RENORBIO

Rede Nordeste de Biotecnologia

Programa de Pós-Graduação em Biotecnologia

BIOPROSPECÇÃO DO EXTRATO DAS FOLHAS DE *Fridericia platyphylla* NA CARDIOPREVENÇÃO EM ROEDORES E OBTENÇÃO DE BIOPRODUTOS

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Coorientadora: Profa. Dra. Marilene Oliveira da Rocha Borges

São Luís – MA
2026

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À minha família, que sempre acreditou em mim e foi meu porto seguro. Aos meus pais, Abel Ferreira e Deusa Coelho, que com amor incondicional, ensinaram-me o valor do conhecimento, do esforço, e da vontade de vencer através da educação, por me mostrarem o quão forte é o poder da dedicação e da resiliência. Obrigada por segurarem minha mão, por suas orações constantes, por celebrarem cada pequena conquista como se fosse a maior vitória do mundo. Tudo o que sou e construí até aqui tem as marcas da educação e do exemplo de vocês.

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competitivo através de comidas que provavelmente não deveriam ser oferecidos em um laboratório que estuda doenças cardiovasculares como um todo. O ambiente de colaboração, os aprendizados diário e a troca de experiências tornaram essa trajetória enriquecedora.

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Esta tese é o reflexo da dedicação e do esforço de todos aqueles que, direta ou indiretamente, fizeram parte desta caminhada — um reflexo de que crescer em um ambiente humilde, não limita sonhos, mas sim fortalece raízes, molda resistências e inspira conquistas. A ciência que produzo carrega as marcas do meu território, das minhas vivências e das pessoas que me ensinaram, desde cedo, a lutar com coragem e dignidade. A vocês, minha eterna gratidão.

“Na vida, não se pode amar mais ou menos, sonhar mais ou menos, lutar mais ou menos, ou se dedicar mais ou menos. Se queremos conquistar algo verdadeiro, precisamos entregar o nosso melhor, pois é assim que deixamos de ser mais ou menos e nos tornamos completos”.

Meu pé de Laranja Lima – José Mauro de Vasconcelos

RESUMO

As doenças cardiovasculares (DCVs) representam a principal causa de morbimortalidade global, englobando condições como doença arterial coronária, hipertensão arterial sistêmica e infarto agudo do miocárdio (IAM), caracterizado pela obstrução das artérias coronárias e consequente morte dos cardiomiócitos. Nesse contexto, esta tese foi estruturada com o objetivo de integrar prospecção tecnológica, revisão científica e investigação experimental acerca do potencial terapêutico da espécie *Fridericia platyphylla* (Cham.) L. G. Lohmann. Inicialmente, realizou-se um estudo de prospecção tecnológica baseado na análise de pedidos de patentes depositados nos principais bancos de dados nacionais e internacionais, incluindo INPI, Espacenet, Google Patents, Derwent Innovations Index e WIPO, considerando depósitos realizados nos últimos 15 anos e utilizando descritores relacionados à espécie e ao seu sinônimo botânico *Arrabidaea brachypoda*, associados a termos correlatos às DCVs. Paralelamente, foi conduzida uma revisão integrativa da literatura, com buscas sistemáticas nas bases PubMed, SciELO e Google Scholar, abrangendo estudos publicados entre outubro de 2014 e dezembro de 2024, incluindo investigações *in vivo*, *in vitro* e etnofarmacológicas. Adicionalmente, desenvolveu-se um estudo experimental a partir do extrato hidroetanólico de *Fridericia platyphylla* (EFP), obtido e caracterizado quimicamente por técnicas cromatográficas avançadas. Ratos machos adultos da espécie *Rattus norvegicus*, linhagem Wistar, foram distribuídos em grupos experimentais (Controle, ISO, EFP50, EFP75 e EFP100) e tratados por 15 dias, sendo o IAM induzido por administração subcutânea de isoproterenol (85 mg/kg) nos dias 14 e 15. Ao final do protocolo, foram realizadas avaliações hemodinâmicas e eletrocardiográficas, seguidas da coleta de amostras biológicas para análises bioquímicas, hematológicas, de hemostasia, morfométricas e histopatológicas (CEUA nº 23115.019856/2023-61). A prospecção tecnológica identificou 66 patentes (2008–2023), majoritariamente de instituições acadêmicas brasileiras, com destaque para a Universidade Estadual de Campinas, seguida pela UFMA e UNESP, evidenciando o interesse na espécie. A revisão integrativa incluiu 20 estudos, mostrando diversidade de extratos e compostos com atividades biológicas relevantes (anti-inflamatória, antioxidante, antiproliferativa, antifúngica e antiparasitária), destacando flavonoides como braquidinas e luteolina. No estudo experimental, a caracterização fitoquímica do EFP revelou predominância de flavonoides glicosilados, especialmente rutina e apigenina. O tratamento com EFP prveniu efeitos deletérios sobre a pressão arterial após administração de isoproterenol. Destaca-se, ainda, que EFP promoveu redução significativa da hipertrofia cardíaca, da área de infarto e dos biomarcadores de lesão miocárdica, incluindo Troponina, CPK, CPK-MB, LDH, AST e proteína C-reativa. Observou-se, ainda, melhor preservação dos parâmetros hepáticos e renais, dos níveis séricos de fósforo, dos achados eletrocardiográficos e da arquitetura miocárdica. Houve ainda redução significativa de edema, infiltração inflamatória, extravasamento de hemácias e mionecrose, bem como menor deposição de colágeno, com efeitos mais pronunciados no grupo tratado com EFP100. Além disso, o FPE promoveu melhora significativa nos parâmetros hematológicos, com redução do número de leucócitos totais e dos níveis plasmáticos de fibrinogênio, indicando efeitos anti-inflamatórios e antitrombóticos consistentes. Adicionalmente, observou-se De forma integrada, os achados experimentais, aliados às evidências da literatura e à análise do panorama de inovação, fundamentaram o desenvolvimento de uma composição farmacêutica inovadora, resultando no depósito de pedido de patente com potencial aplicação no contexto das desordens cardiovasculares, reforçando o caráter farmacológico, tecnológico e translacional da espécie.

Palavras-Chaves: Cardioproteção*;* Extrato hidroetanólico; *Fridericia platyphylla;* Infarto agudo do miocárdio; Prospecção tecnológica.

ABSTRACT

Cardiovascular diseases are the leading cause of morbidity and mortality worldwide, encompassing conditions such as coronary artery disease, systemic arterial hypertension, and acute myocardial infarction (AMI), which is characterized by coronary artery obstruction and subsequent cardiomyocyte death. In this context, this thesis was designed to integrate technological prospection, scientific review, and experimental investigation regarding the therapeutic potential of *Fridericia platyphylla* (Cham.) L. G. Lohmann. Initially, a technological prospection study was conducted based on the analysis of patent applications deposited in major national and international databases, including INPI, Espacenet, Google Patents, Derwent Innovations Index, and WIPO, considering filings from the past 15 years and using descriptors related to the species and its botanical synonym *Arrabidaea brachypoda*, combined with terms associated with cardiovascular diseases. In parallel, an integrative literature review was performed through systematic searches in PubMed, SciELO, and Google Scholar, covering studies published between October 2014 and December 2024, including in vivo, in vitro, and ethnopharmacological investigations. Additionally, an experimental study was developed using the hydroethanolic extract of *Fridericia platyphylla* (FPE), obtained and chemically characterized by advanced chromatographic techniques. Adult male Wistar rats (*Rattus norvegicus*) were allocated into experimental groups (Control, ISO, FPE50, FPE75, and FPE100) and treated for 15 days, with AMI induced by subcutaneous administration of isoproterenol (85 mg/kg) on days 14 and 15. At the end of the protocol, hemodynamic and electrocardiographic assessments were performed, followed by the collection of biological samples for biochemical, hematological, hemostatic, morphometric, and histopathological analyses (CEUA No. 23115.019856/2023-61). Technological prospection identified 66 patents (2008–2023), predominantly from Brazilian academic institutions, with emphasis on the Universidade Estadual de Campinas, followed by UFMA and UNESP, highlighting the growing scientific and technological interest in the species. The integrative review included 20 studies, demonstrating a diversity of extracts and compounds with relevant biological activities (anti-inflammatory, antioxidant, antiproliferative, antifungal, and antiparasitic), particularly flavonoids such as brachydins and luteolin. In the experimental study, phytochemical characterization of FPE revealed a predominance of glycosylated flavonoids, especially rutin and apigenin. FPE treatment prevented deleterious effects on blood pressure following isoproterenol administration. Moreover, FPE significantly reduced cardiac hypertrophy, infarct size, and biomarkers of myocardial injury, including troponin, CPK, CK-MB, LDH, AST, and C-reactive protein. Improved preservation of hepatic and renal parameters, serum phosphorus levels, electrocardiographic findings, and myocardial architecture was also observed. Furthermore, there was a marked reduction in edema, inflammatory infiltration, erythrocyte extravasation, and myonecrosis, along with decreased collagen deposition, with more pronounced effects in the FPE100 group. Additionally, FPE significantly improved hematological parameters, reducing total leukocyte count and plasma fibrinogen levels, indicating consistent anti-inflammatory and antithrombotic effects. Taken together, the experimental findings, combined with literature evidence and innovation landscape analysis, supported the development of an innovative pharmaceutical composition, culminating in a patent application with potential application in cardiovascular disorders, reinforcing the pharmacological, technological, and translational relevance of the species.

Keywords: Cardioprotection; Hydroethanolic extract; *Fridericia platyphylla*; Acute myocardial infarction; Technological prospection.

LISTA DE ABREVIAÇÕES E SIGLAS

15-LOX – 15-Lipoxygenase.

AAS – Ácido Acetilsalicílico.

AGEs – Advanced Glycation End Products.

AINEs – Antiinflamatórios Não Esteroidais.

AMI – Acute Myocardial Infarction.

aPTT – Activated Partial Thromboplastin Time.

BALB/c – Linhagem de Camundongos BALB/c.

Bax – Bcl-2 Associated X Protein.

Bcl-2 - B-Cell Lymphoma 2.

BR-A – Brachydin A. BR-B – Brachydin B.

BRPHE – Brazilian Red Propolis Hydroalcoholic Extract

CBC – Complete Blood Count.

CK – Creatine Kinase (Creatina Quinase).

CK-MB – Creatine Kinase-MB.

COMMIT/CCS-2 – Clopidogrel and Metoprolol in Myocardial Infarction Trial / Second Chinese Cardiac Study.

COX-1 – Ciclooxigenase-1.

CRP – C-Reactive Protein.

CSIC – Consejo Superior de Investigaciones Científicas.

CT – Healthy Control.

CVDs – Cardiovascular Diseases.

DCM – Dichloromethane.

DBP – Diastolic Blood Pressure.

DMSO – Dimethyl Sulfoxide.

DNA – Desoxyribonucleic Acid.

DU145 – Linha Celular de Câncer de Próstata Metastático Humano

ECG – Eletrocardiograma.

EDTA – Ethylenediaminetetraacetic Acid.

EFP – Composição Farmacêutica do Extrato Hidroetanólico de *Fridericia platyphylla.*

ERos – Espécies Reativas de Oxigênio.

ESI – Electrospray Ionization.

EtBr – Ethidium Bromide.

FIA – Flow Injection Analysis.

FLAB-DCM – Fração Diclorometânica da Folha de *Arrabidaea brachypoda*.

FLAB-Et – Fração Etanólica da Folha de *Arrabidaea brachypoda*.

FPE – Pharmaceutical Composition of the Hydroethanolic Extract of *Fridericia platyphylla.*

HBPM – Heparinas de Baixo Peso Molecular.

H&E – Hematoxylin and Eosin.

HEAb – Hydroethanolic Extract of *Arrabidaea brachypoda*.

HDP – Herbal Drug Preparation.

HMG-CoA – 3-Hidroxi-3-Metilglutaril Coenzima A.

HNF – Heparina Não Fracionada.

HPLC – High-Performance Liquid Chromatography.

HPLC-PDA – High-Performance Liquid Chromatography with Photodiode Array Detector.

HPLC-UV-MS – High-Performance Liquid Chromatography coupled to Ultraviolet and Mass Spectrometry Detection.

HT-29 – Linha Celular de Câncer Colorretal Humano.

IC50 – Inhibitory Concentration 50%.

IECA – Inibidores da Enzima Conversora de Angiotensina.

IL-1 – Interleucina 1.

IL-6 – Interleucina 6.

IL-8 – Interleucina 8.

INPI – Instituto Nacional da Propriedade Industrial.

INR – International Normalized Ratio.

ISO – Isoproterenol.

IT – Ion Trap.

IAM – Infarto Agudo do Miocárdio.

IAMCSST – Infarto Agudo do Miocárdio com Supra Desnivelamento do Segmento ST. IAMSSST – Infarto Agudo do Miocárdio sem Supra Desnivelamento do Segmento ST. LC-MS/MS – Liquid Chromatography-Mass Spectrometry/Mass Spectrometry.

LDH – Lactato Desidrogenase.

LDL – Lipoproteínas de Baixa Densidade.

LOX – Lipoxygenase.

MAP – Mean Arterial Pressure.

MCP-1 – Proteína Quimioatraente de Monócitos-1.

ME3 – Microemulsão com 3% de Fração DCM.

ME5 – Microemulsão com 5% de Fração DCM.

MI – Myocardial Infarction.

MMPs – Metaloproteinases de Matriz.

MTT – Ensaio de Viabilidade Celular Baseado na Redução do MTT.

Na^+/Ca^{2+}-ATPase – Sódio/Cálcio – ATPase.

Na^+/K^+-ATPase – Sódio/Potássio – ATPase.

NCI-H460 – Linha Celular de Câncer de Pulmão Humano.

NHA – Normal Human Astrocytes.

NIH – National Institutes of Health.

NO – Óxido Nítrico.

O_2^- – Superóxido.

PBS – Phosphate-Buffered Saline.

PC-3 – Linha Celular de Câncer de Próstata Humano.

PT – Prothrombin Time.

PCR – Proteína C-Reativa.

RBC – Red Blood Cells.

RPMI – Roswell Park Memorial Institute Medium.

RPMI 1640 – Meio de Cultura Celular RPMI-1640.

ROS – Reactive Oxygen Species.

SBP – Systolic Blood Pressure.

SRAA – Sistema Renina-Angiotensina-Aldosterona.

SISGEN – Sistema Nacional de Gestão do Patrimônio Genético e do Conhecimento Tradicional Associado.

SUS – Sistema Único de Saúde.

TGF-β – Fator de Crescimento Transformador Beta.

TNF-α – Fator de Necrose Tumoral Alfa.

TTC – Triphenyl Tetrazolium Chloride.

U-251 – Linha Celular de Glioblastoma Humano.

UFMA – Universidade Federal do Maranhão.

UFPO – Universidade Federal de Ouro Preto.

UNESP – Universidade Estadual Paulista Julio de Mesquita Filho.

UNICAMP – Universidade Estadual de Campinas.

UFRPE – Universidade Federal Rural de Pernambuco.

UPE – Universidade de Pernambuco.

UV – Ultraviolet.

VEGF – Vascular Endothelial Growth Factor.

WIPO – World Intellectual Property Organization.

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APRESENTAÇÃO

Esta tese intitulada “Bioprospecção do extrato das folhas de *Fridericia platyphylla* na cardioprevenção em roedores e obtenção de bioprodutos” buscou investigar os efeitos cardioprotetores do extrato hidroetanólico de *F. platyphylla* (EFP) em um modelo experimental de infarto agudo do miocárdio (IAM) induzido por isoproterenol em ratos *Wistar*.

Apresentamos cada etapa deste estudo a partir da elaboração de 3 diferentes artigos e 1 patente a seguir descritos.

Artigo 1: Prospecção tecnológica: Perspectivas na utilização de *Fridericia platyphylla* para o tratamento de desordens cardiovasculares

Este capítulo da tese aborda o potencial terapêutico e tecnológico da *Fridericia platyphylla* no tratamento de doenças cardiovasculares (DCVs), incluindo hipertensão, insuficiência cardíaca e infarto. A planta tem se destacado por suas propriedades anti-inflamatórias e vasorelaxantes, sugerindo benefícios para a saúde cardiovascular. O estudo realizou uma prospecção tecnológica baseada em pedidos de patentes nas bases de dados do Instituto Nacional da Propriedade Industrial (INPI), European Patent Office (Espacenet), Google Patents, Derwent Innovations Index e World Intellectual Property Organization (WIPO).

Artigo 2: Therapeutic Potential of *Fridericia platyphylla*: An Integrative Review of The Effects of Crude Extracts and Isolated Phytochemicals in Different Experimental Models

Este capítulo da tese aborda o potencial farmacológico da espécie *Fridericia platyphylla*, uma planta endêmica do Cerrado brasileiro em uma revisão abrangente que teve como objetivo avaliar os efeitos do extrato bruto e de compostos isolados desta planta em diferentes modelos experimentais. Para isso, foi realizada uma busca integrativa da literatura em bases de dados como PubMed, Scielo e Google Scholar, considerando estudos publicados entre julho de 2014 e junho de 2024.

Artigo 3: Cardioprotective Potential of *Fridericia platyphylla* (Cham.) L.G. Lohmann: Phytochemical Characterization and Experimental Evidence

Este capítulo da tese investiga o perfil químico e o potencial cardioprotetor de uma formulação farmacêutica a base extrato hidroetanólico de *Fridericia platyphylla* (FPE) em um modelo experimental de infarto agudo do miocárdio

induzido por isoproterenol em ratos *Wistar*. O estudo avaliou parâmetros hemodinâmicos, biomarcadores cardíacos, hipertrofia miocárdica, área de infarto, padrões eletrocardiográficos, além de análises hematológicas, hemostasia e histológicas do ápice cardíaco.

Patente: Composições Farmacêuticas à Base de Cervejinha do Campo (*Fridericia platyphylla*) Para Uso em Desordens Cardiovasculares.

Neste capítulo, apresenta-se o desenvolvimento e a caracterização de formulações farmacêuticas orais inovadoras contendo o extrato hidroalcoólico liofilizado das folhas de *Fridericia platyphylla*, planta popularmente conhecida como cervejinha do campo ou cipó una. A proposta parte de evidências científicas que demonstram o potencial terapêutico deste fitocomplexo, especialmente em distúrbios cardiovasculares associados à isquemia miocárdica

SUMÁRIO

1. INTRODUÇÃO

As doenças cardiovasculares (DCVs) representam um grupo de enfermidades que comprometem o funcionamento do sistema circulatório, sendo a principal causa de morbimortalidade no mundo, responsável por milhões de mortes anualmente (Goretti *et al.*, 2021). Entre as principais DCVs, destacam-se a hipertensão arterial sistêmica (HAS), insuficiência cardíaca, doença arterial coronariana, dislipidemias e, sobretudo, o infarto agudo do miocárdio (IAM), que figura como uma das condições mais críticas (Nicareta *et al.*, 2024).

Nesta perspectiva, por se tratar de patologias com elevada prevalência e impacto significativo na morbimortalidade global, essas condições representam um desafio crítico para os sistemas de saúde, exigindo estratégias integradas e recursos substanciais para sua prevenção e manejo eficaz (Oliveira *et al.*, 2024). No Brasil, essas enfermidades impõem uma sobrecarga significativa ao Sistema Único de Saúde (SUS), gerando elevados custos para garantir o acesso a tratamentos especializados e internações hospitalares, além de exigir investimentos contínuos em infraestrutura e capacitação de profissionais (Costa *et al.*, 2021).

Entre as diversas DCVs, destaca-se o IAM, uma emergência médica caracterizada pela interrupção súbita do fluxo sanguíneo em uma ou mais artérias coronárias, resultando em isquemia do músculo cardíaco e potencialmente em necrose tecidual irreversível (Ruparelia *et al.*, 2023). Os dados mais recentes do Global Burden of Disease (GBD) 2023 indicam que as doenças cardiovasculares (DCVs) foram responsáveis por aproximadamente 19,2 milhões de mortes em nível mudial, além de cerca de 437 milhões de DALYs (Disability-Adjusted Life Years), indicador que corresponde aos anos de vida perdidos por morte prematura somados aos anos vividos com incapacidade. Paralelamente, vale ressaltar que o IAM é a principal causa de óbitos no Brasil, com uma estimativa de 300 a 400 mil casos anuais, dos quais cerca de 30% resultam em morte (Abreu; Branco; Santos, 2021). Ademais, dados demonstram que o SUS realiza mais de 128 mil procedimentos anuais relacionados ao IAM, incluindo angioplastias e cateterismos, com investimentos médios de R$ 500 milhões por ano (Ministério Da Saúde, 2022). Em 2022, houve um aporte adicional de R$ 41 milhões para fortalecer o atendimento especializado e a infraestrutura necessária para o tratamento dessa condição. Esses dados evidenciam o impacto financeiro e social do IAM e a necessidade urgente de novas estratégias de prevenção e tratamento no âmbito do sistema público de saúde (Ministério Da Saúde, 2022).

No campo terapêutico, os avanços farmacológicos têm desempenhado um papel central na melhoria do prognóstico de pacientes com IAM (Silva; Carvalho; Andrade, 2024).

Medicamentos como trombolíticos, inibidores de enzima conversora de angiotensina (IECA), betabloqueadores e agentes antiplaquetários são amplamente utilizados para restaurar o fluxo sanguíneo e prevenir complicações, enquanto intervenções como angioplastia primária têm se mostrado essenciais no manejo agudo (Yasuda *et al.*, 2023). Contudo, os efeitos adversos, o alto custo e a acessibilidade limitada desses tratamentos reforçam a busca por alternativas terapêuticas mais acessíveis e eficazes (Yasuda *et al.*, 2023).

Nesse contexto, os bioprodutos oriundos de fontes naturais têm se destacado como uma abordagem promissora para o manejo de DCVs, incluindo o IAM (Arshad *et al.*, 2021). Plantas medicinais ricas em metabólitos secundários, como flavonoides, saponinas e terpenoides, apresentam propriedades anti-inflamatórias, antioxidantes e cardioprotetoras que podem contribuir para o desenvolvimento de novas terapias (Rodrigues *et al.*, 2022; Pinheiro *et al.*, 2024). Entre essas, a espécie *Fridericia platyphylla*, conhecida popularmente como "cervejinha do campo, cipó-una ou tintureiro", surge como uma alternativa inovadora e acessível para estudos na área de cardioprevenção.

Fridericia platyphylla (Cham.) L. G. Lohmann (sin. *Arrabidaea brachypoda*), pertencente à família Bignoniaceae. Esta é uma espécie nativa do Cerrado brasileiro. Estudos indicam que esta espécie possui diversas atividades biológicas e farmacêuticas, incluindo propriedades anti-inflamatórias, antimicrobianas, antiprotozoárias, analgésicas e citotóxicas contra diversas linhagens de células cancerígenas. Esses efeitos estão principalmente associados ao extrato hidroetanólico obtido das diversas fontes desta planta (raízes, caule, folhas e flores) (Menezes-Filho; Porfiro; Castro, 2021).

Diante desse amplo potencial farmacológico descrito na literatura, o interesse pela investigação da espécie *Fridericia platyphylla* teve início ainda durante a formação em nível de graduação, a partir de estudos voltados à avaliação da rutina, um flavonoide amplamente reconhecido por suas propriedades biológicas e farmacológicas. No contexto do Laboratório de Interfaces em Materiais, buscava-se compreender o potencial de compostos fenólicos em diferentes aplicações, o que conduziu à identificação de espécies vegetais com elevado conteúdo desses metabólitos. Nesse cenário, destacou-se *Fridericia platyphylla*, reconhecida como uma fonte relevante de rutina, despertando o interesse para investigações mais aprofundadas.

A partir dessa constatação, foi estabelecida uma interface com o Laboratório de Farmacologia, sob a orientação da professora Rachel Melo Ribeiro, que já desenvolvia estudos *in vitro* acerca do potencial farmacológico da espécie. Tal aproximação possibilitou o delineamento de uma linha de pesquisa mais estruturada, inicialmente direcionada à avaliação

do efeito vasorelaxante do extrato de *Fridericia platyphylla* em anéis de aorta de ratos. Os resultados obtidos evidenciaram um perfil promissor de atividade vasorelaxante, sugerindo a participação de mecanismos associados à modulação do tônus vascular. Esses achados iniciais foram determinantes para a consolidação do interesse científico na espécie, bem como para o direcionamento de novas abordagens experimentais.

Diante desse contexto, emergiu a necessidade de expandir as investigações para modelos mais complexos e translacionalmente relevantes. Assim, as pesquisas evoluíram para a avaliação do potencial cardiopreventivo de *Fridericia platyphylla* em modelos experimentais com roedores, estabelecendo as bases conceituais e metodológicas que fundamentam o desenvolvimento da presente tese. Nesse sentido, parte-se da hipótese de que o extrato de *Fridericia platyphylla*, rico em compostos fenólicos, especialmente flavonoides, apresenta potencial para promover efeitos cardioprotetores e atenuar alterações estruturais e funcionais associadas ao infarto agudo do miocárdio induzido por isoproterenol.

2. REFERENCIAL TEÓRICO

2.1 FISIOPATOLOGIA DO INFARTO AGUDO DO MIOCÁRDIO

2.1.1 Conceito

O infarto agudo do miocárdio (IAM) é uma condição patofisiológica multifacetada, caracterizada pela necrose do tecido miocárdico em decorrência da interrupção do fluxo sanguíneo coronariano, frequentemente atribuída à oclusão das artérias coronárias (Pellense *et al*., 2021; Bett *et al.*, 2022). A fisiopatologia do IAM envolve um conjunto de processos interligados, que incluem a isquemia miocárdica, a reperfusão, a ativação de respostas inflamatórias e imunológicas, a indução de vias de estresse celular, além de alterações metabólicas e danos celulares irreversíveis. As respostas do miocárdio a estas alterações podem ser avaliadas a partir de sinais eletrocardiográficos que podem dimensionar a possível extensão do comprometimento tecidual cardíaco (Bett *et al.*, 2022; Oliveira *et al.*, 2024). A seguir se abordará detalhadamente as principais fases e mecanismos moleculares envolvidos na fisiopatologia do infarto agudo do miocárdio.

2.1.2 Isquemia Miocárdica e Dano Tecidual Inicial

O tecido cardíaco possui uma alta exigência energética, sendo fortemente dependente da fosforilação oxidativa para a produção de ATP, essencial para a contração e relaxamento do músculo cardíaco (Xavier *et al.*, 2024). A isquemia miocárdica, no entanto, ocorre quando a oferta de oxigênio ao miocárdio se torna insuficiente para atender à sua demanda metabólica. Uma vez que esta demanda de oxigênio é regulada por fatores como frequência cardíaca, contratilidade, tensão parietal e pressão arterial sistêmica, a redução do fluxo sanguíneo coronariano, seja por obstrução aterotrombótica, vasoespasmo ou disfunção endotelial, leva a um déficit na oferta de oxigênio, comprometendo a homeostase energética do miocárdio (Vasconcelos *et al.*, 2024).

A diminuição da produção de ATP afeta a função da bomba Na+/K+-ATPase, resultando no acúmulo de íons intracelulares e na ativação de vias bioquímicas deletérias. O aumento da concentração intracelular de cálcio, por meio do contratansportador Na+/Ca2+, intensifica a demanda metabólica sem suprimento adequado, agravando o estresse celular e

promovendo a ativação de enzimas proteolíticas e lipídicas que deterioram a integridade estrutural das células cardíacas (Vasconcelos *et al.*, 2024). A resposta adaptativa inicial do coração à isquemia envolve mecanismos como a vasodilatação coronariana e o aumento da extração de oxigênio. No entanto, diante de isquemia prolongada, esses mecanismos se tornam insuficientes, levando à disfunção contrátil, necrose celular e resposta inflamatória exacerbada. A perpetuação desse processo pode resultar em infarto do miocárdio, remodelamento ventricular e insuficiência cardíaca (Xavier *et al.*, 2024).

Além disso, o estresse oxidativo decorrente da geração excessiva de radicais livres agrava a lesão miocárdica e pode amplificar a disfunção endotelial, reduzindo ainda mais a perfusão e o fornecimento de oxigênio (Silva *et al.*, 2024). Portanto, estratégias terapêuticas que visam restaurar o equilíbrio entre oferta e demanda de oxigênio são cruciais para a prevenção e tratamento da isquemia miocárdica, incluindo intervenções farmacológicas, angioplastia e modificações no estilo de vida. Em síntese, a isquemia miocárdica é um evento multifatorial que resulta da discrepância entre a demanda metabólica do miocárdio e o suprimento de oxigênio. A sua gravidade e desfechos clínicos dependem da duração da privação de oxigênio e da capacidade do tecido cardíaco de ativar respostas compensatórias (Vasconcelos *et al.*, 2024).

2.1.3 Sobrecarga de Cálcio Intracelular e sua Implicação no Infarto Agudo do Miocárdio

A homeostase do cálcio intracelular é essencial para a manutenção da função celular, uma vez que esse íon atua como um segundo mensageiro em processos como contração muscular, excitação, secreção de neurotransmissores e transdução de sinais (Demontis *et al.*, 2024). A concentração intracelular de cálcio é finamente regulada por transportadores e organelas, incluindo a Na+/Ca2+ -ATPase, mitocôndrias e retículo sarcoplasmático. Entretanto, sob condições de isquemia, a falha desses mecanismos homeostáticos resulta em sobrecarga de cálcio intracelular, precipitando eventos celulares deletérios (Demontis *et al.*, 2024).

Sob condições normais, os níveis de cálcio intracelular são mantidos em baixas concentrações através da ação de diversas bombas e transportadores. A Na^+/K^+-ATPase é uma bomba primária que mantém o gradiente de sódio e potássio através da membrana plasmática, o que por sua vez auxilia a função da Na^+/Ca^{2+} (bomba de sódio e cálcio) na troca de sódio por

cálcio (Landave; Méndez; Moret; Ramos, 2023). Este mecanismo é essencial para garantir que a concentração de cálcio no citosol permaneça baixa, enquanto as mitocôndrias e o retículo endoplasmático sarcoplasmático atuam como reservatórios de cálcio. No entanto, durante a isquemia, essas bombas falham devido à falta de ATP, resultando em um acúmulo de cálcio no citosol (Caorsi; Tortajada; Varela, 2014). A falha na Na^+/K^+-ATPase durante a isquemia ocorre como uma consequência direta da falta de oxigênio e nutrientes, o que compromete a produção de ATP através da fosforilação oxidativa. Com a falha dessa bomba, o sódio intracelular se acumula, gerando um gradiente de sódio alterado que favorece a troca de cálcio extracelular por sódio. O resultado disso é uma influxo maciço de cálcio nas células miocárdicas, um processo fundamental que induz uma série de alterações intracelulares danosas (Caorsi; Tortajada; Varela, 2014).

Durante a isquemia, a hipóxia leva à depleção de ATP, comprometendo a função da Na+/K+-ATPase. Isso promove o acúmulo de sódio intracelular e, consequentemente, altera o gradiente de troca do cálcio, favorecendo sua entrada excessiva no citoplasma e reduzindo a saída do mesmo para o exterior da célula (Demontis *et al.*, 2024). Esse influxo exacerbado desencadeia a ativação de enzimas proteolíticas, como calpaínas, proteases e fosfolipases, que degradam componentes estruturais essenciais, como a tropomiosina, prejudicando a integridade do citoesqueleto e a função contrátil das células miocárdicas. Ademais, o acúmulo de cálcio mitocondrial compromete a cadeia transportadora de elétrons, levando à produção exacerbada de espécies reativas de oxigênio (ROS), o que gera o agravamento ao dano celular (Caorsi; Tortajada; Varela, 2014).

Além disso, a oxidação de proteínas e do DNA celular pode ativar vias apoptóticas e necrosantes, exacerbando a morte celular. Esse fenômeno é particularmente relevante no miocárdio isquêmico, onde a incapacidade de reverter o dano oxidativo contribui para a progressão do infarto miocárdico (Renedo *et al.*, 2021). No contexto sistêmico, a sobrecarga de cálcio intracelular e o estresse oxidativo associado a esta condição induzem alterações na matriz extracelular e no colágeno, promovendo remodelamento miocárdico e fibrose. Essas alterações estruturais resultam em disfunção contrátil, predispondo ao desenvolvimento de insuficiência cardíaca e arritmias. O ciclo patológico estabelecido entre disfunção mitocondrial, sobrecarga de cálcio e produção de ROS representa um dos principais mecanismos na deterioração da função cardíaca pós-isquemia. Esses achados ressaltam a importância de estratégias terapêuticas que visem a regulação do cálcio intracelular como forma de mitigar o dano isquêmico e preservar a função miocárdica (Xiang *et al.*, 2021).

2.1.4 Resposta a Reperfusão e Dano Adicional no Infarto Agudo do Miocárdio

A reperfusão, processo de restauração do fluxo sanguíneo em regiões previamente isquêmicas, é fundamental para a recuperação tecidual pós-infarto do miocárdio. No entanto, de forma paradoxal, essa intervenção pode desencadear um fenômeno deletério conhecido como lesão de reperfusão, caracterizado por agravamento da injúria celular e disfunção tecidual adicional. A principal causa desse dano é o estresse oxidativo exacerbado, resultado da reoxigenação abrupta das células miocárdicas, levando à produção descontrolada de espécies reativas de oxigênio (EROs) (Xiang *et al.*, 2021).

Durante a isquemia, a privacão de oxigênio compromete a fosforilação oxidativa mitocondrial e reduz drasticamente a síntese de ATP, levando à acidose intracelular e à desregulação do metabolismo iônico. A reação abrupta à reintrodução de oxigênio pode gerar um acúmulo de radicais livres, como o superóxido (O_2^-), peróxido de hidrogênio (H_2O_2) e óxido nítrico (NO), que promovem oxidação de lipídeos, proteínas e ácidos nucleicos, intensificando o dano celular (Matter *et al.*, 2021). A lipoperoxidação das membranas celulares desencadeia ruptura estrutural, facilitando a liberação de conteúdo intracelular e exacerbando a resposta inflamatória local. Neutófilos são ativados pelo estresse oxidativo e liberam mediadores inflamatórios, como citocinas, quimiocinas e enzimas proteolíticas (colagenases e elastases), que ampliam a lesão tecidual. Esse fenômeno também aumenta a permeabilidade vascular, contribuindo para infiltração leucocitária e agravamento do dano (Xiang *et al.*, 2021).

Outro fator crítico associado à lesão de reperfusão é o acúmulo de cálcio intracelular, resultado da falha nas bombas iônicas dependentes de ATP. A sobrecarga de cálcio ativa enzimas destrutivas, como fosfolipases, proteases e calpaínas, que degradam componentes celulares essenciais, promovendo morte celular por necrose e apoptose. A ativação da via apoptótica é mediada pela caspase-3, levando à fragmentação do DNA e perda de células funcionais no miocárdio (Ramachandra *et al.*, 2021). A mitocôndria também desempenha papel central na lesão de reperfusão, uma vez que sua disfunção induz a liberação de proteínas pró-apoptóticas, como citocromo c, e intensifica a produção de EROs. Esse ciclo de estresse oxidativo perpetua a degradação tecidual, promovendo a morte celular em larga escala (Zhang *et al.*, 2022).

A reperfusão também pode contribuir para a formação de microtrombos nas arteríolas coronárias, reduzindo a perfusão efetiva do tecido miocárdico e comprometendo a recuperação

funcional do coração. Esse fenômeno, aliado ao remodelamento cardíaco promovido por fibrose miocárdica secundária à inflamação crônica, pode levar ao desenvolvimento de insuficiência cardíaca e arritmias, agravando o prognóstico dos pacientes (Ramachandra *et al.*, 2021). Em suma, a reperfusão, apesar de essencial para a sobrevivência celular, apresenta riscos substanciais devido à indução de estresse oxidativo, inflamação exacerbada, sobrecarga de cálcio intracelular e disfunção mitocondrial. Estratégias terapêuticas direcionadas à modulação da resposta inflamatória, redução da formação de radicais livres e estabilização da homeostase cálcio-mitocondrial são essenciais para minimizar os danos associados à reperfusão e preservar a função cardíaca (Ramachandra *et al.*, 2021; Zhang *et al.*, 2022).

2.1.5 Disfunção Mitocondrial e Estresse Oxidativo no Infarto Agudo do Miocárdio

A mitocôndria é uma organela essencial para a manutenção da homeostase celular, desempenhando um papel central na produção de ATP por meio da fosforilação oxidativa e no controle da concentração intracelular de cálcio. Durante o infarto agudo do miocárdio (IAM), a disfunção mitocondrial desencadeia uma série de eventos deletérios que agravam a lesão celular e contribuem para a morte do tecido miocárdico (Ramachandra *et al.*, 2021).

O primeiro evento crítico ocorre com a isquemia, caracterizada pela redução ou interrupção do fluxo sanguíneo nas artérias coronárias, resultando em hipóxia celular. Na ausência de oxigênio, a mitocôndria apresenta comprometimento na fosforilação oxidativa, levando à depleção de ATP e à ativação de vias metabólicas anaeróbicas (Wal *et al.*, 2023). A produção insuficiente de ATP compromete processos celulares fundamentais, incluindo o transporte iônico, resultando na sobrecarga de cálcio intracelular. Esse aumento excessivo de cálcio, em conjunto com a acidose intracelular induzida pelo acúmulo de lactato, acentua o comprometimento mitocondrial (Wal *et al.*, 2023).

A isquemia mitocondrial leva à disfunção da cadeia transportadora de elétrons e à perda do potencial de membrana mitocondrial, resultando na produção exacerbada de espécies reativas de oxigênio (ROS) (Wal *et al.*, 2023). Durante a reperfusão, ocorre um aumento maciço na formação de ROS, como superóxido (O_2^-) e peróxido de hidrogênio (H_2O_2), que promovem a lipoperoxidação e a oxidação de proteínas e DNA mitocondrial, agravando o estresse oxidativo e comprometendo ainda mais a integridade da mitocôndria (Ramachandra *et al.*, 2021).

A disfunção mitocondrial durante a isquemia e reperfusão leva à liberação do

citocromo c do espaço intermembranoso mitocondrial para o citoplasma, ativando a cascata de apoptose por meio da ativação de caspases. Embora a apoptose possa ser um mecanismo adaptativo para a remoção de células danificadas, sua exacerbação contribui para a perda de células miocárdicas viáveis e para o comprometimento da função cardíaca. Além da apoptose, o estresse oxidativo pode induzir necrose celular, promovendo inflamação exacerbada e contribuindo para a progressão do infarto (Ramachandra *et al.*, 2021).

A reperfusão, apesar de essencial para a recuperação do tecido isquêmico, exacerba a disfunção mitocondrial e a produção de ROS, intensificando a lesão celular. O aumento da permeabilidade mitocondrial facilita a liberação de proteínas pró-apoptóticas da família Bcl-2, como Bax e Bak, que amplificam a morte celular (Yan *et al.*, 2023). Além disso, a ineficiência da cadeia respiratória na dissipação do estresse oxidativo cria um ciclo vicioso, perpetuando a disfunção mitocondrial e a degeneração celular (Wal *et al.*, 2023).

No contexto clínico, a interação entre estresse oxidativo e disfunção mitocondrial representa um dos principais mecanismos na progressão do IAM. A reperfusão, embora necessária, também representa um desafio terapêutico devido à exacerbação do dano oxidativo e da morte celular (Wal *et al.*, 2023). Estratégias que visem a modulação do metabolismo mitocondrial, a redução do estresse oxidativo e a proteção contra o colapso do potencial de membrana mitocondrial são fundamentais para minimizar os danos e preservar a função miocárdica a longo prazo (Ramachandra *et al.*, 2021; Xiang *et al.*, 2021).

2.1.6 Alterações Metabólicas e Distúrbios Energéticos no Infarto Agudo do Miocárdio

A isquemia cardíaca resulta na privação de oxigênio das células miocárdicas, levando a uma série de adaptações metabólicas que, embora inicialmente compensatórias, acabam por contribuir para o agravamento da lesão celular. A primeira resposta metabólica à hipóxia é a transição do metabolismo aeróbico para anaeróbico (Tian *et al.*, 2023). Em condições fisiológicas normais, a geração de ATP ocorre predominantemente pela fosforilação oxidativa mitocondrial, utilizando oxigênio na oxidação de ácidos graxos e glicose. No entanto, a interrupção do suprimento de oxigênio devido à obstrução coronária obriga as células a recorrerem ao metabolismo anaeróbico como fonte primária de energia, o que resulta em uma produção energética ineficiente e na acumulação de metabólitos prejudiciais (Vasconcelos *et al.*, 2024).

Nesse cenário, a glicólise anaeróbica torna-se a principal via metabólica para a geração de ATP. A glicose é convertida em piruvato, que, na ausência de oxigênio, não pode ser completamente oxidado no ciclo de Krebs e é convertido em lactato. Esse acúmulo de lactato leva à acidose intracelular, um fator determinante na disfunção celular durante a isquemia (Tian *et al.*, 2023). A redução do pH celular compromete a atividade enzimática, incluindo a fosfofrutoquinase, essencial para a glicólise, agravando ainda mais a deficiência energética. Além disso, a acidificação do meio intracelular afeta a homeostase iônica, comprometendo o funcionamento das bombas iônicas Na^+/K^+-ATPase e Na^+/Ca^{2+}-ATPase, resultando em sobrecarga de cálcio intracelular, ativação de proteases e degradação estrutural das células miocárdicas (Ramachandra *et al.*, 2021; Tian *et al.*, 2023).

A depleção de ATP afeta diretamente a contratilidade miocárdica, pois impede o funcionamento adequado da miosina ATPase, comprometendo o mecanismo de contração e relaxamento das fibras musculares cardíacas. Além disso, a deficiência energética prejudica a manutenção do potencial de membrana celular, favorecendo a despolarização espontânea e aumentando a suscetibilidade a arritmias letais (Tian *et al.*, 2023). O comprometimento da função mitocondrial, exacerbado pela isquemia prolongada, impede a recuperação energética adequada mesmo após a reperfusão, tornando a recuperação tecidual mais difícil (Han *et al.*, 2022).

Frequentemente observada em pacientes com infarto do miocárdio, a hiperglicemia atua como um importante fator agravante do desequilíbrio metabólico. A elevação dos níveis séricos de glicose intensifica a dependência do metabolismo anaeróbico, contribuindo para o agravamento da acidose. Além disso, a hiperglicemia induz resistência à insulina, prejudicando a captação celular de glicose e reduzindo a utilização de ácidos graxos como substrato energético (Han *et al.*, 2022). Outro aspecto crítico da hiperglicemia é a formação de produtos finais de glicação avançada (AGEs), que promovem inflamação, disfunção endotelial e aumento da fibrose miocárdica, contribuindo para a progressão da insuficiência cardíaca pós-infarto (Ramachandra *et al.*, 2021).

A hipercolesterolemia também desempenha um papel crucial na fisiopatologia do infarto do miocárdio. A presença elevada de lipoproteínas de baixa densidade (LDL) contribui para a formação e progressão das placas ateroscleróticas, que podem se romper e desencadear eventos trombóticos, levando à obstrução coronariana (Upadhyay, 2023). Além disso, durante a isquemia, o metabolismo lipídico torna-se disfuncional, exacerbando a inflamação e o estresse

oxidativo (Han *et al.*, 2022). A lipotoxicidade resultante do acúmulo de ácidos graxos livres no miocárdio pode comprometer ainda mais a função celular e contribuir para a morte celular. No contexto da disfunção metabólica associada ao infarto do miocárdio, durante estados de estresse metabólico, como a isquemia, a oxidação de corpos cetônicos, especialmente o beta-hidroxibutirato, pode oferecer uma via eficiente para a geração de ATP, uma vez que essas moléculas podem ser utilizadas pelo miocárdio sem gerar um acúmulo excessivo de metabólitos acidificantes, como ocorre na glicólise anaeróbica (Upadhyay, 2023).

O impacto metabólico do infarto do miocárdio não se limita à célula isolada, mas afeta a função cardíaca global. A deficiência de ATP reduz a capacidade contrátil do coração, comprometendo o débito cardíaco e a perfusão tecidual sistêmica. Esse comprometimento perfusional pode resultar em falência multiorgânica em casos graves, tornando essencial a implementação de estratégias terapêuticas que minimizem os danos metabólicos associados à isquemia (Tian *et al.*, 2023). Portanto, as alterações metabólicas e os distúrbios energéticos induzidos pela isquemia miocárdica desempenham um importante papel na progressão do infarto e no prognóstico do paciente. Estratégias terapêuticas que visam otimizar a produção de ATP, melhorar a utilização de substratos energéticos e reduzir o estresse metabólico são fundamentais para melhorar os desfechos clínicos e minimizar as sequelas da isquemia cardíaca (Vasconcelos *et al.*, 2024).

2.1.7 Inflamação e Resposta Imunológica no Infarto Agudo do Miocárdio

A resposta inflamatória no infarto agudo do miocárdio (IAM) é um processo complexo e multifásico, desempenhando um papel crucial na tentativa de reparar o dano tecidual, mas também podendo exacerbar a lesão miocárdica e contribuir para a progressão do infarto. Esse fenômeno inicia-se imediatamente após a isquemia, com o recrutamento de células do sistema imunológico e ativação de neutrófilos, as primeiras células deste sistema a responder ao dano (Vasconcelos *et al.*, 2024). A ativação dos neutrófilos ocorre nas primeiras horas após a lesão e é induzida por mediadores químicos, como quimiocinas, citocinas e fatores de crescimento liberados pelas células cardíacas danificadas (Matter *et al.*, 2024).

O recrutamento dos neutrófilos para o local da lesão ocorre por quimiotaxia, onde sinais químicos atraem essas células ao miocárdio isquêmico. Uma vez no local, os neutrófilos liberam enzimas lisossômicas, proteases e espécies reativas de oxigênio (EROs), como o superóxido (O_2^-), que têm a função de degradar células necrosadas e detritos celulares, facilitando a remoção das células mortas (Xiang *et al.*, 2021). No entanto, esse processo não é

seletivo, e essas substâncias reativas podem danificar células miocárdicas viáveis ao redor da área infartada. O superóxido e outras EROs exacerbam o estresse oxidativo no tecido cardíaco, promovendo danos às membranas celulares e mitocôndrias, contribuindo para a lesão adicional. Além disso, a ativação dos neutrófilos aumenta a permeabilidade vascular, resultando em edema intersticial, infiltração de células imunes e acúmulo de proteínas plasmáticas, fatores que podem intensificar a isquemia e prejudicar a perfusão tecidual (Ramachandra *et al.*, 2021).

