UNIVERSIDADE FEDERAL DE MATO GROSSO DO SUL

PROGRAMA DE PÓS-GRADUAÇÃO EM SAÚDE E DESENVOLVIMENTO NA REGIÃO CENTRO-OESTE

BRUNA LARISSA SPONTONI DO ESPIRITO SANTO

EFEITOS DO EXTRATO ETANÓLICO E AQUOSO DAS FOLHAS DE *GARCINIA GARDNERIANA* EM MODELOS EXPERIMENTAIS *IN VIVO*

CAMPO GRANDE, MS

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Orientador: Profº Drº Paulo Roberto Haidamus de Oliveira Bastos

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Banca examinadora: Nota/ Conceito

_____ _____
Paulo Roberto Haidamus de Oliveira Bastos

_____ _____
Danielle Bogo

_____ _____
Ângela Alves Nunes

_____ _____
Aline Lima de Barros

_____ _____
Diana Figuereido de Santana Aquino

DEDICATÓRIA

Aos meus pais, Shirlei e Paulo, meus irmãos Bárbara e Gabriel e meu companheiro, Felipe, que fizeram da caminhada mais leve com seu amor.

AGRADECIMENTOS

A Deus por me amparar nos momentos difíceis, me dar força interior para superar as dificuldades, mostrar os caminhos nas horas incertas e me suprir em todas as minhas necessidades.

Aos meus pais, Paulo e Shirlei, meu infinito agradecimento. Sempre acreditaram em minha capacidade, me incentivando a persistir nos meus sonhos, e me acharam a melhor de todas, mesmo não sendo. Isso só me fortaleceu e me fez tentar, não ser a melhor, mas a fazer o melhor de mim. Obrigada pelo amor incondicional!

Aos meus irmãos, Bárbara e Gabriel, meu agradecimento especial, pois, cada um, a seu modo, sempre se orgulharam de mim e confiaram em meu trabalho. Obrigada pela confiança e pelo apoio!

Ao meu querido esposo, Felipe, por ser tão importante na minha vida. Sempre a meu lado, me fazendo acreditar que eu posso me superar a cada dia. Devido a seu companheirismo, amizade, paciência, compreensão, apoio, alegria e amor, este trabalho pôde ser concretizado.

Aos meus orientadores Profº Drº Paulo Roberto Haidamus de Oliveira Bastos e Profª Drª Karine de Cássia Freitas Gielow por acreditarem em mim, me mostrarem o caminho da ciência, por fazerem parte da minha vida nos momentos bons e ruins. Sempre disponíveis e dispostos a ajudar, querendo que eu aproveitasse cada segundo dentro do doutorado para absorver todo conhecimento possível. Fizeram-me enxergar que, por trás de uma tese, existe mais do que pesquisadores e resultados, existem vidas humanas. Vocês são referências profissionais e pessoais para meu crescimento. Obrigada por estarem ao meu lado e acreditarem tanto em mim! Aos dois, muito obrigada por serem exemplos de profissionais os quais sempre farão parte da minha vida.

À minha grande amiga Lidiani Figueiredo Santana pelos momentos que dividimos juntas. Uma amizade verdadeira que tornou o trabalho muito mais leve mesmo nos dias mais difíceis. Aos poucos nos tornamos mais que amigas, irmãs!!! Obrigada por dividir comigo as angústias e alegrias e ouvir minhas bobagens econfusões. Se hoje eu entrego esse projeto finalizado, foi porque você esteveao meu lado durante todo o tempo me ajudando, me apoiando e confiando emmim, mesmo nos momentos em

que eu mesma duvidava. Eu não poderia teruma parceira melhor do que você. Essa amizade, eu levo dessa etapa para avida toda.

Finalmente, gostaria de agradecer ao Programa de Pós-Graduação em Saúdee Desenvolvimento na Região Centro-Oeste por abrir as portas para que eupudesse realizar este sonho, me proporcionando mais que a busca deconhecimento técnico e científico, mas uma lição de vida.

OBRIGADA!

RESUMO

A obesidade é um problema de saúde crescente no mundo, e sua prevalência aumenta rapidamente nos países desenvolvidos e em desenvolvimento. O estudo de plantas medicinais no tratamento de doenças crônicas não transmissíveis tem despertado o interesse dos pesquisadores. As plantas medicinais e seus constituintes podem representar candidatos promissores para o tratamento da obesidade e comorbidades. Várias plantas medicinais e seus constituintes ativos mostraram efeitos anti-obesidade benéficos *in vivo*. A *Garcinia gardneriana* (Planchon & Triana) Zappi (Clusiaceae), popularmente conhecida com bacupari, possui compostos fitoquímicos bioativos, como compostos fenólicos, principalmente os flavonoides, xantonas e benzofenonas que estão presentes na espécie. Neste contexto, esta proposta caracterizou a folha do Bacupari (*Garcinia gardneriana*) por meio de análises físico-químicas, perfil de bioativos, bem como avaliou os efeitos da administração de diferentes concentrações de extratos, em modelo experimental com consumo de dieta hiperlipídica. Para o experimento, 130 camundongos machos foram separados em 7 grupos, alimentados com as dietas: Dieta normal baseada na ração padrão Nuvital®, Dieta normal baseada na AIN-93M, Dieta hiperlipídica (4% de óleo de soja e 31% de banha), Dieta hiperlipídica (4% de óleo de soja e 31% de banha) + Extrato Aquoso (200mg/kg), Dieta hiperlipídica (4% de óleo de soja e 31% de banha) + Extrato Aquoso (400mg/kg), Dieta hiperlipídica (4% de óleo de soja e 31% de banha) + Extrato Etanólico (200mg/kg), Dieta hiperlipídica (4% de óleo de soja e 31% de banha) + Extrato Etanólico (400mg/kg), pesados semanalmente e monitorados quanto ao consumo das rações. Ao longo de 8 semanas de tratamento, acompanhou-se o consumo alimentar e o peso corporal, e ao final deste período realizou-se a anestesia dos animais e eutanásia por exsanguinação. No sangue, foram avaliados perfis lipídicos, glicemia e citocinas. Na análise de biomarcadores, a citocina IL-10 apresentou maior valor para o grupo HF, quando comparado aos demais grupos ($p<0,001$). Para a citocina MCP-1, os grupos que receberam dieta hiperlipídica apresentaram maiores valores. Os resultados revelam que os grupos não apresentaram diferença no total calórico consumido. O uso do extrato aquoso em 400mg/Kg proporcionou melhorias nos valores de triglicerídeos, e perfil glicêmico, inferindo seu possível uso no tratamento de distúrbios metabólicos associados à obesidade e doenças crônicas não transmissíveis, como a diabetes.

Descritores: Diabetes. Obesidade. Dieta hiperlipídica. Glicemia.

ABSTRACT

Obesity is a growing health issue in the world, and its prevalence is rapidly increasing in developed and developing countries. The chronic study of medicinal plants in the treatment of non-communicable diseases has aroused the interest of researchers. Medicinal plants and their constituents may hold promise for the treatment of obesity and comorbidities. Various medicinal plants and their active anti-obesity constituents beneficial plants in vivo. Garcinia gardneriana (Planchon & Triana) Zappi (Clusiaceae), popularly known as bacupari, has bioactive phytochemical compounds, such as phenolic compounds, mainly flavonoids, xanthones and benzophenones that are present in the species. In this, this proposal was made the leaf of Bac (Garcin gardneriana) through a profile of bioactive diet characteristics, as well as evaluated the effects of the administration of different experimental models with consumption of consumption context. For the experiment, 130 male mice were divided into 7, fed the following groups of diets: Normal diet based on the standard Nuvital® diet, Normal diet based on AIN-93M, High fat diet (4% soybean oil and 31% lard), High fat diet (4% soy oil and 31% lard) + Aqueous extract (200mg/kg), High fat diet (4% soy oil and 31% lard) + Aqueous extract (400mg/kg), High-fat diet (4% soybean oil and 31% lard) + Ethanol Extract (200mg/kg), High-fat diet (4% soybean oil and 31% lard) + Ethanol Extract (400mg/kg), all weekly and monitored in terms of feed consumption. During 8 weeks of treatment, food consumption was monitored and at the end of this period the animals were anesthetized and euthanized by exsanguination. In the blood, lipid profiles, blood glucose and cytokines were recorded. In the analysis of biomarkers, the cytokine IL-10 showed a higher value for the HF group, when compared to the other groups ($p<0.001$). For the MCP-1 cytokine, the groups that received a high-fat diet had higher values. The results reveal that the groups showed no difference in the total calories performed. The use of aqueous stress at 40mg/Kgideo improved triglycemic values and profile, inferring its possible use in the treatment of moderate-to-moderate stress and chronic non-communicable diseases such as diabetes.

Descriptors: Diabetes. Obesity. Hyperlipidic diet. blood glucose.

LISTA DE TABELAS

LISTA DE FIGURAS

CAPÍTULO 1 – REVISÃO DE LITERATURA

RESULTADOS E DISCUSSÃO

ARTIGO 1

ARTIGO 2

LISTA DE ABREVIATURAS E SIGLAS

AGEs - Inibidores de produtos finais de glicação avançada

ALT - alanina aminotransferase

AST - aspartato aminotransferase

CCL-2 - C–C motif chemokine ligand 2 (Ligante de quimiocina 2 C – C)

DNTS – Doenças Crônicas Não Transmissíveis

HDL - High-density lipoprotein (lipoproteína de alta densidade)

HIV - Human Immunodeficiency Virus (Vírus da Imunodeficiência Humana)

IL-10 - Interleucina-10

IL-6 – Interleucina-6

IMC – Índice de Massa Corporal

IpGTT - Intraperitoneal glucose tolerance test (Teste de tolerância à glicose intraperitoneal)

IpITT - Intraperitoneal Insulin Tolerance Test (Teste de tolerância à insulina intraperitoneal)

LDL - Low-density lipoprotein (lipoproteína de baixa densidade)

MCP-1 - Monocyte chemotactic protein-1 (Proteína-1 quimiotática de monócitos)

OMS – Organização Mundial da Saúde

SUS – Sistema Único de Saúde

TNF-α - Fatores de Necrose Tumoral Alfa

VIGITEL - Vigilância de fatores de risco e proteção para doenças crônicas por inquérito telefônico

VLDL - Very low-density lipoprotein (lipoproteína de muito baixa densidade)

SUMÁRIO

1 INTRODUÇÃO

A obesidade é um problema de saúde crescente no mundo, e sua prevalência aumenta rapidamente nos países desenvolvidos e em desenvolvimento. Caracterizada por um acúmulo excessivo de gordura corporal, associa-se a doenças crônicas e alterações de funções fisiológicas, incluindo doenças cardiovasculares, hipertensão, osteoartrite e alguns tipos de câncer (CAI *et al*., 2013; REUTER *et al*., 2013).

As causas da obesidade são complexas, pois envolvem fatores genéticos, metabólicos, ambientais, socioeconômicos e comportamentais. Contudo, o aumento da prevalência da obesidade parece ser consequência especialmente de fatores ambientais, como hábito alimentar, estilo de vida e sedentarismo, mas também de fatores genéticos como predisposição ao sobrepeso e à obesidade (HAUSMAN *et al*., 1997; NAVARRO e PÉREZ-LLAMAS, 2013). A melhoria das condições socioeconômicas da população promoveu uma modernização da sociedade, levando ao consumo de alimentos energéticos, com alto teor de gorduras e ao sedentarismo (KAIN *et al*., 2002; CAI *et al*., 2013).

Atualmente, para o tratamento da obesidade, as principais ferramentas disponíveis e utilizadas são a terapia nutricional realizada por profissional capacitado, mudança no estilo de vida, prática de atividade física e algumas opções de terapias farmacológicas (NAVARRO e PÉREZ-LLAMAS, 2013). Na literatura não há relatos sobre a eficiência das intervenções que são mais eficazes no tratamento da obesidade. A maioria das abordagens relatam que as mudanças no estilo de vida, reeducação alimentar e estímulo ao exercício físico apresentam influência na redução da incidência de doenças crônicas degenerativas, principalmente mortes por causas cardiovasculares (REUTER *et al*., 2013).

O estudo de plantas medicinais no tratamento de doenças crônicas não transmissíveis tem despertado o interesse dos pesquisadores. As plantas medicinais e seus constituintes podem representar candidatos promissores para o tratamento da obesidade, considerando que várias plantas medicinais e seus constituintes ativos mostraram efeitos anti-obesidade benéficos *in vivo*. Por outro lado, o uso dessas plantas para neutralizar e / ou prevenir a obesidade ainda é pouco estudado. Algumas pesquisas mostraram o efeito protetor de poucas plantas e seus

constituintes na obesidade (LARCON-AGUILAR, 2007; SANCHES, 2016; KUMAR, 2016; PALLOMA, 2016; PATIL, 2011)

A *Garcinia gardneriana* (Planchon & Triana) Zappi (Clusiaceae), popularmente conhecida com bacupari, gênero chamado anteriormente por Rhedia, apresenta em torno de 400 espécies, extensamente distribuídas em regiões tropicais do Brasil, Polinésia, Ásia e África. Possui compostos fitoquímicos bioativos, como compostos fenólicos, principalmente os flavonoides, xantonas e benzofenonas que estão presentes em concentrações expressivas nos frutos (FERREIRA; CARVALHO; SILVA, 2012; MELO *et al.,* 2014; LIU *et al*., 2015).

Neste contexto, esta proposta pretende, bem como avaliar os efeitos da administração de diferentes concentrações e tipos de extratos, em modelo experimental com consumo de dieta hiperlipídica.

2 REVISÃO BIBLIOGRÁFICA

2.1 Obesidade

A obesidade é um problema de saúde pública em todo o mundo e equivale a uma doença crônica caracterizada pelo acúmulo excessivo de tecido adiposo. É consequência do balanço energético positivo, devido à redução na prática de atividade física e o aumento no consumo de alimentos com alto teor calórico, principalmente com adição de açúcares e de gordura (DIAS, 2011; PEREIRA, 2003; OMS, 2017).

De acordo com a Organização Mundial da Saúde (OMS), a prevalência mundial da obesidade quase triplicou entre os anos de 1975 e 2016. Em 2016 mais de 1,9 bilhões de adultos estavam acima do peso e, desse número, 650 milhões estavam obesos. Entre crianças e adolescentes os valores chagaram a mais de 340 milhões nessas condições (WHO, 2018).

Além de causar problemas individuais, a obesidade afeta a sociedade em geral e atinge os sistemas de saúde. Indivíduos obesos geralmente apresentam diminuição da qualidade e expectativa de vida, além trazer problemas de ajustes sociais e redução da produtividade o que leva a um gasto público que excede os custos médicos (BAHIA, 2014).

O aumento nas taxas de obesidade tem levado também ao aumento de comorbidades associadas à mesma (FELIZARDO, 2014). A obesidade é uma condição complexa e afeta a funções relacionadas a vários órgãos e é caracterizada tanto como uma doença, como fator de risco para outras doenças crônicas não transmissíveis (DCNT), como doenças cardiovasculares, hipertensão, acidente vascular cerebral, diabetes tipo 2, dislipidemia, doença hepática gordurosa não alcoólica, doenças pulmonares, certos tipos de câncer, osteoartrites, colelitíase, cálculos biliares, entre outras, e até mesmo deficiências nutricionais (ABESO, 2016; AKRAM, 2000; BANERJEE, 2018; HEIDEN, 2018; KULKARNI *et al*., 2016; MANCINI, 2015; NIBLETT, 2015; RAVEENDRAN *et al*., 2017; SÁNCHEZ *et al.,* 2016; SINGH, 2013; VOLLENWEIDER, 2018).

A obesidade tornou-se um dos problemas mais importantes de saúde pública, pois é considerada uma das cinco principais causas de morte no mundo e os

números de casos de obesidade devem continuar afetando 19,5% da população adulta global em 2025 (DI CESARE, 2016). Segundo a OMS, mais de 1,9 bilhão de adultos com mais de 18 anos apresentavam excesso de peso corporal em 2016. Acima de 650 milhões de adultos foram diagnosticados com obesidade, o equivalente à 13% da população adulta do mundo (11% dos homens e 15% das mulheres) (WHO, 2018).

No ano de 2016, as DCNTs foram responsáveis por 71,0% de todas as mortes em todo o mundo e por 76,4% de todas as mortes no Brasil (GBD, 2016). Segundo a pesquisa Vigilância de Fatores de Risco e Proteção para Doenças Crônicas por Inquérito Telefônico (VIGITEL), estima-se que mais da metade dos brasileiros esteja acima do peso, sendo que aqueles com obesidade representam 19,8% da população adulta brasileira, sendo maior entre as mulheres, 20,7%, em comparação aos homens, com 18,7% (BRASIL, 2019).

A obesidade e suas comorbidades estão relacionadas ao aumento dos gastos na saúde pública e as estimativas mostram que até 2030, o aumento com os gastos relacionados ao aumento de peso nos Estados Unidos será de até 66 bilhões de dólares, enquanto no Reino Unido será de 1,9 a 2 bilhões de libras (WANG *et al*., 2011). Estima-se também que o impacto global da obesidade é de aproximadamente 2 trilhões de dólares, o equivalente a 2,8% do produto interno bruto mundial (MCKINSEY GLOBAL INSTITUTE, 2014).

Quanto maior o grau de obesidade, de acordo com o Índice de Massa Corporal (IMC), maiores serão os custos relacionados à doença, tanto diagnósticos quanto tratamentos. Os gastos no cuidado à saúde de indivíduos com peso normal e com sobrepeso são equivalentes. Porém, os custos começam a ser aumentados nas faixas que compreendem a obesidade classe I, apresentando aumentos drásticos nos gastos na obesidade classes II e III (BIENER, CAWLEY E MEYRHOEFER, 2017).

Com relação aos custos do sobrepeso e da obesidade na população brasileira, o Sistema Único de Saúde (SUS) gasta anualmente cerca de R$ 3,6 bilhões com o tratamento dessas doenças. Desses valores, cerca de R$ 2,4 bilhões são gastos em tratamentos hospitalares (68%) e R$ 1,2 bilhões (32%) com tratamentos ambulatoriais (Bahia *et al*, 2012). Ainda existem os custos indiretos,

relativos à perda de produtividade, licenças médicas e morte prematura, logo esses números são uma estimativa conservadora dos gastos púbicos com pacientes obesos, uma vez que o custo real do tratamento é possivelmente maior do que os valores apresentados (BAHIA; ARAÚJO, 2014).

Após a identificação dos impactos das DCNT no desenvolvimento social, econômico e na saúde pública, foi elaborado o Plano de Ação Mundial da OMS para a prevenção e controle de doenças não-transmissíveis 2013-2020, que trouxe intervenções nos fatores causadores de DCNT para a redução em 25% das mortes prematuras por DCNT e desaceleração do aumento da incidência da obesidade global. A meta era reduzir as taxas de mortalidade e morbidade, promover melhorias na qualidade de vida dos indivíduos, minimizar a exposição a fatores de risco por meio de abordagens que promovam o bem-estar e reduzam a desigualdade entre os Estados Membros do Plano. Os principais objetivos eram promover a alimentação saudável para a saúde e bem-estar, e promover vida ativa para prevenir obesidade (OMS, 2017b).

2.2 Classificação da Obesidade

Sobrepeso e obesidade são caracterizados pelo acúmulo excessivo de gordura corporal que podem repercutir negativamente na saúde do indivíduo, com perda considerável da qualidade e expectativa de vida (WHO, 2017b). A classificação de obesidade depende da avaliação do indivíduo em relação a sua adiposidade corporal. É realizado o cálculo do índice de massa corporal (IMC). O IMC é o resultado da divisão entre o peso e a altura elevada ao quadrado (kg/m^2). De acordo com o valor obtido, é possível realizar a classificação, conforme apresentado na tabela 1 (ABESO, 2016; WHO, 2017b; WHO, 2000).

Tabela 1. Classificação internacional da obesidade segundo o índice de massa corporal (IMC) e risco de doença.

Classificação	IMC	Risco de Doença
Peso Normal	18.5 – 24.9 kg/m^2	Normal
Sobrepeso ou pré-obeso	25 – 29 kg/m^2	Aumentado
Obesidade grau I	30 – 34 kg/m^2	Moderado
Obesidade grau II	35 – 39.9 kg/m^2	Severo
Obesidade grau III ou obesidade mórbida	≥40 kg/m^2	Muito Severo

Fonte: Organização Mundial de Saúde (OMS, 2000)

Embora seja o parâmetro mais utilizado para avaliação, o IMC não é a única ferramenta utilizada para avaliação de gordura corporal. Existem diferenças na composição corporal dos indivíduos que variam de acordo com o sexo, idade, etnia, sedentarismo, e em indivíduos edemaciados. Por não ser possível distinguir massa gordurosa de massa magra utilizando apenas o IMC, o mesmo não reflete a distribuição da gordura corporal, sendo que essa é uma informação importante na avaliação de sobrepeso e obesidade, visto que a gordura visceral é um fator de risco para doenças crônicas não transmissíveis, independentemente da gordura corporal total. Ainda, indivíduos com o mesmo IMC podem ter diferentes níveis de massa gordurosa visceral (ABESO, 2016).

Além do IMC, existem outras ferramentas utilizadas para avaliar a adiposidade e sua distribuição corporal nos indivíduos, como a relação circunferência abdominal/quadril, circunferência da cintura, relação altura/circunferência abdominal, bioimpedância, calorimetria indireta, ultrassonografia, tomografia, ressonância magnética e a medição da espessura das pregas cutâneas (ABESO, 2016).

2.3 Etiologia da Obesidade

A obesidade é uma condição clínica multifatorial, consequente da interação de fatores genéticos, ambientais, sociais, emocionais e culturais (OMS, 2017b). Devido ao rápido aumento dos índices de sobrepeso e obesidade nas duas últimas décadas, pressupõe-se que as variações na prevalência de obesidade são influenciadas por fatores ambientais e comportamentais, principalmente pelo aumento da ingestão calórica e redução de atividade física (OMS, 2017b).

Os fatores que influenciam o peso corporal dos indivíduos alteram a ingestão ou o gasto de energia, provocando um estado de balanço energético positivo, que ocorre quando a ingestão de energia é maior em relação ao gasto, gerando aumento no peso corporal do indivíduo, especialmente de tecido adiposo (HILL; WYATT; PETERS, 2012).

Dentre os fatores biológicos associados ao surgimento da obesidade, tem-se a genética, o eixo cérebro-intestinal, as condições neuroendócrinas, os medicamentos, a deficiência física e a microbiota intestinal (KADOUH E ACOSTA, 2017). Com relação à associação da genética, mais de 300 genes diferentes e marcadores de genes relacionados à obesidade foram identificados e interagem com o meio ambiente que podem resultar no desenvolvimento da obesidade (FRIEDMAN, 2003). Segundo Rao e colaboradores (2014) a obesidade pode ser classificada em três subgrupos: obesidade monogênica (defeito de um único gene), obesidade sindrômica (anormalidades cromossômicas) e, obesidade poligênica (obesidade comum).

