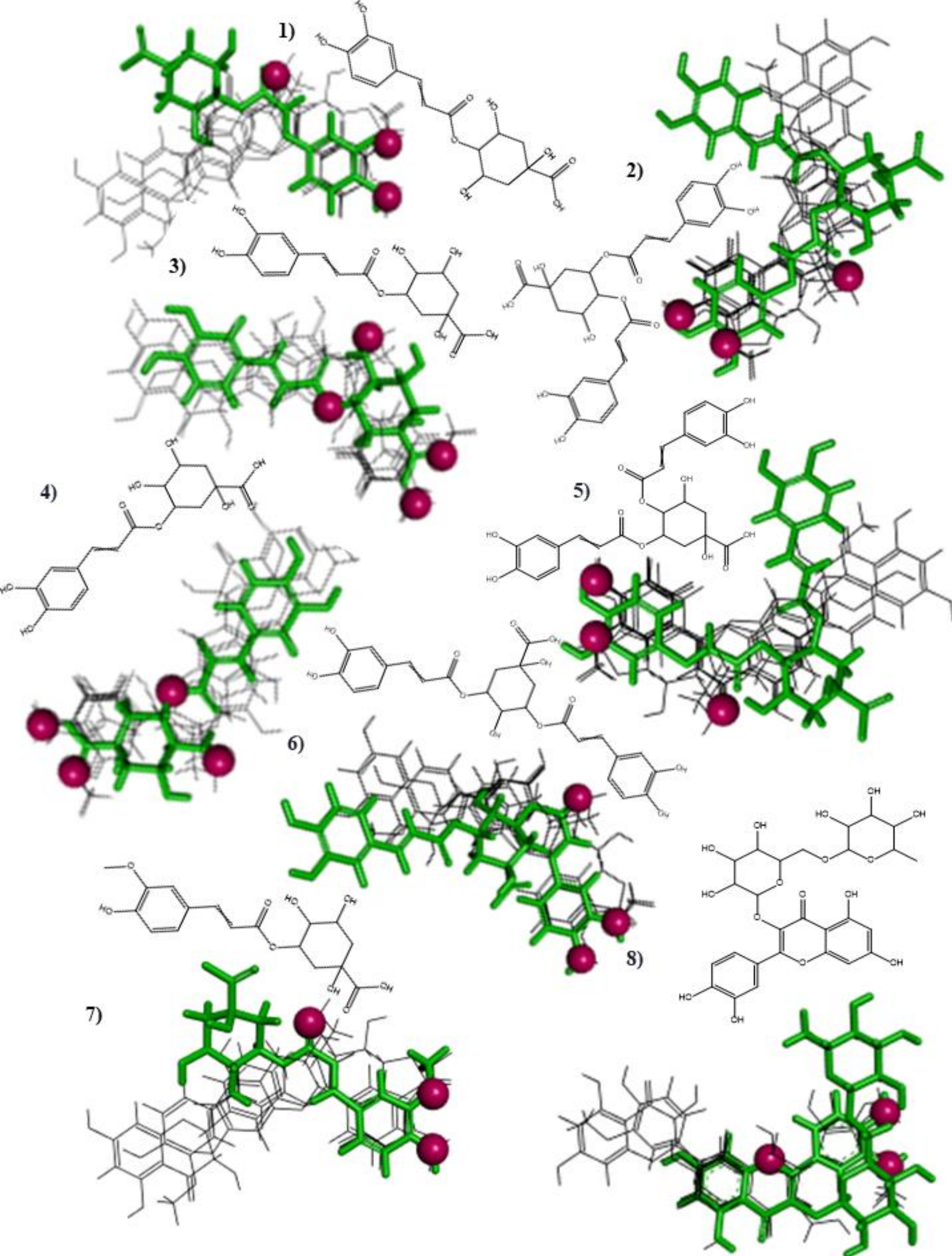

Figure 6 – Molecules identified for *V. polyanthes* coupled with antioxidant molecules. 1) 4-O-caffeoylquinic acid; 2) 4,5-di-O-caffeoylquinic acid; 3) 5-O-caferuloylquinic acid; 4) 3-O-caffeoylquinic acid 5) 3,4-di-O-caffeoylquinic acid 6) 3,5-di-O-caffeoylquinic acid 7) 5-O-feruloylquinic acid and 8) quercetin-3-O-rutinoside

4. Discussion

The survey of active metabolites of *M. lucida*, *M. charantia*, and *V. polyanthes* for potential drugs with antineoplastic potential allowed the choice of damnacanthal, momordicin 1, and quercetin-3-O-rutinoside for performing molecular docking with the estrogen receptor beta (5TOA), the vascular endothelial growth factor Receptor 2 (2RL5) and xanthine dehydrogenase (1JRP), respectively. The compounds Damnacanthal, momordicin 1, and quercetin-3-O-rutinoside were classified as drugs, according to Lipinski(LIPINSKI et al., 1997). This classification is widely used to determine molecular properties that are important for the pharmacokinetic prediction of substances *in vivo*. Lipinski's rule of five states that a candidate molecule is more likely to have favorable properties if the molecular weight is below 500 daltons and the octanol/water partition coefficient (log P) is lower than 5, if there are not more than 5 hydrogen bond donors (OH and NH groups), and if there are not 10 hydrogen bond acceptors (namely N and O) (DAINA; MICHIELIN; ZOETE, 2019; LIPINSKI et al., 1997, 2001).

The molecules damnacanthal, momordicin 1, and quercetin-3-O-rutinoside showed Pa values above 0.7 for antineoplastic, antimutagenic, and chemopreventive activities. According to the PASsonline program, Pa values (probability of being active) > 0.7 mean that the molecule has a high potential to have pharmacological activity (POROIKOV; FILIMONOV, 2002). Additionally, the compounds damnacanthal, momordicin 1, and quercetin-3-O-rutinoside showed no toxicity according to the analyzes performed using the Protox II tool. Toxicological studies using *in silico* methods are widely used, as they have efficient computational methods and mathematical algorithms to simulate possible toxic effects in biological systems (POROIKOV; FILIMONOV, 2002). Understanding the toxicity of a drug is important to ensure therapeutic safety, as drugs with greater toxicity have a smaller therapeutic window and, therefore, may have side effects for users (BANERJEE et al., 2018). Toxicity is calculated by the median lethal dose (LD_{50}), which is the value responsible for leading to the death of 50% of the exposed population. The LD_{50} is classified into 5 classes: class 1 is lethal by ingestion ($LD_{50} \leq 5$), class 2 fatal by ingestion ($5 < LD_{50} \leq 50$), class 3 toxic by ingestion ($50 < LD_{50} \leq 300$), class 4 harmful if swallowed ($300 < LD_{50} \leq 2000$), class 5 may be harmful if swallowed ($2000 < LD_{50} \leq 5000$), class 6 non-toxic ($LD_{50} > 5000$) (BANERJEE et al., 2018).

The possible targets of damnacanthal, momordicin 1, and quercetin-3-O-rutinoside molecules were also predicted. SwissTargetPrediction is a server that allows accurate prediction of bioactive molecule targets based on a combination of 2D and 3D similarity measures with ligands. Mapping predictions by homology within and between different species is possible for

close paralogs and orthologs (DAINA; MICHIELIN; ZOETE, 2019). The targets selected for damnacanthal, momordicin 1, and quercetin-3-O-rutinoside were estrogen receptor beta (5TOA), vascular endothelial growth factor receptor 2 (2RL5), and Xanthine dehydrogenase (1JRP), respectively. Mapping the targets of small bioactive molecules is an important step toward unraveling the molecular mechanisms underlying their bioactivity, helping to prevent potential side effects of these small molecules (GFELLER et al., 2014). Thus, unraveling the interactions between a molecule and its target protein through computational approaches has helped discover new targets for natural products (MAURYA et al., 2020).

The anticancer activity of the molecules selected in this work has been suggested (AKHTAR et al., 2013; DANDAWATE; SUBRAMANIAM; SUBHASH B. PADHYE, 2017; ROCHA et al., 2022b). Damnacanthal is an anthraquinone isolated from *M. lucida* with several health benefits, including anticancer activity. This molecule has demonstrated cytotoxicity against the human breast cancer cell line MCF-7 and the myeloid leukemia cell line K-562 (AKHTAR et al., 2013). Damnacanthal has also been shown to be anti-tumorigenic in human colorectal cancer cells, H1299 and HCT-116, inducing caspase activity and arresting cell growth. Furthermore, damnacanthal increased the transcription factor CCAAT/enhancer binding protein β, which ultimately influences the increase in transcription of gene-1 activated by non-steroidal molecules (NAG-1) (LV et al., 2011; SHAGHAYEGH et al., 2017). Damnacanthal increased the effectiveness of MCF-7-induced cell death and the expression of apoptosis-related genes and proteins (AZIZ et al., 2016). Damacanthal was also able to increase the expression of p21 and caspase-7. Overexpression of p21 directly activated p53 transcription and subsequently increased apoptosis in human breast cancer MCF-7 cells. In this way, damnacanthal may be a useful therapeutic/cancer prevention agent in human breast carcinoma (AZIZ et al., 2016)which corroborates with our results demonstrating a good fit between damnacanthal and the estrogen receptor beta (5TOA).

