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JOÃO RICARDO CRAY DA COSTA

AVALIAÇÃO FARMACOLÓGICA DO EXTRATO DE *Arrabidaea chica* EM MODELO EXPERIMENTAL DE SÍNDROME METABÓLICA INDUZIDA POR MÚLTIPLOS FATORES DE RISCO

Umuarama
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Orientação: Dra. Francislaine Aparecida dos Reis Lívero

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JOÃO RICARDO CRAY DA COSTA

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“O futuro tem muitos nomes.
Para os fracos é o inalcançável.
Para os temerosos, o desconhecido.
Para os valentes é a oportunidade”.
(Victor Hugo, 1802 a 1885)

COSTA, João Ricardo Cray. **Avaliação farmacológica do extrato de** *Arrabidaea chica* **em modelo experimental de síndrome metabólica induzida por múltiplos fatores de risco.** Orientador: Francislaine Aparecida dos Reis Lívero. 2025. 76f. Dissertação (Mestrado em Plantas Medicinais e Fitoterápicos na Atenção Básica) - Universidade Paranaense, Umuarama, 2025.

RESUMO

A Síndrome Metabólica (SM) é caracterizada pela presença simultânea de fatores de risco que aumentam a probabilidade de desenvolvimento de doenças cardiovasculares e diabetes tipo 2 (DM2), como hiperglicemia, dislipidemia e resistência à insulina. Entre esses fatores, o DM2 e a dislipidemia, especialmente a elevação do colesterol LDL, associados ao consumo crônico de álcool, estão fortemente relacionados ao desenvolvimento da esteatose hepática. O tratamento convencional, que combina mudanças no estilo de vida e uso de fármacos, apresenta eficácia limitada devido à baixa adesão dos pacientes, o que justifica a busca por alternativas terapêuticas complementares, como o uso de plantas medicinais. *Arrabidaea chica* é uma planta amplamente utilizada na medicina tradicional da região amazônica para o tratamento de distúrbios inflamatórios, metabólicos e hepáticos. Estudos prévios sugerem propriedades antioxidantes, anti-inflamatórias e hepatoprotetoras. Nesse contexto, este estudo teve como objetivo avaliar a toxicidade e os efeitos terapêuticos da fração solúvel em etanol de *A. chica* sobre parâmetros hepáticos, renais e lipídicos em um modelo pré-clínico de síndrome metabólica induzida por múltiplos fatores em ratos. O experimento foi conduzido com ratos Wistar machos, mantidos em condições ambientais controladas. Na primeira etapa, foi conduzido um teste de toxicidade oral aguda em ratos (n = 5-6) em doses de até 2.000 mg/kg, com monitoramento de mortalidade, alterações comportamentais, parâmetros bioquímicos, hematológicos e histopatológicos. Na segunda etapa foi realizado um estudo de eficácia farmacológica em que os animais (n = 6-7) foram submetidos a um protocolo de indução da SM que incluiu: diabetes induzido por estreptozotocina (60 mg/kg, i.p.), dislipidemia induzida por dieta enriquecida com colesterol (0,5%) e consumo livre de etanol 5% na dieta líquida, por cinco semanas. Durante as duas últimas semanas, os animais receberam tratamento por gavagem com veículo (controle negativo), extrato de *A. chica* (30, 100 ou 300 mg/kg) ou combinação de sinvastatina (2,5 mg/kg) e insulina (6 UI, s.c.) no controle positivo. Um grupo basal, composto por ratos normoglicêmicos, normolipidêmicos e não expostos ao etanol, foi incluído como referência. Ao final do tratamento, os animais foram submetidos à eutanásia e avaliados quanto a glicemia plasmática, perfil lipídico (colesterol total e triglicerídeos plasmáticos e hepáticos), enzimas hepáticas (AST, ALT), marcadores renais (ureia, creatinina)

e peso de órgãos. Exames histopatológicos hepáticos permitiram verificar alterações estruturais e acúmulo lipídico. Os resultados mostraram ausência de mortalidade ou efeitos adversos nos testes de toxicidade. Em relação ao grupo controle negativo, o tratamento com *A. chica* promoveu normalização significativa da glicemia e dos lipídios plasmáticos, redução da esteatose hepática e restauração dos marcadores de função renal. Notavelmente, o tratamento com o extrato foi capaz de normalizar completamente os níveis de AST e ALT, efeito não observado no grupo controle positivo. As análises histológicas confirmaram efeitos hepatoprotetores e nefroprotetores, com preservação da arquitetura tecidual e menor acúmulo de lipídios. Em conclusão, os achados sustentam o potencial terapêutico seguro e multifuncional de *A. chica* no manejo da SM, reforçando seu uso tradicional e destacando a necessidade de estudos adicionais para elucidar seus mecanismos de ação.

Palavras-chave: álcool, diabetes, dislipidemia, efeito hipolipidêmico, hepatoproteção, nefroproteção.

COSTA, João Ricardo Cray. P**harmacological evaluation of** *Arrabidaea chica* **extract in an experimental model of metabolic syndrome induced by multiple risk factors.** Advisor: Francislaine Aparecida dos Reis Lívero. 2025. 76p. Dissertation (Master's degree in Medicinal Plants and Phytotherapeutics in Basic Attention) - Universidade Paranaense, Umuarama, 2025.

ABSTRACT

Metabolic Syndrome (MS) is defined by the coexistence of risk factors that increase the likelihood of cardiovascular diseases and type 2 diabetes (T2DM), including hyperglycemia, dyslipidemia, and insulin resistance. Among these factors, T2DM and dyslipidemia particularly elevated LDL cholesterol together with chronic alcohol consumption, are strongly associated with the development of hepatic steatosis. Conventional treatment, which combines lifestyle modification and pharmacological therapy, often shows limited efficacy due to poor patient adherence, supporting the search for complementary therapeutic alternatives such as medicinal plants. *Arrabidaea chica* is traditionally used in the Amazon region for the treatment of inflammatory, metabolic, and hepatic disorders. Previous studies have suggested antioxidant, anti-inflammatory, and hepatoprotective properties. This study aimed to evaluate the toxicity and therapeutic effects of the ethanol-soluble fraction of *A. chica* on hepatic, renal, and lipid parameters in a multifactor-induced preclinical model of MS in rats. Male Wistar rats were maintained under controlled environmental conditions. In the first phase, an acute oral toxicity test (n = 5–6) was conducted at doses up to 2,000 mg/kg, monitoring mortality, behavioral changes, and biochemical, hematological, and histopathological parameters. For the efficacy study, rats (n = 6–7) were subjected to an MS induction protocol including streptozotocin-induced diabetes (60 mg/kg, i.p.), cholesterol-enriched diet (0.5%), and chronic alcohol consumption through free access to a liquid diet containing 5% ethanol for five weeks. During the last two weeks, animals were treated by oral gavage with vehicle (negative control), *A. chica* extract (30, 100, or 300 mg/kg), or a combination of simvastatin (2.5 mg/kg) and insulin (6 IU, s.c.) as a positive control. A basal group of normoglycemic, normolipidemic, and ethanol-free rats was included as reference. At the end of treatment, plasma glucose, lipid profile (total cholesterol and plasma/hepatic triglycerides), hepatic enzymes (AST, ALT), renal markers (urea, creatinine), and organ weights were assessed. Hepatic histopathology evaluated structural alterations and lipid accumulation. Toxicity testing revealed no mortality or adverse effects. Compared with the negative control group, *A. chica* significantly normalized plasma glucose and lipid levels, reduced hepatic steatosis, and restored renal function markers. Remarkably, extract treatment fully normalized AST and ALT levels, an effect not observed in the positive control group. Histological analyses confirmed hepatoprotective and nephroprotective actions,

with preserved tissue architecture and reduced lipid deposition. In conclusion, the findings support the safe and multifunctional therapeutic potential of *A. chica* in the management of MS, reinforcing its traditional use and highlighting the need for further studies to clarify its mechanisms of action.

Keywords: alcohol, diabetes, dyslipidemia, hepatoprotection, hypolipidemic effect, nephroprotection.

LISTA DE FIGURAS

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Artigo - Therapeutic potential of the traditional amazonian medicinal plant *Arrabidaea chica* in a multifactorial experimental model of metabolic syndrome

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Artigo - Therapeutic potential of the traditional amazonian medicinal plant *Arrabidaea chica* **in a multifactorial experimental model of metabolic syndrome**

LISTA DE SIGLAS

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CONCEA	Brazilian National Council for the Control of Animal Experimentation
UNIVEL	Cascavel University Center
HDL-c	Colesterol de lipoproteína de alta densidade
LDL-c	Colesterol de lipoproteína de baixa densidade
CAPES	Coordenação de Aperfeiçoamento de Pessoal de Nível Superior
COPG	Coordenadoria de Pós-Graduação
DCV	Doenças Cardiovasculares
DM	Diabetes Mellitus
DM1	Diabetes Mellitus tipo 1
DM2	Diabetes Mellitus tipo 2
RNS	Espécie reativa de nitrogênio
ERRO	Espécies Reativas de Oxigênio
TNF-α	Fator de necrose tumoral alfa
UFGD	Federal University of Grande Dourados
H&E	Hematoxylin and eosin
HAS	Hipertensão arterial sistêmica
INSU	Insulin
IL-6	Interleucina-6
MAFLD	Doença Hepática Gordurosa Associada à Disfunção Metabólica
CNPq	National Council for Scientific and Technological Development
(NCEP-ATP) III	Programa Nacional de Educação sobre Colesterol dos Estados Unidos modificado, Painel de Tratamento de Adultos
OMS	Organização Mundial de Saúde
PAD	Pressão arterial diastólica
PAS	Pressão arterial sistólica
RENISUS	Relação Nacional de Plantas Medicinais de Interesse ao Sistema Único de Saúde
SM	Síndrome Metabólica
SIM	Simvastatin
SEM	Standard error of the mean

UEPG	State University of Ponta Grossa
CCl_4	Tetracloreto de carbono
UFPR	Universidade Federal do Paraná
UNIPAR	Universidade Paranaense

LISTA DE SÍMBOLOS

@	Arroba
β	Beta
cm	Centímetro
dL	Decilitro
g	Grama
ºC	Graus Celsius
C–	Grupo Controle
≥	Maior ou igual
+	Mais
±	Mais ou menos
®	Marca Registrada
<	Menor
–	Menos
Hg	Mercúrio
µg	Micrograma
mg	Miligrama
mL	Mililitros
mm	Milímetros
n	Número
%	Porcentagem
Kg	Quilograma
IU	Unidade Internacional

SUMÁRIO

CAPÍTULO 1

REVISÃO DA LITERATURA

PANORAMA DA SÍNDROME METABÓLICA E POTENCIAL TERAPÊUTICO DA *Arrabidaea chica*

1.1 Introdução

A Síndrome Metabólica (SM) é caracterizada por um conjunto de alterações que, em associação, elevam significativamente o risco de complicações graves à saúde (NOUBIAP et al., 2022). Entre seus principais componentes, destacam-se a obesidade abdominal, hipertensão arterial sistêmica (HAS), hiperglicemia, dislipidemia e resistência à insulina (RAMOS, 2022). A presença de três ou mais desses fatores de risco aumenta substancialmente o risco global para o desenvolvimento de doenças cardiovasculares (DCV; BRAUER et al., 2022). Além disso, indivíduos com SM apresentam maior probabilidade de desenvolver diferentes graus de esteatose hepática (GANGIREDDY et al., 2022).

Entre as alterações associadas à SM, destaca-se a Doença Hepática Gordurosa Associada à Disfunção Metabólica (MAFLD), que afeta aproximadamente um quarto da população mundial. Essa condição está relacionada à resistência à insulina, à limitada expansibilidade e à disfunção do tecido adiposo, fatores que favorecem a resistência insulínica e contribuem para a fisiopatologia do diabetes mellitus (DM; GODOY-MATOS, SILVA JÚNIOR e VALERIO, 2020).