Distúrbios endócrinos também podem estar associados com o desenvolvimento do sobrepeso e obesidade, como o hipotireoidismo, deficiência do hormônio do crescimento, hipogonadismo em homens, ovariectomia e síndrome dos ovários policísticos (RIBEIRO, 2015; GURNANI; BIRKEN; HAMILTON, 2015), além de períodos reduzidos de sono (TAHERI *et al*., 2004) e deficiência de vitamina D (DING *et al*., 2012).

O desenvolvimento de tecnologias industriais para a produção e processamento de alimentos calóricos associados à grandes técnicas de marketing e facilidade no acesso pela população, associado à baixas adesões de atividades físicas determina um ciclo vicioso de uma ingestão alimentar com altos níveis

calóricos e leva à população à “epidemia de obesidade” que pode levar ao desenvolvimento de Doenças Crônicas Não Transmissíveis (DCNT) (ASTRUP, 2000; JEFFERY, 2003).

O aumento do consumo de alimentos ultraprocessados tem sido associado à obesidade e às DCNT, hipertensão e alguns tipos de câncer (COSTA, 2018; FIOLET, 2018; JUUL, 2018; MENDONÇA, 2017; RAUBER, 2018). Alimentos ultraprocessados são produtos industriais, que em além de sal, açúcar, óleos e gorduras adicionam substâncias que podem trazer qualidades sensoriais aos alimentos minimamente processados e suas preparações culinárias (MONTEIRO, 2016).

Dietas com alta quantidade de alimentos ultraprocessados tendem a ser nutricionalmente desequilibradas, promover o consumo excessivo de alimentos e bebidas, sendo prejudiciais à saúde (MONTEIRO, 2018a; MONTEIRO, 2018b; MOUBARAC, 2015). Esses fatores têm fomentado a discussão sobre a utilização de medidas econômicas para conter a epidemia de obesidade no país (CLARO, 2010; CLARO 2012). Segundo a OMS (2017) é importante a criação de tributações que aumentaria o preço das bebidas adoçadas em 20% com o intuito de reduzir a compra destes produtos, já que, estudos anteriores, sugerem uma associação inversa entre preços de alimentos não saudáveis e estado nutricional (BEYDOUN, 2011; COTTI, 2013; GROSSMAN, 2014; POWELL, 2009).

O estudo de plantas medicinais no tratamento de doenças crônicas não transmissíveis tem despertado o interesse dos pesquisadores. As plantas medicinais e seus constituintes podem representar candidatos promissores para o tratamento da obesidade. Várias plantas medicinais e seus constituintes ativos mostraram efeitos anti-obesidade benéficos in vivo. Por outro lado, o uso dessas plantas para neutralizar e / ou prevenir a obesidade ainda é pouco estudado. Algumas pesquisas mostraram o efeito protetor de poucas plantas e seus constituintes na obesidade (KUMAR, 2016; LARCON-AGUILAR, 2007; PALLOMA, 2016; PATIL, 2011; SANCHES, 2016)

2.4 Plantas do Cerrado

O cerrado é considerado uma das mais ricas vegetações do mundo e ocorre principalmente na região centro-norte do Brasil, representando cerca de um terço da biota brasileira, cobrindo mais de 20% do território brasileiro, sendo a segunda em termos de cobertura de área nacional (FELFILI; SILVA-JUNIOR,1993).

O bioma do Cerrado é caracterizado como um hotspot, ou seja, um dos ambientes mais ricos e ameaçados do mundo. É conhecida devida sua biodiversidade, que se destaca por conta das inúmeras espécies pouco conhecidas que fornecem frutos com características peculiares e que podem assumir um importante papel na economia da população, como a comercialização in natura ou processados, como também na questão nutricional, que através do seu consumo pode favorecer a diminuição da insegurança alimentar (HAMACEK *et al*., 2013).

No cerrado podem ser encontradas várias espécies de frutas que são consideradas fontes de proteínas, fibras, ácidos graxos, calorias, vitaminas e minerais como o cálcio e o fósforo e possuem grande potencial antioxidante. Geralmente são consumidas *in natura* ou utilizadas como ingredientes em algumas preparações, com grande aceitação popular (CALDEIRA *et al*., 2004; MORAIS *et al*., 2013; RAMOS *et al*., 2008). De acordo com Costa *et al*. (2013) e Santos (2014) um maior consumo de frutas e verduras está associado com a diminuição do risco de doenças cardiovasculares, câncer, obesidade e diabetes.

O Cerrado e o Pantanal apresentam uma grande riqueza de espécies que podem ser consideradas “Plantas do Futuro”, que ainda não foram estudadas e outras que são pouco utilizadas por comunidades locais. Isso faz com que muitas propriedades dessas plantas sejam desconhecidas em relação às propriedades delas. A substituição da vegetação natural e o manejo inadequado de muitas culturas têm levado à perda de oportunidades que poderiam alavancar o comércio regional (ROESLER, 2007; VIEIRA, 2010).

As plantas encontradas no Cerrado têm despertado interesse crescente, devido às suas propriedades nutricionais e funcionais aliadas ao potencial para agregar valor e conservar a biodiversidade deste bioma. As plantas possuem fontes de vitaminas, minerais e fibras e alguns apresentam um grande potencial antioxidante. Neste contexto, pode-se afirmar que os valores nutricionais e

terapêuticos provêm de compostos bioativos, sendo que estes estão presentes em pequenas quantidades nos alimentos, porém são vitais na manutenção da saúde, como os polifenóis, que são capazes de promover benefícios à saúde (COSTA *et al*., 2013).

2.5 Gênero Garcinia

Garcinia é um gênero de plantas clusiáceas, pentencente a família Guttiferae que compreende cerca de 40 gêneros e 1200 espécies amplamente distribuídas na Ásia tropical, África, Nova Caledônia, Polinésia e Brasil. As espécies do gênero Garcinia são uma fonte rica e valiosa de compostos bioativos com importantes propriedades terapêuticas, como atividade anti-inflamatória e analgésica (ALMEIDA *et al*., 2008; PANTHONG *et al*., 2007).

As espécies de Garcinia são ricas em metabólitos secundários, como xantonas preniladas e oxigenadas (CUI *et al*., 2010) que apresentam atividades biológicas, tais como antifúngicos (SORDAT-DISERENS, 1991), anti-inflamatórios (KHANUM, 2004), antitumorais (DIAZ-CARBALLO, 2003), antioxidante (MERZA, 2004), propriedades inibidoras do Vírus da Imunodeficiência Humana (HIV) (GUSTAFSON, 1992) e antilipidêmicos (DIAZ-CARBALLO, 2003; HAY, 2004).

O gênero Garcinia contém uma ampla variedade de metabólitos biologicamente ativos, sendo que nas últimas décadas, as plantas das espécies de Garcinia receberam considerável atenção devido à composição química de seus extratos, que são ricos em derivados de benzofenonapoliisoprenilada, polifenóis, biflavonóides e xantonas (ACUÑA, 2012). Extratos do pericarpo, epicarpo e sementes de Garcinia demonstraram atividade antioxidante, anti-inflamatória, leishmanicida e antiprotozoária (PEREIRA, 2010; SANTA-CECÍLIA, 2011) e na medicina tradicional, a fruta da Garcinia tem sido utilizada na forma de chá no tratamento de feridas, úlceras e disenteria (ACUÑA, 2012).

Outro estudo relatou também a presença dos biflavonóides volkensiflavone e fukugetin (BOTTA, 1984) e xantonas preniladas (DELLE, 1984). Esses compostos estão associados a atividades biológicas, tais como sequestrador de radicais livres e efeito antiúlcera (YAMAGUCHI, 2000), citotoxicidade, inibição de óxido nítrico

sintase (CRUZ, 2006), quimioprevenção de câncer (ITO, 2003), indução de apoptose (PAN, 2001), atividade anti-HIV (PICCINELLI, 2005) e efeitos tripanocidas (ABE, 2004; ALVES, 1999).

A espécie Garcinia brasiliensis (Mart.), também conhecida como *Rheedia brasiliensis Planch* e Triana, é nativa da região amazônica, cultivada em todo o Brasil, sendo popularmente conhecida como bacuri, bacupari, porocó e bacuripari, e na Bolívia, é chamada guapomo. Esta espécie possui fruto amarelo com polpa mucilaginosa, branca e comestível e é utilizada pela população como anti-inflamatório (CASTARDO *et al*., 2008; SANTA-CECÍLIA *et al*., 2011), antinociceptiva (SANTA-CECÍLIA *et al*., 2011), antioxidante e antitumoral (COELHO *et al*., 2008). Em alguns lugares como Tailândia, Sri Lanka, Malásia, Filipinas e Índia, as frutas maduras são usadas na medicina tradicional para tratar a dor abdominal, diarreia, disenteria, feridas infectadas, supuração e úlcera crônica (CUI *et al*., 2010).

Alguns compostos foram encontrados na casca da fruta, sendo eles, sesquiterpenos oxigenados - óleo volátil obtido por hidrodestilação- apresentando em sua composição g-muuroleno (10,3%), espatulenol (8,7%), d-cadineno (8,3%), torreíolo (8,0%), acadinol (7,0%), cadaleno (6,3%) e g-cadineno (5,3%) (MARTINS, 2008). Quando testado em animais, o óleo essencial apresentou atividade anti-inflamatória nas doses de 100mg/kg (MARTINS, 2008; SANTA-CECÍLIA, 2011a).

No epicarpo do fruto da Garcinia brasiliensis foram isolados os seguintes componentes: uma nova biflavonona glicosilada - morelloflavona-4000-ObD-glicosil e os compostos conhecidos 1,3,6,7-tetrahidroxixantona, morelloflavona (fukugetina) e morelloflavona-700-ObD-glicosil (fukugesideo). Esses compostos apresentaram atividade antioxidante após o isolamento de biflavonoides naturais da planta (GONTIJO, 2012).

O consumo de extrato etanólico da folha de *Garcinia brasiliensis* na concentração de 300mg/kg reduziu o estresse oxidativo e a inflamação em ratos obesos portadores de insuficiência cardíaca, e apresentou uma estratégia promissora para modulação benéfica da microbiota. Isso demonstra os potenciais efeitos protetores dos compostos fenólicos, moreloflavona e 7-epiclusianona, presentes no extrato (ARAÚJO, 2019).

A *Garcinia pedunculata Roxb*. é uma espécie da família Clusiaceae. Trata-se de uma árvore perene e endêmica de algumas regiões da Ásia, como partes de Mianmar e partes orientais da Índia. Tradicionalmente, a fruta da *Garcinia pedunculata* vem sendo utilizada pela população para tratar diferentes tipos de desordens gastrointestinais (SARMA E DEVI, 2015). Também é uma planta medicinal indígena. A fruta de G. pedunculata é comumente conhecida como “Taikor” no Bangladesh e "Amlavetasa" na Índia (MUNDUGARU, 2014a). O fruto da *Garcinia pedunculata* é amarelo esverdeado e utilizado como ingrediente na culinária para preparo de diferentes tipos de carne e frango (ISLAM, 2015).

Benefícios da fruta foram relatados, incluindo efeito antioxidante (ISLAM, 2015; MUDOI, 2012), antimicrobiano (NEGI, 2008), antiinflamatório (MUNDUGARU, 2014b; RAVI, 2014), hipolipemiante (SARMA, 2016), hepatoprotetor (MUNDUGARU, 2014a), nefroprotetor (MUNDUGARU, 2016), além de propriedades cardioprotetoras (MUNDUGARU, 2016). A Garcinia pedunculata tem sido tradicionalmente usada na cozinha como um adstringente, um cardiotônico e um emoliente. Também é utilizada no tratamento de asma, tosse, bronquite, diarreia e febre (KAGYUNG, 2010).

A *Garcinia cambogia*, também conhecida como tamarindo malabar, é uma planta nativa do sudeste da Ásia. A fruta é comumente usada como alimento agente conservante, carminativo e aromatizante (SAITO, 2005). O extrato da *Garcinia cambogia* é usado na medicina indiana para o tratamento de úlceras, hemorróidas, diarreia, disenteria e certos tipos de câncer tais como leucemia (DUKE, 2002). Estudos iniciais sobre sementes de *Garcinia cambogia* confirmaram também que elas possuem efeitos antifúngicos (IWU, 1999), anticancerígenos (HO, 2002; PAN, 2001), anti-histamínicos (NAKATANI, 2000), antiulcerogênicos (Mahendran, 2000), antimicrobianos (IWU, 1999), antivirais (CHEN, 1996) e vasodilatadores (SRIPRADHA, 2015). Os efeitos gastroprotetores parecem estar relacionados à capacidade de diminuir a acidez e aumentar a defesa da mucosa (MAHENDRAN *et al*., 2002a, 2002b). Além disso, o extrato apresenta propriedades hipolipidêmicas (MAHENDRAN e DEVI, 2001), efeito antiadipogênico e supressor do apetite em animais experimentais por meio da inibição da expressão do fator de transcrição adipogênica precoce, a proteína de ligação ao elemento CCAAT (C/EBP) alfa que regula a adipogênese (KIM *et al*., 2004; ISHIHARA *et al*., 2000).

Garcinia mangostana Linn é uma fruta nativa do sudeste da Ásia conhecida por conter constituintes, incluindo xantonas, flavonóides, triterpenóides e benzofenonas (RECALDE-GIL, 2019). Em muitos países da Ásia, a casca do mangostão tem sido usada na medicina tradicional para curar várias doenças, como diarreia, disenteria, infecções de pele, micoses, inflamação, cólera e febre (OBOLSKIY,2009; PEDRAZA-CHAVERRI, 2008). Extratos da fruta exibiram efeitos antioxidantes (YOSHIKAWA, 1994; JUNG, 2006), anti-inflamatórios (CHAIRUNGSRILERD, 1996; CHEN, 2008), antibacterianos (CHOMNAWANG, 2009) e antidepressivos (OBERHOLZER, 2018). Em particular, a α-mangostin (AM), um componente primário da GML, apresenta propriedades farmacológicas substanciais (NAKAGAWA, 2007; SAKAGAMI, 2005), incluindo atividade antioxidante (FANG, 2016).

As propriedades farmacêuticas da *Garcinia mangostana Linn* são atribuídas à presença de polifenóis, como xantonas, antocianinas, ácidos fenólicos e flavonóides (JUNG, 2006; TJAHJANI, 2014). Possui propriedades antioxidantes, anti-inflamatórias, antitumorais, antibacterianas, antifúngicas, antivirais e antialérgicas (TJAHJANI, 2014; TOUSIAN, 2020). A alfa-mangostina é uma das xantonas mais abundantes da G. mangostana (mangostão). Ela apresenta efeitos anti-inflamatórios, evidenciado pela redução nos níveis de TNF-α e IL-6 (BUMRUNGPERT, 2009; JARIYAPONGSKUL, 2015). Apresenta também efeitos anti-hiperglicêmicos, antioxidantes e anti-inflamatórios, fluxo sanguíneo e integridade da retina melhorados (JARIYAPONGSKUL, 2015; KARIM, 2019). O fruto também já apresentou melhora nos resultados de adiposidade, hiperlipidemia, resistência à insulina e lesão hepática relacionadas ao envelhecimento em estudo realizado em animais (LI, 2019).

2.6 Espécie *Garcinia gardneriana*

A *Garcinia gardneriana* (Planchon&Triana) Zappi. (Clusiaceae) é uma árvore nativa da mata Atlântica, frutífera e da família Clusiaceae (Figura 1), de fácil cultivo, sendo comum de se encontrar em pomares domésticos. Cresce em todo o Brasil, onde é popularmente conhecida como “Bacupari”, “bacopari”, “bacopari miúdo” ou “mangostão amarelo” (GUIMARÃES, 2004). A fruta de *Garcinia gardneriana* é

inicialmente verde escura, tornando-se verde amarelado e laranja-alaranjado quando amadurece. A pele da fruta é lisa e coriácea, sendo formada pelo exocarpo. A polpa é branca, comestível com sabor doce, sendo derivada principalmente do endocarpo (ASINELLI, 2011; SANTOS *et al*.,1999).

Também conhecida como *Rheedia gardneriana*, a planta é geralmente aplicada na medicina popular para várias finalidades, como problemas inflamatórios, incluindo desordens da pele e feridas, tratamento da dor e infecções (CASTARDO *et al*., 2008).

As folhas, cascas e raízes são as partes mais utilizadas e estas podem ser preparadas como infusões, decocções ou macerados, individualmente ou em combinação com outros produtos naturais (CASTARDO *et al*., 2008). O extrato etanólico confere um efeito benéfico adicional à pele pelo fato de a planta conter uma grande quantidade de biflavonóides que são considerados capazes de reduzir o potencial dano oxidativo produzido na pele após exposição à radiação ultravioleta (SOLANO *et al*., 2006).

Garcinia gardneriana é uma planta muito rica em metabólitos secundários e algumas análises fitoquímicas identificaram xantonas, esteróides, triterpenos e flavonóides de diferentes partes da planta (DELLEMONACHE *et al*., 1983; BRAZ FILHO *et al*., 1970), os quais estão associados a efeitos farmacológicos, tais como antiinflamatórios, antinociceptivos, antibacterianos e antiparasitário (SUBEKI et al., 2004; VERDI *et al*., 2004; CASTARDO *et al*., 2008; OTUKI *et al*., 2011; MELO *et al*., 2014).

A análise fitoquímica de *Garcinia gardneriana* detectou várias classes de compostos como esteróides, triterpenos, biflavonóides e xantonas (CECHINEL FILHO, 2000a). Vários biflavonóides encontrados possuem efeito analgésico (LUZZI *et al*., 1997). Os mesmos foram identificados como volkensiflavone, 13-naringenina-II 8-eriodictyol (GB-2a), fukugetin (ou morelloflavone) e fukugeside. Um novo biflavonóide isolado de folhas de *Garcinia gardneriana*, chamado de GB2a-OMe, também apresentou efeito analgésico significativo no teste da formalina em camundongos (CECHINEL FILHO, 2000b; LUZZI, 1997). Na tabela 2, pode-se observar os compostos já encontrados na planta e suas respectivas atividades.

O composto GB-2a inibiu significativamente o teor de melanina, sem reduzir a viabilidade celular, sugerindo um grande potencial para usos médico como agente despigmentante, para aplicações cosméticas e clínicas no clareamento da pele (CAMPOS, 2015). O composto fukugetin (ou morelloflavone), mostrou uma atividade antiinflamatória contra edema de pata de camundongo induzido por carragenina na concentração de 300 mg/kg, tornando a planta um alvo potencial para o desenvolvimento de novos compostos que podem ser explorados como alternativas às drogas que já estão em uso com atividade antiinflamatória (CASTARDO, 2008).

Os biflavonóides isolados de *Garcinia gardneriana*, tais como moreloflavona (1), Gb-2a (2) e Gb-2a-7-O-glicose (3) foram submetidos ao ensaio in vitro a fim de se avaliar o efeito modulador da aromatase, utilizados para o tratamento de câncer. Como resultados verificaram-se que todos os biflavonóides foram capazes de inibir a enzima, com valores de IC50 variando de 1,35 a 7,67μM. Isso demonstra que os biflavonóides são uma importante fonte para o desenvolvimento de novos inibidores da aromatase, com foco no desenvolvimento de novos agentes anticâncer (RECALDE-GIL, 2019).

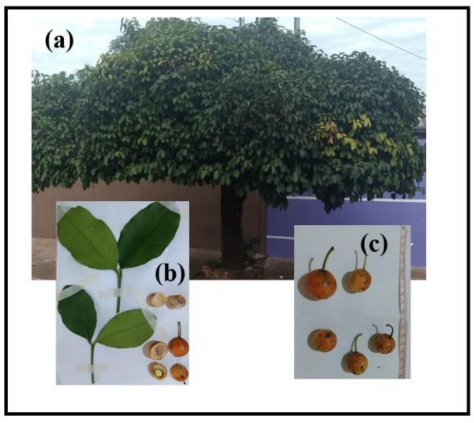

Figura 1: Imagens da *Garcinia gardneriana* (Planchon & Triana) Zappi. (a) Árvore, (b) folhas e (c) frutos. Fonte: O autor.

Tabela 2: Lista de compostos encontrados na *Garcinia gardneriana.* Fonte: ESPIRITO SANTO (2020).

Garcinia gardneriana		
Biflavonóides		
Composto	**Parte da Planta**	**Atividade**
GB-2a	Folha(CAMPOS, 2015),galhos(OTUKI, 2011)	anti-edematogênica(CAMPOS, 2015), anti-inflamatória(CAMPOS, 2015), anticâncer(RECALDE-GIL, 2019)
Gb-2a-7-O-glicosídeo	Galhos(OTUKI, 2011)	Anticâncer(RECALDE-GIL, 2019)
volkensiflavona	Folha(FERREIRA, 2012)	Analgésico(FERREIRA, 2012)
fukugentin	Folha(FERREIRA, 2012)	Analgésico(FERREIRA, 2012); anti-inflamatório (OTUKI, 2011); antioxidante(GONTIJO, 2012)
fukugiside	Folha(FERREIRA, 2012)	Analgésico(FERREIRA, 2012); antioxidante(GONTIJO, 2012)
GB-2a-II-4'-OMe	Folha(FERREIRA, 2012)	Analgésico(FERREIRA, 2012)
Flavonoides		
Composto	**Parte da Planta**	**Atividade**
Epicatechin	Folha(VERDI, 2004)	Antibacteriano(VERDI, 2004)
Fitoesteróis		
Composto	**Parte da Planta**	**Atividade**
sitosterol	Frutos(SANTOS, 1999)	antiinflamatória e anticâncer(MARTINS, 2008)
estigmasterol	Frutos(SANTOS, 1999)	antiinflamatória e anticâncer(MARTINS, 2008)

Benzofenonas		
Composto	**Parte da Planta**	**Atividade**
7-epiclusanone	Casca(SANTOS, 1999)	antinociceptivo e anti-inflamatório (SANTA-CECÍLIA, 2011)antimicrobiana(NALDONI, 2009), anticancerígeno(SALES, 2015), leishmanicida(PEREIRA, 2010), esquistossomicida(CASTRO, 2015)
Sesquiterpenos		
Composto	**Parte da Planta**	**Atividade**
α-copeno	Casca(SANTOS, 1999)	-
α-muuroleno	Casca(SANTOS, 1999)	-
γ-cadineno	Casca(SANTOS, 1999)	-
cadineno	Casca(SANTOS, 1999)	-
Triterpenos		
Composto	**Parte da Planta**	**Atividade**
Ácido oleanólico	Casca(SANTOS, 1999)	-

3. OBJETIVOS

Objetivo Geral

Avaliar os efeitos do extrato aquoso e etanólico em animais recebendo dieta hiperlipídica quanto ao perfil bioquímico, estado inflamatório e nutricional dos animais.