Momordicin I, isolated from *M. charantia* species, is a triterpenoid of the cucurbitan type and is known to have antitumor, antiviral, antidiabetic, cytotoxic antioxidant, anti-inflammatory, antibacterial, antiobesity, and immunomodulatory effects (DANDAWATE; SUBRAMANIAM; SUBHASH B. PADHYE, 2017). Momordicin I showed a significant effect against pancreatic carcinoma cells *in vitro* and *in vivo* by inhibiting cell proliferation, inducing apoptosis, and activating protein kinases (KAUR et al., 2013). The ethanolic extract of the leaves had an antimetastatic effect on prostate cancer in rats, also demonstrating a decrease in the percentage of lung area occupied by metastatic lesions (PITCHAKARN et al., 2010). Momordicin I is also known to have an important action in tumor angiogenesis (RAINA;

KUMAR; AGARWAL, 2016). The VEGFR-2 selected for molecular docking with momodicin I is closely linked to the process of tumor angiogenesis by promoting the production of new vessels, which ensures the supply of oxygen and nutrients to proliferating cells, leading to cancer progression and metastasis (CAPP et al., 2009; FONTANELLA et al., 2014). For VEGF, there are three types of receptors belonging to the tyrosine kinase receptor family: VEGFR-1, VEGFR-2, and VEGFR-3, with VEGFR-2 being responsible for mediating most of the angiogenic effects (CAPP et al., 2009; FONTANELLA et al., 2014). Bevacizumab (Avastin®), an IgG monoclonal antibody, was the first approved therapy to inhibit tumor angiogenesis, precisely the vascular endothelial growth factor 2 (VEGF) inhibition (DEL DEBBIO; TONON; SECOLI, 2007).

Quercetin-3-O-rutinoside, also known as rutoside, rutin, and sophorin, is an active flavonoid widely distributed in various vegetables, fruits, and medicinal plants, including *V. polyanhes* (NOURI et al., 2020; ROCHA et al., 2022b). Studies have shown that quercetin-3-O-rutinoside can neutralize various types of cancer through multiple mechanisms, for example, inhibition of malignant cell growth, induction of cell cycle arrest and apoptosis, and modulation of angiogenesis, inflammation, and oxidative stress, all mediated by the regulation of multicellular signaling pathways (NOURI et al., 2020). The inhibitory activity of flavonoids on xanthine dehydrogenase was determined in terms of inhibition of uric acid synthesis from xanthine (KHOBRAGADE et al., 2008). Quercetin-3-O-rutinoside induced xanthine dehydrogenase inhibition in mouse liver homogenate (ZHU et al., 2004). Some mediators of angiogenic signaling, including caspases, estrogen receptor beta, vascular endothelial growth factor 2, and xanthine inhibition, are associated with the anticancer potential of rutin (NOURI et al., 2020). Xanthine dehydrogenase mRNA expression has been detected in human cancers originating from the liver, bladder, breast, colon, bile duct, kidney, and hematolymphoid system. The prognostic potential of XDH mRNA expression was also significant in some other cancers, including HCC, breast cancer, kidney or bladder carcinoma, gastric cancer, mesothelioma, lung cancer, and ovarian cancer (LIN et al., 2021). In this sense, the inhibition of xanthine dehydrogenase may be important in cancer therapy.

Recently, we demonstrated the protective effect of *V. polyanthes* against *in vivo* doxorubicin-mediated toxicity (ROCHA et al., 2022b). Phytochemical compounds have shown to be promising in overcoming the side effects of DXR in preclinical models in different types of cancer (SALZILLO et al., 2021).. In this study, using pharmacophoric modeling, we observed common characteristics shared by a group of compounds of molecules identified in *V.polyanthes* with ascorbic acid, luteolin, catechin, silybin, and curcumin, that presented good

results as adjuvant compounds in DXR therapies during preclinical studies. Ascorbic acid, also known as vitamin C or ascorbate, is a promising adjuvant compound in cancer therapy when administered intravenously (DU; CULLEN; BUETTNER, 2012; EL-GARAWANI et al., 2021; SHENOY et al., 2018). The flavonoids luteolin, catechin, silybin, and coumarin also have antioxidant, anti-inflammatory, and anticancer activities. Luteolin's anticancer property is associated with apoptosis induction and cell proliferation, metastasis, and angiogenesis inhibition. These observations suggest that luteolin may be an anticancer agent for several types of cancer. Furthermore, recent epidemiological studies have attributed luteolin as a cancer-preventing property (FASOULAKIS et al., 2021; LIN et al., 2008; TUORKEY, 2016). Catechins, mainly identified in green tea, have antioxidant activity, which implicates in their anticancer and anti-inflammatory properties, cell cycle regulation, inhibition of the pathway involving the tyrosine kinase receptor, modulation of the immune system, and epigenetic control (MUSIAL; KUBAN-JANKOWSKA; MAGDALENA GORSKA-PONIKOWSKA, 2021; SHIRAKAMI; SHIMIZU, 2018). Silybin presents chemopreventive and chemosensitizing activities in various types of cancer. It can act on the metabolizing enzymes (phase I and phase II) to protect normal cells against toxic effects or side effects promoted by chemotherapeutic agents in normal cells (TEHRANI et al., 2021). Moreover, silybin exerts a chemopreventive influence by inducing intrinsic and extrinsic pathways and reactivating cell death pathways performed by pro-apoptotic/anti-apoptotic proteins and synergizing with agonists of death domain receptors (BORGES et al., 2018; DELMAS et al., 2020; TEHRANI et al., 2021). Curcumin belongs to the most promising group of bioactive natural compounds, exhibiting anticancer capacity by targeting different cell signaling pathways, including growth factors, cytokines, transcription factors, and genes that modulate cell proliferation and apoptosis (GIORDANO; TOMMONARO, 2019; WANG et al., 2016).

5. Conclusion

M. lucida, *M. charantia*, and *V. polyanthes* are widely used in folk medicine and are rich in compounds with antioxidant and anticancer potential. The compounds damnacanthal, momordicin I, and quercetin-3-O-rutinoside showed the highest scores in *in silico* predictions and show potential for interacting with estrogen beta receptors, vascular endothelial growth factor receptor 2 (VEGFR-2), and xanthine dehydrogenase, respectively. The present *in silico* study opens perspectives for the *in vitro* and *in vivo* verification of the selected compounds damnacanthal, momordicin I, and quercetin-3-O-rutinoside to be used as adjuvant compounds in cancer therapy. Moreover, previously reported *V. polyanthes* molecules could reduce DXR

side effects, which make them potential candidates to be tested as adjuvant compounds in a therapeutic scheme with DXR.

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Considerações Finais

4. Considerações Finais

Esta pesquisa iniciou-se com revisão na literatura sobre a toxicidade de plantas do Cerrado. O estudo de toxicidade é importante para avaliar os possíveis efeitos tóxicos de substâncias químicas sob diferentes condições de exposições, ou seja, concentrações que permitem a sobrevivência dos organismos, mas que afetam suas funções biológicas, tais como reprodução. Apesar de inúmeros trabalhos na literatura sobre o tema, não há até o momento uma revisão sistemática no assunto. Como contribuição científica foi mostrado as atividades citotóxicas, genotóxicas, antibactericidas, antifúngicas, antivirais, inseticidas e antiparasitas. Todas estas propriedades tornam estas espécies uma fonte de compostos para desenvolvimento de novos produtos (medicamentos, cosméticos, dar mais exemplos de produtos.).

Dentre todas as espécies, nosso grupo tem interesse particular no assa-peixe. Isto porque em trabalhos anteriores já detectamos o *Vp*Lae e suas frações foram capazes de interagir com a DXR. A pergunta a ser respondida no presente trabalho foi se os extratos de *V. polyanthes* (aquoso, n-butanol, e acetato de etila) são tóxicos *in vivo* usando modelo murino e como interagem com a droga DXR. Nossos resultados mostraram que em associação com DXR o *Vp*Lae e sua fração n-BF demonstraram um alto potencial quimiopreventivo e antioxidante contra os causados pela DRX.

A análise destes resultados nos direcionaram a investigar quais componentes presentes neste extrato seriam responsáveis pela atividade observada *in vivo*. Para responder isso foi realizada a análise de espectrometria de massas que identificou 8 moléculas (5-O-feruloilquínico, quercetina 3-O-rutinosídeo, 3,4-ácido di-O-cafeoilquínico, ácido 3,5-di-O-cafeoilquínico, ácido 4,5-di-O-cafeoilquínico, 3-O-cafeoilquínico ácido, ácido 5-O-cafeoilquínico e ácido 4-O-cafeoilquínico).

A identificação das moléculas nos direcionou ao seguinte questionamento, qual a função descrita em bancos de dados de atividade destas moléculas e com quais outras moléculas orgânicas estes compostos identificados podem interagir? Para responder isso, selecionamos as análises de triagem bioativas *in sílico* (ADMET prediction, Biological activities prediction, Toxicity prediction e Molecular Docking). Como resultados observamos que o composto quercetina-3-O-rutinoside identificado de *V. polyanthes* mostrou as pontuações mais altas em previsões *in sílico* com potencial para interagir com receptor xantina desidrogenase. Este estudo *in sílico* abre perspectivas para a verificação *in vitro* e *in vivo* dos de quercetin-3-O-rutinoside para ser usado como composto adjuvante na terapia do câncer.

Por fim, concluímos que apesar dos inúmeros dados obtidos ainda não podemos responder se o uso do chá de *V. polyanthes* é benéfico ou não para uso das pessoas saudáveis, e em pessoas sob o tratamento da DXR. Para responder isso seriam necessários análises mais estudos in vivo e in vitro devem ser realizados.