O DM é um distúrbio metabólico caracterizado pela hiperglicemia, decorrente de deficiência na secreção de insulina nas células β das ilhotas pancreáticas de Langherans e/ou resistência periférica à sua ação sendo classificada em tipo 1 (DM1) e tipo 2 (DM2). O DM1, também denominado insulinodependente, resulta da destruição autoimune das células β. Já o DM2, ou não insulinodependente, ocorre predominantemente por resistência à insulina e/ou da redução na sensibilidade celular ao hormônio (TEHSEEN et al., 2024). Evidências científicas apontam o DM2 como um dos principais fatores de risco para a MAFLD (VARGAS et al., 2024).

Outro componente importante relacionado à SM é a dislipidemia, caracterizada por níveis elevados de triglicerídeos e das concentrações de colesterol de lipoproteína de baixa densidade (LDL-c), condição frequentemente presente em indivíduos com a síndrome (XU et al., 2018). O aumento da absorção de lipídios, especialmente do colesterol de LDL-c, contribui para o acúmulo de triglicerídeos no fígado e favorece o transporte e a mobilização de gordura hepática (VARGAS et al., 2024).

Quanto ao consumo de álcool, estudos apontam que a ingestão elevada aumenta significativamente o risco de desenvolvimento da SM e está associada a diversos de seus componentes (ARSHADI et al., 2025; HERNÁNDEZ-RUBIO et al., 2022). O consumo excessivo, seja de forma regular ou episódica, tem sido descrito como um importante determinante comportamental para o aumento desse risco. Evidências sugerem que indivíduos com esse padrão de ingestão apresentam maior probabilidade de manifestar SM quando comparados a abstêmios (SAKBOONYARAT; RANGSIN; MITTLEMAN, 2022; SULIGA et al., 2019).

Dessa forma, diante dos desafios para o controle efetivo da SM, como a baixa adesão às mudanças no estilo de vida, a necessidade frequente de polifarmácia e os efeitos adversos associados ao tratamento farmacológico convencional (ALAWDI et al., 2024; SARAH MATHEW et al., 2024), o uso de plantas medicinais tem sido considerado uma alternativa viável. Historicamente, as plantas têm sido amplamente empregadas como recursos terapêuticos no tratamento de diversas enfermidades (PEDROSO; ANDRADE; PIRES, 2021).

No Brasil, a Relação Nacional de Plantas Medicinais de Interesse ao Sistema Único de Saúde (RENISUS), publicada em 2009, inclui a *Arrabidaea chica* (Humb. & Bonpl.) B. Verlot dentre as espécies de maior relevância na medicina tradicional, especialmente na região amazônica (SILVA-SILVA et al., 2021). Diversos efeitos biológicos e farmacológicos de extratos e frações de *A. chica* têm sido amplamente documentados. Estudos *in vitro* demonstraram o efeito hepatoprotetor do extrato das folhas (DE-SOUZA et al., 2009), confirmado também em modelos *in vivo* utilizando extrato etanólico a 70% em ratos Wistar (MEDEIROS et al., 2011). A ação anti-inflamatória foi evidenciada *in vivo*, destacando-se a capacidade do extrato etanólico e de sua fração aquosa em inibir angiogênese e reduzir a migração de células inflamatórias (RIBEIRO, 2012). Além disso, a inibição *in vitro* do fator de transcrição nuclear kappa B foi relatada para o extrato das folhas (ZORN et al., 2001). Também foi observada atividade antioxidante significativa do extrato etanólico, avaliada pela capacidade de sequestro do radical livre 1,1-difenil-2-picrilidrazila (DPPH; AMARAL et al., 2012).

Diante do potencial terapêutico de produtos naturais e da ampla utilização de *A. chica* na medicina popular, o presente estudo propõe avaliar a atividade protetora dessa espécie frente a múltiplos fatores de risco associados à SM, reforçando sua importância como planta medicinal contemplada na RENISUS.

1.2 Revisão da Literatura

1.2.1 Síndrome Metabólica

A SM não é uma doença única, mas sim um conjunto de fatores de risco inter-relacionados que, quando presentes simultaneamente, aumentam de forma significativa a probabilidade de complicações cardiometabólicas (SWARUP, 2024). É caracterizada por obesidade abdominal, resistência à insulina, HAS e dislipidemia, combinação que eleva substancialmente o risco de desenvolvimento de DCV e DM2 (SOUTO BATISTA et al., 2025). A presença desses fatores impacta diversos órgãos, com destaque para o fígado, essencial no metabolismo de nutrientes e lipídios, aumentando a predisposição à esteatose hepática em diferentes graus (GANGIREDDY et al., 2022; VARGAS et al., 2024).

As definições clínicas da SM se baseiam nos critérios do Programa Nacional de Educação sobre Colesterol dos Estados Unidos, modificados pelo Painel de Tratamento de Adultos (NCEP-ATP III), e da Federação Internacional de Diabetes. Esses parâmetros consideram, entre outros: pressão arterial sistólica (PAS) ≥ 130 mm Hg ou diastólica (PAD) ≥ 85 mm Hg; triglicerídeos ≥ 150 mg/dL; colesterol de lipoproteína de alta densidade (HDL-c) < 40 mg/dL em homens e < 50 mg/dL em mulheres; glicemia de jejum ≥ 110 mg/dL; e circunferência abdominal ≥ 102 cm em homens e ≥ 88 cm em mulheres (ARSHADI, 2025).

Apesar dos avanços globais, os mecanismos patogênicos que sustentam a SM permanecem complexos e ainda não totalmente elucidados. Fatores ambientais e comportamentais, como o sedentarismo associado a uma dieta hipercalórica, desempenham papel central na fisiopatologia multifatorial da síndrome (ROCHLANI et al., 2017). Além disso, a predisposição genética ou étnica e o processo de envelhecimento atuam como moduladores importantes (OBEIDAT et al., 2025). A gênese da SM resulta da interação entre vias metabólicas e processos inflamatórios. Embora a resistência à insulina e a obesidade central sejam reconhecidas como determinantes primários, evidências recentes destacam a inflamação crônica de baixo grau como mecanismo central na progressão da síndrome (CIFUENTES et al., 2024).

Diversas teorias buscam explicar esses processos, incluindo o aumento do fluxo de ácidos graxos associado à resistência à insulina, a ativação neuro-hormonal e a manutenção de um estado inflamatório persistente, todos considerados determinantes para a iniciação e evolução da SM (JHA et al., 2023). O excesso de tecido adiposo visceral, em particular, exerce efeito deletério ao induzir disfunção adipocitária, caracterizada pelo aumento da liberação de ácidos graxos livres e citocinas pró-inflamatórias, concomitante à redução de adipocinas com

propriedades protetoras, como a adiponectina. Essas alterações comprometem a sinalização insulínica, favorecendo disfunção endotelial e o desenvolvimento de hipertensão, dislipidemia e hiperglicemia (DHONDGE et al., 2024; OBEIDAT et al., 2025).

A elevação dos ácidos graxos livres circulantes interfere diretamente na cascata de sinalização da insulina em diversos órgãos, intensificando a resistência insulínica (GIROUSSE et al., 2013). Esse processo decorre, em parte, da incapacidade da insulina em inibir a lipólise no tecido adiposo resistente, sobretudo na região visceral, o que amplifica a liberação de ácidos graxos e impacta negativamente o metabolismo hepático (FREEMAN; ACEVEDO; PENNINGS, 2025).

O tecido adiposo, que desempenha função semelhante à de uma glândula endócrina, secreta compostos biologicamente ativos denominados adipocinas ou adipocitocinas, fundamentais para a regulação da homeostase metabólica. Alterações no padrão de secreção dessas moléculas em indivíduos com obesidade central constituem um dos principais mecanismos associados às manifestações clínicas da SM. A produção excessiva de adipocinas inflamatórias favorece a manutenção de um estado inflamatório crônico, contribuindo para o agravamento progressivo das complicações relacionadas à síndrome (JHA et al., 2023).

Nesse contexto, o estabelecimento de um ambiente pró-inflamatório configura-se como aspecto crucial da SM. O excesso de gordura visceral promove a secreção exacerbada de citocinas, como o fator de necrose tumoral alfa (TNF-α), a interleucina-6 (IL-6) e a proteína C reativa, que intensificam o processo inflamatório sistêmico. Esses mediadores interferem na sinalização insulínica, exacerbam a disfunção endotelial e participam diretamente do desenvolvimento de hipertensão, alterações lipídicas e distúrbios glicêmicos (DHONDGE et al., 2024; OBEIDAT et al., 2025).

A etiologia da SM é multifatorial, sendo os padrões alimentares inadequados, o sedentarismo e outros determinantes relacionados ao estilo de vida reconhecidos como fatores centrais em seu desenvolvimento (BORGES NETO, 2021). Pacientes com SM apresentam risco aproximadamente duas vezes maior de desenvolver doenças cardiovasculares ateroscleróticas e até cinco vezes maior de desenvolver diabetes mellitus em comparação à população geral (SAMSON; GARBER, 2014). Uma metanálise conduzida por Noubiap et al. (2022) estimou prevalência global da SM entre 12,5% e 31,4%, enquanto no Brasil a taxa é de cerca de 33%, com marcada heterogeneidade regional (DE SIQUEIRA VALADARES et al., 2022).

Apesar da existência de terapias eficazes, a adesão às recomendações das diretrizes permanece aquém do ideal (PASSAGLIA et al., 2023). Estratégias preventivas e de manejo da

SM incluem políticas públicas voltadas à promoção de hábitos saudáveis, programas de cessação do tabagismo, combate à obesidade, incentivo à atividade física e redução do consumo nocivo de álcool (OPAS, 2017; WHO, 2013). No entanto, países de baixa e média renda frequentemente enfrentam dificuldades para implementar programas integrados de atenção primária que permitam a detecção e o tratamento precoces de indivíduos em risco, o que agrava o impacto socioeconômico da síndrome (NASCIMENTO et al., 2018).

Embora políticas de saúde tenham contribuído para a redução da mortalidade, o número absoluto de casos segue em crescimento, impulsionado pelo envelhecimento populacional e pelo aumento da incidência de doenças crônicas (PRÉCOMA et al., 2019). Um dos fatores mais preocupantes nesse cenário é o DM2, cuja prevalência global deve alcançar 578 milhões de pessoas até 2030, configurando-se como problema de saúde pública de caráter emergencial. O Brasil ocupa atualmente a quarta posição no ranking mundial de países com maior número de indivíduos diagnosticados, reflexo de um crescimento expressivo nas últimas três décadas (SANTOS-DE-ARAÚJO et al., 2024).

A hiperglicemia e a resistência à insulina presentes no DM2 promovem inflamação crônica, estresse oxidativo e disfunção endotelial, favorecendo a aterogênese (MESQUITA; KER, 2021). Alterações no peso corporal, envelhecimento populacional e mudanças socioeconômicas têm contribuído para o aumento da incidência global (BRAUER et al., 2022). Além disso, há evidências de relação bidirecional entre DM2 e esteatose hepática associada à disfunção metabólica, o que reforça a necessidade de detecção precoce e intervenção oportuna (MARTÍNEZ et al., 2021; VARGAS et al., 2024).

Outro componente central da SM é a dislipidemia, especialmente a elevação do LDL-c, um dos fatores de risco modificáveis mais relevantes (YUSUF et al., 2004). A dislipidemia caracteriza-se por alterações no perfil lipídico, incluindo aumento do colesterol total, triglicerídeos e LDL-c, além da redução do HDL-c (NOGUEIRA DE SÁ et al., 2022). Esse perfil lipídico aterogênico contribui de forma expressiva para o aumento do risco de DCV (RAHMAN et al., 2024; SINGH; JIALAL, 2024). Estudos indicam que a redução intensiva do LDL-c está associada a benefícios significativos na diminuição de eventos cardiovasculares e mortalidade (FALUDI et al., 2017). Segundo dados da Organização Mundial da Saúde (OMS, 2009), níveis elevados de colesterol sérico são responsáveis por aproximadamente 2,6 milhões de mortes anuais no mundo. Além disso, níveis inadequados de HDL-c aumentam a probabilidade de desenvolvimento de esteatose hepática (SCHILD, SANTOS; ALVES, 2013).