Na fase subsequente, ocorre a infiltração de macrófagos, células essenciais para a remoção do tecido necrótico por meio da fagocitose. Os macrófagos também secretam citocinas inflamatórias e fatores de crescimento, como o fator de necrose tumoral alfa (TNF-α) e interleucinas (IL-1 e IL-6), que modulam a resposta inflamatória e coordenam a reparação tecidual (Matter *et al.*, 2024). O TNF-α intensifica a inflamação e está envolvido em processos de apoptose, remodelamento tecidual e fibrose. Já as interleucinas promovem a quimiotaxia de leucócitos, ativação endotelial e amplificação dos sinais inflamatórios para as áreas adjacentes ao infarto. Embora essas respostas sejam necessárias para a reparação tecidual, a inflamação excessiva pode prolongar o dano e comprometer a função cardíaca (Matter *et al.*, 2024).

Um dos desfechos do processo inflamatório é a formação de fibrose miocárdica, caracterizada pela substituição do tecido muscular cardíaco por matriz extracelular rica em colágeno (Matter *et al*., 2024; Frantz *et al.*, 2024). Esse tecido cicatricial, desprovido de função contrátil, compromete a mecânica cardíaca e pode levar à redução da função ventricular. A fibrose também altera a arquitetura do miocárdio, impactando a condução elétrica e aumentando o risco de arritmias potencialmente fatais, como fibrilação ventricular e taquicardia ventricular (Fonseca; Izar, 2022).

Além da fibrose, a resposta inflamatória está intrinsecamente associada ao remodelamento cardíaco, processo caracterizado por dilatação ventricular, alongamento das fibras musculares cardíacas e degradação da matriz extracelular mediada por enzimas proteolíticas, como as metaloproteinases de matriz (MMPs) (Matter *et al.*, 2024). Essas alterações estruturais podem aumentar a rigidez ventricular e comprometer o desempenho hemodinâmico do coração, favorecendo a progressão para insuficiência cardíaca. A inflamação também contribui para a formação de microtrombos nas artérias coronárias, especialmente após a reperfusão, devido à agregação plaquetária exacerbada pela liberação de citocinas inflamatórias e radicais livres. Esses microtrombos podem obstruir pequenos vasos do miocárdio, aumentando o risco de isquemia residual e retardando a recuperação do tecido infartado, o que pode agravar o prognóstico clínico (Fonseca; Izar, 2022).

Portanto, a resposta inflamatória, embora essencial para o reparo tecidual, pode ter efeitos deletérios no IAM. A produção excessiva de mediadores inflamatórios, como TNF-α, interleucinas e radicais livres, contribui para o agravamento da lesão tecidual e para alterações estruturais no miocárdio, como fibrose e remodelamento ventricular (Vasconcelos *et al.*, 2024). Esses processos são determinantes na progressão do infarto e no desenvolvimento de complicações a longo prazo, como insuficiência cardíaca e arritmias. Assim, intervenções terapêuticas direcionadas à modulação da resposta inflamatória podem ser essenciais para melhorar os desfechos clínicos e reduzir o impacto do IAM sobre a função cardíaca (Fonseca *et al.*, 2024).

2.1.8 **Fases Histológicas e Reparação no Infarto Agudo do Miocárdio**

A progressão histológica do infarto agudo do miocárdio (IAM) ocorre em uma sequência altamente regulada de eventos, envolvendo necrose tecidual, resposta inflamatória e subsequente reparação cicatricial. Esse processo é coordenado por interações entre células inflamatórias, fatores de crescimento, matriz extracelular e proteínas estruturais, determinando a extensão do dano miocárdico e suas consequências funcionais a longo prazo (Hilgendorf; Frantz; Frangogiannis, 2024). A privação de oxigênio e nutrientes, resultante da obstrução arterial, desencadeia um rápido colapso da homeostase celular, levando à morte celular irreversível em aproximadamente 30 minutos de isquemia. Entretanto, as alterações histológicas tornam-se evidentes somente após algumas horas (Hilgendorf; Frantz; Frangogiannis, 2024).

Nas primeiras 12 a 24 horas, as fibras miocárdicas começam a exibir sinais de necrose coagulativa isquêmica, caracterizada pela eosinofilia citoplasmática devido à desnaturação proteica, e por alterações nucleares como picnose (condensação da cromatina), cariorréxis (fragmentação nuclear) e cariólise (dissolução do núcleo) (Yap *et al.*, 2023). Embora a arquitetura celular seja preservada nessa fase, a perda funcional dos cardiomiócitos já é definitiva. Entre 24 e 48 horas, ocorre intensa infiltração de neutrófilos, mobilizados pela liberação de quimiocinas como a interleucina-8 (IL-8) e a proteína quimioatraente de monócitos-1 (MCP-1). Essas células desempenham um papel essencial na degradação do tecido necrótico, liberando metaloproteinases de matriz (MMPs) e elastases, que fragmentam componentes estruturais e facilitam a remoção celular. Entretanto, a liberação de espécies reativas de oxigênio (EROs) nesse processo pode ampliar o dano miocárdico devido ao aumento do estresse oxidativo (Hilgendorf; Frantz; Frangogiannis, 2024).

A partir do terceiro ao quinto dia, ocorre a transição para uma resposta inflamatória predominantemente mediada por macrófagos, que fagocitam os restos celulares e secretam citocinas pró-reparação, como o fator de crescimento derivado de plaquetas (PDGF) e o fator de crescimento transformador beta (TGF-β) (Yap *et al.*, 2023). Esses mediadores estimulam a proliferação de fibroblastos e a deposição de colágeno, iniciando a formação do tecido de granulação. Entre 7 e 10 dias, a degradação completa do tecido necrótico já ocorreu, e a área infartada é progressivamente substituída por tecido de granulação, caracterizado pela presença de fibroblastos proliferativos, neovasos e macrófagos ativados. O processo de angiogênese, mediado pelo fator de crescimento do endotélio vascular (VEGF), é essencial para assegurar o suprimento adequado de oxigênio e nutrientes às células envolvidas na reparação (Yap *et al.*, 2023).

A partir da segunda semana, inicia-se o remodelamento miocárdico, no qual fibroblastos continuam a sintetizar colágeno tipo I e tipo III, conferindo maior resistência à área cicatricial (Leancă *et al.*, 2022). Esse processo, que pode se estender por semanas a meses, culmina na formação de uma matriz extracelular densa e fibrosa, substituindo permanentemente o tecido contrátil por um tecido não funcional. Embora a fibrose seja um mecanismo essencial para evitar a ruptura da parede ventricular, também leva a complicações estruturais e funcionais, incluindo dilatação ventricular, redução da função contrátil global e predisposição à insuficiência cardíaca crônica. A remodelação excessiva pode comprometer a condução elétrica do coração, favorecendo arritmias ventriculares graves, como fibrilação ventricular e taquicardia ventricular (Leancă *et al.*, 2022; Hilgendorf; Frantz; Frangogiannis, 2024).

A compreensão detalhada da progressão histológica do IAM tem implicações terapêuticas diretas. Estratégias que modulam a resposta inflamatória, reduzem o estresse oxidativo, estimulam a angiogênese e limitam a deposição excessiva de colágeno são fundamentais para otimizar a recuperação funcional do miocárdio (Cong *et al.*, 2021; Hilgendorf; Frantz; Frangogiannis, 2024). Em suma, a evolução histológica do IAM reflete uma interação dinâmica entre morte celular, inflamação e reparação tecidual. O equilíbrio entre esses processos é determinante na extensão do dano final e na recuperação funcional do coração. A identificação de alvos terapêuticos ao longo dessa cascata de eventos abre novas perspectivas para a redução das sequelas do infarto e a melhoria da qualidade de vida dos pacientes acometidos (Ramachandra *et al.*, 2021; Xiang *et al.*, 2021; Leancă *et al.*, 2022).

2.2 DIAGNÓSTICO DIFERENCIAL DO INFARTO AGUDO DO MIOCÁRDIO: PAPEL DOS MARCADORES BIOQUÍMICOS E AVALIAÇÃO ELETROCARDIOGRÁFICA

O IAM é uma das principais emergências cardiovasculares e o diagnóstico precoce e preciso do IAM depende da correlação entre achados clínicos, bioquímicos e eletrocardiográficos (Kasar; Al-Bahrani; Mohsin, 2022). Biomarcadores de necrose miocárdica, como a creatina quinase total (CPK), sua fração MB (CK-MB), a desidrogenase lática (LDH) e a proteína C-reativa (PCR) quantitativa, desempenham papéis fundamentais na detecção e prognóstico da síndrome coronariana aguda (Kasar; Al-Bahrani; Mohsin, 2022). Além disso, a avaliação do segmento ST no eletrocardiograma (ECG) é um parâmetro crucial para a definição do tipo de IAM, direcionando condutas terapêuticas e sendo amplamente utilizada em modelos *in vivo* de IAM para validação de estratégias terapêuticas (Xiong; Lee; Chan, 2022).

Neste sentido, os biomarcadores de necrose miocárdica refletem a ruptura da integridade celular dos cardiomiócitos, permitindo a liberação de proteínas e enzimas intracelulares na circulação sistêmica (Xu *et al.*, 2022). A CPK é uma enzima citoplasmática que participa do metabolismo energético celular, atuando na regeneração do ATP por meio da conversão de creatina-fosfato em creatina (Kasar; Al-Bahrani; Mohsin, 2022). Dentre suas isoenzimas, a fração CK-MB é altamente específica para o tecido cardíaco e apresenta um padrão cinético característico após a injúria miocárdica: elevação entre 3 e 6 horas, pico em 12 a 24 horas e retorno aos níveis basais em 48 a 72 horas. Este perfil permite a identificação precoce do IAM e a avaliação da extensão da lesão. Além disso, a relação CK-MB/CPK total auxilia na diferenciação entre lesão miocárdica e lesões musculares esqueléticas, que cursam com aumento predominante da CPK total sem elevação proporcional da CK-MB (Xu *et al.*, 2022).

A LDH, por outro lado é uma enzima envolvida na conversão de piruvato em lactato, apresenta cinco isoformas, das quais a LDH-1 é a predominante no miocárdio. Durante um evento isquêmico, a inversão da razão LDH-1/LDH-2 ocorre devido à liberação seletiva da LDH-1 dos cardiomiócitos necróticos (Wu *et al.*, 2021). Contudo, a elevação da LDH é mais tardia que a CK-MB, atingindo seu pico entre 24 e 48 horas e permanecendo elevada por até 10 dias, tornando-se útil para o diagnóstico retrospectivo do IAM em pacientes por exemplo com apresentação tardia de um evento isquêmico (Wu *et al.*, 2021). A PCR quantitativa é um

marcador inflamatório que reflete a resposta sistêmica ao dano tecidual e à ativação da cascata inflamatória induzida pelo IAM. Sua elevação precoce pode ser observada em resposta ao estresse oxidativo e à liberação de citocinas pró-inflamatórias, como a interleucina-6 (IL-6) e o fator de necrose tumoral-alfa (TNF-α), associando-se a maior risco de eventos adversos e remodelamento ventricular patológico (Lafta; Issa; Hazza; Abed, 2021). Além disso, estudos indicam que níveis persistentemente elevados de PCR após o IAM correlacionam-se com um pior prognóstico, aumentando o risco de insuficiência cardíaca e reinfarto (Lafta; Issa; Hazza; Abed, 2021). A Figura 1 evidencia os principais mecanismos relacionados ao dano tecidual e as alterações que levam ao aumento de marcadores bioquímicos de necrose miocárdica.

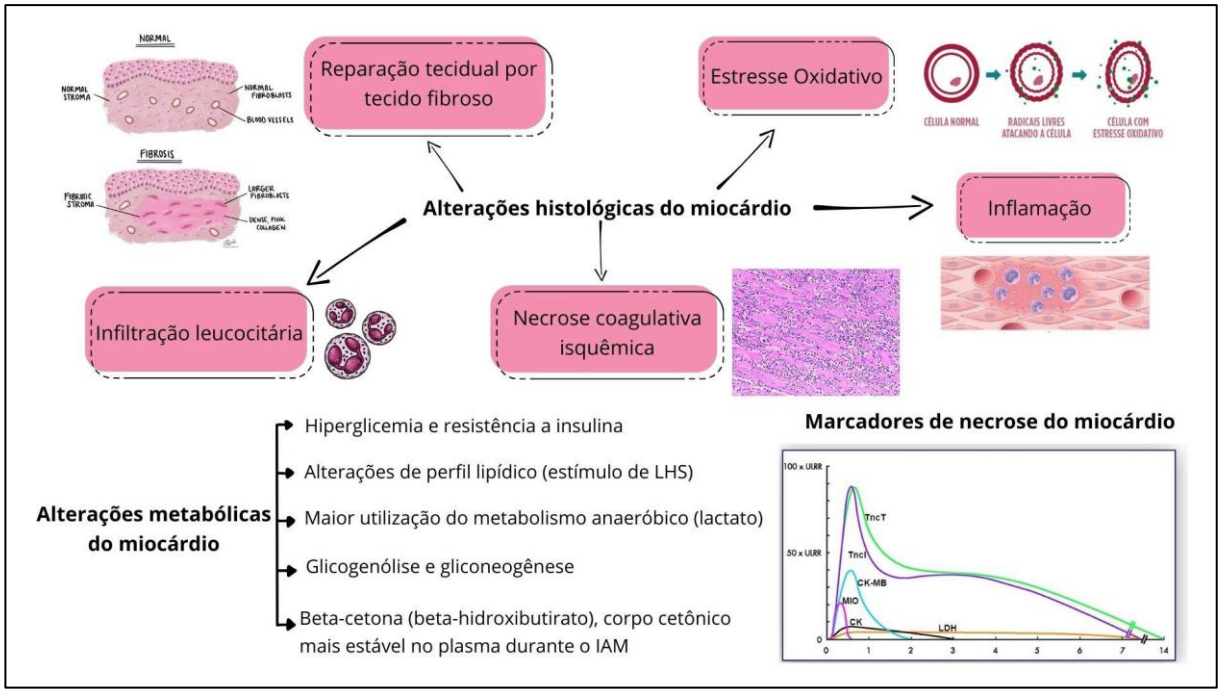

Figura 1. Mecanismos de dano tecidual e marcadores de necrose miocárdica.
Fonte**:** Elaborado pelo autor.

O eletrocardiograma é uma ferramenta essencial na identificação e classificação do IAM, permitindo a distinção entre IAM com supra de ST (IAMCSST) e IAM sem supra de ST (IAMSSST) (Xiong; Lee; Chan, 2022). O IAMCSST caracteriza-se pela elevação persistente do segmento ST em duas ou mais derivações contíguas, refletindo a oclusão total e sustentada de uma artéria coronária epicárdica. Esse achado é resultado da despolarização anômala do miocárdio isquêmico, associado ao fenômeno de "corrente de lesão", que leva a um deslocamento ascendente do segmento ST (Oliveira *et al.*, 2024). Pacientes com IAMCSST apresentam alto risco de complicações, incluindo arritmias malignas e choque cardiogênico, demandando reperfusão imediata via angioplastia primária ou trombólise. O IAMSSST, por

outro lado, manifesta-se com alterações inespecíficas do segmento ST e da onda T, como depressão do ST ou inversão da onda T, sugerindo isquemia subendocárdica secundária a obstrução coronariana parcial ou intermitente. Esse padrão eletrocardiográfico indica um risco aumentado de progressão para oclusão total, sendo necessário um monitoramento rigoroso e estratégias terapêuticas baseadas na estratificação de risco (Oliveira *et al.*, 2024).

A análise do segmento ST tem sido amplamente empregada em modelos experimentais de IAM em animais, principalmente em roedores e suínos, que apresentam padrões eletrofisiológicos comparáveis aos humanos (Jia; Chang; Song, 2024; Low; Azahar; Samson; Rane, 2024; Eddin *et al.*, 2025). Esses modelos permitem o estudo dos mecanismos celulares e terapias emergentes, como agentes cardioprotetores e intervenções regenerativas. A indução do IAM nesses modelos é frequentemente realizada por oclusão da artéria coronária descendente anterior, reproduzindo o padrão eletrocardiográfico de supra de ST observado na prática clínica ou por indução farmacológica utilizando fármacos específicos para este objetivo (Eddin *et al.*, 2025). A avaliação contínua do segmento ST em modelos *in vivo* permite a monitorização em tempo real da progressão da isquemia, auxiliando na validação de estratégias terapêuticas. Estudos demonstram que a atenuação do desvio de ST após a administração de terapias citoprotetoras, como inibidores da apoptose e antioxidantes, correlaciona-se com menor extensão da lesão miocárdica. Além disso, a resolução do supra de ST após a reperfusão é um indicativo prognóstico importante, refletindo a eficácia da restauração do fluxo sanguíneo miocárdico (Song *et al.*, 2024). A seguir, a figura 2 evidencia os principais fatores relacionados as alterações no padrão eletrocardiográfico no IAM.

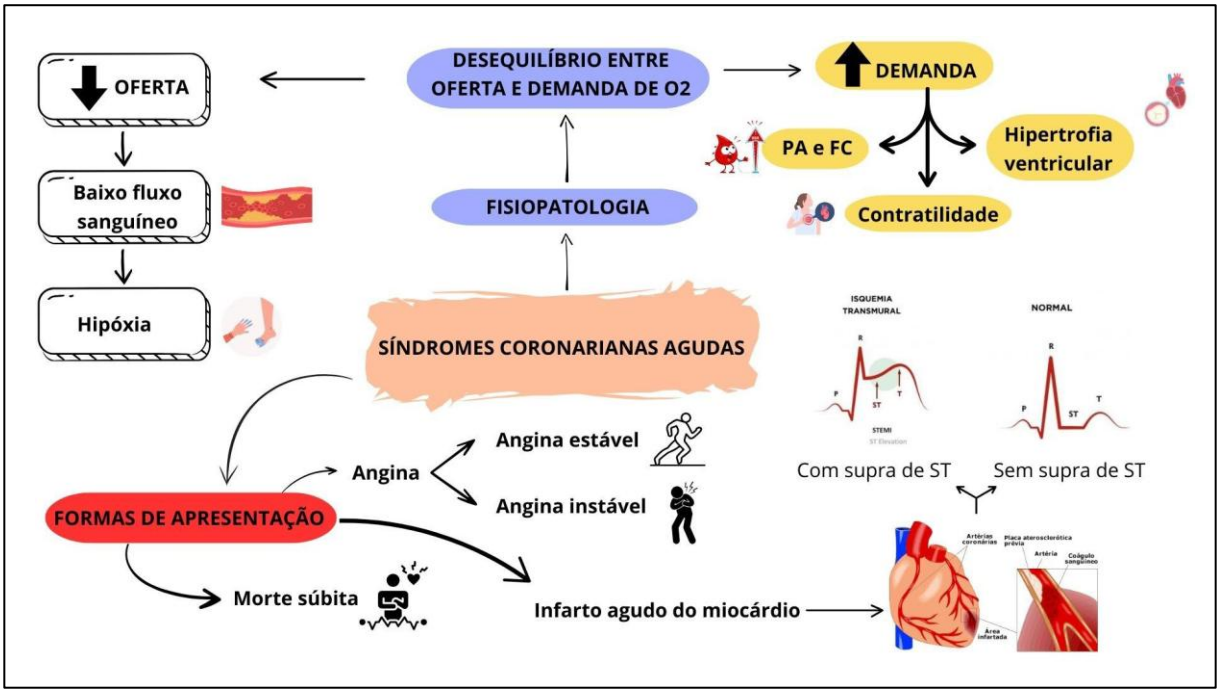

Figura 2. Fatores associados a alterações no padrão eletrocardiográfico após o IAM.
Fonte**:** Elaborado pelo autor.

A compreensão do diagnóstico diferencial do IAM baseia-se na integração entre achados clínicos, biomarcadores bioquímicos de necrose miocárdica e análise eletrocardiográfica. A CK-MB e a LDH desempenham papéis fundamentais na detecção da lesão miocárdica, enquanto a PCR quantitativa auxilia na avaliação inflamatória e prognóstica (Xu *et al.*, 2021). No contexto eletrocardiográfico, a distinção entre IAMCSST e IAMSSST direciona a abordagem terapêutica e define a necessidade de reperfusão imediata. Além de sua importância clínica, a avaliação do segmento ST tem sido amplamente utilizada em modelos *in vivo* de IAM, permitindo a validação de novas estratégias terapêuticas. Desta forma, a combinação dessas ferramentas diagnósticas possibilita um manejo mais eficaz do IAM (Song *et al.*, 2024; Eddin *et al.*, 2025).

2.3 MODELO DE INDUÇÃO DO INFARTO AGUDO DO MIOCÁRDIO POR ISOPROTERENOL

O infarto agudo do miocárdio (IAM) é uma condição cardiovascular de alta morbimortalidade, caracterizada por processos patológicos complexos que envolvem necrose tecidual, inflamação e remodelamento ventricular (Eddin *et al.*, 2025). A compreensão desses

mecanismos é essencial para o desenvolvimento de novas abordagens terapêuticas, e modelos experimentais têm sido amplamente utilizados para simular os aspectos fisiopatológicos do IAM. Entre esses, o modelo de indução do IAM por isoproterenol é amplamente empregado devido à sua capacidade de reproduzir, de forma controlada, as alterações cardíacas observadas no infarto humano (Eddin *et al.*, 2025).

O isoproterenol é um agonista sintético dos receptores beta-adrenérgicos, com afinidade por receptores beta-1 e beta-2, promovendo efeitos inotrópicos e cronotrópicos positivos (Mattoo; Shamim; Alam, 2024). Quando administrado em doses elevadas, provoca aumento da demanda miocárdica por oxigênio e, simultaneamente, reduz o fluxo coronário, levando à isquemia e consequente necrose miocárdica. A isquemia induzida compromete a oxidação eficiente dos substratos energéticos, favorecendo o metabolismo anaeróbico, o acúmulo de lactato e a acidose intracelular. Além disso, a sobrecarga de cálcio resultante da disfunção mitocondrial e da falência das bombas iônicas ativa proteases e metaloproteinases, promovendo degradação estrutural e apoptose (Mattoo; Shamim; Alam, 2024).

O modelo de isoproterenol também mimetiza a intensa resposta inflamatória característica do IAM. A injúria isquêmica induz a liberação de citocinas pró-inflamatórias, como fator de necrose tumoral alfa (TNF-α), interleucinas (IL-1β, IL-6) e quimiocinas, resultando na ativação e infiltração de neutrófilos e macrófagos no tecido infartado (Matarrese *et al.*, 2021). A ação dessas células intensifica o dano tecidual pela liberação de enzimas proteolíticas e espécies reativas de oxigênio (EROs), exacerbando a inflamação e contribuindo para o remodelamento ventricular. Além disso, a reperfusão pós-isquemia, essencial para restaurar o fluxo sanguíneo, pode gerar agravar a lesão miocárdica devido ao estresse oxidativo e ao aumento da permeabilidade vascular, intensificando a morte celular e a disfunção endotelial (Mattoo; Shamim; Alam, 2024).

A Figura 3 sintetiza os principais mecanismos celulares e moleculares envolvidos na lesão miocárdica, evidenciando a estreita inter-relação entre isquemia, depleção de ATP, sobrecarga intracelular de Ca^{2+}, disfunção mitocondrial, estresse oxidativo e hiperestimulação β-adrenérgica (Mattoo; Shamim; Alam, 2024). A redução da disponibilidade energética compromete a atividade das bombas iônicas, favorecendo o acúmulo intracelular de Ca^{2+} e a ativação de enzimas degradativas, enquanto a disfunção mitocondrial intensifica a produção de espécies reativas de oxigênio (EROs) (Mattoo; Shamim; Alam, 2024). Esses eventos estabelecem um ciclo de retroalimentação positiva que amplifica progressivamente o dano às membranas celulares e mitocondriais, culminando em perda da integridade e morte celular.

No contexto do modelo experimental induzido por isoproterenol, a hiperestimulação dos receptores β-adrenérgicos e a ativação da via AMPc/PKA potencializam a sobrecarga de Ca^{2+}, o desequilíbrio energético e o estresse oxidativo, reproduzindo importantes aspectos fisiopatológicos da lesão miocárdica (Matarrese *et al.*, 2021). A compreensão desses mecanismos não apenas fundamenta a ampla utilização desse modelo experimental, mas também permite identificar alvos terapêuticos estratégicos para interromper ou atenuar a cascata de eventos responsáveis pela progressão do dano cardíaco (Matarrese *et al.*, 2021).

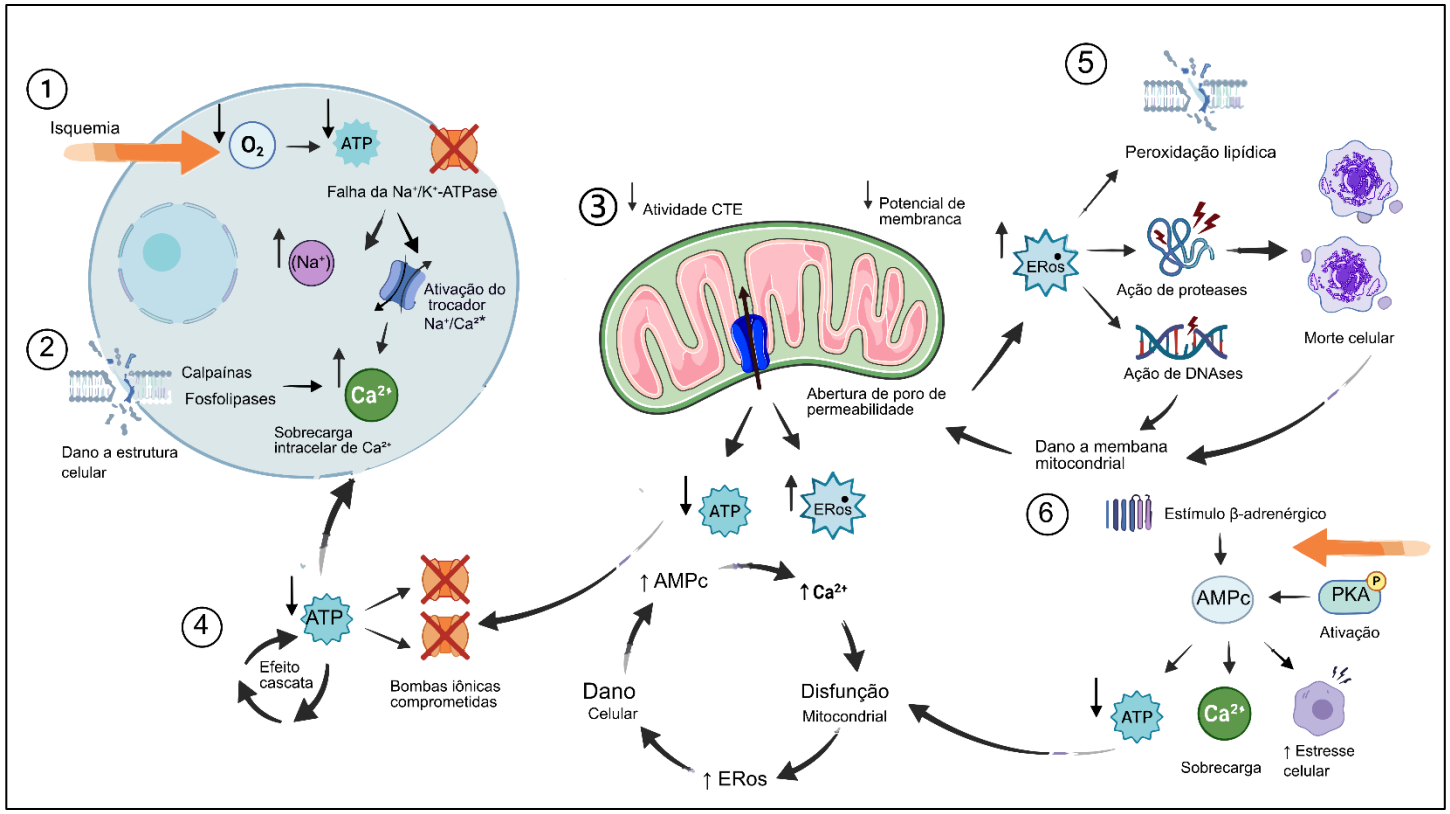

Figura 3. Mecanismos celulares e moleculares envolvidos na lesão miocárdica induzida por isquemia e hiperestimulação β-adrenérgica. AMPc, adenosina monofosfato cíclico; ATP, adenosina trifosfato; Ca^{2+}, íon cálcio; CTE, cadeia transportadora de elétrons; EROs, espécies reativas de oxigênio; Na^{+}, íon sódio; Na^{+}/Ca^{2+}, trocador sódio/cálcio; Na^{+}/K^{+}-ATPase, bomba de sódio e potássio dependente de ATP; O_2, oxigênio molecular; PKA, proteína quinase A. Fonte: Elaborado pelo autor.

Devido à sua relevância, o modelo experimental de isoproterenol tem sido empregado na avaliação de estratégias terapêuticas voltadas à cardioproteção. Estudos têm demonstrado que antioxidantes, como flavonoides e compostos fenólicos, reduzem o estresse oxidativo e minimizam a apoptose celular (Verma *et al.,* 2024; Xu *et al.*, 2024). Além disso, terapias anti-inflamatórias, incluindo inibidores de citocinas e fatores de crescimento, têm mostrado eficácia na modulação da resposta imune e na redução do recrutamento de células inflamatórias (Jubaidi *et al.*, 2021; Xu *et al.*, 2024). A preservação da função mitocondrial também tem sido alvo de investigação, pois estratégias que previnem a disfunção mitocondrial durante a isquemia e reperfusão apresentam potencial para mitigar o dano cardíaco e preservar a função contrátil do miocárdio (Sharma *et al.,* 2024; Verma *et al.*, 2024).

Embora o modelo de isoproterenol não envolva a formação de trombos coronários, principal etiologia do IAM em humanos, ele continua sendo uma ferramenta robusta para elucidar os mecanismos celulares e moleculares do infarto, bem como para testar novas terapias (Eddin *et al.*, 2025). Esse modelo permite a investigação da isquemia, inflamação, estresse oxidativo e remodelamento ventricular, sendo fundamental para o avanço no desenvolvimento de intervenções terapêuticas direcionadas à proteção miocárdica e à melhora do prognóstico pós-IAM (Eddin *et al.*, 2025). Além disso, pesquisas que exploram estratégias para minimizar a fibrose e preservar a função cardíaca têm utilizado esse modelo para avaliar a eficácia de novas terapias visando a modulação do remodelamento ventricular e a prevenção da insuficiência cardíaca subsequente (Wang *et al.*, 2013; Cebova; Pechanova, 2020). A seguir, a figura 4 demonstra os principais mecanismos associados a utilização do modelo de IAM através da utilização do isoproterenol.

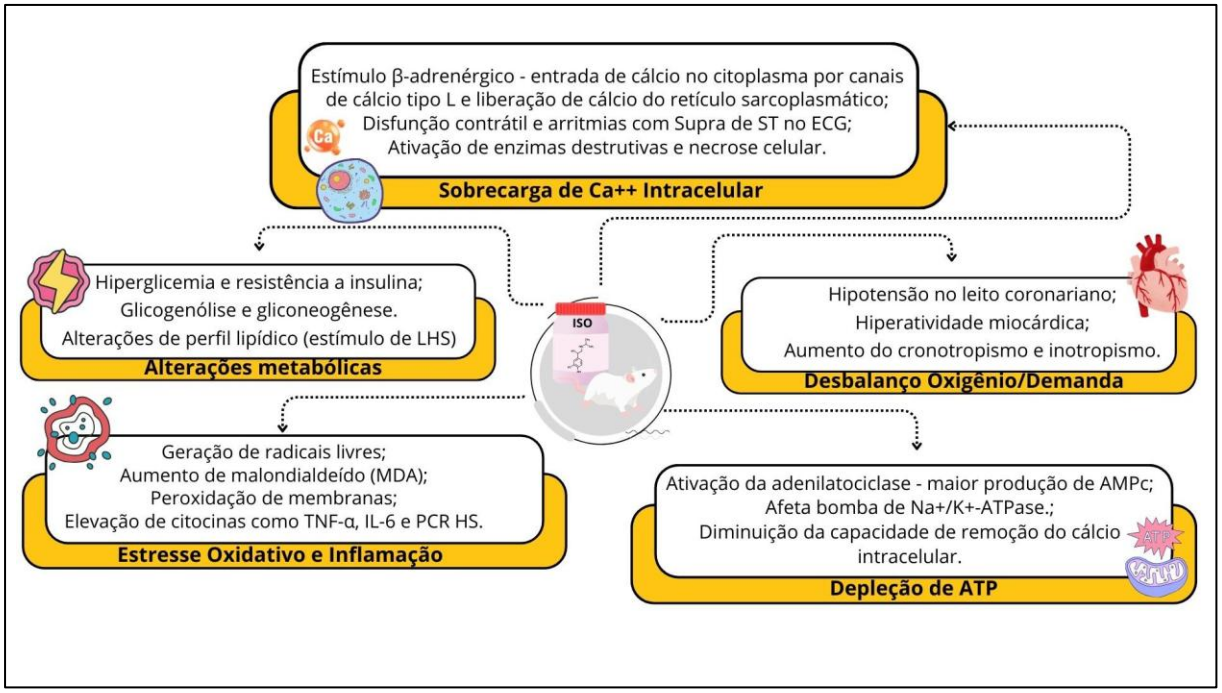

Figura 4. Principais consequências fisiopatológicas decorrentes da hiperestimulação β-adrenérgica induzida por isoproterenol. AMPc, adenosina monofosfato cíclico; ATP, adenosina trifosfato; Ca^{2+}, íon cálcio; ECG, eletrocardiograma; IL-6, interleucina 6; ISO, isoproterenol; LHS, lipase hormônio-sensível; MDA, malondialdeído; Na^{+}/K^{+}-ATPase, bomba de sódio e potássio dependente de ATP; PCR-hs, proteína C-reativa de alta sensibilidade; ST, segmento ST; TNF-α, fator de necrose tumoral alfa. Fonte: Elaborado pelo autor.

Ademais, o modelo de indução do infarto agudo do miocárdio por isoproterenol permanece como uma ferramenta essencial para o entendimento dos mecanismos fisiopatológicos do IAM, permitindo o desenvolvimento e a triagem de novas estratégias terapêuticas. Sua capacidade de simular com precisão a isquemia, a inflamação, o estresse oxidativo e o remodelamento ventricular reforça sua importância na pesquisa translacional, contribuindo para a melhora do manejo clínico e prognóstico dos pacientes acometidos por IAM (Cebova; Pechanova, 2020; Verma *et al.*, 2024; Eddin *et al.*, 2025).

2.4 TERAPIAS DE PRIMEIRA LINHA UTILIZADAS NO TRATAMENTO DO INFARTO AGUDO DO MIOCÁRDIO

O IAM é uma condição cardiovascular grave que exige intervenção terapêutica imediata para restaurar a perfusão coronariana, minimizar a necrose miocárdica e prevenir complicações subsequentes (Feres *et al.*, 2017). As abordagens terapêuticas incluem estratégias farmacológicas e não farmacológicas, sendo a revascularização percutânea um dos principais

tratamentos para restabelecer o fluxo sanguíneo ao miocárdio isquêmico (Feres *et al.*, 2017). No contexto farmacológico, diversos fármacos são empregados para controlar o processo trombótico, reduzir a carga isquêmica e modular a resposta inflamatória, promovendoa estabilização do paciente e prevenindo eventos cardiovasculares futuros (Vasconcelos *et al.*, 2024).

Os antiagregantes plaquetários são essenciais para a prevenção da formação e progressão do trombo intracoronário, uma vez que a ativação plaquetária é um dos eventos centrais na fisiopatologia do IAM (Vale Filho *et al.*, 2024). O ácido acetilsalicílico (AAS) é amplamente utilizado devido à sua capacidade de inibir irreversivelmente a ciclooxigenase-1 (COX-1), reduzindo a síntese de tromboxano A2 e, consequentemente, a agregação plaquetária (Do Vale-Filho *et al.*, 2024). Os inibidores do receptor P2Y12, como clopidogrel, prasugrel e ticagrelor, bloqueiam a ativação plaquetária mediada pelo ADP, proporcionando uma inibição adicional da formação de trombos (Montalvão; Oliveira; Reis, 2022). A terapia antiplaquetária dupla (TAPD), combinando AAS com um inibidor do P2Y12, é recomendada para pacientes submetidos à intervenção coronariana percutânea (ICP), pois reduz significativamente o risco de trombose de stent e eventos isquêmicos recorrentes (Kirsten *et al.*, 2022).

Os anticoagulantes desempenham papel fundamental na prevenção da progressão dos trombos intracoronários. As heparinas, sejam as de baixo peso molecular (HBPM) ou a heparina não fracionada (HNF), atuam potencializando a ação da antitrombina III, inibindo fatores-chave da cascata de coagulação (Bastos; Barreto; Caiafa; Rezende, 2011). A bivalirudina, um inibidor direto da trombina, demonstrou eficácia na redução de complicações hemorrágicas em pacientes submetidos à ICP (Pais *et al.*, 2023). Os anticoagulantes orais diretos (DOACs), como rivaroxabana, também têm sido investigados como adjuvantes na prevenção de eventos tromboembólicos em pacientes de alto risco (Veras *et al.*, 2024).

Os inibidores do sistema renina-angiotensina-aldosterona (SRAA), representados pelos inibidores da enzima conversora de angiotensina (IECA) e bloqueadores dos receptores da angiotensina II (BRA), desempenham um papel crucial na prevenção do remodelamento ventricular, reduzindo a hipertrofia miocárdica, a fibrose e a retenção de sódio (Vasconcelos *et al.*, 2024). Estudos como o SAVE e o VALIANT demonstraram que a administração precoce de IECA ou BRA reduz a mortalidade e melhora a função ventricular após o IAM (Dargie, 2001; Velazquez *et al.*, 2003). Esses fármacos também apresentam efeitos renoprotetores, sendo particularmente indicados para pacientes com diabetes mellitus ou doença renal crônica (Vasconcelos *et al.*, 2024).

As estatinas são amplamente empregadas no manejo do IAM devido aos seus efeitos hipolipemiantes e pleiotrópicos. Ao inibir a HMG-CoA redutase, reduzem a síntese hepática de colesterol e promovem a captação de LDL pelos hepatócitos (Almeida *et al.*, 2024). Além disso, possuem propriedades anti-inflamatórias e antioxidantes, estabilizando placas ateroscleróticas e melhorando a função endotelial. A administração precoce de estatinas de alta intensidade, como atorvastatina e rosuvastatina, é recomendada para reduzir a mortalidade e a recorrência de eventos cardiovasculares (Almeida *et al.*, 2024).

Os betabloqueadores constituem uma classe fundamental no tratamento do IAM, atenuando a resposta simpática e reduzindo a demanda de oxigênio pelo miocárdio. Esses fármacos promovem efeito cronotrópico e inotrópico negativo, diminuindo a frequência cardíaca, a contratilidade e a pressão arterial, favorecendo a perfusão coronariana (Nogueira *et al.*, 2024). Também apresentam ação antiarrítmica, reduzindo o risco de fibrilação ventricular e morte súbita. Estudos como o COMMIT/CCS-2 demonstraram que a introdução precoce de metoprolol reduz a mortalidade e previne complicações hemodinâmicas (Chen; Jiang; Chen, 2005). No entanto, sua administração deve ser individualizada, especialmente em pacientes com disfunção ventricular severa, hipotensão ou bloqueios atrioventriculares (Motawea *et al.*, 2022). A seguir, a figura 5 evidencia um fluxograma da utilização das principais classes de medicamentos para o tratamento do IAM, bem como seus principais efeitos colaterais associados.

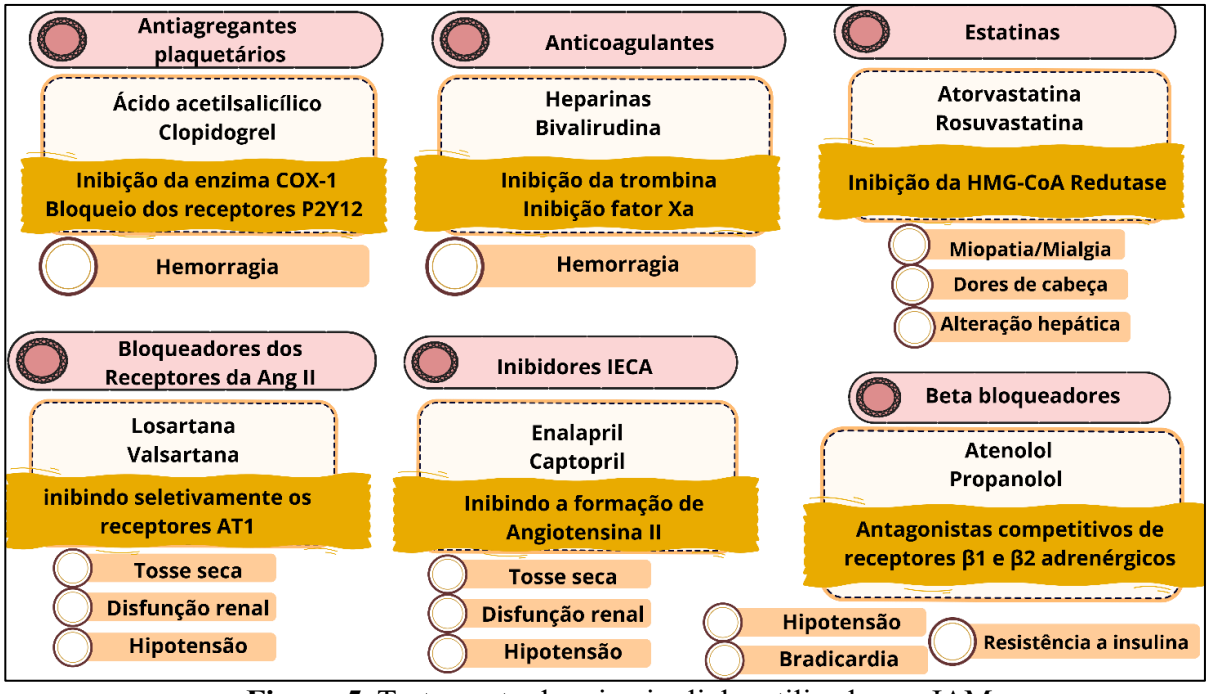

Figura 5. Tratamento de primeira linha utilizados no IAM.
Fonte: Elaborado pelo autor.

As terapias farmacológicas no IAM constituem um arsenal robusto para otimizar a recuperação miocárdica e prevenir complicações. A combinação de antiagregantes plaquetários, anticoagulantes, estatinas, inibidores do SRAA e betabloqueadores proporciona redução significativa na mortalidade e morbidade cardiovascular. A estratégia terapêutica deve ser individualizada, levando em consideração o perfil hemodinâmico e metabólico do paciente, com monitorização rigorosa para minimizar eventos adversos e otimizar os desfechos clínicos a longo prazo (Dargie, 2001; Velazquez *et al.*, 2003; Chen; Jiang; Chen, 2005).

2.5 *Fridericia Platyphylla* (CHAM.) L.G.LOHMANN: CARACTERIZAÇÃO E POTENCIAL FARMACOLÓGICO

Fridericia platyphylla (Cham.) L.G.Lohmann, pertencente à família Bignoniaceae, é uma espécie nativa do Brasil, amplamente distribuída em diferentes biomas, mas encontrada especialmente em regiões de cerrado (Menezes Filho, 2020). Popularmente conhecida como cervejinha do campo, cipó-una ou tintureiro, essa planta tem despertado interesse devido à presença de compostos bioativos com propriedades antioxidantes, anti-inflamatórias e possivelmente cardioprotetoras (Menezes Filho, 2020). A espécie apresenta folhas compostas, flores vistosas e caule lenhoso, características comuns da família Bignoniaceae. A figura 6 evidencia as principais características físicas desta espécie bem como sua distribuição geográfica em território brasileiro.

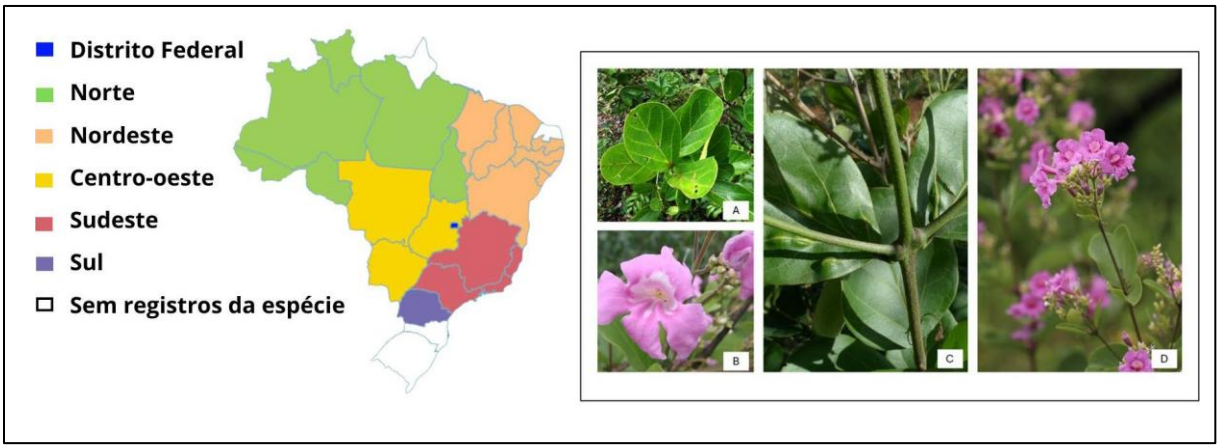

Figura 6. Distribuição geográfica e característica físicas da espécie *F. platyphylla*.
Fonte**:** Adaptado de Menezes Filho (2020). Legenda: A. folhas; b. flor; c. caule; d. *Fridericia platyphylla*.