Independente de não responder diretamente essa questão, nossos resultados contribuem para o entendimento dos possíveis efeitos de *V. polyanthes* e das interação com medicamentos, mostrando a importância

Anexos:

6. Outras atividades acadêmicas e de pesquisa relevantes: disciplinas cursadas, créditos, participação em eventos, publicações, etc.

- Artigos;
- Disciplinas;
- Resumos;
- Participação em eventos (Palestras e Webnares);
- Treinamentos e minicursos;
- Colaborações.

Artigos

Drug and Chemical Toxicology

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In vitro hematotoxicity of *Vernonanthura polyanthes* leaf aqueous extract and its fractions

Jamira Dias Rocha , Janaina da Silva Ferreira , Jeniffer Gabrielle Vieira Silva , Amanda Silva Fernandes , Jefferson Hollanda Véras , Luciane Madureira de Almeida , Aristônio Magalhães Teles , Leonardo Luiz Borges , Lee Chen-Chen & Elisa Flávia Luiz Cardoso Bailão

To cite this article: Jamira Dias Rocha , Janaina da Silva Ferreira , Jeniffer Gabrielle Vieira Silva , Amanda Silva Fernandes , Jefferson Hollanda Véras , Luciane Madureira de Almeida , Aristônio Magalhães Teles , Leonardo Luiz Borges , Lee Chen-Chen & Elisa Flávia Luiz Cardoso Bailão (2020): *In vitro* hematotoxicity of *Vernonanthura polyanthes* leaf aqueous extract and its fractions, Drug and Chemical Toxicology, DOI: 10.1080/01480545.2020.1802481

To link to this article: https://doi.org/10.1080/01480545.2020.1802481

Published online: 06 Aug 2020.

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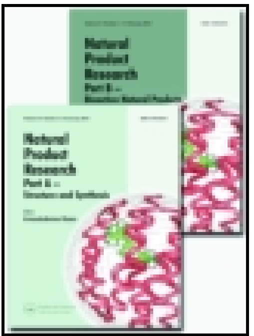


Natural Product Research

Formerly Natural Product Letters

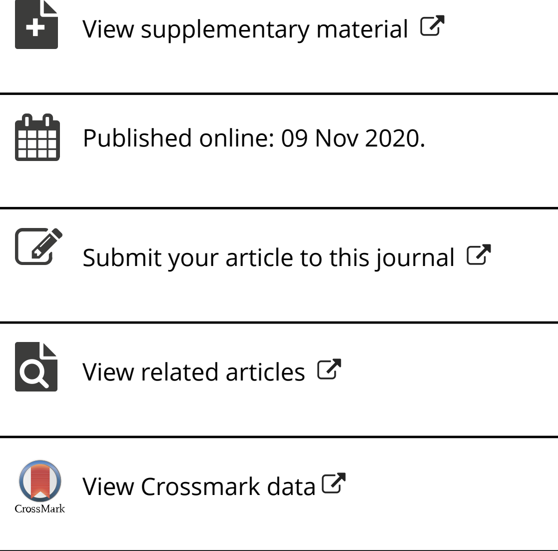
ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/gnpl20

Psidium myrtoides O. Berg fruit and leaves: physicochemical characteristics, antifungal activity and chemical composition of their essential oils in different seasons

Alline L. B. Dias , Hellen R. F. Batista , Wendel C. Sousa , Elisa F. L. C. Bailão , Jamira D. Rocha , Eugenio M. Sperandio , Cassia C. Fernandes , Edson L. Souchie & Mayker L. D. Miranda

To cite this article: Alline L. B. Dias , Hellen R. F. Batista , Wendel C. Sousa , Elisa F. L. C. Bailão , Jamira D. Rocha , Eugenio M. Sperandio , Cassia C. Fernandes , Edson L. Souchie & Mayker L. D. Miranda (2020): *Psidium myrtoides* O. Berg fruit and leaves: physicochemical characteristics, antifungal activity and chemical composition of their essential oils in different seasons, Natural Product Research, DOI: 10.1080/14786419.2020.1844689

To link to this article: https://doi.org/10.1080/14786419.2020.1844689



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Disciplinas

Aluno

Frequência do aluno: JAMIRA DIAS ROCHA

VOLTAR

Dados gerais do aluno

Número Matrícula: 7233397

Curso: Recursos Naturais do Cerrado (RENAC)

Nivel: Mestrado Acadêmico

Câmpus: CÂMPUS CENTRAL - SEDE: ANÁPOLIS - CET

Disciplina

Disciplina: Bioprodutos Vegetais do Cerrado

Tipo: Frequência / Conceito (A a D)

Situação: Aprovado

Total de aulas: 4

Presença: 100.00% - **Faltas:** 0

Aulas

Mês	Dia	Dia da semana	Hora	Status
Março			13:30:00 às 14:30:00	Presente
	05/03/2018	Segunda-feira	14:30:00 às 15:30:00	Presente
			15:30:00 às 16:30:00	Presente
			13:30:00 às 14:30:00	Presente
	12/03/2018	Segunda-feira	14:30:00 às 15:30:00	Presente
			15:30:00 às 16:30:00	Presente
			13:30:00 às 14:30:00	Presente
	19/03/2018	Segunda-feira	14:30:00 às 15:30:00	Presente
			15:30:00 às 16:30:00	Presente
	26/03/2018	Segunda-feira	13:30:00 às 14:30:00	Presente

Mês	Dia	Dia da semana	Hora	Status
			14:30:00 às 15:30:00	Presente
			15:30:00 às 16:30:00	Presente
Abril	02/04/2018	Segunda-feira	13:30:00 às 14:30:00	Presente
			14:30:00 às 15:30:00	Presente
			15:30:00 às 16:30:00	Presente
	09/04/2018	Segunda-feira	13:30:00 às 14:30:00	Presente
			14:30:00 às 15:30:00	Presente
			15:30:00 às 16:30:00	Presente
	16/04/2018	Segunda-feira	13:30:00 às 14:30:00	Presente
			14:30:00 às 15:30:00	Presente
			15:30:00 às 16:30:00	Presente
	23/04/2018	Segunda-feira	13:30:00 às 14:30:00	Presente
			14:30:00 às 15:30:00	Presente
			15:30:00 às 16:30:00	Presente
	30/04/2018	Segunda-feira	13:30:00 às 14:30:00	Presente
			14:30:00 às 15:30:00	Presente
			15:30:00 às 16:30:00	Presente
Maio	07/05/2018	Segunda-feira	13:30:00 às 14:30:00	Presente
			14:30:00 às 15:30:00	Presente
			15:30:00 às 16:30:00	Presente
	14/05/2018	Segunda-feira	13:30:00 às 14:30:00	Presente
			14:30:00 às 15:30:00	Presente
			15:30:00 às 16:30:00	Presente
	21/05/2018	Segunda-feira	13:30:00 às 14:30:00	Presente
			14:30:00 às 15:30:00	Presente
			15:30:00 às 16:30:00	Presente
	28/05/2018	Segunda-feira	13:30:00 às 14:30:00	Presente
			14:30:00 às 15:30:00	Presente

Mês	Dia	Dia da semana	Hora	Status
			15:30:00 às 16:30:00	Presente
Junho	04/06/2018	Segunda-feira	13:30:00 às 14:30:00	Presente
			14:30:00 às 15:30:00	Presente
			15:30:00 às 16:30:00	Presente
	11/06/2018	Segunda-feira	13:30:00 às 14:30:00	Presente
			14:30:00 às 15:30:00	Presente
			15:30:00 às 16:30:00	Presente
	18/06/2018	Segunda-feira	13:30:00 às 14:30:00	Presente
			14:30:00 às 15:30:00	Presente
			15:30:00 às 16:30:00	Presente
	25/06/2018	Segunda-feira	13:30:00 às 14:30:00	Presente
			14:30:00 às 15:30:00	Presente
			15:30:00 às 16:30:00	Presente
Julho	02/07/2018	Segunda-feira	13:30:00 às 14:30:00	Presente
			14:30:00 às 15:30:00	Presente
			15:30:00 às 16:30:00	Presente
	09/07/2018	Segunda-feira	13:30:00 às 14:30:00	Presente
			14:30:00 às 15:30:00	Presente
			15:30:00 às 16:30:00	Presente
	16/07/2018	Segunda-feira	13:30:00 às 14:30:00	Presente
			14:30:00 às 15:30:00	Presente
			15:30:00 às 16:30:00	Presente

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Frequência do aluno: JAMIRA DIAS ROCHA

VOLTAR

Dados gerais do aluno

Número Matrícula: 7233397

Curso: Recursos Naturais do Cerrado (RENAC)

Nivel: Mestrado Acadêmico

Câmpus: CÂMPUS CENTRAL - SEDE: ANÁPOLIS - CET

Disciplina

Disciplina: Ecotoxicologia

Tipo: Frequência / Conceito (A a D)

Situação: Aprovado

Total de aulas: 4

Presença: 100.00% - **Faltas:** 0

Aulas

Mês	Dia	Dia da semana	Hora	Status
Agosto	13/08/2018	Segunda-feira	08:00:00 às 09:00:00	Presente
			09:00:00 às 10:00:00	Presente
			10:00:00 às 11:00:00	Presente
			11:00:00 às 12:00:00	Presente
	14/08/2018	Terça-feira	08:00:00 às 09:00:00	Presente
			09:00:00 às 10:00:00	Presente
			10:00:00 às 11:00:00	Presente
			11:00:00 às 12:00:00	Presente
	15/08/2018	Quarta-feira	08:00:00 às 09:00:00	Presente
			09:00:00 às 10:00:00	Presente