O consumo excessivo de álcool é outro fator de risco relevante para a SM, associado a alterações no metabolismo lipídico e a danos hepáticos (PARK et al., 2022). Padrões de ingestão abusiva elevam o risco de DCV, câncer, cirrose e pancreatite crônica (HERNÁNDEZ-RUBIO et al., 2022; LEE e JANG, 2018). A OMS destaca o alcoolismo como fator modificável que contribui significativamente para o surgimento de doenças metabólicas, incluindo alterações nos níveis de HDL-c e lesões hepáticas (ARSHADI, 2025; LIMA et al., 2013; OMS, 2014). Estudos recentes têm reforçado os efeitos tóxicos do etanol, particularmente sobre o estresse oxidativo e a integridade celular. Modelos experimentais com ratos expostos cronicamente ao etanol revelam alterações estruturais e funcionais no miocárdio, remodelação metabólica precoce e prejuízo na eficiência das proteínas contráteis. Adicionalmente, metabólitos como o acetaldeído, em associação com espécies reativas de oxigênio (ERO), desempenham papel central nos danos celulares e na inflamação tecidual decorrentes do etilismo crônico (AMARAL et al., 2012; YANG et al., 2022).

Os mecanismos exatos que sustentam a interação sinérgica entre o consumo de álcool e a disfunção metabólica ainda não estão totalmente esclarecidos. Contudo, evidências indicam que esse processo pode envolver efeitos combinados sobre a função mitocondrial, aumento do estresse oxidativo, indução da atividade do citocromo P450 (CYP) 2E1, ativação da imunidade inata, estímulo às células estreladas hepáticas, alterações da microbiota intestinal e aumento da permeabilidade da mucosa intestinal. Adicionalmente, alterações no metabolismo dos ácidos biliares e lipídico, bem como a disfunção adipocitária, que resulta em intensificação da lipólise e maior liberação de mediadores pró-inflamatórios, também parecem contribuir para esse quadro (ACIERNO, et al., 2022; ÅBERG et al., 2023). Evidências provenientes de estudos em humanos demonstraram que a intoxicação alcoólica induz modificações rápidas no perfil de lipídios circulantes, sendo que tais efeitos sobre o metabolismo lipídico e a lipotoxicidade são exacerbados na presença de MAFLD (ISRAELSEN et al., 2021; SOGABE, et al., 2023).

O tratamento da SM envolve, prioritariamente, mudanças no estilo de vida, como adoção de dieta equilibrada, prática regular de atividade física e abandono de hábitos nocivos, aliados à terapia farmacológica direcionada a cada componente da síndrome. Entretanto, a adesão a essas medidas é frequentemente baixa, em parte devido à dificuldade de manutenção de hábitos saudáveis a longo prazo, à polifarmácia e aos efeitos adversos associados ao uso contínuo de medicamentos (ALAWDI et al., 2024; GRUNDY, 2016). Além disso, a abordagem farmacológica costuma focar em controlar individualmente os fatores de risco — como hipertensão, dislipidemia ou hiperglicemia — sem necessariamente reverter a fisiopatologia

subjacente da SM (FAHED, 2022). Esses desafios ressaltam a necessidade de novas estratégias terapêuticas mais seguras, acessíveis e capazes de atuar de forma integrada sobre os múltiplos aspectos da síndrome.

Por fim, embora as diretrizes recomendem a combinação de mudanças no estilo de vida com terapias médicas para prevenção e tratamento das doenças associadas à SM, existe um descompasso entre as intervenções propostas e a realidade da atenção primária e das políticas de saúde pública. Essa lacuna contribui para a persistência de altas taxas de morbidade e mortalidade associadas à síndrome (BRAUER et al., 2022).

Como alternativa terapêutica, o uso de plantas medicinais tem se mostrado relevante, baseado no conhecimento empírico e tradicional transmitido por gerações, que ainda hoje é aplicado em muitas comunidades (FERREIRA et al., 2019; FISCHER; STUMPF; MARIOT, 2019). Segundo a OMS, cerca de 80% da população em países em desenvolvimento, como o Brasil, utiliza medicamentos à base de extratos vegetais, sendo essa a única opção terapêutica para muitas comunidades (FERREIRA et al., 2019; SILVEIRA; BANDEIRA; ARRAIS, 2008).

2.1.2 *Arrabidaea chica* dos usos populares aos estudos farmacológicos

Embora o Brasil detenha grande biodiversidade, parte da sua flora ainda é consumida sem comprovação científica adequada, o que pode levar a intoxicações e interações medicamentosas indesejadas (JUNIOR; PINTO; MACIEL, 2005; VENDRUSCOLO; MENTZ, 2006). As práticas integrativas e complementares na Atenção Básica, que incluem o uso de fitoterápicos, aproveitam esse recurso natural, de baixo custo e fácil cultivo. Contudo, é necessária maior orientação aos usuários para garantir um uso consciente, seguro e eficaz, prevenindo riscos e potencializando benefícios (GOÉS; SILVA; CASTRO, 2019; IANK et al., 2017).

O avanço da pesquisa científica tem ampliado o conhecimento sobre o uso correto das plantas, desde aspectos etnobotânicos e fitoquímicos até a comprovação farmacológica, com o objetivo de identificar propriedades terapêuticas e segurança (FERREIRA et al., 2019). O principal foco desses estudos é a descoberta de novos compostos bioativos e a formulação de fitoterápicos seguros e eficazes (ABAD; BERMEJO, 2007). Ademais, o interesse pelo uso de plantas medicinais cresceu diante dos efeitos adversos frequentemente associados a fármacos sintéticos (SOUZA-MOREIRA; SALGADO; PIETRO, 2010).

Nesse contexto, a etnobotânica e a etnofarmacologia desempenham papel central na exploração da biodiversidade, contribuindo para a identificação de compostos bioativos e

promovendo o desenvolvimento tecnológico sustentável dos recursos naturais (SALES; SARTOR; GENTILLI, 2015).

A Amazônia destaca-se como um dos biomas mais ricos em biodiversidade, entre as plantas medicinais, a *Arrabidaea chica* (Humb. & Bonpl.) B. Verlot (popularmente conhecida como "crajiru", "pariri" ou "chica"), da família *Bignoniaceae*, reconhecida pelo potencial na produção de compostos fenólicos utilizados no tratamento de várias enfermidades. A espécie é uma trepadeira lenhosa distribuída por toda a América tropical (Figura 1; DE SIQUEIRA et al., 2022; DO NASCIMENTO et al., 2022).

Figura 1. Espécie adulta da *Arrabidaea chica*, com destaque para as folhas e flores.

Fonte: https://l1nq.com/zsE1O

Diversos estudos identificaram flavonoides, antocianinas, taninos e fitoesteróis em extratos das folhas de *A. chica*, principalmente em plantas cultivadas fora da região amazônica (DEVIA et al., 2002; SIRAICHI et al., 2013). Embora sua eficácia e segurança ainda demandem maiores comprovações científicas, a planta é amplamente utilizada na medicina tradicional, com evidências de propriedades anti-inflamatórias e antimicrobianas nas folhas (MAFIOLETI et al., 2013; MICHEL et al., 2015). Coelho et al. (2019) descreve a utilização da *A. chica* na tradição popular para tratar diversas enfermidades, dentre elas: doenças do sistema cardiovascular, ginecológicas e do trato urinário, doenças infecciosas e imunológicas, envenenamentos e outras.

De Souza et al. (2012) demonstraram atividade anti-inflamatória do extrato das folhas da *A. chica* em estudos *in vitro*, com inibição do fator de transcrição nuclear kappa B a 500 µg/mL, efeito semelhante ao da quercetina presente no solvente. A carajurina, uma 3-

desoxiantocianidina, é apontada como responsável por essa inibição, contribuindo para a ação anti-inflamatória observada *in vivo* (OLIVEIRA et al., 2009; ZORN et al., 2001).

Outras pesquisas destacam ação antimicrobiana do extrato etanólico contra *Staphylococcus aureus* (RIBEIRO, 2008) e atividade cicatrizante tanto *in vitro*, pela estimulação do crescimento de fibroblastos (JORGE, 2008), quanto *in vivo*, em modelo de cicatrização de feridas cirúrgicas em ratos (JORGE et al., 2008). Além disso, extratos de *A. chica* mostraram capacidade significativa para eliminar ERO e espécies reativas de nitrogênio (ERN), sendo o extrato etanólico o mais rico em compostos fenólicos e com maior atividade antioxidante (DE SIQUEIRA et al., 2022).

Estudos experimentais indicam ainda o potencial hepatoprotetor da planta. De Souza et al. (2009) observaram que o extrato inibe a respiração mitocondrial acoplada à fosforilação de adenosina difosfato, reduz taxas de controle respiratório e aumenta a hidrólise de adenosina trifosfato em mitocôndrias isoladas, sugerindo influência no metabolismo hepático. Medeiros et al. (2011) demonstraram que o extrato hidroetanólico protege o fígado de ratos contra lesões induzidas por tetracloreto de carbono (CCl_4), evidenciado pela redução das enzimas hepáticas transaminases (aspartato e alanina aminotransferase) e bilirrubina, indicadores de integridade celular.

Diante da elevada morbimortalidade associada à SM, da baixa adesão aos tratamentos farmacológicos convencionais, frequentemente acompanhados de efeitos adversos e custos elevados e dos promissores resultados obtidos com plantas medicinais, além da carência de modelos experimentais que associem múltiplos fatores de risco com o uso de fitoterápicos, a busca por novos agentes terapêuticos seguros, eficazes e acessíveis torna-se essencial.

Considerando a elevada morbimortalidade associada à síndrome metabólica, as limitações e efeitos adversos dos tratamentos convencionais, e o uso tradicional de *A. chica* como recurso terapêutico, faz-se necessária a investigação científica dos seus efeitos em condições metabólicas complexas. Assim, este trabalho se propõe a avaliar o impacto do extrato de *A. chica* sobre parâmetros hepáticos, renais e lipídicos em um modelo pré-clínico de síndrome metabólica induzida por diabetes, dislipidemia e consumo de álcool em ratos, buscando validar e ampliar o conhecimento sobre seu potencial terapêutico e segurança.

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1.4 Objetivo

Investigar a toxicidade e os efeitos do tratamento com o extrato de *Arrabidaea chica* sobre parâmetros hepáticos, renais e lipídicos em ratos submetidos a um modelo pré-clínico de síndrome metabólica induzida por diabetes, dislipidemia e consumo de álcool.

CAPÍTULO 2

ARTIGO

THERAPEUTIC POTENTIAL OF THE TRADITIONAL AMAZONIAN MEDICINAL PLANT *Arrabidaea chica* IN A MULTIFACTORIAL EXPERIMENTAL MODEL OF METABOLIC SYNDROME

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Therapeutic potential of the traditional Amazonian medicinal plant *Arrabidaea chica* in a multifactorial experimental model of metabolic syndrome

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Abstract

Ethnopharmacological relevance: *Arrabidaea chica* is a medicinal plant traditionally used in the Amazon region for treating inflammatory, metabolic, and liver disorders. **Aim of the study:** This study aimed to evaluate the safety and therapeutic efficacy of *A. chica* extract in a multifactorial rodent model of metabolic syndrome combining diabetes, dyslipidemia, and chronic alcohol intake. **Materials and methods:** Acute oral toxicity was evaluated in rodents at doses up to 2000 mg/kg, monitoring mortality, behavioral changes, and biochemical, hematological, and histopathological parameters. For efficacy, male Wistar rats were subjected to a combined protocol inducing diabetes, dyslipidemia, and chronic alcohol intake for 5 weeks. *A. chica* extract was administered orally at 30 mg/kg daily for 2 weeks. Metabolic parameters measured included plasma glucose, total cholesterol, triglycerides, liver enzymes (AST, ALT), renal biomarkers, and organ weights. Histopathological examination of liver and kidney tissues was performed to assess morphological changes and lipid accumulation. **Results:** No mortality or adverse effects were observed in toxicity testing. Treatment with *A. chica* significantly normalized plasma glucose and lipid levels, reduced hepatic steatosis, and restored renal function markers. Notably, *A. chica* fully normalized AST and ALT levels, whereas simvastatin failed to restore these enzymes. Histological analyses confirmed hepatoprotective and nephroprotective effects with preserved tissue architecture and reduced lipid accumulation. **Conclusion:** These findings validate its traditional use and highlight *A. chica* as a promising, safe, multi-target phytotherapeutic candidate for metabolic syndrome management. Further studies are needed to elucidate mechanisms and clinical applicability.