Estudos fitoquímicos revelaram que diferentes partes da planta contêm metabólitos secundários de relevante atividade biológica, destacando-se os flavonoides, braquidinas e glicosídeos fenólicos (Silva, 2022; Bezerra *et al.*; Nunes, 2024). Os flavonoides, especialmente, possuem ação antioxidante significativa, enquanto as braquidinas exibem um comportamento redox capaz de modular processos inflamatórios e oxidativos, sugerindo um possível mecanismo de ação cardioprotetora (Bezerra *et al.*, 2024).

Os estudos farmacológicos com *F. platyphylla* indicam sua ampla aplicação terapêutica. Compostos presentes na planta demonstraram atividades antibacteriana, antifúngica, antiparasitária, antitumoral, analgésica e antiulcerogênica (Rocha, 2014; Queiroz *et al.*, 2014; Rocha *et al.,* 2017; Rodrigues *et al.*, 2017; Martins; Nascimento, 2019). Análises toxicológicas preliminares sugerem que o extrato não apresenta toxicidade significativa, tornando viável a sua exploração farmacêutica (Serpeloni *et al.*, 2020). No entanto, apesar do potencial cardioprotetor da espécie, ainda são necessários estudos adicionais que avaliem sua segurança e eficácia em modelos experimentais e clínicos, especialmente no contexto do infarto agudo do miocárdio (IAM). A caracterização estrutural detalhada dos metabólitos secundários é essencial para avanços no desenvolvimento de formulações farmacêuticas seguras e eficazes (Arbeláez *et al.*, 2018).

Nesse sentido, a espécie tem sido investigada por suas diversas propriedades, dentre elas sua atividade antiparasitária. Estudos demonstraram que extratos da planta apresentam atividade contra o *Trypanosoma cruzi*, agente etiológico da doença de Chagas, e contra espécies de Leishmania, causadoras da leishmaniose (Rocha *et al.*, 2014; Rocha *et al.*, 2018). Além disso, compostos halogenados derivados do extrato mostraram aumento da seletividade e atividade biológica, sugerindo potencial para tratamentos antiparasitários mais eficazes (Neuenschwander *et al.*, 2020). Estudos recentes apontam para a capacidade do extrato de inibir a atividade de lipoxigenases (LOXs), enzimas envolvidas na síntese de mediadores pró-inflamatórios, indicando ação anti-inflamatória relevante para estudo em diversas patologias (Bertanha *et al.*, 2020).

No campo da oncologia, pesquisas sugerem que metabólitos presentes na *F. platyphylla* podem possuir propriedades antitumorais (Franco *et al.*, 2021; Lima *et al.*, 2022). Estudos mostraram que a luteolina, flavonoide isolado da espécie, demonstrou atividade antiproliferativa contra glioblastomas, reduzindo a proliferação celular de forma mais eficaz do que o fármaco padrão temozolomida (Franco *et al.*, 2021). Outro estudo indica que braquidinas extraídas da planta apresentam citotoxicidade seletiva em células tumorais depróstata,

influenciando vias intracelulares como PI3K/AKT/mTOR. A caracterização molecular desses compostos evidencia sua potencial aplicação como novos agentes quimioterápicos (Serpeloni *et al.*, 2023).

A investigação de propriedades antimicrobianas também tem revelado achados promissores. Extratos de *F. platyphylla* exibiram efeito antifúngico contra cepas de Candida, incluindo *C. albicans, C. tropicalis* e *C. krusei*. Além disso, evidências indicam que seus compostos podem aumentar a eficácia de antibióticos contra bactérias resistentes, sugerindo potencial para desenvolvimento de terapias combinadas (Menezes Filho *et al.,* 2021; Porfiro, 2021). Os avanços na formulação farmacêutica da *F. platyphylla* também têm sido explorados. Estudo recente demonstrara que microemulsões incorporando flavonoides extraídos da planta apresentam liberação controlada e melhor estabilidade físico-química, indicando um sistema promissor para otimização da biodisponibilidade e eficácia terapêutica (Nascimento *et al.*, 2023). Ensaios de toxicidade realizados em modelos *in vitro* e *in vivo* confirmaram a segurança dessas formulações, destacando sua viabilidade para futuras aplicações clínicas (Resende *et al.*, 2017; Serpeloni *et al.*, 2020).

Apesar do amplo potencial farmacológico, ainda se faz necessária a realização de estudos complementares que avaliem a toxicidade crônica e os possíveis efeitos adversos de compostos isolados da *Fridericia platyphylla*. O desenvolvimento de formulações farmacêuticas otimizadas, aliado a estudos básicos rigorosos, permitirá a consolidação dessa espécie como uma relevante fonte de bioativos para aplicações terapêuticas futuras. Em um estudo ainda não publicado de nosso grupo, avaliamos a administração oral aguda de uma dose única de 2000 mg/kg do extrato hidroetanólico de *Fridericia platyphylla* (EHFP) e não foram observados sinais de toxicidade clínica ou alterações significativas nos parâmetros bioquímicos renais, hepáticos e cardíacos. Ainda, no que tange à análise da citotoxicidade do EHFP, feita através do ensaio utilizando o MTT, os dados obtidos mostraram que não houve inviabilidade das células expostas ao extrato, em nenhuma das concentrações testadas e em nenhum tempo de exposição, 24 horas e 48 horas. Esses resultados reforçam a segurança pré-clínica do extrato em estudos iniciais. A seguir, a Figura 6 evidencia os principais compostos investigados extraídos da espécie *F. platyphylla* e seus alvos terapêuticos mediante diferentes abordagens de estudos.

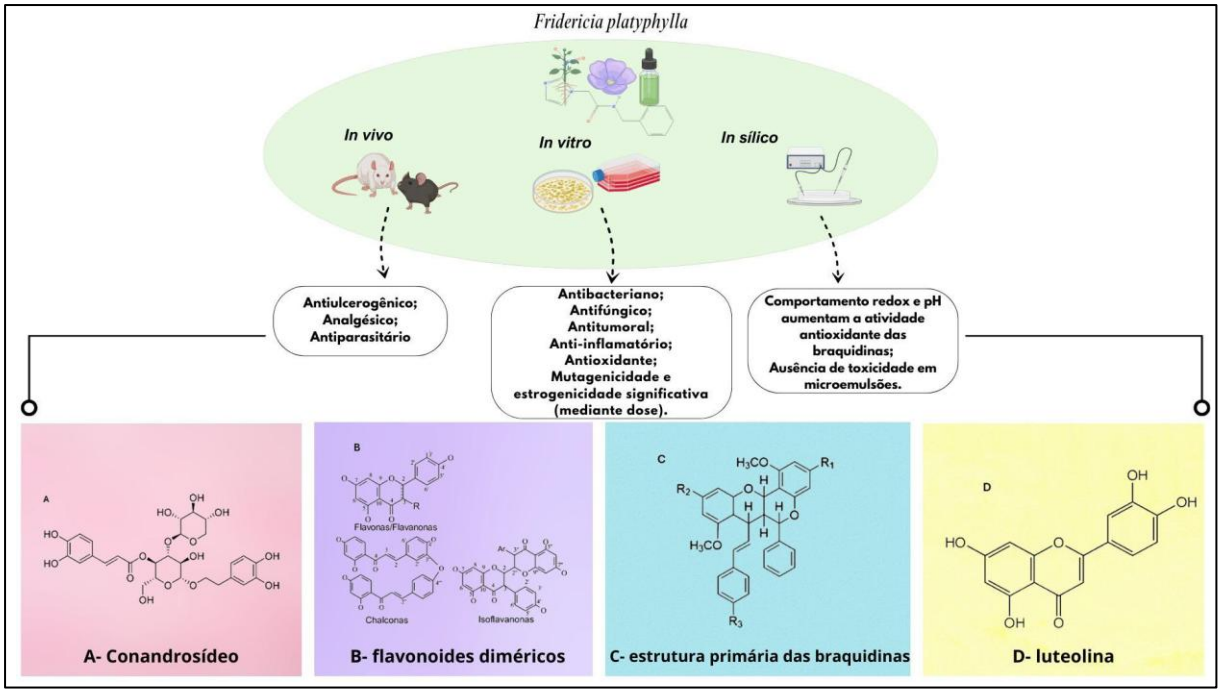

Figura 7. Compostos bioativos de *Fridericia platyphylla* e seus alvos terapêuticos em diferentes abordagens metodológicas.

Fonte**:** Elaborado pelo autor.

Diante desse panorama, a *Fridericia platyphylla* consolida-se como uma espécie de elevado interesse estratégico no contexto da bioprospecção de produtos naturais, reunindo diversidade química, segurança preliminar e amplo espectro de atividades biológicas (Resende *et al.*, 2017; Serpeloni *et al.*, 2020). A presença de flavonoides estruturalmente estáveis, compostos fenólicos bioativos e derivados com potencial de modulação redox confere à espécie um perfil multitarget, particularmente relevante para doenças multifatoriais, como as cardiovasculares, inflamatórias e neoplásicas. Além disso, a combinação entre evidências farmacológicas consistentes, avanços em sistemas de liberação controlada e resultados toxicológicos favoráveis fortalece sua aplicabilidade translacional (Resende *et al.*, 2017; Serpeloni *et al.*, 2020. Nesse sentido, a continuidade de estudos integrando caracterização fitoquímica avançada, validação farmacodinâmica e desenvolvimento tecnológico poderá posicionar a *F. platyphylla* como uma plataforma promissora para inovação farmacêutica baseada em biodiversidade brasileira.

3. OBJETIVOS

3.1 OBJETIVO GERAL

Realizar a bioprospecção farmacológica e tecnológica de *Fridericia platyphylla*, avaliando seu potencial cardioprotetor em modelo experimental de infarto induzido por isoproterenol, integrando evidências científicas e de inovação para o desenvolvimento de uma composição farmacêutica de aplicação cardiovascular.

3.2 OBJETIVOS ESPECÍFICOS

- Analisar o panorama de inovação associado à *Fridericia platyphylla*, identificando aplicações terapêuticas, avanços tecnológicos e lacunas no desenvolvimento científico e tecnológico da espécie.

- Sintetizar e avaliar criticamente as evidências científicas disponíveis sobre o potencial farmacológico de *Fridericia platyphylla*, considerando diferentes compostos, extratos e modelos experimentais.

- Investigar o potencial cardioprotetor de *Fridericia platyphylla*, por meio da análise integrada de desfechos fisiológicos, bioquímicos e estruturais em modelo experimental de injúria miocárdica.

- Integrar evidências experimentais, científicas e tecnológicas visando subsidiar o desenvolvimento de uma inovação farmacêutica com potencial aplicação na prevenção e/ou tratamento de desordens cardiovasculares.

CAPÍTULO 1

PROSPECÇÃO TECNOLÓGICA: PERSPECTIVAS NA UTILIZAÇÃO DE *Fridericia Platyphylla* PARA O TRATAMENTO DE DESORDENS CARDIOVASCULARES

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RESUMO

Introdução: As doenças cardiovasculares (DCVs) são uma das principais causas de morte globalmente, incluindo condições como hipertensão, insuficiência cardíaca e infarto. Estudos recentes têm explorado novas terapias, destacando o uso de compostos naturais de plantas. A *Fridericia platyphylla* mostrou potencial terapêutico para DCVs, devido às suas atividades antiinflamatória e vasorelaxante, sugerindo benefícios para a saúde cardiovascular. Objetivo: Avaliar as perspectivas do uso do extrato e/ou compostos isolados de *F. platyphylla* no tratamento de desordens cardiovasculares a partir de uma prospecção tecnológica. Metodologia: Foi realizada uma prospecção tecnológica baseada em pedidos de patentes nos bancos de dados do Instituto Nacional da Propriedade Industrial (INPI) do Brasil, European Patent Office (Espacenet), Google Patents, Derwent Innovations Index e World Intellectual Property Organization (WIPO). A pesquisa abrangeu patentes depositadas nos últimos 15 anos, utilizando descritores como *Fridericia platyphylla*, *Fridericia platyphylla AND extrato*, *Fridericia platyphylla AND doenças cardiovasculares*, *Arrabidaea brachypoda*, *Arrabidaea brachypoda AND extrato*, *Arrabidaea brachypoda AND doenças cardiovasculares* e seus correlatos em inglês. Resultados: A prospecção tecnológica de patentes entre 2008 e 2023 identificou 66 pedidos, com o maior número de depósitos ocorrendo em 2015, totalizando 20 patentes. A Universidade Estadual de Campinas (UNICAMP) foi a instituição com o maior número de patentes depositadas, seguida pela Universidade Federal do Maranhão e pela Universidade Estadual Paulista Julio de Mesquita Filho. Conclusão: Essas descobertas sugerem potencial terapêutico e tecnológico significativos na utilização do extrato de *F. platyphylla* e de seus compostos isolados, especialmente no contexto das doenças cardiovasculares.

Palavras-chave: *Fridericia platyphylla. Arrabidaea brachypoda*. Prospecção Tecnológica. Doenças Cardiovasculares.

ABSTRACT

Introduction: Cardiovascular diseases (CVDs) are among the leading causes of death globally, encompassing conditions such as hypertension, heart failure, and myocardial infarction. Recent studies have explored new therapies, highlighting the promising potential of natural plant compounds. *Fridericia platyphylla*, with its

anti-inflammatory and vasorelaxant activities, has shown significant therapeutic potential for CVDs. Objective: This study aimed to evaluate the potential use of *F. platyphylla* extract and/or isolated compounds in treatment of cardiovascular diseases based on a comprehensive technological prospecting study. Methodology: A technological prospecting study was conducted based on patent applications in the databases of the Brazilian National Institute of Industrial Property (INPI), European Patent Office (Espacenet), Google Patents, Derwent Innovations Index, and World Intellectual Property Organization (WIPO). The research covered patents filed over the past 15 years, using descriptors such as *Fridericia platyphylla, Fridericia platyphylla* AND extract, *Fridericia platyphylla* AND cardiovascular diseases, *Arrabidaea brachypoda, Arrabidaea brachypoda* AND extract, *Arrabidaea brachypoda* AND cardiovascular diseases, and their word's English equivalents. Results: The technological prospecting of patents between 2008 and 2023 identified 66 applications, with the highest filings in 2015, totaling 20 patents. The University of Campinas (UNICAMP) had the most patent filings, followed by the Federal University of Maranhão and São Paulo State University Julio de Mesquita Filho. Conclusion: These findings suggest therapeutic and technological potential in using F. platyphylla extract and its isolated compounds in treatment of cardiovascular diseases.

Keywords: *Fridericia platyphylla. Arrabidaea brachypoda*. Technological Prospecting. Cardiovascular Disease.

RESUMEN

Introducción: Las enfermedades cardiovasculares (ECV) son una de las principales causas de muerte a nivel mundial, incluyendo condiciones como hipertensión, insuficiencia cardíaca e infarto. Estudios recientes han explorado nuevas terapias, destacando el uso de compuestos naturales de plantas. *Fridericia platyphylla* ha demostrado potencial terapéutico para las ECV, debido a sus actividades antiinflamatorias y vasorrelajantes, lo que sugiere beneficios para la salud cardiovascular. Objetivo: Evaluar las perspectivas del uso del extracto y/o compuestos aislados de *F. platyphylla* en el tratamiento de trastornos cardiovasculares a partir de una prospección tecnológica. Metodología: Se realizó una prospección tecnológica basada en solicitudes de patentes en las bases de datos del Instituto Nacional de la Propiedad Industrial (INPI) de Brasil, la Oficina Europea de Patentes (Espacenet), Google Patents, Derwent Innovations Index y la Organización Mundial de la Propiedad Intelectual (WIPO). La investigación abarcó patentes depositadas en los últimos 15 años, utilizando descriptores como *Fridericia platyphylla*, *Fridericia platyphylla AND extracto, Fridericia platyphylla* AND enfermedades cardiovasculares*, Arrabidaea brachypoda, Arrabidaea brachypoda* AND extracto, *Arrabidaea brachypoda* AND enfermedades cardiovasculares y sus correlatos en inglés. Resultados: La prospección tecnológica de patentes entre 2008 y 2023 identificó 66 solicitudes, con el mayor número de depósitos ocurridos en 2015, totalizando 20 patentes. La Universidad Estatal de Campinas (UNICAMP) fue la institución con el mayor número de patentes depositadas, seguida por la Universidad Federal de Maranhão y la Universidad Estatal Paulista Julio de Mesquita Filho. Conclusión: Estos hallazgos sugieren un potencial terapéutico y tecnológico significativo en

la utilización del extracto de *F. platyphylla* y de sus compuestos aislados, especialmente en el contexto de las enfermedades cardiovasculares.

Palabras clave: *Fridericia platyphylla. Arrabidaea brachypoda*. Prospección Tecnológica. Enfermedades Cardiovasculares.

1 INTRODUÇÃO

Segundo a Organização Mundial da Saúde, as Doenças Cardiovasculares (DCVs) estão entre as principais causas de morte no mundo, correspondendo a 17,7 milhões de óbitos em 2017, o que representa 31% dos casos registrados a nível global (ORGANIZATION, 2016; ROETERS VAN LENNEP; TOKGÖZOĞLU; BADIMON; DUMANSKI *et al.*, 2023; TIMMIS; KAZAKIEWICZ; TORBICA; TOWNSEND *et al.*, 2023). No Brasil, estima-se que ao menos 20% dos óbitos na população acima dos 30 anos sejam causados pelas DCVs (MANSUR; FAVARATO, 2016; OPAS, 2019). Essas formam um grande grupo de patologias, no qual estão inclusas a hipertensão arterial sistêmica, insuficiência cardíaca, doença coronariana, doença arterial periférica, infarto agudo do miocárdio, entre outras doenças. Dessa maneira, diversos são os tratamentos e diretrizes empregados, com o objetivo de cura e sobrevida (GAIDAI; CAO; LOGINOV, 2023; MANSUR; FAVARATO, 2016; SHAITO; THUAN; PHU; NGUYEN *et al.*, 2020).

Diante da alta incidência dessas patologias e do significativo impacto na qualidade de vida da população afetada, há uma busca constante pelo desenvolvimento de novos agentes e alternativas terapêuticas eficazes. O objetivo é encontrar tratamentos que não apenas mantenham níveis pressóricos ideais, mas também ofereçam menor risco de efeitos adversos em comparação com as opções atualmente disponíveis no mercado. (DIACONU; DRAGOI; BRATU; NEAGU *et al.*, 2018). Nessa perspectiva, a utilização de compostos biologicamente ativos presentes nas plantas têm sido alvo de estudos científicos para identificação das moléculas e seus mecanismos de ação (COLALTO, 2018). Compostos que exibem boa atividade sobre o sistema cardiovascular e que possuam efeitos anti-hipertensivos têm demonstrado grande potencial no

tratamento das DCVs. Nesse contexto, plantas medicinais ricas em metabólitos secundários, como saponinas, terpenoides, alcaloides e polifenóis, emergem como fontes renováveis e valiosas de agentes terapêuticos para a prevenção de doenças cardiovasculares. (BARBOSA; FERNANDES, 2014).

Uma dessas espécies vegetais com potencial para uso no tratamento de DCVs é a *Fridericia platyphylla* (Cham.) L. G. Lohmann (sin. *Arrabidaea brachypoda*), pertencente a família Bignoniaceae e ao gênero *Fridericia Mart* e é conhecida popularmente por “cipó-una” ou “cervejinha do campo” (DE MENEZES FILHO; PORFIRO; DE SOUZA CASTRO, 2021). Estudos relataram que *F. platyphylla* apresenta atividades biológicas e farmacêuticas com ações antiinflamatória, antimicrobiana e antiprotozoária, assim como ações citotóxicas contra células cancerígenas do sistema gástrico, bem como ação analgésica, promovidas pelo extrato hidroetanólico de suas raízes (DE LIMA; CUBERO; FRANCO; RODRIGUES et al., 2022a; DE SOUZA MONTEIRO; DA SILVA COSTA; MARTINS; DA ROCHA et al., 2020; RESENDE; NOGUEIRA; ESPANHA; BOLDRIN et al., 2017; WENG; ZENG; WANG; GUO et al., 2024).

O estudo das folhas dessa espécie por nosso grupo de pesquisa sugere atividade antiespasmódica para o extrato hidroetanólico das folhas de F. platyphylla (EHFP) em jejuno isolado de rato, cuja ação se deu através da inibição do influxo de Ca2+ através de canais de cálcio voltagem dependentes (DE SOUZA MONTEIRO; DA SILVA COSTA; MARTINS; DA ROCHA *et al.*, 2020). Ainda, estudos preliminares mostram potencial vasorelaxante do extrato sobre anéis de aorta isoladas de ratos.

A espécie *Fridericia platyphylla* se destaca como uma candidata promissora para exploração terapêutica no contexto cardiovascular, dada sua relevância para a saúde pública e as limitações dos tratamentos farmacológicos atuais, como efeitos colaterais adversos e dificuldades no controle ideal da pressão arterial em diversos pacientes. Estudos preliminares já demonstraram atividades biológicas significativas, incluindo efeitos anti-inflamatórios, antimicrobianos, citotóxicos contra células cancerígenas e ação analgésica (DE LIMA; CUBERO; FRANCO; RODRIGUES *et al.*, 2022b; REZENDE-JÚNIOR; ANDRADE; LEAL; MESQUITA *et al.*, 2020; WENG; ZENG; WANG; GUO *et al.*,

2024). No sistema cardiovascular, seu potencial vasorelaxante pode ser especialmente benéfico no tratamento de condições como hipertensão e outras desordens cardiovasculares (DE SOUZA MONTEIRO; DA SILVA COSTA; MARTINS; DA ROCHA *et al.*, 2020).

Essa prospecção tecnológica sobre *F. platyphylla* não apenas amplia o conhecimento sobre os efeitos de seu extrato bruto e compostos isolados em doenças cardiovasculares, mas também oferece uma base para o desenvolvimento de medicamentos naturais com menos efeitos colaterais, apresentando alternativas terapêuticas acessíveis. Além disso, a exploração dessa planta valoriza a biodiversidade brasileira, gerando oportunidades para a biotecnologia e a indústria farmacêutica, promovendo tanto o avanço científico quanto aplicações clínicas e industriais. Portanto o objetivo deste trabalho é avaliar as perspectivas do uso do extrato e/ou compostos isolados de *F. platyphylla* no tratamento de desordens cardiovasculares a partir de uma prospecção tecnológica.

2 METODOLOGIA

2.1 ESTRATÉGIAS DE REVISÃO EM BANCO DE PATENTES

A presente prospecção tecnológica foi realizada com base nos pedidos de patente depositados no banco de dados brasileiro do Instituto Nacional da Propriedade Industrial (INPI) do Brasil, visando à análise das patentes depositadas em território nacional. Adicionalmente, também foram realizadas pesquisas nas bases de dados European Patent Office (Espacenet), Google Patents e na Derwent Innovations Index. Além disso, foi acessada a base de dados internacional World Intellectual Property Organization (WIPO), uma vez que esta possui maior abrangência de patentes. A busca foi limitada a patentes depositadas nos últimos 15 anos (2008-2023). Utilizou-se os seguintes descritores para busca: *Fridericia platyphylla; Fridericia platyphylla* AND extrato; *Fridericia platyphylla* AND doenças cardiovasculares; *Arrabidaea brachypoda*;

Arrabidaea brachypoda AND extrato; *Arrabidaea brachypoda* AND doenças cardiovasculares e seus correlatos em inglês.

3 RESULTADOS E DISCUSSÕES

A busca pelos efeitos biológicos de extratos e compostos bioativos isolados de *F. platyphylla*, em diferentes modelos experimentais, tem sido uma preocupação constante da comunidade científica, que se empenha na prospecção tecnológica para compreender os mecanismos farmacológicos associados a essa espécie (DA ROCHA; VILELA; CAVALCANTE; SANTA-CECÍLIA *et al.*, 2011; DE LIMA; CUBERO; FRANCO; RODRIGUES *et al.*, 2022b; DE SOUSA ANDRADE; DE OLIVEIRA; LEAL; DE ALCÂNTARA OLIVEIRA *et al.*, 2020). Desta forma, ressalta-se o elevado potencial antioxidante e antiinflamatório deste composto, destacando-se neste artigo prospecções tecnológicas que enfatizam seu possível impacto terapêutico no sistema cardiovascular.

Nesta perpectiva, vale destacar a prevalência da distribuição geográfica da espécie *Fridericia platyphylla* no Brasil. Na Figura 1 observa-se que sua distribuição é bastante homogênea nas diferentes regiões do país. Fato evidenciado pelas extensas áreas de cerrado, sendo o segundo maior bioma encontrado no território nacional. É notório que a espécie *F. platyphylla* possui grande abrangência a nível nacional, uma vez que habita majoritariamente áreas do Cerrado brasileiro, segundo maior bioma nacional, mas possuindo também exemplares ao redor de quase todo território brasileiro (DA ROCHA; VILELA; CAVALCANTE; SANTA-CECÍLIA *et al.*, 2011; DE LIMA; CUBERO; FRANCO; RODRIGUES *et al.*, 2022b). Essa observação é significativa, pois, se a *F. platyphylla* for validada como um agente eficaz contra DCVs, haverá uma demanda substancial por sua coleta e distribuição, potencializando seu desenvolvimento como medicamento.

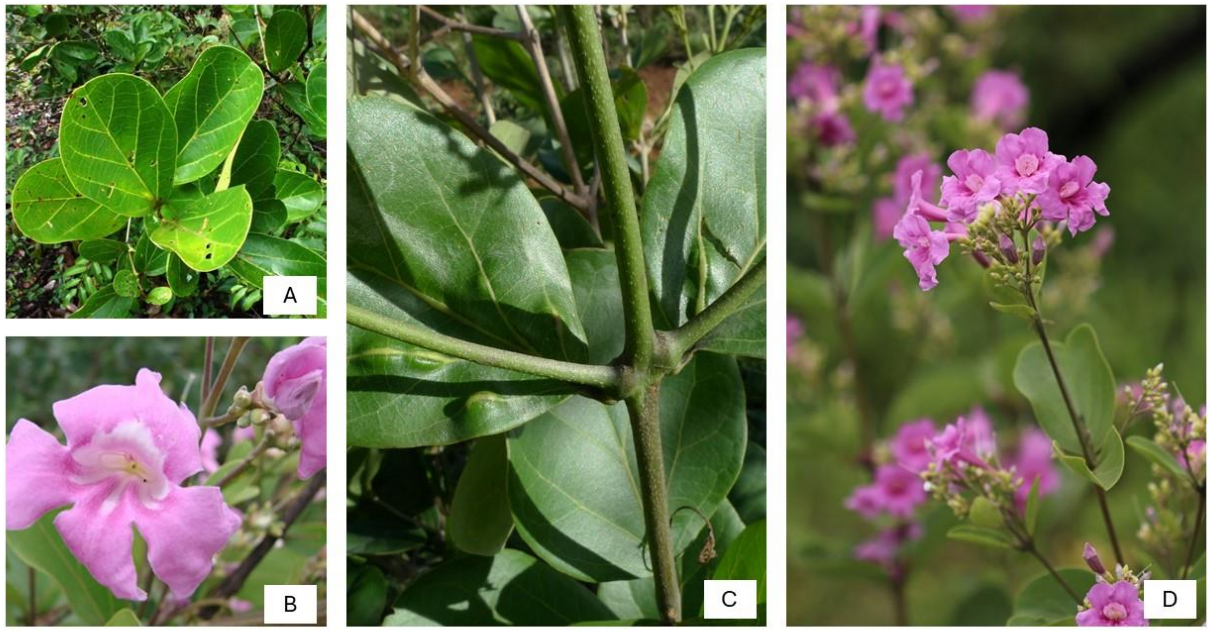
Figura 1. Distribuição geográfica de *Fridericia platyphylla* no Brasil

Legenda: Ocorrências confirmadas: Norte (Acre, Amazonas, Pará, Rondônia, Roraima, Tocantins); Nordeste (Alagoas, Bahia, Ceará, Maranhão, Paraíba, Pernambuco, Piauí, Sergipe); Centro-Oeste (Distrito Federal, Goiás, Mato Grosso do Sul, Mato Grosso); Sudeste (Espírito Santo, Minas Gerais, Rio de Janeiro, São Paulo); Sul (Paraná).
Fonte: http://floradobrasil.jbrj.gov.br

A Figura 2 evidencia as principais partes da espécie *F. platyphylla* utilizadas para obtenção de compostos bioativos, como flavonoides e taninos. Conforme se destaca nesta figura, diferentes partes da *F. platyphylla* podem ser utilizadas para a formulação farmacêutica (DE LIMA; CUBERO; FRANCO; RODRIGUES *et al.*, 2022b; DE SOUZA MONTEIRO; DA SILVA COSTA; MARTINS; DA ROCHA *et al.*, 2020; REZENDE-JÚNIOR; ANDRADE; LEAL; MESQUITA *et al.*, 2020). Os flavonoides são particularmente proeminentes, distribuídos em várias partes da planta: as flores contêm flavonoides, especialmente chalconas; as raízes apresentam flavonoides, triterpenos, saponinas, taninos e outros polifenóis; e as folhas são ricas principalmente em flavonoides. Esse perfil fitoquímico é de grande relevância, uma vez que plantas medicinais com alto teor de metabólitos secundários, como saponinas, terpenoides, alcaloides e polifenóis, são fontes renováveis de agentes terapêuticos importantes na prevenção de DCVs. Isso ressalta o potencial da *F.*

platyphylla para investigação dos seus efeitos no sistema cardiovascular (ALCERITO; BARBO; NEGRI; SANTOS *et al.*, 2002; DE SOUZA MONTEIRO; DA SILVA COSTA; MARTINS; DA ROCHA *et al.*, 2020).

Figura 2. Características físicas da espécie *Fridericia platyphylla*



Legenda: A. folhas; b. flor; c. caule; d. *Fridericia platyphylla*.
Fonte: Elaborado pelos autores deste artigo.

A análise de depósitos de patentes ao longo do tempo oferece uma visão valiosa sobre o progresso tecnológico e a inovação relacionada a determinadas espécies vegetais. No caso de *Fridericia platyphylla* e seu sinônimo *Arrabidaea brachypoda*, a investigação de patentes depositadas entre 2008 e 2023 revela tendências importantes no desenvolvimento de produtos e aplicações envolvendo essa espécie. A seguir, são apresentados os principais achados em relação ao número de patentes depositadas, sua distribuição entre diferentes bancos de dados e a evolução temporal dessas submissões.

Em relação as pesquisas em banco de dados de depósitos de patentes, foram identificados 66 pedidos depositados para a espécie *F. platyphylla* ou seu sinônimo *A. brachypoda* (Tabela 1). Vale ressaltar que o Google Patents apresentou o maior número de resultados (25), seguido do WIPO (20), Derwent

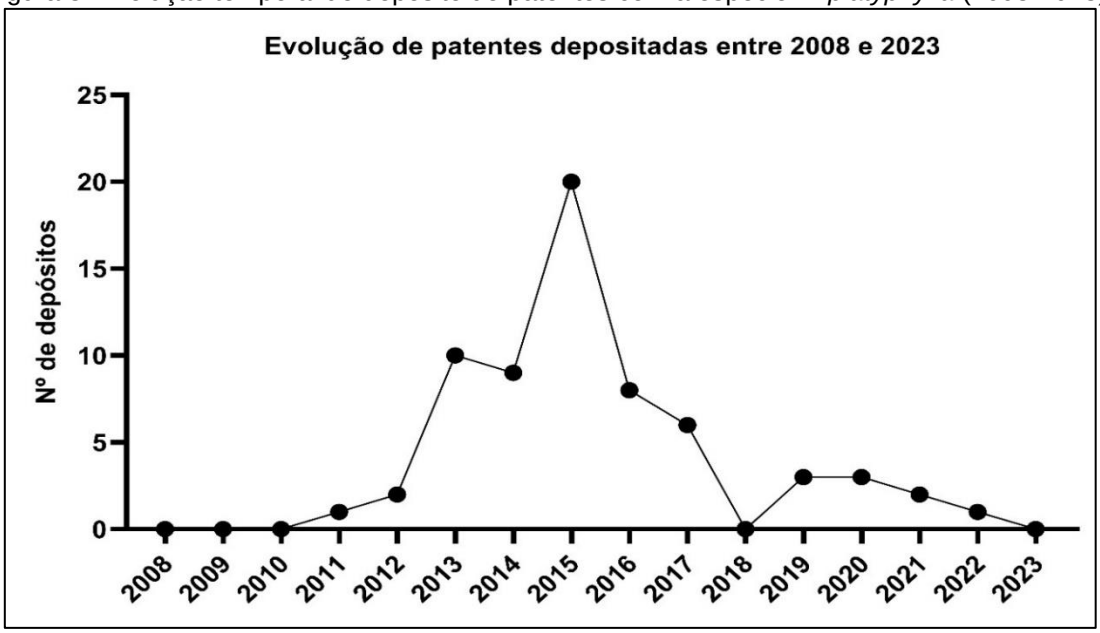
Innovations Index (11), INPI (05) e Spacenet (05). Em relação a evolução temporal das patentes depositadas observou-se que a maior demanda se deu no ano de 2015 com 20 patentes depositadas neste período, em 2018, no entanto, não houve nenhum registro de depósito (Figura 3).

Tabela 1. Busca em bases de patente de produtos depositados entre setembro de 2008 e agosto de 2023 com a espécie *F. platyphylla* ou seu sinônimo *A. brachypoda*

Descritores	**INPI**	**Spacenet**	**Google Patents**	**Derwent Innovations Index**	**WIPO**
Arrabidaea brachypoda	04	05	09	05	10
Arrabidaea brachypoda AND extrato	00	00	07	05	08
Arrabidaea brachypoda AND doenças cardiovasculares	00	00	00	00	00
Fridericia platyphylla	01	00	06	01	01
Fridericia platyphylla AND extrato	00	00	03	00	01
Fridericia platyphylla AND doenças cardiovasculares	00	00	00	00	00
Total: 66	05	05	25	11	20

Legenda: INPI: Instituto Nacional da Propriedade Industrial do Brasil; WIPO: World Intellectual Property Organization.
Fonte: Elaborado pelos autores deste artigo partir da base de dados INPI, Spacenet, Google Patents, Derwent Innovations Index e WIPO.

Figura 3. Evolução temporal de depósito de patentes com a espécie *F. platyphylla* (2008-2023).



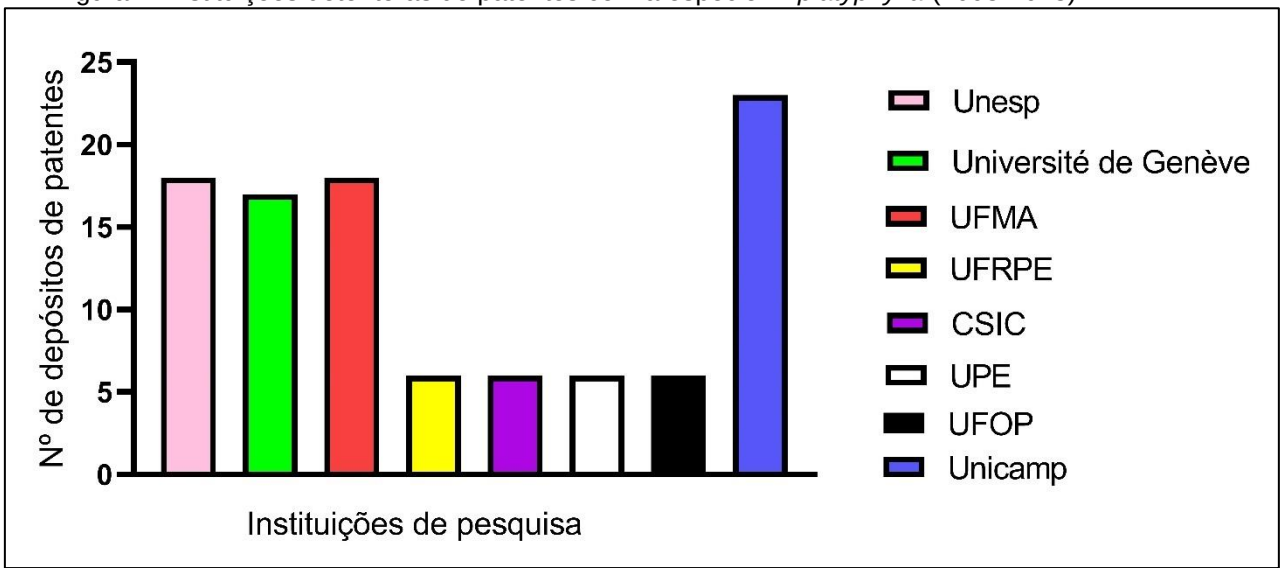
Fonte: Elaborado pelos autores deste artigo a partir da base de dados Google Patents

Interessantemente, entre os anos de 2012 e 2023, os depósitos de patente relacionados à espécie *F. platyphylla* (syn.: *A. brachypoda*)

apresentaram um aumento significativo, refletindo o potencial tecnológico da espécie, seja para potenciais aplicações farmacêuticas, nutracêuticas e/ou cosméticas de seus extratos e compostos isolados. Vale ressaltar que em 2015, houve um pico de número de patentes depositadas (n=20), com posterior redução nos anos subsequentes (Figura 3). O crescimento do número dos depósitos de patentes relacionados a espécie se dá em reflexo a avaliação do seu potencial antiinflamatório, antioxidante, antimicrobiano e/ou antiparasitário oriundos de estudos realizados em universidades brasileiras. Sugerindo um reconhecimento crescente do seu valor comercial e terapêutico (DA ROCHA; VILELA; CAVALCANTE; SANTA-CECÍLIA *et al.*, 2011; REZENDE-JÚNIOR; ANDRADE; LEAL; MESQUITA *et al.*, 2020; ROCHA; QUINTINO DA ROCHA; FERREIRA QUEIROZ; MARCOURT *et al.*, 2018; SERPELONI; RIBEIRO; WEISS; DE OLIVEIRA *et al.*, 2023)

Adicionalmente, foi observado que a Universidade Estadual de Campinas (UNICAMP) apresentou o maior número de patentes depositadas no período, seguida da Universidade Federal do Maranhão e Universidade Estadual Paulista Julio de Mesquita Filho (Figura 4).

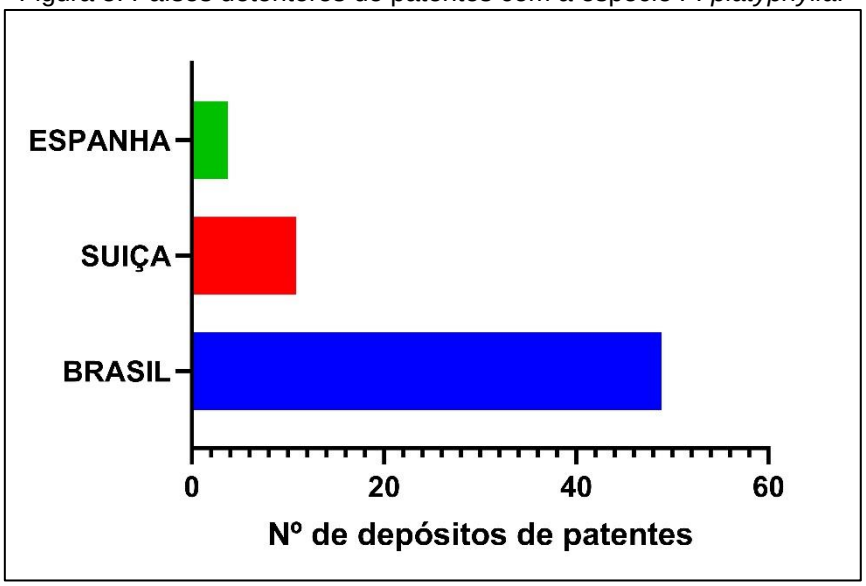
Figura 4. Instituições detentoras de patentes com a espécie *F. platyphylla* (2008-2023).



Legenda: Unesp: Universidade Estadual Paulista Julio de Mesquita Filho; UFMA: Universidade Federal do Maranhão; UFRPE: Universidade Federal Rural de Pernambuco; CSIC: Consejo Superior de Investigaciones Cientificas; UPE: Universidade de Pernambuco; UFPO: Universidade Federal de Ouro Preto; Unicamp: Universidade Estadual de Campinas.
Fonte: Elaborado pelos autores deste artigo a partir da base de dados Google Patents.

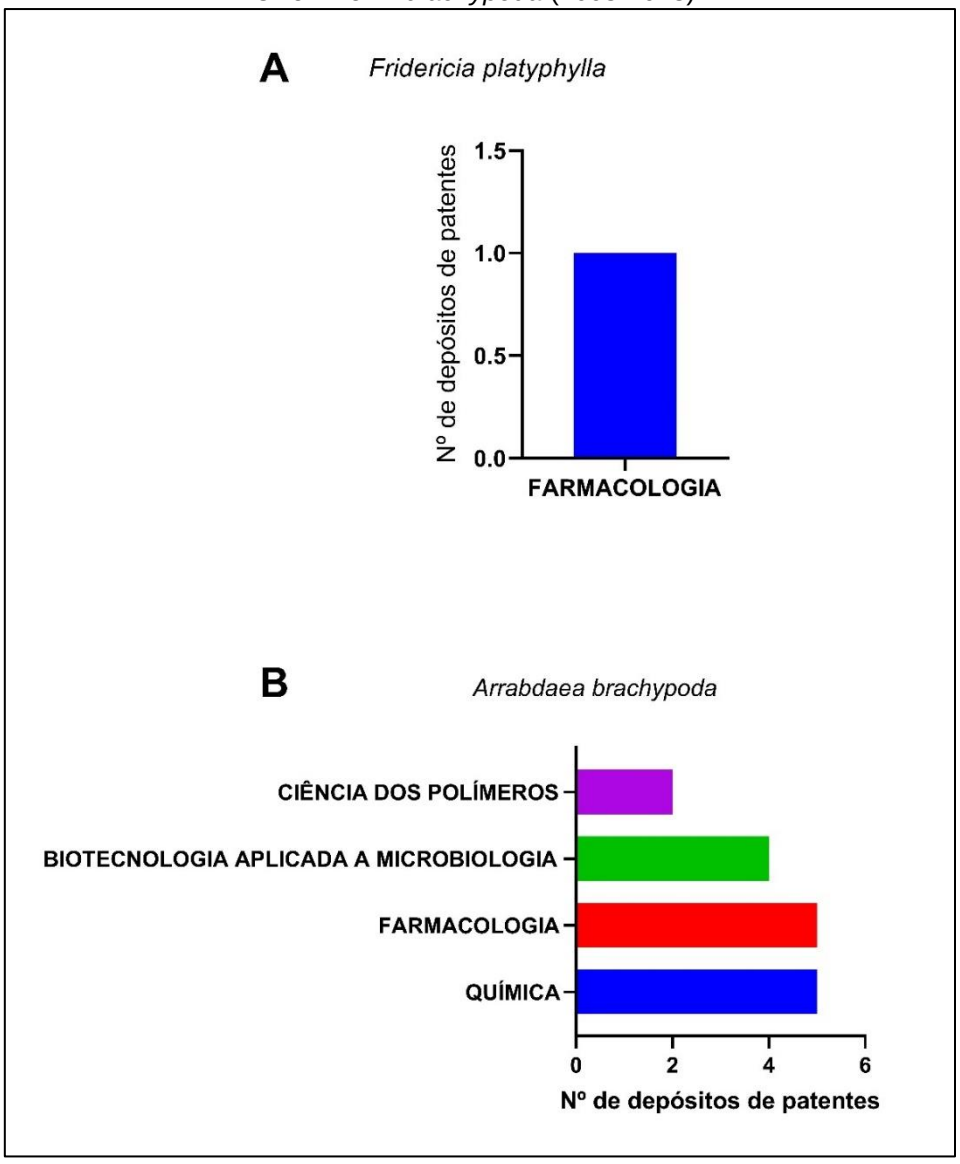
A distribuição geográfica e as áreas de concentração dos depósitos de patentes refletem a importância científica e econômica de uma espécie em diferentes regiões e setores. No caso da *Fridericia platyphylla*, o Brasil destaca-se como o país com o maior número de patentes depositadas, seguido por Suiça e Espanha com números comparativamente menores em relação ao primeiro (Figura 5). Quanto as áreas de concentração de depósitos de patentes, têm-se as áreas da química e farmacologia com maior número de depósitos relacionadas a nomenclatura *A. brachypoda*, seguidos por biotecnologia aplicada a microbiologia e ciência dos polímeros. Em relação a atual nomenclatura, sendo esta *F. platyphylla,* observa-se apenas 1 depósito na área da farmacologia (Figura 6).

Figura 5. Países detentores de patentes com a espécie *F. platyphylla.*



Fonte: Elaborado pelos próprios autores a partir da base de dados Google Patents.

Figura 6. Áreas de concentração de depósitos de patentes com a espécie *F. platyphylla* ou seu sinônimo *A. brachypoda* (2008-2023).



Fonte: Elaborado pelos autores deste artigo a partir da base de dados Derwent Innovations Index.

A discussão sobre o depósito de patentes relacionadas à espécie *F. platyphylla* revela um panorama interessante sobre a utilização desta planta em diferentes campos de pesquisa e desenvolvimento tecnológico. No Brasil, o maior número de patentes depositadas sugere um foco significativo na exploração e aplicação desta espécie, o que pode ser atribuído à biodiversidade rica e ao potencial farmacológico das plantas nativas do país (AGUIAR; SCARANO; BOZELLI; BRANCO *et al.*, 2023). Em contrapartida, Suiça e Espanha apresentam números de depósitos de patentes significativamente

menores, o que pode indicar diferenças na disponibilidade de recursos naturais comparáveis.

