

**CHLOROGENIC ACID
EXTRACTED FROM
CECROPIA PACHYSTACHYA
TRÉCUL. PROMOTES LIVER
PROTECTION THROUGH
CONTROL THE
INFLAMMATION AND
OXIDATIVE STRESS DURING
NON ALCOHOL-HEPATIC
DAMAGE**

**ÁCIDO CLOROGÊNICO EXTRAÍDO DE CECROPIA PACHYSTACHYA TRÉCUL.
PROMOVE A PROTEÇÃO HEPÁTICA ATRAVÉS DO CONTROLE DA
INFLAMAÇÃO E DO ESTRESSE OXIDATIVO DURANTE LESÕES HEPÁTICAS
NÃO ALCOÓLICAS**

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is a complex metabolic disorder associated with insulin resistance, oxidative stress, inflammation, and lipid metabolism dysregulation. Despite its growing prevalence, no pharmacological therapy has been specifically approved for its treatment. We propose that chlorogenic acid, a bioactive polyphenol abundantly present in *Cecropia pachystachya* leaf extracts, may exert therapeutic effects in NAFLD by modulating hepatic lipid accumulation, oxidative stress, and inflammatory responses. Chlorogenic acid possesses antioxidant, anti-inflammatory, and antilipogenic properties, acting on key molecular targets such as CPT-1, SREBP-1c, and PPAR- α . It enhances β -oxidation, attenuates lipid peroxidation, and reduces mitochondrial dysfunction induced by free fatty acids. Moreover, it modulates gut-living axis activity and intestinal microbiota composition, contributing to hepatic lipid homeostasis. The hypothesis can be tested in murine models of diet-induced NAFLD, evaluating the hepatoprotective effects of *C. pachystachya* extracts rich in chlorogenic acid through biochemical, histological, and molecular analyses. If confirmed, this hypothesis could lead to the development of novel phytotherapeutic strategies for NAFLD management, positioning chlorogenic acid as a potential natural alternative or adjuvant to existing interventions.

Keywords: Chlorogenic acid. *Cecropia pachystachya*. Non-alcoholic fatty liver disease. Hepatic steatosis. Natural products.

RESUMO

A doença hepática gordurosa não alcoólica (DHGNA) é uma desordem metabólica complexa associada à resistência à insulina, estresse oxidativo, inflamação e desregulação do metabolismo lipídico. Apesar de sua crescente prevalência, nenhuma terapia

farmacológica foi especificamente aprovada para o seu tratamento. Propomos que o ácido clorogênico, um polifenol bioativo abundantemente presente nos extratos das folhas de *Cecropia pachystachya*, pode exercer efeitos terapêuticos na DHGNA modulando o acúmulo de lipídios hepáticos, o estresse oxidativo e as respostas inflamatórias. O ácido clorogênico possui propriedades antioxidantes, anti-inflamatórias e antilipogênicas, atuando em alvos moleculares chave como CPT-1, SREBP-1c e PPAR- α . Ele aumenta a β -oxidação, atenua a peroxidação lipídica e reduz a disfunção mitocondrial induzida por ácidos graxos livres. Além disso, modula a atividade do eixo intestino-cérebro e a composição da microbiota intestinal, contribuindo para a homeostase lipídica hepática. A hipótese pode ser testada em modelos murinos de DHGNA induzida por dieta, avaliando os efeitos hepatoprotetores de extratos de *C. pachystachya* ricos em ácido clorogênico por meio de análises bioquímicas, histológicas e moleculares. Se confirmada, essa hipótese poderá levar ao desenvolvimento de novas estratégias fitoterápicas para o tratamento da DHGNA, posicionando o ácido clorogênico como uma potencial alternativa natural ou adjuvante às intervenções existentes.

Palavras-chave: Ácido clorogênico. *Cecropia pachystachya*. Doença hepática gordurosa não alcoólica. Esteatose hepática. Produtos naturais.

Introduction

Obesity is increasing at an alarming rate and it has already reached epidemic proportions, leading the World Health Organization (WHO) to classify it as a global health problem. This metabolic disorder affects more than a billion people, both in developed and developing countries, with a worrying increase among children and

adolescents [1,2]. The consequences of obesity have a significant negative impact on physical and mental health, contributing to the emergence of metabolic syndrome and several comorbidities that affect nearly every organ, such as kidneys, liver, heart, brain, joints, and reproductive organs. Furthermore, obesity is associated with an increased risk of developing several of the leading causes of death, including cardiovascular disease, respiratory disease, type 2 diabetes, cancer, neurological disorders, and non-alcoholic fatty liver disease (NAFLD) [3].