Mês	Dia	Dia da semana	Hora	Status
			10:00:00 às 11:00:00	Presente
			11:00:00 às 12:00:00	Presente
	17/08/2018	Sexta-feira	08:00:00 às 09:00:00	Presente
			09:00:00 às 10:00:00	Presente
			10:00:00 às 11:00:00	Presente
			11:00:00 às 12:00:00	Presente
			13:00:00 às 14:00:00	Presente
			14:00:00 às 15:00:00	Presente
			15:00:00 às 16:00:00	Presente
			16:00:00 às 17:00:00	Presente
	20/08/2018	Segunda-feira	08:00:00 às 09:00:00	Presente
			09:00:00 às 10:00:00	Presente
			10:00:00 às 11:00:00	Presente
			11:00:00 às 12:00:00	Presente
	21/08/2018	Terça-feira	08:00:00 às 09:00:00	Presente
			09:00:00 às 10:00:00	Presente
			10:00:00 às 11:00:00	Presente
			11:00:00 às 12:00:00	Presente
	22/08/2018	Quarta-feira	08:00:00 às 09:00:00	Presente
			09:00:00 às 10:00:00	Presente
			10:00:00 às 11:00:00	Presente
			11:00:00 às 12:00:00	Presente
	24/08/2018	Sexta-feira	08:00:00 às 09:00:00	Presente
			09:00:00 às 10:00:00	Presente
			10:00:00 às 11:00:00	Presente
			11:00:00 às 12:00:00	Presente
			13:00:00 às 14:00:00	Presente
			14:00:00 às 15:00:00	Presente

Mês	Dia	Dia da semana	Hora	Status
			15:00:00 às 16:00:00	Presente
			16:00:00 às 17:00:00	Presente
	27/08/2018	Segunda-feira	08:00:00 às 09:00:00	Presente
			09:00:00 às 10:00:00	Presente
			10:00:00 às 11:00:00	Presente
			11:00:00 às 12:00:00	Presente
	28/08/2018	Terça-feira	08:00:00 às 09:00:00	Presente
			09:00:00 às 10:00:00	Presente
			10:00:00 às 11:00:00	Presente
			11:00:00 às 12:00:00	Presente
	29/08/2018	Quarta-feira	08:00:00 às 09:00:00	Presente
			09:00:00 às 10:00:00	Presente
			10:00:00 às 11:00:00	Presente
			11:00:00 às 12:00:00	Presente
	31/08/2018	Sexta-feira	08:00:00 às 09:00:00	Presente
			09:00:00 às 10:00:00	Presente
			10:00:00 às 11:00:00	Presente
			11:00:00 às 12:00:00	Presente
			13:00:00 às 14:00:00	Presente
			14:00:00 às 15:00:00	Presente
			15:00:00 às 16:00:00	Presente
			16:00:00 às 17:00:00	Presente

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Aluno

Frequência do aluno: JAMIRA DIAS ROCHA

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Dados gerais do aluno

Número Matrícula: 7233397

Curso: Recursos Naturais do Cerrado (RENAC)

Nivel: Mestrado Acadêmico

Câmpus: CÂMPUS CENTRAL - SEDE: ANÁPOLIS - CET

Disciplina

Disciplina: Princípios de Epistemologia da Ciência

Tipo: Frequência / Conceito (A a D)

Situação: Aprovado

Total de aulas: 4

Presença: 100.00% - **Faltas:** 0

Aulas

Mês	Dia	Dia da semana	Hora	Status
Março	20/03/2018	Terça-feira	08:30:00 às 09:30:00	Presente
			09:30:00 às 10:30:00	Presente
			10:30:00 às 11:30:00	Presente
			11:30:00 às 12:30:00	Presente
			12:30:00 às 13:30:00	Presente
			13:30:00 às 14:30:00	Presente
			14:30:00 às 15:30:00	Presente
			15:30:00 às 16:30:00	Presente
Abril	03/04/2018	Terça-feira	08:30:00 às 09:30:00	Presente
			09:30:00 às 10:30:00	Presente

Mês	Dia	Dia da semana	Hora	Status
			10:30:00 às 11:30:00	Presente
			11:30:00 às 12:30:00	Presente
			12:30:00 às 13:30:00	Presente
			13:30:00 às 14:30:00	Presente
			14:30:00 às 15:30:00	Presente
			15:30:00 às 16:30:00	Presente
	10/04/2018	Terça-feira	08:30:00 às 09:30:00	Presente
			09:30:00 às 10:30:00	Presente
			10:30:00 às 11:30:00	Presente
			11:30:00 às 12:30:00	Presente
			12:30:00 às 13:30:00	Presente
			13:30:00 às 14:30:00	Presente
			14:30:00 às 15:30:00	Presente
			15:30:00 às 16:30:00	Presente
	24/04/2018	Terça-feira	08:30:00 às 09:30:00	Presente
			09:30:00 às 10:30:00	Presente
			10:30:00 às 11:30:00	Presente
			11:30:00 às 12:30:00	Presente
			12:30:00 às 13:30:00	Presente
			13:30:00 às 14:30:00	Presente
			14:30:00 às 15:30:00	Presente
			15:30:00 às 16:30:00	Presente
Maio	08/05/2018	Terça-feira	08:30:00 às 09:30:00	Presente
			09:30:00 às 10:30:00	Presente
			10:30:00 às 11:30:00	Presente
			11:30:00 às 12:30:00	Presente
			12:30:00 às 13:30:00	Presente
			13:30:00 às 14:30:00	Presente

Mês	Dia	Dia da semana	Hora	Status
			14:30:00 às 15:30:00	Presente
			15:30:00 às 16:30:00	Presente
	15/05/2018	Terça-feira	08:30:00 às 09:30:00	Presente
			09:30:00 às 10:30:00	Presente
			10:30:00 às 11:30:00	Presente
			11:30:00 às 12:30:00	Presente
			12:30:00 às 13:30:00	Presente
			13:30:00 às 14:30:00	Presente
			14:30:00 às 15:30:00	Presente
			15:30:00 às 16:30:00	Presente
	22/05/2018	Terça-feira	08:30:00 às 09:30:00	Presente
			09:30:00 às 10:30:00	Presente
			10:30:00 às 11:30:00	Presente
			11:30:00 às 12:30:00	Presente
			12:30:00 às 13:30:00	Presente
			13:30:00 às 14:30:00	Presente
			14:30:00 às 15:30:00	Presente
			15:30:00 às 16:30:00	Presente
	29/05/2018	Terça-feira	08:30:00 às 09:30:00	Presente
			09:30:00 às 10:30:00	Presente
			10:30:00 às 11:30:00	Presente
			11:30:00 às 12:30:00	Presente

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Aluno

Consulta alunos

VOLTAR

Frequência do aluno: JAMIRA DIAS ROCHA

Dados gerais do aluno

Número Matrícula: 7233397

Curso: Recursos Naturais do Cerrado (RENAC)

Nivel: Mestrado Acadêmico

Câmpus: CÂMPUS CENTRAL - SEDE: ANÁPOLIS - CET

Disciplina

Disciplina: Estatística Aplicada a Dados Ambientais

Tipo: Frequência / Conceito (A a D)

Situação: Aprovado

Total de aulas: 4

Presença: 100.00% - **Faltas:** 0

Aulas

Mês	Dia	Dia da semana	Hora	Status
Outubro	01/10/2018	Segunda-feira	08:30:00 às 09:30:00	Presente
			09:30:00 às 10:30:00	Presente
			10:30:00 às 11:30:00	Presente
			11:30:00 às 12:30:00	Presente
			13:30:00 às 14:30:00	Presente
			14:30:00 às 15:30:00	Presente
			15:30:00 às 16:30:00	Presente
			16:30:00 às 17:30:00	Presente
	08/10/2018	Segunda-feira	08:30:00 às 09:30:00	Presente
			09:30:00 às 10:30:00	Presente

Mês	Dia	Dia da semana	Hora	Status
			10:30:00 às 11:30:00	Presente
			11:30:00 às 12:30:00	Presente
			13:30:00 às 14:30:00	Presente
			14:30:00 às 15:30:00	Presente
			15:30:00 às 16:30:00	Presente
			16:30:00 às 17:30:00	Presente
	15/10/2018	Segunda-feira	08:30:00 às 09:30:00	Presente
			09:30:00 às 10:30:00	Presente
			10:30:00 às 11:30:00	Presente
			11:30:00 às 12:30:00	Presente
	22/10/2018	Segunda-feira	08:30:00 às 09:30:00	Presente
			09:30:00 às 10:30:00	Presente
			10:30:00 às 11:30:00	Presente
			11:30:00 às 12:30:00	Presente
			13:30:00 às 14:30:00	Presente
			14:30:00 às 15:30:00	Presente
			15:30:00 às 16:30:00	Presente
			16:30:00 às 17:30:00	Presente
	29/10/2018	Segunda-feira	08:30:00 às 09:30:00	Presente
			09:30:00 às 10:30:00	Presente
			10:30:00 às 11:30:00	Presente
			11:30:00 às 12:30:00	Presente
			13:30:00 às 14:30:00	Presente
			14:30:00 às 15:30:00	Presente
			15:30:00 às 16:30:00	Presente
			16:30:00 às 17:30:00	Presente
Novembro	05/11/2018	Segunda-feira	08:30:00 às 09:30:00	Presente
			09:30:00 às 10:30:00	Presente