Keywords: Alcohol-induced metabolic disorders, diabetes, dyslipidemia, hepatoprotection, hypolipidemic effect, nephroprotection.

1. Introduction

Metabolic syndrome is a complex cluster of metabolic disorders characterized by insulin resistance, hyperglycemia, dyslipidemia, central obesity, and hypertension, and is recognized as a major risk factor for cardiovascular diseases and type 2 diabetes (Souto Batista et al., 2025; Swarup, 2024). The global prevalence of metabolic syndrome is increasing, driven by multiple risk factors such as poor diet, physical inactivity, excessive alcohol consumption, and genetic predisposition, highlighting the urgent need for integrated therapeutic strategies to manage this condition (Grundy, 2016).

Rodent models that mimic metabolic syndrome by simultaneously inducing diabetes, dyslipidemia and alcohol consumption are essential tools for investigating underlying pathophysiological mechanisms and evaluating potential therapeutic agents. However, most existing models induce only one or a few risk factors in isolation, limiting the understanding of the complex interactions present in human metabolic syndrome (Wong et al., 2016; Ionita et al., 2024). The development of a novel animal model combining multiple risk factors such as diabetes, dyslipidemia, and chronic alcohol intake, represents a significant advancement in preclinical research, allowing for a more accurate simulation of the clinical complexity of metabolic syndrome and a more realistic assessment of natural product efficacy.

Arrabidaea chica (Humb. & Bonpl.) B. Verlot, known as ‘crajiru’, ‘pariri’, or ‘chica’, is a woody vine of the Bignoniaceae family widely distributed across tropical Americas, particularly in the Amazon (De Siqueira et al., 2022; Do Nascimento et al., 2022). It occupies a prominent role in traditional medicine among Indigenous and local communities, being used to treat a broad spectrum of ailments such as skin wounds, inflammation, gastrointestinal disorders, anemia, and cardiovascular diseases (Mafioletti et al., 2013; Michel et al., 2015). Ethnobotanical studies document that infusions of its leaves are commonly employed for wound healing, intestinal colic, blood disorders, and leukemia (Lorenzi & Matos, 2008), while preparations from the whole plant address cardiovascular, gynecological, urinary tract diseases, infections, and poisoning (Coelho et al., 2019). Additionally, the plant’s distinctive reddish pigment, mainly due to anthocyanins like carajurina, confers cultural and ritual significance, serving as body paint or in ceremonies among some Indigenous groups (Chapman et al., 1927).

Phytochemical investigations have identified flavonoids, tannins, anthocyanins, and phytosterols as the main bioactive constituents, with documented antioxidants, anti-inflammatory, antimicrobial, and hepatoprotective properties (Devia et al., 2002; Michel et al., 2015). Experimental studies demonstrate that extracts of *A. chica* can inhibit pro-inflammatory

pathways such as NF-κB and stimulate fibroblast proliferation aiding wound repair (Ribeiro et al., 2012; Zorn et al., 2001) and protect hepatic tissue against chemical-induced injury (De Souza et al., 2012; Medeiros et al., 2011).

Despite extensive ethnopharmacological evidence and preliminary pharmacological findings, there is a paucity of studies investigating the therapeutic potential of *A. chica* in multifactorial metabolic disorders. Therefore, the present study aims to rigorously evaluate the pharmacological effects of *A. chica* extract using a novel rat model of metabolic syndrome induced by diabetes, dyslipidemia, and chronic alcohol consumption, thereby contributing to the scientific validation of its traditional applications and providing foundational data to support its development as a phytotherapeutic agent for metabolic syndrome.

2. Material and Methods

2.1. Preparation of Arrabidaea chica

Leaves of *Arrabidaea chica* were collected from the medicinal plant garden of Federal University of Grande Dourados (UFGD) in Dourados, MS, in May 2022. The leaves were cleaned and dried in a forced air circulation oven at 35 ºC for 3 days. From the dried and powdered plant material, the aqueous extract was prepared through infusion. The infusion was prepared with 100 g of dried and powdered plant material to 1 L of chlorinated water at boiling point. The extraction took place for a period of 5 to 6 hours, until reaching room temperature (25 ºC) (Coelho et al., 2019). Subsequently, the infusion was treated with three volumes of ethanol to precipitate proteins and polysaccharides, allowing separation between the precipitate and the ethanolic supernatant. The supernatant was then concentrated and lyophilized (Barbosa et al., 2020). The final extract was stored frozen at -20 ºC until further use.

2.1.1. Toxicological studies of Arrabidaea chica

2.1.2. Acute toxicity evaluation

2.1.2.1. Animals

Male Wistar rats (200–250 g) obtained from the State University of Ponta Grossa (UEPG, Brazil) were utilized to evaluate the toxicological profile of *Arrabidaea chica* extract. Animals were maintained in the Cardiometabolic Pharmacology Laboratory at the Federal University of Paraná (UFPR), housed in controlled conditions with unrestricted access to standard chow and water. The environmental parameters were carefully regulated, maintaining an ambient temperature of 22 ± 2 °C, relative humidity at 50 ± 10%, and a 12-hour light/dark

cycle. Enrichment strategies were implemented to promote animal welfare throughout the experimental period. All experimental procedures conformed to the ethical guidelines established by the Brazilian National Council for the Control of Animal Experimentation (CONCEA) and adhered to the ARRIVE standards for in vivo research reporting (Percie du Sert et al., 2020). The Institutional Animal Care and Use Committee of UFPR approved the protocol under number 1536.

2.1.2.2. Experimental design

Acute toxicity evaluation followed the OECD guideline 423 (2001). Male Wistar rats ($n = 6$) were fasted for 8 hours prior to receiving a single oral administration of *A. chica* extract. Given the lack of previous toxicological data for this extract, an initial dose of 300 mg/kg was chosen. Subsequent dosing was adjusted based on observed clinical signs of toxicity or survival outcomes. The assessment proceeded until one of the following criteria was met: (i) manifestation of significant toxic effects; (ii) occurrence of mortality; (iii) absence of adverse effects at the highest administered dose; or (iv) deaths observed at the lowest tested dose. A basal control group ($n = 5$) received only the vehicle (filtered water) under identical experimental conditions.

2.1.2.3. Assessment of clinical signs

After oral administration of the *A. chica* extract, animals were closely monitored at specific intervals: during the first 30 minutes, followed by assessments at 1, 2, 3, and 4 hours post-treatment. Observations included evaluation of behavioral and clinical parameters such as grooming, piloerection, respiratory distress, abdominal contractions, diarrhea, lethargy, impaired coordination, sedation, coma, and mortality. Once the initial 4-hour period concluded, animals were given unrestricted access to food and water. Thereafter, daily monitoring was conducted over a 14-day period to detect any delayed clinical manifestations or mortality (Silva et al., 2022).

2.1.2.4. Euthanasia, material collection and analysis

On the 15th day, after a 12-hour fasting period, the animals were euthanized by anesthetic overdose using 20% isoflurane in a sealed chamber. Blood was collected by decapitation for subsequent hematological and biochemical analyses. Serum glucose was quantified with a glucometer (Accu-Chek Active®, Roche, Mannheim, Germany).

Hematological assessments included red blood cell count, total and differential leukocyte counts. Biochemical parameters such as serum cholesterol, triglycerides, aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea, and creatinine were measured using a semi-automated analyzer along with commercial assay kits. The liver, spleen, heart, and kidneys were carefully excised, rinsed with saline, and weighed on an analytical balance. Relative organ weights were calculated as the ratio of organ weight to body weight multiplied by 100 (%). Tissue samples from these organs were fixed in 10% buffered formalin, processed according to standard histological protocols, embedded in paraffin, and sectioned. Sections were stained with hematoxylin and eosin (H&E) and examined under a Leica DM 2500® light microscope by a veterinary pathologist to evaluate possible morphological changes linked to the treatment.

2.2. ***Pharmacological studies***

2.2.1. Animals

Male Wistar rats weighing between 200 and 250 g were sourced from the Central Animal Facility at the Federal University of Paraná (UFPR) and housed in the Laboratory of Cardiometabolic Pharmacology's animal facility. The animals were kept under controlled environmental conditions, including a temperature of 22 ± 2 °C, relative humidity of 50 ± 10%, and a 12-hour light/dark cycle, with environmental enrichment provided. Food and water were available *ad libitum*, and all experimental procedures took place during the light phase. Subjects were randomly allocated into experimental groups consisting of 6 to 7 animals each. Sample sizes were established based on prior research using similar protocols, while also considering the 3Rs principles (Replacement, Reduction, and Refinement) to optimize animal use (Percie du Sert et al., 2020; Amaral et al., 2022; Auth et al., 2022; Albuquerque et al., 2023; Silva et al., 2024). Weekly body weight measurements were taken using an analytical scale. The study was conducted under the approval of the Institutional Animal Care and Use Committee of UFPR (protocol number 1536) and adhered strictly to both national and international regulations, including compliance with ARRIVE guidelines (Percie du Sert et al., 2020).

2.2.2. Experimental design and treatments

The metabolic syndrome model employed in this study was established by combining multiple risk factors, including diabetes, dyslipidemia, and chronic alcohol intake. Diabetes was induced by a single intraperitoneal injection of streptozotocin (60 mg/kg) dissolved in 10 mM

citrate buffer (pH 4.5) following a 12-hour fasting period (Souza et al., 2020; Vit et al., 2002). Blood glucose levels were assessed from tail vein samples using an Accu-Chek Active® glucometer (Roche) three days after streptozotocin administration. Animals with glycemia ≥ 250 mg/dL were classified as diabetic. Dyslipidemia was induced by feeding a cholesterol-enriched diet (0.5%) for five weeks, prepared by mixing 150 g of standard chow with one egg yolk, 13.5 mL of corn oil, and water. The mixture was dried in a laboratory oven at 50°C for 36 hours and stored in vacuum-sealed bags. Each 150 g portion contained approximately 225 mg cholesterol, 1.8 g saturated fat, 2.16 g monounsaturated fatty acids, and 0.72 g polyunsaturated fatty acids (Silva et al., 2024). Additionally, animals had free access to a liquid diet containing 5% ethanol, following the protocol by Lívero et al. (2016). During the final two weeks, animals were treated by oral gavage with either filtered water (negative control group [C–]), *A. chica* extract at doses of 30, 100, or 300 mg/kg, or a combination of simvastatin (2.5 mg/kg) and insulin (6 IU) administered subcutaneously (SIM+INSU group). A basal control group of normoglycemic, normolipidemic rats not exposed to ethanol received only filtered water.

2.2.3. Euthanasia, sample collection and biochemical analysis

At the conclusion of the treatment period, after a 12-hour fasting interval, the animals were euthanized via anesthetic overdose using 20% isoflurane in a sealed chamber. Blood was collected through decapitation for biochemical analyses. Serum glucose concentrations were measured using a glucometer (Accu-Chek Active®, Roche, Mannheim, Germany). Plasma levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol, triglycerides, urea, and creatinine were quantified by colorimetric enzymatic methods employing a semi-automated analyzer (Global Analyzer®, model GTA-300, Calgary, AB, Canada). The liver was excised, weighed using an analytical balance, and processed accordingly. Portions of the organ were fixed for histopathological analysis, while the remaining tissue samples were stored at –20°C for subsequent assays assessing lipid profiles.

2.2.4. Measurement of hepatic cholesterol and triglycerides

Liver samples were freeze-dried and subjected to lipid extraction via a gravimetric technique as described by Lívero et al. (2016). For extraction, samples were combined with hexane in a 1:10 ratio (sample to solvent) and incubated at 80°C for 2 hours. The resulting supernatant was collected in a vial and allowed to evaporate at ambient temperature. This

extraction was performed in triplicate to maximize lipid yield. The lipid content was then calculated as a percentage using the formula:

$$\text{Lipid (\%)} = 100 \times (\text{final vial weight} / \text{initial vial weight}) / 0.1 \text{ g}.$$

The recovered lipids were weighed and dissolved in a mixture of 1 mL chloroform and 2 mL isopropanol. Concentrations of cholesterol and triglycerides were determined by enzymatic colorimetric assays using an automated analyzer.