Objetivos Específicos

- Realizar o levantamento literário dos compostos encontrados nos gêneros Garcinia;

- Avaliar o estado nutricional e o percentual de gordura corporal dos grupos experimentais;

- Realizar análise histológica do fígado dos grupos experimentais;

- Analisar o perfil lipídico e glicemia;

- Avaliar o desenvolvimento da resistência à insulina (teste de tolerância à glicose (ipGTT) e à insulina (ipITT));

- Realizar a dosagem de citocinas: IL-10 e MCP-1.

4. METODOLOGIA

4.1 Coleta das folhas.

As folhas foram coletadas em região urbana da cidade de Campo Grande sob a coordenada geográfica Latitude −20.533720 e longitude −54.675146, no Estado de Mato Grosso do Sul, Brasil e a espécie foi cadastrada no Sistema Nacional De Gestão Do Patrimônio Genético e Do Conhecimento Tradicional Associado (Sisgen) sob o número de cadastro A26D547. Em seguida em laboratório da Unidade de Ciência de Alimentos (UNICAL) da Faculdade de Ciências Farmacêuticas, Alimentos e Nutrição (FACFAN) da Universidade Federal de Mato Grosso do Sul, as folhas foram secas em estufa de circulação de ar a 40 °C, e utilizadas no preparo de amostras para análises. Após a secagem, foram trituradas e homogeneizadas em turrax, obtendo-se uma massa homogênea que foi adequadamente embalada em embalagem escura e identificada para confecção do extrato.

4.2 Preparo dos extratos.

Para o extrato etanólico, o material foi triturado com etanol por maceração na proporção de 1 kg de folha em pó para 10 L de solvente durante sete dias e depois foi filtrado. O resíduo foi reextraído com etanol mais cinco vezes seguindo o mesmo procedimento. O extrato etanólico resultante da folha da Garcinia gardneriana foi concentrado sob pressão reduzida a 37 °C e liofilizado. Para o extrato aquoso, o material triturado com água destilada por maceração na proporção de 1 kg de folha em pó para 1L de solvente durante um dia e filtrado. O extrato aquoso resultante da folha da *Garcinia gardneriana* foi concentrado sob pressão reduzida a 37 °C e liofilizado.

4.3 Experimento.

O presente estudo foi aprovado pela Comissão de Ética no uso de Animais/ CEUA da Universidade Federal de Mato Grosso do Sul, registrado com o nº 1.050/2019. Foram utilizados 130 camundongos machos Swiss da linhagem Mus Musculus, adultos, com 60 dias de vida. Os camundongos foram alojados em gaiolas coletivas na sala de experimentação animal do Biotério da Universidade Federal de Mato Grosso do Sul, no qual as condições ambientais foram

controladas a fim de manter a temperatura em 22 ± 2 °C, umidade relativa do ar 50-60% e ciclo claro/escuro de 12 horas. Os animais experimentais foram divididos em 6 grupos de acordo com a ração e tratamento recebido via gavagem: 1) Grupo controle com dieta padrão (Nuvital®) 2) Grupo controle (AIN-93M); 3) Grupo High Fat (HF); 4) Grupo dieta hiperlipídica + Extrato Aquoso da folha da *Garcinia gardneriana* 200mg/kg (HFAQ200); 5) Grupo dieta hiperlipídica + Extrato Aquoso da folha da Garcinia gardneriana 400 mg/kg (HFAQ400); 6) Grupo dieta hiperlipídica + Extrato Etanólico da folha da Garcinia gardneriana 200 mg/kg (HFET200); 7) Grupo dieta hiperlipídica + Extrato Etanólico da folha da Garcinia gardneriana 400 mg/kg (HFET400) (n= 20 em cada grupo), sendo a composição das rações descritas na tabela 1.

Os grupos 1 (Nuvital), grupo 2 (AIN-93M) e grupo 3 (HF) foram mantidos nas mesmas condições alimentares, não receberam os extratos das plantas e foram submetidos ao mesmo estresse, com a oferta de água no mesmo volume que os extratos. Os demais grupos foram tratados com os extratos da Garcinia, 4) HF AQ 200 (dieta hiperlipídica + extrato aquoso 200mg/kg); 5) HF AQ 400 (dieta hiperlipídica + extrato aquoso 400 mg/kg); 6) HF ET 200 (dieta hiperlipídica + extrato etanólico 200mg/kg); 7) HF ET 400 (dieta hiperlipídica + extrato etanólico 400 mg/kg) e acompanhados por 8 semanas de estudo (Figura 1). Após o período estudado, os animais foram submetidos a eutanásia com dose excessiva do anestésico isoflurano seguido de exsanguinação pela veia cava inferior.

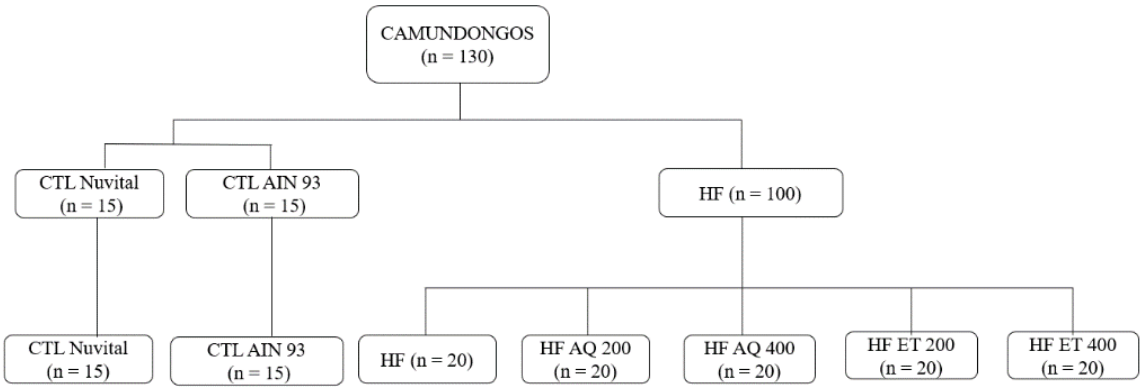

Figura 1. Distribuição de animais nos grupos estudados. 1) Grupo controle com dieta padrão (Nuvital®) 2) Grupo controle (AIN-93M); 3) Grupo High Fat (HF); 4) Grupo dieta hiperlipídica +

Extrato Aquoso da folha da Garcinia gardneriana 200 mg/kg (HFAQ200); 5) Grupo dieta hiperlipídica + Extrato Aquoso da folha da Garcinia gardneriana 400mg/kg (HFAQ400); 6) Grupo dieta hiperlip-ídica + Extrato Etanólico da folha da Garcinia gardneriana 200 mg/kg (HFET200); 7) Grupo dieta hiperlipídica + Extrato Etanólico da folha da *Garcinia gardneriana* 400 mg/kg (HFET400).

Tabela 1. Composição das dietas experimentais (g/kg ração).

	AIN-93M	**Nuvital®**	**Hiperlipídica**
Ingredientes (g/kg)			
Amido	620,692	725,67	320,692
Caseína (≥85% de proteína)	140,00	40,00	140,00
DL-metionina	-	100,00	
Banha de porco	-	-	320,00
Açúcar	100,00	-	100,00
Óleo de soja	40,00	40,00	20,00
Celulose	50,00	100,00	50,00
Mix minerais**	35,00	35,00	35,00
Mix vitaminas*	10,00	10,00	10,00
L-cistina	1,80	1,80	1,80
Bitartarato de colina	2,50	2,50	2,50
Tertbutil hidroquinona	0,008	0,008	0,008
Energia (kcal/kg)	3.802,80	4.360,00	5.302,80
Carboidratos (%)	75,81%	75,75%	31,73%
Proteínas (%)	14,73%	16,00%	10,56%

Lipídeos (%)	9,47%	8,25%	57,71%
Calorias/g dieta	3,80	4,36	5,30

*Vitaminas e **Minerais presentes no mix de acordo com a ração padronizada AIN-93M.

4.4 Ingestão Alimentar/Consumo de Ração.

Cada grupo teve acesso ad libitum a água e comida durante o período experimental. O controle da ingestão de ração foi monitorado semanalmente. Considerando a diferença em gramas entre a quantidade ofertada e a quantidade restante (por animal).

4.5 Ganho de Peso.

A avaliação do peso corporal dos animais foi verificada semanalmente em balança semi-analítica (Bel®).

4.6 Avaliação da Gordura Corporal.

Após a eutanásia, os sítios de gorduras (epididimal, mesentérica, omental, perrirenal, retroperitonial) de cada animal foram totalmente removidos e pesados em balança analítica.

4.7 Histologia do Fígado.

Após a retirada, o fígado foi banhado em solução fisiológica para extração de sangue acumulado e, em seguida, fragmentos do lobo maior foram colo-cados em grades histológicas para fixação. As amostras foram fixadas em solução de formalina a 10% por 12 horas e depois mantidas em álcool 70% até o processamento his-tológico. Após a fixação, os espécimes foram desidratados em baterias de álcool e xilol, incluídos em parafina, cortados em micrótomo com espessura de 5 mm cada e corados com hematoxilina-eosina (HE). A esteatose hepática foi graduada quanto à intensidade.

4.8 Análises Séricas.

Para a realização das análises séricas, o sangue de todos os ani-mais foi coletado ao final do período experimental e obtido o soro. As amostras de soro dos animais foram utilizadas para a determinação dos seguintes parâmetros: glicemia de jejum, triglicerídeos, colesterol total e frações (HDL-c, LDL-c, VLDL-c). Foram avaliadas por kits colorimétricos (Labtest Diagnostics SA™).

4.9 Teste de tolerância oral à glicose (OGTT)

Foram determinados 5 dias antes de fina-lizar o experimento. Os animais dos grupos estudados, após 12 h de jejum, foram pesados, e após foi verificada a glicemia de jejum via caudal (tempo 0), com o uso de um glicosímetro. Em seguida os animais receberam glicose via gavagem na concentração de 2 g/kg de peso corporal. A glicemia foi verificada aos 15, 30, 60 e 120 min após a aplicação da glicose.

4.10 Teste de sensibilidade à insulina (IPITT).

Foram determinados 5 dias antes de finalizar o experimento. Para o ipITT os animais dos grupos em estudo, no estado alimentado, foram pesados e, em seguida, foi verificada a glicemia no estado alimentado (tempo 0). Após, foi aplicado 1,5 U/kg de insulina (NovoRapid®) via intraperitoneal, e a glicemia verificada nos tempos 0, 15, 30 e 60 minutos, conforme Lenquiste *et al*., 2012.

4.11 Concentração de adipocinas: IL-10 e MCP-1.

A concentração de adipocinas IL-10 e MCP-1 foi mensurada utilizando kit comercial MADKMAG-71K®, Merck Sigma-Aldrich. Para tanto foi separado soro a partir da centrifugação. Em seguida 10 µL do soro de cada animal foram distribuídos e acondicionados em uma placa com 96 poços juntamente com 10 µL de solução Assay buffer e 25 µL de solução contendo duas adipocinas. Foram preparados os parâmetros brancos, padrão e controle conforme instruções do fabricante (Milliplex® MAP kit, USA). Após, foi realizada a leitura da placa no Luminex® pelo soft-ware MAGPIX® e obtidos valores de concentrações em µg/mL.

4.12 Análise dos dados.

A análise estatística foi realizada com os softwares Jandel Sigma Stat®, versão 3.5 (Sys-tal software, Inc., EUA) e Sigma Plot, versão 12.5 (Systat Software Inc., EUA) e apresentados como média ± erro padrão da média. Os grupos foram comparados entre si por meio da análise de variância (ANOVA), seguido pelo pós-teste de Tukey. Os valores foram considerados significativos quando $p < 0,05$.

5. RESULTADOS E DISCUSSÃO

5.1 ARTIGO 1

Objetivo: Realizar o levantamento de compostos bioativos presentes nas espécies do gênero Garcinia;

*Artigo publicado na Revista *Molecules* no dia 01 de outubro de 2020.

Review

Medicinal Potential of *Garcinia* Species and Their Compounds

Bruna Larissa Spontoni do Espirito Santo [1], Lidiani Figueiredo Santana [1], Wilson Hino Kato Junior [2], Felipe de Oliveira de Araújo [3], Danielle Bogo [1], Karine de Cássia Freitas [1,*], Rita de Cássia Avellaneda Guimarães[1], Priscila Aiko Hiane[1], Arnildo Pott [4], Wander Fernando de Oliveira Filiú[5], Marcel Arakaki Asato[6], Patrícia de Oliveira Figueiredo[7] and Paulo Roberto Haidamus de Oliveira Bastos [1]

1 Graduate Program in Health and Development in the Central-West Region of Brazil, Federal University of Mato Grosso do Sul-UFMS, 79079-900 Campo Grande, Brazil; bruna.spontoni@gmail.com (B.L.S.d.E.S.); lidi_lfs@hotmail.com (L.F.S.); daniellebogo@hotmail.com (D.B.); rita.guimaraes@ufms.br (R.d.C.A.G.); priscila.hiane@ufms.br (P.A.H.); phaidamus43@gmail.com (P.R.H.d.O.B.)

2 Graduate of Pharmaceutical Sciences, Federal University of Mato Grosso do Sul-UFMS, 79079-900 Campo Grande, Brazil; hinokato@gmail.com (W.H.K.J)

3 Graduate of Electrical Engineering, Federal University of Mato Grosso do Sul-UFMS, 79079-900 Campo Grande, Brazil; felipe@nexsolar.com.br (F.d.O.A.)

4 Laboratory of Botany, Institute of Biosciences, Federal University of Mato Grosso do Sul, 79070-900 Campo Grande, Mato Grosso do Sul, Brazil; arnildo.pott@gmail.com (A.P.)

5 Faculty of Pharmaceutical Sciences, Food and Nutrition, Federal University of Mato Grosso do Sul-UFMS, 79079-900 Campo Grande, Brazil; wander.filiu@gmail.com (W.F.d.O.F.)

6 Medical School, Federal University of Mato Grosso do Sul, 79070-900 Campo Grande, Brazil; marcel_arakakiasato@hotmail.com (M.A.A.)

7 Laboratory PRONABio (Bioactive Natural Products)-Chemistry Institute, Federal University of Mato Grosso do Sul-UFMS, 79079-900 Campo Grande, Brazil; patricia.figueiredo@ufms.br (P.d.O.F.)

* Correspondence: kcfreitas@gmail.com; Tel.: +55-67-3345-7416

Academic Editor: Derek J. McPhee

Received: 7 July 2020; Accepted: 30 July 2020; Published: date

Abstract: *Garcinia* is a genus of Clusiaceae, distributed throughout tropical Asia, Africa, New Caledonia, Polynesia, and Brazil. *Garcinia* plants contain a broad range of biologically active metabolites which, in the last few decades, have received considerable attention due to the chemical compositions of their extracts, with compounds which have been shown to have beneficial effects in several diseases. Our work had the objective of reviewing the benefits of five *Garcinia* species (*G. brasiliensis*, *G. gardneriana*, *G. pedunculata*, *G. cambogia*, and *G. mangstana*). These species provide a rich natural source of bioactive compounds with relevant therapeutic properties and anti-inflammatory effects, such as for the treatment of skin disorders, wounds, pain, and infections, having demonstrated antinociceptive, antioxidant, antitumoral, antifungal, anticancer, antihistaminic, antiulcerogenic, antimicrobial, antiviral, vasodilator, hypolipidemic, hepatoprotective, nephroprotective, and cardioprotective properties. This demonstrates the relevance of the genus as a rich source of compounds with valuable therapeutic properties, with potential use in the prevention and treatment of nontransmissible chronic diseases.

Keywords: Clusiaceae; phytochemical compounds; therapeutic effects

1. Introduction

Research into medicinal plants can provide essential knowledge about drugs from plants and for the production of phytotherapeutic agents. Understanding the chemical compositions of herbs is a necessary step in obtaining standards for their quality specifications, using both analytical and phytochemical determinations. Thus, materials destined for medicinal purposes must be submitted to a protocol of evaluation for their quality standards, applying all possible means of botanical and chemical analyses before commercialization [1].

The nutraceutical properties of medicinal plants can be determined by their carbohydrates, proteins, vitamins, minerals, and metabolites, such as flavonoids and antioxidants. Secondary metabolites, such as phenols and flavonoids, also contribute considerably to their medicinal functions. Fruits also have medicinal properties, their most relevant secondary metabolites being phenols and flavonoids [2].

Among medicinal plants, the former family *Guttiferae*, comprising circa 140 genera and 1200 species [3] (which was split into various families), and *Clusiaceae*, with 14 genera and 600 species, stand out. *Garcinia* (=*Rheedia*) is a plant genus of *Clusiaceae*, distributed throughout tropical Asia, Africa, New Caledonia, Polynesia, and Brazil. Species of *Garcinia* are rich and valuable sources of bioactive compounds with relevant therapeutic properties, such as anti-inflammatory and analgesic properties [4–9]. A great variety of compounds, mainly polyisoprenylated benzophenones, flavonoids, and xanthones have been isolated from *Clusiaceae* species. Thus, species of the genus *Garcinia* have proved to be rich sources of compounds with relevant therapeutical properties [7,8,10,11]. *Garcinia* species are rich in secondary metabolites, such as prenylated and oxygenated xanthones [11] with biological activities such as antifungal [12], anti-inflammatory [13], antitumoral [14], antioxidant [15,16], Human Immunodeficiency Virus (HIV)-inhibitory [7], and antilipidemic properties [14,17].

The genus *Garcinia* contains a broad range of biologically active metabolites, and these, in the last few decades, has received considerable attention for the chemical composition of their extracts, being rich in derivates of polyisoprenylated benzophenones, polyphenols, bioflavonoids, and xanthones [18–20].

In traditional medicine, the fruits of *Garcinia* have been utilized in infusions for treating wounds, ulcers, and dysentery [20]. Extracts of the pericarp, epicarp, and seeds of *Garcinia* have demonstrated antioxidant, anti-inflammatory, leishmanicidal, and antiprotozoal activities [21–23]. Another study also reported the presence of the bioflavonoids volkensiflavone, fukugetin [24], and prenylated xanthones [25]. These compounds have been associated with biological activities such as free-radical scavenging, antiulcer effects [26], cytotoxicity, inhibition of nitric oxide synthase [27], chemoprevention of cancer [28], induction of apoptosis [29], anti-HIV [30], and trypanocidal effects [31].

Some metabolites isolated from the genus *Garcinia* have already shown anticancer activities. Garcinol, a polyisoprenylated benzophenone obtained from *Garcinia*, was evaluated in vitro and in vivo, and induced apoptosis and arrest of the cellular cycle, inhibition of angiogenesis, and modulation of the gene expression of carcinogenic cells [32]. Xanthones found in *Garcinia* species have demonstrated effects against human cervical cancer, lung cancer cells, and hepatocellular carcinomas [33,34].

Some biflavonoids derived from *Garcinia* have also been evaluated for various activities, including chemoprevention properties. Among these, kolaviron has been pointed out, which presents the capacity to eliminate free radicals, inhibit proteins related to the stress response, and interfere with the DNA-binding activities of some transcription factors [35], as well as showing inhibitory activity against aromatase [36], the enzyme which catalyses the final step of the biosynthesis of estrogen, considered a key target for the development of drugs against estrogen-dependent breast cancers [37].

Given the presence of various compounds with several functions in these organisms, our work had the objective of reviewing the benefits presented by five species of *Garcinia* (*G. brasiliensis*, *G. gardneriana*, *G. pedunculata*,*G. cambogia,* and *G. mangstana*).

2. *Garcinia* Species and Bioactive Compounds

2.1. Garcinia Brasiliensis

Garcinia brasiliensis Mart. (*Rheedia brasiliensis* (Mart.) Planch. & Triana) is a species native to the Amazonian region, which is cultivated all over Brazil and which is commonly known as “bacuri”, “bacupari”, “porocó”, “bacuripari”, and, in Bolivia, “guapomo”. This tree has yellow fruit with mucilaginous, white, and edible sour-sweet pulp, which is utilized by the local people for its anti-inflammatory [22,38], antinociceptive [22], antioxidant, and

antitumoral [39] properties. In some countries, such as Thailand, Sri Lanka, Malasia, the Philipines, and India, the ripe fruits are used in traditional medicine to treat abdominal pain, diarrhea, dysentery, infected wounds, suppuration, and chronic ulcers [11].

Some compounds found in the fruit peel are oxygenated sesquiterpenes—volatile oils obtained by hydrodistillation—presenting γ-muurolene (**1**; 10.3%), spathulenol (**2**; 8.7%), δ-cadinene (**3**; 8.3%), torreiol (**4**; 8.0%), α-cadinol (**5**; 7.0%), cadalene (**6**; 6.3%), and γ-cadinene (**7**; 5.3%) [31]. When tested, the essential oil presented anti-inflammatory activity at a dose of 100 mg/kg [22,31].

The ethanolic extract of *G. brasiliensis* leaves at concentrations of 30 and 300 mg/kg demonstrated anti-inflammatory action in rats and antinociceptive action in mice, corroborating the traditional use of species of *Garcinia* against inflammation of the urinary tract and inflammatory pains such as arthrosis. The biflavonoids procyanidin (**8**), fukugetin (**9**), amentoflavone (**10**), and podocarpusflavone A (**11**), isolated from *G. brasiliensis*, represent a therapeutic strategy to control diseases related to oxidative stress, controlling inflammation and reducing the harmful effects of reactive species of oxygen (ROSs). Furthermore, biflavonoids have exhibited potent inhibition of the oxidative hemolysis and lipidic peroxidation induced by 2,2′-azobis amidinopropane (AAPH) in human erythrocytes, demonstrating the anti-inflammatory and antioxidant properties of the compounds present in *G. brasiliensis* [40].

Another effect presented by the species is leishmanicidal activity [21,41]. The leishmanicidal activities of the hexane extract and ethyland ethanolic acetate at 5.0 mg/mL were evaluated, as well as those of molecules obtained from the extraction of the pericarp of *G. brasiliensis* in an in vitro model. The hexane extract presented the best activity on extracellular (promastigote) and intracellular (amastigote) forms of *Leishmania* (*L.*) *amazonensis*, compared with other extracts. Following those results, fractions of the most efficient extract were made, resulting in three purified prenylated benzophenones, 7-epi-clusianone (**12**), garciniaphenone (**13**), and guttiferone-a (**14**) [21,42]. These results suggested that the hexane extract and the polyprenylated benzophenones isolated from *G. brasiliensis* have relevant leishmanicidal activities and provide potential compounds for the development of new drugs against leishmaniasis. The compound found in the extract, morelloflavone-7,4′,7″,3‴,4⁗-penta-*O*-acetyl (**15**), was prepared by acylation and alkylation reactions from the compound morelloflavone isolated from the ethyl acetate extract of *G. brasiliensis* fruits, which demonstrated leishmanicidal, antiproteolytic, and antioxidant activities, as well as low cytotoxicity in in vitro models, at a concentration of 400 μg/mL [41].