Mês	Dia	Dia da semana	Hora	Status
			10:30:00 às 11:30:00	Presente
			11:30:00 às 12:30:00	Presente
			13:30:00 às 14:30:00	Presente
			14:30:00 às 15:30:00	Presente
			15:30:00 às 16:30:00	Presente
			16:30:00 às 17:30:00	Presente
	12/11/2018	Segunda-feira	08:30:00 às 09:30:00	Presente
			09:30:00 às 10:30:00	Presente
			10:30:00 às 11:30:00	Presente
			11:30:00 às 12:30:00	Presente
	19/11/2018	Segunda-feira	08:30:00 às 09:30:00	Presente
			09:30:00 às 10:30:00	Presente
			10:30:00 às 11:30:00	Presente
			11:30:00 às 12:30:00	Presente
	26/11/2018	Segunda-feira	08:30:00 às 09:30:00	Presente
			09:30:00 às 10:30:00	Presente
			10:30:00 às 11:30:00	Presente
			11:30:00 às 12:30:00	Presente
			13:30:00 às 14:30:00	Presente
			14:30:00 às 15:30:00	Presente
			15:30:00 às 16:30:00	Presente
			16:30:00 às 17:30:00	Presente

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Aluno

Início Consulta alunos Frequência

Frequência do aluno: JAMIRA DIAS ROCHA

VOLTAR

Dados gerais do aluno

Número Matrícula: 7233397

Curso: Recursos Naturais do Cerrado (RENAC)

Nivel: Mestrado Acadêmico

Câmpus: CÂMPUS CENTRAL - SEDE: ANÁPOLIS - CET

Disciplina

Disciplina: Tópicos Especiais - Introdução ao R

Tipo: Frequência / Conceito (A a D)

Situação: Aprovado

Total de aulas: 2

Presença: 100.00% - **Faltas:** 0

Aulas

Mês	Dia	Dia da semana	Hora	Status
Maio	23/05/2018	Quarta-feira	09:00:00 às 10:00:00	Presente
			10:00:00 às 11:00:00	Presente
			11:00:00 às 12:00:00	Presente
			12:00:00 às 13:00:00	Presente
			13:00:00 às 14:00:00	Presente
			14:00:00 às 15:00:00	Presente
			15:00:00 às 16:00:00	Presente
			16:00:00 às 17:00:00	Presente
	30/05/2018	Quarta-feira	09:00:00 às 10:00:00	Presente
			10:00:00 às 11:00:00	Presente

Mês	Dia	Dia da semana	Hora	Status
			11:00:00 às 12:00:00	Presente
			12:00:00 às 13:00:00	Presente
			13:00:00 às 14:00:00	Presente
			14:00:00 às 15:00:00	Presente
			15:00:00 às 16:00:00	Presente
			16:00:00 às 17:00:00	Presente
Junho	05/06/2018	Terça-feira	09:00:00 às 10:00:00	Presente
			10:00:00 às 11:00:00	Presente
			11:00:00 às 12:00:00	Presente
			12:00:00 às 13:00:00	Presente
			13:00:00 às 14:00:00	Presente
			14:00:00 às 15:00:00	Presente
			15:00:00 às 16:00:00	Presente
			16:00:00 às 17:00:00	Presente
	06/06/2018	Quarta-feira	09:00:00 às 10:00:00	Presente
			10:00:00 às 11:00:00	Presente
			11:00:00 às 12:00:00	Presente
			12:00:00 às 13:00:00	Presente
			13:00:00 às 14:00:00	Presente
			14:00:00 às 15:00:00	Presente

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Aluno

JAMIRA DIAS ROCHA

Início Consulta alunos

Frequência

Frequência do aluno: JAMIRA DIAS ROCHA

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Dados gerais do aluno

Número Matrícula: 7233397

Curso: Recursos Naturais do Cerrado (RENAC)

Nivel: Mestrado Acadêmico

Câmpus: CÂMPUS CENTRAL - SEDE: ANÁPOLIS - CET

Disciplina

Disciplina: Tópicos Especiais - Revisão Sistemática e Informetria aplicada às Ciências Ambientais

Tipo: Frequência / Conceito (A a D)

Situação: Aprovado

Total de aulas: 2

Presença: 100.00% - **Faltas:** 0

Aulas

Mês	Dia	Dia da semana	Hora	Status
Maio	03/05/2018	Quinta-feira	08:30:00 às 09:30:00	Presente
			09:30:00 às 10:30:00	Presente
			10:30:00 às 11:30:00	Presente
			11:30:00 às 12:30:00	Presente
	04/05/2018	Sexta-feira	08:30:00 às 09:30:00	Presente
			09:30:00 às 10:30:00	Presente
			10:30:00 às 11:30:00	Presente
			11:30:00 às 12:30:00	Presente
	10/05/2018	Quinta-feira	08:30:00 às 09:30:00	Presente
			09:30:00 às 10:30:00	Presente

Mês	Dia	Dia da semana	Hora	Status
			10:30:00 às 11:30:00	Presente
			11:30:00 às 12:30:00	Presente
	11/05/2018	Sexta-feira	08:30:00 às 09:30:00	Presente
			09:30:00 às 10:30:00	Presente
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			11:30:00 às 12:30:00	Presente
	17/05/2018	Quinta-feira	08:30:00 às 09:30:00	Presente
			09:30:00 às 10:30:00	Presente
			10:30:00 às 11:30:00	Presente
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	18/05/2018	Sexta-feira	08:30:00 às 09:30:00	Presente
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	24/05/2018	Quinta-feira	08:30:00 às 09:30:00	Presente
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			10:30:00 às 11:30:00	Presente
			11:30:00 às 12:30:00	Presente
	25/05/2018	Sexta-feira	08:30:00 às 09:30:00	Presente
			09:30:00 às 10:30:00	Presente

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D E C L A R A Ç Ã O

Declaramos, para os devidos fins, que **Jamira Dias Rocha** cursou a disciplina **Tópicos Especiais em Produtos Naturais e Biossintéticos I: Estudos de Produtos Naturais Utilizando Espectrometria de Massas com Ionização por Electrospray (IES-EM)**, da Pós-Graduação em Produtos Naturais e Sintéticos Bioativos (Mestrado e Doutorado), código 1608146, com 02 créditos correspondentes à 30 horas/aula, no período letivo de 2020.2, na qualidade de **ALUNO ESPECIAL**, obtendo a nota 9,0 (nove vírgula zero), e sua frequência foi de 100% das aulas.

Coordenação do Programa de Pós-Graduação em Produtos Naturais e Sintéticos Bioativos (Mestrado e Doutorado), em João Pessoa/PB, 06 de novembro de 2020.

PROGRAMA DE PÓS-GRADUAÇÃO EM PRODUTOS NATURAIS E SINTÉTICOS BIOATIVOS - PGPNSB
PROF. DR. MARCELO SOBRAL DA SILVA
COORDENADOR
SIAPE 63322923

Instituto de Pesquisa em Fármacos e Medicamentos – IPeFarM – Universidade Federal da Paraíba
Recanto da Milona, Via Ipê Amarelo - Cidade Universitária – João Pessoa – PB – Brasil CEP: 58051-900
Fone: 55 83 3216-7502 E-mail: pos-graduacao@ltf.ufpb.br Site: www.ufpb.br/pos/pgpnsb

Ementa de tópicos especiais

Título do curso: Estudos de produtos naturais utilizando espectrometria de massas com ionização por Electrospray (IES-EM)

Período: 29/09/2020 a 29/10/2020 (terças e quintas de 9:00-12:00)

Docente: Prof. Dr. Lucas Silva Abreu

Número de créditos: 02 créditos (30 horas)

Ementa: Princípios da Espectrometria de Massas, Técnicas de Ionização (com foco em IES), Analisadores, Detectores, Espectrometria de Massas Tandem, Interpretação de Espectros – IES (com foco em estudos de fragmentação), Aplicações da Espectrometria de Massas.

Objetivo: Ao final do período o aluno deverá ser capaz de: compreender os princípios fundamentais da técnica de ionização por electrospray e tipos de analisadores, identificar os principais tipos de fragmentações ocorridas por dissociação induzida por colisão e capacidade de desenhar um estudo com IES-EM até a sua publicação.

Estratégias de Ensino: As aulas teóricas e apresentação de seminários utilizando a plataforma digitais do Google for Education (Classroom e Meet).

Método de avaliação de aprendizagem: A avaliação do ensino-aprendizagem será realizada através de duas avaliações. Uma delas, a avaliação continuada em sala de aula virtual e a outra uma apresentação em forma de seminário de estudos envolvendo espectrometria de massas aplicado a produtos naturais.

Conteúdos:

1. Técnicas de ionização e tipos de analisadores.
2. Principais reações de fragmentação (EM-IES).
3. Estudos de fragmentação de terpenoides.
4. Estudos de fragmentação de polifenóis.
5. Estudo de fragmentação de alcaloides.
6. Aplicações da EM-IES em produtos naturais.
7. Da criação do estudo a publicação.

Referências:

SILVERSTEIN, R. M.; WEBSTER, F. X. **Identificação Espectrométrica de Compostos Orgânicos**, 8ª edição, LTC, 2014.

PAVIA, D. L. et al. **Introdução à espectroscopia**. 5ª edição, Cengage Learning, 2015.