2.2.5. Histopathological analysis

Liver tissue samples were fixed in 10% buffered formalin, subjected to a graded dehydration process using ethanol and xylene, then embedded in paraffin wax. Sections of 6 µm thickness were cut and stained with hematoxylin and eosin (H&E) to assess cellular morphology and tissue alterations, as well as with Sudan Black to evaluate lipid accumulation. Microscopic analysis was performed using a Leica DM 2500® light microscope to detect histopathological changes. Hepatic lesions were semi-quantitatively evaluated following the criteria established by Kleiner et al. (2005), which classify ballooning and steatosis (both microvesicular and macrovesicular) according to the extent of tissue involvement: 0 (absent), 1 (mild; 5–33%), 2 (moderate; 34–66%), and 3 (severe; 67–100%).

2.3. Statistical analysis

Prior to statistical analysis, data were evaluated for normality and homogeneity of variance. Comparisons between groups were performed using one-way analysis of variance (ANOVA), followed by Tukey's post hoc test for multiple comparisons. Statistical significance was set at $p < 0.05$. Results are expressed as mean ± standard error of the mean (SEM). All statistical analyses were conducted using GraphPad Prism software version 9.0 (GraphPad Software, San Diego, CA, USA).

3. Results

3.1. Safety assessment of Petiveria alliacea extract

3.1.1. Evaluation of clinical signs, relative organs and body weight of rats

Animals administered a single oral dose of *A. chica* extract at 300 mg/kg and 2000 mg/kg exhibited no behavioral or physiological alterations during the entire observation period (from 30 minutes up to 14 days) compared to the untreated basal group (**Table 1**).

Summarizes the body and organ weight data for all groups. Over the 14-day study period, all animals exhibited a gradual increase in body weight. The basal group reached a final mean weight of 328.60 ± 13.57 g, while rats receiving 300 mg/kg and 2000 mg/kg of *A. chica* extract attained 325.40 ± 16.23 g and 325.80 ± 5.89 g, respectively. Weight gain patterns were comparable across groups, suggesting that extract administration did not interfere with normal growth. No statistically significant differences were detected in body weight gain or in the relative weights of key organs, including liver, spleen, heart, and kidneys, between treated and basal groups (**Table 2)**.

3.1.2. Biochemical serum parameters in Wistar rats treated with Arrabidaea chica extract

The biochemical evaluation of serum parameters in Wistar rats treated with *A. chica* extract revealed no statistically significant differences among the groups (**Figure 1**). Total cholesterol levels ranged from 47.60 ± 6.03 mg/dL in the basal group to 51.54 ± 1.79 mg/dL and 52.82 ± 3.26 mg/dL in the 300 mg/kg and 2000 mg/kg groups, respectively (**Figure 1A**). Triglyceride concentrations remained stable, with values of 54.20 ± 3.14 mg/dL in the basal group, 53.90 ± 2.49 mg/dL in the 300 mg/kg group, and 47.95 ± 2.12 mg/dL in the 2000 mg/kg group (**Figure 1B**). Similarly, hepatic enzyme activities showed no relevant variations. AST values were 130.9 ± 14.74 U/L in the basal group, 113.1 ± 10.28 U/L in the 300 mg/kg group, and 122.0 ± 10.85 U/L in the 2000 mg/kg group (**Figure 1C**). ALT levels were 66.23 ± 2.59 U/L, 61.30 ± 1.52 U/L, and 62.88 ± 3.78 U/L in the respective groups (**Figure 1D**). Renal function markers also remained within physiological ranges, with no significant differences observed. Serum urea levels were 31.10 ± 0.87 mg/dL in the basal group, 32.94 ± 2.29 mg/dL in the 300 mg/kg group, and 30.50 ± 2.78 mg/dL in the 2000 mg/kg group (**Figure 1E**). Serum creatinine values were similar across groups, ranging from 0.4750 ± 0.0479 mg/dL to 0.4833 ± 0.0601 mg/dL (**Figure 1F**).

3.1.3. Hematological profile of rats treated with Arrabidaea chica extract

Hematological evaluation revealed no evidence of systemic hematotoxicity associated with *A. chica* extract administration at any tested dose. Red blood cell parameters, including total erythrocyte count, hemoglobin concentration, and hematocrit values, remained statistically similar across all experimental groups when compared to the basal group, indicating preserved erythropoietic function. Likewise, white blood cell counts showed no significant variations, suggesting the absence of extract-induced inflammatory or immunosuppressive effects.

Differential leukocyte analysis demonstrated stable proportions of neutrophils, lymphocytes, monocytes, eosinophils, and basophils, with no dose-dependent trends. Platelet counts and mean platelet volume also remained unaltered, further supporting the hematological safety of the extract.

3.2.5. Arrabidaea chica does not induce hepatic, cardiac and renal cellular alterations

Microscopic evaluation of liver, spleen, heart, and kidney tissues from rats treated with *A. chica* extract at 300 mg/kg and 2000 mg/kg doses revealed preserved normal histological features comparable to those observed in the basal control group (**Figure 2**). Liver sections showed hepatocytes arranged in typical cords with intact cytoplasm and nuclei, without any indication of fat accumulation, inflammatory infiltration, cell swelling, or necrotic changes. The splenic architecture remained unaltered, displaying well-defined white and red pulp regions without lymphocyte depletion or tissue disruption. Cardiac muscle fibers appeared normal, with no signs of structural disorganization, inflammatory presence, or fibrosis. Kidney histology demonstrated well-preserved glomerular and tubular structures, lacking evidence of necrosis, edema, or inflammatory cell infiltration.

3.2. Pharmacological effects of Arrabidaea chica extract

3.2.1. Arrabidaea chica extract displayed partial glycemic control and lipid-lowering effects

The concomitant induction of diabetes, dyslipidemia, and alcohol intake resulted in marked metabolic disturbances. Plasma glucose levels (**Figure 3A**) significantly increased in the untreated disease model group (C–: 448.60 ± 18.31 mg/dL) compared with the healthy control group (Basal: 115.3 ± 3.75 mg/dL). Treatment with *A. chica* extract at 30 mg/kg (305.70 ± 24.42 mg/dL) and 100 mg/kg (359.50 ± 16.01 mg/dL) partially reduced glycemia, whereas the 300 mg/kg dose (408.10 ± 17.60 mg/dL) showed no significant improvement. Complete normalization of glucose was observed only in the SIM+INSU group (165.30 ± 16.21 mg/dL). Regarding lipid metabolism, plasma total cholesterol (**Figure 3B**) rose from 58.57 ± 4.01 mg/dL in the basal group to 610.30 ± 22.29 mg/dL in the C– group, and triglycerides (**Figure 3C**) increased from 58.71 ± 4.25 mg/dL to 537.30 ± 8.79 mg/dL. Hepatic cholesterol (**Figure 3D**) and triglycerides (**Figure 3E**) also significantly increased, from 29.57 ± 3.26 mg/dL and 27.90 ± 3.50 mg/dL in the basal group to 108.80 ± 4.53 mg/dL and 211.70 ± 20.70 mg/dL, respectively, in the C– group. Treatment with 30 mg/kg of *A. chica* and SIM+INSU fully

normalized both plasma and hepatic lipid profiles, while intermediate doses (100 mg/kg and 300 mg/kg) promoted only partial improvements

3.3.2. Arrabidaea chica demonstrates significant hepatic protective properties

After metabolic syndrome induction, the C- group showed a significant increase in relative liver weight (5.29 ± 0.18%) compared to the basal group (3.01 ± 0.06%). Treatment with *A. chica* at 30 mg/kg and the combination therapy of simvastatin plus insulin (SIM+INSU) fully reversed the liver weight increase, with values comparable to the basal group. The 100 mg/kg dose of *A. chica* produced a partial reversal, while the 300 mg/kg dose did not significantly alter liver weight compared to the C− group (**Figure 4A**). Serum levels of liver enzymes ALT and AST were significantly elevated in the C− group relative to basal (ALT: 107.0 ± 4.75 U/L vs. 34.7 ± 3.01 U/L; AST: 155.9 ± 6.19 U/L vs. 48.0 ± 3.81 U/L; $p < 0.05$). For ALT (**Figure 4B)**, only the 30 mg/kg treatment completely reversed the elevation, showing levels close to basal values, whereas the 100 mg/kg, 300 mg/kg, and SIM+INSU treatments showed partial reversal, with ALT levels remaining significantly higher than basal. Regarding AST (**Figure 4C**), the 30 mg/kg dose was the only treatment to fully normalize the enzyme levels, bringing them close to basal values. The 100 mg/kg and 300 mg/kg doses induced partial reductions, with intermediate values between C− and basal groups. The SIM+INSU treatment did not produce a statistically significant decrease in AST levels.

3.3.3. Arrabidaea chica reversed hepatocellular alterations

The group subjected to combined metabolic risk factors (C–) exhibited a significant increase in relative liver lipid content, reaching 45.11 ± 3.69%, compared to 13.63 ± 0.77% in the basal control group. Treatment with *A. chica* extract at 30 mg/kg and the combination therapy of SIM+INSU effectively normalized hepatic lipid accumulation, showing values close to the basal group (19.10 ± 1.57% and 16.10 ± 1.33%, respectively). Intermediate reductions in liver lipid content were observed with the 100 mg/kg and 300 mg/kg doses of *A. chica*, with percentages of 28.42 ± 1.57% and 37.39 ± 1.07%, respectively (**Figure 5A**). Microscopic examination of hepatic sections showed that the basal group displayed normal architecture with no signs of steatosis. In contrast, pronounced pathological changes were evident in the C– group, characterized by severe ballooning degeneration (grade 3), marked microvesicular steatosis (grade 3), and moderate macrovesicular steatosis (grade 2). Administration of *A. chica* extract mitigated these alterations in a dose-responsive manner. At 30 mg/kg, all three

parameters, ballooning, microvesicular, and macrovesicular steatosis, were reduced to grade 1. A 100 mg/kg dose yielded ballooning and microvesicular steatosis at grade 2, with macrovesicular steatosis remaining at grade 1. Similarly, 300 mg/kg resulted in ballooning and microvesicular steatosis graded as 2, and macrovesicular steatosis as 1. The SIM+INSU group showed only mild ballooning (grade 1) and complete absence of both microvesicular and macrovesicular steatosis (grade 0), as depicted in **Figures 5B** and **Figure 5C**.

3.4.4. Arrabidaea chica extract partially restores renal morphology and function

A significant increase in relative kidney weight was observed in the disease model group (C–) compared to the basal group. Treatment with *A. chica* at 30 mg/kg completely normalized kidney weight, while the 100 mg/kg dose and SIM+INSU treatment induced partial reversal. The 300 mg/kg dose did not significantly reduce kidney weight **(Figure 6A)**. Plasma urea levels were significantly elevated in the C– group. Complete reversal of urea elevation was observed with the 30 mg/kg *A. chica* dose and SIM+INSU treatment, while the 100 mg/kg dose promoted a partial reduction. The 300 mg/kg dose did not significantly alter urea levels **(Figure 6B)**. Creatinine levels were also elevated in the C– group. Complete normalization of creatinine was achieved with the 30 mg/kg *A. chica* dose and SIM+INSU treatment, whereas the 100 mg/kg and 300 mg/kg doses did not produce significant changes **(Figure 6C)**.

4. Discussion

The present study provides experimental evidence supporting the safety and therapeutic potential of *Arrabidaea chica*, a medicinal species traditionally used in the Amazon region for treating inflammatory, metabolic, and liver disorders. In our experimental model combining diabetes, dyslipidemia, and chronic alcohol intake, a multifactorial approach that mimics the complexity of human metabolic syndrome, oral administration of *A. chica* extract demonstrated absence of acute toxicity and exerted hypolipidemic, hepatoprotective, and nephroprotective effects. These results are particularly relevant considering the ethnopharmacological background of *A. chica*, which has been historically employed for treating liver ailments and improving general health in indigenous and rural populations of South America.