The compound 7-epiclusianone (**12**) found in the pericarp of *G. brasiliensis* fruits exhibited biological activity in vitro against trypomastigotes of *Trypanosoma cruzi* [9], and a potent vasodilatory effect on the endothelium [42]; antianaphylactic [43], anti-HIV [29], antimicrobial [5,44–46], antispasmodic [39], antiproliferative [45], and leishmanicidal activities, have also been attributed to this benzophenone [21].

A study evaluated the analgesic and anti-inflammatory effects of benzophenone 7-epiclusianone extracted from the epicarp of *G. brasiliensis* using experimental models of rats and mice [22]. In the test, benzophenone 7-epiclusianone (**12**) exerted an anti-inflammatory effect, which was verified through the reduction of mouse paw edema induced by carrageenin and the inhibition of recruitment of leucocytes to the peritoneal cavity, as well as the nociception induced by intraperitoneal injection of acetic acid. The substances associated with the extract components were capable of absorbing ultraviolet-B (UVB) radiation, preventing the induced inflammatory process. The absorption of UVB radiation by components of the ethanolic extract could impede the installation of oxidative stress and, consequently, lipidic peroxidation, antioxidant capacity, and removal of free radicals, contributing to a photoprotective effect [47].

Treatment with 7-epiclusianone (**12**) altered the cell-cycle progression; furthermore, the capacity to form cell colonies was significantly reduced, demonstrating long-term effects. This demonstrated that 7-epiclusianone (**12**) is a relevant natural benzophenone with antineoplastic activity in a model of glioblastoma—a tumor with chemoresistance, demonstrating influence on growing cells, cell-cycle dynamics, apoptosis, and ability to form colonies [48]. The 7-epiclusianone (**12**) was isolated from *G. brasiliensis* for the treatment of schistosomiasis, showing efficacy against *Schistosoma mansoni* adult worms, cercariae, and schistosomula in vitro [49].

Administration of the ethanolic extract to rats at a concentration of 300 mg/kg produced an increased antioxidant activity through the reduction of inflammation and adiposity in obese rats. The antiobesity effect of the treated group was related to the negative regulation of the lipogenic gene of the lipoprotein lipase (LPL), the proteins of Tumor Necrosis Factor Alpha (TNF-α) and Interleukin 1 (IL-1), diminishing adipogenesis, adipocyte size, and body weight, when compared with the control group [50].

The following components have been isolated from the epicarp of *G. brasiliensis* fruit: a new glycosylated biflavonone, morelloflavone-4‴-*O*-β-D-glycosyl (**16**), and the known compounds 1,3,6,7-tetrahydroxyxanthone (norathyriol; **17**), morelloflavone (fukugetin; **9**), and morelloflavone-7″-*O*-β-D-glycosyl (fukugesid; **18**). These compounds presented antioxidant activity after the isolation of natural biflavonoids from the plant [41].

The ethanolic extract of *G. brasiliensis*,at a concentration of 300 mg/kg, reduced oxidative stress and inflammation in obese rats with cardiac insufficiency, and presented a promising strategy for beneficial microbiota modulation. That demonstrates the potential protective effects of two phenolic compounds, morelloflavone and 7-epiclusianone (**12**), present in the extract [51].

It is worth noting the method of extraction of the bioactive compounds. The use of the solvent N-hexane has demonstrated to be the most adequate for extracting guttiferone A and/or 7-epiclusianone, whereas the highest levels of fukugetin and norathyriol (**17**) were detected in the ethyl acetate fraction [37]. Table 1 and Figure 1 summarize the main compounds, plant part from which they were extracted, and their related activities.

Table 1. Compounds present in different parts of *Garcinia brasiliensis* and their related activities.

Garcinia Brasiliensis		
Sesquiterpenes		
Compounds	**Plant Part**	**Activity**
α-Ylangene; α-Copaene; β-Bourbonene; β-Elemene; β-Caryophyllene; β-Gurjunene; Aromadendrene; α-Humulene; Drima-7,9(**11**)-diene; y-Muurolene-10; Germacrene D; β-Selinene; Viridiflorene; α-Muurolene; γ-Cadinene; cis-Calamenene; Cadina-1,4-diene; α-Cadinene; α-Calacorene; Longicamphenylone; Ledol; Spathulenol; Globulol; Salvial-4(**14**)-en-1-one; Guaiol; Viridiflorol; Humuleneepoxide II; 1,10-Diepicubenol; 1-Epicubenol; Cubenol; Cedr-8(**15**)-en-9a–ol; Torreyol; Selin-11-en-4a-ol; α-Cadinol; Khusinol; Cadalene; 14-Oxy-α-muurolene.	Peel [31]	Anti-inflammatory and antioxidant [21] (correlation of all compounds)
Biflavonoids		
Compound	**Plant Part**	**Activity**
Fukugetin	Fruit [43]	Analgesic [52], antioxidant [43]
Fukugiside	Fruit [43]	Analgesic [52], antioxidant [12]
morelloflavone-4‴-*O*-β-D-glycoside	Fruit [43]	Antioxidant [12]
Amentoflavone	Leaf [41]	Anti-inflammatory and antioxidant [41]
Podocarpusflavone A	Leaf [41]	Anti-inflammatory and antioxidant [41]
Benzophenones		
Compound	**Plant Part**	**Activity**
Garcinol	Leaf [41]	Anti-inflammatory and antioxidant [41], anticancer, antiparasitic, action in nervous system [24]

7-epiclusianone	Leaf [22]/Fruit [47]	Antinociceptive and anti-inflamatory [22], antimicrobial [47], anticarcinogenic [49], leishmanicidal [21], schistosomicidal [50]
Organic Acid		
Compound	**Plant Part**	**Activity**
Galic acid	Leaf [41]	Anti-inflammatory and antioxidant [41]
Flavonoid		
Compound	**Plant Part**	**Activity**
Procyanidine	Leaf [41]	Anti-inflammatory and antioxidant [41]
Xanthones		
Compound	**Plant Part**	**Activity**
Guttiferone-A	Seeds [47]/Fruits [21]	Antimicrobial [47], photoprotective, and photochemopreventive [20] Leishmanicidal [21]
1,3,6,7-tetrahydroxyxanthone	Fruit [43]	Antioxidant [43]

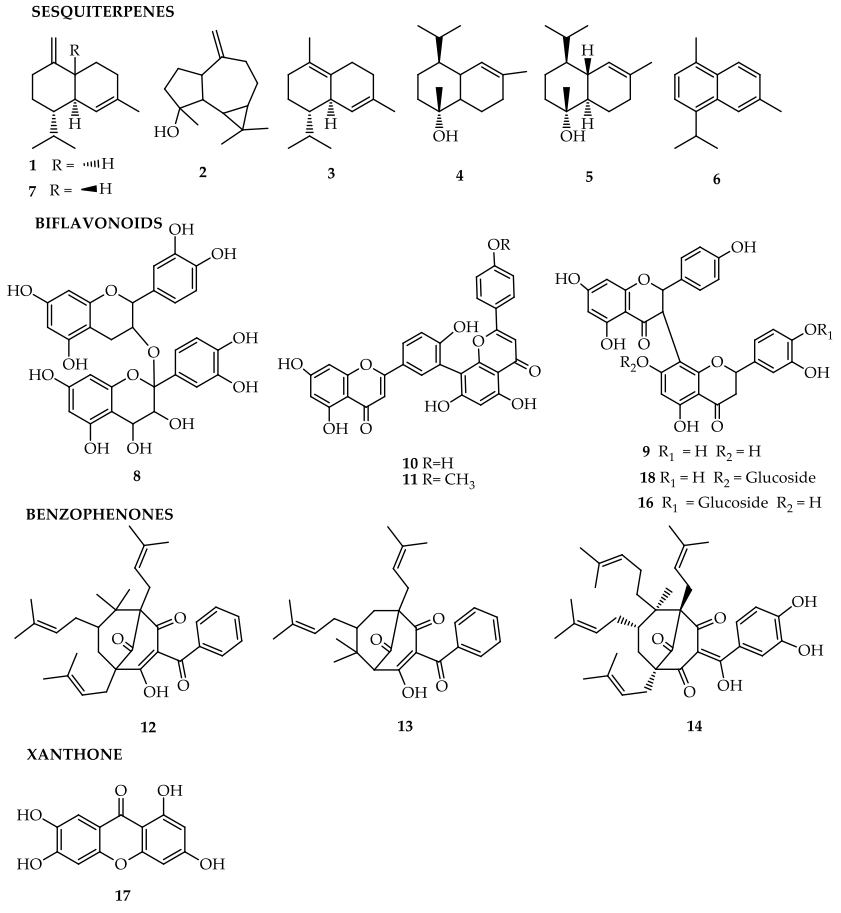

Figure 1. Bioactive compounds of *Garcinia brasiliensis.*

2.2. Garcinia gardneriana

Garcinia gardneriana (Planch. & Triana) Zappi (*Rheedia gardneriana* Planch. & Triana) (*Clusiaceae*) is native to the Atlantic forest and grows throughout Brazil. It is an easily cultivated fruit tree which is often found in domestic orchards. It is regionally known as "bacupari", "bacopari", "bacopari-miúdo", or "mangostão-amarelo" [53]. The fruit is initially dark green, becoming yellowish-green or yellow-orangish when ripe. The fruit peel (or epicarp) is smooth and coriaceous. The pulp is white, edible, and sour-sweetish, formed by the mesocarp and endocarp [52,54]. A study on its fruits identified two phytosterols—sitosterol and stigmasterol—which have already presented anti-inflammatory and anticancer activities in other studies, with the isolation of these compounds achieved in fruits of the genus *Garcinia* [37,52]. Furthermore, four sesquiterpenes—α-copaene (**19**), α-muurolene (**20**), γ-cadinene (**7**), and cadinene (**21**)—were identified in the fruit peel, besides triterpene oleanolic acid (**22**) [52].

The plant has generally been applied for several purposes in folk medicine, such as inflammatory problems including skin disorders and wounds, as well as for the treatment of pain and infections [38]. The leaves, bark, and roots are the most utilized parts, typically prepared as infusions, decoctions, or macerates, either separately or combined with other natural products [38].

Evaluation of a hydroalcoholic extract of *G. gardneriana* revealed that it diminished the quantity of melanin in B16F10 melanoma cells and, specifically, promoted the inhibition of tyrosinase activity [55]. The ethanolic extract conferred an additional beneficial effect to the skin as the plant has a high content of bioflavonoids, which are considered to be able to reduce the potential oxidative damage produced in the skin after exposure to ultraviolet radiation [56]. *G. gardneriana* presented a potential source of bioactive compounds with a significant antiproliferative effect in breast neoplastic lines in animals [57].

Garcinia gardneriana is very rich in secondary metabolites.Some phytochemical analyses have identified xanthones, steroids, triterpenes, and flavonoids in different parts of the plant [14,41–43], which have been associated with pharmacological effects such as anti-inflammatory, antinociceptive, antibacterial, and antiparasitic activities [38,58–60].

Phytochemical analyses of *G. gardneriana* detected several classes of compounds, such as steroids, triterpenes, biflavonoids, and xanthones [61]. Several biflavonoids found and identified as volkensiflavone (**23**), 13-naringenin-II 8-eriodictyol (GB-2a; **24**), fukugetin (or morelloflavone; **9**), and fukugesid (**18**) have demonstrated analgesic effects [62]. A new biflavonoid isolated from *G. gardneriana* leaves, named GB2a-OMe (**25**), also presented a significant analgesic effect in the formalin test in mice in the neurogenic and inflammatory phases [63].

The compound GB-2a significantly inhibited the melanin content without reducing cell viability, suggesting its great potential for medical use as a hypopigmentation agent, for cosmetic and clinical applications related to skin clearing [64]. The compound fukugetin (or morelloflavone) showed an anti-inflammatory activity in mouse paw edema induced by carrageenin at a concentration of 300 mg/kg, rendering the plant a potential target for the development of new compounds to be explored as alternatives to drugs with anti-inflammatory activity that are already in use [65].

The biflavonoids isolated from *G. gardneriana*, such as morelloflavone (**9**), Gb-2a (**24**), and Gb-2a-7-*O*-glucose (**26**) were submitted to an in vitro trial in order to evaluate their modulatory effects on aromatase, utilized for cancer treatment. The results showed that all biflavonoids were able to inhibit the enzyme, with IC_{50} values varying from 1.35 to 7.67 μM. This demonstrates that these biflavonoids are a relevant source of new aromatase inhibitors, with focus on the development of new anticancer agents. This reinforces that the species is an important source of bioactive compounds, with applications concentrated mainly in the treatment of estrogen-dependent breast cancers [65]. Table 2 and Figure 2 summarize the main compounds of *Garcinia gardneriana*, the plant parts from which they were extracted, and their related activities.

Table 2. List of compounds presented in different parts of *Garcinia gardneriana* and related activities.

Garcinia gardneriana		
Biflavonoids		
Compound	**Plant Part**	**Activity**
GB-2a	Leaf [64],	Antiedematogenic [64], anti-inflammatory [64],

	branches [59]	anticancer [65]
Gb-2a-7-*O*-glucoside	Branches [59]	Anticancer [65]
Volkensiflavone	Leaf [52]	Analgesic [52]
Fukugentin	Leaf [52]	Analgesic [52], anti-inflammatory [59], antioxidant [43]
Fukugiside	Leaf [52]	Analgesic [52], antioxidant [52]
GB-2a-II-4′-OMe	Leaf [52]	Analgesic [52]
Flavonoid		
Compound	**Plant Part**	**Activity**
Epicatechin	Leaf [58]	Antibacterial [58]
Phytosterols		
Compound	**Plant Part**	**Activity**
Sitosterol	Fruits [52]	Anti-inflammatory and anticancer [31]
stigmasterol	Fruits [52]	Anti-inflammatory and anticancer [31]
Benzophenones		
Compound	**Plant Part**	**Activity**
7-epiclusanone	Peel [52]	Antinociceptive and anti-inflammatory [22], antimicrobial [47], anticarcinogenic [49], leishmanicidal [21], schistossomicidal [50]
Sesquiterpenes		
Compound	**Plant Part**	**Activity**
α-copene	Peel [52]	-
α-muurolene	Peel [52]	-
γ-cadinene	Peel [52]	-
Cadinene	Peel [52]	-
Triterpene		
Compound	**Plant Part**	**Activity**
Oleanolic acid	Peel [52]	-

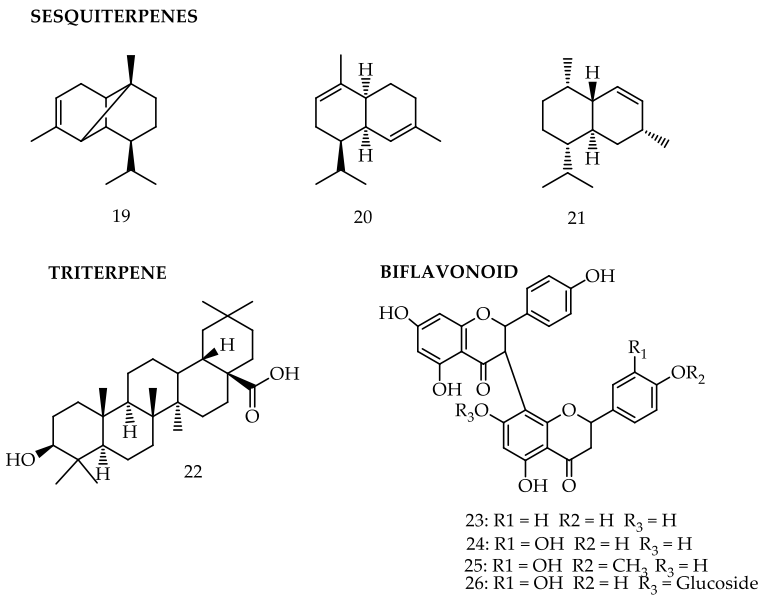

Figure 2. Bioactive compounds of *Garcinia gardneriana.*

2.3. Garcinia Pedunculata

Garcinia pedunculata Roxb. (*Clusiaceae*) is a tree endemic to some Asian regions—namely to parts of Myanmar and oriental parts of India. The fruit is known as "taikor" in Bangladesh and "amlavetasa" in India [66]. It also is an indigenous medicinal plant. Traditionally, the fruit has been utilized by people to treat several gastrointestinal disorders [67], as a cardiotonic, and as an emollient. It is also utilized in the treatment of asthma, cough, bronchitis, diarrhea, and fever [68].

The fruit is greenish-yellow and is utilized as an ingredient in several meat dishes as a culinary adstringent [69]. The fruit of *G. pedunculata* contains 7.93% carbohydrates, 0.95% reducing sugars, 4.93% total proteins, and 0.20% total fats. Regarding the composition of vitamins and minerals, it has 2.48 mg/100 g sodium, 27.3 mg/100 g potassium, 13.21 mg/100 g calcium, 35.43 mg/100 g magnesium, 10.12 mg/100 g iron, 4.32 mg/100 g phosphorus, 49 μg/100 g thiamine, 276 μg/100 g riboflavin, 47 μg/100 g niacin, 35.43 μg/100 g ascorbic acid, and 8.12 μg/100g vitamin B12 [2].

Phytochemical studies have shown that the dry fruits contain hydroxylcitric acid, benzophenones, garcinol, pedunculol, and isogarcinol (cambogin), the first having been reported as possessing antioxidant activity [16], and the second and third with anticancer, anti-inflammatory, and antiparasitic activities [24,70]. Dry fruits have been selected for different actions and have shown anti-inflammatory, hepatoprotective, cardioprotective, and antioxidant pharmacological activities in vitro [71,72]. Phytochemical analyses have revealed the presence of phytochemicals such as pedunculol (**27**), garcinol (**28**), cambogin (**29**) [73], and (α)-hydroxylcitric acid (**30**) [70]. Hexane and chloroform extracts of *Garcinia pedunculata* showed antioxidant activity, helping in the elimination of free radicals and showing strong antimutagenicity, the hexane extract being more reactive than that of the chloroform extract [73].

Among the reported benefits of *G. pedunculata* fruit are antioxidant [70–75], antimicrobial [76], anti-inflammatory [71], hypolipidemic [77], hepatoprotective [66], and nephroprotective effects [71], as well as cardioprotective properties [77]. The peel and the pericarp of dry fruits have been shown to contain benzophenones, pedunculol (**27**), garcinol (**28**), cambogin (**29**), and hydroxycitric acid (HCA; **30**) [70], some of which are potent antioxidants. Some

research has suggested that benzophenones and garcinol present protective effects against the toxicity of carbon tetrachloride in hepatocytes of rats [70] and anti-inflammatory effects in hepatocytes of mice [78]. An ethanolic extract of the fruit showed significant hepatoprotective, cardioprotective, and hypoglycemic activities in the treatment of Long Evans rats with a daily dose of 1000 mg/kg for 21 days [79]. The nephroprotective effect detected with the administration of a water extract of the fruit peel at concentrations of 200 and 400 mg/kg of weight was attributed to its general cytoprotective effect, which promptly impeded the ischemic damage caused by acute toxicity by cisplatin, a cytotoxic agent that has effects on the kidneys, liver, and neural tissues [80].

Administration of the extract of *G. pedunculata* fruit significantly reduced blood glucose levels, demonstrating the possibility of reduction of hyperglycemia, diabetes, diabetic comorbidities, and protection against damages induced by oxidative stress [81]. Administration of methanolic extract at a concentration of 200 mg/kg attenuated hyperlipidemia and oxidative stress in the studied animals [77]. Evaluation of a methanolic extract of the fruit showed antioxidant activity, having free-radical scavengers and the capacity to protect cells from lipidic peroxidation, which is associated with the treatment of degenerative diseases and diabetes [77,82].

A recent study on an aqueous extract of fruits of *G. pedunculata* given to rats at 200 and 400 mg/kg of body weight observed a significant reduction in damage caused by colitis, preventing oxidative peroxidation. At the dose of 400 mg/kg, the lipidic peroxidation was reverted significantly, and in several parameters of inflammation generated in the colon showed improvement (i.e., the punctuation of macroscopic damage, lipidic peroxidation, and histopathological exam of the colon tissue), demonstrating its therapeutical potential for the treatment of colitis [83].

Analysis of pericarp and peel separately reported a diversity of xanthones in the form of the compounds peduxanthone-D (**31**), -E (**32**), and –F (**33**), standing out in the pericarp [33], which have shown anticancer activity [65]; meanwhile, garbogiol (**34**), present in the peel [33], has been reported as an inhibitor of α-glucosidase [33].

Besides the fruits, a study on the heartwood of the species [19] identified benzophenone2,4,6,3′,5′-pentahydroxybenzophenone (**35**) and the xanthones 1,3,6,7-tetrahydroxyxanthone (**36**) and 1,3,5,7-tetrahydroxyxanthone (**37**) to have antioxidant activity [42] and LDL-c-oxidation-inhibitory activity, respectively; additionally, the biflavonoids GB-1a (**38**) and volkensiflavone (**23**) have shown antioxidant activity [84] and antitumoral activity [74], respectively. Table 3 and Figure 3 summarize the main compounds, the plant parts they have been extracted from, and their related activities.

Table 3. List of compounds present in different parts of *Garcinia pedunculata* and related activities.

