DISCIPLINARUM SCIENTIA *Disciplinarum Scientia.* **Série: Naturais e Tecnológicas**
Santa Maria, v. 27, n. 3, p. 123-142, 2026
Recebido em: 26.03.2026. Aprovado em: 12.06.2026.
ISSN 2176-462X | DOI: doi.org/10.37779/nt.v27i1.5767

THERAPEUTIC EFFECTS OF CARNAUBA (*Copernicia prunifera* MILLER) BASED BIOPRODUCTS IN METABOLIC DISEASES

EFEITOS TERAPÊUTICOS DE BIOPRODUTOS À BASE DE CARNAÚBA (Copernicia prunifera MILLER) EM DOENÇAS METABÓLICAS

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ABSTRACT

Background: Copernicia prunifera (carnauba), a palm species native to the Brazilian semiarid region, is recognized for its economic importance and its potential as a source of bioactive compounds. In this context, metabolic disorders, including diabetes, hyperlipidemia, oxidative stress, and inflammation, represent major public health challenges, increasing interest in the investigation of novel therapeutic alternatives derived from this species. **Objective:** This study aimed to systematically review the scientific evidence regarding the therapeutic effects of carnauba-derived bioproducts published between 2015 and 2024. Methods: A systematic literature review was conducted using the Google Scholar, ScienceDirect, PubMed, SciELO, and Web of Science databases. Twenty-two studies met the predefined inclusion and exclusion criteria and were included in the qualitative synthesis. **Results:** The findings indicate that carnauba-derived bioproducts possess significant pharmacological and technological potential, particularly in the context of metabolic disorders, while demonstrating favorable biocompatibility and safety profiles in experimental animal models. Carnauba wax emerged as a promising matrix for controlled drug delivery systems, improving the stability and bioavailability of bioactive compounds. Scientific production in this field is predominantly concentrated in Brazil, although international collaboration has increased in recent years. **Conclusions:** Despite these promising findings, further translational and clinical studies are required to validate the therapeutic and industrial applications of carnauba-derived bioproducts.

Keywords: Natural products; hyperlipidemia; diabetes; oxidative stress.

RESUMO

Contexto: A carnaúba (Copernicia prunifera), palmeira nativa do semiárido brasileiro, destaca-se por sua relevância econômica e por seu potencial como fonte de compostos bioativos. Nesse contexto, distúrbios metabólicos, como diabetes, hiperlipidemia, estresse oxidativo e inflamação, constituem importantes desafios de saúde pública, reforçando o interesse na investigação de novas alternativas terapêuticas derivadas dessa

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espécie. ***Objetivo:*** *Este estudo teve como objetivo revisar sistematicamente as evidências científicas relacionadas aos efeitos terapêuticos de bioprodutos derivados da carnaúba entre 2015 e 2024. Métodos: Por meio de uma revisão sistemática realizada nas bases de dados Google Scholar, Science Direct, PubMed, SciELO e Web of Science. Vinte e dois (22) estudos atenderam aos critérios de inclusão e exclusão previamente definidos e foram incluídos na síntese qualitativa.* ***Resultados:*** *Os resultados indicam que bioprodutos derivados da carnaúba apresentam significativo potencial farmacológico e tecnológico, especialmente no contexto dos distúrbios metabólicos, além de demonstrarem elevados perfis de biocompatibilidade e segurança em diferentes modelos experimentais animais. A cera de carnaúba destaca-se como uma matriz promissora para liberação controlada de fármacos, melhorando a estabilidade e a biodisponibilidade de compostos ativos. A produção científica é majoritariamente brasileira, com crescente colaboração internacional.* ***Conclusões:*** *Contudo, ainda são necessários estudos translacionais e clínicos para validar suas aplicações terapêuticas e industriais.*

Palavras-chave: *Produtos naturais; hiperlipidemia; diabetes; estresse oxidativo.*

1 INTRODUCTION

Metabolic diseases, such as diabetes mellitus (DM), arterial hypertension, and obesity, represent significant and growing challenges for global health systems (Chew *et al*., 2023). The pathophysiological mechanisms underlying these metabolic disorders are closely interconnected and constitute major risk factors for cardiovascular diseases (CVD). Metabolic diseases are characterized by chronic metabolic dysfunctions that substantially increase the risk of CVD, stroke, and other severe health complications. Moreover, multiple metabolic disorders frequently coexist in the same individual, thereby collectively exacerbating adverse health outcomes (Jin *et al*., 2023). They represent a substantial burden on global health and currently rank among the leading causes of morbidity and mortality worldwide (Miao *et al*., 2024).