A análise das áreas de concentração dos depósitos de patentes com esta espécie mostra uma predominância da química e farmacologia. Esta tendência reflete o interesse na exploração dos compostos bioativos desta planta e suas propriedades terapêuticas ou aplicabilidade na produção de novos fármacos. O fato de a biotecnologia aplicada à microbiologia e ciência dos polímeros também estar entre as áreas com número considerável de depósitos sugere uma abordagem multifacetada na exploração das propriedades da espécie, abrangendo desde o desenvolvimento de novos materiais até a modificação genética ou uso de microrganismos para ampliação do seu potencial de aplicação. Vale ressaltar que as patentes depositadas estão, principalmente, na subclasse A61K (preparações para finalidades médicas, odontológicas ou higiênicas).

A identificação das propriedades farmacológicas de uma espécie e seu potencial para aplicações terapêuticas é um aspecto crucial na inovação biotecnológica. A seguir, são apresentados os principais depósitos de patentes relacionados a *Fridericia platyphylla*, destacando as propriedades farmacológicas de maior interesse, conforme evidenciado na Tabela 2.

Tabela 2. *Registros de patentes* com a espécie *F. platyphylla* ou seu sinônimo *A. brachypoda*

Título	**Instituição/PAÍS**	**Data de depósito**	**Nº de registro**
Compostos obtidos a partir de extratos da *Arrabidaea brachypoda* e composições farmacêuticas compreendendo os mesmos	Univ. Estadual Paulista Julio/BRASIL; Univ. Geneve/SUIÇA	10/12/2014	BR1320140308678E2
Uso de compostos obtidos a partir de extratos da *Arrabidaea brachypoda* como antiparasitário	Univ. Estadual Paulista Julio/BRASIL; Univ. Geneve/SUIÇA	12/12/2013	BR1020130319279A2
Uso de compostos produzidos a partir de extratos de *Arrabidaea brachypoda* como agentes antiulcerogênicos.	Univ. Estadual Paulista Julio/BRASIL; Univ. Geneve/SUIÇA; Unicamp/BRASIL	12/12/2013	BR102013031926A
Composição farmacêutica do extrato em pó de cipó-una (*Fridericia platyphylla*) na reparação de fraturas ósseas	Universidade Federal do Maranhão/BRASIL	08/08/2019	BR102019016399A2

Fonte: Elaborado pelos próprios autores a partir da base de dados Derwent Innovations Index.

A investigação das patentes destacadas na Tabela 2, envolvendo a espécie *Fridericia platyphylla* ou seu sinônimo *Arrabidaea brachypoda*, destaca a relevância dessa planta no contexto nacional, refletida em múltiplos estudos voltados para a avaliação de seus efeitos. A primeira patente, intitulada "Compostos obtidos a partir de extratos da *Arrabidaea brachypoda* e composições farmacêuticas compreendendo os mesmos," busca compreender os compostos bioativos presentes na planta. Para isso, foram realizadas diversas análises químicas, resultando na obtenção de extratos e formulações farmacêuticas, visando um entendimento mais aprofundado das propriedades terapêuticas da espécie.

A segunda patente intitulada “Uso de compostos obtidos a partir de extratos da *Arrabidaea brachypoda* como antiparasitário” abrange o uso de compostos derivados dos extratos de *A. brachypoda* como agentes antiparasitários. Parasitas como os causadores da malária e da doença de Chagas são responsáveis por patologias de alto risco de mortalidade, especialmente em regiões tropicais, como o Brasil. Essas doenças têm graves implicações cardiovasculares: a malária pode comprometer o endotélio e afetar a coagulação sanguínea, enquanto a doença de Chagas frequentemente leva à cardiomiopatia chagásica, manifestada por arritmias, insuficiência cardíaca, dilatação cardíaca e tromboembolismo. Assim, o uso de antiparasitários é crucial no controle desses patógenos. A patente investigou a atividade farmacológica de extratos e compostos de *A. brachypoda* contra *Plasmodium falciparum* (malária), *Trypanosoma cruzi* (doença de Chagas) e *Leishmania amazonensis* (leishmaniose), demonstrando que dois compostos apresentaram potente atividade antiparasitária, comparável ao benznidazol, medicamento de referência.

Já a terceira patente que se intitula “Uso de compostos produzidos a partir de extratos de *Arrabidaea brachypoda* como agentes antiulcerogênicos”, explora o uso de compostos derivados dos extratos de *A. brachypoda* como agentes antiulcerogênicos, sugerindo uma possível ação anti-inflamatória desses compostos. A atividade antiulcerogênica está frequentemente relacionada à capacidade de um agente de reduzir a inflamação e proteger as células da

mucosa gástrica contra danos causados por estresse oxidativo e inflamação. A inflamação crônica no trato gastrointestinal pode ser exacerbada pelo uso prolongado de medicamentos anti-inflamatórios não esteroides (AINEs), frequentemente prescritos para pacientes com doenças cardiovasculares. Portanto, a introdução de um agente anti-inflamatório natural que também ofereça proteção gástrica pode ser uma adição valiosa à terapia, minimizando os efeitos colaterais gastrointestinais associados ao uso de AINEs e melhorando a qualidade de vida dos pacientes.

Nesse sentido, o aspecto anti-inflamatório da patente é particularmente relevante no contexto de desordens cardiovasculares, onde a inflamação desempenha um papel central na patogênese e progressão de condições como aterosclerose, infarto do miocárdio e insuficiência cardíaca. A capacidade de reduzir a inflamação sistêmica pode, portanto, ter um impacto direto na melhoria dos resultados clínicos desses pacientes. Além disso, um agente anti-inflamatório derivado de plantas, com efeitos colaterais potencialmente menores em comparação aos antiinflamatórios não esteroides (AINEs) tradicionais, oferece uma alternativa promissora para o manejo de inflamações em pacientes com risco cardiovascular elevado.

Quanto a quarta e última patente destacada intitulada “Composição farmacêutica do extrato em pó de cipó-una (*Fridericia platyphylla*) na reparação de fraturas ósseas”, se refere à composição farmacêutica do extrato em pó de *F. platyphylla* para a reparação de fraturas ósseas, que também pode estar intrinsecamente ligada a efeitos anti-inflamatórios. A inflamação é uma resposta inicial essencial no processo de reparação óssea, mas a resolução eficiente dessa inflamação é crucial para a cicatrização adequada. Se o extrato de *F. platyphylla* possui propriedades que modulam a inflamação durante a reparação óssea, ele pode não apenas acelerar o processo de cicatrização, mas também reduzir complicações associadas, como a inflamação crônica e a dor prolongada.

Vale ressaltar que não se encontrou nenhuma patente voltada exclusivamente para análise direta dos efeitos cardioprotetores da planta. No entanto, a exploração das propriedades antiparasitárias e anti-inflamatórias de *F. platyphylla* podem levar ao desenvolvimento de novas terapias integradas que

não apenas tratam a inflamação e os patógenos de forma eficaz, mas também oferecem proteção adicional contra as complicações gastrointestinais, ósseas e cardiovasculares frequentemente encontradas em populações vulneráveis. Isso reforça a relevância da planta, a qual possui ainda diversos campos a serem estudados, e a importância de uma abordagem multifacetada no desenvolvimento de medicamentos para obtenção de tratamentos mais seguros e eficazes para desordens cardiovasculares e outras condições crônicas.

4 CONCLUSÃO

O presente estudo teve como objetivo avaliar as perspectivas do uso do extrato bruto e compostos isolados de *Fridericia platyphylla* no tratamento de desordens cardiovasculares, por meio de uma abordagem de prospecção tecnológica. Os achados indicam o elevado potencial terapêutico dessa espécie, particularmente em relação ao sistema cardiovascular, atribuível às suas propriedades anti-inflamatórias, antioxidantes e vasorelaxantes. Esses resultados sugerem que a espécie *F. platyphylla* representa uma fonte promissora para o desenvolvimento de novas terapias, com potencial para originar fármacos eficientes e minimizando efeitos adversos frente aos tratamentos atuais disponíveis.

Vale destacar que a relevância social deste estudo está na possibilidade de oferecer alternativas terapêuticas importantes para a saúde pública, ao mesmo tempo em que promove o uso sustentável da biodiversidade brasileira. No âmbito acadêmico, este estudo contribui significativamente para a ampliação do conhecimento sobre os compostos bioativos de plantas nativas e seus mecanismos de ação no sistema cardiovascular, estimulando o desenvolvimento de novas linhas de pesquisa e produtos farmacêuticos. Paralelamente, o crescente interesse por substâncias naturais reforça o impacto positivo que esses compostos podem ter no avanço da ciência e da inovação tecnológica no setor farmacêutico.

No entanto, esta pesquisa apresenta algumas limitações. A maioria dos estudos disponíveis até o momento são preliminares e baseados em

experimentos in vitro, o que limita a extrapolação dos resultados para a prática clínica. Assim, é imperativo que futuras investigações incluam estudos in vivo e ensaios clínicos rigorosos para confirmar a eficácia e segurança dos compostos isolados de F. platyphylla no tratamento de desordens cardiovasculares. Ademais, recomenda-se a prospecção de novas moléculas bioativas dessa espécie, além da análise das possíveis interações com outros fármacos, visando à ampliação da aplicabilidade clínica e à garantia da segurança terapêutica em diferentes contextos.

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CAPÍTULO 2

THERAPEUTIC POTENTIAL OF *Fridericia Platyphylla*: AN INTEGRATIVE REVIEW OF THE EFFECTS OF CRUDE EXTRACTS AND ISOLATED PHYTOCHEMICALS IN DIFFERENT EXPERIMENTAL MODELS

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Andressa Coelho Ferreira*; Raphael Furtado Marques; Ícaro Rodrigo Dutra Cunha; Jhonata Costa Moura; Rebekha Matos Oliveira; Kellen de Jesus Farias da Luz; Ludmila Tavares dos Santos Silva; Mateus Balbino Barbosa de Carvalho; Lara Possapp Andrade; Júlia Karla de

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Review

Therapeutic Potential of *Fridericia platyphylla* (Cham.) L.G. Lohmann: An Integrative Review of the Effects of Crude Extracts and Isolated Phytochemicals in Different Experimental Models

Published as part of ACS Omega special issue "Chemistry in Brazil: Advancing through Open Science".

Andressa Coelho Ferreira,* Raphael Furtado Marques, Icaro Rodrigo Dutra Cunha, Jhonata Costa Moura, Rebekha Matos Oliveira, Kellen De Jesus Farias Da Luz, Ludmila Tavares dos Santos Silva, Mateus Balbino Barbosa de Carvalho, Lara Possapp Andrade, Júlia Karla de Albuquerque Melo Xavier, Joel Felix Silva Diniz Filho, Cláudia Quintino Rocha, and Rachel Melo Ribeiro*

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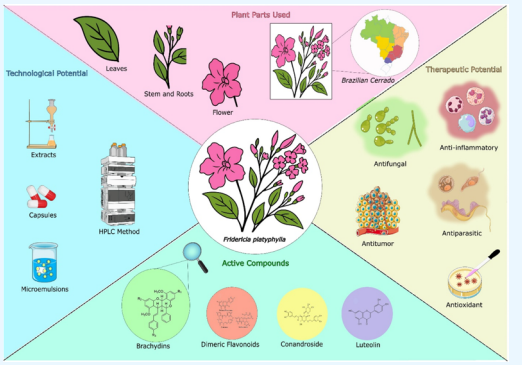
ABSTRACT: *Fridericia platyphylla* (Cham.) L.G. Lohmann is a species endemic to the Brazilian Cerrado, commonly known as "cervejinha do campo," "cipó-una," or 'tintureiro," traditionally used to treat kidney stones and joint pain. This species has garnered scientific interest due to its potential pharmacological properties. This review evaluated the pharmacological effects of crude extracts and isolated compounds from *F. platyphylla*, as well as its ethnopharmacological relevance. A comprehensive literature search was conducted across PubMed, Scielo, and Google Scholar for studies published between October 2014 and December 2024, using the descriptors "*F. platyphylla*" and "*A. brachypoda*" combined with terms related to *in vivo*, *in vitro*, and ethnopharmacological research. Of 896 records, 20 studies met the inclusion criteria. The included studies conducted comprehensive isolation and structural elucidation of the bioactive compounds, confirming their chemical identities and supporting their pharmacological relevance through robust analytical and spectroscopic validation. Different extracts and isolated compounds from the roots, leaves, and flowers of *F. platyphylla* have antiulcerogenic, antitumor, antiproliferative, anti-inflammatory, and antifungal action. Brachydins demonstrated cytotoxicity against prostate cancer cells and exhibited biological potential against intracellular amastigotes of *Trypanosoma cruzi*. Luteolin reduced proliferation in U-251 glioblastoma cells with low toxicity to nontumor cells. Additionally, the microemulsion and encapsulation of the active fraction obtained from the roots of this plant showed relevant biological activity for pharmaceutical applications. However, despite these promising findings, potential mutagenic effects raise concerns about the safety of using the plant. In conclusion, *F. platyphylla* and its phytochemicals hold significant therapeutic and technological potential. Nevertheless, further *in vivo* studies are necessary to ensure safety and better understand its pharmacological mechanisms, thereby paving the way for the development of novel therapeutic agents derived from this species.



1. INTRODUCTION

Plant species rich in flavonoids have proven to be a potential alternative in bioprospecting for bioactive compounds that act in various pathologies, as these species possess anti-inflammatory, antioxidant, and antimicrobial properties.[1−4] One of these plant species with potential for therapeutic use is *Fridericia platyphylla* (Cham.) L.G. Lohmann or its synonym *Arrabidaea brachypoda* (DC.) Bureau, also popularly known as "cervejinha do campo", "cipó-una", or "tintureiro".[1,5,6]

The genus Fridericia Mart., Bignoniaceae, comprises climbing plants native to Tropical America, ranging from Mexico to Argentina, with several species found predominantly in the Brazilian Cerrado. These plants have been traditionally used for diverse therapeutic purposes, including astringent, antioxidant, anti-inflammatory, antimicrobial, antitumor, and

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Table 1. Plant Part-Based Analysis of Phytochemical Composition, Detection Methods, and Biological Activities[a]

plant part	extraction method	structural elucidation and analytical parameters*	bioactive compounds	concentration–effect parameters	biological activity (highlights)	references
Roots	Percolation at room temperature with ethanol: water (7:3). Extracts were fractionated with dichloromethane (CH_2Cl_2) and methanol: water (7:3)	The active compounds were identified as dimeric flavonoids (brachydin A, B, and C). MPLC; Injection volume not specified; Stationary phase C18 (460 × 70 mm^2, 15–25 μm); Mobile phase: MeOH + 0.002% HCOOH in H_2O; Flow rate: 3.5 mL/min; Gradient: 5–100% MeOH over 50 h; with structures elucidated using HPLC-PDA, UV–vis, ^1H and ^{13}C NMR, COSY, NOESY, HSQC, HMBC, HRMS, Acetyl derivatization.	Brachydin B	**Concentration**: 0.24–20 μM	Focus on the antiparasitic effect against *Trypanosoma cruzi* in both *in vivo* and *in vitro* models	Rocha et al.
		Control not specified	Brachydin C	**Analysis Software**: GraphPad Prism v5.01.		
				Positive Control: Benznidazole (IC_{50} = 11.3 μM)	*In vitro*: based on parasite viability against *T. cruzi*. Parasites were incubated with test compounds for 24 h at 37 °C and 5% CO_2. Viability was assessed by direct counting in a Neubauer chamber	
				Brachydin B: IC_{50} = 5.3; **Brachydin C**: IC_{50}= 6.6 μM	*In vivo* (parasitized mice)	
				Replicates: Triplicate assays.	*in vitro:* LC_{50} = 15.6 μM (brachydin B), 17.3 μM (brachydin C); *in vivo* (mice): 100 mg/kg brachydin B reduced parasitemia by 92%, no apparent toxicity	
	Percolation (300 g of roots) at room temperature with ethanol/water (7:3)	09 compounds were isolated, including two phenylethanoid glycosides and seven glycosylated dimeric flavonoids, designated as brachydins D to J	N.A.	**Concentration**: 10–300 mg/kg—gavage; main effects observed at 300 mg/kg	Focus on gastroprotective effect *in vivo* model	Rocha et al.
		MPLC and HPLC-PDA-MS was performed; Injection volume not specified; Stationary phase: C18 (460 × 49 mm, 15–25 μm); Mobile phase: MeOH in H_2O + 0.002% HCOOH over 30 h; Flow rate: 10 mL/min; Gradient: 10–100% MeOH in H_2O + 0.002% HCOOH over 30 h; with structures elucidated using HPLC-PDA, UV–vis, NMR (^1H, ^{13}C, COSY, NOESY, HSQC, HMBC), HRMS, and ECD spectroscopy		**Analysis Software**: GraphPad Prism v5.01.	No signs of toxicity after 7 and 14 days of treatment; no adverse effects on organ weights or body weight progression	
		Control not specified		**Replicates**: 5–6 assays		
	Percolation (300 g of roots) at room temperature. with ethanol/water (7:3)	The active compounds were identified as dimeric flavonoids (brachydin A, B and C)	N.A.	**Concentrations**: 10, 30, and 100 mg/kg (oral); Main effect at 30 mg/kg	focus on nociceptive and mechanistic pain assays	Rodrigues et al.
		HPLC–PDA was performed; Injection volume: 10 μL		**Analysis Software**: GraphPad Prism v5.00.	*In vitro*: No signs of toxicity Immediate postdose. No signs of toxicity were observed at doses up to 300 mg/kg. Rotarod test confirmed absence of sedation or motor impairment. The extract was considered behaviorally safe under the tested conditions	
		Stationary phase: XBridge C18 (250 × 4.6 mm, 5 μm); Mobile phase: MeOH + 0.002% HCOOH (A) and H_2O + 0.002% HCOOH (B); Gradient: 5–100% A over 60 min +10 min hold; Flow rate: 1 mL/min; with structures elucidated using HPLC-PDA, UV–vis (210 and 254 nm)		**Replicates**: Not performed. Each experimental group consisted of 8–10 mice.		
		Control not specified				
	Percolation (amount not specified) at room temperature with ethanol/water (7:3). Extracts were fractionated with dichloromethane (CH_2Cl_2)	The active compounds were identified as dimeric flavonoids (brachydin A, B and C).	Brachydin B	**Concentrations**: Against promastigote form: 0.25–20 μM (72 h); Against amastigotes form: 0.24–20 μM (72 h)	Focus on antiparasitic effect against *Leishmania amazonensis in vitro* model	Rocha et al.

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Table 1. continued

plant part	extraction method	structural elucidation and analytical parameters*	bioactive compounds	concentration–effect parameters	biological activity (highlights)	references
		UHPLC-HRMS was performed; Column and injection volume not detailed; purity confirmed by MS-based profiling; purity >98%; with structures elucidated using		IC_{50} for brachydin B: 2.2 ± 0.09 μM (amastigotes); **Analysis Software**: GraphPad Prism v5.01.	*In vitro:* No cytotoxic effects were observed in host macrophages at concentrations up to 50 μM, as confirmed by Alamar Blue viability assay and automated nuclear staining (Hoechst 33342). Menadione was used as a positive control.	
		UHPLC-HRMS, UV–vis (Alamar Blue at 570 and 600 nm); High-Content Imaging (Hoechst 33342 fluorescence); ^{1}H, ^{13}C NMR and HRMS		**Replicates**: Quadruplicate assays.		
		Control not specified				
	Percolation at room temperature with ethanol/water (7:3)	10 compounds were isolated and identified as dimeric flavonoids (brachydins A to J)	N.A.	**Concentrations**: Hydroethanolic extract. Viability assays: 5–100 mg/mL	Intracellular ROS detection using CM-H2DCFDA; concentrations: 5, 30, and 60 mg/mL; time points: 1–24 h; no significant ROS modulation	Serpeloni et al.
		LC-MS dereplication was performed; column and injection volume not specified; comparison with previously characterized hydroethanolic extract. In addition, the structures were elucidated using LC-MS dereplication through detection of specific $[M - H]^-$ ions in the m/z range of 573–603, consistent with previously isolated dimeric flavonoids		EC_{50}: 56.16 μg/mL (GAS), 43.68 μg/mL (ACP02), 42.57 μg/mL (HepG2)	*In vitro*: Cytotoxicity was evaluated using multiple assays: MTT assay (570 nm) and Neutral Red uptake assessed cell viability; LDH release assay (340 nm) measured membrane damage; AO/EB fluorescence microscopy (515–560 nm) and Annexin V/PI flow cytometry distinguished apoptotic and necrotic cells. The extract showed selective cytotoxicity toward tumor cells, with necrosis at 30–60 mg/mL, increased NBUDs, and downregulation of BCL-XL, BIRC5, and MET, suggesting genomic instability and impaired cell survival mechanisms	
		Control not specified		**Analysis Software**: GraphPad Prism v5.01. **Replicates**: Triplicate assays.		
	Percolation at room temperature with 70% EtOH. Further liquid–liquid partitioning was done using CH_2Cl_2 and MeOH-H_2O (7:3)	The active compounds were identified as brachydin A, B and C and halogenated brachydins	Halogenated brachydins	**Concentrations**: Compounds were tested at concentrations of 1.25, 2.5, 5, and 10 μM for IC_{50} determination, and 100 μM for cytotoxicity screening. IC_{50} values against L. amazonensis amastigotes were 1.0 ± 0.3 μM (4,9,11-Tribromobrachydin C) and 1.2 ± 0.4 μM (11-Chlorobrachydin C); against *T. cruzi* amastigotes, 1.4 μM for both compounds 4,11-Dibromobrachydin C, 4-Iodobrachydin B, 11-Chorobrachydin B, and 11-Chlorobrachydin C. CC_{50} for macrophages was >100 μM in all cases. Selectivity indices ranged from >71 to >100 . **Positive control**: Amphotericin B and benznidazole.	Focus on antiparasitic potential	Neuenschwander et al.
		UHPLC-PDA-ELSD-MS and HPLC-PDA. Full scan: 150–1000 m/z. Injection volume: 4 μm (UHPLC), 20 μL (HPLC). Stationary phase: BEH C18 (50 × 2.1 mm^2, 1.7 μm) for UHPLC, PF C18 HQ (250 × 4.6 mm, 10 μm) for HPLC. Mobile phase: MeCN/H_2O both with 0.1% formic acid. Gradient (UHPLC): 5–98% MeCN in 4.0 min, held 0.8 min, re-equilibrated; flow rate: 600 μL/min (UHPLC), 1 mL/min (HPLC). UV detection at 254 and 280 nm; with structures elucidated using UHPLC-PDA-ELSD-MS, HRESIMS, and 1D/2D NMR (^{1}H, ^{13}C, HMBC, ROESY). Halogenation patterns were		**Analysis software**: Not specified.	*In vitro*: Based on viability of mouse peritoneal macrophages exposed to halogenated biflavonoids derived from A. brachypoda. Cytotoxicity was assessed by resazurin metabolism assay (AlamarBlue). None of the tested compounds (4–19) showed toxicity at the maximum concentration of 100 μM; CC_{50} values were all >100 μM	

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Table 1. continued

plant part	extraction method	structural elucidation and analytical parameters*	bioactive compounds	concentration–effect parameters	biological activity (highlights)	references
		confirmed by aromatic shift analysis and HMBC/ROESY correlations				
		Control not specified		**Replicates**: Assays were performed in triplicate (three biological replicates).		
	Hydroethanolic extraction (70% ethanol), followed by fractionation with dichloromethane. Compounds were diluted in DMSO and PBS to a final concentration of 0.5% DMSO for cell culture assays	The active compounds were identified as brachydin A, B and C	Brachydin A	**Concentration**: Cells were treated with nine concentrations of each compound (0.24 to 30.72 μM) for 24 h. IC_{50} values in PC-3 cells were 23.41 μM (brachydin A), 4.28 μM (brachydin B), and 4.44 μM (brachydin C).	Focus on the antioxidant assay and antitumor activity. *In vitro*: All compounds showed cytotoxicity against PC-3 prostate cancer cells. Brachydin B and brachydin C, (0.96–6 μM) for 1–24 h, induced both apoptosis and necrosis, while brachydin A (6 μM, 24 h) predominantly induced necrosis at higher concentrations. Elevated cleaved PARP expression supported apoptosis. Brachydin B and brachydin C upregulated p21, suggesting G1 arrest; brachydin A and brachydin B decreased phospho-AKT levels. No genotoxicity was observed in the comet assay	Nunes et al.
		UHPLC-HRMS was performed. Structural elucidation was performed using NMR and HRMS	Brachydin B	**Analysis Software**: Statistical analysis was performed using RStudio v1.1.442. ImageJ was used for densitometric analysis of Western blots, and Comet Imager v2.2 was used for comet assay image analysis.		
		Control not specified	Brachydin C	**Replicates**: Three biological and four technical replicates were used for viability assays.		
	Two extracts were prepared: a hydroethanolic extract of *A. brachypoda* (HEAB) and a dichloromethane fraction of *A. brachypoda* (DCMAB)	The active compounds were identified as brachydin A, B and C	Brachydin A	**Concentration**: HEAB and DCMAB were tested at 3–100 μg/mL; brachydins A, B and C at 3–100 μM. IC_{50} values for IL-6 inhibition were: 62 ± 2 μM (brachydin A), 17 ± 3 μM (brachydin B), 19 ± 3 μM (brachydin C); and 31 μg/mL for DCMAB. HEAB showed no significant effect (IC_{50} > 100 μg/mL)	Focus on anti-inflammatory effects in an osteoarthritic inflammation model	Salgado et al.
		HPLC-PDA and UHPLC-MS/MS were employed for analysis and quantification. The HPLC-PDA method used a Waters X-Bridge C18 column (250 × 4.6 mm^2, 5 μm), gradient elution (5–100% MeOH with 0.1% FA), flow rate 1 mL/min, and detection at 254 nm. Quantification was performed by UHPLC-MS/MS (BEH C18 column, 50 × 2.1 mm^2, 1.7 μm) using MRM mode. Calibration curves ranged from 31 to 500 ng/mL with r^2 > 0.99	Brachydin B	**Analysis Software**: GraphPad Prism 8.3.	*In vitro*: Cytotoxicity was assessed using the WST-1 assay. DCMAB showed concentration-dependent cytotoxicity to HFLS. HEAB was noncytotoxic up to 100 μg/mL . Among the isolated compounds, brachydin B and C reduced HFLS viability at 50 μM, while 1 was cytotoxic only at 100 μM	
		Control not specified	Brachydin C	**Replicates**: Experiments were run in six replicates (two experiments per donor, three donors; n = 6)		
	Percolation with 70% ethanol. The extract was evaporated under reduced pressure at a temperature below 40 °C and then lyophilized. The crude extract underwent liquid–liquid partitioning with CH_2Cl_2 and H_2O/MeOH (7:3). The dichloromethane phase was fractionated on a silica gel column using hexane/ethyl acetate and ethyl acetate/methanol gradients, yielding 19 fractions. Compounds were further purified based on HPLC-PDA and TLC profiles.	Brachydins A, B, and C were identified by comparison with previously isolated and characterized standards. HPLC-PDA and TLC. Structural identity was established in earlier studies *via* NMR and HRMS. Column chromatography: silica gel 60 (0.063–0.200 mm, Merck) as the stationary phase. A linear polarity gradient of hexane/ethyl acetate to ethyl acetate/methanol was applied.	Brachydin A	**Compounds**: Electrochemical analyses were performed using brachydins A, B, and C at a fixed concentration of 0.300 mmol L^{-1}. Solutions were prepared in methanol and diluted with 0.04 mol L^{-1} Britton-Robinson buffer containing 0.1 mol L^{-1} KCl and 20% methanol to ensure solubility	Focus on antioxidant assay using electrochemical behavior. Electrochemical oxidation profiles were used as an indirect measure of antioxidant potential. Differential pulse voltammetry revealed that brachydin A had the lowest oxidation potential (+0.48 V), followed by brachydin C (+0.57 V) and brachydin B (+0.71 V). Oxidation peak potentials shifted to less positive values with increasing pH	Nascimento et al.
			Brachydin B	**Analysis Software**: GPES software (Eco Chemie, Autolab PGSTAT 302N system)		
			Brachydin C	**Replicates**: The number of replicates was not explicitly stated		

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Table 1. continued

plant part	extraction method	structural elucidation and analytical parameters*	bioactive compounds	concentration–effect parameters	biological activity (highlights)	references
	Hydroethanolic extraction, followed by liquid–liquid partitioning with dichloromethane (CH_2Cl_2) and H_2O-MeOH (7:3)	The isolated compounds were Brachydin E and Brachydin F	Brachydin E	**Concentrations**: 1.6, 3.12, 6.25, 12.5, 25, 50, and 100 μg/mL. IC_{50} values for PC-3 cells were 5.9 ± 1.3 μg/mL for Brachydin E and 33.1 ± 7.4 μg/mL for Brachydin F.	Focus on antiproliferative, cytotoxic, and pro-apoptotic activities	Lima et al.
		HPLC-PDA, NMR and HR-ESI-MS. HPLC was conducted using a reverse-phase C18 column with gradient elution of water (0.1% formic acid) and acetonitrile (0.1% formic acid), at a flow rate of 0.5 mL/min. Detection was achieved *via* PDA at 254 nm. MS analysis was performed using electrospray ionization (ESI) in positive ion mode. ESI-MS revealed $[M + Na]^+$ ions at m/z 883 and 913, and high-resolution electrospray ionization mass spectrometry (HR-ESIMS) confirmed $[M - H]^-$ ions at m/z 859.2457 and 889.2586.	Brachydin F	**Positive control**: Doxorubicin at concentrations of 0.16, 0.31, 0.62, 1.25, 2.5, 5, and 10 μg/mL (100 μL/well)	*In vitro:* Brachydins E and F showed selective cytotoxicity against PC-3 (prostate) tumor cells without affecting HaCaT (nontumoral) cells at similar concentrations, suggesting low systemic toxicity	
		Control not specified		**Analysis Software**: IC_{50} values were calculated *via* linear regression using Origin software. **Replicates**: Assays were performed in triplicate, in three independent experiments.		
	Percolation at room temperature with ethanol/water (7:3). Extracts were fractionated with dichloromethane (CH_2Cl_2) and methanol:water (7:3). The purified compound (≥98%) was lyophilized. The stock solution was prepared in DMSO at −20 °C	Brachydin A was the only compound investigated	Brachydin A	**Concentrations**: Brachydin A was tested at concentrations ranging from 10 to 100 μM. Cytotoxic effects were observed from 60 μM at 48 h, and 40 μM at 168 h. IC_{50} values were not explicitly calculated in this study	Focus on Antioxidant assay. Antioxidant activity was indirectly assessed *via* high-content screening using the mitochondrial superoxide indicator MitoSOX Red, which measures ROS production. Brachydin A did not significantly increase MitoSOX Red fluorescence, indicating it did not promote mitochondrial ROS generation under the tested conditions.	Ribeiro et al.
		The article does not describe the chromatographic method used for BrA isolation in this study, nor does it mention the use of commercial reference standards. All compound-related details, including purity, were obtained from previous work		**Positive control**: Docetaxel **Negative control**: RPMI 1640. **Solvent control**: DMSO 1%. **Analysis Software**: GraphPad Prism 7.0 software. **Replicates**: All assays were conducted with six replicates (n = 6) per group in three independent experiments (n = 3)	*In vitro*: Toxicity was evaluated using DU145 metastatic prostate tumor spheroids. Brachydin A decreased cell viability in a time- and dose-dependent manner, starting from 40 μM at 48 h. Flow cytometry showed increased apoptosis and necrosis, with >61% apoptosis at concentrations ≥80 μM. High-content screening revealed mitochondrial depolarization. Western blotting confirmed increased markers of DNA damage (cleaved-PARP, p-γ-H2AX), apoptosis (CASP3, CASP7, CASP8), and inflammation (NF-kB, TNF-α), suggesting brachydin A induces cell death by PARP-related	
	Percolation at room temperature with ethanol/water (7:3). Extracts were fractionated with dichloromethane (CH_2Cl_2) and methanol:water (7:3).The extraction process involved lyophilization, and the compound was dissolved in dimethyl sulfoxide (DMSO) and PBS for experimental use	No chromatographic method or analytical validation using reference standards was detailed in this study. The compound brachydin B was characterized and provided by collaborating institutions based on prior studies	Brachydin B	**Concentrations**: Brachydin B showed cytotoxicity at concentrations ≥ 1.50 μM after 24 h (MTT assay), with an IC_{50} value of 7.45 μM in 2D models. In 3D spheroids, cytotoxicity was observed at concentrations ≥ 50 μM after 48 h, and ≥30 μM after 168 h.	Focus on antitumoral, antiproliferative, and antimigratory effects of brachydin B	Sperloni et al.
				Positive control: Docetaxel **Negative control**: PBS.	*In vitro*: Brachydin B demonstrated selective cytotoxicity toward DU145 cancer cells	

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Table 1. continued

plant part	extraction method	structural elucidation and analytical parameters*	bioactive compounds	concentration–effect parameters	biological activity (highlights)	references
				Analysis Software: GraphPad Prism 7.0. TScratch software; AxioVision SE64 Rel. 4.9.1.	without affecting nontumoral HGF cells at low doses. In 2D culture, cytotoxicity was confirmed *via* MTT, LDH release, and triple staining, which showed no signs of apoptosis/necrosis at lower concentrations. In 3D spheroids, brachydin B inhibited viability and volume growth at high concentrations and long exposure times. No *in vivo* toxicity assessment was performed	
				Replicates: All experiments were performed in biological triplicates (n = 3)		
	Percolation at room temperature with 70% ethanol. The resulting hydroethanolic extract was evaporated, lyophilized, and fractionated *via* liquid–liquid partition using dichloromethane and methanol–water (7:3). The dichloromethane fraction (FDCM) was selected for microemulsion incorporation	Three dimeric flavonoids—brachydins A, B, and C—were identified. The FDCM was analyzed using HPLC-UV/PDA with a C18 column (5 μm , 150 × 4.6 mm^2, 100 Å). A gradient mobile phase of methanol and water (both acidified with 0.01% formic acid) was used at a flow rate of 1 mL/min, with UV detection at 254 nm. No external reference standards were specified; identification was based on UV spectra and retention times	N.A.	**Concentrations**: FDCM was incorporated into microemulsions (ME) at 3% (ME3) and 5% (ME5) w/w. Particle size (DLS: 36.7–75.4 nm), PDI (0.248–0.604) , and ζ-potential were measured. Release kinetics used Franz cells (6 h; 63.5% cumulative release for ME3). The study did not report IC_{50} or IG_{50} values	Focus on physicochemical stability, *in vitro* release, and *in vivo* toxicity	Nascimento et al.
		Control not specified		**Negative control (*in vivo*)**: trauma and DMSO	*In vivo*: toxicity was evaluated using *Tenebrio molitor* larvae injected with ME3 or FDCM (1–100 μg/mL). No toxicity or behavioral changes were observed over 7 days	
				Software Analysis: GraphPad Prism 6 and DDsolver.	Survival was 100% in all treated groups, indicating the safety of both the microemulsion and the isolated fraction	
				Replicates: 3 (triplicate) for physicochemical assays, *in vitro* release, and stability studies.		
	Maceration at room temperature with ethanol/water (7:3). Extracts were fractionated with dichloromethane (CH_2Cl_2) and methanol:water (7:3). The crude DCM and aqueous-methanolic fractions were obtained after decantation and evaporated under a vacuum at approximately 40 °C	The DCM fraction enriched with brachydin A was analyzed using HPLC-UV/PDA-MS with a C18 column (5 μm, 150 × 4.6 mm^2, 100 Å). A gradient mobile phase of methanol and water, both acidified with 0.01% formic acid, was employed at a flow rate of 1 mL/min, with UV detection at 254 nm. No external reference standards were specified; identification was based on UV spectra and retention times.	Brachydin A	**Concentrations**: The encapsulation of the brachydin A compound into micelles formed by the F127 copolymer was carried out using the solid dispersion method. This process resulted in the formation of brachydin-loaded micelles at final concentrations of 0.5%, 0.25%, or 0.125% (w/v) of F127, with a fixed brachydin A concentration of 500 μg/mL	Focus on physicochemical characterization, encapsulation efficiency, *in vitro* release kinetics, leishmanicidal activity, and cytotoxicity	Costa et al.
		Control not specified		**Control**: Micelles containing only F127 were prepared in parallel and used as controls in all experiments	*In vitro*: The study evaluated the physicochemical properties (particle size, Polydispersity Index, ζ-potential), drug release kinetics using Franz diffusion cells, and antileishmanial activity against *L. amazonensis* promastigotes. In addition, brachydin A demonstrated selective cytotoxicity in mouse macrophage cell line (RAW 264.7)	
				Replicates: All the measurements were performed in triplicate		
				Software Analysis: ORIGIN 10.0		
	Percolation at room temperature with ethanol:water (7:3). The crude extract was subjected to liquid–liquid partitioning with CH_2Cl_2 and H_2O/MeOH (7:3) to obtain DCMF	The DCM fraction enriched with brachydins A, B, and C was analyzed using HPLC-PDA and LC-MS. Nanoparticles were characterized by DLS, ζ-potential, AFM, FTIR, and DSC. Chromatographic conditions were not described in detail in this study, but are available in a previous work (Da Rocha et al., 2017). No external reference standards were specified; identification was based	Brachydin A, Brachydin B, Brachydin C	**Concentration**: Promastigote and amastigote assays: 0.06 to 125 μg/mL	Focus on physicochemical characterization, encapsulation efficiency, stability, leishmanicidal activity, and cytotoxicity	Neves et al.
				Cytotoxicity assay: up to 500 μg/mL	*In vitro:* ZNP-DCMF exhibited potent activity against *L. amazonensis*, with IC_{50} = 36.33 μg/mL (promastigotes) and 0.72 μg/mL (amastigots). In contrast, nonencapsulated DCMF showed IC_{50} = 253.1 μg/mL and 6.96 μg/mL,	
				–**Negative controls**: 1% DMSO; blank zein nanoparticles		
				Replicates: All experiments were performed in triplicate		

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Table 1. continued

plant part	extraction method	structural elucidation and analytical parameters*	bioactive compounds	concentration–effect parameters	biological activity (highlights)	references
		on retention profiles and published data on brachydin content		**Analysis Software**: GraphPad Prism 9.0	respectively. The formulation demonstrated high selectivity (SI = 694.44) and low cytotoxicity in RAW 264.7 macrophages (CC_{50} > 500 μg/mL). Physicochemical analysis confirmed a mean particle size of 206 nm, PDI < 0.2, encapsulation efficiency >99%, and 49-day stability	
Leaves Stalks and Roots	Percolation at room temperature with ethanol/water (7:3)	The active compounds were identified as dimeric flavonoids (brachydin A, B and C).	Brachydin A	**Concentration**: RYA assay—Increasing concentrations from 10 to 300 μg/mL.	Focus on estrogenic and mutagenic assays	Resende et al.
		HPLC was performed; Injection volume not specified; Stationary phase: C18 (150 × 49 mm^2, 5 μm); Mobile phase: A gradient of methanol (MeOH) and water (H_2O), both containing 0.002% formic acid (HCOOH), from 5 to 100% MeOH over 60 min. Flow rate: 10 mL/min; with structures elucidated using HPLC-PDA, UV–vis, ^{1}H and ^{13}C NMR, and Direct MS	Brachydin B	**Ames test**: 1, 10, 50, 100, and 500 μg/plate	*In vitro*: Estrogenicity (RYA): EC_{50} = 56.2 μg/mL (leaves), 191.3 μg/mL (roots); Estradiol Equivalent Concentration (EEQ): EEQ 7.4 ± 2.3 nM (leaves), EEQ 2.16 ± 0.9 nM (roots). Estrogenic activity mediated by ERα	
		Control not specified	Brachydin C	**Controls used**: **Positive controls**: 4-nitro-*o*-phenylenediamine (NPD), sodium azide, mitomycin C, 2-anthramine **Negative control**: DMSO With and without metabolic activation (±S9 mix) **Analysis Software**: GraphPad Prism v5.00 **Replicates**: 6 experiments in triplicate	Mutagenic activity in TA98 (Ames test); DNA damage potential; flavonoids implicated	
Aerial parts - branches	Maceration with ethanol (P.A) at room temperature. Solvent removed under reduced pressure. solid-phase extraction with CH_3OH-H_2O (30, 50, 100%)	Conandroside (phenylethanoid glycoside)	Conandroside	**Concentrations**: Crude ethanol extract: 25 μg/mL	Focus on anti-inflammatory activity	Bertanha et al.
		HPLC-DAD and HPLC-HRMS were performed. Injection volume not specified. Stationary phase: C18 column (Onyx Monolithic 100 × 10 mm^2); mobile phase: CH_3OH-H_2O + 0.1% acetic acid; gradient 5–100% MeOH in 30 min; flow rate 4 mL/min; HRMS: ESI-TOF mode with methanol gradient 95% H_2O to 100% CH3OH over 35 min. In addition, the structure was detected and characterized by HPLC-DAD, HRMS, ^{1}H and ^{13}C NMR		Conandroside and quercetin were evaluated at concentrations ranging from 1.25 to 80 μM	*In vitro* (normal human fibroblasts, GM07492A): CC_{50} > 2500 μM (conandroside); extract: CC_{50} = 2352.0 ± 28.5 μg/mL. The data shows that both crude ethanol extract and conandroside are not presented as cytotoxic	
		Control not specified		Crude ethanol extract-IC_{50}: 49.4 ± 2.5 μg/mL Conandroside- IC_{50}: 7.8 ± 1.1 μM; Quercetin (control) -IC_{50}: 7.6 ± 0.3 μM **Analysis Software**: not specified **Replicates**: triplicate assays		
Leaves	Percolation at room temperature with ethanol/water (7:3). Crude extract evaporated under vacuum (~40 °C); liquid–liquid partitioning with hexane, ethyl acetate, and methanol/water (7:3)	HPLC-UV/vis and MS/NMR.Injection volume not specified. Stationary phase: Silica gel 60 (0.063–0.200 mm)	Luteolin	**Concentrations**: Luteolin: 5, 9.7, 19.5, 39.2, 78.5, 157–314 μM	Focus on antiproliferative and pro-apoptotic activity	Franco et al.
		Mobile phase: Gradient elution with hexane:ethyl acetate followed by ethyl acetate:methanol. Gradient: Increasing polarity with two-step solvent system (hexane/EtOAc, then EtOAc/MeOH); no proportions or timing provided. Control not specified		**U-251 (glioblastoma)**- IG_{50}: 6.6 ± 1.3 μM **NCI-ADR/RES (resistant ovarian cancer)**-IG_{50}: 15.0 ± 1.3 μM **NCI-H460 (lung cancer)**-IG_{50}: 8.0 ± 0.3 μM	*In vitro*: U-251 cells were the most sensitive to luteolin, followed closely by HaCaT and NCI-H460, while HT-29 and 786–0 cells showed the highest resistance. Selectivity Index (SI) ≈ 0.98 (U-251 *vs*	

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Table 1. continued

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				786–0 (kidney cancer)-IG_{50}: 55.2 ± 9.7 μM **PC-3 (prostate cancer)**-IG_{50}: 26.2 ± 2.0 **HT-29 (colon cancer)**- IG_{50}: 60.8 ± 11.1 μM **HaCaT (nontumoral** keratinocyte line)-IG_{50}: 7.6 ± 2.4 μM **Analysis Software**: ORIGIN 8.0 and GraphPad Prism **Replicates**: Triplicate assays	NHA), suggesting low selectivity between tumor and nontumor cells	
Flowers	Percolation at room temperature with ethanol/water (7:3). Extracts were fractionated with dichloromethane (CH_2Cl_2)	The active compounds were identified as dimeric flavonoids (brachydin A, B and C)	Brachydin A	**Concentrations**: MIC assay: 8–512 μg/mL; Norfloxacin/EtBr modulation at 128 and 256 μg/mL (1/8 and 1/4 MIC)	Focus on antimicrobial activity and Norfloxacin modulation (inhibition of the Norfloxacin efflux pump).	Andrade et al.
		HPLC-PDA was performed; Injection volume: 10 μL. Stationary phase: Luna C18 (250 × 4.6 mm^2, 5 μm); Mobile phase: A (2% acetic acid in H_2O), B (2% acetic acid in MeOH); Gradient: 5–95% B over 30 min; Flow rate: 1 mL/min; In addition, the structures were elucidated using LC-ESI-MS analysis provided *m*/*z* fragments ranging from 573 to 603 $[M - H]^-$. HPLC-PDA, UV–vis (210–254 nm)	Brachydin B	**Analysis Software**: GraphPad Prism v5.00	*In vitro*: antimicrobial activity of floral extracts rich in brachydins A, B, and C was evalueted. The Minimum Inhibitory Concentration (MIC) was determined over a concentration range of 8–512 μg/mL. Additionally, efflux pump modulation was assessed using norfloxacin combined with ethidium bromide at subinhibitory concentrations (128 and 256 μg/mL), indicating interference with bacterial resistance mechanisms	
		Control not specified	Brachydin C	**Replicates**: triplicate assays		
	Hydrodistillation using a Clevenger apparatus for 3 h; organic phase washed with dichloromethane and dried with anhydrous sodium sulfate	15 compounds identified; major: trans-anethole (11.10%), β-thujene (14.87%), 3-carene (21.07%), γ-terpinene (32.01%)	N.A	**Concentrations**: 1.0, 2.0, 4.0, 6.0, 8.0, 10.0, 20.0, 30.0, 40.0 e 50.0 μL/mL. IC_{50} value not calculated; **Analysis Software**: PAST 3.0	*Focus on antioxidant potential*	Menezes-Filho
		GC-MS was performed. Injection volume not specified. Stationary phase: Restek Rtx-5 ms capillary column (30 m × 0.25 mm × 0.25 μm), nonpolar Mobile phase: Helium (carrier gas) at 57.4 kPa. Temperature gradient: 60 °C (3 min), then +3 °C/min to 200 °C, then +15 °C/min to 280 °C (1 min hold). Injector/Detector: temperatures: 230/300 °C. Ionization mode: Electron Impact (EI) at 70 eV. Detection by GC-MS (mass range: 43–550 *m*/*z*). and comparison with Kovats Index and NIST 11 library.		**Replicates**: triplicate assays	*In vitro:* The essential oil extracted presented 15 volatile compounds—mainly γ-terpinene and 3-carene, both known for their antioxidant properties. Antioxidant activity was assessed using the DPPH radical scavenging assay. The extract showed dose-dependent radical scavenging activity across concentrations from 1.0 to 50.0 μL/mL, indicating relevant antioxidant potential likely attributed to its high content of monoterpenes	
		DPPH radical scavenging assay in 96-well microplate; absorbance read at 517 nm; incubation at 1 °C for 1 h in the dark.				
		Control not specified				
	The flowers were macerated in 1 L of 70% hydroethanolic solution for 48 h at room temperature in amber glass containers. After filtration, the extract was concentrated under reduced pressure, frozen at −12 °C, and lyophilized. The lyophilized ex-	No specific compounds were isolated or identified	N.A.	**Concentration**: The extract was tested at concentrations of 500, 250, 125, 62.5, 31.25, and 15.62 mg/mL. Inhibition halos ranged from 26.1–9.1 mm for *Candida albicans*, 19.7–4.6 mm for *Candida guilliermondii*, 16.9–6.4 mm for *Candida tropicalis*, and 11.8–8.7 mm for *Candida*	Focus on antifungal evaluation	Menezes-Filho, Porfiro e Castro

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Table 1. continued

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	tract was stored at −12 °C until further use			*krusei*. **Positive control**: Cetoconazole (50 μg/mL) **Negative control**: DMSO		
		No chromatographic profiling or reference standard quantification was performed. Only organoleptic (color, aroma, clarity), pH (5.25 ± 0.04), and relative density (0.9699 g/mL at 20 °C) parameters were reported for extract characterization		**Analysis Software**: Statistical analysis was conducted using the Scott-Knott test at a 5% significance level. No software was specified in this study **Replicates**: All assays were performed in triplicate.	*In vitro:* The extract showed antifungal activity against *Candida* species, with inhibition halos ranging from 26.1 mm (*C. albicans*) to 4.6 mm (*C. guilliermondii*), depending on the concentration (15.62 to 500 mg/mL). *C. albicans* was the most sensitive, while *C. krusei* and *C. tropicalis* showed moderate inhibition. The antifungical activity was dose-dependent	
	Flowers were macerated in 1 L of 70% hydroethanolic solution for 72 h at room temperature. Extracts were concentrated under reduced pressure using a rotary evaporator and dried in a forced-air oven at 35 °C	No specific compounds were isolated or identified. No chromatographic or phytochemical profiling was performed. No internal or external standards were used for compound identification or quantification. Only the crude extracts were evaluated for biological activity	N.A.	**Concentrations**: 100, 50, 25, and 12.5 mg/mL for antifungal assays. The largest inhibition zones were 18.6 mm (F. platyphylla, C. albicans) and 14.3 mm (Fridericia florida, C. krusei) at 100 mg/mL. Cytotoxicity (LC_{50}) against *Artemia salina* was 237.81 μg/mL for *F. platyphylla* and 301.20 μg/mL for *F. florida*	Focus on antifungal and cytotoxic evaluations	Menezes-Filho
				Positive control: Ketoconazole (50 μg/mL; antifungal assay). Potassium dichromate (cytotoxicity assay) **Negative control**: 70% hydroethanolic solution (antifungal assay). 5 mL seawater +100 μL DMSO (cytotoxicity assay) **Analysis Software**: LC_{50} was calculated *via* best-fit line using Assistat Software Free. Statistical analysis was performed using ANOVA and the Scott-Knott test at 5% significance. **Replicates**: Assays were conducted in quadruplicate	*In vitro*: Cytotoxicity was assessed through the brine shrimp lethality test (*A. salina*). Both floral extracts showed growth inhibiting activity for most strains, indicating biologically relevant cytotoxic potential. No *in vivo* toxicological assays were conducted	

[a]Prepared by the authors from the PubMed, Scielo, and Google Scholar databases. **Legend**: ACP02—Human gastric adenocarcinoma cell line; AFM—Atomic Force Microscopy; CC_{50}—Cytotoxic Concentration 50%; CH_2Cl_2—Dichloromethane; COSY—Correlation Spectroscopy; DAD—Diode Array Detector; DLS—Dynamic Light Scattering; DMSO—Dimethyl Sulfoxide; DNA—Deoxyribonucleic Acid; DPV—Differential Pulse Voltammetry; DSC—Differential Scanning Calorimetry; DU145—Human metastatic prostate cancer cell line; ECD—Electronic Circular Dichroism; EC_{50}—Effective Concentration 50%; EEQ—Estradiol Equivalent Concentration; ELSD—Evaporative Light Scattering Detector; EtOH—Ethanol; EtOAc—Ethyl Acetate; FA—Formic Acid; FGH—Human Gingival Fibroblasts; GC-MS—Gas Chromatography–Mass Spectrometry; GAS—Primary human gastric cells; H_2O—Water; HaCaT—Human keratinocyte cell line; HCOOH—Formic Acid; HMBC—Heteronuclear Multiple Bond Correlation; HPLC—High Performance Liquid Chromatography; HRMS—High Resolution Mass Spectrometry; HSQC—Heteronuclear Single Quantum Coherence; IC_{50}—Inhibitory Concentration 50%; IG_{50}—Inhibitory Growth 50%; LDH—Lactate Dehydrogenase; LC-MS—Liquid Chromatography–Mass Spectrometry; ME3—Microemulsion 3%; MeOH—Methanol; MET—Mesenchymal Epithelial Transition factor gene; MIC—Minimum Inhibitory Concentration; MTT—3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; NBUDs—Nucleoplasmic Bridges and Nuclear Buds; NHA—Normal Human Astrocytes; NOESY—Nuclear Overhauser Effect Spectroscopy; NMR—Nuclear Magnetic Resonance; PARP—Poly (ADP-ribose) polymerase; PBS—Phosphate Buffered Saline; PDA—Photodiode Array Detector; PDI—Polydispersity Index; PC-3—Human prostate cancer cell line; RMS—Root Mean Square; ROS—Reactive Oxygen Species; RP-HPLC—Reverse Phase High Performance Liquid Chromatography; RPMI 1640—Roswell Park Memorial Institute medium; RYA—Recombinant Yeast Assay; SI—Selectivity Index; TA98—*Salmonella typhimurium* strain for Ames test; TLC—Thin Layer Chromatography; TScratch—Software for scratch wound healing assay analysis; UHPLC—Ultra High Performance Liquid Chromatography; UV–vis—Ultraviolet–Visible Spectroscopy; WST-1 —Water-soluble tetrazolium salt 1.