Garcinia Pedunculata		
Xanthones		
Compound	**Plant Part**	**Activity**
1,3,6,7-tetrahydroxyxanthone	Heartwood [19]	Antioxidant [43]
1,3,5,7-tetrahydroxyxanthone	Heartwood [19]	Inhibits oxidation of LDL-c [45]
1,5-dihydroxy-3-methoxy-6′,6′-dimethyl-2*H*-pyrano(2′,3′:6,7)-4-(3-methylbut-2-enyl)xanthone	Peel [69]	-
1,5-dihydroxy-3-methoxy-4-(3-methylbut-2-enyl)xanthone	Peel [69]	-
Dulxanthone A	Peel [69]	-
Garbogiol	Peel [69]	Inhibition of α-glucosidade [10]
Pedunxanthone-A	Peel [69]	-
Pedunxanthone-B	Peel [69]	-
Pedunxanthone-C	Peel [69]	-

Pedunxanthone-D	Pericarp [33]	Anticancer [65]
Pedunxanthone-E	Pericarp [33]	Anticancer [65]
Pedunxanthone-F	Pericarp [33]	Anticancer [65]
1,6-dihydroxy-7-methoxy-8-(3-methyl-2-butenyl)-6′,6′-dimethylpyrane-(2′,3′:3,2)-xanthone	Pericarp [33]	-
6-O-demethyloliverixanthone	Pericarp [33]	-
Fuscaxanthone A	Pericarp [33]	Cytotoxic [16]
Cowanin	Pericarp [33]	Antimalarial [65]
Norcowanin	Pericarp [33]	Antiplasmodic [65]
Cowanol	Pericarp [33]	Antimalarial [65]
α-mangostin	Pericarp [33]	-
Mangostanol	Pericarp [33]	-
3-isomangostin	Pericarp [33]	-
1,7-dihydroxyxanthone	Pericarp [33]	-
Benzophenones		
Compound	**Plant Part**	**Activity**
Pedunculol	Dry fruits [70]	Antioxidant [16]
Isogarcinol	Dry fruits [70]	Anticancer, anti-inflammatory, antiparasitic, action in nervous system [24]
Garcinol	Dry fruits [70]	Anticancer, anti-inflammatory, antiparasitic, action in nervous system [24]
2,4,6,3′,5′-pentahydroxybenzophenone	Heartwood [19]	-
Biflavonoids		
Compound	**Plant Part**	**Activity**
GB-1a	Heartwood [19]	Antioxidant [84]
volkensiflavone	Heartwood [19]	Antitumoral [74]
Triterpene		
Compound	**Plant part**	**Activity**
Oleanolic acid	Peel [69]	-

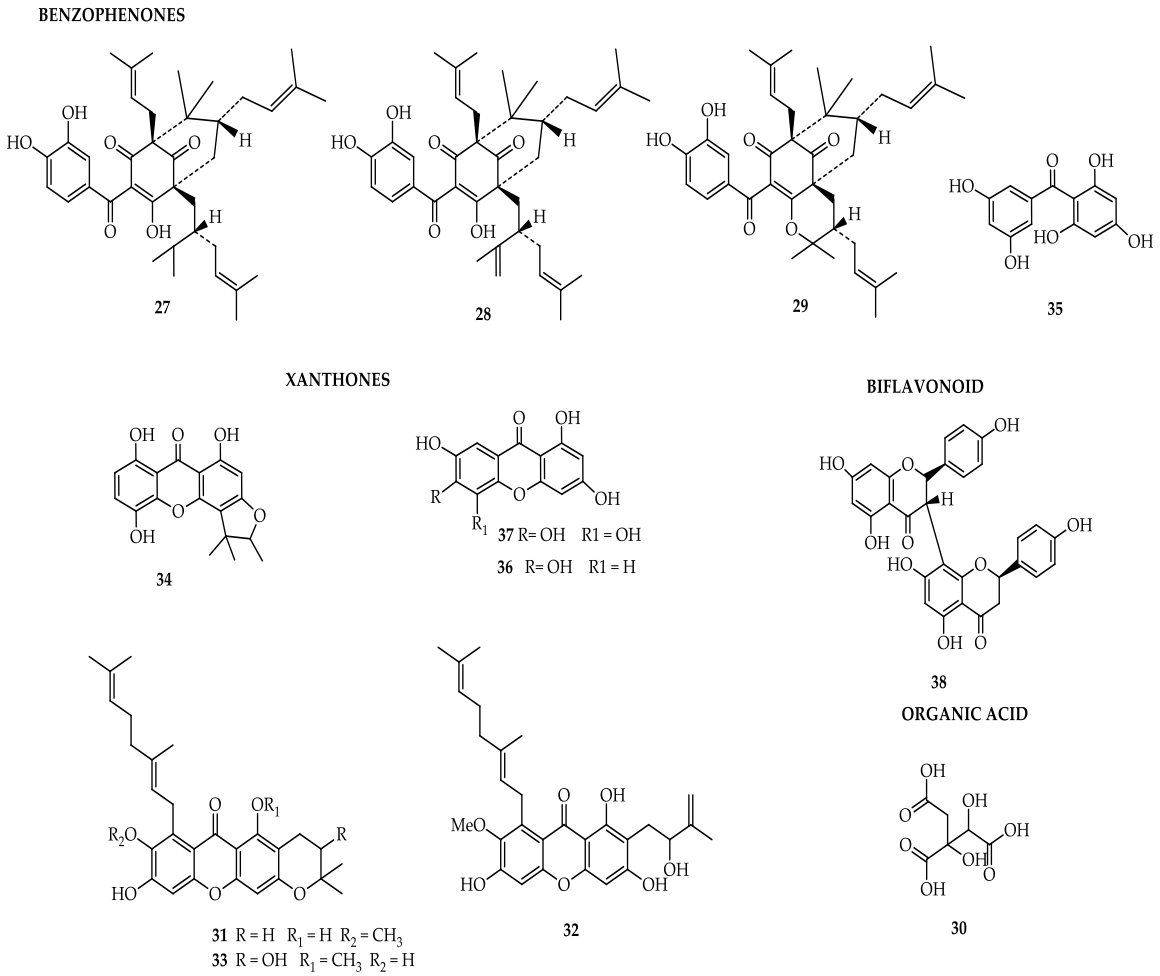

Figure 3. Bioactive compounds of *Garcinia pedunculata*.

2.4. Garcinia Cambogia

Garcinia cambogia L., known as Malabar tamarind, is a plant native to Southeast Asia. The fruit is used as a food preservative, carminative, and flavoring agent [82]. The fruit contains hydroxycitric acid (HCA; **30**) and is a popular ingredient utilized for weight reduction [85,86]. Semwal [85] presented a revision of the species, citing the presence of organic acids, such as HCA, in the fruits, as well as the xanthones oxy-guttiferone-I (**40**), -K (**41**), -K2 (**42**), and -M(**43**), and the benzophenones guttiferone-I (**44**), -J (45), -K (**46**), -N(**47**), and -M (**48**). Guttiferone-K (**46**) and guttiferone-M (**48**) are inhibitors of topoisomerase II [87]. In that same study, the presence of the xanthone garbogiol was reported in the roots. In the peel, the presence of rheediaxanthone-A [86], benzophenonesgarcinol (**28**), and isogarcinol (**29**) was also reported.

In Indian medicine, the extract of *G. cambogia* is used to treat ulcers, hemorrhoids, diarrhea, dysentery, and some types of cancer, such as leukemia [88]. Initial studies on seeds confirmed that they have antifungal [89], anticancer [28,90], antihistaminic [91], antiulcerogenic [92], antimicrobial [93], antiviral [94], and vasodilatory effects [95]. The gastroprotective effects seem to be related to its capacity to diminish acidity and increase the mucosal defenses [92,96]. Furthermore, the extract presented hypolipidemic [95], antiadipogenic, and appetite-suppression effects in experimental animals through the inhibition of the expression of the early adipogenic transcription factor CCAAT enhancer-binding protein alpha (C/EBP alpha), which regulates adipogenesis [97–99].

The hypolipidemic effect of the *G. cambogia* extract has been attributed to its high content of flavonoids [100]. The generated anti-inflammatory effects resulted in the improvement of some parameters analyzed in experimental colitis, where 2,4,6-Trinitrobenzenesulfonic acid (TNBS)/ethanol caused lesions characterized by severe necrosis of the mucosa, hyperemia, and focal adhesion to adjacent organs. Administration of the extract by oral gavage at a dose of 1.0 g/kgreduced the length of the lesions observed macroscopically; thus, it may provide a source to search for new anti-inflammatory compounds useful in the treatment of intestinal inflammatory diseases [101].

Garcinia cambogia showed an antiobesity effect and a significant reduction in the values of triacylglycerol (TAG) of the adipose tissue and liver of the tested groups; however, it significantly increased the TAG pool of the gastrointestinal system [95,102,103]. The plant also reduced the serum levels of total cholesterol, triglycerides, and insulin, as well as the intolerance of glucose and levels of alpha-TNF associated with hyperlipidic diets [95,102–105]. *G. cambogia* extracts have also been shown to trigger the myotubes and skeleton cells to absorb glucose and to equilibrate the glucose levels in the blood [106].

This species also has already shown favorable results in tests in humans—either healthy or bearing some nontransmissible chronic disease—for 6 months. Treatment with 500 mg of HCA, twice a day, promoted weight loss and reduction of fatty mass, visceral fat, total cholesterol, and glycemic profile. Furthermore, an increase of the basal metabolic rate was perceived, independent of sex, age, or bearing hypertension, diabetes mellitus type 2, or dyslipidemia [107].

The HCA (**30**) present in *G. cambogia* is a potent and competent inhibitor of adenosinetriphosphate (ATP) citrate lyase, which is a key enzyme in the synthesis of fatty acids, cholesterol, and triglycerides [85,108]. It also regulates the level of serotonin, which has been associated with satiety, increased oxidation of fat, and decreased gluconeogenesis [85,109]. This explains how the compound exerts weight-loss activity, with reduced food ingestion and reduction of accumulated gain of body fat [85,108–110]. HCA (**30**) presents a chemical structure similar to citric acid and, therefore, inhibits the action of adenosine triphosphate (ATP) citrate lyase in the citric acid cycle. This action inhibits the conversion of citric acidinacetyl-coenzyme A (CoA) and suppresses the synthesis of fatty acids. The increased quantity of citric acid that is not converted into acetyl-CoA leads to acceleration of the production of glycogen from glucose. Thus, the ingestion of HCA (**30**) stabilizes glucose levels in the blood, resulting in the suppression of feelings of hunger. Therefore, it is also expected to show a preventive effect against hyperphagia [111–115]. Earlier studies showed that HCA (**30**) reduced the build-up of lipidic droplets and accelerated the energy metabolism, besides protecting cells from oxidative stress, as well as increasing the antioxidant status and mitochondrial functions [116,117].

Despite the benefits present in the species, some studies have shown that its consumption can cause adverse effects, such as headache, dizziness, dry mouth, nausea, and diarrhea [118]. Recent studies have described (hypo)mania and/or psychosis after the consumption of *G. cambogia* [87,119–121]. Some liver complications have also been reported, such as hepatotoxicity, with acute hepatic lesions, acute hepatitis, and hepatic insufficiency requiring transplant [122–125]. The complications from *G. cambogia* include mania or hypomania, mania with psychosis, and serotonin syndrome [10,126]. When taken over the recommended dose, individuals should be aware that the extract of *G. cambogia* can also lead to ocular complications [127].

HCA (**30**), the main active ingredient of *G. cambogia* extracts, presents effects of inhibiting the recapture of serotonin, inhibiting acetylcholinesterase, increasing the oxidation of fatty acids, and reducing lipogenesis [85]. The serotoninergic effects of HCA (**30**) are worrisome and can contribute to serotonin syndrome when combined with serotonin recapture inhibitors [109].

Some cases have been reported of acute pancreatitis secondary to the use of *G. cambogia* [128,129]. The pathogenesis of how such an increased risk of acute pancreatitis may occur is not clear; however, there is evidence that active oxygen species may play a central role in this pathogenesis. *Garcinia cambogia* increases lipidic peroxidation and positively regulates the expression of superoxide dismutase and glutathione peroxidase messenger ribonucleic acid (RNA) [130]. Lipidic peroxidation also increases oxidative stresss and can increase the risk of acute pancreatitis in patients using the species [131]. *G. cambogia* can cause other severe adverse events, including hepatoxicity and secondary acute hepatic insufficiency [124,132]. Other studies have also shown acute necrotizing eosinophilic myocarditis, rhabdomyolysis, serotonin toxicity, and nephropathy secondary to the use of *G. cambogia* [87,121,122,128–136]. Table 4 and Figure 4 describe the main compounds, the plant parts they have been extracted from, and their related activities.

Table 4. List of compounds presented in different parts of *Garcinia cambogia* and their related activities.

Garcinia Cambogia		
Xanthones		
Compound	**Plant Part**	**Activity**
Garbogiol	Roots [85]	Inhibition of α-glucosid [10]
Rheedia xanthone A	Peel [85]	-
Oxy-guttiferone i	Fruits [85]	-
Oxy-guttiferone k	Fruits [85]	-
Oxy-guttiferone k2	Fruits [85]	-
Oxy-guttiferone m	Fruits [85]	-
Benzophenones		
Compound	**Plant Part**	**Activity**
garcinol	Peel [85]	Anticancer, anti-inflammatory, antiparasitic, action on nervous system [24]
isogarcinol	Peel [85]	Anticancer, anti-inflammatory, antiparasitic, action on nervous system [24]
Guttiferone i	Fruits [85]	-
Guttiferone n	Fruits [85]	-
Guttiferone j	Fruits [85]	-
Guttiferone k	Fruits [85]	Topoisomerase II inhibitor [87]
Guttiferone m	Fruits [85]	Topoisomerase II inhibitor [87]
Organic Acids		
Compound	**Plant Part**	**Activity**
Heterocyclic amines	Fruits [85]	Antiobesity [137]
Tartaric acid	Fruits [85]	-
Citric acid	Fruits [85]	-
Malic acid	Fruits [85]	Antimicrobial [138]
Garcinialactone	Fruits [85]	-

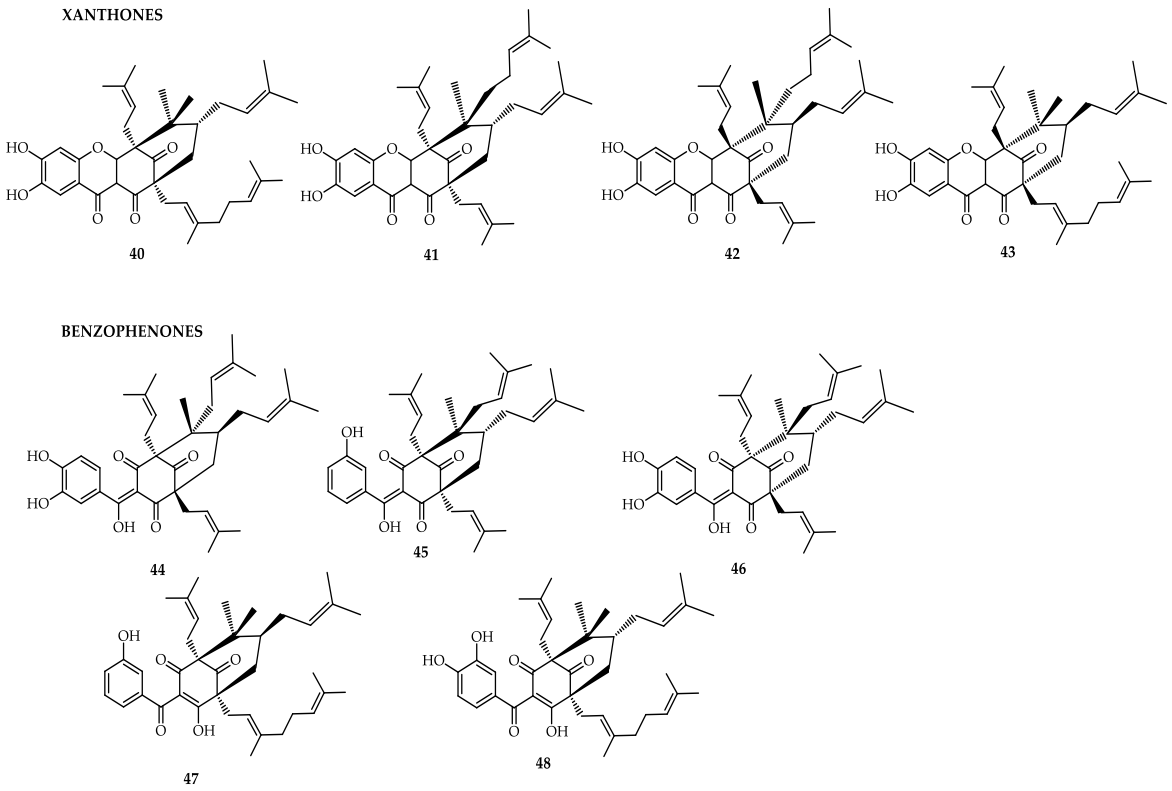

Figure 4. Bioactive compounds of *Garcinia cambogia.*

2.5. Garcinia Mangostana

Garcinia mangostana L. is a tropical evergreen fruit tree native to Southeast Asia, with the popular name of mangosteen, known for containing several constituents including xanthones, flavonoids, triterpenoids, and benzophenones [64]. In many Asian countries, the peel of *G. mangostana* has been used in traditional medicine to cure various diseases, such as diarrhea, dysentery, skin infections, mycosis, inflammation, cholera, and fever [139,140]. Fruit extracts have exhibited antioxidant [141,142], anti-inflammatory [143,144], antibacterial [145], and antidepressive effects [146]. In particular, α-mangostin (AM; **49**), a primary component of *G. mangostana*, has presented substantial pharmacological properties [147,148], including antioxidant activity in the treatment of age-related macular degeneration and protecting the retina from light damage [149].

Its pharmacological properties have been attributed to the presence of polyphenols such as xanthones, anthocyanins, phenolic acids, and flavonoids [142,150]. It has demonstrated antioxidant, anti-inflammatory, antitumoral, antibacterial, antifungal, antiviral, and anti-allergic properties [150,151]. Alfa-mangostin (**49**) is one of the most abundant xanthones in *G. mangostana*. The presented anti-inflammatory effects have been evidenced by reduced levels of TNF-α and IL-6 [152,153]. It has also shown antihyperglycemic, antioxidant, and anti-inflammatory effects, as well as improved blood flux and integrity of the retina [153,154]. The fruit has also produced improved results in terms of adiposity, hyperlipidemia, insulin resistance, and hepatic lesion related to ageing [155].

Mangosteen is used, in the form of an infusion, as a tonic for fatigue and as a digestive [139]. It can also be utilized for its medicinal properties in hemorrhoids, flood allergies, arthritis, tuberculosis, mycosis, mouth sores, fever, candidiasis, abdominal pain, suppuration, leucorrhea, and convulsions [140].

Some studies have shown the antihyperglycemic power and antidiabetic activity of mangosteen. Mangosteen pericarp extract has shown efficacy in the reduction of cholesterol levels and lipidic peroxidation, besides improving the kidney structure and function in fastening diabetic rats [156,157]. The hypoglycemic power is due to the inhibition of the activity of α-glucosidase and α-amylase: the enzymes responsible for the digestion of carbohydrates [158]. The xanthones mangostaxanthone-I (**50**), -II (**51**), and -VIIII (**52**), found in the pericarp, have been reported as inhibitors of the activity of α-amylase [133]; meanwhile, mangostenone-F (**53**), gartanin (**54**), α-magostin (**49**), and γ-magostin (**55**) have been shown to be inhibitors of the activity of α-glucosidase. Besides these compounds, the presence of the xanthones β-magostin (**56**), 3-isomangostin (**57**), magostenone-C (**58**) and -D (**59**), as well as the flavonoids

aromadendrin-8-C-β-*D*-glucopyranoside (**60**) and epicatechin (**61**), in the fruits corroborates those studies, which have presented hypoglycemic and antiobesity activities [134].

A hepatoprotective effect, which has previously been shown as one of the actions of α-mangostin [159], and renoprotective action were also found in streptozotocin-induced diabetic mice [160]. Some authors have cited the compound α-mangostin (**49**) as having anticancer activities, being capable of inducing cell death via apoptosis of human colorectal carcinomas [161,162]. This compound has presented antioxidant activity and evidences the benefits of the fruit in improving the kidney structure and function in diabetic rats [157]. In human melanoma, breast cancer, and epidermoid carcinoma, the compound α-mangostin had a cytotoxic effect, inducing the death of the cited cells [163,164].

One study on the mangosteen pericarp demonstrated a wide range of activities, including antifungal, antioxidant, antiobesity, and antidiabetic properties [139]. Its hypoglycemic power is due to the inhibition of the activity of α-glucosidase and α-amylase, enzymes responsible for the digestion of carbohydrates [158].

Some studies have presented satisfactory results with respect to the endogenous antioxidant system, demonstrating a high level of antioxidant enzymes in the organisms of the tested animals. Such effects suggest the capacity of the fruit to eliminate free radicals from the biological system [165]. Human adipocytes treated with α-mangostin (**49**) showed a decrease in the expression of inflammatory genes, as well as reducing insulin resistance [166]. Indeed, the daily consumption of a mangosteen drink for 30 days in healthy adults resulted in reduction of the inflammatory markers and increased the antioxidant capacity of human blood, due to reduction of the inflammatory marker C-reactive protein, reducing the risk of inflammation and chronic diseases related to immunity [167]. Thus, it has been proven that the mangosteen is a plant which can provide benefits in the development of drugs for the prevention and treatment of numerous diseases, mainly as it is a rich source of xanthones and other bioactive substances [159].

A study on rats fed daily with an aqueous extract of mangosteen pericarp (100 and 200 mg/kg, 38 days) showed that they exhibited significant improvements in memory loss. The extract, rich in xanthones, was also capable of restoring acetylcholinesterase activity in the dysfunction induced by lead in red blood cells and brain tissue. The presence of the xanthones α- and γ-mangostin (**55**), 3-isomangostin (**57**), gartanin (**54**), garciniafuran (**62**), 9-hydroxycalabaxanthone (**63**), and garcinone -C (**64**) and -D (**65**) was verified [134]. Table 5 and Figure 5 list the main compounds of *Garcinia mangostana*, the plant part where they have been extracted from, and their related ativities.

Table 5. List of compounds presented in different parts of *Garcinia mangostana* and their related activities.