HOFFMANN, E.; STROOBANT, **Mass Spectrometry: Principles and Applications**, V. 3ª ed. Wiley, 2007

THROCK WATSON, J. E DAVID SPARKMAN, O., **Introduction to Mass Spectrometry**: Instrumentation, Applications and Stategies for Data Interpretation, 4ª ed., Wiley, 2007

DEMARQUE, Daniel P. et al. Fragmentation reactions using electrospray ionization mass spectrometry: an important tool for the structural elucidation and characterization of synthetic and natural products. **Natural Product Reports**, v. 33, n. 3, p. 432-455, 2016.

Artigos recentes dos seguintes periódicos:

- J. of mass spectrometry
- Organic mass spectrometry
- J. Am. Soc. mass spectrometry
- Analytical Chemistry
- Mass spectrometry Reviews
- Phytochemical Analysis
- J. of mass spectrometry and rapid communications in mass spectrometry

Aluno

Frequência do aluno: JAMIRA DIAS ROCHA

VOLTAR

Dados gerais do aluno

Número Matrícula: 12733397

Curso: Recursos Naturais do Cerrado (RENAC)

Nivel: Doutorado

Câmpus: CÂMPUS CENTRAL - SEDE: ANÁPOLIS - CET

Disciplina

Disciplina: REDAÇÃO E A DINÂMICA NA PRODUÇÃO CIENTÍFI CA

Tipo: Frequência / Conceito (A a D)

Situação: Aprovado

Total de aulas: 4

Presença: 100.00% - **Faltas:** 0

Aulas

Mês	Dia	Dia da semana	Hora	Status
Abril	10/04/2020	Sexta-feira	08:00:00 às 09:00:00	Presente
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	20/04/2020	Segunda-feira	08:00:00 às 09:00:00	Presente
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	23/04/2020	Quinta-feira	08:00:00 às 09:00:00	Presente
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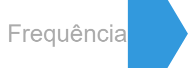

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Número Matrícula: 12733397

Curso: Recursos Naturais do Cerrado (RENAC)

Nivel: Doutorado

Câmpus: CÂMPUS CENTRAL - SEDE: ANÁPOLIS - CET

Disciplina

Disciplina: TÓPICOS ESPECIAIS: EXPERIMENTOS MANIPULATIVOS EM CIÊNCIAS AMBIENTAIS

Tipo: Frequência / Conceito (A a D)

Situação: Aprovado

Total de aulas: 2

Presença: 100.00% - **Faltas:** 0

Aulas

Mês	Dia	Dia da semana	Hora	Status
Maio	04/05/2020	Segunda-feira	08:00:00 às 09:00:00	Presente
			09:00:00 às 10:00:00	Presente
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			16:00:00 às 17:00:00	Presente
	11/05/2020	Segunda-feira	08:00:00 às 09:00:00	Presente
			09:00:00 às 10:00:00	Presente

Mês	Dia	Dia da semana	Hora	Status
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Junho	01/06/2020	Segunda-feira	08:00:00 às 09:00:00	Presente
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Curso: Recursos Naturais do Cerrado (RENAC)

Nivel: Doutorado

Câmpus: CÂMPUS CENTRAL - SEDE: ANÁPOLIS - CET

Disciplina

Disciplina: TRABALHO DE CAMPO MULTIDISCIPLINAR

Tipo: Frequência / Conceito (A a D)

Situação: Aprovado

Total de aulas: 4

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Aulas

Mês	Dia	Dia da semana	Hora	Status
Agosto	10/08/2020	Segunda-feira	08:30:00 às 09:30:00	Presente
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			11:30:00 às 12:30:00	Presente
	31/08/2020	Segunda-feira	08:30:00 às 09:30:00	Presente
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			11:30:00 às 12:30:00	Presente
Setembro	29/09/2020	Terça-feira	08:30:00 às 09:30:00	Presente
			09:30:00 às 10:30:00	Presente

Mês	Dia	Dia da semana	Hora	Status
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			11:30:00 às 12:30:00	Presente
Outubro	27/10/2020	Terça-feira	08:30:00 às 09:30:00	Presente
			09:30:00 às 10:30:00	Presente
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			11:30:00 às 12:30:00	Presente
Janeiro	19/01/2021	Terça-feira	08:30:00 às 09:30:00	Presente
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			10:30:00 às 11:30:00	Presente
			11:30:00 às 12:30:00	Presente
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			14:00:00 às 15:00:00	Presente
			15:00:00 às 16:00:00	Presente
			16:00:00 às 17:00:00	Presente
	20/01/2021	Quarta-feira	08:30:00 às 09:30:00	Presente
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Mês	Dia	Dia da semana	Hora	Status
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			11:30:00 às 12:30:00	Presente

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Resumos

Avaliação da citogenotoxicidade *in vivo* do extrato aquoso de folhas de *Vernonanthura polyanthes* pelo teste do micronúcleo.

Vitória Silva Ferreira (IC), Jamira Dias Rocha (PG), Abel Vieira de Melo Bisneto (PG), Lee Chen-Chen e Elisa Flávia Luiz Cardoso Bailão (PQ)*

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Laboratório de Radiobiologia e Mutagênese, Departamento de Genética, Instituto de Ciências Biológicas I, Universidade Federal de Goiás, CEP: 74045-155, Goiânia, GO, Brasil.

Introdução

Plantas medicinais com propriedades terapêuticas e fitoterápicas vêm sendo utilizadas ao longo da história devido aos baixos custos e conhecimento generalizado (VELOSO e LARROSA, 2012). Denominada como assapeixe, *Vernonanthura polyanthes* (Spreng.) A.J. Vega & Dematt., destaca-se pelas suas várias propriedades terapêuticas (Alves e Neves, 2003). Comummente conhecida e utilizada no tratamento de afecções como: bronquite, tosses persistentes, tratamento de hemoptises e abscessos internos, além de apresentar propriedades diurética, balsâmica e antirreumática (Jorgetto et al., 2008; Silva, 2010; Silva, 2007).Recentemente foi demonstrado que o extrato aquoso de folhas de *V. polyanthes* e suas frações (aquosa, n-butanol e acetato de etila) apresentaram citotoxicidade e genotoxicidade contra linfócitos humanos. Substâncias genotóxicas são aquelas capazes de causar danos no material genético. Normalmente esses danos são reparados pelo próprio organismo ou há apoptose. O agente é considerado mutagênico se a alteração é fixada e passada as células filhas durante a replicação (OBE et al., 2004; WHITE & RASMUSSEN 1998). De acordo o com o Banco de Células do Rio de Janeiro (BCRJ), a capacidade específica de um composto em favorecer alterações metabólicas em culturas de células ocasionando ou não em sua morte é denominada citotoxicidade.

Quando previamente tratado com uma droga citotóxica chamada doxorrubicina (DXR) o extrato ou suas frações (aquosa, n-butanol ou acetato de etila), foi constatado o aumento da citotoxicidade da DXR contra linfócitos, contudo a genotoxicidade da DXR diminuiu cerca de 15% (ROCHA et al.,2020).

Caraterizado como um antibiótico antiblástico e citotóxico, a DXR é um medicamento que pertence a classe das antraciclinas utilizado na quimioterapia contra tumores sólidos, linfomas e leucemias (PEREIRA, 2016; SWIFT et al. 2006). Além de produzir espécies reativas de oxigênio que afetam o coração (BERTHIAUME; WALLACE, 2007), também podem lesar o DNA, gerando instabilidade genômica, sendo importante no desenvolvimento de mutações e canceres (KRYSTON et al., 2011).

Neste sentido, objetivamos avaliar os efeitos citogênotoxicos e anti-citogênotóxios em modelo sistêmico, uma vez que neste ocorre a metabolização de substâncias exógenas. O modelo murino foi escolhido para dar continuidade no estudo com o extrato aquoso de folhas de *V. Polyanthes* com ou sem associação de DXR usando o teste do micronócleo (MN).

Material e Métodos

Exposição e manejo dos animais

Esta etapa do projeto já executa e materiais armazenados adequadamente para análises. Grupos contendo 5 camundongos Swiss Webster foram tratados via gavagem,com o extrado aquoso de folhas de *V. polyanthes* associados ou não a DXR. O grupo controle positivo recebeu DXR intraperitonealmente (ip) e o grupo controle negativo recebeu água mineral. Os animais foram eutanasiados por deslocamento cervical e os fêmures foram retirados, o sangue da medula óssea foi extraído utilizando soro fetal bovino. Este material foi usado para a confecção dos esfregaços sanguíneos. Todo procedimento experimental juntamente com o manejo dos animais foi aprovado pela Comissão de Ética no Uso de Animais/CEUA da UFG (protocolo nº 069/2018).

A contagem de micronúcelos foi realizada com lâminas previamente preparadas. A partir dos métodos relatados por von Ledebur & Schimid (1973), o teste do micronúcleo foi executado. Para a confecção de esfregaços celulares em lâminas vidro foram usadas as células da medula óssea de camundongos, que após a secagem foram fixadas em metanol absoluto durante 5 min, e posteriormente coradas em solução de Giemsa tamponada (fosfato de sódio dibásico e fosfato de sódio monobásico) com pH 6,8. Para cada animal, quatro lâminas foram preparadas. Conforme orientação da OECD TG 474 (2014), foram analisados 4.000 eritrócitos policromáticos (EPCs) para cada animal para determinar a frequência de eritroblastos policromáticos micronucleados (EPCMN). A genotoxicidade e a antigenotoxicidade foram avaliadas pela frequência de EPCMN com relação ao total de células analisadas. Enquanto a citotoxicidade e a anticitotoxicidade forma avaliadas pela razão de EPC e eritroblastos normocromáticos (ENC). A análise das lâminas será realizada em microscópio óptico de luz com aumento de 1000X (PrimoStar, Zeiss).