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wound-healing applications.[7−10] In traditional Brazilian medicine, particularly in the Southeast and Northeast regions, the roots and leaves of *F. platyphylla* are used to treat kidney stones and joint pain.[11] Among the species in the genus, *F. platyphylla* stands out for its chemical diversity, with at least 29 isolated substances, predominantly flavonoids, followed by terpenes, which are widely known for their pharmacological relevance.[12,13]

Flavonoids, as a significant class of phenolic secondary metabolites, are broadly distributed throughout the plant kingdom, with over 4,200 identified structures and well-established biological activities. Compared to other species, *F. platyphylla* exhibits a vibrant and diverse phytochemical profile with significant pharmacological potential.[3,14] A subclass of unusual dimeric flavonoids called brachydins (originating from the name *A. brachypoda*) was isolated from this species for the first time.[15,16]

Recent studies have reported various biological properties for *F. platyphylla* extracts obtained from distinct plant parts. The flowers are rich in chalcones and enhance the efficacy of norfloxacin through synergistic effects.[17] The leaves contain flavonoids with estrogenic and mutagenic activities, while the branches exhibit inhibition of lipoxygenase enzymes. The roots concentrate the most potent bioactive compounds, including flavonoids, triterpenes, saponins, tannins, and other polyphenols, which confer anti-inflammatory, antinociceptive, antiproliferative, cytotoxic, estrogenic, mutagenic, gastroprotective, antileishmanial, and trypanocidal effects.[11,13,15,18−21]

In addition to these findings, our research group demonstrated the antispasmodic effect of the hydroethanolic leaf extract in isolated rat jejunum, mediated by inhibition of Ca^{2+} influx through voltage-dependent calcium channels.[19] These results highlight the potential of *F. platyphylla* for developing bioproducts that modulate smooth intestinal muscle contractility. More recently, efforts have focused on formulating suspensions containing crude or purified extracts to enhance oral bioavailability and mitigate toxicity.

Despite the increasing number of pharmacological studies on *F. platyphylla*, significant gaps remain, particularly regarding the lack of standardized methodologies, limited toxicological data, and heterogeneity in experimental designs, which hinder comparative analysis and the translational potential of these findings. To address these challenges, this review systematically compiles and critically analyzes preclinical evidence from *in vitro* and *in vivo* models, encompassing both crude extracts and isolated compounds. By identifying consistent pharmacological patterns, mechanistic insights, and safety concerns, this work provides a consolidated foundation to guide future investigations and support the rational development of *F. platyphylla*-based therapeutic strategies.

2. RESULTS

Table 1 shows the chromatographic parameters, phytochemical compounds isolated, as well detection methods, and biological activities of the studies included in the systematic review. Tables 2 and 3 highlights the main characteristics (experimental model, *in vivo* administration, strain, *in vitro* design, groups, *in vivo* monitoring, and dose or concentration administered *in vivo*/*in vitro*) and main findings obtained from the use of the crude extract or phytochemical compounds isolated from the species *F. platyphylla*.

The chemical structures of the isolated compounds listed in Table 1 are shown in Figure 1, allowing for easier visualization and identification of each described substance.

Figure 2 shows the temporal evolution of the studies published using the crude extract and/or phytochemical compounds isolated from the species *F. platyphylla* in different experimental models. It shows that most of the publications of studies with this species were between 2019 and 2021.

Figure 3 illustrates the pharmacological effects observed in response to different doses of the crude extract or isolated phytochemical compounds from *F. platyphylla*. The figure highlights dose-dependent relationships, supporting the potential therapeutic relevance of both the crude extract and its active constituents.

Figure 4A,B illustrate the diverse effects of *F. platyphylla* across *in vitro*, *in vivo*, and *in silico* models.

Figure 5 illustrates the proposed mechanism of action and pharmacological activities of the bioactive compounds isolated from *F. platyphylla*. The figure integrates experimental evidence from *in vitro* and *in vivo* assays, highlighting key effects such as antiparasitic, antitumoral, anti-inflammatory, antioxidant, antimicrobial, and analgesic actions. These effects are primarily attributed to brachydins, which modulate cellular targets including efflux pumps, inflammatory mediators (such as IL-6), reactive oxygen species (ROS), and apoptotic pathways. The schematic representation provides a comprehensive overview of how these compounds interact with molecular targets, supporting their therapeutic potential in different experimental models.

Figure 6 illustrates the advanced drug delivery systems developed using Fridericia platyphylla and its bioactive compounds. The diagram highlights three main nanotechnological approaches: microemulsions, polymeric micelles, and zein nanoparticles, each designed to improve solubility, stability, and bioavailability. These delivery platforms have demonstrated enhanced encapsulation efficiency, sustained release profiles, low cytotoxicity, and high selectivity in *in vitro* and *in vivo* models

3. DISCUSSION

The growing phytochemical and pharmacological exploration of *F. platyphylla* underscores its promise as a source of bioactive compounds with diverse therapeutic potential. The data compiled in this review consolidate evidence for antioxidant, anti-inflammatory, antiparasitic, antitumor, antinociceptive, and antimicrobial effects associated with both crude extracts and isolated compounds, particularly dimeric flavonoids such as brachydins (A−F), luteolin, and cuneatin. These findings suggest that structural diversity and chemical complexity significantly influence pharmacological activity, modulated by electron-donating and withdrawing substituents, medium pH, lipophilic properties, and controlled-release formulations such as microemulsions.

Notably, both *in vitro* and *in vivo* studies demonstrate not only therapeutic efficacy but also selectivity and low cytotoxicity in nontumor cells, with well-characterized molecular mechanisms of action. These include inhibition of inflammatory pathways (*e.g.*, LOX, IL-6), mitochondrial-mediated apoptosis, ion channel modulation related to nociception, and interference with cell proliferation signaling (*e.g.*, pAKT pathway). Standardization of extracts, rigorous structural characterization, and the use of robust analytical methodologies—such as HPLC, UHPLC-MS/MS, NMR, and

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Table 2. Experimental Design and Main Outcomes of *In Vitro* Studies with *F. platyphylla*[a]

experimental model	study design	groups	concentration	main findings	references
Cytotoxicity in macrophages	Culture of macrophage cells obtained from BALB/c mice	Control, Benznidazole, Amphotericin B, brachydin A, brachydin B, and brachydin C (n = 6)	100 mg/kg (*in vivo*); 1.23−100 μg/mL (*in vitro*)	Brachydin B and C reduced parasitemia in *T. cruzi*	Rocha et al.
Mutagenicity and estrogenic activity	Mutagenic activity: *S. typhimurium*. Estrogenic activity: *Saccharomyces cerevisiae* strains	G1: *A. brachypoda* leaf extract. G2: *A. brachypoda* stem extract. G3: *A. brachypoda* root extract.	3 a 24 mg per culture plate	Extracts showed mutagenic activity; leaf and root extracts had significant estrogenic activity	Resende et al.
Effect against *L. amazonensis*	Macrophages from BALB/c	Control, Amphotericin B and brachydin B	*In vitro:* dose de 0.25 a *20 μM*	Brachydin B was effective against *L. amazonensis* promastigotes with no significant toxicity	Rocha et al.
Antimicrobial and drug-resistance modulation	*Staphylococcus aureus*; *Escherichia coli* and *C. albicans*	Control group: Chlorpromazine (CPZ); Crude extract of *A. brachypoda* leaves (FLAB-Et) extract; Dichloromethane fraction of *A. brachypoda* leaves (FLAB-DCM) extract; Brachydin A; Brachydin B and associations with Norfloxacin and Ethidium bromide	They were prepared in DMSO, followed by dilution in sterile water to a fin-0-al concentration of 1024 μg/mL	FLAB-Et, FLAB-DCM, and brachydin B enhanced antibiotic efficacy against resistant bacteria	Andrade et al.
Cell viability assay using MTT test was used	Tumor cells (ACP02) and normal human gastric primary cells obtained by biopsy (GAS) were used	Cytotoxic activity: *F. platyphylla* extracts in different concentrations Apoptotic activity: *F. platyphylla* roots extracts (5.0, 30, or 60 mg/mL) or vehicle (PBS) and doxorubicin (DXR 0.2 mg/mL).	*F. platyphylla* root extracts (5−500 mg/mL) for 24 h	*F. platyphylla* root extracts have cytotoxic and antiproliferative effects by inducing necrosis and reducing expression of apoptosis (BCL-XL, BIRC5) and cell cycle (MET) genes	Serpeloni et al.
15-LOX inhibition assay and cytotoxicity test	Enzymatic assay with human cells in culture	Control group (enzymatic assay): Quercetin; Control group (cytotoxicity): Doxorubicin	Use of 25 μg/mL for enzymatic and cytotoxicity assays	*F. platyphylla* extract inhibited 15-LOX without cytotoxicity, and conandroside showed strong LOX inhibition potential	Bertanha et al.
Antiproliferative activity of luteolina	Culture of tumor cells of U-251 glioblastomas and cultures of nontumor cells HaCaT and NHA.	Control group: Dimethyl sulfoxide (DMSO) and Temozolomide (TMZ). Luteolin compound group	For antitumor activity, concentrations of 314, 157, 78.5 39.2, 19.5, 9.7 e 5 μM were used	Luteolin reduced proliferation in U-251 glioblastoma cells with low toxicity to nontumor cells	Franco et al.
Phytopathological antifungal activity	Phytopathological antifungal activity—*Sclerotinia sclerotiorum*, Colletotrichum acutatum and *Aspergillus flavus* strains; Antifungal activity in *Candida* strains - *C. albicans*; *C. guilliermondi*, *C. krusei* and *C. tropicalis*	Phytopathological antifungal activity: Negative control - untreated and DMSO; Positive control - Frowncide 500 SC; Essential oil (EO) tested at various concentrations Antifungal activity for *Candida*: Negative control—Tween 80; Positive control- Ketoconazole *(50 μg/mL)*; Essential oil tested at various concentrations	For phytopathological antifungal activity, doses of 100 (EO); 50; 25; 12.5; 6.25; 3.13; and 1.56 μL/mL of EO were used; Antifungal activity for Candida strains at concentrations (2, 4, 6 and 8% of EO) and antioxidant activity by DPPH at concentrations 50; 40; 30; 20; 10; 8.0; 6.0; 4.0; 2.0 and 1.0 μm/mL	EO inhibited fungal growth with high antioxidant activity at higher concentrations	Menezes-Filho
Halogenated flavonoids for antiparasitic effects	Mouse macrophages infected with *L. amazonensis* and *T. cruzi*	Antiparasitic: halogenated brachydins, at different concentrations Group 1: amastigote forms of *L. amazonensis*, using halogenated brachydins Group 2: amastigote forms of *T. cruzi*, using halogenated brachydins	Oxidative halogenation was performed with 50 mg of the dichloromethane fraction (DCM), obtaining 16 derivatives Antiparasitic activity and IC_{50}: 10, 5, 2.5, and 1.25 μM	Halogenated brachydins showed high selectivity for *L. amazonensis* especially compounds 4,9,11-Tribromobrachydin C and 11-Chlorobrachydin C. In addition, was observed best activity for *T. cruzi* in 4,11-Dibromobrachydin C, 4-Iodobrachydin B, 11-Chorobrachydin B, and 11-Chlorobrachydin C	Neuenschwander et al.
Cytotoxicity on prostate cancer	Human prostate cancer cell line PC-3 to evaluate the cytotoxic effects of brachydins	Control (PBS, Doxorubicin), brachydins A, B, C	Concentrations of 0.24 to 30.72 μM of brachydin A, B and C were used to determine cell viability and cytotoxic effects on PC-3 prostate cancer cells. Then, doses of 1.5, 3.84, and 6 μM were administered	Brachydins showed cytotoxicity in PC-3 cells, affected cell cycle genes, and modulated the PI3K/AKT/mTOR pathway. pathways, such as the PI3K/AKT/mTOR pathway, suggesting therapeutic potential for the treatment of prostate cancer	Nunes et al.
Anti-inflammatory effect	IL-1β-activated human synoviocytes	IL-1β-activated arthritic synoviocytes were treated with varying concentrations of *F. platyphylla* extracts and compounds. Neg-	Concentrations of *F. platyphylla* extracts and isolated compounds ranging from 3 to 100 μg/mL	Root extract of *F. platyphylla* inhibited IL-6 release in arthritic synoviocytes	Salgado et al.

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Table 2. continued

experimental model	study design	groups	concentration	main findings	references
		ative control (untreated) was likely included for comparison			
Antifungal activity	The fungal strains used were *C. tropicalis*, *C. guilliermondii*, *C. albicans*, and *C. krusei*	Negative control group: Dimethyl sulfoxide (DMSO); Positive control group: Ketoconazole at a concentration of 50 $\mu g\ mL^{-1}$; *F. platyphylla* floral extract group at different concentrations	*In vitro:* 500; 250; 125; 62.5; 31.25 e 15.62 mg/mL diluted in DMSO	*F. platyphylla* floral extract showed antifungal activity at high concentrations	Menezes-Filho, Porfiro e Castro
Antifungal and cytotoxicity assay	Fungal strains of *C. albicans*, *C. krusei*, *C. tropicalis*, and *C. guilliermondii* were used	Antifungal assay: hydroethanolic solution (negative control) and ketoconazole (50 μg/mL, positive). In the cytotoxic assay: DMSO with seawater (control negative) and potassium dichromate with seawater (positive control). Extract was tested at various concentrations	*In vitro:* 100; 50; 25 e 12.5 mg/mL diluted in hydroethanolic solution (70%) for the antifungal assay 1.000; 500; 100; 50; 25 e 1 μg/mL diluted in hydroethanolic solution (35%) for the lethality assay	*F. platyphylla* extract inhibited *Candida* with greater activity in *C. krusei*; low toxicity in cytotoxicity test	Menezes-Filho
In silico: electrochemical analysis of brachydins	Glassy carbon electrodes in buffered solution	Fractions 14, 15, and 16 of the extract were analyzed, which contained compounds called brachydins A, B and C, respectively.	The brachydin stock solutions brachydin A, brachydin B and brachydin C were prepared at 0.300 mmol/L in methanol	Brachydin A exhibited high oxidation at high pH, which affected its antioxidant capacity and redox behavior	Nascimento et al.
Cytotoxic activity	Panel of commercial human cell lines, four tumoral (U-251-glioblastoma, NCI-H460-lung, PC-3-prostate, and HT-29-colorectal), and one nontumorous (HaCat-keratinocyte)	(Doxorubicin hydrochloride—control group) Hydromethanolic subfraction group of the extract of *F. platyphylla* brachydin E and brachydin F	*In vitro:* concentrations of 1.6, 3.12, 6.25, 12.5, 25, 50, and 100 μg/mL in triplicate	Brachydins E and F exhibited cytotoxic effects in almost all cell lines tested, with selectivity for the PC-3 lines	Lima et al.
Prostate cancer cells	Three-dimensional tumor models created from metastatic prostate cells of the DU145 lineage isolated from a metastatic brain site and reproduced in oncological models of the tumor spheroid type	Negative control RPMI 1640 Solvent control DMSO (1%) Positive control group: Docetaxel (50 μM) Brachydin A group: Spheroids were treated with different concentrations of brachydin A	*In vitro:* Brachydin A solutions were prepared in DMSO to reach final concentrations of 10, 20, 40, 60, 80, and 100 μM	Brachydin A showed cytotoxicity and reduced invasiveness and migration in tumor spheroids	Ribeiro et al.
Antitumor effects	DU145 metastatic prostate cancer cells in 2D and 3D models	PBS (Negative control): Solvent group with 0.25% DMSO; Brachydin B groups in 2D model: 0.24, 0.75, 0.96, 1.50, 3.84, 6.00, 15.36, 24.00, and 30.72 μM. Brachydin B groups in 3D model: 5, 10, 20, 30, 40, 50, and 60 μM.	Brachydin B solutions were prepared in DMSO to reach final concentrations of 0.24, 0.75, 0.96, 1.50, 3.84, 6.00, 15.36, 24.00, and 30.72 μM of brachydin B for 2D culture and concentrations of 5, 10, 20, 30, 40, 50, and 60 μM for 3D culture	Brachydin B reduced cell viability in 2D model, inhibited spheroid growth and migration in 3D model.	Sperloni et al.
Antiparasitic and Cytotoxic effects	Nanotechnological formulation of brachydin A for antileishmania and cytotoxicity effects	Polymer F127 m/v 0.125%, 0.25% and 0.5% (negative control) Brachydin A Brachydin A-loaded F127 m/v 0,125% Brachydin A-loaded F127 m/v 0.25% Brachydin A-loaded F127 m/v 0,50%	Brachydin-loaded micelles were prepared in concentrations of 0.5%, 0.25%, or 0.125% (w/v) of F127, with a fixed brachydin A concentration of 500 μg/mL	The nanotechnological formulation of Brachydin A presented promising leishmanicidal activity, selective toxicity, and a favorable safety profile.	Costa et al.
Antiparasitic effect	*In vitro* exposure for 48 h (promastigotes and intracellular amastigotes); cytotoxicity in RAW 264.7 macrophages	ZNP-DCMF, DCMF, Blank ZNP, Pentamidine, Negative control (1% DMSO)	0.06−125 μg/mL; CC_{50} > 500 μg/mL	ZNP-DCMF: IC_{50} = 36.33 μg/mL (promastigotes), 0.72 μg/mL (amastigotes), SI = 13.77 and 694.44, respectively. DCMF: IC_{50} = 253.1 μg/mL (promastigotes), 6.96 μg/mL (amastigotes), SI = 1.98 and 71.84. Both formulations showed low cytotoxicity (CC_{50} > 500 μg/mL)	Neves et al.

[a]Prepared by the authors from the PubMed, Scielo, and Google Scholar databases. **Legend**: 15-LOX—15-Lipoxygenase; ACP02—Human gastric adenocarcinoma cell line; BCL-XL—B-cell lymphoma-extra large (antiapoptotic gene); BIRC5—Baculoviral IAP Repeat Containing 5 (Survivin gene); CC_{50}—Cytotoxic Concentration 50%; DCMF—Dichloromethane fraction of extract; DMSO—Dimethyl Sulfoxide; DXR—Doxorubicin; EO—Essential Oil; F127—Pluronic F127 copolymer; FLAB-DCM—Dichloromethane extract of F. platyphylla; FLAB-Et—Ethanol extract of F. platyphylla; FP—Fridericia platyphylla; GAS—Primary human gastric cells; HT-29—Human colorectal adenocarcinoma cell line; IC_{50}—Inhibitory Concentration 50%; IL-1β—Interleukin 1 β; IL-6—Interleukin 6; MET—Mesenchymal Epithelial Transition factor gene; MTT—3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; NHA—Normal Human Astrocytes; PBS—Phosphate Buffered Saline;

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Table 2. continued

PC-3—Human prostate cancer cell line; PI3K/AKT/mTOR—Phosphoinositide 3-kinase/Protein kinase B/Mechanistic target of rapamycin pathway; RAW 264.7—Murine macrophage cell line; SI—Selectivity Index; TMZ—Temozolomide; U-251—Human glioblastoma cell line; ZNP—Zein nanoparticles; ZNP-DCMF—Zein nanoparticles containing dichloromethane fraction.

ECD—strengthen the reliability of these findings and provide a solid scientific foundation for translational research. This is particularly relevant when coupled with nanotechnological strategies aimed at improving bioavailability, stability, and therapeutic safety.

Additionally, a new visual summary (Figure 5) was inserted to illustrate the mechanisms of action and pharmacological activities of the major bioactive compounds, facilitating a clearer understanding of their biological relevance.

The following sections discuss the main pharmacological activities reported for crude extracts and isolated bioactive compounds of *F. platyphylla* as documented in the studies included in this review.

3.1. Biological Potential, Antioxidant Effect and Possible Pharmacological Mechanisms. The search for the biological effects of extracts and bioactive compounds isolated from *F. platyphylla*, in different experimental models, has been a constant concern of the scientific community, which strives to produce studies that explain the pharmacological mechanisms associated with this species.[19,20,22] Interestingly, between 2019 and 2021, the number of published studies related to the species F. platyphylla increased significantly, reflecting the technological potential of the species for potential pharmaceutical, nutraceutical, and/or cosmetic applications of its extracts and isolated compounds. It is worth mentioning that in 2020, there was a peak in the number of published studies (n = 6), with a subsequent reduction in subsequent years (Figure 2). The growth in the number of publications related to the species reflects the evaluation of its anti-inflammatory, antioxidant, antimicrobial, and/or antiparasitic potential.

It is noteworthy that several pharmacological applications were observed due to the different characteristics of the extracts and their fractions obtained in the studies included in this review.[8,9,23] In a survey conducted by Nascimento et al., the diversity of pharmacological applications related to the characteristics of the extracts, particularly the fractions of the F. platyphylla plant, was highlighted. The research focused on the electrochemical investigation of three unusual dimeric flavonoids, Brachydins A, B and C (Figure 1), which were isolated and identified for the first time by the research group. To isolate brachydins, *F. platyphylla* roots were subjected to exhaustive percolation extraction using a mixture of ethanol and water (7:3). The crude hydroethanolic extract obtained was then subjected to a liquid/liquid partition using dichloromethane (CH_2Cl_2) and a water/methanol solution (7:3). The resulting fraction was analyzed by high-performance liquid chromatography with photodiode array detection (HPLC-PDA) at λ = 254 nm. Cyclic voltammetry (CV) and differential pulse voltammetry (DPV) revealed that brachydin A is more easily oxidized, presenting an oxidation peak at +0.48 V, compared to brachydins B (+0.71 V) and C (+0.57 V) due to the presence of an hydroxyl group (−OH) in the D ring. The research also highlights the significant influence of the substituent in the D ring and the pH of the environment on the antioxidant capacity and redox behavior of the brachydins. With increasing pH, the oxidation potentials of the three brachydins shift to less positive values, confirming a direct relationship between pH and the facilitation of flavonoid oxidation, where oxidation is more pronounced for brachydin A due to its chemical structure.[18] Another important discussion was the influence of chemical substituents attached to the aromatic rings of flavonoids. The results indicate that

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Table 3. Experimental Design, Dosing, and Outcomes of *In Vivo* Studies with *F. platyphylla*[a]

experimental model	administration form	model system specifications	groups	*In vivo* monitoring	dose or concentration administered *in vivo*/*in vitro*	main findings	references
Effect on mice infected with *T. cruzi*	Oral gavage (once a day) for consecutive days	BALB/c mice (female, 6−8 weeks)	Control, Benznidazole, Amphotericin B, brachydin A, brachydin B, and brachydin C (n = 6)	30 days postinfection	100 mg/kg (*in vivo*); 1.23−100 μg/mL (*in vitro*)	Brachydin B and C reduced parasitemia in *T. cruzi*	Rocha et al.
Antiulcer effect in rats (induced ulcers)	Single dose, oral gavage	Wistar rats (male, 6−8 weeks)	Control group: (saline 10 mL/kg) Lansoprazole group: (60 mg/kg) HEAb groups (10, 30, 100, and 300 mg/kg)	Days 0, 7, and 14 postinduction	10, 30, 100 e 300 mg/kg	HEAb demonstrated antiulcer activity comparable to that of lansoprazole	Rocha et al.
Nociception test in adult mice	Oral gavage, once a day, single dose	Adult male Swiss mice, 20−35 g, n = 8	Saline solution 10 mL/kg DEAB fraction 30 mg/kg Morphine 2.5 mg/kg	Immediate postdose	10, 30 ou 100 mg/kg	DEAB reduced pain in mice in the formalin test	Rodrigues et al.
Effect against *L. amazonensis*	Oral gavage, once a day, for 3 *weeks*	Female BALB/c mice (4−8 weeks); macrophages from BALB/c	Control, Amphotericin B and brachydin B	3 weeks after treatment	*In vitro:* dose de 0.25 a 20 μM *In vivo*: maximum of 2 μM	Brachydin B was effective against *L. amazonensis* promastigotes with no significant toxicity	Rocha et al.
DCM fraction in microemulsion	Single-dose injection	*In vivo:* Evaluation of cytotoxicity of healthy larvae of the species *Tenebrio molitor* weighing approximately 100−200 mg *In vitro:* ME of DCM fraction were formulated at concentrations of 3% and 5% (ME3 and ME5)	Control group with 1% DMSO, DCM fraction (10 μL), and ME3 groups with concentrations of 1 μg/kg, 5 μg/kg, 10 μg/kg, 50 μg/kg , and 100 μg/kg. For the *in vitro* test, a solution containing DCM fraction (LC) was compared with microemulsion groups containing DCM at concentrations of 3 and 5%	The viability of the larvae was monitored 24 h after the injections were administered, assessing the absence of movement over 7 days	*In vivo:* were administered 10 μL doses of DCM fraction; microemulsion groups received 1−100 μg/mL *In vitro:* Tests used a saturated DCM fraction solution compared with microemulsions at 3 and 5% DCM	The microemulsion demonstrated high stability and a safe release of DCM in larvae	Nascimento et al.

[a]Source: Prepared by the authors from the PubMed, Scielo, and Google Scholar databases. Legend: BALB/c—Albino laboratory-bred mouse strain (Bagg Albino Laboratory-Bred); DCM—Dichloromethane; DEAB—Dichloromethane extract of F. platyphylla; F. platyphylla—Fridericia platyphylla; HEAb—Hydroethanolic extract of F. platyphylla; LC—Liquid Chromatography (or DCM solution, context-dependent); ME3—Microemulsion 3%; ME5—Microemulsion 5%; Tenebrio molitor—Larvae used as *in vivo* toxicity model organism; Wistar—A common strain of albino rats used in laboratory research.

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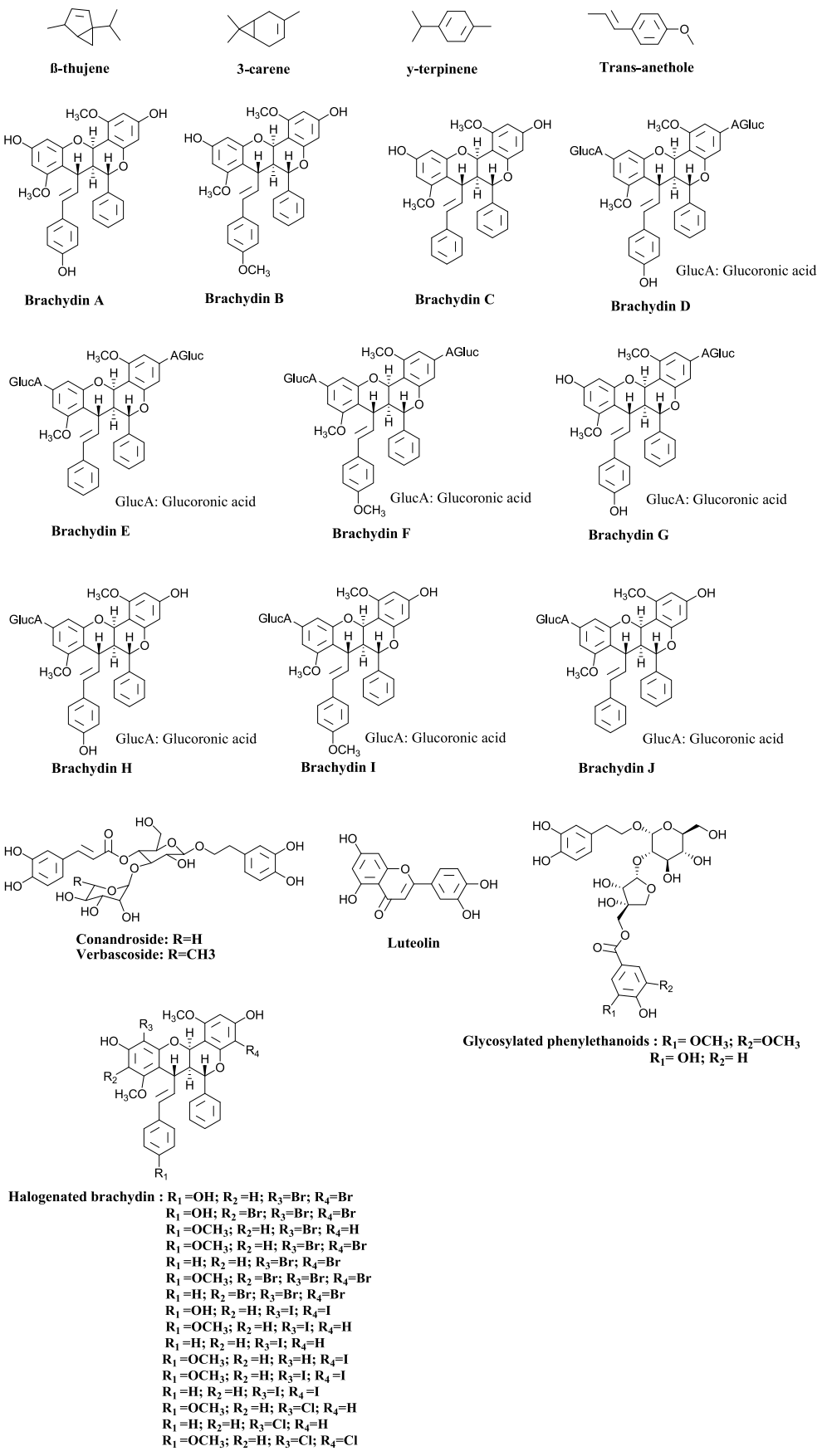

Figure 1. Structure of identified compounds from *F. platyphylla* or its synonym *A. brachypoda*.

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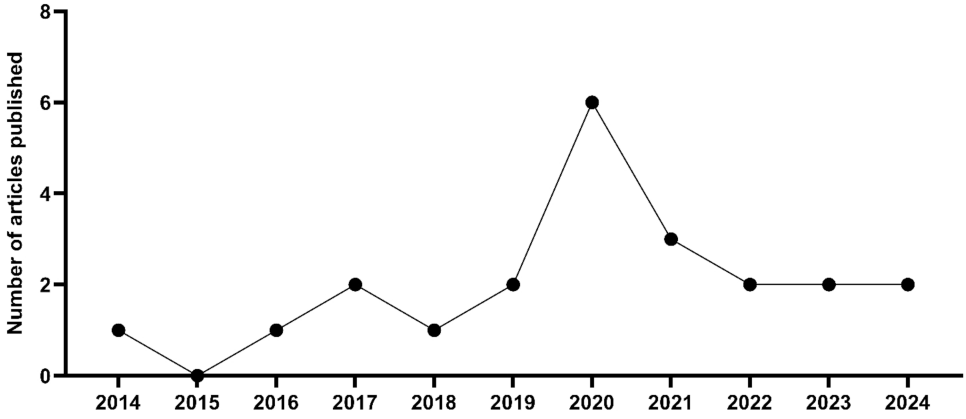

Figure 2. Temporal evolution of articles published with the species *F. platyphylla* or its synonym *A. brachypoda* (2014−2024). **Source**: Prepared by the authors from the PubMed, Scielo and Google Scholar databases.

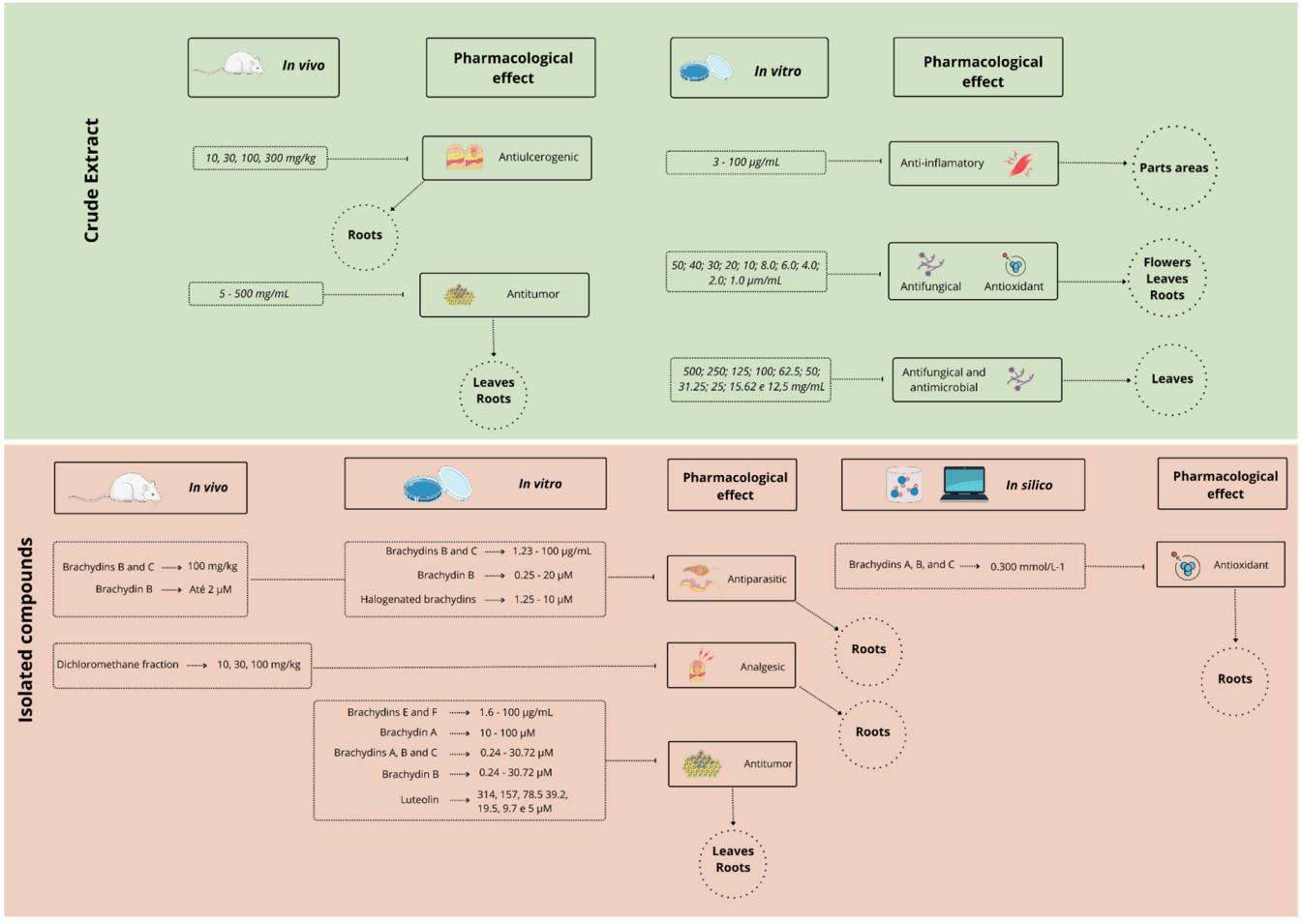

Figure 3. Pharmacological effects related to the dose of crude extract or phytochemical compounds isolated from *F. platyphylla*. **Source**: Prepared by the authors based on the studies included in this review. This Figure was created using Servier Medical Art (https://smart.servier.com/), licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

electron-attracting groups, such as nitro ($-NO_2$) and carbonyl (C═O) groups, tend to hinder oxidation, while electron-donating groups, such as methoxyl ($-OCH_3$) and hydroxyl (−OH), can facilitate electron loss, reflecting how chemical substitution can impact the redox behavior of flavonoids. Furthermore, everything revealed that the hydroxyl groups of ring B of flavonoids did not undergo oxidation. This is due to the lack of resonance between rings B and C, as well as the absence of a double bond and electronegative groups, which justify the electrochemical inactivity of ring B.[24]

Phenolic compounds, especially flavonoids, are known for their antioxidant properties, which are closely linked to the presence of hydroxyl groups.[24] In previous studies, such as that carried out by Gomes et al.,[25] it was observed that the addition of more hydroxyl groups to flavones and 2-styrylchromones led to a decrease in the anodic peak potential, indicating that these

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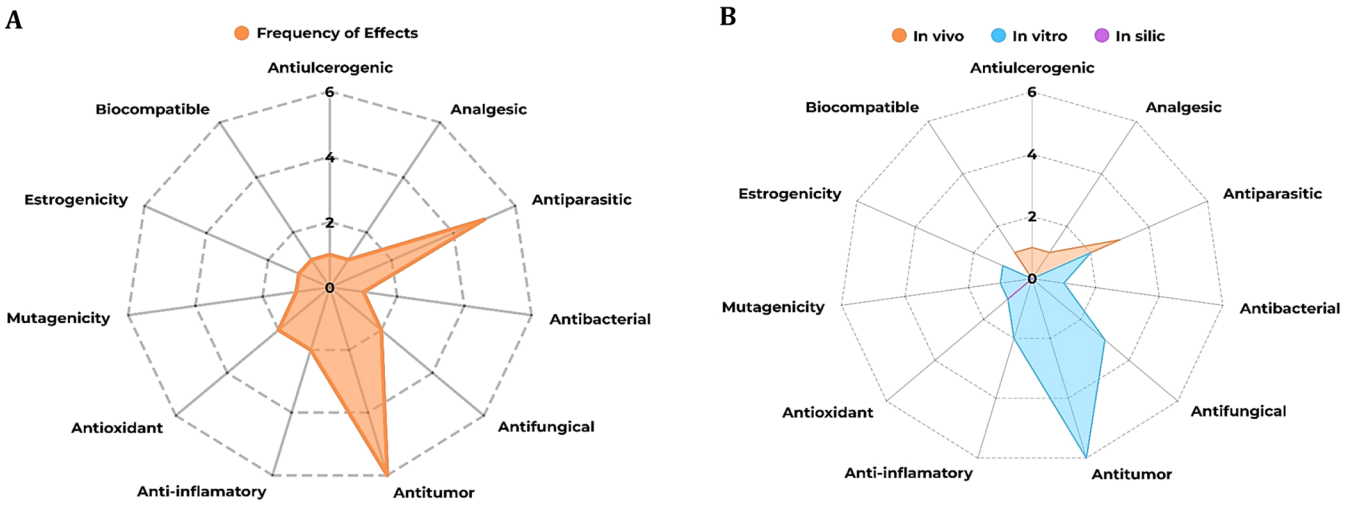

Figure 4. Effects related to the use of *F. platyphylla* or its synonym *A. brachypoda in vitro, in vivo*, and *in silico* models. Summary of pharmacological data related to *F. platyphylla*. (A) Frequency of pharmacological effects attributed to the crude extract or bioactive compounds. (B) Frequency distribution of study types investigating these effects, categorized *as in vitro, in vivo*, and *in silico*. **Source**: Prepared by the authors based on the studies included in this review.

compounds became progressively more susceptible to oxidation. However, the oxidation dynamics of brachydins—a specific type of phenolic dimers—reveal a different behavior. Despite also containing hydroxyl groups, the molecular structure of brachydins modifies their electrochemical properties. Specifically, the −OH group located in ring B is not in resonance with ring C. The lack of resonance implies that the electron density is not efficiently shared between the rings, resulting in greater difficulty in oxidizing the −OH group of ring B, particularly when compared to compounds with rings that present effective resonance between hydroxyl groups and aryl structures.[24]