Garcinia Mangostana		
Xanthones		
Compound	**Plant Part**	**Activity**
α-Mangostin	Pericarp, whole fruit, stem, arils, and seed [159]	Antibacterial, antifungal, antihistamine, antiobesity, anticancer [159], neuroprotective, antineoplastic [134], antioxidant [168]
β-Mangostin	Pericarp, whole fruit, stem [159]	Antiparasitic, hypoglycemic, antiobesity [134], antioxidant [168]
γ-Mangostin	Pericarp, whole fruit [159]	Antibacterial, anti-inflammatory, antihistamine, anticancer, hepatoprotective [159], antineoplastic, hypoglycemic, antiobesity, neuroprotective [134]
(16E)-1,6-Dihydroxy-8-(3-hydroxy-3-methylbut-1-enyl)-3,7-dimethoxy-2-(3-methylbut-2-	Not stated [159]	-

enyl)-xanthone		
(16E)-1-Hydroxy-8-(3-hydroxy-3-methylbut-1-enyl)-3,6,7-trimethoxy-2-(3methylbut-2-enyl)-xanthone	Whole fruit [159]	-
1,2-Dihydro-1,8,10-trihydroxy-2-(2-hydroxypropan-2-yl)-9-(3-methylbut-2-enyl)furo [3,2-a]xanthen-11-one	Heartwood [159]	-
1,3,6,7-Tetrahydroxy-xanthone	Pericarp [159]	-
1,3,6,7-Tetrahydroxy-2,8-(3-methyl-2-butenyl)-xanthone-P1	Pericarp [159]	-
1,3,6-Trihydroxy-7-methoxy-2,8-(3-methyl-2-butenyl)-xanthone-P2	Leaves [159]	-
1,3,8-Trihydroxy-4-methyl-2,7-diisoprenylxanthone	Heartwood [159]	-
1,3,7-Trihydroxy-2,8-di-(3-methylbut-2-enyl)-xanthon	Leaves [159], Pericarp [169]	-
1,3-Dihydroxy-2-(2-hydroxy-3-methylbut-3-enyl)-6,7-dimethoxy-8-(3-methylbut-2-enyl)-xanthone	Heartwood [159]	-
1,5-Dihydroxy-2-(3-methylbut-2-enyl)-3-methoxy-xanthone	Heartwood, stem [159]	-
1,5-dihydroxy-2-isopentyl-3-methoxy xanthone	Heartwood [159]	-
1,5,8-Trihydroxy-3-methoxy-2-(3-methylbut-2-enyl) xanthone	Heartwood [159], Pericarp [159]	-
1,6-Dihydroxy-2-(2-hydroxy-3-methylbut-3-enyl)-3,7-dimethoxy-8-(3-methylbut-2-enyl)-xanthone	Pericarp [159]	-
1,6-Dihydroxy-3-methoxy-2-(3-methyl-2-buthenyl)-xanthone	Pericarp [159]	-
1,6-Dihydroxy-3,7-dimethoxy-2-(3-methylbut-2-enyl)-8-(2-oxo-3-methylbut-3-enyl)-xanthone	Whole fruit [159]	-
1,6-Dihydroxy-3,7-dimethoxy-2-(3-methylbut-2-enyl)-xanthone	Heartwood [159]	-
1,6-Dihydroxy-8-(2-hydroxy-3-methylbut-3-enyl)-3,7-	Heartwood [159]	-

dimethoxy-2-(3-methylbut-2-enyl)-xanthone		
1,7-Dihydroxy-2-(3-methylbut-2-enyl)-3-methoxy-xanthone	Pericarp [159]	-
1,7-dihydroxy-2-isopentyl-3-methoxy xanthone	Pericarp [159]	-
11-Hydroxy-1-isomangostin	Not stated [159]	-
1-Hydroxy-2-(2-hydroxy-3-methylbut-3-enyl)-3,6,7-trimethoxy-8-(3-methylbut-2-enyl)-xanthone	Heartwood [159]	-
1-Isomangostin	Pericarp [159]	-
1-Isomangostin hydrate	Pericarp [159]	-
2-(γ,γ-Dimethylallyl)-1,7-dihydroxy-3-methoxyxanthone	Pericarp, arils [159]	-
2,3,6,8-Tetrahydroxy-1-isoprenylxanthone	Not stated [159]	-
2,8-bis-(γ,γ-Dimethyallyl)-1,3,7-trihydroxyxanthone	Arils [159]	-
3-Isomangostin	Pericarp [159]	Hypoglycemic, antiobesity, neuroprotective [134]
3-Isomangostin hydrate	Pericarp [159]	-
5,9-Dihydroxy-8-methoxy-2,2-dimethyl-7-(3-methylbut-2-enyl)-2H,6Hpyrano-(3,2,6)-xanthene-6-one	Fruit hull [159]	-
6-Deoxy-7-demethylmangostanin	Whole fruit [159]	
6-methoxy–bis pyrano xanthone	Pericarp [159]	Antioxidant [170]
6-*O*-Methylmangostanin	Not stated [159]	
7-*O*-Demethyl mangostanin	Pericarp [159]	Anticancer [169]
8-Deoxygartanin	Pericarp, whole fruit [159]	-
8-Hydroxycudraxanthone	Pericarp [159]	-
9-hydroxycalabaxanthone	Bark [171]	Neuroprotective [134]
BR-Xanthone-A	Pericarp [159]	-
BR-Xanthone B	Pericarp [159]	-

Calabaxanthone	Arils [159]	-
Cratoxyxanthone	Pericarp, stem, whole fruit [169]	-
Cudraxanthone	Pericarp [159]	-
Demethylcalabaxanthone	Whole fruit, arils, seed [159]	Antibacterial [159]
Dulxanthone-A	Bark [171]	Antibacterial [171]
Garcimangosone A	Fruit hull [159]	-
Garcimangosone B	Pericarp [159]	-
Garcimangosone C	Pericarp [159]	-
Garciniafuran	Heartwood [159]	Neuroprotective [134]
Garcinone B	Pericarp, whole fruit [159]	-
Garcinone C	Whole fruit [159]	Neuroprotective [134]
Garcinone D	Pericarp, whole fruit, stem [159]	Antibacterial [161], neuroprotective [134], antioxidant [47]
Garcinone E	Pericarp, whole fruit [159]	-
Garcinoxanthone-A	Not stated [134]	Antinociceptive, anti-inflammatory [134]
Garcinoxanthone-B	Not stated [134]	Antinociceptive, anti-inflammatory [134]
Garcinoxanthone-C	Not stated [134]	Antioxidant [46], antinociceptive, anti-inflammatory [134]
Garcinoxanthone-D	Not stated [134]	Antinociceptive, anti-inflammatory [134]
Garcinoxanthone-E	Not stated [134]	Antinociceptive, anti-inflammatory [138], antibacterial [171]
Garcinoxanthone-F	Not stated [134]	Antinociceptive, anti-inflammatory [134]
Garcinoxanthone-G	Not stated [134]	Antinociceptive, anti-inflammatory [134]
Garmoxanthone	Bark [171]	Antibacterial [171]
Gartanin	Pericarp, whole fruit [159]	Antineoplastic, hypoglycemic, antiobesity, neuroprotective [134], antioxidant [170]
Isogarcinol	Not stated [134]	Antinociceptive, anti-inflammatory [134], antibacterial [43]
Mangosharin	Stem [159]	-
Mangostaxanthone-I	Pericarp [133]	α-amylase inhibitor [136]

Mangostaxanthone-II	Pericarp [133]	α-amylase inhibitor [136]
Mangostaxanthone-III	Pericarp [168]	AGE* inhibitor, antioxidant [168]
Mangostaxanthone-IV	Fruits [172] Pericarp [164]	AGE* inhibitor, antioxidant [168]
Mangostaxanthone-V	Fruits [172]	-
Mangostaxanthone-VI	Fruits [172]	-
Mangostaxanthone-VII	Pericarp [136]	-
Mangostanaxanthone-VIIII	Pericarp [136]	α-Amylase inhibitory [136]
Mangostanate	Pericarp [172]	-
GlucosidaMangostanin	Pericarp [159]	Antibacterial [159]
Mangostanol	Wholefruit, stem [159]	-
Mangostenol	Pericarp [159]	-
Mangostenone A	Pericarp [159]	-
Mangostenone B	Pericarp [159]	-
MangostenoneC	Whole fruit [159]	Hypoglycemic, antiobesity [134]
Mangostenone D	Whole fruit [159]	Hypoglycemic, antiobesity [134]
Mangostenone E	Whole fruit [159]	
Mangostenone F	Not stated [134]	α-glucosidase inhibitor, antineoplastic [134]
Mangostinone	Pericarp, whole fruit [159]	-
Nigrolineaxanthone T	Bark [171]	-
Nor-mangostin	Fruits [172]	-
Rubraxantone	Pericarp [168]	Antioxidant [168]
Smeathxanthone A	Pericarp [159]	-
Thwaitesixanthone	Whole fruit [159]	-
Tovophyllin A	Pericarp [159]	-
Tovophyllin B	Pericarp [159]	-
Toxyloxanthone A (trapezifolixanthone)	Pericarp [159]	-
trapezifolixanthone	Pericarp [169]	-
1,7-dihydroxyxanthone	Pericarp [159]	-

Euxanthone	Pericarp [159]	-
Caloxanthone A	Pericarp [159]	-
Macluraxanthone	Pericarp [159]	-
Mangostingone [7-methoxy-2-(3- isoprenyl)-8-(3-methyl-2-oxo-3-buthenyl)-1,3,6-trihydroxyxanthone	Pericarp [159]	-
Benzophenones		
Compound	**Plant Part**	**Activity**
2,4,6,3′,5′-pentahydroxybenzophenone		
Garcimangosone D	Pericarp [159]	-
Maclurin	Pericarp, heartwood [159]	-
maclurin-6-*O*-β-D-glucopyranoside	Pericarp [134]	Hypoglycemic, antiobesity [134]
Kolanone	Pericarp [159]	-
Anthocyanidins		
Compound	**Plant Part**	**Activity**
Chrysanthemin	Pericarp [159]	-
Cyanidin-3-*O*-glucoside	Not stated [159]	-
Biflavonoid		
Compound	**Plant Part**	**Activity**
proanthocyanidin A2	Pericarp [173]	Anti-HIV [174]
Flavonoid		
Compound	**Plant Part**	**Activity**
Epicatehin	Pericarp [159]	Antidiabetic, antioxidant [173], hypoglycemic, antiobesity [134]
Aromadendrin-8-C-β-D-glucopyranoside	Pericarp [134]	Hypoglycemic, antiobesity [134]
Megastigmanesulphoglycoside		
Compound	**Plant Part**	**Activity**
4-*O*-sulpho-β-D-glucopyranosylabscisate	Pericarp [173]	Antioxidant [173]

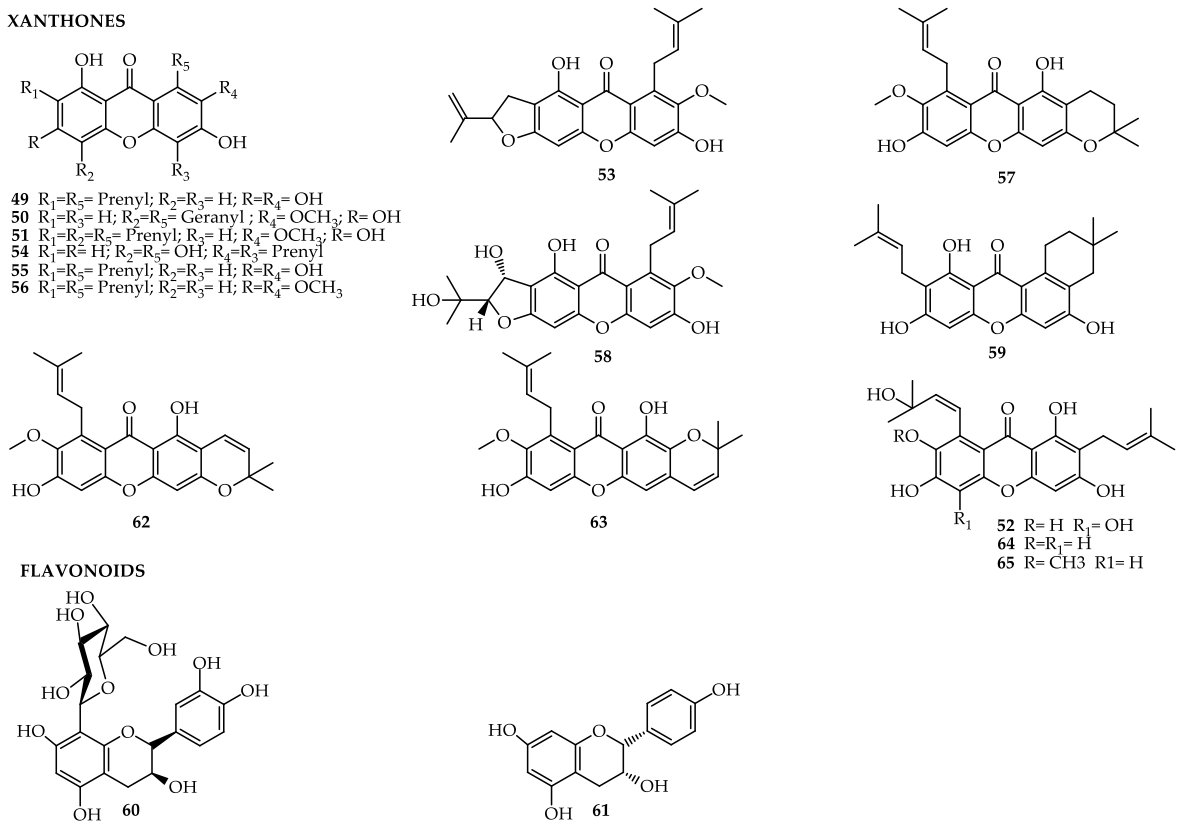

Figure 5. Bioactive compounds of *Garcinia mangostana.*

3. Conclusions

Plant species of the genus *Garcinia* are a relevant source of bioactive compounds. This review compiled the bioactive compounds found in five species of the genus *Garcinia*, as well as the effects of several types of extracts of different plant parts. Plants from genus *Garcinia* exhibits healing properties with anti-inflammatory effects, for the treatment of such ailments as skin disorders, wounds, pain, and infections, as well as presenting antinociceptive, antioxidant, antitumoral, antifungal, anticancer, antihistaminic, antiulcerogenic, antimicrobial, antiviral, vasodilatory, hypolipemic, hepatoprotective, nephroprotective, and cardioprotective properties. It was possible to observe that, across all the species mentioned in the present review, most of the studies carried out were in vitro experiments. Some tests have already been started in in vivo models; however, these are recent studies evaluating the effectiveness of the plant in treating diseases in animal models. These studies are promising and open up new perspectives on the use of the compounds present in these species, offering new perspectives on the possibility of developing new drugs. For this to be effective, it is necessary to initiate plant-use tests in humans, in order to analyze their effectiveness in treating diseases. Therefore, considering the high number of compounds found in plants of the genus and their beneficial effects, additional studies are required to support the development of new products with therapeutic properties for the prevention and treatment of various diseases; most importantly, non-transmissible chronic diseases. Therefore, these plants provide a promising potential source of natural biomolecules for pharmaceutical and medicinal applications.

Author Contributions: B.L.S.d.E.S., L.F.S., F.d.O.A.; P.A.H.; and M.A.A.: writing—original draft preparation; W.H.K.J., D.B., K.d.C.F., R.d.C.A.G., A.P., W.F.d.O.F., P.d.O.F and P.R.H.d.O.B.: writing—review and editing.

Funding: This work was carried out with support from the Federal University of Mato Grosso do Sul-UFMS/MEC-Brazil. This study was financed, in part, by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior-Brasil (CAPES); FinanceCode 001".

Acknowledgments: Graduate Program in Health and Development in the Central-West Region of Brazil, Federal University of Mato Grosso do Sul-UFMS.

Conflicts of Interest: The authors declare no conflict of interest.

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5.2 ARTIGO 2

Objetivo: Avaliar o estado nutricional e o percentual de gordura corporal (Epididimal, mesentérica, omental, perrirenal, retroperitoneal) dos grupos experimentais; realizar análise histológica do fígado, pâncreas e tecido adiposo dos grupos experimentais; analisar indicadores bioquímicos plasmáticos: HDL, LDL, VLDL, colesterol total, triglicerídeos e glicose; Avaliar o desenvolvimento da resistência à insulina (teste de tolerância à glicose (ipGTT) e à insulina (ipITT)); Realizar a dosagem de citocinas: IL-10 e MCP-1

*Artigo em processo de submissão para a Revista *Journal of Medicinal Food*.

Effects of the ethanolic and aquous extract of of *Garcinia gardneriana* leaves in *in vivo* experimental model induced by hyperlipidic diet

Bruna Larissa Spontoni do Espirito Santo[1], Lidiani Figueiredo Santana[1], Wilson Hino Kato Junior[2], Felipe de Oliveira de Araújo[3], Mariana Bento Tatara[4], Júlio Croda[4], Danielle Bogo[1], Karine de Cássia Freitas[1*], Rita de Cássia Avellaneda Guimarães[1], Priscila Aiko Hiane[1], Arnildo Pott[5], Wander Fernando de Oliveira Filiú[6], Bernardo Bacelar de Faria[7], Patrícia de Oliveira Figueiredo[8], Frederico Louveira Ayres[9] and Paulo Roberto Haidamus de Oliveira Bastos[1]

[1]Graduate Program in Health and Development in the Central-West Region of Brazil, Federal University of Mato Grosso do Sul-UFMS, 79079-900 Campo Grande, Brazil; bruna.spontoni@gmail.com (B.L.S.d.E.S.); lidi_lfs@hotmail.com (L.F.S.); daniellebogo@hotmail.com (D.B.); rita.guimaraes@ufms.br (R.d.C.A.G.); priscila.hiane@ufms.br (P.A.H.); phaidamus43@gmail.com (P.R.H.d.O.B.)

[2]Graduate of Pharmaceutical Sciences, Federal University of Mato Grosso do Sul-UFMS, 79079-900 Campo Grande, Brazil; hinokato@gmail.com (W.H.K.J)

[3]Graduate of Electrical Engineering, Federal University of Mato Grosso do Sul-UFMS, 79079-900 Campo Grande, Brazil; felipe@nexsolar.com.br (F.O.A)

[4]Health Science Research Laboratory, Federal University of Grande Dourados, 79804-970, MS, Brazil. School of Medicine Federal University of Mato Grosso do Sul, Campo Grande, Brazil. Oswaldo Cruz Foundation, Campo Grande, Brazil; juliocroda@gmail.com (J.H.R.C.); maria-nabtatara@gmail.com (M.B.T.)

[5]Laboratory of Botany, Institute of Biosciences, Federal University of Mato Grosso do Sul, 79070-900 Campo Grande, Mato Grosso do Sul, Brazil; arnildo.pott@gmail.com (A.P)

[6]Faculty of Pharmaceutical Sciences, Food and Nutrition, Federal University of Mato Grosso do Sul-UFMS, 79079-900 Campo Grande, Brazil; wander.filiu@gmail.com (W.F.O.F)

[7]Diagnostic Medicine Laboratory-Scapulatempo. Campo Grande 79002-17, MS, Brazil; bacelarfaria@gmail.com (B.C.F)

[8]Laboratory of Pronabio (Bioactive Natural Products)-Chemistry Institute, Federal University of Mato Grosso do Sul-UFMS, 79079-900 Campo Grande, Brazil; patricia.oliveira@ufms.br (P.O.F.)

[9]Medical School, Federal University of Mato Grosso do Sul, 79070-900 Campo Grande, Brazil; flouveira@hotmail.com (F.L.A)

*Correspondence: kcfreitas@gmail.com; Tel.: +55-67-3345-7416

Abstract: The study of medicinal plants in treating chronic non-transmissible diseases has raised the interest of researchers, such as the genus *Garcinia* (Clusiaceae). We evaluated the effects of aqueous and ethanolic extract of *Garcinia gardneriana* (Planch. & Triana) Zappi leaves in animals receiving a hyperlipidic diet. We utilized male adult Swiss mice: 1) Control (standard diet Nuvital®); 2) Control (AIN-93M); 3) HF (hyperlipidic diet); 4) HFAQU 200 (hyperlipidic diet + aqueous extract 200mg/kg); 5) HFAQU 400 (hyperlipidic diet + aqueous extract 400mg/kg); 6) HFET200 (hyperlipidic diet + aqueous extract 200mg/kg); 7) HFET400 (hyperlipidic diet + ethanolic extract 400mg/kg).

We verified the food consumption, weight gain, body fat, fastening glycemia, triglycerides, total cholesterol and fractions, and dosage of cytokines. Mice under the hyperlipidic diet presented higher weight gain and lower glucose tolerance and insulin resistance than the control group ($p<0.005$). HDL-c levels increased in those treated with the aqueous extract. *Garcinia gardneriana* revealed antioxidant and anti-inflammatory properties that can be related to our results. The aqueous extract prevented weight gain and comorbidities, indicating the possibility of use as an alternative method of weight control.

Keywords: Brazilian plant. Bacupari. Medicinal plant. Glycemy

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Introduction

Obesity is a growing health problem worldwide, and its prevalence increases rapidly in developed and developing countries. Characterized by an excessive accumulation of body fat, it is associated with non-transmissible chronic diseases and alterations of physiological functions, including cardiovascular diseases, hypertension, osteoarthritis, some types of cancer and is also being related to Cerebrovascular Accident [1–4].

The excess of lipids inside the adipocytes leads to increased pressure in the plasmatic membrane to expand, so inducing extracellular stress, leading to a pro-inflammatory state in the adipose tissue.

The oxidative stress and the inflammatory process produced by the free radicals (ROS) resulting from metabolic processes of the human body can be factors contributing to the development of non-transmissible chronic diseases[5,6].

At present, research has looked for alternatives to treat such diseases with metabolites obtained from plants. An example of secondary metabolites found in plants is polyphenols. They have excellent antioxidant activity as eliminators of ROS, reducing inflammation and inhibiting the liberation of pro-inflammatory mediators [5,6].

Therefore, plant products have been used as dietetic supplements or medicaments based on their various activities [7]. There is an increased interest in developing materials of plant origin [8] for treatments of non-transmissible chronic diseases, and experimental models *in vivo* induced by hyperlipidic diet can contribute to evaluating and understanding the effect of such plants on comorbidities affecting the human beings [5].

Garcinia gardneriana (Planch. & Triana) Zappi (Clusiaceae) is locally known as "bacupari", previously genus *Rhedia*, with c. 400 species, extensively distributed in tropical regions do Brazil, Polinesia, and continents as Asia and Africa. They contain bioactive substances, such as phenolic compounds, mainly flavonoids, xanthones and benzophenones present in expressive concentrations, with anti-inflammatry, antioxidant and antiobesity effects [9–15].

In this context, we evaluated the effects of the aqueous and ethanolic extract of *G. gardneriana* leaves on animals receiving a hyperlipidic diet, verifying alterations concerning serum pattern and the inflammatory and nutritional state of the animals.

Materials and Methods

Leaf collection. We collected leaves of *Garcinia gardneriana* in the urban area of Campo Grande (latitude 20.533720 and longitude 54.6751460), State of Mato Grosso do Sul, Brazil. The species was registered no. A26D547 in the National Administration System of the Genetic Patrimony and Associated Traditional Knowledge (Sisgen). In the laboratory of the Food Science Unit (UNICAL) of the Faculty of Pharmaceutical Sciences, Foods and Nutrition (FACFAN) of the Federal University of Mato Grosso do Sul (UFMS), the leaves were dried in an air circulation oven at 40 °C, and utilized to prepare the samples for analyses. The dry leaves were ground and homogenized in a turrax mixer, obtaining a homogeneous mass that was adequately placed in dark packages and identified to prepare the extracts.

Extract prepararation. We obtained the ethanolic extract by macerating 1 kg of powdered *Garcinia gardneriana* leaves in 10 L of ethanol for seven days and then filtered. The residue was reextracted with ethanol five times more, repeating the same procedure. The ethanolic extract was concentrated under reduced pressure at 37 °C and lyophilized. For the aqueous extract, 1 kg of powdered *G. gardneriana* leaves was macerated in 1L distilled water for one day and filtered. The aqueous extract was concentrated under reduced pressure at 37 °C and lyophilized.