Análises estatísticas

A avaliação de genotoxicidade dos grupos controles a partir do teste de MN foi feita por análise de variância (ANOVA) seguida pelo teste de Tukey. A citotóxicidade dos controles a partir da razão EPC/ENC foi comparda pelo teste do Qui-quadrado (X^2), com nível de significância de $p < 0,05$ para ambos os testes.

Resultados e Discussão

O teste do micronúcleo foi desenvolvido com a finalidade de avaliar a propensão de substancias em provocar danos cromossômico estrutural e/ou numérico em células em processo de divisão celular (SCHMID, 1975; SALVADORI et al., 2006). Os micronúcleos são comumente presenciados em Células que passaram pela divisão celular, em telófase, em células de formato binucleado. Na fase de interfase, os microcnúcleos se apresentam na forma de agregados de DNA de coloração semelhante à do núcleo principal, e com 5 a 30% de seu tamanho (OECD, 2016). O

aumento de unidade de células que contem micronúcleos, juntamente com a quantidade no citoplasma das células examinadas, podem indicar a presença de dano genotóxico (Speit, Zeller e Neuss, 2011).

Neste estudo a genotoxicidade dos controles foi avaliada pela frequência de eritrócitos policromáticos micronucleados (EPCMN) a partir de 4.000 EPCs (Figura 1a). De acordo com análise estatística houve uma diferença significativa entre os grupos controle negativo e DXR. Evidenciando o efeito genotóxico da DXR no controle positivo (Tabela 1). Essa diferença estatística também foi observada para o efeito citotóxico avaliadopela razão de EPC e eritrócitos normocromáticos (ENC) (Figura 1b). A diminuição dos valores da razão EPC/ENC evidencia que a citotoxicidade no grupo controle positivo é maior em comparação ao grupo controle negativo (Tabela 1).

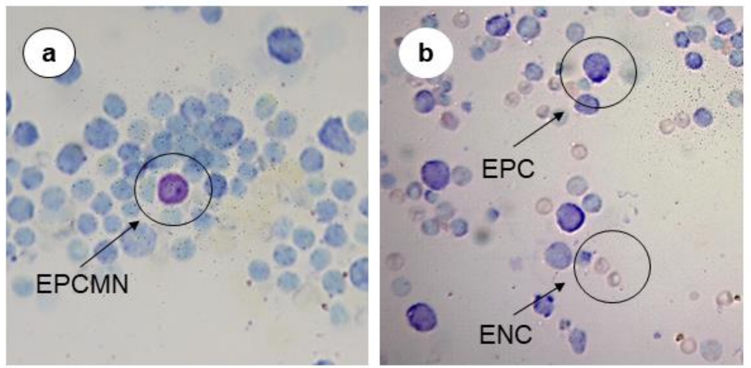

Figura 1. Fotomicrografia de esfregaço de sangue da medula óssea de camundongos mostrando: eritrócitos policromáticos micronucleados (EPCMN), eritrócitos policromáticos (EPC) e eritrócitos normocromáticos (ENC). **a)** EPCMN indicado pela seta. **b)** EPC e ENC indicados pelas setas.

Durante o processo de divisão celular, os eritrócitos duplicam os cromossomos pela última vez dando origem aos EPCc. São eritrócitos jovens e ricos em ribossomos, sendo facilmente corados em tom rosado e se distinguem dos ENCs que são corados em tom azulado. Fragmentos cromossômicos podem ser gerados a partir de agentes clastogênicos (que quebram cromossomos) e/ou agentes aneugênicos (que induzem aneuploidia ou segregação anormal) (MACGREGOR et al., 1987; HAYASHI et al., 1994). Esses fragmentos podem não se incorporar ao núcleo principal das células filhas logo após à mitose dando origem ao MN (JUNQUEIRA, 2006). Esses

fragmentos se mantem no citoplasma e são visualizados com facilidade em EPCs, que por sua vez, apresenta tempo de vida razoavelmente curto, o que possibilita a tese de que os MNs que foram formados a partir de danos cromossômicos recentes causados pela presença de substâncias lesivas (SCHMID, 1975).

Tabela 1. Resultados do ensaio de micronúcleo em camundongo. Citotoxicidade da medula óssea expressa como eritrócitos policromático (PCE) entre eritrócitos totais (eritrócitos normocromáticos (PCE/NCE), a genotoxicidade é expressa através da média e desvio padrão da frequência de eritrócitos policromáticos micronucleados (PCEMN) para cada 4000 PCEs.

Grupos	*n*	Tratamentos	Tempo de exposição	Razão EPC/ENC	EPCMN/400EPC
G1	5	Negative cotrol	24 h	1.03 ± 0.09^{a}	17^{a}
G2	5	DXR	24 h	0.28 ± 0.01^{b}	192^{b}

CN: Controle negativo:(H2O); DXR: controle positivo (doxorrubicina 50ug). Os resultados são expressos como média ± desvio padrão. Letras iguais indicam que não há diferenças entre os grupos.

Neste estudo foi utilizado a DXR que já é amplamente usada como controle positivo em pesquisas relacionadas a avaliação citogenotoxicas de diferentes compostos por causar mutações e aberrações cromossômicas devido a produção excessiva de radicais livres. (KEIZER et al., 1990; RESENDE et al., 2007; GUERRA-SANTOS et al., 2016; ROCHA et al.,2020). Como já é relatado na literatura que a DRX possui um efeito citotóxico e genotóxico o que corrobora para os resultados encontrados neste estudo.

Considerações Finais

A partir da contagem de EPCs foi possível avaliar a citogenotoxicidade do controle positivo contendo DXR em comparação ao controle negativo contendo água mineral. Constatas-se então um maior efeito citogenotoxico nas células dos camundongos Swiss Webster na presença da DXR. Contudo, devido a atual situação pandêmica, não foi possível realizar as análises necessárias para avaliar o efeito citogenotoxico e anticitogenotoxico do estrato aquoso e suas frações da *V. polyanthes*.

Agradecimentos

Inserir aqui Agradecimentos (Fonte: Arial, 10).

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Avaliação da genotoxicidade *in vivo* do extrato aquoso de folhas de *Vernonanthura polyanthes*

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Introdução

Vernonanthura polyanthes (Spreng.) A.J. Vega & Dematt. (sin.: *Vernonia polyanthes* Less), conhecida popularmente como assa-peixe, é considerada uma planta silvestre nativa do Brasil e apresenta ampla distribuição nas regiões sul, sudeste e centro-oeste, sendo encontrada principalmente nos estados de Goiás, Minas Gerais, São Paulo, Mato Grosso e no entorno da Mata Atlântica (LORENZI & MATOS, 2008; RAMOS, 2014; KISSMANN, 1999; ALVES, 2003; HATTORE, 2008). A espécie multiplica-se com facilidade, sendo frequentemente encontrada em regiões de Cerrado, principalmente, em áreas abertas, como beira de estradas, pastagens e solos pouco férteis e terrenos baldios (LORENZI & MATOS, 2008; BRASIL, 2014; RAMOS, 2014; KISSMANN, 1999; ALVES, 2003; BIREME, 2014).

As folhas de *V. polyanthes* são empregadas na medicina popular para o tratamento de afecções do aparelho respiratório, como pneumonia, bronquite, tosses, gripes e resfriados, bem como doenças renais, infecções do útero, úlcera, hipertensão, leishmaniose, febre, hemorragias e afecções gástricas (RODRIGUES & CARVALHO, 2001; SILVEIRA et al., 2003; SILVEIRA et al., 2000; BRAGA et al., 2007; BARBASTEFANO et al., 2007; LORENZI & MATOS, 2008; SILVA et al., 2012; JORGETO et al., 2011).

Foi demonstrado por Guerra-Santos e colaboradores (2016), por meio do teste de recombinação e mutação somática em asa de *Drosophila melanogaster* (SMART/asa), que o extrato aquoso das folhas de *V. polyanthes* não é tóxico, genotóxico ou antigenotóxico. Porém, este extrato foi capaz de potencializar a genotoxicidade da doxorrubicina, um agente quimioterápico que induz quebras simples e duplas no DNA. No entanto, a genotoxicidade desta droga vegetal ainda não foi testada em modelo animal utilizando o ensaio cometa, em que ocorre a metabolização de moléculas exógenas. Assim, o objetivo deste trabalho foi o de avaliar o potencial genotóxico do extrato de *V. polyanthes* usando células da medula óssea de camundongos.

Material e Métodos

Exposição e manejo dos animais

Foram utilizados camundongos *Mus musculus* (Swiss Webster) out bred, do sexo masculino, pesando entre 20 a 30g com idade variando de 7 a 12 semanas, procedentes do Biotério Central da Universidade Federal de Goiás. Para a realização dos testes *in vivo*. Os animais foram tratados via gavagem com o extrato aquoso de folhas de *V. polyanthes* (EA*Vp*) em diferentes concentrações (250, 500 ou 1000 mg/kg). O grupo controle positivo recebeu doxorrubicina (50mg/kg) intraperitonealmente (ip) e o grupo controle negativo foi tratado com água destilada. Após 24 h de tratamento, os animais foram sacrificados por deslocamento cervical, os fêmures foram retirados e as células da medula óssea foram coletadas em soro fetal bovino. Parte dessas células foi utilizada para a confecção das lâminas do ensaio cometa. Os procedimentos experimentais e manejo dos animais foram aprovados pela Comissão de Ética no Uso de Animais/CEUA da UFG (protocolo no 069/2018).