Acute oral administration of *A. chica* extract at doses up to 2000 mg/kg did not induce mortality or behavioral alterations, nor did it produce changes in biochemical, hematological, or histopathological parameters in vital organs. The absence of toxicological effects aligns with previous studies reporting a wide safety margin for *A. chica* preparations in rodents,

corroborating its traditional use as a safe herbal remedy. The maintenance of normal liver enzyme levels and preserved tissue histoarchitecture in both acute and efficacy protocols suggests a low hepatotoxic potential, which is a critical parameter for plants intended for long-term management of chronic metabolic disorders.

In the efficacy model, the concomitant induction of hyperglycemia, dyslipidemia, and hepatic steatosis successfully reproduced key pathophysiological aspects of metabolic syndrome. This multifactorial model, by integrating several human-relevant risks factors, provides a more translationally valid platform compared to single-insult models. Treatment with *A. chica* at 30 mg/kg emerged as the most consistent dose in restoring metabolic parameters, completely normalizing plasma glucose, hepatic lipid accumulation, and renal function markers. These effects suggest a broad-spectrum activity, potentially linked to the presence of bioactive secondary metabolites such as anthocyanidins, flavonoids, and phenolic acids, known for their antioxidants, anti-inflammatory, and lipid-lowering properties (Farzei et al., 2019; Naseri et al., 2018; Gasmi et al., 2022).

The hypolipidemic effect observed in both plasma and liver reinforces the potential of *A. chica* for managing dyslipidemia. The marked reduction in hepatic triglyceride and cholesterol levels may involve decreased de novo lipogenesis and enhanced β-oxidation, although these mechanisms require further investigation. Simvastatin, a widely used statin, lowers lipid levels primarily through inhibition of HMG-CoA reductase, effectively reducing plasma LDL cholesterol. However, despite its efficacy, simvastatin is known to cause adverse effects such as hepatotoxicity, often reflected by elevated serum liver enzymes such as AST and ALT (Adhyaru & Jacobson, 2018). In our study, simvastatin treatment did not normalize AST and ALT levels, indicating persistent liver injury, whereas *A. chica* treatment fully restored these enzymes to baseline values, demonstrating a superior hepatoprotective effect. Importantly, the lipid-lowering and hepatoprotective effects of *A. chica* were distinct from those of the simvastatin plus insulin combination, suggesting that the plant's mechanisms involve complementary metabolic pathways and may offer a safer alternative or adjunct therapy in managing metabolic syndrome.

The hepatoprotective activity of *A. chica* was evidenced by reductions in liver weight, hepatic lipid content, and serum aminotransferases in treated animals. The histological analysis confirmed attenuation of steatosis and preservation of hepatic architecture, which could be attributed to the plant's antioxidant capacity and ability to modulate inflammatory cascades. These findings mirror reports on closely related species, where antioxidant and anti-

inflammatory properties confer protection against fatty liver and associated inflammatory damage (Auth et al., 2022; Rodrigues Albuquerque et al., 2023; Silva et al., 2024; Mendes et al., 2021; Amaral et al., 2021, Barbosa et al., 2020).

Inflammation represents a central pathophysiological axis in metabolic syndrome, driving hepatic steatosis, dyslipidemia, and insulin resistance through activation of transcriptional regulators such as nuclear factor kappa B (NF-κB). Persistent low-grade inflammation promotes lipogenesis, hepatocellular injury, and elevated aminotransferases, thereby linking metabolic alterations to organ dysfunction (Cavalieri et al., 2023; Mohamed et al., 2016). In this context, the anti-inflammatory activity of *A. chica* emerges as a plausible mechanism underlying the metabolic improvements observed in our study. De Souza et al. (2012) demonstrated that leaf extracts inhibit NF-κB activation at concentrations of 500 μg/mL, an effect attributed to carajurina, a 3-deoxyanthocyanidin. This inhibitory action has been confirmed in both *in vitro* and *in vivo* models (Oliveira et al., 2009; Zorn et al., 2001), suggesting that modulation of inflammatory cascades may contribute to reduced hepatic lipid accumulation, normalization of AST and ALT levels, and attenuation of tissue injury observed here. Thus, beyond its antioxidant and lipid-lowering effects, the anti-inflammatory potential of *A. chica* provides a mechanistic explanation for its hepatoprotective and systemic benefits in the multifactorial model of metabolic syndrome.

Renal protection was also evident, particularly at the 30 mg/kg dose, which normalized kidney weight and renal function biomarkers. Oxidative stress and inflammation are major contributors to kidney injury in metabolic syndrome, and the presence of antioxidant flavonoids in *A. chica* may mitigate these processes. Preservation of renal function is a critical endpoint, as kidney impairment often coexists with metabolic and hepatic disorders in clinical practice (Wang et al., 2022).

A key strength of this investigation lies in the use of a multifactorial animal model that integrates major components of human metabolic syndrome, including hyperglycemia, dyslipidemia, and alcohol exposure. Our group has extensively employed and validated such models in recent studies involving *Baccharis dracunculifolia*, *Baccharis trimera*, *Croton urucurana*, and *Pereskia grandifolia*, which collectively simulate the complex interplay of metabolic and lifestyle factors observed clinically (Silva et al., 2024; Amaral et al., 2023; Auth et al., 2022; Albuquerque et al., 2023; Zago et al., 2021). This modeling approach enhances translational relevance by enabling the assessment of botanical therapies that exert pleiotropic effects on interconnected metabolic pathways, as demonstrated here with *A. chica*.

Importantly, the complex phytochemical composition of *A. chica* extract likely underpins its broad pharmacological effects through polypharmacological and synergistic mechanisms. Plant extracts contain diverse bioactive molecules—flavonoids, anthocyanidins, phenolic acids, and others—that can target multiple biochemical pathways simultaneously. This multiplicity may produce additive or synergistic actions that amplify therapeutic efficacy beyond what isolated compounds could achieve alone (Süntar, 2020; Chopra & Dhingra, 2020; Leonti & Casu, 2013; Yuan et al., 2016). For example, combined antioxidant and anti-inflammatory activities can simultaneously reduce oxidative damage and modulate inflammatory cascades, central processes in metabolic syndrome pathogenesis. Furthermore, interactions between different flavonoids may enhance lipid metabolism modulation, insulin signaling, and cellular protection, contributing to the holistic improvement observed in multiple organ systems. This polypharmacological profile aligns with a growing recognition that botanical therapies offer distinct advantages in managing complex chronic diseases with multifactorial etiologies, such as metabolic syndrome. By targeting several interrelated pathological mechanisms concurrently, extracts like that of *A. chica* can achieve more comprehensive and potentially safer therapeutic outcomes compared to single-target synthetic drugs. However, elucidating the precise interactions and identifying the key bioactive components require further phytochemical and mechanistic studies.

Taken together, our findings validate traditional uses of *A. chica* and highlight its potential as a phytotherapeutic candidate for the integrated management of metabolic syndrome and its complications. The safety profile observed here supports the feasibility of chronic administration, while the broad metabolic improvements suggest a multi-target mechanism of action. Nevertheless, some limitations must be acknowledged. The present study was conducted in an animal model, which limits direct extrapolation to humans, and the relatively short treatment duration may not fully capture long-term effects. Additionally, the lack of detailed mechanistic investigations leaves open questions about the molecular pathways involved. Future research should address these aspects and aim to validate the findings in clinical settings.

Despite these limitations, this study makes a significant contribution to ethnopharmacology by demonstrating the efficacy of *A. chica* extract in normalizing key metabolic parameters in a multifactorial model of metabolic syndrome. Our results reinforce the therapeutic potential of this medicinal plant as a complementary approach for managing metabolic disorders and emphasize the importance of investigating native plants with traditional uses for novel drug discovery. The data generated herein provides a robust foundation to guide

future preclinical and clinical studies, potentially leading to safer, more accessible, and evidence-based treatments for patients affected by metabolic syndrome.

Acknowledgements

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Conflict of Interest Statement

The authors declare that there are no conflicts of interest regarding the publication of this article.

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616
617 **Legends for figures**
618
619 **Figure 1.** Biochemical parameters in Wistar rats treated with *Arrabidaea chica* extract at doses
620 of 300 mg/kg and 2000 mg/kg compared to the basal control group. Serum levels of **(A)** total
621 cholesterol; **(B)** triglycerides; **(C)** aspartate aminotransferase (AST); **(D)** alanine
622 aminotransferase (ALT); **(E)** urea levels; and **(F)** creatinine levels. Data are presented as mean
623 ± standard error of the mean (S.E.M.). No statistically significant differences were observed
624 among groups ($p > 0.05$, one-way ANOVA followed by Tukey's post hoc test).

Figure 2. Representative histological images of tissues from Wistar rats treated with *Arrabidaea chica* extract (300 and 2000 mg/kg) and basal controls. **(A)** Spleen, **(B)** heart, **(C)** liver, **(D)** kidney. All tissues show preserved morphology without evidence of damage or abnormalities. Hematoxylin & Eosin-stained tissue sections show no significant morphological alterations at both dosages of the extract. Magnification: 20 *x*.

Figure 3. Levels of glucose (**A**), total cholesterol **(B)** and triglycerides **(C)** in serum, along with hepatic cholesterol **(D)** and triglycerides **(E)** content. Treatment groups received *Arrabidaea chica* extract at 30, 100, or 300 mg/kg doses, or a combination therapy of simvastatin (2.5 mg/kg) plus insulin (6 IU) (SIM+INSU). The basal group corresponds to healthy controls, while the C– group represents untreated animals subjected to diabetes, dyslipidemia, and ethanol intake. Data are presented as mean ± SEM (n = 6–7). Data are presented as mean ± SEM. [a] $p < 0.05$ *vs*. basal; [b] $p < 0.05$ *vs*. C– (one-way ANOVA followed by Tukey's post hoc test).

Figure 4. Relative liver weight (%) **(A)** and serum levels of alanine aminotransferase (ALT) **(B)** and aspartate aminotransferase (AST) **(C)** in rats submitted to experimental metabolic syndrome and treated with *Arrabidaea chica* extract at doses of 30, 100, and 300 mg/kg, simvastatin plus insulin (SIM+INSU), or vehicle (C−). Data are presented as mean ± SEM (n = 6–7). Data are presented as mean ± SEM. [a] $p < 0.05$ *vs*. basal; [b] $p < 0.05$ *vs*. C– (one-way ANOVA followed by Tukey's post hoc test).

Figure 5. (A) Relative hepatic lipid percentage, **(B)** scores of liver damage, and **(C)** representative liver histology sections stained with hematoxylin and eosin (H&E). Experimental groups received *Arrabidaea chica* extract at doses of 30, 100, or 300 mg/kg, or a combination treatment of simvastatin (2.5 mg/kg) and insulin (6 IU) (SIM+INSU). Basal represents healthy controls; C– is the untreated metabolic syndrome model group (diabetes + dyslipidemia + ethanol). Data are presented as mean ± SEM (n = 6–7). [a] $p < 0.05$ *vs*. basal; [b] $p < 0.05$ vs. C– (one-way ANOVA followed by Tukey's post hoc test). In the histological sections, black arrows indicate areas of hepatic macrovesicular steatosis, while empty (hollow) arrows point to regions of microvesicular steatosis. Images captured at 40× magnification.