NAFLD is the most prevailing form of chronic liver disease, representing a clinicopathological syndrome that includes a spectrum of histopathological changes in the liver, from steatosis to non-alcoholic steatohepatitis (NASH) [4]. In some cases, the term can also refer to early and benign stages of the disease, before progression to NASH. In adults, NAFLD increases the risk of cirrhosis and hepatocellular carcinoma, in addition to contributing to the development of type 2 diabetes mellitus, cardiovascular disease, and chronic kidney disease. For this reason, NAFLD is increasingly seen as a multisystem condition [5,6]. Due to its high prevalence, NAFLD is expected to become the leading cause of end-stage liver disease, which will have a significant impact on public health. This impact is reflected in high medical costs, especially the growing demand for liver transplants, with non-alcoholic steatohepatitis being one of the main indications for this procedure [7].

The pathogenesis of NAFLD is complex and involves several factors. Genetic and environmental factors play fundamental roles in this condition, including genetic polymorphisms, epigenetic alterations, inadequate diet, sedentary lifestyle, obesity, insulin resistance, adipokine dysfunction, lipotoxicity, endoplasmic reticulum stress,

oxidative stress, intestinal dysbiosis, and exposure to endocrine disruptors [8,9,10]. These mechanisms result in a limited capacity of the adipocytes to store fat, increasing the release of free fatty acids into the circulation and in consequence the accumulation of fat in the liver. If this condition is not treated, it promotes the infiltration of immune cells into the liver, triggering an inflammatory process [11].

The accumulation of free fatty acids in the liver during NAFLD activates several hepatic immune cells, such as Kupffer cells, dendritic cells, and hepatic stellate cells. The lipotoxicity intensifies the inflammatory response, leading to the infiltration of neutrophils, monocytes, T lymphocytes, and macrophages [12]. The activation of these cells, combined with the interaction with Toll-like receptors (TLR4), which recognize lipopolysaccharides from the intestinal microbiota and free fatty acids as Damage-Associated Molecular Patterns (DAMPs), triggers NF- κ B-mediated proinflammatory signaling, stimulating the synthesis of cytokines such as IL-1, IL-6, and TNF- α [13,14].

The increase of the serum levels of free fatty acid also intensifies mitochondrial and peroxisomal oxidation processes, leading to increased production of reactive oxygen species (ROS). This results in oxidative stress, depleting components of the antioxidant system, such as the enzymes superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT), in addition to increasing lipid peroxidation, reflected in high levels of malondialdehyde (MDA). This inflammatory and oxidative stress cycle contributes to chronic inflammation, fibrosis, and eventually the development of hepatocellular carcinoma due to persistent inflammation [15,16].

Despite advances in the field, there are still no established therapies to treat NAFLD [17,18]. However, non-pharmacological interventions, such as lifestyle changes and vitamin C supplementation, are considered alternatives in the treatment of the disease, but there is low patient adherence. In contrast, lipid-lowering medicines such as fenofibrate and statins are effective in reducing blood lipids, however, their use is associated with adverse effects that can limit the therapy [19]. Therefore, the scientific community has intensified the search for new therapeutic approaches, such as innovative and promising strategies for the treatment of NAFLD with minimal or no side effects, such as the use of natural components [20].

Phytomedicine, which utilizes active plant compounds, has emerged as a promising approach, long used in the treatment of various diseases [21]. Bioactive compounds from various plants are widely studied in phytomedicine due to their numerous health benefits, such as quinine, curcumin, flavonoids, saponins, alkaloids, essential oils, tannins, and chlorogenic acid. Some of these bioactives, already present in herbal medicines, have a high safety profile and cause fewer side effects than synthetic medications, which is beneficial in long-term treatments [22].

The *Cecropia pachystachya* is a tropical tree native to Central and South America, widely found in Brazil, known as embaúba, umbaúba, or embaúva. Traditionally, it is used in folk medicine as a diuretic and in the treatment of asthma, cough, hypertension, diabetes, and inflammation [21]. Several compounds have been identified in this species, such as isoorientin, orientin, catechin, epicatechin, isoquercitrin, isovitexin, procyanidin B2, sitosterol, α -amyrin, and ursolic, pomolic, oleanolic, and chlorogenic acids [22,23].