Experiment. Our study was approved by the Ethics Committee in the Use of Animals (CEUA) of the Federal University of Mato Grosso do Sul (UFMS), register no. 1.050/2019. We utilized 130 male Swiss mice lineage of *Mus*

musculus, adults 60 days of age. The mice were kept in collective cages in the animal experimentation room of the Biotherium of the Federal University of Mato Grosso do Sul, under controlled conditions of temperature at 22 ± 2 °C, relative air humidity of 50-60% and light/dark cycle of 12/12 h. The experimental animals were split into 6 groups according to the food and treatment via gavage: 1) Control group with a standard diet (Nuvital®); 2) Control group (AIN-93M); 3) Group High Fat (HF); 4) Group hyperlipidic diet + Aqueous Extract of *Garcinia gardneriana* leaves 200mg/kg (HFAQU 200); 5) Group hyperlipidic diet+ Aqueous Extract of *G. gardneriana* leaves 400 mg/kg (HFAQU 400); 6) Group hyperlipidic diet + Ethanolic Extract of *G. gardneriana* leaves 200 mg/kg (HFET200); 7) Group hyperlipidic diet + Ethanolic Extract of *G. gardneriana* leaves 400 mg/kg (HFET400) (n= 20 in each group). The composition of diets is described in table 1. The groups 1 (Nuvital), 2 (AIN-93M) and 3 (HF) were kept under the same feeding conditions, did not receive plant extracts and were submitted to the same stress, with water supplied in equal volume as the extracts. The other groups were treated with *G. gardneriana* extracts; 4) HF AQU200 (hyperlipidic diet + Aqueous Extract 200mg/kg); 5) HF AQU400 (hyperlipidic diet + Aqueous Extract 400 mg/kg); 6) HF ET 200 (hyperlipidic diet + Ethanolic Extract 200mg/kg); 7) HF ET 400 (hyperlipidic diet + Ethanolic Extract 400 mg/kg) and followed for 8 weeks of study (Figure 1). After the trial, the animals were submitted to euthanasia with an overdose of the anesthetic isoflurane followed by exsanguination through the cava vein.

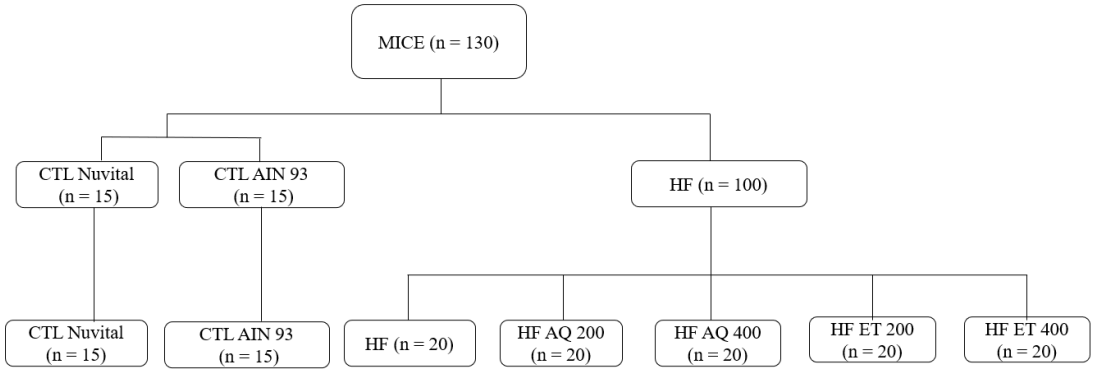

Figure 1. Distribution of animals into the studied groups. 1) Control group with standart diet (Nuvital®) 2) Control group (AIN-93M); 3) Group High Fat (HF); 4) Group hyperlipidic diet + Aqueous Extract of *Garcinia gardneriana* leaves 200 mg/kg (HF AQU 200); 5) Group hyperlipidic diet + Aqueous Extract of *G. gardneriana* leaves 400mg/kg (HFAQU 400); 6) Group hyperlipidic diet + Ethanolic Extract of *G. gardneriana* leaves 200 mg/kg (HFET200); 7) Group hyperlipidic diet + Ethanolic Extract of *G. gardneriana* leaves 400 mg/kg (HFET400).

Table 1. Composition of the experimental diets (g/kg food).

	AIN-93M	**Nuvital®**	**Hyperlipidic**
Ingredients (g/kg)			
Starch	620.692	725.67	320.692
Casein (≥85% of protein)	140.00	40.00	140.00
DL-methionine	-	100.00	
Lard	-	-	320.00
Sugar	100.00	-	100.00
Soybean oil	40.00	40.00	20.00
Celulose	50.00	100.00	50.00
Mix minerals**	35.00	35.00	35.00

Mix vitamines*	10.00	10.00	10.00
L-cystine	1.80	1.80	1.80
Colin bitartrate	2.50	2.50	2.50
Tertbutil hidroquinone	0.008	0.008	0.008
Energy (kcal/kg)	3802.80	4360.00	5302.80
Carbohydrates (%)		75.75%	31.73%
Proteins (%)		16.00%	10.56%
Lipids (%)		8.25%	57.71%
Calorias/g diet	3.80	4.36	5.30

*Vitamines and **Minerals present in the mix according to standard food AIN-93M.

Food Ingestion/Food Consumption. Each group had access ad libitum to water and food during the experimental period. Food ingestion was monitored weekly, considering the difference in grams between the offered quantity and the left-over (per animal).

Weight Gain. The animal body weights were evaluated weekly on a semi-analytic balance (Bel®).

Evaluation of Body Fat. After euthanasia, the fat sites (epididymal, mesenteric, omental, perirenal, retroperitonial) of each animal were totally removed and weighed on an analytic balance [16–18].

Liver Histology. After removal, the liver was bathed in physiological solution to extract accumulated blood and fragments of the right lobe were placed in histological grids for fixation. The samples were fixed in formaldehyde solution at 10% for 12 h and then kept in alcohol 70% until histological processing. After fixation, the specimens were dehydrated in batteries of alcohol and xylol, included in paraffin, cut in microtom 5 mm thick sections and stained with hematoxylin-eosin (HE) [19]. The hepatic steatosis was graded for intensity [20].

Serum Analyses. Blood of all animals was collected at the end of the experimental period for serum analyses. The serum samples were utilized to determine the following parameters: fastening glycemia, triglycerides, total cholesterol and fractions (HDL-c, LDL-c, VLDL-c), evaluated by colorimetric kits (Labtest Diagnostics SA™).

Oral glucose tolerance test (OGTT). The test was performed 5 days before finishing the experiment. The animals of the studied groups were weighed after 12 h fastening, and then the fastening glycemia was verified via caudal (time 0), using a glucometer. Next, the animals received glucose via gavage at the concentration of 2 g/kg body weight. The glycemia was determined at 15, 30, 60 and 120 min after the application of glucose.

Insulin sensitivity test (IPITT). The test was performed 5 days before finishing the experiment. For the ipITT, the animals of the studied groups were weighed, and the glycemia was verified at a fed state (time 0). Then, 1.5 U/kg of insulin (NovoRapid®) was applied via intraperitoneal, and the glycemia was assessed in the times 0, 15, 30 and 60 minutes, according to Lenquiste et al. [21] .

Concentration of adipokines: IL-10 e MCP-1. The concentration of adipokines IL-10 and MCP-1 was measured utilizing the commercial kit MADKMAG-71K®, Merck Sigma-Aldrich. Therefore, the serum was separated by centrifugation. Then, 10 μL of serum of each animal were distributed and placed in a 96-well plate with 10 μL of Assay buffer solution and 25 μL of a solution containing two adipokines. Standard and control blank parameters were prepared according to the label instructions (Milliplex® MAP kit, USA). Next, plate reading on Luminex® utilized the software MAGPIX®, with concentrations given in pg/mL.

Analyses of data. The statistical analyses were performed using Jandel Sigma Stat®, version 3.5 (Sys-tal software, Inc., EUA) and Sigma Plot, version 12.5 (Systat Software Inc., EUA) and presented as mean ± standard error of the mean. The groups were compared through analysis of variance (ANOVA), followed by the post-hoc Tukey test. Differences were considered significant when $p < 0.05$.

Results

2.1. Experimental

Regarding body weight gain at the end of 60 days of study, the groups that consumed hyperlipidic diet presented higher weight gain than the control group with Nuvital standard diet ($p \leq 0.001$). The group AIN-93M also exhibited non-significant lower weight gain than the hyperlipidic diet (HF) (Figure 2). The group HFAQU 200 gained less weight than the other groups under the hyperlipidic diet and showed values close to the control group AIN-93M ($p=1.0$) [22].

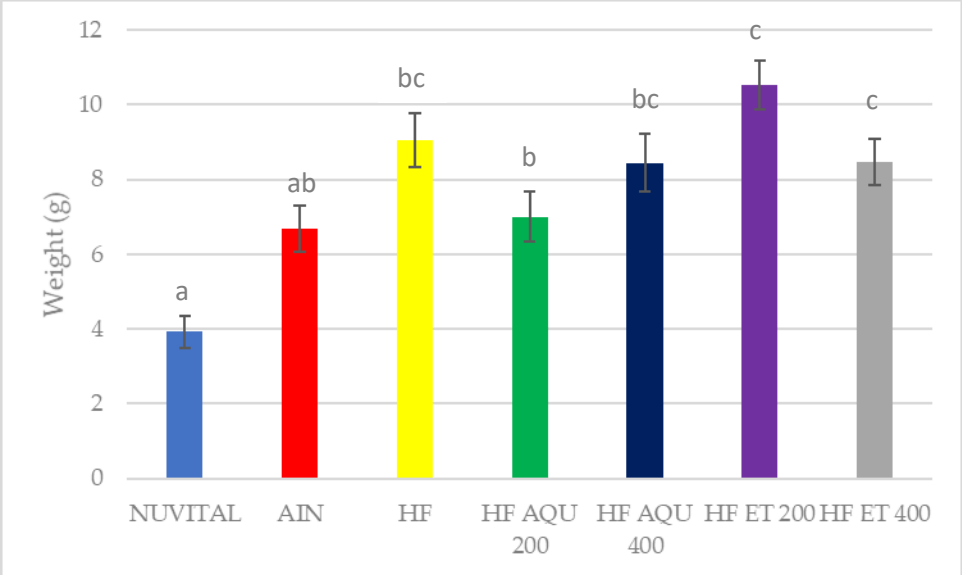

Figure 2. Total weight gain of the studied groups, in grams. 1) Control group with standard diet (Nuvital®) 2) Control group (AIN-93M); 3) Group High Fat (HF); 4) Group hyperlipidic diet + Aqueous Extract of *Garcinia gardneriana* leaves 200 mg/kg (HFAQU 200); 5) Group hyperlipidic diet + Aqueous Extract of *G. gardneriana* leaves 400 mg/kg (HFAQU 400); 6) Group hyperlipidic diet + Ethanolic Extract of *G. gardneriana* leaves 200 mg/kg (HFET200); 7) Group hyperlipidic diet + Ethanolic Extract of *G. gardneriana* leaves 400 mg/kg (HFET400). Letters indicate significant difference between groups. Mean ± standard error of the mean. Analysis of variance (ANOVA) followed by post-hoc Tukey test.

Concerning the food intake depicted in figure 3, the groups that consumed normocaloric diets (group Nuvital and group AIN-93) presented higher ingestion than those consuming hyperlipidic diets ($p<0.001$). The administration of aqueous and ethanolic extracts of *Garcinia gardneriana* reduced the intake of the hyperlipidic diet compared with the group HF, showing significant differences between the treated groups (HFAQU 200 , HFAQU 400 , HFET200, HFET400) and non-treated (HF) ($p \leq 0.001$).

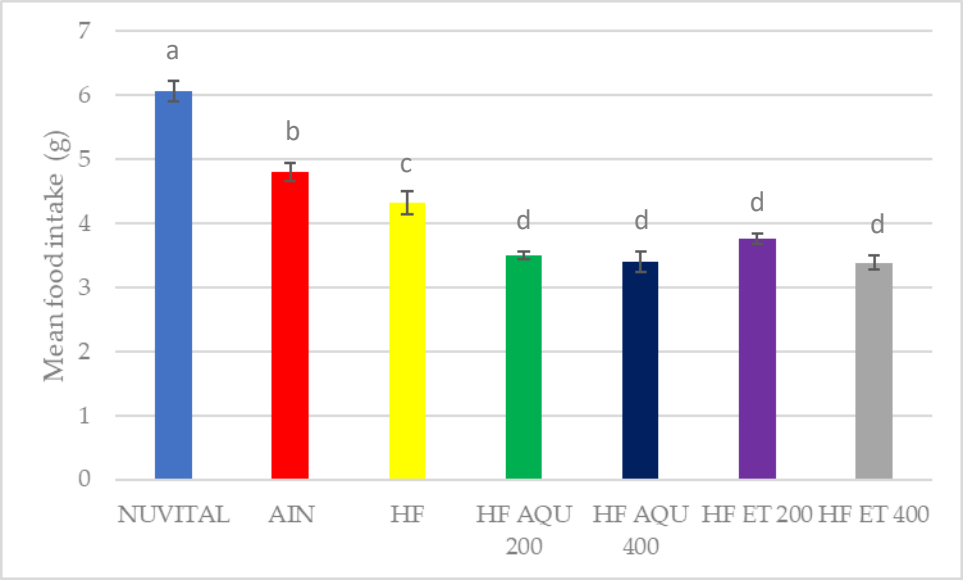

Figure 3. Mean food intake of the studied groups, in grams. 1) Control group with standard diet (Nuvital®) 2) Control group (AIN-93M); 3) Group High Fat (HF); 4) Group hyperlipidic diet + Aqueous Extract of *Garcinia gardneriana* leaves 200 mg/kg (HFAQU 200); 5) Group hyperlipidic diet + Aqueous Extract *G. gardneriana* leaves 400 mg/kg (HFAQU 400); 6) Group hyperlipidic diet + Ethanolic Extract of *G. gardneriana* leaves 200 mg/kg (HFET200); 7) Group hyperlipidic diet + Ethanolic Extract of *G. gardneriana* leaves 400 mg/kg (HFET400). Letters indicate significance between groups. Mean ± standard error of the mean. Analysis of variance (ANOVA) followed by post-hoc Tukey test.

At the end of treatments, the weights of omental, epidydimal, perirenal, retroperitoneal and mesenteric adipose tissues were evaluated. As shown in table 2, the hyperlipidic diet significantly increased the weight of all studied sites, compared with the groups fed with Nuvital and AIN-93 ($p \leq 0.001$).

Table 2. Comparison of weights of sities of adipose tissue between the studied groups.

Sites of adipose tissue	NUVITAL	AIN	HF	HF AQU 200	HF AQU 400	HF ET 200	HF ET 400	P
Mesenteric	454.800 ± 57.724[a]	697.818 ± 72.908[b]	961.950 ± 70.817[b]	1071.117 ± 108.671[b]	856.867 ± 95.687[b]	1035.394 ± 100.743[b]	1064.011 ± 94.405[b]	<0.001
Omental	77.013 ± 11.319	58.373 ± 10.549	65.975 ± 5.130	65.400 ± 6.822	83.153 ± 6.937	72.150 ± 7.517	110.184 ± 37.466	0.437
Perirenal	125.467 ± 20.070[a]	169.282 ± 21.033[abc]	263.335 ± 22.272[b]	238.272 ± 24.722[b]	249.583 ± 25.552[b]	287.994 ± 31.012[bd]	312.637 ± 22.726[bd]	<0.001
Retro peritoneal	303.220 ± 57.442[a]	653.818 ± 82.254[b]	917.405 ± 69.429[b]	722.233 ± 62.966[b]	765.206 ± 59.738[b]	744.333 ± 55.520[b]	759.316 ± 50.806[b]	<0.001
Epidydimal	872.613 ± 95.015[a]	1691.118 ± 168.116[bc]	2309.035 ± 110.559[b]	2254.744 ± 167.444[b]	2070.900 ± 132.692[b]	2345.261 ± 113.758[bd]	2143.626 ± 136.399[b]	<0.001
Total fat	1622.967 ± 144.897[a]	3233.145 ± 320.828[bc]	4393.684 ± 205.897[bd]	4322.039 ± 340.853[b]	3999.082 ± 199.997[b]	4467.556 ± 178.390[bd]	4319.205 ± 231.899[b]	<0.001

Sites of adipose tissue (mg). Standard diet based on Nuvital®, Standard diet based on AIN-93M [22], Hyperlipidic diet (4% of soybean oil and 31% of lard), Hyperlipidic diet (4% of soybean oil and 31% of lard) + Aqueous Extract (200 mg/kg), Hyperlipidic diet (4% of soybean oil and 31% of lard) + Aqueous Extract (400 mg/kg), Hyperlipidic diet (4% of soybean oil and 31% of lard) + Ethanolic Extract (200 mg/kg), Hyperlipidic diet (4% of soybean oil and 31% of lard) + Ethanolic Extract (400 mg/kg). Letters indicate significance between groups. Mean ± standard error of the mean. Analysis of variance (ANOVA) followed by post-hoc Tukey test.

The total fat weight in the groups fed with hyperlipidic diets was lower in the groups with administration in group HFAQU 400; however, it did not significantly from the treated groups.

At the end of the study, we assessed the glycemic profile of the animals, performing the oral glucose tolerance test and the insulin sensitivity test to determine the impact of the plant aqueous and ethanolic extracts on glucose homeostasis and insulin sensitivity. The dosage of fastening glucose did not show significant differences between groups ($p=0.031$).

As shown in figure 4, after glucose administration via gavage, mice that received the extracts HFAQU 200 , HFAQU 400 , HFET200 and HFET400 had the glucose level reduced faster than mice of untreated groups. The area under the curve (AUC) demonstrated that the group HFAQU 200 had reduced glycemia ($p<0.005$).

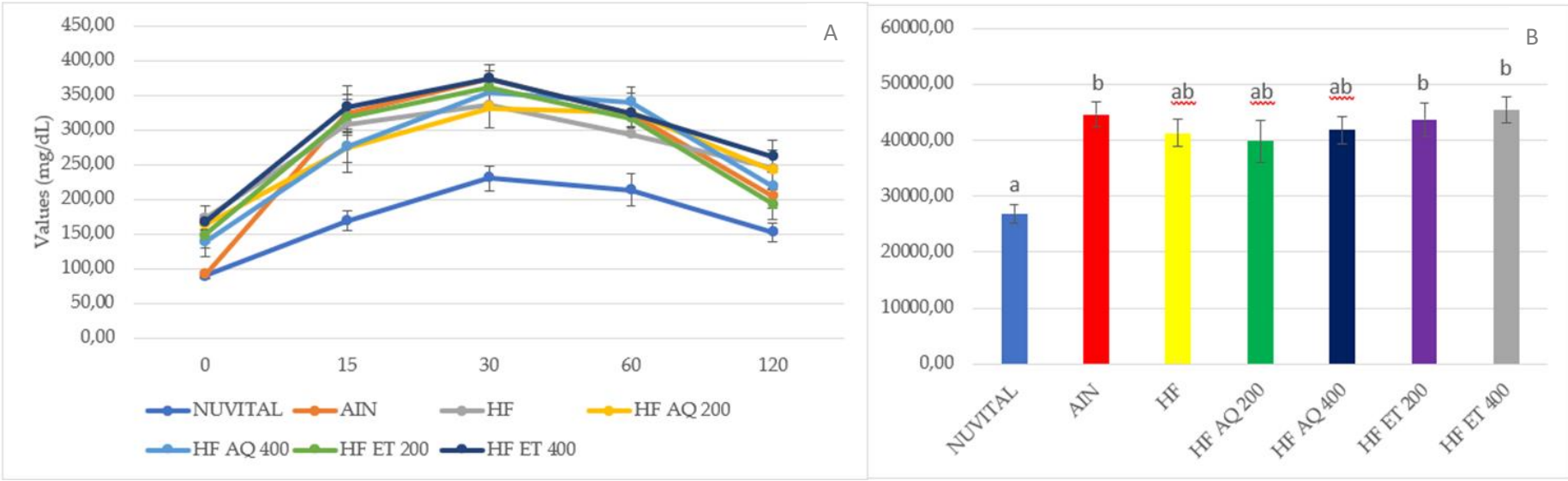

Figure 4. A- Oral Glucose Tolerance Test; B- Area Under the Curve of Glucose Tolerance Test. 1) Control Group (Nuvital®) 2) Control Group (AIN-93M); 3) Group High Fat (HF); 4) Group hyperlipidic diet + Aqueous Extract of *Garcinia gardneriana* leaf 200 mg/kg (HFAQU 200); 5) Group hyperlipidic diet + Aqueous Extract of *G. gardneriana* leaf 400 mg/kg (HFAQU 400); 6) Group hyperlipidic diet + Ethanolic Extract of *G. gardneriana* leaf 200 mg/kg (HFET200); 7) Group hyperlipidic diet + Ethanolic Extract of *G. gardneriana* leaf 400 mg/kg (HFET400). Mean ± standard error of the mean. Analysis of variance (ANOVA).

The area under the curve did not show a significant difference within experimental groups, but we verified a trend of its reduction in the group HF AQU200. The area under the curve in the group Nuvital was smaller, indicating that the normocaloric diet reduces the probability of developing glucose intolerance due to the lower values obtained in this group. The bigger the AUC, the higher is the glucose intolerance, as shown in figure 5.

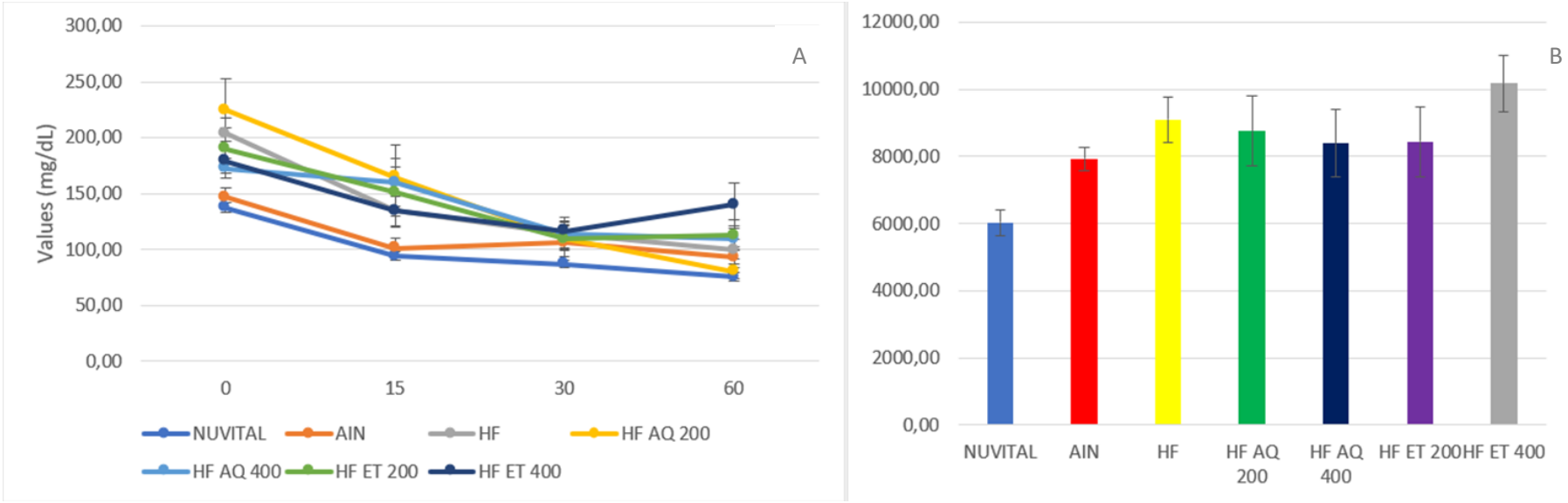

Figure 5. A- Insulin sensitivity test; B- Area Under the Curve of the Insulin sensitivity test. 1) Control group (Nuvital®) 2) Control group (AIN-93M); 3) Group High Fat (HF); 4) Group hyperlipidic diet + Aqueous Extract of *Garcinia gardneriana* leaf 200 mg/kg (HFAQU 200); 5) Group hyperlipidic diet + Aqueous Extract of *G. gardneriana* leaf 400 mg/kg (HFAQU 400); 6) Group hyperlipidic diet + Ethanolic Extract of *G. gardneriana* leaf 200 mg/kg (HFET200); 7) Group hyperlipidic diet + Ethanolic Extract of *G. gardneriana* leaf 400 mg/kg (HFET400). Mean ± standard error of the mean. Analysis of variance (ANOVA).