The underlying etiology of metabolic disorders is multifactorial. Proposed contributors include genetic predisposition and multiple environmental and lifestyle-related factors, such as obesity, physical inactivity, and unhealthy dietary patterns (Xu *et al*., 2018).

Pharmacological therapy is commonly recommended for the management of metabolic disorders. Medications used to address insulin resistance include metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and pioglitazone (Bednarz *et al*., 2022). Recent studies have reported evidence supporting the potential role of plant extracts in controlling metabolic disorders and its components; however, current clinical guidelines do not endorse their use (Arozal *et al*., 2020). Further research is required to clarify the efficacy and safety of medicinal plants in the management of metabolic disorders. Patients with metabolic disorders often require multiple pharmacological agents to control dyslipidemia, hypertension, insulin resistance, and obesity, making close monitoring of treatment adherence essential (Swarup *et al*., 2025).

In the context of advancing scientific research and bioproduct development, the carnauba palm [*Copernicia prunifera* (Miller) H. E. Moore], an endemic species of Northeastern Brazil, stands

out. The mature leaves of this palm constitute the primary source of carnauba wax, a material composed of a complex mixture of fatty acid esters, fatty alcohols, and hydrocarbons, widely employed in the pharmaceutical, food, textile, and electronics industries. This species occurs predominantly in the Caatinga biome (Vianna, 2018), a region renowned for its unique biodiversity and characterized by species highly adapted to severe, arid environmental conditions. Although the carnauba palm is considered a domesticated crop, wax extraction still relies largely on traditional extractivist practices (Macêdo *et al*., 2024).

Despite significant scientific advances, few contemporary studies specifically investigate bioproducts and structural derivatives derived from Copernicia prunifera, particularly in experimental models of metabolic disorders. This scientific gap highlights the need for systematic reviews and critical syntheses that integrate established biochemical knowledge with recent findings regarding molecular mechanisms, bioavailability, safety, and therapeutic efficacy. In this context, understanding the potential of carnauba is highly relevant not only for advancing scientific knowledge but also for the bioprospection of bioactive compounds of Brazilian origin, thereby promoting pharmaceutical innovation and the valorization of national sociobiodiversity. Therefore, this study aimed to systematically review the scientific evidence published between 2015 and 2024 regarding the therapeutic potential, safety, and technological applications of carnauba-derived bioproducts, with particular emphasis on their effects in metabolic disorders and their potential use in pharmaceutical and biomedical fields.

2 METHODOLOGY

2.1. SYSTEMATIC LITERATURE REVIEW PROTOCOL

The present review was conducted to compile and critically analyze recent scientific evidence regarding the metabolic effects of bioproducts derived from *Copernicia prunifera*. Accordingly, a systematic review was conducted through an extensive bibliographic search carried out up to March 2025, covering studies published between 2015 and 2024. The review included scientific articles, master's dissertations, and doctoral theses published in English, Spanish, or Portuguese. The search was performed across several specialized databases, including PubMed, SciELO, ScienceDirect, Google Scholar, and Web of Science, which collectively provide broad access to peer-reviewed scientific literature (Page *et al*., 2021).

Studies were considered eligible when they investigated bioproducts derived from *Copernicia prunifera*, including plant extracts, carnauba wax-derived compounds, isolated bioactive molecules, or pharmaceutical and technological formulations. Eligible publications comprised original experimental studies, including *in vitro* assays, *in vivo* animal studies, phytochemical and physicochemical characterization studies, and investigations addressing biological, pharmacological, metabolic,

antioxidant, anti-inflammatory, hypoglycemic, hypolipidemic, hepatoprotective, or technological outcomes. Master's dissertations and doctoral theses meeting these criteria were also included.

Studies were excluded if they were review articles, editorials, letters to the editor, conference abstracts or proceedings, preprints, scientific reports, website publications, duplicate records, or studies not directly related to *Copernicia prunifera* bioproducts and their biological or technological applications.