Recently, phenolic acids, such as chlorogenic acid, have been highlighted for their biological and pharmacological effects [24].

Chlorogenic acid is a biologically active polyphenol with antioxidant, antibacterial, hepatoprotective, cardioprotective, anti-inflammatory, antipyretic, neuroprotective, anti-obesity, and antiviral properties. In addition to obliterating free radicals, it improves immune regulation and modulates lipid and glucose metabolism, influencing essential proteins such as AMPK and ERK1/2 [25]. By inhibiting lipid-binding enzymes and regulating AMPK and CPT-1, chlorogenic acid reduces triglyceride and fatty acid levels in animal models fed with a high-fat diet. It also facilitates cholesterol elimination by regulating bilirubin and bile acid homeostasis through the FXR and PGC-1 α receptor pathways [26].

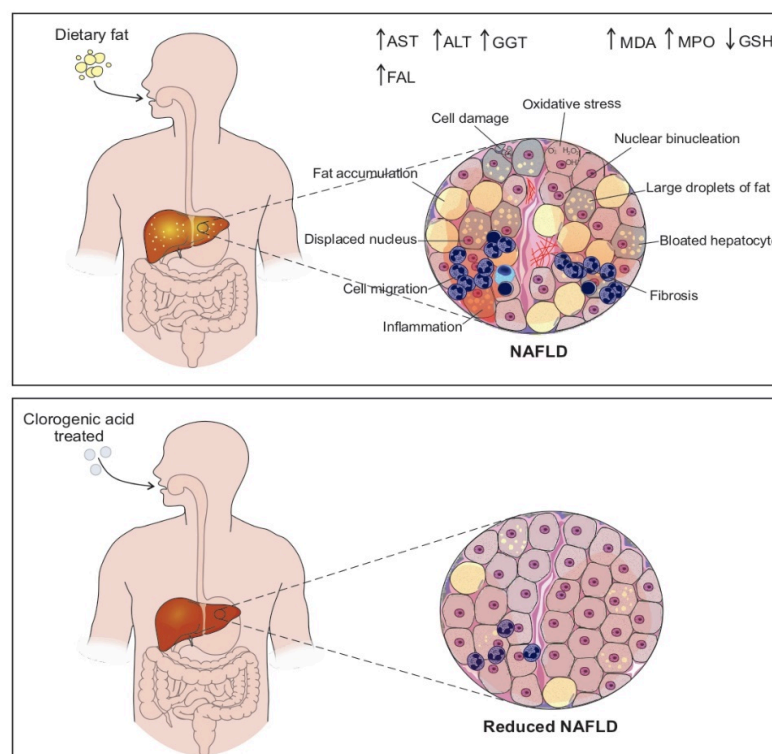
According to the literature, which demonstrates the crucial role of chlorogenic acid in regulating lipid and glucose metabolism, its use may help in the treatment of various disorders, such as hepatic steatosis. The use of *Cecropia pachystachya* extracts, rich in chlorogenic acid, emerges as a potential intervention strategy to control the pathophysiological consequences of NAFLD, including weight gain, insulin resistance, oxidative stress, and inflammation. Thus, these extracts may contribute as a therapeutic tool for people living with this condition.

The hypothesis

Due to the lack of a standard treatment for NAFLD and the medications used to minimize adverse effects, studies have demonstrated that a variety of natural products can regulate this disease, both *in vivo* and *in vitro* models [27,28]. Among these

products, *Cecropia pachystachya* leaf extracts stand out for their antioxidant, wound-healing, and anti-inflammatory activities. One of the main bioactive compounds present in these extracts is the chlorogenic acid, which has a broad and multifaceted biological function. We propose that chlorogenic acid, through its anti-inflammatory, antioxidant, and lipid metabolism-modulating characteristics, fulfill a therapeutic function in the control and prevention of NAFLD, acting in an integrated manner to reduce hepatic inflammation, combat oxidative stress, and regulate liver fat accumulation. This suggests its potential as an effective approach for the treatment of this clinical condition (**Figure 1**).

Figure 1



Hypothesis Evaluation

This hypothesis evaluates the biological activity of chlorogenic acid, a phenolic compound and chemical marker present in *Cecropia pachystachya* leaf extracts, reducing oxidative stress in hepatocytes

caused by excess fatty acids. The free radicals, which cause oxidative damage, are chemically active atoms or molecules that are unstable due to having an odd number of electrons in their outer orbit. They sequester electrons from other molecules, damaging cells, proteins, carbohydrates, lipids, and DNA [29].