3.2. Potential Antiparasitic Treatment. Rocha et al. evaluated the efficacy of nonpolar fraction of an aqueous ethanol extract of the roots of *F. platyphylla* against *T. cruzi*, the parasite responsible for Chagas disease. The extract was subjected to liquid−liquid partitioning with dicloromethane (CH_2Cl_2) and water:methanol (H_2O-MeOH, 7:3) and then fractionated by medium-pressure liquid chromatography (MPLC) using a Zeoprep C18 column. This resulted in 235 fractions, among these, Brachydins A, B, and C were identified. Their structures were elucidated using Ultraviolet spectroscopy (UV), Nuclear Magnetic Resonance (NMR), and High-Resolution Mass Spectrometry (HRMS) analysis, as well as by chemical derivatization. Brachydin A showed no activity against trypomastigotes *T. cruzi* (IC_{50} > 20 μM), while Brachydins B and C exhibited selective activity with inhibitory concentration (IC_{50}) values of 5.3 and 6.6 μM, respectively. Both inhibited the parasite's invasion and intracellular development, comparable to benznidazole (IC_{50} 11.3 μM), reference compound. Against intracellular amastigotes of *T. cruzi*, Brachydins B and C demonstrated IC_{50} values of 6.0 μM and 6.8 μM. In comparison, the reference drug benznidazole exhibited an IC_{50} value of 14.0 μM in the same assay. This indicates that Brachydins B and C could potentially inhibit the parasite's intracellular development effectively, making them promising candidates for the development of new anti-*T. cruzi* drugs.[11]

In 2019, the same group evaluated the antileishmanial activity of flavonoids Brachydins A, B and C against promastigotes and amastigotes of three *Leishmania* species (*L. amazonensis*, *Leishmania infantum* and *Leishmania braziliensis*) using the viability assay based on the metabolism of Alamar Blue. Similar to *T. cruzi* activity, Brachydin A also demonstrated no significant activity against *Leishmania* species, with an IC_{50} greater than 20 μM. While Brachydin B and C demonstrated activity against all three tested species of *Leishmania* promastigotes, it was Brachydin B (*L. amazonensis*, IC_{50} = 9.16 μM; *L. braziliensis*, IC_{50} = 7.05 μM; *L. infantum*, IC_{50} = 12.90 μM) that stood out significantly. Brachydin B not only exhibited superior potency compared to the other compounds, but it was also the most effective against intracellular amastigotes of *L. amazonensis*, with an IC_{50} value of approximately 2.20 μM. Its ability to inhibit the proliferation of intracellular forms of the parasite without causing toxicity to host cells makes Brachydin B a promising candidate for the development of new treatments for leishmaniasis. The positive control used was amphotericin B, which presented an IC_{50} of 0.14 μM against *L. amazonensis*, 0.11 μM against *L. braziliensis* and 0.05 μM against *L. infantum*. Notably, Brachydin B showed a significant reduction in lesion size in an experimental model of cutaneous leishmaniasis.[23]

The studies demonstrate that, although Brachydin A does not present significant activity against *T. cruzi* and *Leishmania* spp, Brachydins B and C exhibit promising potencies. The presence of functional groups and the structural configuration of Brachydins, such as methoxylated groups and substituents that promote greater lipophilicity, are fundamental for their ability to penetrate the cell membranes of parasites and enhance their antiprotozoal activity. Brachydin B, in particular, demonstrated remarkable selectivity and efficacy in inhibiting the proliferation of intracellular amastigotes, and also stands out for not causing toxicity to host cells.[11,17]

The study carried out by Neuenshwander et al. described how the halogenation process can increase the biological activity of phenolic compounds present in the dichloromethane (CH_2Cl_2) fraction of *F. platyphylla* root extract against *L. amazonensis* and *T. cruzi*. The halogenation reactions used eco-friendly conditions with sodium bromide (NaBr), sodium iodide (NaI), and sodium chloride (NaCl), monitored

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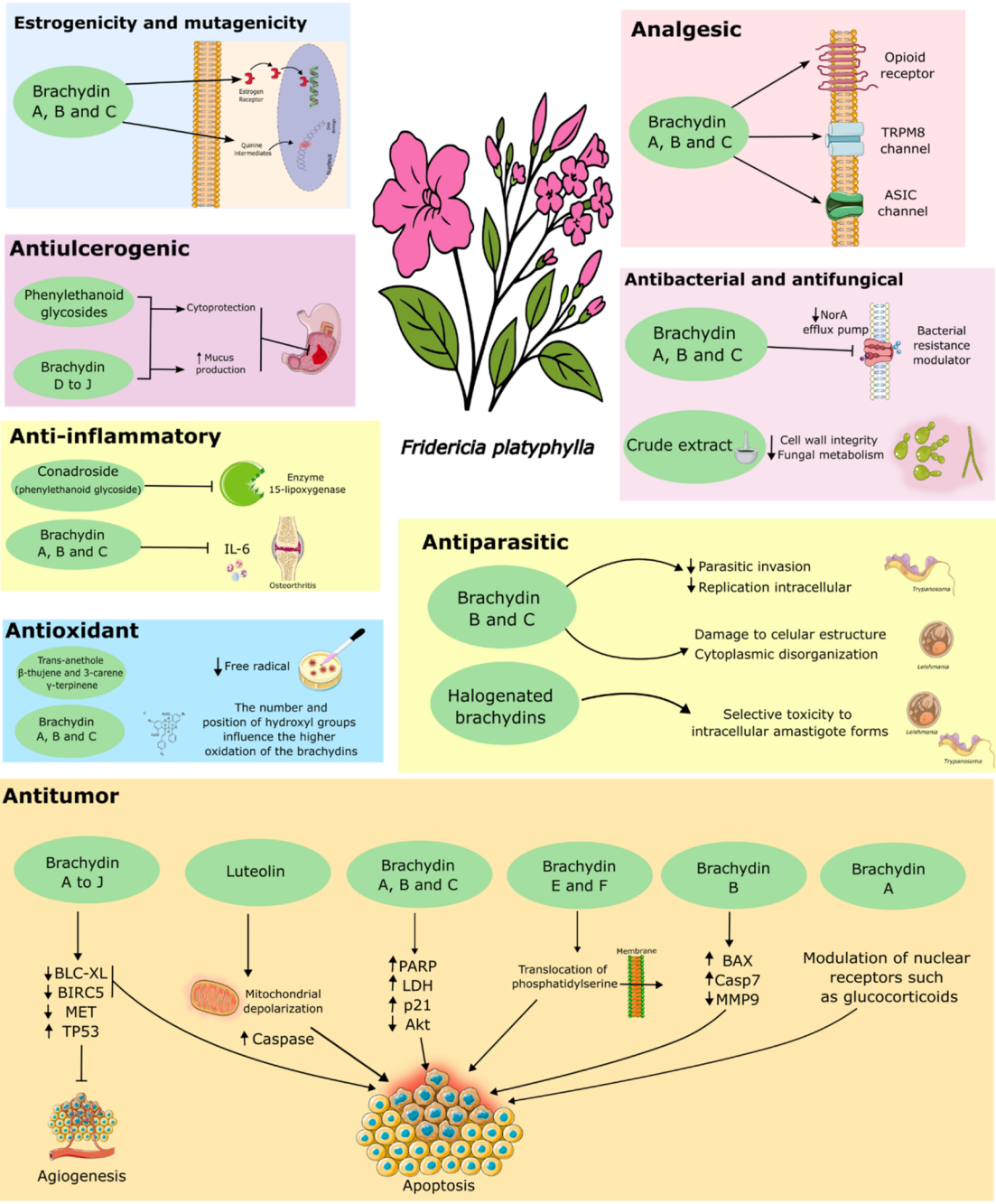

Figure 5. Mechanism of action and pharmacological activies of bioactive compounds from *F. platyphylla*. Representative image of the main results obtained from the use of the extract and/or compounds isolated from the species *F. platyphylla* in different experimental models. **Source**: Prepared by the authors based on the studies included in this review. This Figure was created using Servier Medical Art (https://smart.servier.com/), licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

by Ultra-High Performance Liquid Chromatography with Photodiode Array, Evaporative Light Scattering, and Mass Spectrometry (UHPLC-PDA-ELSD-MS). The halogenated derivatives were isolated *via* semipreparative High-Performance Liquid Chromatography (HPLC-UV) and characterized by Nuclear Magnetic Resonance (NMR) and High-Resolution Mass Spectrometry (HR-MS). All the 16 halogenated derivatives were evaluated for their antiparasitic activities against the parasites *L. amazonensis* and *T. cruzi*. Compounds 10 (IC_{50} = 1.0 μM) and 18 (IC_{50} = 1.2 μM) exhibited particularly strong selective antiparasitic activity against *L. amazonensis*. In contrast, compounds 8, 14, 17, and 18 demonstrated significant efficacy against *T. cruzi*, with IC_{50} values ranging from 1.4 to 1.6 μM. When compared to the positive control, amphotericin B, which has an IC_{50} of 0.2 μM, these compounds show promising potential as effective treatments for these parasitic infections. The study demonstrated that the introduction of halogens, such as bromine and iodine, in specific positions of these molecules contribute significantly to the expansion of antiparasitic efficacy, highlighting the potential of these halogenated derivatives as promising therapeutic agents against these parasitic infections.[19]

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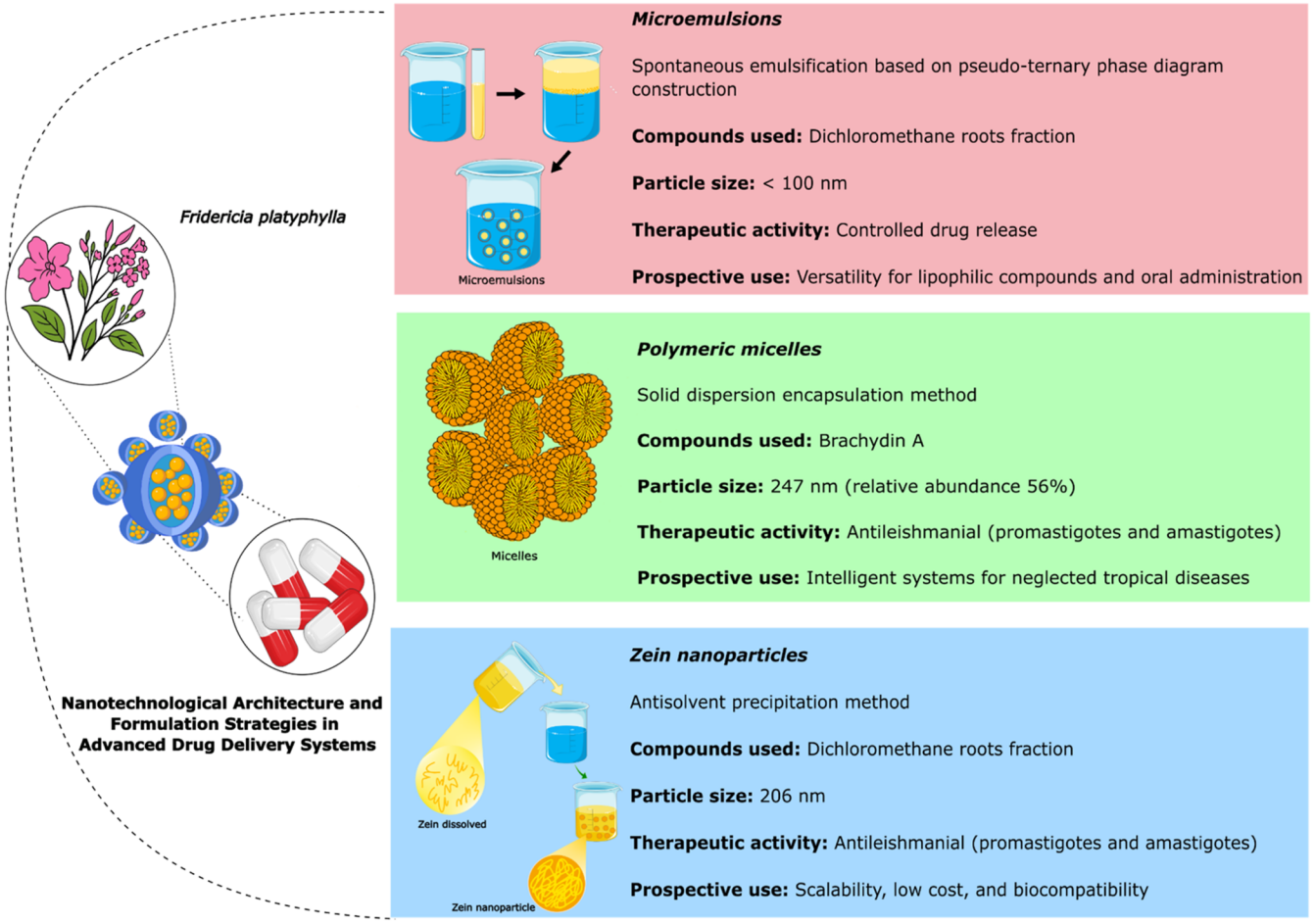

Figure 6. Advanced Drug Delivery Systems Based on *F. platyphylla*: Microemulsions, Polymeric Micelles, and Zein Nanoparticles Representative image of the main results obtained in advanced drug delivery systems based on *F. platyphylla*. **Source**: Prepared by the authors based on the studies included in this review. This Figure was created using Servier Medical Art (https://smart.servier.com/), licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

In parallel, a study evaluated the antiparasitic activity of brachydin A after its encapsulation into F127 polymeric micelles (LF-B500: Brachydin A-loaded F127 m/v 0,125%; Brachydin A-loaded F127 m/v 0,25%; and Brachydin A-loaded F127 m/v 0,50%), which exhibited significant activity against *L. amazonensis* promastigotes, with an IC_{50} of 16.06 μg/mL for the LF-B500 formulation.[26] Simultaneously, the formulation showed low cytotoxicity against murine RAW 264.7 macrophages, with a 50% cytotoxic concentration (CC_{50}) of 171 μg/mL. The difference between the IC_{50} for the parasite and the CC_{50} for the host cells resulted in a high selectivity index (SI = 10.64) for promastigotes compared to RAW cells, suggesting that the formulation is more toxic to the parasite than to host cells - an essential factor in the development of safe and effective treatments for leishmaniasis.[26]

Neves et al. investigated the antileishmanial potential of the DCMF (roots), which are known to be enriched in the dimeric flavonoids Brachydins A, B, and C. The crude extract was obtained by percolation with an ethanol/water mixture (7:3) and subjected to liquid−liquid partitioning to isolate the DCMF.[27] Chemical profiling using HPLC-PDA and LC-MS confirmed the predominance of brachydins in the fraction. To enhance the solubility, bioavailability, and biological performance of these compounds, DCMF was incorporated into zein nanoparticles (ZNP-DCMF) *via* antisolvent precipitation in the presence of Pluronic F-68.[27] Among the concentrations tested (0.5 to 10 mg/mL), the formulation containing 0.5 mg/mL of DCMF showed the most outstanding colloidal stability and was selected for further assays. The physicochemical properties of ZNP-DCMF were evaluated through dynamic light scattering (DLS), ζ-potential, and atomic force microscopy (AFM), revealing particles with an average diameter of 206 nm, a polydispersity index below 0.2, and spherical shape.[27] Encapsulation was further confirmed by Fourier-transform infrared spectroscopy (FTIR), which evidenced physical interactions through the suppression of characteristic DCMF signals, and by differential scanning calorimetry (DSC), which showed thermal shifts indicative of matrix−flavonoid integration.[27] The formulation achieved an encapsulation efficiency above 94% and maintained structural stability for at least 49 days at room temperature. Biological evaluation of ZNP-DCMF against promastigote and intracellular amastigote forms of *L. amazonensis* revealed an IC_{50} of 36.33 and 0.72 μg/mL, respectively—the latter significantly outperforming the free DCMF (IC_{50} = 6.96 μg/mL). In cytotoxicity assays with RAW 264.7 murine macrophages, the formulation demonstrated low toxicity (CC_{50} > 500 μg/mL), resulting in a high SI (694.44). Overall, these results highlight that nanoencapsulation markedly improves the physicochemical and pharmacological attributes of DCMF, underscoring

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the promise of ZNP-DCMF as a candidate for innovative antileishmanial therapies.[27]

3.3. Potential Antinociceptive and Anti-Inflammatory. Rocha et al. investigated the mechanisms of action of the bioactive compounds of the hydroethanolic extract of the root of *F. platyphylla*. obtained by method of percolation with ethanol and water (70% v/v). The characterization of the compounds included UV spectroscopy, nuclear magnetic resonance (NMR), and high-resolution mass spectrometry (HRMS), resulting in the identification of seven glycosylated dimeric flavonoids and two unprecedented derivatives of phenylethylamine glycosides in literature. The absolute configuration of the isolated dimeric flavonoids was determined using electronic circular dichroism (ECD) spectroscopy. The gastroprotective effects were tested in male Wistar rats in several models of gastric ulcer, showing a significant reduction in gastric damage at a dose of 300 mg/kg, similar to lansoprazole (60 mg/kg). The metabolization of the compounds suggests that glycosides and aglycones may be involved in the observed effects. Appropriate controls, including carbenoxolone (100 mg/kg), confirmed that the extract did not affect motor coordination, validating that its gastroprotective effects were not due to sedation. The results highlight its potential as a gastroprotective agent and corroborate its use in folk medicine.[4]

In addition, the study examined the mechanisms of action of bioactive compounds present in the dichloromethane fraction (DEAB) from the roots of *F. platyphylla*.[20] The DEAB fraction was obtained through liquid−liquid extraction, using dichloromethane as a solvent. The characterization of the compounds was performed by high-performance liquid chromatography (HPLC), which accurately identified three dimeric flavonoids known as brachydins A, B, and C. The antinociceptive activity of DEAB was tested in male Swiss mice using formalin and hot plate tests. The fraction demonstrated efficacy at doses ranging from 10 to 100 mg/kg, indicating its potential as an antinociceptive agent. The study also investigated the mechanisms of action, identifying the involvement of ion channels such as TRPV1 (transient receptor potential vanilloid 1), ASIC (acid-sensing ion channels), TRPM8 (transient receptor potential melastatin 8), and TRPA1 (transient receptor potential ankyrin 1) in pain modulation. Control tests were conducted, including groups treated with a vehicle and diazepam (2 mg/kg) as a positive control, which induced a sedative effect and allowed for the assessment of whether DEAB affected the motor coordination of the mice. Locomotor performance was evaluated using a rotarod apparatus, revealing that DEAB did not significantly influence the motor coordination of the animals, confirming that the antinociceptive effect was specific and not due to a sedative effect.[20]

F. platyphylla is associated with inflammatory process regulation in several pathologies, such as rheumatoid arthritis, atherosclerosis, and cancer.[20,28,29] Research carried out by Bertanha et al. investigated the anti-inflammatory potential of *F. platyphylla* through the inhibition of lipoxygenase (LOX), an enzyme involved in inflammatory processes. The ethanolic extract from the aerial parts of the plant was subjected to microfractionation using high-performance liquid chromatography (HPLC-DAD) to identify bioactive compounds. The microfractions were collected and tested in *in vitro* assays to evaluate their ability to inhibit LOX. Additionally, the crude extract was analyzed by high-resolution mass spectrometry (HPLC-HRMS) to identify the components present, while the extract was purified through solid-phase chromatography and semipreparative HPLC. The isolated compound, identified as conandroside, exhibited LOX inhibitory activity with a IC_{50} of 7.8 μM, similar to quercetin (IC_{50} of 7.6 Mm). The study found no significant toxicity of conandroside in normal cells, suggesting its potential as a lipoxygenase inhibitor and its value in the search for new anti-inflammatory agents.[3]

Given the similarity in lipoxygenase (LOX) inhibitory activity between conandroside and quercetin, molecular docking simulations of the two compounds become essential for elucidating their interactions. Conandroside forms hydrogen bonds with His373 and Ile676, stabilizing the enzyme complex and inhibiting the enzyme's activity. Its interaction with the Fe^{3+} ion modifies the redox cycle of LOX, while π-π and cationic interactions with Phe192 and Arg429 enhance its efficacy. Quercetin, although it has fewer hydrogen bonds, possesses a compact structure that promotes strong interactions with LOX, resulting in a similar inhibition profile. This understanding of the structure−activity relationship (SAR) is crucial for the development of new LOX inhibitors.[3]

On the other hand, Salgado et al. focused on the modulation of the levels of the pro-inflammatory cytokine IL-6 from the dichloromethane (DCMAB) and hydroethanolic (HEAB) fractions derived from the root extract of *F. platyphylla*. High-performance liquid chromatography with photodiode array detection (HPLC-PDA) was used to analyze the fractions, while the DCMAB was fractionated by medium-pressure liquid chromatography (MPLC), and the dimeric compounds brachydins A, B, and C were isolated using high-speed counter-current chromatography (HSCCC). For quantification, the fractions were analyzed by UHPLC-MS/MS, increasing the sensitivity in determining the bioactive compounds present. The Enzyme-Linked Immunosorbent Assay (ELISA) method was used to quantify anti-inflammatory activity. This assay measured the levels of the pro-inflammatory cytokine IL-6 in synoviocytes activated with IL-1β after incubation with extracts and isolated compounds. The results demonstrated that the DCMAB effectively inhibited the release of IL-6, while the HEAB showed no significant effect. The higher presence of brachydins B and C in the DCMAB is related to its anti-inflammatory potential, highlighting the role of these compounds in the traditional use of the plant to treat inflammatory conditions such as osteoarthritis.[16]

3.4. Potential Antitumor Agent. In the study conducted by Franco et al., luteolin, a flavonoid isolated from *F. platyphylla*, demonstrated significant antiproliferative activity against glioblastoma multiforme (GBM), one of the most aggressive types of brain tumors. The dried leaves of *F. platyphylla* were extracted by exhaustive percolation with 70% ethanol at room temperature, followed by liquid−liquid partitioning and isolation of luteolin from the ethyl acetate fraction using silica gel column chromatography. The compound was identified through ultraviolet (UV) spectroscopy, nuclear magnetic resonance (NMR) spectroscopy, and mass spectrometry (MS). The cytotoxic activity of luteolin was evaluated against a panel of tumor cell lines (U-251, NCI-ADR/RES, 786−0, NCI-H460, PC-3, HT-29) and nontumor cell lines (HaCaT and NHA) using the MTT assay (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide), which measures mitochondrial metabolic activity as an indirect indicator of cell viability. After 48 h of exposure, luteolin exhibited potent antiproliferative effects, achieving a GI_{50} value

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of 6.6 μM for U-251 cells, significantly lower than that of the standard chemotherapeutic agent Temozolomide (TMZ), which presented a GI_{50} of 873 μM. Although the selectivity index (SI) of luteolin (0.98) did not reach the ideal threshold ($\geq$2.0), it was substantially higher than that of TMZ (0.06), suggesting relatively greater selectivity of luteolin toward tumor cells. Moreover, luteolin demonstrated lower toxicity to nontumor cells compared to TMZ. Additional functional assays revealed that luteolin significantly inhibited the migration and colony formation of U-251 cells, reducing the number of colonies by 82% after 21 days of treatment. Mechanistic studies indicated that luteolin induced apoptosis in U-251 cells through mechanisms involving mitochondrial membrane depolarization, phosphatidylserine externalization, cleavage of PARP and caspase-9, and increased phosphorylation of ERK and H2AX proteins, suggesting mitochondrial-mediated apoptosis and DNA damage.[30]

Studies carried out with the extract of *F. platyphylla* roots demonstrated selectivity in tumor cells, inducing necrosis and altering the expression of genes related to apoptosis and the cell cycle.[22] The researchers investigated the cytotoxic and antiproliferative effects of *F. platyphylla* roots on normal (GAS) and tumor cells (ACP02 and HepG2). The extract was prepared by exhaustive percolation using a mixture of ethanol and water in a 7:3 ratio, at room temperature, and was analyzed by liquid chromatography coupled to mass spectrometry (LC/MS), identifying the presence of dimeric flavonoids, known as brachydins (A to J), which have recognized pharmacological properties, including cytotoxic activity. The effects of the extract were measured by cell viability assays, such as MTT and neutral red. The effective concentrations (EC_{50}) obtained indicated significant efficacy: 56.16 mg/mL for GAS cells, 43.68 mg/mL for ACP02 and 42.57 mg/mL for HepG2. Furthermore, the data suggested a significant decrease in nuclear division rates in tumor cells treated with the extract, although this decrease was not reflected in the cell proliferation curves, implying that although the extract causes cell death, this does not necessarily translate into short-term cell growth inhibition. This complexity may be due to underlying mechanisms, such as the induction of apoptosis or necrosis, which may not manifest in a linear manner in the cell growth curves.[22]

The cytotoxic effects of Brachydins A, B, and C, dimeric flavonoids isolated from the roots of *F. platyphylla*, were investigated in a study using prostate cancer PC-3 cells. The isolation and structural elucidation of the brachydins were detailed in the work by Rocha et al., where advanced techniques such as nuclear magnetic resonance (NMR) and high-resolution mass spectrometry (HRMS) were utilized. The structural differences among the three brachydins are subtle, with BrA containing a hydroxyl group, BrB having a methoxy group, and BrC consisting of a single hydrogen. The study assessed the cytotoxic effects of brachydins on the PC-3 cell line using concentrations ranging from 0.24 to 30.72 μM and employed three viability assays: MTT, neutral red, and LDH release. Results indicated that brachydins significantly decreased cell viability compared to the negative control (PBS), with brachydins B exhibiting the highest cytotoxicity. The IC_{50} values were determined as 23.41 μM for brachydins A, 4.28 μM for brachydins B, and 4.44 μM for brachydins C. Morphological analysis showed increased apoptosis induced by the brachydins, particularly with brachydins B at 6 μM, significantly reducing cell viability. Compared to the positive control (Docetaxel at 10 μM), brachydins demonstrated promising effects, especially brachydins B, implying its potential as an alternative or complementary cancer treatment. Furthermore, elevated levels of p21 protein were observed in cells treated with brachydins B and brachydins C, suggesting a potential G1 phase cell cycle arrest. Analysis of pAKT protein expression showed significant reductions following treatment with BrA and BrB, indicating that these brachydins impact cell proliferation pathways. Overall, these findings highlight brachydin B as an appealing candidate for future investigations in cancer therapies.[8]

The studies carried out on the flavonoids Brachydin A and Brachydin B illustrate the promising antitumor effects and the mechanisms of action in DU145 metastatic prostate cancer cells, emphasizing their potential therapeutic applications.[21,24] Brachydin A demonstrates significant cytotoxic properties in tumor spheroids of DU145, with cytotoxicity observed in concentrations of 60 to 100 μM, as evidenced by acid phosphatase and resazurin assays. The antitumor activity of BrA has been attributed to mechanisms that include the promotion of DNA damage and the induction of parthanatos, a form of cell death mediated by the activation of poly(ADP-ribose) polymerase (PARP). Furthermore, Brachydin A increases the activity of caspases and alters the levels of anti/pro-apoptotic markers, indicating their interference in the signaling pathways of cell survival, making tumor cells more susceptible to apoptose. Brachydin A also demonstrates effectiveness in inhibiting cellular migration and invasion, addressing a critical challenge in the management of metastatic spread of prostate cancer. Compared to the positive control Docetaxel (50 μM), which is a parent chemotherapeutic agent, or Brachydin A can offer a therapeutic alternative with lower toxicity potential for normal cells, promoting a safer and more effective approach in the treatment of the disease.[21]

Similarly, the study on the flavonoid Brachydin B in metastatic DU145 cells revealed promising antitumor and antimigratory effects. O Brachydin B exhibited cytotoxicity from 1.50 μM after 24 h in 2D cultures, as measured by MTT and resazurin assays. In 3D tumor spheroid models, cytotoxicity was observed in higher concentrations after prolonged periods. BrB also reduces clonogenicity in 2D cultures and reduces the volume of tumor spheroids. Furthermore, we inhibited cell migration at 6 μM in 2D monolayers and showed antimigratory effects in spheroids starting at 30 μM. These results highlight BrB as a potential therapy for metastatic prostate cancer, encouraging additional research.[24] The details regarding the extraction, isolation, and identification of Brachydin A and B were previously reported by Rocha et al.

These compounds, Brachydin A and Brachydin B showed potential as therapeutic agents against metastatic prostate cancer. While Brachydin A can induce cell death through specific mechanisms, offering a safer alternative in relation to conventional chemotherapy drugs such as Docetaxel, Brachydin B ability to promote cytotoxicity in 2D and 3D models further reinforces its therapeutic promise. Together, these studies encourage additional exploration of Brachydins as viable options for the treatment of metastatic prostate cancer, possibly with lower toxicity for normal cells.[21,24]

The antiproliferative and cytotoxic potential of the crude hydroethanolic extract and its subfraction, which contains 59.3% of Brachydin E and 40.7% of Brachydin F, as well as two composts isolated from the roots of *F. platyphylla* foram

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investigated. The crude hydroethanolic extract, subfractionated and the Brachydin E and Brachydin F composts obtained according to Rocha et al., Por meio liquido−liquido partição com CH_2Cl_2 e H_2O-MeOH (7:3). The hydromethanolic fraction was fractionated by column chromatography, resulting in a subfraction containing Brachydin E and F, whose quantity was determined by HPLC-PDA and analyzed by NMR to confirm purity. Cytotoxic activity was assessed using the MTT method in cell lymphocytes from glioblastoma (U-251), lung (NCI-H460), prostate (PC-3) and colon (HT-29). The data indicate that the isolated extracts and composts of *F. platyphylla* present variable cytotoxic activities according to the form of the extract and the cell lines tested. The crude hydroethanolic extract had an IC_{50} of 95.8 μg/mL in U-251 (glioblastoma) and did not show significant effects in other cases, suggesting the presence of components that could dilute its effectiveness. In contrast, a subfraction, enriched in dimeric flavonoids Brachydin E and F, exhibited better performance, with IC_{50} of 47.7 μg/mL in U-251 and 42.5 μg/mL in PC-3 (prostate). Noteworthy is Brachydin E, which presented an IC_{50} of 5.9 μg/mL in PC-3, indicating promising therapeutic potential. Comparing doxorubicin as a positive control, which has an IC_{50} of 2.1 μg/mL in PC-3, the flavonoids show antitumor efficacy, but with lower potencies. The IC_{50} values for Brachydin F foram reported as 33.1 μg/mL in PC-3 and 44.1 μg/mL in U-251, indicating that, although less potent than Brachydin E, it also presents significant cytotoxic activity. The selectivity of two composts, especially Brachydin E, against tumor cells in relation to healthy cells, suggests potential therapeutic use in oncological treatments, deserving more in-depth investigation.[9]

3.5. Potential Antimicrobial Agent. Studies with *F. platyphylla* demonstrate its antifungal potential against several strains of Candida, including *C. tropicalis*, *C. guilliermondii*, *C. albicans*, and *C. krusei*, with the hydroethanolic extract showing inhibitory activity.[31] The flower extract was obtained by maceration method with a 70% hydroethanolic solution. The antifungal activity on Candida sp. was carried out using paper disk diffusion methodology, and the cytotoxic activity on *A. salina*, both assays in different concentrations of extract. The results will show that the *F. platyphylla* floral extract presents significant inhibitory activity against *C. guilliermondii*, with inhibition zones varying from 13.8 to 9.7 mm and against *C. albicans*, with measurements of 18.6 to 14.5 mm in higher concentrations of 50 to 100 mg/mL, respectively. Furthermore, the cytotoxicity of extracts of *F. platyphylla* was evaluated in tests with *A. salina*. The extracts demonstrate toxicity, with Letal concentration (LC_{50}) values of 237.81 μg/mL, which highlights its potential as a source of antifungal and cytotoxic agents.[25] Unfortunately, minimum inhibitory concentrations (MIC) and chemical composition were not determined.

The essential oil in the flower also inhibits phytopathogenic fungi such as *S. sclerotiorum* and has antioxidant activity. *Brachydin-B* demonstrated antifungal activity against *C. albicans*, and the hydroethanolic extract and the dichloromethane fraction increased the efficacy of the antibiotic Norfloxacin against *S. aureus*, suggesting a potential to alter microbial resistance. These results highlight *F. platyphylla* as a promising source of antifungal compounds, indicating the need for further studies on its mechanisms of action and therapeutic potential.[22]

3.6. Microemulsion is a Potential Delivery System for Enhanced Therapeutic Efficacy and Safety. The research by Nascimento et al. showed that microemulsion developed, incorporating a flavonoid-rich compound from the roots of *F. platyphylla*, releases the active compound more efficiently than soluble forms and presents excellent physical and chemical stability. The fraction dichloromethane (DCM) extracted from the roots of *F. platyphylla* is rich in dimeric flavonoids, specifically the composts made as brachydins A, B and C. The development of microemulsion used a pseudoternary diagram to identify the ideal proportions of water, isopropyl myristate and surfactants, resulting in white microemulsifiers (ME), with 3% (ME3) and 5% (ME5) of the DCM fraction. ME3 has particle sizes less than 100 nm, stability under extreme conditions and favorable organoleptic characteristics, such as transparency, physiologically oily pH, refractive index of 1.42 and density of 1.017 g/cm^3. Stability tests indicate that microemulsifiers do well even after exposure to extreme thermal conditions, with minimal variations in pH and the concentration of the incorporated fraction. The *in vitro* release study showed that ME3 provided a controlled release of the fraction, with more than 60% released in 6 h. Additionally, toxicity tests of the DCM fraction and the ME3 microemuls were carried out using *Tenebrio molitor* larvae as an experimental model. The larvae, saudaveis and weighing between 100 and 200 mg, were distributed in 14 groups, with injections of 10 μL of substances in concentrations of 1 to 100 μg/mL. Control groups were used to ensure precise results. The viability was monitored for 7 days, and the results will show that both substances do not cause toxicity, indicating a safety profile suitable for potential therapeutic applications. The toxicity assessment in *T. molitor* larvae confirmed the safety of both the microemulsion and the flavonoid-rich DCM fraction, with no evidence of toxicity at the levels tested. These results indicate that microemulsions can improve the efficacy of *F. platyphylla* extracts, enhancing their therapeutic effects and ensuring safety and stability. In this sense, the integration of microemulsions in the formulation of herbal medicines can represent a significant advance for the clinical use of *F. platyphylla* compounds.[32]

3.7. Potential Pharmacological Agents: Benefits and Safety Considerations. Studies on *F. platyphylla* reveal several potential pharmacological uses of the extract and essential oil.[33] However, as mentioned above, it is crucial to consider the possible mutagenic effects of plant extracts.[33,34] Research by Resende et al. indicated that all extracts and the aqueous fraction of *F. platyphylla* leaves were mutagenic, with the crude extract showing better activity. Furthermore, only the hydroalcoholic extract of the roots showed significant estrogenic activity.[35] Although it was noted many pharmacological benefits, most studies were *in vitro*, which highlights the need for further *in vivo* investigations to deepen the understanding of the plant's mechanisms of action.

3.8. Therapeutic and Nanotechnological Prospects of Bioactive Compounds from *F. platyphylla*: Toward Clinical Application. Among the bioactive constituents derived from *F. platyphylla*, brachydins (notably A, B, C, E, and F) have emerged as key pharmacophores, exhibiting a wide range of therapeutic activities linked to their unique dimeric flavonoid structures. These dimeric flavonoids have been implicated in various biological activities, including antiparasitic, antitumor, antifungal, anti-inflammatory, antioxidant, and antinociceptive effects, highlighting their potential as

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selective antitumor agents.[8,9,11,28,36] Luteolin, a well-studied flavonoid, exhibits significant antiproliferative effects on glioblastoma cells with minimal toxicity to nontumor cells, reinforcing its relevance as a therapeutic candidate. Additionally, conandroside has emerged as a potential inhibitor of lipoxygenase, an enzyme involved in the inflammatory cascade, thereby positioning this compound as a potential anti-inflammatory agent.[5]

Halogenated compounds derived from this species have also demonstrated crucial antiparasitic activity against *L. amazonensis* and *T. cruzi*, presenting high selectivity. These findings underscore the feasibility of developing new antiparasitic drugs based on these compounds. Also, *F. platyphylla* exhibits promising antifungal and antibacterial potential, with extracts inhibiting *Candida spp.* and bacteria such as *S. aureus*. Compounds like brachydin B show antifungal activity, and the leeves extracts enhance the efficacy of antibiotics such as norfloxacin, suggesting a modulatory effect on microbial resistance.[17] These findings support its potential use in antimicrobial therapies and highlight the need for further studies investigating mechanisms of action, safety, and clinical efficacy.

In parallel, nanotechnology-based systems have proven to be highly effective strategies for improving the bioavailability of active compounds, regulating their release profiles, enhancing solubility, and minimizing systemic toxicity.[4,10,37] The application of advanced drug delivery systems, such as microemulsions, has further strengthened the therapeutic prospects of *F. platyphylla*.[32] These attributes are critical to optimizing the pharmacokinetic and pharmacodynamic profiles of phytocompounds in translational medicine.

In the technological context, the microemulsion formulated with dimeric flavonoids isolated from *F. platyphylla* exhibits key nanopharmaceutical attributes, including nanometric droplet size (ME3:65.4 ± 9.8 nm), physicochemical stability, and sustained drug release (>60% within 6 h). Although the formulation presented a moderate polydispersity index (PDI = 0.543 ± 0.11), its favorable ζ-potential and near-physiological pH reinforce its potential for biomedical use. Importantly, *in vivo* toxicity assays using *Tenebrio molitor* larvae confirmed the safety of both the dichloromethane extract and ME3, supporting its viability as a nanocarrier system for bioactive phytocompounds.[32]

The encapsulation of brachydin A in F127 micelles—an FDA-approved copolymer—resulted in high encapsulation efficiency (92.65 ± 0.48%) and favorable nanometric profiles, with particle sizes ranging from 157 to 359 nm and low polydispersity indices. These characteristics ensure pharmacokinetic stability and enhance bioavailability. Notably, the worm-like micellar architecture may prolong plasma half-life and reduce macrophage uptake, contributing to selective leishmanicidal activity with minimal cytotoxicity. Collectively, these findings highlight the potential of nanostructured systems to enhance brachydin A delivery and therapeutic precision.[21]

In parallel with previous strategies, zein nanoparticles encapsulating the dichloromethane fraction (DCMF) of *F. platyphylla*, rich in brachydins A, B, and C, demonstrated excellent nanotechnological performance, with high encapsulation efficiency (99.8%), narrow size distribution (mean diameter ∼ 206 nm), and structural stability. This formulation significantly enhanced the antiparasitic activity of the bioactive fraction, reducing IC_{50} values from 253.1 to 36.33 μg/mL (promastigotes) and from 6.96 to 0.72 μg/mL (amastigotes) of *L. amazonensis*. Moreover, cytotoxicity to RAW 264.7 macrophages remained minimal (CC_{50} > 500 μg/mL), yielding a high selectivity index (SI = 694.4) for the intracellular form. These findings suggest that zein-based nanocarriers promote improved bioavailability, membrane permeability, and targeted delivery of flavonoid compounds, offering a promising platform for the development of plant-derived antileishmanial therapies.[27]

Although preliminary *in vitro* and *in vivo* findings are encouraging, comprehensive preclinical studies remain essential to ensure these compounds' safe and effective translation into clinical use.[38,39] In particular, acute and subchronic toxicity assessments and pharmacokinetic and pharmacodynamic analyses in animal models are critical for understanding how these substances behave in a complex biological system.[40] *In vivo* studies are indispensable because they provide insights into absorption, distribution, metabolism, and excretion (ADME) and potential systemic effects and organ-specific toxicity—factors that cannot be fully predicted by *in vitro* assays alone.[39,40] These evaluations form the scientific basis for defining safe dose ranges and identifying potential risks.[40] Following this stage, phase I clinical trials are required to confirm human safety, tolerability, and preliminary pharmacological responses, serving as the gateway to further therapeutic development.[41]

In addition, future research should prioritize several key areas to support the translational development of *F. platyphylla* compounds. One critical focus is the investigation of pharmacological synergism,[42] particularly the interaction between brachydins and luteolin, as well as their combined application with conventional chemotherapeutic agents. These combinations should be evaluated using tools such as the Combination Index (CI), which can quantify synergistic effects and potentially enable effective dose reduction while minimizing toxicity.[42,43]

Equally important is the standardization of extracts and their isolated compounds, which includes the quantification of key bioactive markers, such as brachydins and luteolin, through chromatographic techniques. This process should be complemented by formulation studies that evaluate the stability, solubility, and viability of various dosage forms, including tinctures, capsules, and microemulsions, which may improve pharmacokinetic profiles and patient adherence.[44]

To ensure translational relevance, clinical validation through Phase I trials is essential. These studies will provide fundamental data on human safety, tolerability, and initial pharmacodynamics, forming the basis for subsequent clinical development.[45,46] Furthermore, assessing the technological scalability and pharmaceutical viability of these compounds, through feasibility studies on large-scale extraction, formulation, and production, will be vital for their incorporation into therapeutic protocols.[46,47]

While *F.* platyphylla and its isolated compounds—particularly brachydin B—have demonstrated promising pharmacological activities in preclinical models, including selective antitumor, antiparasitic, and anti-inflammatory effects, their potential clinical application must be interpreted with caution. The absence of clinical trials, combined with reports of mutagenic and estrogenic activity in some extracts, highlights the urgent need for comprehensive safety assessments. Until robust toxicological and pharmacokinetic data are available, the therapeutic use of these compounds should be

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considered exploratory and restricted to experimental investigation.

4. CONCLUSIONS

This integrative review provides, for the first time, a consolidated and critical overview of the phytochemical diversity, pharmacological properties, and toxicological data available on *F. platyphylla*. By synthesizing fragmented findings from 20 original studies across both *in vitro* and *in vivo* models, this work highlights the scientific relevance of the species as a promising yet underexplored platform for natural product-based drug discovery. The systematic presentation of data according to plant parts, compound classes, and experimental models underscores the novelty and utility of this compilation, which fills a significant gap in the literature.

Among the bioactive constituents, the dimeric flavonoids known as brachydins (A−F) emerged as the most pharmacologically potent, particularly brachydin B, which demonstrated selective antitumor and antimetastatic effects in 2D and 3D prostate cancer models. Novel compounds such as brachydins E and F, identified for the first time in this species, exhibited selective cytotoxicity against tumor cells. Luteolin, another relevant compound, exhibited antiproliferative effects on glioblastoma cells with minimal toxicity to nontumor cells, further supporting the therapeutic potential of this phytochemical group.

Technologically, the development of a microemulsion incorporating a dichloromethane root extract resulted in a stable delivery system with controlled release and favorable *in vivo* tolerability, thereby reinforcing the potential for translational pharmaceutical applications.

Nevertheless, the clinical applicability of these findings remains hypothetical and should be approached with caution. Reports of mutagenic and estrogenic activity in some extracts, particularly from leaves and roots, raise significant safety concerns. Moreover, the lack of clinical trials and the predominance of preliminary *in vitro* data limit the immediate translational relevance of these compounds. Thus, while the pharmacological evidence is encouraging, no therapeutic recommendation can be made at this stage.

To bridge this gap, future investigations should prioritize the characterization of pharmacokinetic behavior, bioavailability, dose−response relationships, and long-term toxicity of both crude extracts and isolated constituents. Robust *in vivo* validation, mechanistic elucidation, and standardized preclinical protocols will be essential to support the rational and safe development of *F. platyphylla*-derived bioactive agents for potential clinical use.

5. MATERIALS AND METHODS

5.1. Integrative Review Strategies. A scientific review was conducted to probe relevant studies through an integrative literature search in the PubMed, Scielo, and Google Scholar databases. The search was limited to articles written in the last ten years, between October 2014 and December 2024. The search included keywords such as "*F. platyphylla* AND *in vivo* studies", "*F. platyphylla* AND *in vitro* studies", "*F. platyphylla* AND ethnopharmacological studies", "*A. brachypoda* AND *in vivo* studies", "*A. brachypoda* AND *in vitro* studies", and "*A. brachypoda* AND ethnopharmacological studies" in English. Additionally, the reference lists of the retrieved studies were scanned to identify any potentially missed articles.

After searching the databases using the keywords, 896 studies addressing the theme of this review were identified (Table 4). Of this total, the results associated with the keyword *A. brachypoda* obtained the most published articles. Furthermore, the Google Scholar database yielded the most available articles (874), followed by PubMed (20) and Scielo (2).

Table 4. Search of Databases for Scientific Articles Published between October 2014 and December 2024 with the Species *F. platyphylla* or Its Synonym *A. brachypoda*[a]

keywords	PubMed	Scielo	Scholar Google
A. brachypoda	10	01	363
A. brachypoda AND *in vivo* studies	02	00	74
A. brachypoda AND *in vitro* studies	00	00	117
A. brachypoda AND ethnopharmacological studies	00	00	24
F. platyphylla	07	01	221
F. platyphylla AND *in vitro* studies	01	00	27
F. platyphylla AND *in vivo* studies	00	00	20
F. platyphylla AND ethnopharmacological studies	00	00	28
Total: 896	20	02	874

[a]Prepared by the authors from the PubMed, Scielo, and Google Scholar databases.

5.2. Study Selection Criteria. After conducting the searches, the records were imported into EndNote software. Any duplicate articles were then removed. Two researchers independently reviewed the titles and abstracts of all citations to select only the relevant studies.

In the characterization aspects of the included studies, several criteria were adopted, such as the type of study, study objective, administration of the formulation, and treatment effects. Then, all the necessary data were organized and presented in tabular form. Data not identified in the studies were filled with n.a (not evaluated). An overview of the excluded and included studies is presented in Figure 7, prepared under the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement (PRISMA).[48] Also, two investigators independently determined whether the studies met the inclusion criteria, with a third resolving any disputes as necessary.

Of the 896 records initially identified through database searches, 395 were excluded as duplicates. The remaining 501 records were screened based on title and abstract, resulting in the exclusion of 479 articles that did not meet the eligibility criteria—namely: not written in English or Portuguese, classified as reviews or meta-analyses, lacking experimental data, not reporting relevant outcomes for this review, or not using *F. platyphylla* (or its synonym *A. brachypoda*) or their constituents as the primary focus of investigation. After full-text assessment, 22 studies met all inclusion criteria and were retained for detailed qualitative analysis in this review.

5.3. Data Extraction, Methodology, and Findings. A data extraction form was developed in Microsoft Excel and included information regarding study design, group characteristics, pharmaceutical formulation identification, and main findings (Tables 2, 3, and 4). Data extraction was performed independently by two reviewers and compared for disparities.