Figure 6. **(A)** Relative kidney weight, **(B)** plasma urea levels, and **(C)** plasma creatinine levels in rats. Animals were treated with *Arrabidaea chica* at doses of 30, 100, or 300 mg/kg, or with

658 a combination of simvastatin (2.5 mg/kg) and insulin (6 IU) (SIM+INSU). Basal: healthy
659 control group; C–: untreated disease model group (diabetes + dyslipidemia + ethanol). Data are
660 presented as mean ± SEM (n = 6–7). Data are presented as mean ± SEM. [a] $p < 0.05$ *vs*. basal;
661 [b] $p < 0.05$ *vs*. C– (one-way ANOVA followed by Tukey's post hoc test).
662

Figures

Figure 1

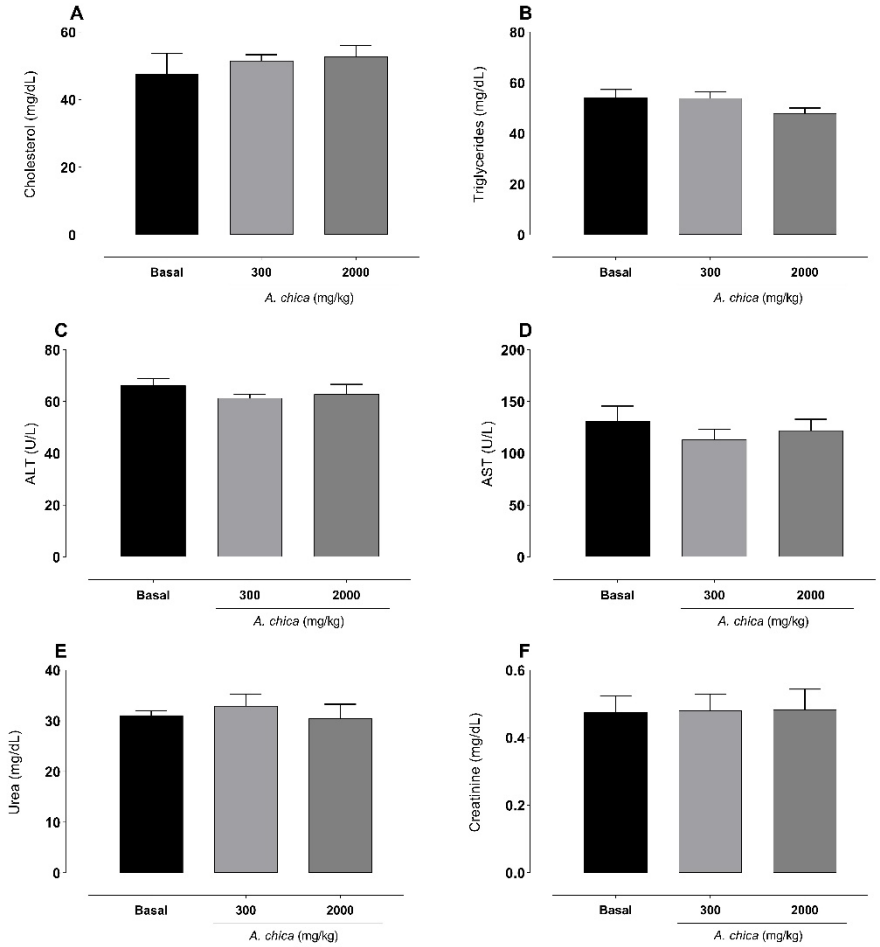


Figure 2

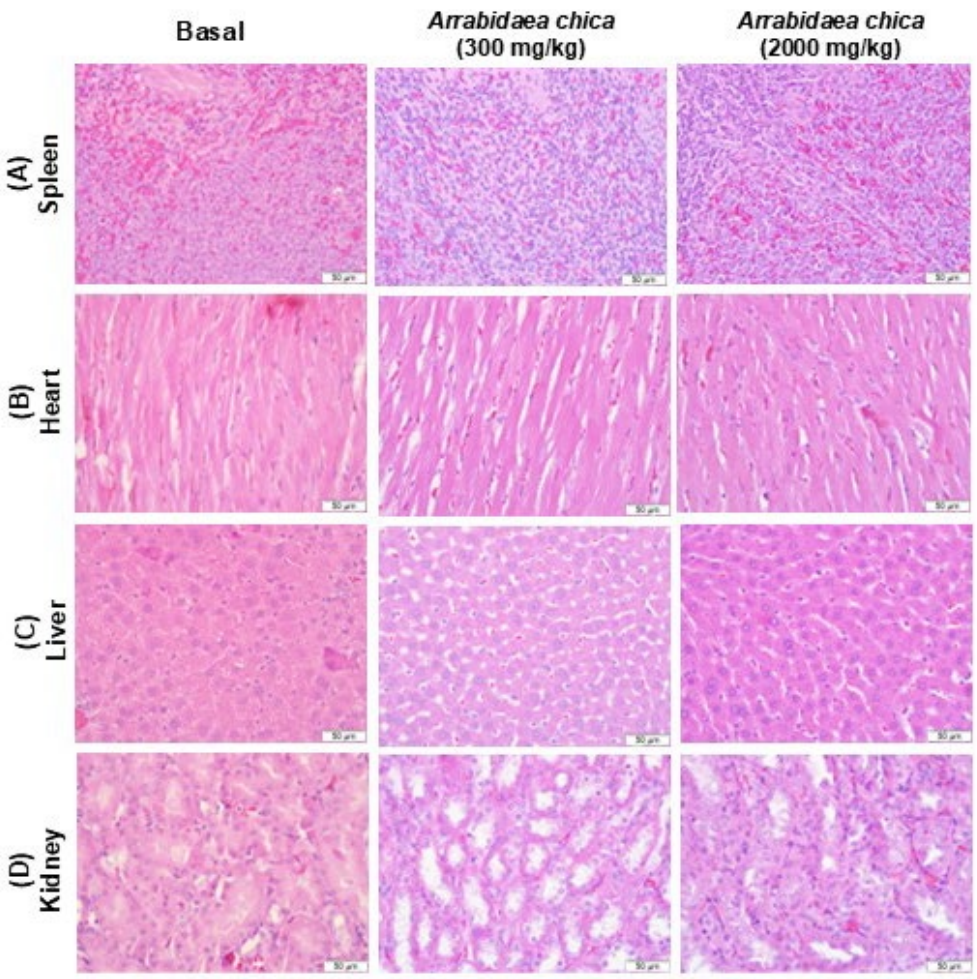

Basal
Arrabidaea chica (300 mg/kg)
Arrabidaea chica (2000 mg/kg)
(A) Spleen
(B) Heart
(C) Liver
(D) Kidney

Figure 3

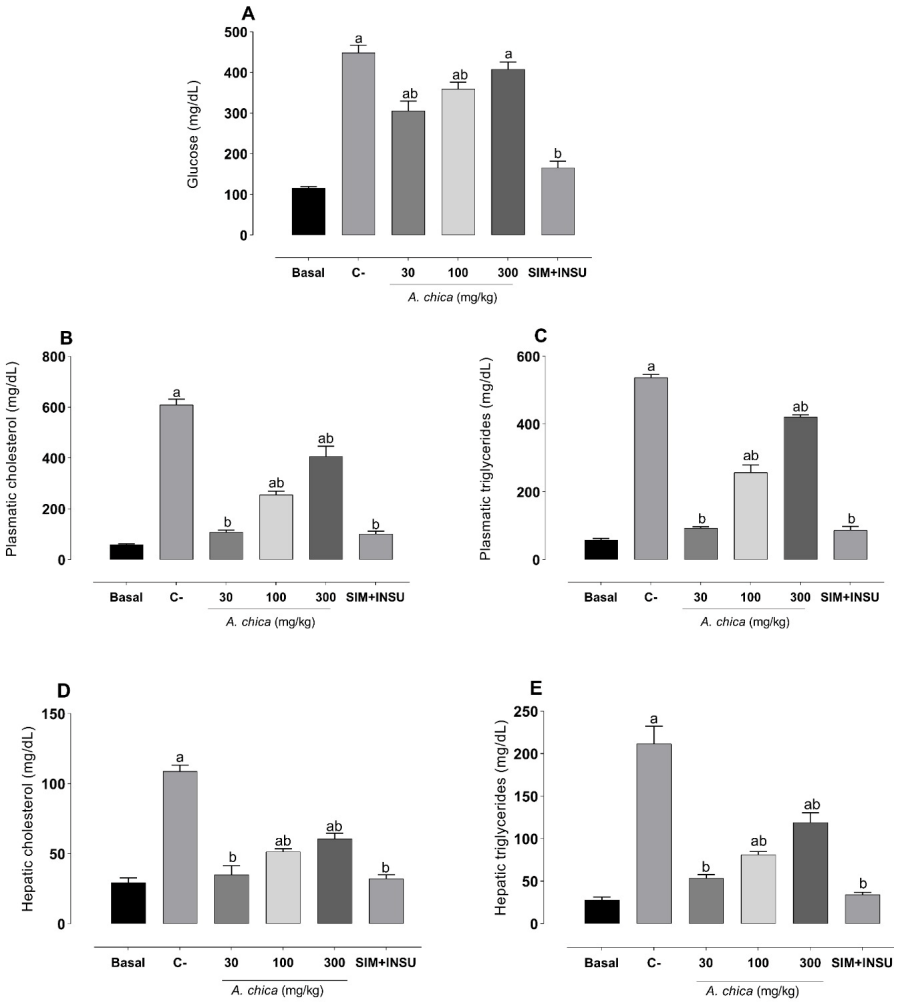


Figure 4

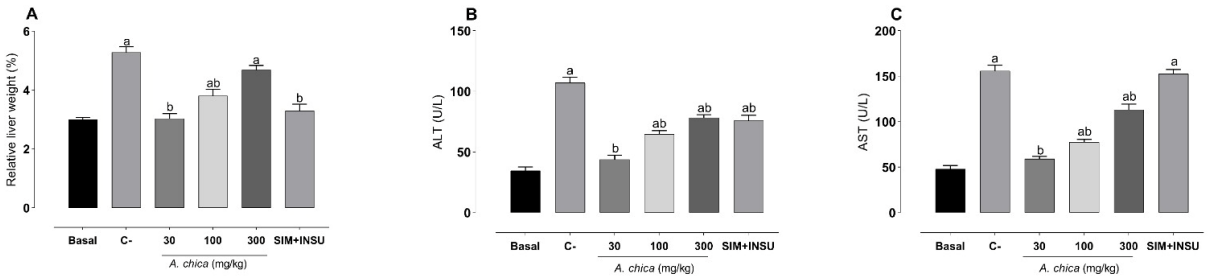
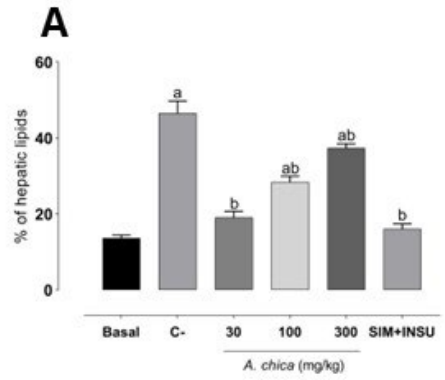


Figure 5



B

	Ballooning	Microvesicular steatosis	Macrovesicular steatosis
Basal	0	0	0
C-	3	3	2
AC 30	1	1	1
AC 100	2	2	1
AC 300	2	2	1
SIM+INSU	1	0	0

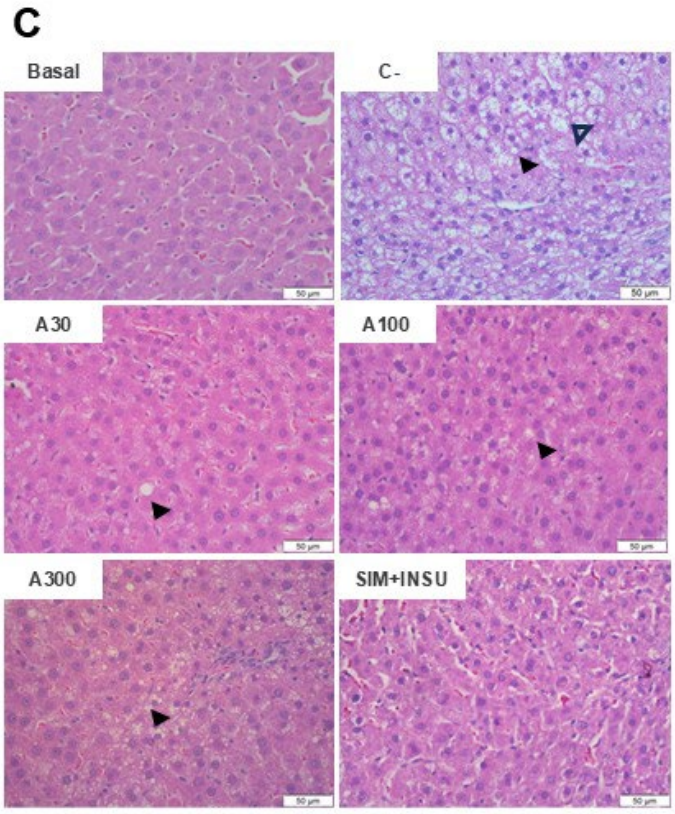
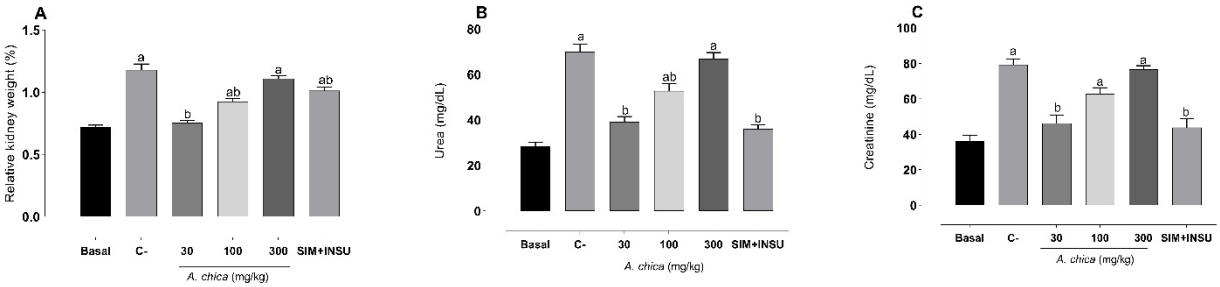


Figure 6



826 **Tables**

827 **Table 1.** Assessment of clinical signs in Wistar rats treated with vehicle or *Arrabidaea chica*
828 extract (300 or 2000 mg/kg), orally, in a single dose.