In mice, the hyperlipidic diet induced a relevant increase in total cholesterol levels ($p<0.001$), as only the group HFET200 maintained a value similar to the control groups AIN93M and Nuvital, with a significant difference from groups under hyperlipidic diets (Figure 6). Regarding the High-density Lipoprotein (HDL cholesterol), the group HFAQU 200 had significantly increased values in comparison with the other groups of our study, considering the groups Nuvital ($p<0.001$) and AIN93M ($p=0.002$).

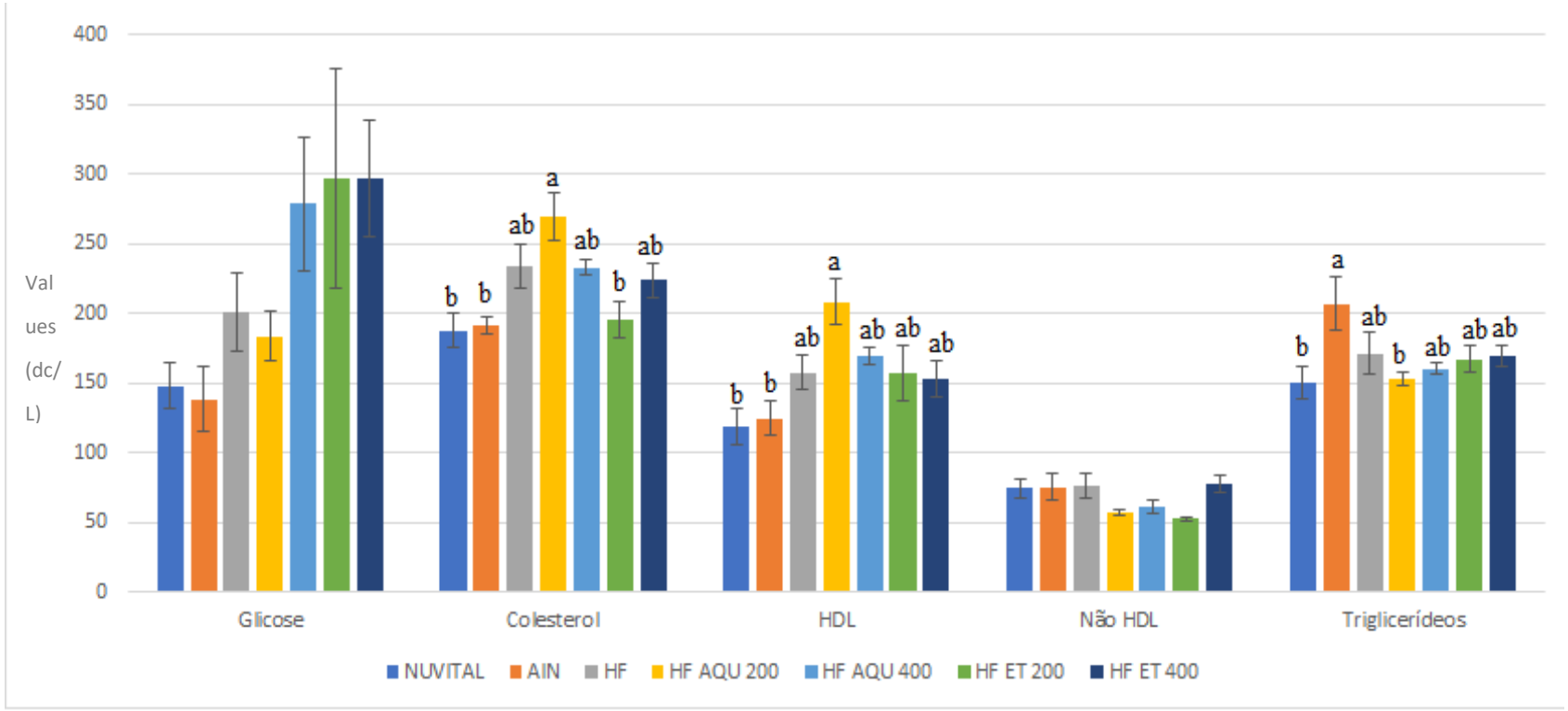

Figure 6. Serum patterns of the studied groups. 1) Control group (Nuvital®) 2) Control group (AIN-93M); 3) Group High Fat (HF); 4) Group hyperlipidic diet + Aqueous Extract of *Garcinia gardneriana* leaf 200 mg/kg (HFAQU 200); 5) Group hyperlipidic diet + Aqueous Extract of *G. gardneriana* leaf 400 mg/kg (HFAQU 400); 6) Group hyperlipidic diet + Ethanolic Extract of *G. gardneriana* leaf 200 mg/kg (HFET200); 7) Group hyperlipidic diet + Ethanolic Extract of *G. gardneriana* leaf 400 mg/kg (HFET400). Mean ± standard error of the mean. Analysis of variance (ANOVA).

Concerning triglycerides, an increase in group AIN-93M occurred with significant differences from the control groups Nuvital and HFAQU 200 ($p=0,022$). The groups treated with the leaf extract (HFAQU 200 , HFAQU 400 , HFET200, HFET400) had non-significant lower values than the non-treated group (HF).

The histological analysis of the liver pointed that the treatment HFAQU 400 avoided the build-up of lipids in the hepatic tissue. The groups AIN, Nuvital and HFAQU 400 presented lower percentages of steatosis and had a significant difference compared with the other groups (Table 3). These results were confirmed at evaluating the presence of microvesicular steatosis. Furthermore, the group HFAQU 400 exhibited the lowest hepatic weight between mice fed with hyperlipidic diets compared with the other groups, though non-significant.

Table 3. Evaluation of steatosis, microvesicular steatosis, lobular inflammation, ballooning, Mallory's hyaline and apoptosis in the liver.

Evaluated parameters		Nuvital	AIN	HF	HF AQU 200	HF AQU 400	HF ET 200	HF ET 400	p
		%	%	%	%	%	%	%	
Steatosis	until 5%	81.8	75.0	8.3	10.0	41.7	18.2	8.3	<0.001
	5 to 33%	9.1	25.0	25.0	30.0	33.3	36.4	16.7	
	33 to 66%	0.0	0.0	25.0	50.0	25.0	18.2	41.7	
	over 66%	9.1[a]	0.0[a]	41.7[b]	10.0[b]	0.0[a]	27.3[b]	33.3[b]	
Microvesicular steatosis	Absent	90.9	87.5	33.3	30.0	83.3	45.5	33.3	<0.001
	Present	9.1[a]	12.5[a]	66.7[b]	70.0[b]	16.7[a]	54.5[b]	66.7[b]	
Lobular inflammation	Absent	72.7	12.5	41.7	20.0	25.0	0.0	0.0	<0.001
	<2 foci per field of 200x	27.3[a]	87.5[b]	50.0[a]	80.0[b]	58.3[b]	72.7[b]	83.3[b]	
	2-4 foci per field of 200x	0.0	0.0	8.3	0.0	16.7	27.3	16.7	
Ballooning	Absent	100.0[b]	37.5[a]	58.3[b]	30.0[a]	66.7[b]	81.8[b]	66.7[b]	0.005
	Few cells	0.0	62.5	25.0	50.0	16.7	18.2	33.3	
	Many cells	0.0	0.0	16.7	20.0	16.7	0.0	0.0	
Mallory's Hyaline	Absent	100.0	87.5	75.0	80.0	83.3	100.0	100.0	-
	Present	0.0	12.5	25.0	20.0	16.7	0.0	0.0	
Apoptosis	Absent	100.0	87.5	91.7	100.0	100.0	90.9	100.0	-
	Present	0.0	12.5	8.3	0.0	0.0	9.1	0.0	

Standart diet based on Nuvital®, Normal diet based on AIN-93M [22], Hyperlipidic diet (4% of soybean oil and 31% of lard), Hyperlipidic diet (4% of soybean oil and 31% of lard) + Aqueous Extract (200 mg/kg), Hyperlipidic diet (4% of soybean oil and 31% of lard) + Aqueous Extract (400 mg/kg), Hyperlipidic diet (4% of soybean oil and 31% of lard) + Ethanolic Extract (200 mg/kg), Hyperlipidic diet (4% of soybean oil and 31% of lard) + Ethanolic Extract (400 mg/kg). Values expressed in percent. Differents Letters indicate significance between groups. Fisher's exact test or the chi-square test.

Regarding the presence of cellular apoptosis, the groups AIN, HFET200 and HF presented cell death, in contrast with the other groups. Occurred significant differences in lobular inflammation and ballooning in the studied groups. The treatments AIN, HFAQU 200, HFAQU 400, HFET200 and HFET400 showed more inflammation than the HF and Nuvital diets ($p<0.001$). At analyzing the ballooning process, the groups AIN and HFAQU 200 had more ballooning than HF, HFAQU 40 , HFET200, HFET400 and Nuvital ($p=0.01$).

In the analysis of biomarkers, the cytokine IL-10 presented the highest value for the group HF ($p<0.001$). For cytokine MCP-1, the groups under hyperlipidic diet exhibited higher values, pointing out HF ET 400 with the highest level between groups; in contrast, Nuvital showed the lowest value, though without significant differences between groups, as detailed in table 4.

Table 4. Analysis of the Cytokines IL-10 and MCP-1 of the studied groups.

Cytokines	Nuvital	AIN	HF	HF AQU 200	HF AQU 400	ET 200	ET 400	p
IL-10 (pg/mg)	6.936 ± 2.357[b]	2.541 ± 0.549[b]	7.604 ± 1.371[a]	2.928 ± 0.610[b]	3.216 ± 0.575[b]	5.924 ± 0.769[b]	4.165 ± 0.354[b]	<0.001
MCP-1 (pg/mg)	9.290 ± 3.283	11.356 ± 2.752	18.572 ± 3.497	16.694 ± 2.621	13.473 ± 3.285	13.527 ± 3.370	27.033 ± 7.994	0.058

Standart diet based on Nuvital®, Normal diet based on AIN-93M [22], Hyperlipidic diet (4% of soybean oil and 31% of lard), Hyperlipidic diet (4% of soybean oil and 31% of lard) + Aqueous Extract (200 mg/kg), Hyperlipidic diet (4% of soybean oil and 31% of lard) + Aqueous Extract (400 mg/kg), Hyperlipidic diet (4% of soybean oil and 31% of lard) + Ethanolic Extract (200 mg/kg), Hyperlipidic diet (4% of soybean oil and 31% of lard) + Ethanolic Extract (400 mg/kg). Letters indicate significance between groups. Mean ± standard error of the mean. Analysis of variance (ANOVA) followed by post-hoc Tukey test.

Discussion

Medicinal plants and their constituents can be promising candidates for the treatment of obesity; they showed anti-obesity effects such as reducing body fat in animals treated with particular species of plants [23,24].

Of all pharmaceuticals available in therapeutics, around 25 – 30% are produced from natural products (plants, microorganisms and animals) or are derived from those products and produce several secondary metabolites, with various therapeutical activities including inflammations and pains [25–28]. One of the sources of chemical derivations is the family Clusiaceae, composed of a vast spectrum of biological activities [29–31]. *Rheedia*, a genus of Clusiaceae, is used in various disorders in folk medicine, including constipation, rheumatism, inflammation and pain [32,33]. The literature shows that plants of this family are rich in flavonoids and biflavonoids, benzophenones, xanthones, triterpenes and steroids [34,35].

In this context, *Garcinia gardneriana* (Planch. & Triana) Zappi (synonym *Rheedia gardneriana*) is used in herbal treatments as inflammatory, and its extracts and isolated compounds have confirmed such recommendations [36]. The chemical investigation of the genus *Rheedia* revealed biflavonoids among numerous other compounds in several species. Analyses of the root peel of *Rheedia benthamiana* Planch. & Triana, *R. brasiliensis* (Mart.) Planch. & Triana and *R. gardneriana* led to the isolation of many xanthones and the biflavonoids volkensiflavone, fukugetin and GB-2a, also present in fruits of *R. madruno* (Kunth) Planch. & Triana, together with GB-1a, proved the investigated anti-inflammatory effect [37].

Studies suggested that any alteration in the normal weight of the human body leads to abnormal functions [38,39]. It is presumed that animals induced by hyperlipidic diets are a helpful model compatible with the excessive fat intake in the human diet [38–40].

In our study, the groups under hyperlipidic diet presented lower food consumption, as the characteristics of hyperlipidic food can influence food intake. Foods with high fat and carbohydrates content are well accepted by rodents [41,42]. The lower food ingestion observed in animals under the HF diet can be consequent from more satiety promoted by the high ingestion of lipids. The diet utilized in this study had high-fat content, that induced weight gain in mice. Previous research has shown that foods rich in fat increase the build-up of adipose tissue significantly for their high density of energy, and, consequently, induce increased body weight [2,43,44].

Given that the consumption of plant origin foods rich in polyphenols has effects in protecting against metabolic syndrome, obesity induced by diet, and insulin resistance, such foods were tested in obesity models [45,46]. In the present study, we evaluated the impact of extracts from *Garcinia gardneriana* leaves in the protection against weight gain and associated comorbidities, including glucose intolerance, dyslipidemia, hepatic build-up of lipids and inflammatory factors, in a model utilizing male mice, consuming hyperlipidic diets.

Studies show that the hyperlipidic diet resulted in dyslipidemic alterations by increased triglycerides, total cholesterol and reduced level of High-density Lipoprotein cholesterol (HDL) [40,47]. Our study observed these beneficial effects that probably are associated with antioxidant enzymes, such as the polyamides that play a relevant role in eliminating free radicals [48–50]. The total antioxidant capacity (TAC) increased; in contrast, total cholesterol, LDL cholesterol and triglycerides in mice under hyperlipidic diet decreased after the supplementation of ethanolic extract of *G. gardneriana*. We highlight the lower values in groups under hyperlipidic diet compared with groups treated with the extract.

We observed that the administration of the leaf extract of *G. gardneriana* prevented the weight gain induced by hyperlipidic diets and the accumulation of fat mass in mice. Furthermore, the *G. gardneriana* extract also improved glucose tolerance and insulin resistance in mice fed with hyperlipidic diets. According to Demenciano et al. [51], *G. gardneriana* contains compounds classified as xanthones [52,53], Biflavonoids [54,55] and Benzophenones [56,57] that have as main activities the antioxidant and anti-inflammatory function. That is consistent with previous studies reporting that these

compounds can improve insulin sensitivity in mice in initial development when treated with plants of this genus [49,50,58–60].

Much is studied on natural bioactive substances – the phytochemicals present in plants that can benefit health, such as preventing chronic and metabolic diseases. The potential dos bioactive components in the treatment and prevention of weight gain is under investigation, representing an alternative and attractive strategy for developing anti-obesity products [61]. The genus *Garcinia* exhibits other therapeutical properties with anti-inflammatory effects, such as skin disorders and wounds, pain and infections. For the number of compounds found in plants of the genus which show therapeutical properties that can be utilized to prevent and treat non-transmissible chronic diseases, Thus, the study in an experimental model as herein described is justified.

Reports suggest that high levels of cholesterol, triglycerides (TG), (Low-density Lipoprotein cholesterol (LDL-c) and Very Low-density Lipoprotein cholesterol (VLDL-c) increase the risk factor for cardiovascular diseases, hypertension, obesity and diabetes mellitus [62–64]. In the present study, mice fed with hyperlipidic diets had a significant rise in serum lipidic constituents; however, the treatment with the extracts of *G. gardneriana* lowered LDL cholesterol levels. The reduced build-up of triglycerides can be partially attributed to the suppression of hepatocellular apoptosis via the improved potential of mitochondrial membrane and ameliorated cellular functions in general [65].

The increase of apoptosis of hepatocytes can lead to fast cell death and incapacity of cells to effectively modulate the lipidic metabolism, leading to hyperlipidemia. An alternative explanation for the reduced levels of apoptosis in treated groups could be caused by the improved antioxidant capacity, as increased activity of antioxidant enzymes can lead to reduced oxidative damage and plays a relevant role in mediating apoptosis [66].

Garcinia gardneriana presents pharmacological properties attributed to the presence of biflavonoids such as GB-2a [67], Fukugentin [13] and Fukugiside [13]. They exhibit antioxidant [13,68] and anti-inflammatory properties [69], probably related to our results. The association of some compounds administered through extracts can provide a promising potential source of natural biomolecules for pharmaceutical and medicinal applications [36].

Pro-inflammatory cytokines, such as MCP-1, are necessary to initiate an inflammatory response. MCP-1 or CCL2 is produced by macrophages and endothelial cells and is responsible for recruiting immune system cells for the inflammation sites [70]. Its expression is increased in obese persons, mainly with insulin resistance [71]. In contrast, anti-inflammatory cytokines such as IL-10 regulate the immune system; therefore, they are relevant to inhibiting the synthesis of pro-inflammatory cytokines[72]. An anti-inflammatory cytokine acts in the suppression of the signal transduction of pro-inflammatory cytokines [72,73]. The expression of IL-10 is associated with adiposity and shows low levels in obese individuals [74]. It is possible to observe that secondary metabolites from plants, such as triterpenes, flavonoids and steroids, can modulate the inflammation and metabolic dysfunctions associated with obesity [75]. In the present work, increased doses of extracts did not interfere significantly with IL-10 and MCP-1 levels. However, it was also observed that IL-10 could exert anti-inflammatory effects due to inhibiting pro-inflammatory cytokines [76].

Conclusions

In the carried out experimental model, the treatments with *Garcinia gardneriana* demonstrated to reduce the risks of comorbidities associated with obesity induced by hyperlipidic diets. That effect was proven by lower food intake, less weight gain, improved insulin sensitivity, increased HDL-c levels and lower hepatic steatosis levels in the groups that received the aqueous extract, especially at the dose of 200 mg/kg. The leaf aqueous extract of *G. gardneriana* can prevent obesity and the metabolic syndrome induced by the diet, indicating the possibility to use *G. gardneriana* as an alternative method of weight control. The utilization of the aqueous extract in low doses should be further investigated to achieve even better results to prevent and treat non-transmissible chronic diseases.

Author Contributions: Author Contributions: B.L.S.d.E.S., L.F.S., F.d.O.A.; P.A.H.; and M.A.A.: writing—original draft preparation; D.B., K.d.C.F., R.d.C.A.G., A.P., W.F.d.O.F., P.R.H.d.O.B., W.H.K.J. and P.d.O.F: writing—review and editing.

Institutional Review Board Statement: The study was approved by Ethics Committee of Federal University of Mato Grosso do Sul (protocol code 1.050/2019).

Funding: This work was carried out with support from the Federal University of Mato Grosso do Sul-UFMS/MEC-Brazil. This study was financed, in part, by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior-Brasil (CAPES); Finance Code 001.

Acknowledgments: Graduate Program in Health and Development in the Central-West Region of Brazil, Federal University of Mato Grosso do Sul-UFMS.

Conflicts of Interest: The authors declare no conflict of interest.

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6. CONCLUSÃO

Espécies vegetais do gênero Garcinia são uma fonte relevante de compostos bioativos com possíveis efeitos benéficos. Estudos adicionais são necessários para subsidiar o desenvolvimento de novos produtos com propriedades terapêuticas para a prevenção e tratamento de diversas doenças; mais importante, doenças crônicas não transmissíveis.

No modelo experimental executado, o tratamento com *Garcinia gardneriana* demonstrou reduzir os riscos de comorbidades que acompanham a obesidade induzida por dieta hiperlipídica.

Esse efeito foi comprovado pelo menor consumo de dieta, menor ganho de peso, melhor sensibilidade à insulina, aumento dos níveis de HDL-c e níveis mais baixos de esteatose hepática nos grupos que receberam extrato aquoso, especialmente na dose de 200 mg/kg.

O extrato aquoso da *Garcinia gardneriana*, neste modelo, pode prevenir a obesidade e a síndrome metabólica induzida pela dieta, indicando a possibilidade do uso da Garcinia gardneriana como método alternativo de controle de peso.

O uso do extrato aquoso em menores doses devem ser investigado para analisar melhor os resultados no tratamento.

Portanto, essas plantas fornecem uma fonte potencial promissora de biomoléculas naturais para aplicações farmacêuticas e medicinais.

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ANEXO 1 – APROVAÇÃO PELA COMISSÃO DE ÉTICA ANIMAL

Serviço Público Federal
Ministério da Educação
Fundação Universidade Federal de Mato Grosso do Sul

CERTIFICADO

Certificamos que a proposta intitulada "Efeitos do extrato etanólico e aquoso das folhas de *Garcinia gardneriana* em modelos experimentais *in vivo*", registrada com o nº 1.050/2019, sob a responsabilidade de **Karine de Cássia Freitas Gielow** - que envolve a utilização de animais pertencentes ao filo Chordata, subfilo Vertebrata, para fins de pesquisa científica – encontra-se de acordo com os preceitos da Lei nº 11.794, de 8 de outubro de 2008, do Decreto nº 6.899, de 15 de julho de 2009, e com as normas editadas pelo Conselho Nacional de Controle de Experimentação Animal (CONCEA), e foi aprovada pela COMISSÃO DE ÉTICA NO USO DE ANIMAIS/CEUA DA UNIVERSIDADE FEDERAL DE MATO GROSSO DO SUL/UFMS, na 4ª reunião ordinária do dia 22/05/2019.

FINALIDADE	( ) Ensino (x) Pesquisa Científica
Vigência da autorização	26/03/2018 a 26/02/2022
Espécie/Linhagem/Raça	*Mus musculus* / Swiss
Nº de animais	130 Machos + 15 Fêmeas = 145
Peso/Idade	25g / 60 dias
Sexo	Machos e Fêmeas
Origem	UT-Biotério/UFMS

Fábio José Carvalho Faria

Coordenador da CEUA/UFMS

Campo Grande, 24 de maio de 2019.

Documento assinado eletronicamente por **Fabio Jose Carvalho Faria, Professor do Magisterio Superior**, em 27/05/2019, às 18:41, conforme horário oficial de Mato Grosso do Sul, com fundamento no art. 6º, § 1º, do Decreto nº 8.539, de 8 de outubro de 2015.

COMISSÃO DE ÉTICA NO USO DE ANIMAIS
Av Costa e Silva, s/nº - Cidade Universitária
Fone:
CEP 79070-900 - Campo Grande - MS