5.4. Data Synthesis and Analysis. A narrative synthesis was performed, categorizing the studies according to their

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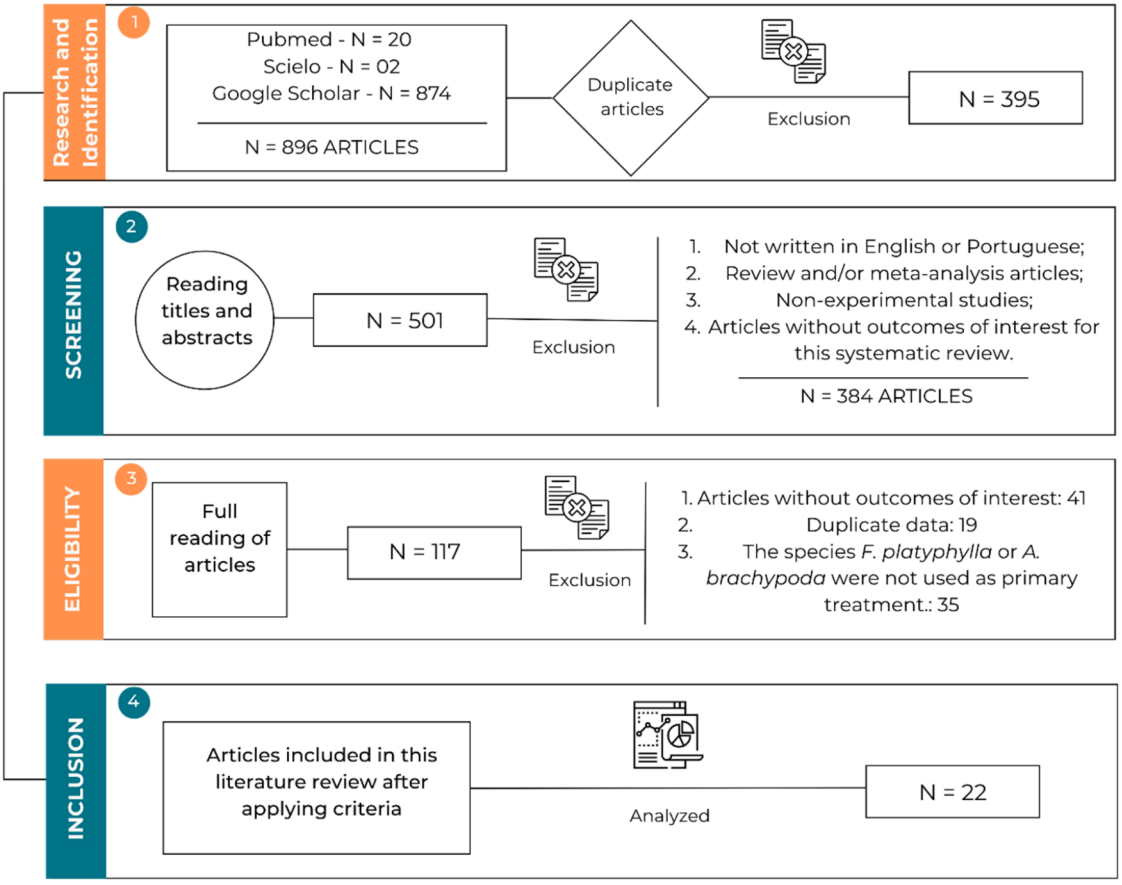

Figure 7. Flowchart of the search strategy and study selection **Source**: Prepared by the authors based on the studies included in this review and prepared under the PRISM 2020.

characteristics and settings. The effects of the pharmaceutical formulation were inferred using experimental trials. The researchers chose not to conduct a meta-analysis because the included studies varied in aspects such as study designs, participant groups, pathologies evaluated, variable definitions, comparisons, and analytical strategies. The structure of this methodology was taken as an example from the one recommended by Donato and Donato.[49]

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CAPÍTULO 3

CARDIOPROTECTIVE POTENTIAL OF *Fridericia platyphylla* (Cham.) L.G. Lohmann: PHYTOCHEMICAL CHARACTERIZATION AND EXPERIMENTAL EVIDENCE

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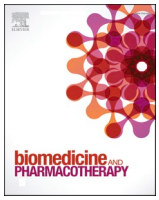

Cardioprotective potential of *Fridericia platyphylla* (Cham.) L.G. Lohmann: Phytochemical characterization and experimental evidence

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ABSTRACT

Background: The isoproterenol (ISO)–induced myocardial injury (MI) model is widely used to investigate cardioprotective strategies in the context of sustained β-adrenergic overstimulation, oxidative stress, and disruption of calcium homeostasis. Plant-derived products rich in phenolic compounds have attracted interest due to their antioxidant, anti-inflammatory, and cytoprotective properties. *Fridericia platyphylla* (Cham.) L.G. Lohmann is a medicinal species traditionally recognized as a source of bioactive compounds and represents a promising candidate for experimental cardioprotection.

Purpose: To characterize the phytochemical profile of a hydroethanolic extract of *F. platyphylla* (FPE) and evaluate its cardioprotective effects and dose-related responses in an ISO-induced MI model.

Methods: Phytochemical characterization was performed using LC–MS/MS, enabling the annotation of phenolic acids and flavonoids. Male Wistar rats were orally treated with FPE at different doses for 15 days, followed by ISO-induced myocardial injury. Hemodynamic and electrocardiographic parameters were recorded. Biochemical markers of cardiac injury, systemic biochemical and hematological parameters, coagulation indices, infarct size, cardiac hypertrophy, and histopathological alterations were assessed.

Results: LC–MS/MS identified rutin as the major constituent in a phenolic-rich profile. FPE treatment conferred dose-related cardioprotection, with more pronounced effects at doses of 75 and 100 mg/kg in the ISO-induced MI model. FPE restored electrocardiographic alterations, reduced infarct size, attenuated cardiac hypertrophy, decreased circulating cardiac injury markers, and mitigated collagen deposition. Additionally, FPE improved hematological parameters and reduced plasma fibrinogen levels, indicating anti-inflammatory and antithrombotic effects.

Abbreviations: AMI, acute myocardial infarction; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CPK, creatine phosphokinase; CPK-MB, creatine phosphokinase-MB fraction; CRP, C-reactive protein; CT, healthy control; CVF, collagen volume fraction; CVDs, cardiovascular diseases; EDTA, ethylenediaminetetraacetic acid; ECG, electrocardiogram; EHSA, FPE, *Fridericia platyphylla* extract; H&E, hematoxylin and eosin; HDP, herbal drug preparation; HDL, high-density lipoprotein; HPLC, high-performance liquid chromatography; HPLC–MS/MS, high-performance liquid chromatography–tandem mass spectrometry; INR, international normalized ratio; ISO, isoproterenol; LC–ESI–IT–MS, liquid chromatography–electrospray ionization–ion trap mass spectrometry; LC–MS/MS, liquid chromatography–tandem mass spectrometry; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; LPS, lipopolysaccharide; MI, myocardial injury *m/z* – mass-to-charge ratio; MS2, second-stage fragmentation; MS3, third-stage fragmentation; N2, nitrogen; NIH, National Institutes of Health; PT, prothrombin time; SisGen, National System for the Management of Genetic Heritage and Associated Traditional Knowledge; TTC – 2, 3,5, triphenyltetrazolium chloride; UFMA, Universidade Federal do Maranhão; UPLC, ultra-performance liquid chromatography; VLDL, very-low-density lipoprotein.

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Conclusions: FPE treatment for 15 days produced dose-dependent cardioprotective effects against ISO-induced MI, reinforcing its pharmacological potential as a source of bioactive compounds for experimental cardioprevention.

1. Introduction

Cardiovascular diseases (CVDs) represent a set of illnesses that impair the circulatory system's function and remain the leading cause of global morbidity and mortality, being responsible for millions of deaths annually [1]. Among these, acute myocardial infarction (AMI) stands out as one of the most critical conditions, characterized by the abrupt interruption of blood flow in coronary arteries, leading to ischemia and often to irreversible necrosis of cardiac tissue [2]. According to epidemiological data from the World Health Organization, cardiovascular diseases account for 32% of all global deaths, responsible for approximately 19.8 million fatalities annually. Of these deaths, 85% were due to heart attack and stroke [3]. In this sense, cardioprotection encompasses all strategies aimed at reducing or preventing myocardial damage, and evaluating substances that mitigate cardiac injury following experimental interventions is considered a key cardioprotective approach [4,5].

Isoproterenol (ISO) is a synthetic β-adrenergic agonist widely employed to induce experimental myocardial injury (MI) [6]. At high doses, ISO promotes sustained cardiac overstimulation, leading to oxidative stress, calcium overload, inflammation, and cardiomyocyte necrosis, thereby reproducing several pathological features of AMI [7,8]. In parallel, ISO-induced MI is widely employed as a standard experimental model to assess the cardioprotective effects of phytochemicals and plant extracts [9]. The pathological manifestations of ISO-induced MI closely resemble those observed in human infarction, making it a valuable tool for investigating potential therapeutic agents. Several studies have demonstrated the cardioprotective potential of natural compounds in ISO-induced MI models [6,10,11], emphasizing the scientific importance of exploring naturally derived compounds as promising therapeutic strategies for myocardial ischemia. In this context, natural products have emerged as promising sources of new drugs, given the therapeutic potential of secondary metabolites such as flavonoids, saponins, and terpenoids, which possess anti-inflammatory, antioxidant, and cardioprotective properties [12].

Fridericia platyphylla (syn. *Arrabidaea brachypoda*) (Cham.) L.G. Lohmann, a member of the Bignoniaceae and native to the Brazilian Cerrado, is noted for diverse biological and pharmaceutical activities, including anti-inflammatory, antimicrobial, antiprotozoal, analgesic, and cytotoxic properties against tumor cells [13–16]. These properties have been associated with the hydroethanolic extract from various plant parts, including roots, stems, leaves, and flowers [13,17,18]. Recent phytochemical investigations demonstrated that leaf extracts of *F. platyphylla* are rich in phenolic compounds, particularly flavonoids and phenolic acid derivatives, including rutin, quercetin, and kaempferol derivatives, apigenin glycosides, caffeoylquinic acid, and feruloylquinic acid [14,16]. This phytochemical profile is particularly relevant to the present study because these metabolites have been associated with antioxidants, anti-inflammatory, cytoprotective, and anti-remodeling effects, all of which are directly involved in the pathophysiology of ISO-induced MI. [8]. In this context, the bioactive constituents of *F. platyphylla* provide a pharmacological basis for investigating its cardioprotective potential. Flavonoids and related phenolic metabolites have been reported to modulate oxidative stress, inflammatory signaling, extracellular matrix remodeling, and cell survival pathways, all of which contribute to the progression of myocardial injury following ISO administration. In addition, isolated compounds from this species, such as brachydins, have been reported to interfere with pathways related to oxidative stress and inflammation, reinforcing the therapeutic relevance of *F. platyphylla* in cardiovascular disorders, including AMI [14,15].

To the best of our knowledge, this is the first study to investigate the cardioprotective potential of a hydroethanolic extract of *F. platyphylla* in an experimental model of ISO-induced MI. By integrating phytochemical characterization with functional, biochemical, electrocardiographic, morphometric, and histopathological analyses, this study provides experimental evidence supporting the pharmacological relevance of this species as a source of bioactive compounds with cardioprotective potential.

2. Materials and methods

2.1. Material collection

Fridericia platyphylla (Cham.) L. G. Lohmann leaves were collected in Sant'Ana da Serra, João Pinheiro, Minas Gerais, Brazil (coordinates 17°44'04.500 S, 46°10'04.400 W) in February 2021. The botanist, Dr. Ana Maria Cristina Teixeira Braga, identified the plant at the Jose Badine Herbarium of the Federal University of Ouro Preto (Voucher 17.935). Access to botanical material was registered in the National System for the Management of Genetic Heritage and Associated Traditional Knowledge (SisGen, A4551DE4).

Preparation of Hydroethanolic Extract of *Fridericia platyphylla* (FPE).

The plant material was first dehydrated in a forced-air oven (Hexasystems, SSDic, São Paulo, Brazil) maintained at 40–50 °C. After drying, the leaves were ground to a fine powder using a knife mill (Trapp, Santa Catarina, Brazil). From 150 g of dried and milled material, extraction was performed with 70% ethanol (Êxodo Científica, Campinas, Brazil). The solvent-to-plant ratio was 7:3, yielding a total extraction volume of 4.10 mL. Exhaustive percolation was adopted as an extraction technique, consisting of sequential 24-hour cycles. In each cycle, 216 mL of 70% ethanol was added to ensure complete solvent renewal. After percolation, the extract was filtered and concentrated under reduced pressure using a rotary evaporation system composed of a vacuum pump (Tecnal, model TE−058, Piracicaba, Brazil), a rotary evaporator (Fisatom, model 802, São Paulo, Brazil), and an ultrathermostatic bath (SolidSteel, model SSDu-20L, Piracicaba, Brazil), keeping the temperature below 40 °C to avoid degradation of thermolabile constituents. The concentrated extract was then freeze-dried in a lyophilizer (Liotop, model K105, São Carlos, Brazil) for 48 h at −95 °C under reduced pressure (12 μHg vacuum pressure). At the end of the process, the ethanolic extract yielded a dry mass of 29.35 g, corresponding to an extraction yield of 19.56%.

2.2. Liquid Chromatography-Mass Spectrometry (LC-MS/MS) analysis

Chemical analysis for metabolite annotation using LC-MS/MS data processing with molecular networking was performed by liquid chromatography-electrospray ionization ion trap mass spectrometry (LC-ESI-IT-MS) on a spectrometer (amaZon SL, Bruker Daltonics®, Billerica, MA, USA). The chromatographic analysis was performed on a Luna 5 μm C18 100 Å column (250 × 4.6 mm, Phenomenex, Torrance, CA, USA), with HPLC Prominence Shimadzu®. The binary gradient mobile phase consisted of 0.1% formic acid (Sigma-Aldrich, St. Louis, MO, USA) in water (solvent A) and 0.1% formic acid in methanol (Sigma-Aldrich, St. Louis, LO, USA) (solvent B). Samples (1 mg mL^{-1}) were eluted from the analytical column with a 40 min gradient ranging from 5% to 100% solvent B at a constant 1 mL min^{-1} flow rate. The injection volume was 2 μL. Column compartment temperature set to 40

∘C. Data acquisition was performed in both negative and positive modes, with fragmentation in multiple stages (MS^2 and MS^3), using a Data-Dependent Acquisition (DDA) method, according to the following parameters: nebulization gas pressure, 50.0 psi; capillary temperature, 300 ºC; transfer capillary input voltage, 4500 V; desolvation gas, nitrogen (N_2), flow 10 $L.min^{-1}$; collision gas, helium (He); range acquisition, *m/z* 50–1200. Raw data were analyzed and converted to the mzML format using Data Analysis, Version 4.3 (Bruker, Billerica, MA, USA, 2014).

2.3. Animals

Normotensive male Wistar rats (Rattus norvegicus), weighing 200–250 g, sourced from the Central Animal Facility of the Federal University of Maranhão, Brazil, were used to evaluate pharmacological activity. Animals were housed in polypropylene cages (four animals per cage) under controlled environmental conditions (22–24 °C; 12 h light/12 h dark cycle), with free access to food and water throughout the study. All procedures were conducted by the Guidelines for the Care and Use of Laboratory Animals, published by the National Institutes of Health (NIH Publication No. 85–23, revised 1996) and were approved by the Animal Ethics and Research Committee/UFMA, following the Guidelines for the Care and Use of Laboratory Animals under protocol No. 23115.019856/2023–61. During the pharmacological tests, exclusion criteria included non-Wistar strains, female subjects, and any pathology.

2.4. Pharmacological evaluation

2.4.1. Experimental design

The pharmacological evaluation was conducted using a randomized, controlled experimental design to investigate the *in vivo* effects of the FPE. The protocol was specifically developed to assess the cardioprotective properties of the extract in ISO-induced MI model, which mimics β-adrenergic overstimulation and its associated pathophysiological alterations. After an initial adaptation period, the animals were randomly assigned to experimental groups to ensure reproducibility and internal validity.

Due to the lipophilic characteristics of the crude extract, dimethyl sulfoxide (DMSO) is typically employed as a solubilizing agent. However, to ensure compatibility with oral administration and minimize potential biological interference, the extract was formulated in a vehicle consisting of propylene glycol (10%) and sorbitol, which was previously standardized in the laboratory. This vehicle efficiently dispersed the extract and demonstrated good tolerability, particularly given the low volume of administration (0.1 mL/100 g body weight). For consistency, both the Health Control (CT) and ISO-induced MI groups (ISO, FPE50, FPE75, and FPE100) received the same vehicle (propylene glycol and sorbitol) without the addition of the extract [24]. In addition, the selected FPE doses (50, 75, and 100 mg/kg) were based on previous toxicological investigations demonstrating a high safety profile for the extract. These doses correspond to approximately 5–10% of the reported LD50 value and were selected to investigate dose-related cardioprotective effects while maintaining a substantial safety margin.

Following the acclimatization period, the animals were randomly allocated to the experimental groups for pharmacological evaluation (Fig. 1). The study was designed to assess the cardioprotective effects and potential mechanisms of action of FPE using a 15-day treatment protocol. FPE or vehicle was administered once daily by oral gavage at a volume of 0.1 mL/100 g body weight. All formulations were freshly prepared immediately before administration.

Throughout the experiment, animals had free access to food and water, and their intake was monitored every three days as an indicator of animal welfare. MI was induced in all experimental groups, except the Healthy Control group, by subcutaneous administration of ISO (85 mg/kg) on days 14 and 15 of the protocol. ISO was prepared in 2 mL of isotonic 0.9% NaCl solution and administered using two 1 mL syringes, with one injection delivered on each side of the animal. The CT received equivalent subcutaneous saline injections.

After completion of the treatment period, the animals were fasted for 12 h. On day 16, anesthesia was induced by intraperitoneal administration of ketamine (75 mg/kg) and midazolam (5 mg/kg) [19]. Hemodynamic parameters and rectal temperature were then recorded, followed by the collection of blood and organ samples for subsequent

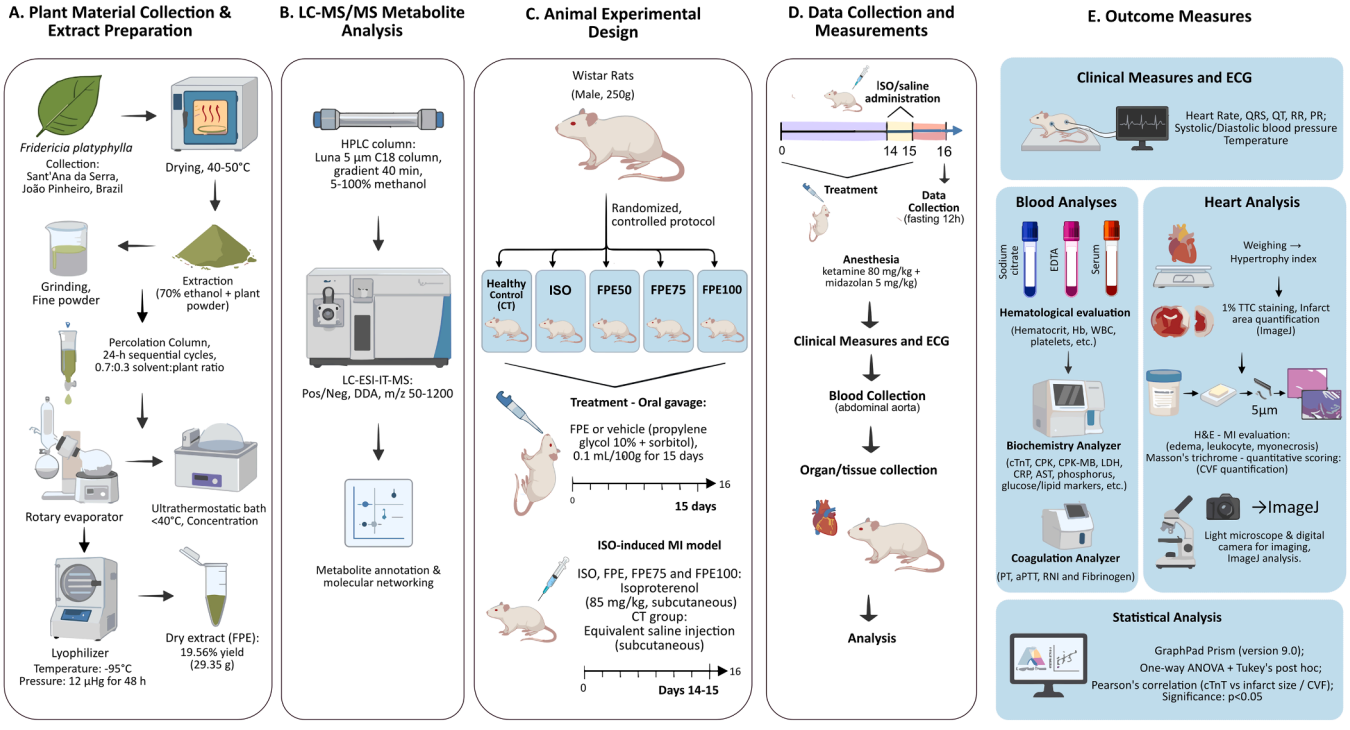

Fig. 1. Illustrative Diagram of the Research Protocol.

biochemical, hematological, and histopathological analyses.

2.5. Determination of electrocardiogram (ECG) and clinical parameters

At the end of the treatment, the animals underwent electrocardiographic (ECG) analysis, which was performed at 1–5-minute intervals to observe the heart rate, QRS duration, and QT segment, as well as the RR and PR interval through lead and reference electrodes connected to a biopotential amplifier (Multiparametric Monitor VET DL 1000 – Delta Life®, São Paulo, Brazil). The QTc interval was calculated using Bazzet's equation. Additionally, the Multiparametric Monitor VET DL 1000 enabled measurement of systolic and diastolic blood pressure and rectal temperature in the animals.

2.6. Blood collection and hematological, biochemical, and coagulation analyses

Following a 12-hour fasting period, the animals were anesthetized and euthanized for blood collection. Samples were obtained from the abdominal aorta and distributed into tubes containing anticoagulants (EDTA and sodium citrate) and tubes without anticoagulants, according to the requirements of each analysis (hematological, biochemical, or hemostatic).

Whole blood collected in EDTA was used for hematological evaluation by complete blood count (CBC) performed on a 5-part automated analyzer (HEMATOCLIN 5.4®). The parameters analyzed included erythrocyte count, hemoglobin concentration, hematocrit, reticulocyte count, total leukocyte count, and platelet count.

Blood samples were collected in tubes without anticoagulant and allowed to clot at room temperature. The samples were then centrifuged at 3500 rpm for 15 min using a digital clinical centrifuge (80–2B-DM, Daiki®, China) to obtain serum. The separated serum was aliquoted and stored at −20°C until further biochemical analyses. Serum obtained from these samples was used to assess cardiac, inflammatory, and metabolic biomarkers, including cardiac troponin T (cTnT), creatine phosphokinase (CPK), creatine phosphokinase-MB fraction (CPK-MB), lactate dehydrogenase (LDH), quantitative C-reactive protein (CRP), aspartate aminotransferase (AST, U/L), phosphorus, and markers of glycemic and lipid metabolism. These analyses were performed using a cobas® c513 analyzer, except for cTnT, which was measured using the Roche Cobas® h232 system. Additionally, ketonemia was measured using the FreeStyle Optium Xceed® meter (Abbott Diabetes Care, Alameda, CA, USA) and FreeStyle Optium β-Ketone test strips.

For coagulation analysis, plasma samples collected in sodium citrate were used to determine prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen levels. These parameters were measured using a semi-automatic analyzer COAGMASTER BR 2.0®, following the manufacturer's instructions.

2.7. Evaluation of cardiac hypertrophy and morphometry

At the end of the treatment, the anesthetized animals and those subjected to euthanasia had their hearts removed for macroscopic verification and morphometric analysis. The hearts were washed in cold 0.9% saline to remove clots, then weighed to estimate cardiac hypertrophy by calculating relative weight [20]. Next, the hearts were frozen at −20°C for 20 min, sectioned, stained with 1% triphenyltetrazolium chloride (TTC) [20] at pH 7.0 for 30 min, photographed, and the images were analyzed using ImageJ® software to quantify the infarcted area [21].

2.8. Histological examination

The hearts collected during euthanasia were fixed in 10% buffered formalin at room temperature for 24 h. After fixation, the samples were transferred to 70% ethanol until histological processing. Subsequently, the tissues were dehydrated through ascending grades of ethanol, cleared in xylene, and embedded in paraffin. 5 μm thick) were obtained from the paraffin blocks for histopathological evaluation [22].

Additionally, a transverse section was taken in the ventricle at the midpoint between the cardiac apex and the atrioventricular groove, specifically at the papillary muscle. Hematoxylin and Eosin (H&E) staining was utilized to visualize structural components. Histopathological myocardial injury was assessed in H&E-stained sections using a semi-quantitative scoring system (0–3) [23]. The evaluation was based on the presence and severity of interstitial edema, leukocyte infiltration, and myonecrosis. Six randomly selected high-power fields (400 ×) were examined per tissue section, and the mean score was calculated for statistical analysis [24]. To evaluate myocardial fibrosis and collagen volume fraction (CVF), tissue sections were stained with Masson's trichrome. The CVF was quantified using ImageJ software (NIH, USA) as the ratio between the collagen-positive area in the myocardial interstitium and the total field area (CVF = collagen area / total area). For each tissue section, six high-power fields (HPF, 400 ×) were randomly selected, and the mean value was calculated. Histological images were acquired using a digital camera (Nikon, Japan) coupled to a light microscope (Nikon, Japan) [25].

2.9. Statistical analysis

Data were expressed as mean ± standard error of the mean (SEM). Statistical analyses were performed using GraphPad Prism (version 9.0; GraphPad Software, San Diego, CA, USA). Normality of data distribution was assessed using the Shapiro–Wilk test. Comparisons among multiple groups were conducted by one-way analysis of variance (ANOVA), followed by Tukey's post hoc test, when appropriate. Pearson's correlation coefficient (r) was calculated to evaluate the associations between serum cardiac troponin T levels and (i) infarct size (CVS) and (ii) collagen volume fraction (CVF). Correlation analyses were conducted as exploratory analyses to investigate the relationships between biochemical markers of myocardial injury and structural remodeling parameters, without implying causality. A p-value < 0.05 was considered statistically significant.

3. Results

3.1. Phytochemical profiling of the ethanolic extract obtained from Fridericia platyphylla leaves

To characterize the chemical constituents of the FPE, LC-MS/MS analyses were conducted in both negative and positive modes. The determination of each compound's structure was guided by the characteristic fragments produced during LC-MS/MS analysis. Fifteen phenolic molecules were identified, revealing the presence of chlorogenic acid derivatives and various glycosylated flavonoids belonging to the subclass of flavones and flavonols. In parallel, LC–MS/MS identified rutin as the major constituent of this extract. Their proposed structures, based on literature-supported fragmentation comparisons, are depicted in Fig. 2, while the chemical structures of the identified compounds are presented in Fig. 3.

3.2. Effects of FPE on body weight, food intake, and water consumption

To assess the animals' general health status during the experimental period, basic welfare parameters were monitored. In Fig. 4, the animal welfare assessment revealed no significant differences in weight gain, feed consumption, or water intake after 15 days of FPE treatment.

3.3. FPE attenuates hemodynamic and electrocardiographic alterations

Table 1 shows the values for systolic blood pressure, diastolic blood pressure, mean arterial pressure, and temperature. After 15 days of FPE

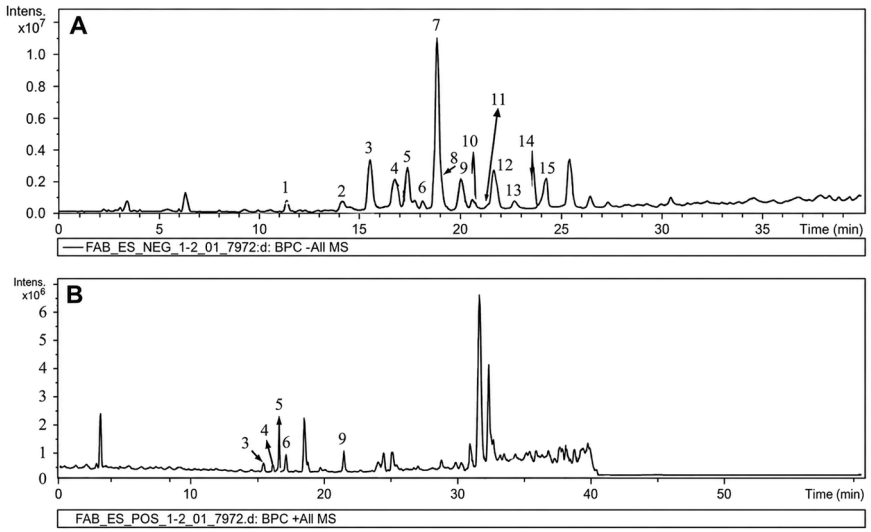

Fig. 2. Base peak chromatograms of *Fridericia platyphylla* leaf extract in (A) negative and (B) positive modes.

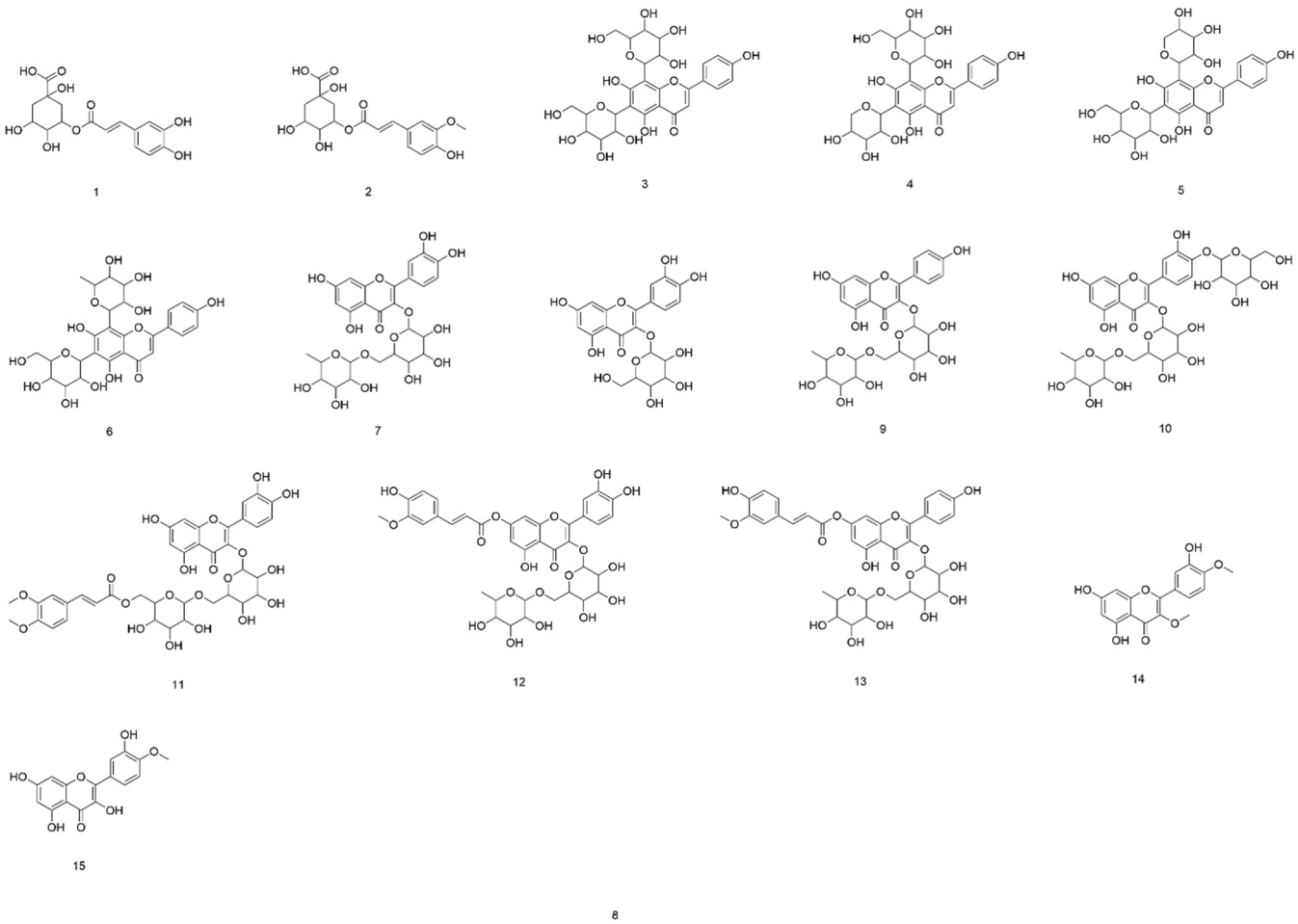

Fig. 3. Chemical constituents annotated in the hydroethanolic extract of *Fridericia platyphylla* leaves: (1) caffeoylquinic acid; (2) feruloylquinic acid; (3) apigenin 6,8-C-dihexoside; (4) apigenin 6-C-pentosyl−8-C-hexoside; (5) apigenin 6-C-hexosyl−8-C-pentoside; (6) apigenin 6-C-hexosyl−8-C-deoxihexoside; (7) rutin; (8) quercetin-O-hexoside; (9) kaempferol-O-deoxyhexosyl-O-hexoside; (10) quercetin -O-deoxyhexosyl-O-dihexoside; (11) quercetin-O-dimethoxycaffeoyl-O-hexosyl-Ohexoside; (12) quercetin-O-feruloyl-O-deoxyhexosyl-O-hexoside; (13) kaempferol-O-feruloyl-O-deoxyhexosyl-O-hexoside; (14) 3,4-dimethoxy-quercetin; (15) tamarixetin.

treatment, these parameters did not differ significantly.

Electrocardiographic analysis in Fig. 5 revealed significant alterations in cardiac electrical activity following ISO administration. Representative Lead II recordings demonstrated marked waveform

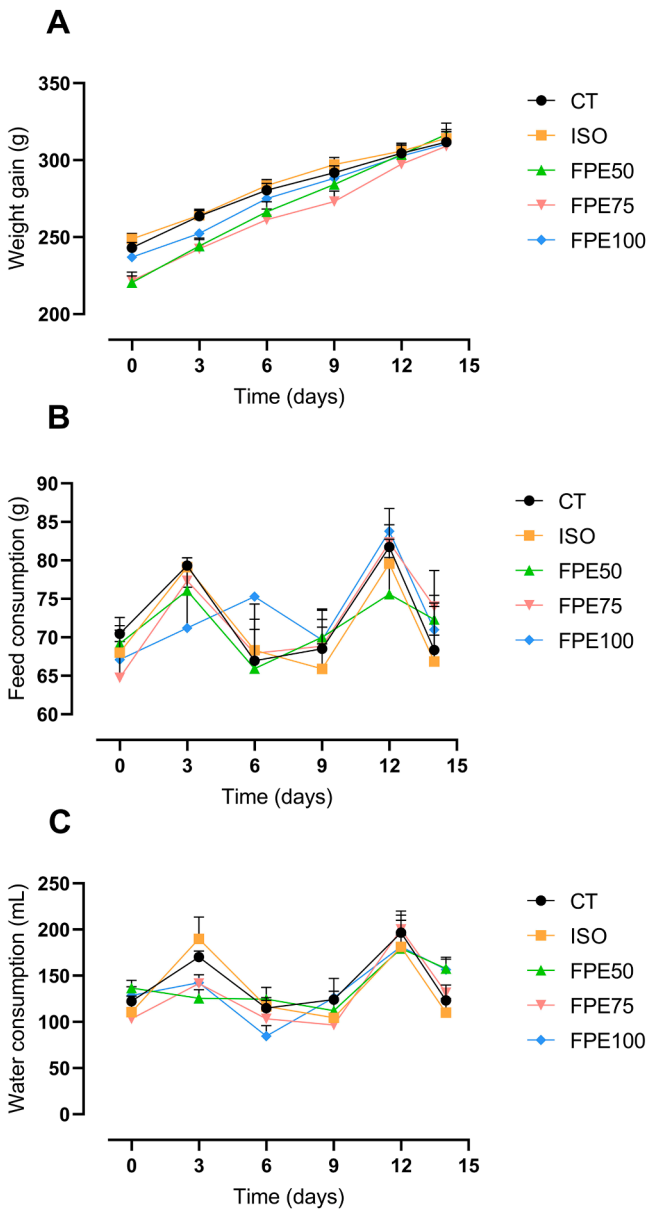

Fig. 4. Animal welfare parameters. FPE: *Fridericia platyphylla* extract; Fig. 4A-Weight gain after 15 days of treatment; Fig. 4B-Feed consumption after 15 days of treatment; Fig. 4C-Water consumption after 15 days of treatment. Results expressed as mean ± SEM.

abnormalities in ISO group compared with the CT group. Quantitative analysis showed that ISO significantly increased heart rate while reducing the R–R interval, consistent with enhanced β-adrenergic stimulation. In addition, ISO prolonged QT and QTc intervals and produced a modest increase in QRS duration, indicating disturbances in ventricular depolarization and repolarization associated with MI. Treatment with FPE attenuated these electrocardiographic abnormalities in a dose-dependent manner. Animals receiving FPE50 exhibited partial improvement, whereas FPE75 promoted greater normalization of electrical parameters. Notably, FPE100 produced the most pronounced protection, restoring heart rate, R–R interval, QT, and QTc values toward control levels. The representative ECG tracings corroborated the quantitative findings, showing progressive recovery of rhythm organization and electrical stability with increasing FPE doses.

Table 1
Hemodynamic variables and temperature.

Parameters	CT	ISO	FPE50	FPE75	FPE100
Systolic blood pressure (mmHg)	154.60 ± 1.42	131.50 ± 9.60	167.50 ± 7.93	165.20 ± 4.99	154.80 ± 16.03
Diastolic blood pressure (mmHg)	125.20 ± 16.77	113.50 ± 9.60	160.50 ± 9.04	149.20 ± 3.81	137.80 ± 18.76
Mean arterial pressure (mmHg)	143.20 ± 14.13	122.60 ± 9.77	160.80 ± 3.40	158.00 ± 4.72	145.50 ± 20.57
Heart rate (beats/min)	290.00 ± 8.40	421.50 ± 19.60*	360.70 ± 17.93	335.20 ± 14.52#	306.80 ± 16.03#
Temperature (T °C)	36.82 ± 0.29	36.13 ± 0.26	36.40 ± 0.15	36.94 ± 0.27	36.85 ± 0.28

CT: Healthy Control; ISO: Isoproterenol; FPE: *Fridericia platyphylla* extract; Results expressed as mean ± standard error of the mean. *$p < 0,05$ *vs.* CT; #$p < 0.05$ *vs.* ISO.

3.4. FPE attenuates cardiac morphometric alterations and reduces biomarkers of myocardial injury

Table 2 shows the relative weight of the organs after 15 days of treatment with FPE. Compared to the control group, animals exposed to ISO had a statistically significant increase in heart weight. However, this difference was not observed in animals treated with FPE100. In addition, no statistically significant differences were observed in other organs, including the liver, right kidney, left kidney, and the liver-spleen ratio.

ISO treatment significantly increased cardiac hypertrophy and infarcted areas ($p < 0.05$ vs. CT). In contrast, FPE treatments, especially at the 100 mg/kg dose (FPE100), demonstrated protective effects by significantly reducing these parameters (#$p < 0.05$ *vs.* ISO, #&$p < 0.05$ *vs.* ISO and FPE50). Representative heart images further confirm these findings, with FPE100 showing visibly smaller infarcted regions than the ISO group (Fig. 6).

Injury cardiac markers, including cTnT, CPK, CPK-MB, LDH, AST, and CRP, were significantly elevated ($p < 0.05$) in the ISO group compared to the CT group. FPE treatment significantly reduced these markers, with FPE100 showing the most pronounced effect, as observed in Fig. 7.

3.5. FPE improves renal function, phosphorus homeostasis, and metabolic profiles

In Table 3, the ISO treatment increased urea levels, whereas the FPE100 treatment showed the greatest improvement in this parameter. Furthermore, an elevation in serum phosphorus was observed in the ISO-treated groups. However, the FPE75 and FPE100 treatments partially mitigated this increase. In parallel, ISO-treated animals exhibited marked hyperglycemia compared with the CT group, accompanied by significant increases in triglycerides, LDL cholesterol, non-HDL cholesterol, beta-ketone levels, and atherogenic indices (CHO/HDL, Log[TG/HDL], and Non-HDL/HDL). FPE treatment promoted partial to substantial improvement in these metabolic disturbances.

3.6. FPE preserves myocardial structure and attenuates myocardial fibrosis

Fig. 8 shows intact cardiac muscle FPE50, a central nucleus, and acidophilic cytoplasm (CT); FPE75 and FPE100 show normal myocardial structure, except for some cardiac muscle fibers with a central nucleus and wide Spaces. FPE50 shows structural changes: fragmented and separated cardiac muscle fibers and edema; ISO fragmented and separated cardiac muscle fibers, vacuolation and extreme edema, pale cytoplasm, pyknotic nuclei, and extravasated RBC's. Regarding edema formation, leukocyte infiltration, and myonecrosis, FPE treatment at the

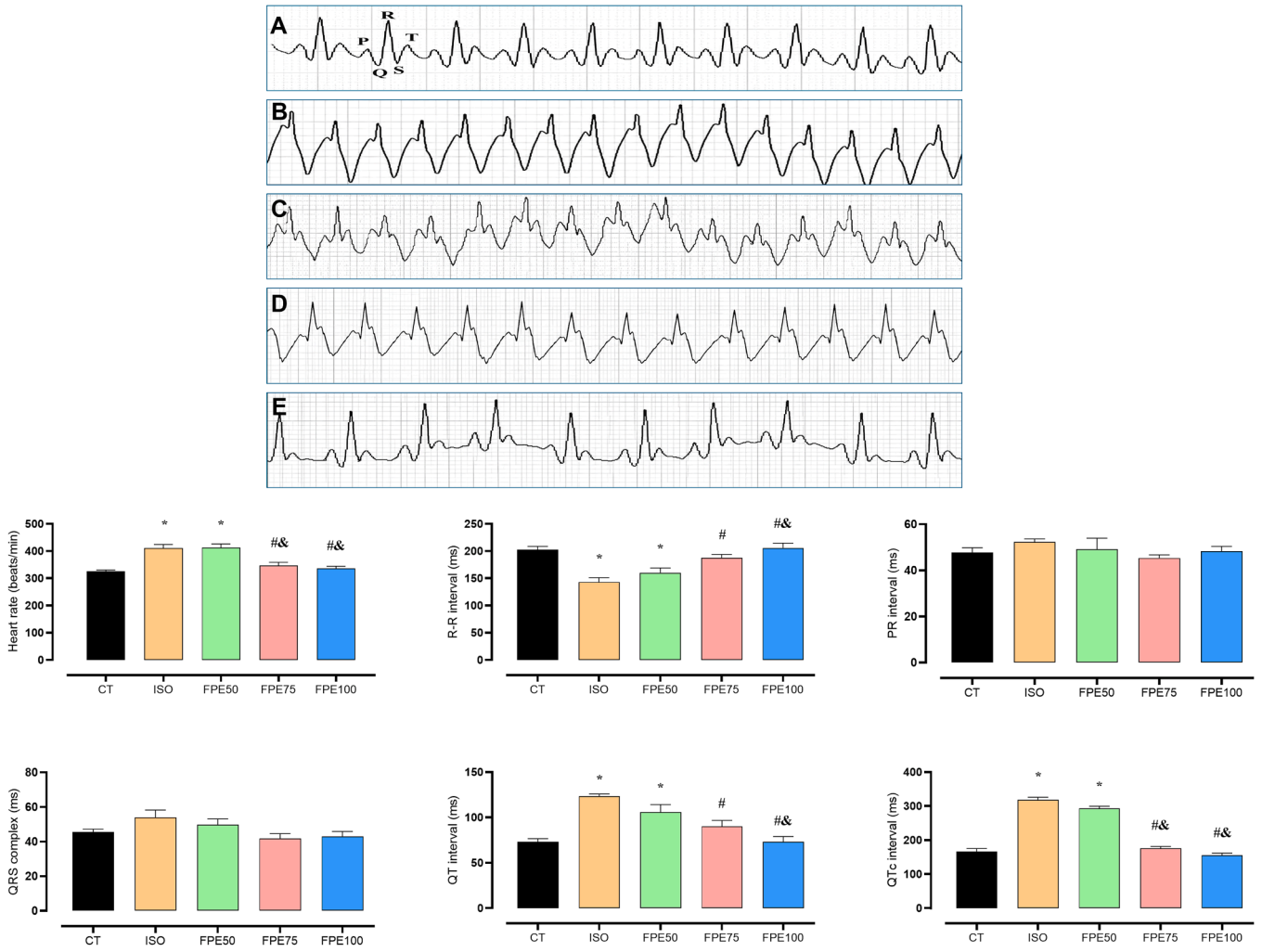

Fig. 5. Electrocardiographic evaluation of rats treated with FPE and subjected to ISO-induced MI. Representative Lead II electrocardiographic tracings from experimental groups: (A) CT, (B) ISO, (C) FPE50, (D) FPE75, and (E) FPE100. Representative recordings illustrate the electrocardiographic alterations induced by ISO and their attenuation following FPE pretreatment. Quantitative analysis of electrocardiographic parameters included heart rate, R–R interval, PR interval, QRS duration, QT interval, and corrected QT interval (QTc). CT: Healthy Control; ISO: Isoproterenol; FPE: *Fridericia platyphylla* extract; Results expressed as mean ± standard error of the mean. *p < 0,05 vs. CT; #p < 0.05 vs. ISO; &p < 0.05 vs. FPE50.

Table 2
Relative weight of organs.