This secondary metabolite significantly improves acute and chronic liver injury through antioxidant and anti-inflammatory activities [30]. As a polyphenol, this metabolite is effective in breaking free radical chain reactions, as the phenolic groups are readily ionized and act as weak acids, being able to stabilize free radicals by donating an electron and/or hydrogen, consequently, the resulting aromatic structures are not reactive and are stabilized by resonance [31].

Hepatic steatosis resulting from the progression of NAFLD arises from the increased influx of free fatty acids into the liver or the decreased disposal of lipids. The main sources of free fatty acids in the liver are non-esterified plasma fatty acids from lipolysis in adipose tissue, lipogenesis from carbohydrates, glucose, and dietary free fatty acids in the form of chylomicrons. In the liver, fatty acids can be oxidized through beta-oxidation in the mitochondria or are linked to the production of triglycerides, which are exported to the circulation as VLDL or can accumulate in lipid concentrates in hepatocytes, leading to steatosis [32].

In NAFLD, insulin resistance is an important characteristic in the development of this disease, as it induces increased peripheral lipolysis, decreased mitochondrial beta-oxidation, and induction of triglyceride biosynthesis. This is caused by an imbalance of pro-inflammatory mediators such as leptin, resistin, IL-6, tumor necrosis factor alpha (TNF- α), and intestinal lipopolysaccharides (bacterial

endotoxins), creating a barrier to insulin signaling pathways and impairs glucose uptake by the hormone. High levels of TNF- α in liver tissue cause mitochondrial dysfunction, which, instead of oxidizing fatty acids, causes lipid peroxidation. Peroxidized fatty acids increase ROS concentrations in the environment [33]. Consequently, high ROS production leads to the oxidation of nucleic acids, proteins and lipids, compromising cellular function and inducing the production of pro-inflammatory cytokines (TNF- α , IL-6, IL-1 β and TGF- β) [34,35,36].

Lipid peroxidation is one of the most prominent types of damage caused by the excess of free radicals in the cellular environment. It occurs in a cascade of biochemical reactions in unsaturated lipids of cell membranes, altering their structure, causing permeability damage, and altering ionic movement, this leads to a loss of selectivity for the entry and/or exit of nutrients and toxic substances from cells, inactivation of metabolic exchange mechanisms, release of organelle subject matters, formation of cytotoxic products such as malondialdehyde and conjugated dienes, and DNA alterations, resulting in cell death [37].

Excessive oxidation of cellular biomolecules causes damage such as apoptosis or tissue damage, leading to diseases such as cancer, liver disease, diabetes, and atherosclerosis [38]. Oxidative stress is closely related to chronic diseases such as Alzheimer's disease and chronic obstructive pulmonary disease, which validates the importance of research on redox balance for the formulation of antioxidant drugs [39]. Therefore, it is important to understand the pathways and mechanisms of action of the non-enzymatic antioxidant system, composed of low molecular weight elements such as ascorbic acid

(vitamin C), tocopherol (vitamin E), carotenoids, anthocyanins, polyphenols, ubiquinol, and glutathione [40].

Chlorogenic acid, when acting on the gut-liver axis, has antilipogenic and anti-inflammatory activity, in addition to regulating the intestinal microbiota through the degradation of fatty acids by activating hepatic autophagy linked to ALKBH5 (Alk B demethylase homolog 5), reducing hepatic steatosis [41]. The acid also improves the expression of carnitine palmitoyltransferase (CPT-1), which conjugates long-chain fatty acids to carnitine in the mitochondria, causing β -oxidation [42,43].

Another action mechanism of the polyphenol in reducing liver damage is the decrease in lipogenesis by downregulating sterol regulatory element-binding protein 1c (SREBP-1c), increasing fatty acid β -oxidation through the upregulation of peroxisome proliferator-activated receptor gamma (PPAR α), optimizing insulin sensitivity, reducing oxidative stress, and inflammatory processes [44].