		Clinical sign	Time					
			30 min	1h	2h	3h	4h	14 days
Basal (vehicle)		*Self-cleaning absence*	0/5	0/5	0/5	0/5	0/5	0/5
		Piloerection	0/5	0/5	0/5	0/5	0/5	0/5
		Dyspnea	0/5	0/5	0/5	0/5	0/5	0/5
		Abdominal constriction	0/5	0/5	0/5	0/5	0/5	0/5
		Diarrhea	0/5	0/5	0/5	0/5	0/5	0/5
		Prostration	0/5	0/5	0/5	0/5	0/5	0/5
		Ataxia	0/5	0/5	0/5	0/5	0/5	0/5
		Sedation	0/5	0/5	0/5	0/5	0/5	0/5
		Coma	0/5	0/5	0/5	0/5	0/5	0/5
		Death	0/5	0/5	0/5	0/5	0/5	0/5
Extract of *Arrabidaea chica*	**300 mg/kg**	*Self-cleaning absence*	0/6	0/6	0/6	0/6	0/6	0/6
		Piloerection	0/6	0/6	0/6	0/6	0/6	0/6
		Dyspnea	0/6	0/6	0/6	0/6	0/6	0/6
		Abdominal constriction	0/6	0/6	0/6	0/6	0/6	0/6
		Diarrhea	0/6	0/6	0/6	0/6	0/6	0/6
		Prostration	0/6	0/6	0/6	0/6	0/6	0/6
		Ataxia	0/6	0/6	0/6	0/6	0/6	0/6
		Sedation	0/6	0/6	0/6	0/6	0/6	0/6
		Coma	0/6	0/6	0/6	0/6	0/6	0/6
		Death	0/6	0/6	0/6	0/6	0/6	0/6
	2000 mg/kg	*Self-cleaning absence*	0/6	0/6	0/6	0/6	0/6	0/6
		Piloerection	0/6	0/6	0/6	0/6	0/6	0/6
		Dyspnea	0/6	0/6	0/6	0/6	0/6	0/6
		Abdominal constriction	0/6	0/6	0/6	0/6	0/6	0/6
		Diarrhea	0/6	0/6	0/6	0/6	0/6	0/6
		Prostration	0/6	0/6	0/6	0/6	0/6	0/6
		Ataxia	0/6	0/6	0/6	0/6	0/6	0/6

	Sedation	0/6	0/6	0/6	0/6	0/6	0/6
	Coma	0/6	0/6	0/6	0/6	0/6	0/6
	Death	0/6	0/6	0/6	0/6	0/6	0/6

Table 2. The body weight and relative organ weight of Wistar rats treated with vehicle or *Arrabidaea chica* extract (300 or 2000 mg/kg), orally, in a single dose.

	Basal	**Extract of** *Arrabidaea chica*	
		300 mg/kg	**2000 mg/kg**
	Body weight (g)		
Day 1	291.00 ± 9.93	288.40 ± 7.94	288.20 ± 13.77
Day 7	315.20 ± 12.05	309.20 ± 9.24	308.40 ± 14.80
Day 14	328.60 ± 13.57	325.40 ± 16.23	325.80 ± 5.89
	Relative organ weight (%)		
Liver	3.31 ± 0.09	3.07 ± 0.08	3.17 ± 0.13
Spleen	0.18 ± 0.005	0.19 ± 0.006	0.19 ± 0.005
Heart	0.36 ± 0.009	0.35 ± 0.006	0.34 ± 0.006
Kidneys	0.77 ± 0.03	0.74 ± 0.02	0.71 ± 0.013

Data are presented as mean ± S.E.M., n = 6-7. Statistical analysis was performed using one-way ANOVA followed by Tukey's post hoc test.

3. CONCLUSÃO

Os resultados obtidos indicam que o extrato de *Arrabidaea chica* apresenta um potencial promissor como candidato fitoterápico para o manejo integrado da síndrome metabólica e suas complicações. Esse potencial foi evidenciado por seus efeitos hipolipidêmico, hepatoprotetor e nefroprotetor, além de demonstrar um perfil de segurança favorável. Embora o estudo tenha revelado efeitos positivos em diversos parâmetros, são necessárias investigações adicionais para compreender com mais profundidade os mecanismos envolvidos e ampliar o conhecimento sobre o potencial terapêutico da planta. Nossos achados reforçam a relevância de *A. chica* como uma abordagem complementar no tratamento de distúrbios metabólicos e destacam a importância de explorar plantas nativas com uso tradicional na busca por novos medicamentos.

4 ANEXOS

ANEXO 1 - Normas para publicação no *Journal of Ethnopharmacology*

About the journal
Aims and scope
The Journal of Ethnopharmacology is the Official Journal of the International Society for Ethnopharmacology. The journal is dedicated to the exchange of information and understandings about people's use of plants, fungi, animals, microorganisms and minerals and their biological and pharmacological effects based on the principles established through international conventions.
The Journal of Ethnopharmacology publishes original articles concerned with the observation and experimental investigation of the biological activities of plant and animal substances used in the traditional medicine of past and present cultures, which document indigenous medical knowledge, study indigenous medicines in order to contribute in the long-run to improved health care in the regions of study, and which report on pharmacologically unique principles from existing indigenous remedies.
The journal will particularly welcome interdisciplinary papers with an ethnopharmacological, an ethnobotanical or an actinochemical approach to the study of indigenous drugs. It is imperative that experimental studies are aligned and related to the traditional use(s).
Furthermore:
Reports of anthropological and ethnobotanical field studies fall within the journal's scope.
Studies involving pharmacological and toxicological mechanisms of action are especially welcome.
Clinical studies on efficacy will be considered if contributing to the understanding of specific ethnopharmacological problems.
The journal welcomes review articles in the above-mentioned fields especially those highlighting the multi-disciplinary nature of ethnopharmacology.
Article types
The Journal of Ethnopharmacology will accept the following contributions:
Original research articles - whose length is not limited and should include Title, Abstract, Methods and Materials, Results, Discussion, Conclusions, Acknowledgements and References. As a guideline, a full-length paper normally occupies no more than 10 printed pages of the journal, including tables and illustrations.
Short Communications - whose average length is not more than 4 pages in print (approx. 2000-2300 words, including abstract and references). A maximum of 2 illustrations (figures or tables) is allowed. See paragraph below for description and format.
Letters to the Editors.
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Van der Geer, J., Handgraaf, T., Lupton, R.A., 2020. The art of writing a scientific article. J. Sci. Commun. 163, 51–59. https://doi.org/10.1016/j.sc.2020.00372.
Reference to a journal publication with an article number:
Van der Geer, J., Handgraaf, T., Lupton, R.A., 2022. The art of writing a scientific article. Heliyon. 19, e00205. https://doi.org/10.1016/j.heliyon.2022.e00205.
Reference to a book:
Strunk Jr., W., White, E.B., 2000. The Elements of Style, fourth ed. Longman, New York.
Reference to a chapter in a book:
Mettam, G.R., Adams, L.B., 2023. How to prepare an electronic version of your article, in: Jones, B.S., Smith, R.Z. (Eds.), Introduction to the Electronic Age. E-Publishing Inc., New York, pp. 281–304.
Reference to a website:
Cancer Research UK, 2023. Cancer statistics reports for the UK. http://www.cancerresearchuk.org/aboutcancer/statistics/cancerstatsreport/ (accessed 13 March 2023).
Reference to a dataset:
Oguro, M., Imahiro, S., Saito, S., Nakashizuka, T., 2015. Mortality data for Japanese oak wilt disease and surrounding forest compositions [dataset]. Mendeley Data, v1. https://doi.org/10.1762/xwj98nb39r.1.
Reference to software:
Coon, E., Berndt, M., Jan, A., Svyatsky, D., Atchley, A., Kikinzon, E., Harp, D., Manzini, G., Shelef, E., Lipnikov, K., Garimella, R., Xu, C., Moulton, D., Karra, S., Painter, S., Jafarov, E., & Molins, S., 2020. Advanced Terrestrial Simulator (ATS) v0.88 (Version 0.88) [software]. Zenodo. https://doi.org/10.5281/zenodo.3727209.
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ANEXO 2 - Comissão de Ética no Uso de Animais do Setor de Ciências Biológicas da UFPR (CEUA/BIO–UFPR; protocolo número: 1536).

MINISTÉRIO DA EDUCAÇÃO
UNIVERSIDADE FEDERAL DO PARANÁ
SETOR DE CIÊNCIAS BIOLÓGICAS
COMISSÃO DE ÉTICA NO USO DE ANIMAIS

UFPR

Nº 1536

CERTIFICADO

A Comissão de Ética no Uso de Animais do Setor de Ciências Biológicas da Universidade Federal do Paraná (CEUA/BIO – UFPR), instituída pela Resolução Nº 86/11 do Conselho de Ensino Pesquisa e Extensão (CEPE), de 22 de dezembro de 2011, **CERTIFICA** que os procedimentos utilizando animais no projeto de pesquisa abaixo especificado estão de acordo com a Diretriz Brasileira para o Cuidado e a Utilização de Animais para fins Científicos e Didáticos (DBCA) estabelecidas pelo Conselho Nacional de Controle de Experimentação Animal (CONCEA) e com as normas internacionais para a experimentação animal.

STATEMENT

The Ethics Committee for Animal Use from the Biological Sciences Section of the Federal University of Paraná (CEUA/BIO – UFPR), established by the Resolution Nº 86/11 of the Teaching Research and Extension Council (CEPE) on December 22nd 2011, **CERTIFIES** that the procedures using animals in the research project specified below are in agreement with the Brazilian Guidelines for Care and Use of Animals for Scientific and Teaching purposes established by the National Council for Control of Animal Experimentation (CONCEA) and with the international guidelines for animal experimentation.

PROCESSO/PROCESS: 23075.026096/2023-62

APROVADO/APPROVAL: 13/06/2023 – R.O. 05/2023.

TÍTULO: Padronização de um modelo de estudo de doença hepática para triagem de compostos bioativos com atividade hepatoprotetora.

TITLE: Standardization of a liver disease study model for screening bioactive compounds with hepatoprotective activity.

AUTORES/AUTHORS: Francislaine Aparecida dos Reis Lívero.

DEPARTAMENTO/DEPARTAMENT: Farmacologia.

Coordenador(a) da CEUA

Documento assinado eletronicamente por **ANGELA CRISTINA DA FONSECA DE OLIVEIRA, INSTITUCIONAL**, em 03/07/2023, às 14:22, conforme art. 1º, III, "b", da Lei 11.419/2006.

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