Parameters	CT	ISO	FPE50	FPE75	FPE100
Lung	0.0050 ± 0.0001	0.0055 ± 0.0004	0.0068 ± 0.0006	0.0062 ± 0.0004	0.0066 ± 0.0001
Heart	0.003776 ± 0.0001	0.0049 ± 0.0001*	0.0048 ± 0.0001*	0.0045 ± 0.0001*	0.0044 ± 0.0002
Liver	0.0328 ± 0.0002	0.0342 ± 0.0007	0.0360 ± 0.0019	0.0341 ± 0.0012	0.0303 ± 0.0012
Right kidney	0.0039 ± 0.0001	0.0042 ± 0.0002	0.0040 ± 0.0002	0.0035 ± 0.0002	0.0033 ± 0.0001
Left kidney	0.0040 ± 0.0001	0.0041 ± 0.0002	0.0041 ± 0.0003	0.0036 ± 0.0002	0.0035 ± 0.0001
Spleen	0.0020 ± 0.0001	0.0018 ± 0.0001	0.0017 ± 0.0001	0.0018 ± 0.0001	0.0016 ± 0.0002
Liver/ spleen ratio	16.62 ± 1.04	18.12 ± 0.77	20.23 ± 0.86	18.24 ± 0.96	16.82 ± 0.49

CT: Healthy Control; ISO: Isoproterenol; FPE: *Fridericia platyphylla* extract; Results expressed as mean ± standard error of the mean. *p < 0.05 *vs.* CT.

evaluated dose showed significant differences compared with the ISO group. Furthermore, as shown in Fig. 8(E) and 8(F), the degree of myocardial fibrosis and the positive areas of myocardial fiber staining were significantly increased ($p < 0.05$) in the ISO group. At the same time, collagen deposition and the CVF were significantly reduced ($p < 0.05$) after FPE treatment. In addition, correlation analysis in animals treated with FPE at 100 mg/kg demonstrated significant positive associations between serum cTnT levels and both the infarcted area and the collagen volume fraction. cTnT levels were strongly correlated with infarct size ($r = 0.8241$, $p = 0.0119$), indicating that greater biochemical myocardial injury was associated with increased infarct extension. Similarly, a significant positive correlation was observed between cTnT levels and collagen volume fraction ($r = 0.9363$, $p = 0.0006$), suggesting that more severe myocardial damage was associated with greater fibrotic remodeling. Together, these findings support a close relationship between biochemical injury markers and structural myocardial damage at the optimal FPE dose.

3.7. FPE attenuates hematological disturbances and hyperfibrinogenemia induced by ISO

In Table 4, the ISO treatment significantly altered hematological parameters, including reductions in red blood cell count, hemoglobin, hematocrit, and total leukocyte count. These alterations were mitigated by FPE treatment, particularly in the EFP75 and EFP100 groups, which

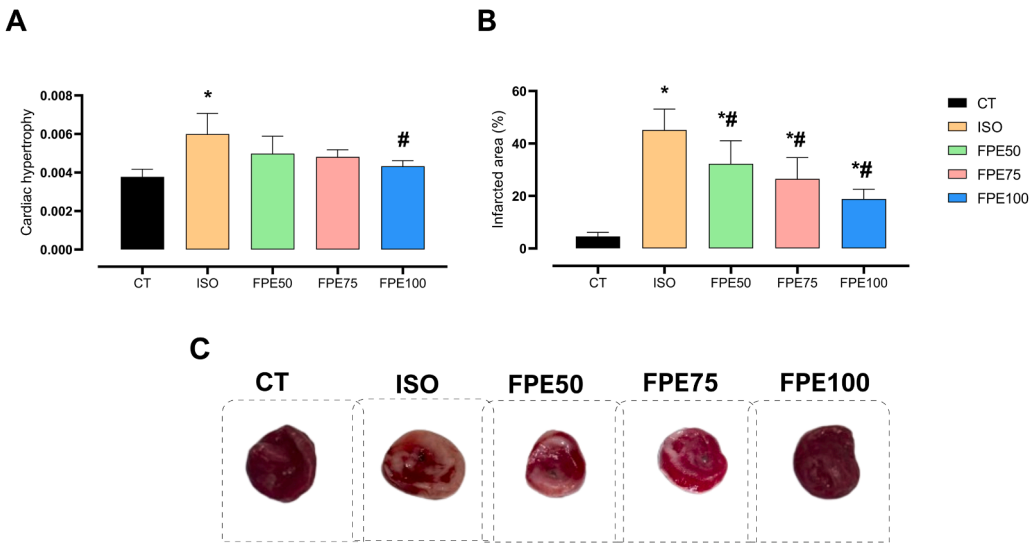

Fig. 6. Cardiac hypertrophy, infarcted area, and representative heart sections after 15 days of treatment. Fig. 5A- Cardiac hypertrophy after 15 days of treatment; Fig. 5B- infarcted area after 15 days of treatment, and Fig. 5C- representative heart sections after 15 days of treatment. CT: Healthy Control; ISO: Isoproterenol; FPE: *Fridericia platyphylla* extract; Results expressed as mean ± SEM. *p < 0.05 vs. CT; #p < 0.05 vs. ISO; &p < 0.05 vs. FPE50.

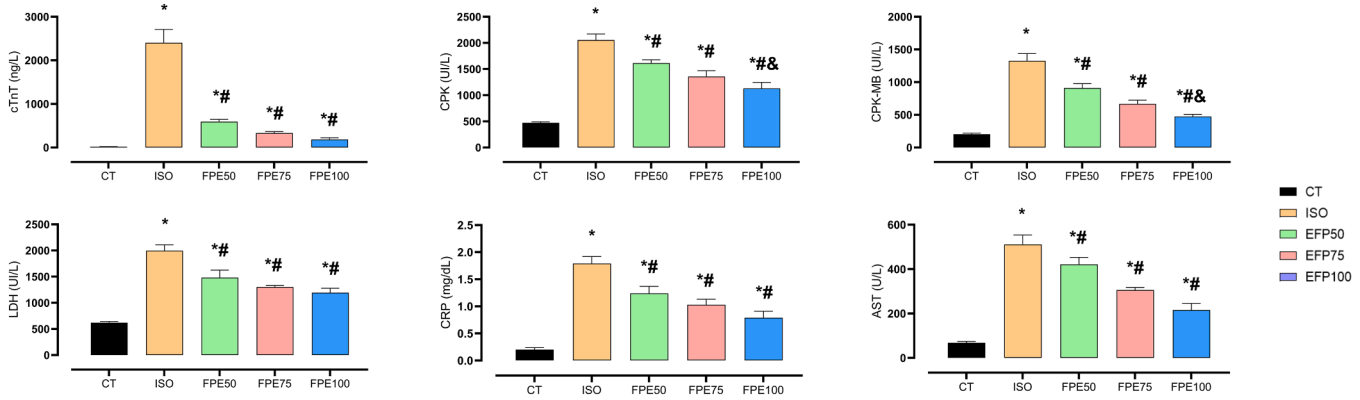

Fig. 7. Effects of *Fridericia platyphylla* extract on cardiac injury biomarkers in isoproterenol-induced myocardial infarction. Bar graphs represent serum levels of cardiac troponin T (cTnT), creatine phosphokinase (CPK), creatine phosphokinase-MB (CK-MB), lactate dehydrogenase (LDH), C-reactive protein (CRP), and aspartate aminotransferase (AST) across experimental groups. CT: Healthy Control; ISO: Isoproterenol; FPE: *Fridericia platyphylla* extract; Results expressed as mean ± SEM. *p < 0.05 vs. CT; #p < 0.05 vs. ISO; &p < 0.05 vs. FPE50.

Table 3
Biochemical, metabolic, and atherogenic profile.

Parameters	CT	ISO	FPE50	FPE75	FPE100
Urea (mg/dL)	36.02 ± 2.51	68.40 ± 6.60*	58.85 ± 3.79	58.20 ± 6.35	40.00 ± 2.00#
Creatinine (mg/dL)	0.37 ± 0.03	0.50 ± 0.02*	0.43 ± 0.04	0.38 ± 0.02	0.44 ± 0.04
Uric acid (mg/dL)	1.04 ± 0.14	1.54 ± 0.10	1.17 ± 0.17	1.02 ± 0.11	1.44 ± 0.17
Phosphorus (mg/dL)	7.89 ± 0.17	9.92 ± 0.34*	7.69 ± 0.38#	7.72 ± 0.28#	7.35 ± 0.20#
Glucose (mg/dL)	116.70 ± 7.55	165.20 ± 9.71*	145.30 ± 3.87	138.60 ± 6.00	100.80 ± 4.55#&@
Glycated hemoglobin (mg/dL)	3.78 ± 0.05	3.75 ± 0,03	3.60 ± 0,06	3.56 ± 0.09	3.62 ± 0.12
Total cholesterol (mg/dL)	72.45 ± 4.80	80.20 ± 2.81	73.65 ± 4.59	78.01 ± 4.24	70.80 ± 6.37
Triglycerides (mg/dL)	58.13 ± 9.08	99.22 ± 5.10*	70.20 ± 4.63*	64.33 ± 3.39#	68.45 ± 10.91#
HDL cholesterol (mg/dL)	48.15 ± 2.21	33.53 ± 2.57	42.25 ± 4.90	42.14 ± 3.07	43.14 ± 2.48
LDL cholesterol (mg/dL)	12.67 ± 3.73	26.83 ± 2.78*	17.36 ± 1.12	18.67 ± 1.96	13.97 ± 5.15#
VLDL cholesterol (mg/dL)	11.73 ± 3.45	19.84 ± 1.02	14.04 ± 0.92	12.87 ± 0.68	13.69 ± 1.72
Non-HDL cholesterol (mg/dl)	24.30 ± 4.23	46.67 ± 4.45*	31.4 ± 6.15	37.90 ± 3.25	27.70 ± 4.72#
Beta-ketone (mg/dL)	1.48 ± 0.09	1.85 ± 0.08*	1.77 ± 0.07*	1.74 ± 0.09*	1.63 ± 0.02
Atherogenic risk 1 (CHO/HDL)	1.50 ± 0.09	2.39 ± 0.11*	1.78 ± 0.13*#	1.94 ± 0.21*#	1.64 ± 0.19#
Atherogenic risk 2 (LDL/HDL)	0.32 ± 0.11	0.49 ± 0.12	0.41 ± 0.08	0.49 ± 0.02	0.34 ± 0.13
Atherogenic risk 3 (Log [Triglycerides/HDL])	0.08 ± 0,01	0.48 ± 0.05*	0.22 ± 0.04*#	0.21 ± 0.01*#	0.20 ± 0.01*#
Atherogenic risk 4 (Non-HDL/HDL)	0.50 ± 0.11	1.39 ± 0.11*	0,74 ± 0.11#	0,94 ± 0.11	0,64 ± 0.11#

CT: Healthy Control; ISO: Isoproterenol; FPE: *Fridericia platyphylla* extract; Results expressed as mean ± standard error of the mean. *p < 0,05 *vs.* CT; $^{\#}$p < 0.05 *vs.* ISO; $^{\&}$p < 0.05 *vs.* FPE50; $^{@}$p < 0.05 *vs.* FPE75.

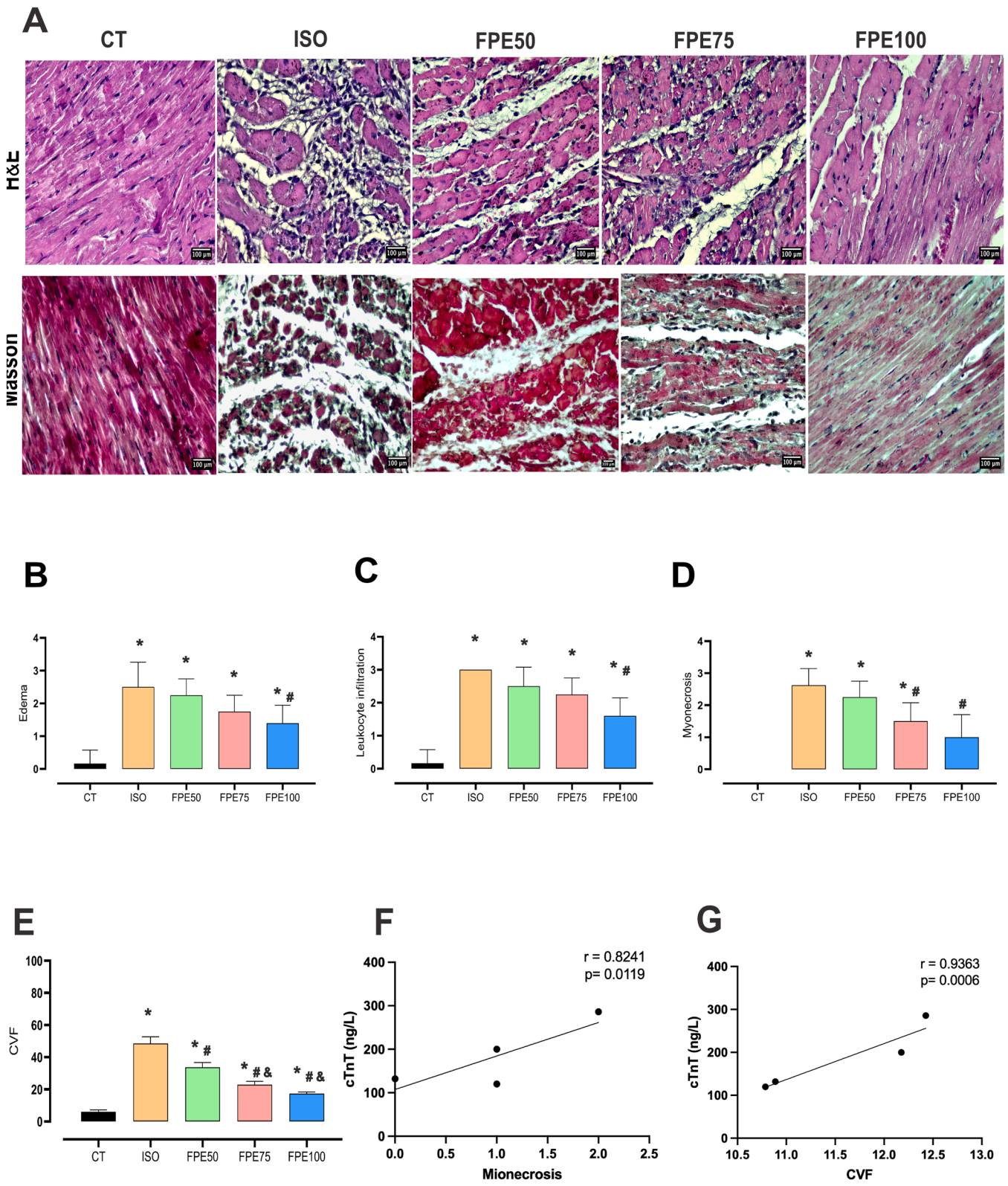

Fig. 8. (A) Representative photomicrographs of rat myocardial sections (from right to left; scale bar = 100 μm). Collagen fibers are stained light green, whereas myocardial fibers appear red. (B–D) Semi-quantitative histopathological scores related to edema (B), leukocyte infiltration (C), and myonecrosis formation (D) in the evaluated cardiac tissue. (E) Masson's trichrome staining of heart tissue (from right to left; scale bar = 100 μm). (F) Scores related to collagen volume fraction (CVF). (G–H) Correlation analyses in animals treated with *Fridericia platyphylla* extract (FPE) at 100 mg/kg, showing the association between serum cTnT levels and infarcted area (%) (G), and between cTnT levels and collagen volume fraction (CVF) (H). Pearson's correlation analysis demonstrated significant positive correlations between cTnT and infarct size ($r = 0.8241$, $p = 0.0119$) as well as CVF ($= 0.9363$, $p = 0.0006$), indicating that biochemical myocardial injury is closely associated with infarct extension and fibrotic remodeling at the optimal FPE dose ($n = 5$). CT: Healthy Control; ISO: Isoproterenol; FPE: *Fridericia platyphylla* extract. Results are expressed as mean ± SEM. *$p < 0.05$ vs. CT; #$p < 0.05$ vs. ISO; &$p < 0.05$ vs. FPE50.

Table 4
Hematological and hemostasis parameters.

Parameters	CT	ISO	FPE50	FPE75	FPE100
Red blood cells (10^6 cells/mm^3)	8.55 ± 0.10	6.81 ± 0.14*	7.07 ± 0.14*	8.00 ± 0.27#&	8.00 ± 0.29#&
Hemoglobin (g/dL)	16.22 ± 0.21	12.74 ± 0.39*	12.98 ± 0.61*	14.68 ± 0.54#	16.04 ± 0.12#&
Hematocrit (%)	48.28 ± 0.37	37.06 ± 1.27*	37.63 ± 1.73*	43.82 ± 1.27#&	48.38 ± 0.28#&
Reticulocytes (10^9 cells/L)	248.50 ± 12.17	454.40 ± 24.58*	442.80 ± 22.11*	361.30 ± 6.58*#	337.10 ± 24.02#
Leukocytes (cells/mm^3)	3042.00 ± 157.90	7735.00 ± 235.30*	6150.00 ± 222.30*	3756.00 ± 180.00#&	3589.00 ± 160.30#&
Platelets (10^3/mm^3)	625.30 ± 34.60	643.80 ± 39.28	610.30 ± 35.53	527.80 ± 34.84	618.60 ± 28.85
Prothrombin Time (s)	11.70 ± 0.45	10.49 ± 0.48	10.10 ± 0.34	9.96 ± 0.32	11.06 ± 0.28
INR	0.93 ± 0.04	0.82 ± 0.04	0.78 ± 0.03	0.77 ± 0.03	0.87 ± 0.03
Aptt	19.84 ± 0.70	18.00 ± 0.58	17.48 ± 0.49	17.86 ± 0.34	21.08 ± 0.95
Fibrinogen (mg/dL)	144.00 ± 18.39	354.70 ± 15.88*	212.50 ± 23.15*	262.00 ± 12.90*#	244.60 ± 11.81*#

CT: Healthy Control; ISO: Isoproterenol; FPE: *Fridericia platyphylla* extract; International Normalized Ratio (INR); Activated Partial Thromboplastin Time (aPTT). Results expressed as mean ± standard error of the mean. *$p < 0.05$ *vs.* CT; #$p < 0.05$ *vs.* ISO; $^{\&}p < 0.05$ *vs.* FPE50.

showed values comparable to the control group. In addition, the neutrophil-to-lymphocyte ratio showed a statistically significant difference between the FPE100 and ISO groups. In addition, prothrombin activity and activated partial thromboplastin time did not differ significantly among the FPE-treated, CT, and ISO groups. However, fibrinogen levels were higher after ISO administration than in the CT group. Besides, pre-treatment with FPE (FPE50, FPE75, and FPE100) significantly decreased plasma fibrinogen levels by 9.28%, 20.39%, and 24.21%, respectively, compared with untreated infarcted rats ($P < 0.05$).

4. Discussion

This study presents integrated experimental evidence supporting the cardioprotective effects of FPE in an ISO-induced MI model. The combination of phytochemical characterization with comprehensive biochemical, functional, hematological, hemostatic, and histopathological analyses provides robust scientific evidence for the potential cardioprotective efficacy of this plant extract in a pharmacologically induced model of cardiac dysfunction.

The phytochemical profile of the FPE revealed phenolic compounds, particularly hydroxycinnamoylquinic acid derivatives and flavonoids, which provide strong biological plausibility for the observed cardioprotective effects. In parallel, LC–MS/MS identified rutin as its major compound. The annotation of caffeoylquinic and feruloylquinic acid derivatives, supported by characteristic LC-MS/MS fragmentation patterns [26], is relevant given the well-established antioxidant and membrane-protective properties of hydroxycinnamic acids, mechanisms consistent with the reduction in myocardial injury markers and infarct size reported in this study. In addition, the presence of apigenin C-glycosides, structurally confirmed by characteristic fragmentation behavior [27], indicates a chemically stable flavonoid fraction with established anti-inflammatory and anti-fibrotic activities, which may contribute to the preservation of myocardial architecture and the attenuation of fibrosis. The detection of O-glycosylated flavonols, including rutin, quercetin, and kaempferol derivatives, further supports a multitarget cardioprotective profile [11,15,26–28], as these compounds are known to modulate oxidative stress, inflammation, and thrombotic pathways, aligning with the hematological and hemostatic improvements observed following FPE treatment.

Notably, in this study, the assessment of animal welfare showed no significant changes in body weight, feed intake, or water consumption over the 15-day treatment period (Fig. 4), supporting tolerability and safety under the conditions evaluated. Given that oxidative stress, inflammation, and microvascular dysfunction are key contributors to MI and post-infarction remodeling, the phytochemical composition of FPE provides a mechanistic basis for its potential protective effects in AMI.

AMI is characterized by irreversible MI, progressive impairment of contractile function, and maladaptive ventricular remodeling resulting from sustained myocardial ischemia secondary to coronary artery obstruction [26,27]. In experimental research, the synthetic β-adrenergic agonist ISO reliably reproduces the major biochemical, functional, and histological hallmarks of AMI, supporting its extensive use as a preclinical model for cardioprotective evaluation [11,29]. The myocardial alterations induced by ISO closely resemble those observed in human AMI, reinforcing the translational relevance of this model [11]. Therefore, understanding the mechanisms underlying ISO-induced MI is essential for interpreting the protective effects of therapeutic interventions in this experimental setting.

Sustained β-adrenergic overstimulation induced by ISO initiates a cascade of pathophysiological events involving increased myocardial oxygen demand, intracellular calcium overload, oxidative stress, and energetic imbalance, ultimately leading to cardiomyocyte injury and ventricular remodeling. Chronic activation of β-adrenergic signaling is also associated with the development of left ventricular hypertrophy and functional deterioration, reflecting a hypercontractile yet energetically compromised phenotype [30]. Under these conditions, FPE administration did not exacerbate hemodynamic alterations, indicating that the extract did not impose additional cardiovascular burden within the experimental setting [30,31]. Importantly, the cardioprotective effects of FPE were not observed across all tested doses; protection was consistently more pronounced at higher doses, particularly at 100 mg/kg, indicating a dose-related effect under the experimental conditions.

These pathophysiological disturbances are accompanied by structural alterations in the myocardium, among which tissue edema represents one of the earliest manifestations of injury. Consistent with this mechanism, the increase in heart weight observed in ISO-treated animals indicates myocardial edema resulting from interstitial fluid accumulation and intracellular swelling secondary to β-adrenergic–mediated calcium overload. Excessive activation of L-type calcium channels and disruption of intracellular Ca^{2+} homeostasis promote osmotic imbalance, cardiomyocyte swelling, and extracellular matrix destabilization, thereby increasing myocardial volume [10,11,32]. In this context, even modest increases in myocardial water content may substantially impair cardiac performance [33]. In contrast, attenuation of the pathological increase in heart weight was predominantly observed in animals treated with the highest FPE dose, suggesting that mitigation of edema-associated myocardial alterations requires sufficient extract exposure. The absence of significant changes in organ weights, aside from the heart, further supports the cardiac specificity of ISO-induced injury and the targeted protective effect of FPE [34,35].

Given the limited regenerative capacity of the myocardium, infarct size remains a critical determinant of disease severity and prognosis following ischemic injury [36]. In the ISO model, excessive β-adrenergic stimulation accelerates oxygen consumption, promotes calcium overload, and enhances reactive oxygen species generation, leading to membrane lipid peroxidation, loss of sarcolemmal integrity, and cardiomyocyte necrosis. These events result in the release of cytosolic injury biomarkers, including CPK, CPK-MB, LDH, CRP, and AST, into the circulation [37,38]. In the present study, FPE significantly reduced

infarct size, attenuated cardiac hypertrophy, and suppressed serum cardiac injury markers, with greater effects observed at higher doses, reinforcing the pharmacological consistency of the cardioprotective response across independent outcome measures [39].

Histopathological analyses corroborated these findings, revealing marked disruption of myocardial architecture in the ISO group, including cardiomyocyte distortion, vacuolization, edema, nuclear pyknosis, and fiber fragmentation, accompanied by an increased CVF, indicative of early fibrotic remodeling [40]. These alterations are commonly attributed to sustained β-adrenergic overstimulation, inflammatory cell infiltration, and fibroblast activation, resulting in excessive extracellular matrix deposition [41]. Given the central role of inflammation in driving these structural alterations, attenuating inflammatory responses may help limit fibrotic progression. Consistent with this mechanism, FPE preserved myocardial architecture and reduced collagen accumulation in a dose-related manner, with the most pronounced effects at higher doses, suggesting mitigation of inflammation-associated fibrotic remodeling.

In parallel with structural remodeling, ISO induces electrophysiological disturbances that contribute to cardiac dysfunction. The combined effects of cardiomyocyte injury, inflammatory infiltration, and extracellular matrix accumulation can disrupt normal impulse generation and propagation, leading to electrophysiological abnormalities [42]. Electrophysiological disturbances, therefore, represent an important functional component of ISO-induced MI and arise from impaired calcium influx, oxidative stress, and structural disorganization of cardiomyocytes [43]. Such alterations may compromise impulse generation and conduction, contributing to electrocardiographic alterations and arrhythmogenic susceptibility. In this context, electrocardiographic assessment serves as a valuable complementary tool for integrating electrophysiological, structural, and biochemical findings, enabling functional correlation with the cardioprotective effects observed following FPE treatment [43].

The electrocardiographic findings further support the cardioprotective effects of FPE against ISO-induced MI. Excessive β-adrenergic stimulation by ISO is known to promote calcium overload, oxidative stress, and electrophysiological disturbances, resulting in alterations of ventricular depolarization and repolarization. Consistent with these mechanisms, the ISO group showed tachycardia, shortening of the R–R interval, prolongation of the QT and QTc intervals, and disorganized ECG waveforms, reflecting increased electrophysiological instability after MI. In parallel, treatment with FPE attenuated these alterations in a dose-dependent manner. While FPE50 produced only a partial improvement, FPE75 and, particularly, FPE100 markedly restored electrocardiographic parameters toward physiological values. The reduction in QT and QTc prolongation suggests improved ventricular repolarization, whereas the normalization of heart rate and R–R interval indicates attenuation of the excessive adrenergic stimulation induced by ISO. Importantly, the electrophysiological improvements were accompanied by parallel reductions in infarct size, CPK-MB and troponin levels, collagen deposition, and histopathological injury scores, reinforcing the consistency of the cardioprotective response across functional, biochemical, and structural endpoints. Overall, FPE appears to preserve electrophysiological function and reduce myocardial susceptibility to ISO-induced deleterious effects.

In addition to the effects on heart tissue, excessive β-adrenergic stimulation exerts systemic consequences. ISO-mediated activation of β_1- and β_2-adrenoceptors enhances intracellular cAMP signaling, promoting oxidative stress and inflammatory pathways that contribute to metabolic disturbances and alterations in fluid and electrolyte homeostasis [44,45]. The elevations in urea and phosphorus levels observed in the ISO group may reflect enhanced catabolism, cardiomyocyte injury, and loss of membrane integrity associated with myocardial necrosis, thereby releasing intracellular phosphate into the circulation [10,32]. These alterations may be further aggravated by impaired tissue perfusion during myocardial dysfunction. Partial normalization of these parameters following FPE treatment suggests a protective effect on systemic metabolic balance and electrolyte regulation in the ISO-induced MI model.

ISO exposure also induced metabolic disturbances characterized by hyperglycemia and dyslipidemia, reflecting β-adrenergic activation of glycogenolysis, gluconeogenesis, lipolysis, and ketogenesis, consistent with a hypercatabolic state [6]. The attenuation of these alterations by FPE, more evident at higher doses, supports a dose-related modulation of metabolic imbalance during myocardial injury.

Hematological changes were observed in the ISO group, including reductions in erythrocyte indices and leukocytosis, which reflect systemic inflammatory activation and leukocyte recruitment to injured myocardial tissue [9]. FPE at doses of 75 and 100 mg/kg mitigated these alterations, restoring hematological parameters to control values and indicating dose-dependent preservation of hematological homeostasis.

Elevated plasma fibrinogen levels following ISO administration further indicate activation of acute-phase and prothrombotic pathways associated with MI. Fibrinogen plays a central role in platelet aggregation, plasma viscosity, endothelial dysfunction, and thrombus formation and is recognized as a predictor of cardiovascular risk [38–41,44,46–49]. The dose-dependent reduction in fibrinogen levels observed after FPE treatment suggests a graded modulation of inflammation-associated thrombotic pathways, thereby contributing to the extract's cardioprotective profile [39].

The correlation analyses further reinforce the integrated cardioprotective profile of FPE at the optimal dose (100 mg/kg). The significant correlations between cTnT levels, infarct size, and CVF suggest that attenuation of myocardial injury is closely associated with reductions in structural damage and fibrotic remodeling. These findings support the concept that the cardioprotective effects of FPE extend beyond isolated biochemical improvements, reflecting coordinated preservation of myocardial integrity and extracellular matrix organization under ISO-induced stress.

Notably, the cardioprotective effects of FPE were observed following a 15-day treatment period before MI induction, suggesting that prolonged exposure to the extract may play a critical role in the development of cardioprotective responses. The consistent dose-related responses observed across structural, biochemical, histopathological, and systemic parameters further support a pharmacologically meaningful relationship between FPE exposure and cardioprotection. Although the present experimental design does not permit conclusions about acute administration or therapeutic intervention after injury onset, the findings underscore the combined importance of treatment duration and dose in modulating myocardial vulnerability under ISO-induced stress conditions.

While these findings provide compelling evidence of the cardioprotective potential of FPE, some limitations should be considered when interpreting the underlying mechanisms. Although clear anti-inflammatory and anti-fibrotic effects were observed, the molecular pathways underlying these responses were not directly investigated and therefore warrant further study. Furthermore, although the present study demonstrated dose-dependent cardioprotective effects of FPE, the absence of a reference cardioprotective drug limits direct comparisons with established pharmacological interventions in the ISO-induced MI model. Likewise, more detailed characterization of ventricular performance using invasive hemodynamic measurements was beyond the scope of the present investigation. In addition, the experimental design was focused on cardioprevention through pretreatment and therefore does not permit conclusions regarding therapeutic efficacy after MI has been established. Finally, identifying the specific bioactive constituents responsible for the observed effects and characterizing their individual contributions to myocardial and vascular remodeling remain important objectives for future research.

5. Conclusion

This study demonstrates the cardioprotective effects of FPE in an ISO-induced MI model in rats. Phytochemical analysis identified a phenolic- and flavonoid-rich profile, with rutin as a major constituent. FPE, particularly at 75 and 100 mg/kg, markedly attenuated ISO-induced MI, as evidenced by reduced infarct size, cardiac hypertrophy, and circulating injury biomarkers (cTnT, CPK-MB, LDH, CRP, and AST), indicating preservation of cardiomyocyte integrity. Histopathological analysis corroborated these findings, demonstrating a substantial reduction in myocardial disorganization, edema, and cellular degeneration in the FPE100 group. Characterizing their individual contributions to myocardial and vascular remodeling remains an important objective. In parallel, FPE improved hematological disturbances and reduced plasma fibrinogen levels in a dose-dependent manner, suggesting anti-inflammatory and antithrombotic effects. Collectively, these results support the pharmacological relevance of FPE as a source of bioactive compounds with cardioprotective potential, warranting further investigation to elucidate its molecular mechanisms and active constituents.

CRediT authorship contribution statement

Jhonathas Aparecido Rodrigues Brito: Methodology, Investigation, Formal analysis, Data curation. **Bianca de Fátima Assunção Sodré:** Methodology, Investigation. **Carlos Henrique de Barros da Costa Sobrinho:** Methodology, Investigation. **Ellen Caroline da Silva Penha:** Methodology, Investigation, Formal analysis, Data curation. **Carine Novaes Paes Leme:** Methodology, Investigation. **Rachel Melo Ribeiro:** Writing – review & editing, Investigation, Funding acquisition, Conceptualization. **Raphael Furtado Marques:** Writing – original draft, Methodology, Investigation. **Jhonata Costa Moura:** Investigation, Formal analysis, Data curation. **Carlos Alberto Alves Dias Filho:** Funding acquisition, Conceptualization. **Marilene de Oliveira da Rocha Borges:** Writing – review & editing, Investigation. **Andressa Coelho Ferreira:** Writing – original draft, Methodology, Investigation. **Júlia Karla de Albuquerque Melo Xavier:** Methodology, Investigation, Conceptualization. **Cláudia Quintino Rocha:** Funding acquisition, Conceptualization.

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Declaration of Competing Interest

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

Data availability

No data was used for the research described in the article.

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CAPÍTULO 4

COMPOSIÇÕES FARMACÊUTICAS À BASE DE CERVEJINHA DO CAMPO (*Fridericia Platyphylla*) PARA USO EM DESORDENS CARDIOVASCULARES

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PATENTE DE INVENÇÃO

TÍTULO: COMPOSIÇÕES FARMACÊUTICAS À BASE DE CERVEJINHA DO CAMPO (FRIDERICIA PLATYPHYLLA) PARA USO EM DESORDENS CARDIOVASCULARES.

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RESUMO:

A presente invenção refere-se ao desenvolvimento de composições farmacêuticas contendo *Fridericia platyphylla* (popularmente conhecida como cervejinha do campo), com aplicação profilática e/ou terapêutica em distúrbios cardiovasculares. As composições são obtidas por meio da incorporação do extrato vegetal a veículos farmacologicamente aceitáveis que promovem adequada solubilização, estabilidade físico-química, palatabilidade e características organolépticas compatíveis com diferentes formas de administração, preferencialmente oral. A invenção apresenta como diferencial técnico a otimização da biodisponibilidade do extrato bioativo, aliada à facilidade de administração, baixo custo de produção e potencial para aplicação em larga escala. As propriedades farmacológicas observadas incluem atividade antioxidante e efeito regenerativo, conferindo à formulação um perfil terapêutico promissor para uso preventivo e/ou complementar ao tratamento convencional de doenças cardiovasculares. As formulações contêm compostos inertes que garantem boa solubilidade do componente ativo, melhor palatabilidade, sabor adocicado, sem alteração do odor original, com elevada biodisponibilidade oral, sem riscos de toxicidade. A invenção também fornece uma nova aplicação médica para *Fridericia platyphylla*.

CONSIDERAÇÕES FINAIS

Os resultados deste estudo demonstram que o tratamento com FPE, especialmente nas doses de 75 e 100 mg/kg/dia, exerceu efeitos cardioprotetores significativos no modelo experimental de infarto do miocárdio induzido por isoproterenol. O FPE promoveu redução expressiva do tamanho da área de infarto e da hipertrofia cardíaca, contribuindo para a preservação da integridade estrutural e funcional do miocárdio. A análise fitoquímica evidenciou a presença de múltiplos compostos, com destaque para o flavonoide glicosilado rutina, identificado como constituinte majoritário do extrato. Adicionalmente, a presença de compostos fenólicos com reconhecida atividade antioxidante, como rutina, apigenina e luteolina, pode estar diretamente associada à capacidade do FPE de atenuar os efeitos deletérios do isoproterenol sobre o tecido cardíaco.

Observou-se ainda uma redução significativa nos principais biomarcadores de lesão miocárdica, incluindo Troponina T, CPK, CK-MB, LDH, AST e proteína C-reativa, indicando menor extensão da lesão tecidual e atenuação da resposta inflamatória sistêmica. O tratamento com FPE100 conferiu proteção substancial contra as alterações estruturais induzidas pelo isoproterenol, preservando a integridade histológica das fibras musculares cardíacas e reduzindo a formação de edema, a infiltração leucocitária e o grau de mionecrose. Esses achados contrastam de forma significativa com o grupo ISO, no qual foram observadas fragmentação das fibras cardíacas, vacuolização, edema acentuado, citoplasma pálido e extravasamento de hemácias. Tais alterações histopatológicas corroboram o papel do FPE, especialmente na dose de 100 mg/kg/dia, na preservação da arquitetura miocárdica e do interstício celular frente à agressão isquêmica.

Além dos efeitos cardíacos diretos, o tratamento com FPE contribuiu para a restauração de parâmetros hematológicos, atenuando a redução na contagem de hemácias, nos níveis de hemoglobina e no hematócrito, bem como normalizando a contagem total de leucócitos, o que reforça seu potencial anti-inflamatório. Outro achado relevante foi a modulação do risco trombótico, evidenciada pela redução significativa dos níveis plasmáticos de fibrinogênio, sugerindo um efeito protetor frente a eventos pró-trombóticos comumente associados ao modelo de infarto do miocárdio induzido por isoproterenol. Esses efeitos tornam-se particularmente relevantes diante do papel central da inflamação sistêmica e do estado pró-coagulante na progressão e agravamento das lesões cardiovasculares.

A ausência de alterações significativas nos parâmetros hemodinâmicos e de bem-estar animal, como peso corporal, consumo hídrico e ingestão alimentar ao longo do protocolo

experimental, reforça o perfil de segurança do tratamento com FPE nas condições avaliadas. Dessa forma, os dados obtidos posicionam *Fridericia platyphylla*, especialmente na dose de 100 mg/kg/dia, como um potencial agente terapêutico na prevenção e no tratamento de danos cardíacos decorrentes do infarto do miocárdio, com efeitos benéficos sobre marcadores bioquímicos de lesão cardíaca, parâmetros hematológicos, redução da área de infarto, modulação do risco trombótico e preservação histológica do miocárdio.

Do ponto de vista integrativo, os achados experimentais são fortalecidos pelos resultados do artigo de prospecção tecnológica, que evidenciou um cenário promissor de inovação envolvendo *F. platyphylla*, bem como pela revisão integrativa da literatura, que consolidou evidências prévias sobre o potencial farmacológico e tecnológico da espécie em diferentes modelos experimentais. A convergência entre esses três eixos (experimental, científico e tecnológico) possibilitou a translação do conhecimento gerado para o desenvolvimento de uma composição farmacêutica inovadora, culminando no depósito de um pedido de patente voltado à aplicação cardiovascular. Assim, este conjunto de resultados não apenas amplia o conhecimento científico sobre *Fridericia platyphylla*, mas também estabelece bases sólidas para futuras investigações pré-clínicas e clínicas, bem como para o avanço de estratégias terapêuticas inovadoras no contexto das DCVs.

PERSPECTIVAS FUTURAS

Apesar dos resultados promissores, são necessários estudos adicionais para aprofundar a compreensão dos mecanismos moleculares envolvidos na ação do FPE. Uma das principais perspectivas é a avaliação dos impactos do tratamento sobre o perfil inflamatório, por meio da quantificação das citocinas pró-inflamatórias IL-6 e TNF-α, com o objetivo de elucidar os mecanismos imunomoduladores associados à redução da extensão do infarto e à preservação da função cardíaca.

Dado que o modelo de isoproterenol envolve sobrecarga β-adrenérgica, estresse oxidativo e desregulação do cálcio intracelular, torna-se relevante investigar a participação de vias relacionadas ao estresse oxidativo e à homeostase redox, incluindo avaliação de marcadores de peroxidação lipídica como malondialdeído (MDA). A correlação observada entre CPK-MB, área infartada e fração volumétrica de colágeno sugere que o FPE pode atuar em etapas iniciais da lesão oxidativa, prevenindo a progressão para remodelamento fibrótico.

A expressiva redução da fração volumétrica de colágeno (CVF) observada nas doses mais altas indica potencial modulação de vias pró-fibróticas. Assim, estudos futuros devem avaliar a expressão de TGF-β1, colágeno tipo I e III,, com o objetivo de elucidar o impacto do FPE no remodelamento ventricular pós-lesão

A avaliação dos níveis de angiotensina II em estudos de cardioprevenção também se configura como uma ferramenta importante na prospecção de agentes terapêuticos naturais ou sintéticos com potencial efeito cardioprotetor. Como componente central do sistema renina-angiotensina-aldosterona, a angiotensina II está diretamente envolvida em processos de vasoconstrição, inflamação, estresse oxidativo e remodelamento cardíaco, que são mecanismos-chave na progressão das DCVs. Assim, a redução de seus níveis ou da expressão de seus receptores em modelos experimentais, após a administração de compostos bioativos, pode indicar um possível mecanismo de ação cardioprotetora, orientando o desenvolvimento de novas estratégias para a prevenção do infarto do miocárdio e outras cardiopatias. Com base nessas abordagens, espera-se consolidar o conhecimento sobre os mecanismos cardioprotetores de *Fridericia platyphylla*, reforçando seu potencial terapêutico e estabelecendo fundamentos para futuras investigações clínicas no campo das DCVs.

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ANEXOS

ANEXO 1 – PATENTE SUBMETIDA

INSTITUTO NACIONAL DA PROPRIEDADE INDUSTRIAL

870260005772
21/01/2026 15:43
29409162350104989

Número do Processo: BR 10 2026 001434 6

Dados do Depositante (71)

Depositante 1 de 1

Nome ou Razão Social: UNIVERSIDADE FEDERAL DO MARANHÃO
Tipo de Pessoa: Pessoa Jurídica
CPF/CNPJ: 06279103000119
Nacionalidade: Brasileira
Endereço: Cidade Universitária Dom Delgado, Av. dos Portugueses, 1966, Vila Bacanga.
Cidade: São Luis
Estado: MA
CEP: 65080-805
País: Brasil
Telefone: (98) 32728710
Fax:
Email: ageufma.cprp@ufma.br

PETICIONAMENTO ELETRÔNICO Esta solicitação foi enviada pelo sistema Peticionamento Eletrônico em 21/01/2026 às 15:43, Petição 870260005772

Dados do Pedido

Natureza Patente:	10 - Patente de Invenção (PI)
Título da Invenção ou Modelo de Utilidade (54):	COMPOSIÇÕES FARMACÊUTICAS À BASE DE CERVEJINHA DO CAMPO (FRIDERICIA PLATYPHYLLA) PARA USO EM DESORDENS CARDIOVASCULARES
Resumo:	A presente invenção refere-se ao desenvolvimento de composições farmacêuticas contendo Fridericia platyphylla (popularmente conhecida como cervejinha do campo), com aplicação profilática e/ou terapêutica em distúrbios cardiovasculares. As composições são obtidas por meio da incorporação do extrato vegetal a veículos farmacologicamente aceitáveis que promovem adequada solubilização, estabilidade físico-química, palatabilidade e características organolépticas compatíveis com diferentes formas de administração, preferencialmente oral. A invenção apresenta como diferencial técnico a otimização da biodisponibilidade do extrato bioativo, aliada à facilidade de administração, baixo custo de produção e potencial para aplicação em larga escala. As propriedades farmacológicas observadas incluem atividade antioxidante e efeito regenerativo, conferindo à formulação um perfil terapêutico promissor para uso preventivo e/ou complementar ao tratamento convencional de doenças cardiovasculares. As formulações contêm compostos inertes que garantem boa solubilidade do componente ativo, melhor palatabilidade, sabor adocicado, sem alteração do odor original, com elevada biodisponibilidade oral, sem riscos de toxicidade. A invenção também fornece uma nova aplicação médica para Fridericia platyphylla.
Figura a publicar:	02

ANEXO 2 – COMPROVANTE DE CADASTRO DE ACESSO - SISGEN

Ministério do Meio Ambiente
CONSELHO DE GESTÃO DO PATRIMÔNIO GENÉTICO

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

Comprovante de Cadastro de Acesso

Cadastro nº A451DE4

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

Número do cadastro:	**A451DE4**
Usuário:	**Cláudia Quintino da Rocha**
CPF/CNPJ:	**068.952.376-90**
Objeto do Acesso:	**Patrimônio Genético**
Finalidade do Acesso:	

☑ **Pesquisa Científica** ☑ **Bioprospecção** ☑ **Desenvolvimento Tecnológico**

Espécie

Arrabidaea brachypoda

Título da Atividade:	**Estudo Quimico e Biológico de Arrabidaea brachypoda**

Equipe

Cláudia Quintino da Rocha	**UFMA**
MILENA BOTELHO PEREIRA SOARES	**FIOCRUZ**
Emerson Ferreira Queiroz	**Université de Genève**
Wagner Vilegas	**Unesp**
Jean-Luc.Wolfender	**Université de Genève**
Marcelo Henrique Dos Santos	**Universidade Federal de Viçosa**
Maria Perpétua Oliveira Ramos	**UNIPAM**
Giovanna Barbarini Longato	**UFS**

Data do Cadastro:	**03/10/2018 08:39:50**
Situação do Cadastro:	**Concluído**

Conselho de Gestão do Patrimônio Genético
Situação cadastral conforme consulta ao SisGen em **10:03** de **05/11/2018**.

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

ANEXO 3 – APROVAÇÃO DA COMISSÃO DE ÉTICA NO USO DE ANIMAIS – CEUA

UNIVERSIDADE FEDERAL DO MARANHÃO
Av. dos Portugueses, 1966, - Bairro Vila Bacanga, São Luís/MA, CEP 65080-805
Telefone: (98) 3272-8000 - https://www.ufma.br

Certificado Eletrônico nº 0943286/2024/CEUA/CCBS
NUP 23115.019856/2023-61.

CERTIFICADO

Comissão de Ética no Uso de Animais
CIAEP: 02.0341.2019

Certificamos que a proposta intitulada: "**Bioprospecção do extrato das folhas de Fridericia platyphylla na cardioprevenção em roedores e obtenção de bioprodutos" Processo n. 23115.019856/2023-61**, sob a responsabilidade da **Profa. Dra. Rachel Melo Ribeiro**, 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 considerado **APROVADO** pela Comissão de Ética no Uso de Animais (CEUA - UFMA) da Universidade Federal do Maranhão, **na reunião realizada em 06/02/2024**.

We certify the proposal: "**Bioprospecting of *Fridericia platyphylla* leaf extract for cardioprevention in rodents and obtaining bioproducts", Process n. 23115.019856/2023-61**, under the responsibility of **Profa. Dra. Rachel Melo Ribeiro**, which involves the production, maintenance or use of animals belonging to the phylum Chordata, sub-phylum Vertebrata (except human beings) for scientific research purposes (or teaching) - is following Law No. 11,794, of October 8, 2008, Decree No. 6.899, of July 15, 2009, as well as with the rules issued by the National Council for Control of Animal Experimentation (CONCEA), and was **APPROVED** by the Ethics Committee on Animals Use of the Federal University of Maranhão (CEUA - UFMA), **in meeting of 02/06/2024.**