It is important to highlight the lack of targeted pharmacotherapy for the treatment of NAFLD, as well as the lack of any specific medicine recommendation by the Food and Drug Administration (FDA). Therefore, drug intervention is directed at patients with associated comorbidities such as type 2 diabetes mellitus, dyslipidemia, and obesity. Pharmacological treatment aims to reduce hepatic inflammation, fibrosis, and steatosis, decrease insulin resistance, and lipid peroxidation. An example of a nonspecific drug for the treatment of NAFLD is metformin, an insulin sensitizer that reduces hepatic glucose production and increases its peripheral utilization,

thus reducing the synthesis of inflammatory mediators and oxidative stress [45]

Hypothesis Testing

The hypothesis outlined above could be tested using experimental murine models. Such models are indispensable tools for evaluating the involvement of different factors in the pathogenesis of NAFLD, as well as understanding its multifaceted etiology and therapeutic options. Since the risks arising from research in humans are significant, these models can be used as long as they reproduce similar characteristics in humans. Since through the biochemical parameters assess liver function through levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), increased concentrations of the enzyme myeloperoxidase, and increased levels of malonaldehyde (MDA), glutathione (GSH), superoxide dismutase (SOD), and myeloperoxidase (MPO).

The animal model of NAFLD induction through a hypercaloric diet is associated with lipid metabolism involving the exogenous pathway, in other words, the organism's contact with dietary fat [46]. Fat is transported by lipoproteins, chylomicrons, produced by enterocytes synthesized after fat ingestion, released into the lymphatic channels, reaching the bloodstream, transporting lipids to body tissues for use or storage. In hepatocytes, the endogenous pathway begins, with deposition followed by the synthesis of triglycerides, and subsequent segregation in the form of VLDL (very low-density lipoproteins). In extrahepatic tissues, lipids are transformed into IDL (intermediate-density lipoproteins) and LDL (low-density lipoproteins) [47]. This experimental hypercaloric diet model is well-known and widely used because it reproduces the effects of NAFLD

in humans, particularly when considering clinical and histopathological characteristics and biochemical measurements.

Hepatic steatosis is the key symptom for evaluating the induction of NAFLD in animal models by a hypercaloric diet. The condition occurs when there is a dysfunction in lipid transport, excessive fat accumulation in hepatocytes, and is directly related to dyslipidemia and type 2 diabetes *mellitus* [48]. In this condition, adipose tissue releases pro-inflammatory cytokines that interfere with insulin signal transduction pathways [47]. In the context of hepatic steatosis, the relationship between increased VLDL levels, lipogenesis, and a hypercaloric diet is well-known [49].

The model could be reproduced in groups of animals treated with phytochemicals rich in chlorogenic acid from *Cecropia pachystachya* leaf extracts. As a polyphenol, chlorogenic acid targets a variety of pathways related to the pathophysiology of NAFLD, especially in decreasing lipid peroxidation and maintaining mitochondrial beta-oxidation, while phytochemical exhibits therapeutically significant activity [50].

Implications

The hypothesis presents a range of implications that could positively impact the understanding and treatment of NAFLD. If confirmed, the biological activity of chlorogenic acid from *Cecropia pachystachya* leaves, particularly its antioxidant activity, would establish leaf extracts from this taxon as an essential phytochemical for the treatment of NAFLD and associated comorbidities. The confirmation of the hypothesis will lead to the development of a targeted therapy, as the polyphenol found in

Cecropia pachystachya leaves acts directly on the developmental pathways of this condition, inhibiting or modulating liver damage due to its antioxidant and anti-inflammatory properties.

A better understanding of how chlorogenic acid acts to reduce liver damage caused by a high-calorie diet could lead to the development of new therapeutic strategies. Therefore, the phytochemical from *Cecropia pachystachya* leaves could be a significant adjunct in the treatment of NAFLD, combined with the adoption of healthy habits (a lower-calorie diet and physical activity). By developing more targeted therapies and better understanding the mechanisms of NAFLD, it is expected to improve the quality of the patients' life, reducing symptoms such as steatosis, hepatic fibrosis, dyslipidemia, and insulin resistance.

Conclusion

Based on the evidence supporting our hypothesis regarding the hepatoprotective activity of the secondary metabolite chlorogenic acid from *Cecropia pachystachya* leaves in the treatment of NAFLD, it is suggested that the phytochemical may play a role in reducing the inflammatory response and oxidative stress, enhancing its antioxidant action, contributing to the maintenance of fatty acid beta-oxidation, reduction of lipid peroxidation, and insulin resistance, culminating in the modulation of pro-inflammatory cytokines in liver tissue, demonstrating its therapeutic activity.

However, further research is needed to validate this scientific hypothesis, exploring its impact on various metabolic pathways and biomarkers of liver function more comprehensively. Understanding how this phenolic compound affects these processes may reveal

mechanisms that influence liver health, leading to new therapeutic strategies that modulate the pathways that lead to NAFLD.

Declaration of conflict of interest

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

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