Ensaio cometa

A versão alcalina do ensaio cometa (eletroforese em gel de célula única) foi utilizada conforme descrito por Singh e colaboradores (1988), com pequenas modificações descritas a seguir: foram utilizados 10 µl de células de medula óssea de camundongo foram diluídas em soro fetal bovino e em seguida foram suspensas em 120µl de 0,5% (p/v) de agarose de baixo ponto de fusão, esta solução foi colocada sobre uma lâmina microscópica previamente revestida com uma camada de 1,5% de agarose normal. As lâminas foram imersas em solução de lise de pH 10 (Triton X-100, DMSO e solução lise estoque) e deixadas durante a noite. Em seguida, foram transferidas para uma câmara de eletroforese horizontal contendo solução alcalina (NaOH 300 mM, pH>13) a 4 ºC por 30 min para que o DNA se desenovelasse. Usando a mesma solução alcalina, a eletroforese foi realizada por 30 min (300 mA, 25V). E, então, lavadas três vezes com tampão neutralizante (tampão Tris-HCl 0,4 M, pH 7,5). A coloração foi realizada usando DiamondTM Nucleic Acid Dye (Promega, Madison, WI, USA) diluído 1:10.000 em tampão fosfato salino (PBS: 1,4 mM KH_2PO_4, 8 mM Na_2HPO_4, 140 mM NaCl, 2,7 mM KCl; pH 7.2) por 30 min. A análise ocorreu utilizando o microscópio de fluorescência Axio Imager 2 (Carl Zeiss, Jena, Alemanha), onde alguns campos foram capturados em objetiva de 20× (comprimento de excitação do filtro 510–560 nm) utilizando o software Zen (Carl Zeiss, Jena, Alemanha). As imagens obtidas foram analisadas usando o Software CometScore^{TM} (versão 1.5). O dano ao DNA foi quantificado pela porcentagem de DNA na cauda. Serão analisados 100 nucleóides.

Análise estatística

Os diferentes tratamentos e os controles foram comparados entre si pelo teste ANOVA seguido pelo teste de Tukey. Serão considerados significativos valores de $p<0,05$.

Resultados e Discussão

O EA*Vp* foi genotóxico em todas as concentrações utilizadas neste trabalho (250, 500 e 1000 mg/kg) quando comparadas com o controle negativo (Figuras 1 e 2). Tais resultados são congruentes com os apresentados por Jorgetto et al (2011), onde foram observadas diferenças entre os grupos de animais controle negativos e tratamento na maior concentração (2000 mg/kg), o que sugeriu uma leve predisposição aos efeitos genotóxicos desse extrato a partir de uma dosagem acima de 1500 mg/Kg. Já no estudo realizado por Guerra-Santos et al (2016), foi evidenciado a ausência de atividade genotóxica nas condições experimentais testadas (0.25-1 mg/ml), usando o teste de recombinação e mutação somática de asa (SMART/asa). A divergência dos resultados pode estar associada principalmente pela diferença das doses (concentrações) e modelo experimental usado.

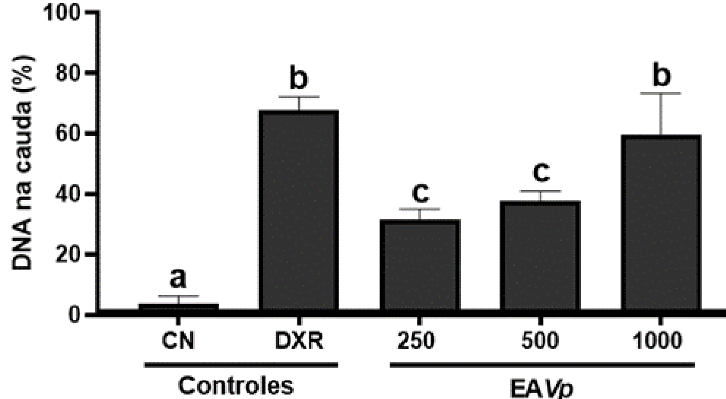

Figura 1. **Atividade genotóxica do extrato aquoso de folhas de *Vernonanthura polyanthes* (EA *Vp*).** A avaliação da genotoxicidade foi realizada pelo ensaio cometa em medula óssea de camundongos. O parâmetro utilizado para avaliar o dano no material genético foi a %DNA na cauda medida pelo software CometScore 1.5. Foram utilizados 5 animais para cada condição de tratamento e um total de 100 nucleóides por animal foram analisados. CN, controle negativo (água mineral); CP, controle positivo (doxorrubicina, DXR, 50 mg/kg ip). Os resultados são expressos como média ± desvio padrão e os grupos foram comparados por Anova seguida por teste de Tukey. Letras diferentes indicam que houve diferenças estatisticamente significativas entre os grupos ($p < 0,05$).

Uma analise qualitativa das imagens capturadas também foi realizada usando como parâmetro o tamanho da cauda do cometa. Assim, como na análise qualitativa

também foi possivél observar a similaridade entre a maior dose do EA *Vp* (1000 mg/kg) e doxurrubicina usada como controle positivo. Neste sentido podemos dizer que a genotoxicidade apresentada por esta dose foi mais expressiva (Figura 1 e 2). Em concordância com essa afirmação estão os resultados apresentados por Rocha et al (2020) que avaliou a genotoxicidade do EA *Vp* e de suas frações (aquosa, n-butanol e acetato de etila) em linfócitos de sangue periférico humano. Os resultados demonstraram atividade genotóxica para o extrato aquoso e suas frações nas condições e concentrações testadas (0.25-1 mg/ml). A presença de flavonoides e taninos foi demonstrada para o EA *Vp* e em suas frações (aquosa, n-butanol e acetato de etila) (ROCHA et al., 2020). Esse resultado pode indicar que a presença desses compostos podem estar relacionada a genotoxicidade demonstrada pelo EA *Vp* neste estudo. A presença de componentes genotóxicos pode levar ao acometimento de danos genéticos em regiões de fundamental importância para o controle do ciclo celular e apoptose.

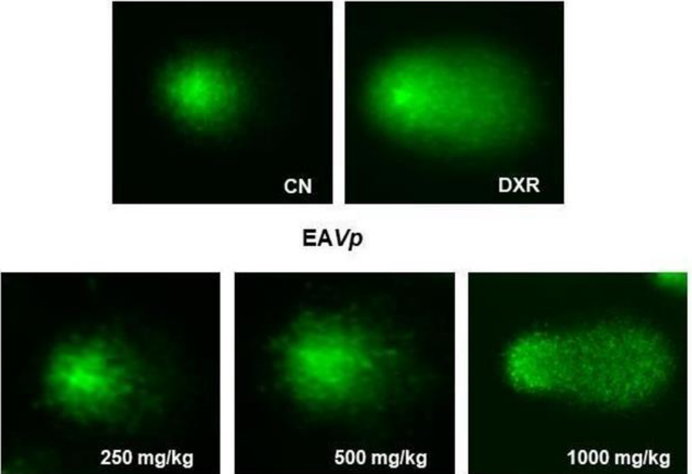

Figura 2. **Fotomicrografias representativas da atividade genotóxica do extrato aquoso de folhas de *Vernonathura polyanthes* (EA *Vp*) pelo ensaio cometa em medula óssea de camundongos**. As células foram coradas com Diamond^{TM} Nucleic Acid Dye (Promega®, Austrália) e as imagens foram capturadas com um microscópio de fluorescência (Axio Imager® A2 e software Zen 2.3 Carl Zeiss AG, Alemanha, com filtro de excitação de 510-560 nm e filtro barreira de 590 nm, em objetiva de 20×)..CN: controle negativo, água mineral; DXR: doxorrubicina 50 mg/kg ip, controle positivo.

Assim, esses achados permitem inferir que o papel exercido por *V. polyanthes* nas condições testadas possui potencial genotóxico que pode estar relacionado com as condições de tratamento e o modelo experimental.

Considerações Finais

Em conclusão, o EA *Vp* nas doses de 250, 500 e 1000 mg/kg foram capazes de induzir danos no material genético das células da medula óssea de camundongos. Deste modo, sugere-se que *V. polyanthes* é capaz de causar lesões no DNA. Porém, isso pode ser um problema em indivíduos que não têm um sistema de reparo eficiente, tipo de tratamento e ou concentração usada. Mais estudos são necessários para que o uso de *V. polyanthes* possa ser usado com segurança.

Agradecimentos

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DECLARAÇÃO DE AUTORIA E RESPONSABILIDADE

Eu, Luana Magalhães Pelegrine de CPF n° 700.342.121-67, residente no endereço Rua PB 46 QD.06 LT.43, Parque Brasília, Anápolis – Goiás, declaro, para fins de submissão de trabalho para avaliação e publicação junto ao 7º Congresso de Ensino, Pesquisa e Extensão, da Universidade Estadual de Goiás, que o artigo o resumo Avaliação da genotoxicidade *in vivo* do extrato aquoso de folhas de *Vernonanthura polyanthes*, é original e de completa autoria dos pesquisadores relacionados como autores do estudo, tendo todos eles equivalente participação no trabalho.

Declaro, também, na qualidade de autor do manuscrito Avaliação da genotoxicidade *in vivo* do extrato aquoso de folhas de *Vernonanthura polyanthes*, que participei da construção e formação desse estudo, e assumo a responsabilidade pública pelo conteúdo desse.

Anápolis-GO, 30 de setembro de 2020.

Luana Magalhães Pelegrine
Responsável pela submissão