Duplicate records and studies that did not meet the predefined inclusion criteria were excluded from the systematic review. Unreliable sources, such as drafts, website articles, preprints, scientific reports, and conference proceedings, were also omitted. The remaining articles were manually screened to ensure full compliance with the established criteria.

The search strategy combined terms related to *Copernicia prunifera* and its bioproducts with terms associated with metabolic disorders and related biological processes. The following search string was adapted according to the indexing requirements of each database: ("*Copernicia prunifera*" OR carnauba OR "carnauba wax" OR bioproducts) AND ("metabolic disorders" OR " metabolic disorders" OR diabetes OR hyperlipidemia OR dyslipidemia OR obesity OR "oxidative stress" OR inflammation). The search terms were applied to titles, abstracts, and keywords whenever permitted by the database.

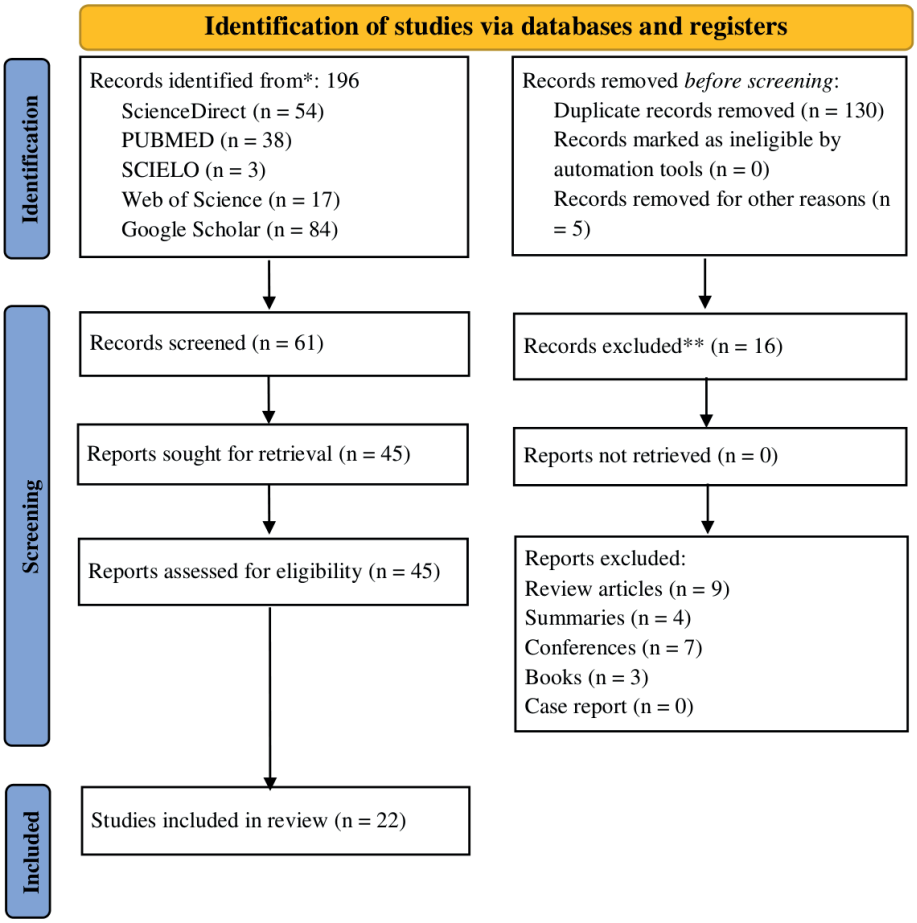
The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were applied to ensure a rigorous and transparent systematic review process (Page *et al.*, 2021). This framework systematically directs the identification, screening, and inclusion of relevant studies, thereby promoting a structured and comprehensive synthesis of the scientific literature (Alharbi *et al.*, 2024).

2.2. DATA EXTRACTION

Data from the included studies were independently extracted by the researchers using a standardized spreadsheet, with consensus reached through discussion. Extracted variables encompassed bibliographic details, characteristics, study design, experimental conditions, assays, main outcomes and conclusions. Corresponding authors were contacted to obtain missing information when necessary. Due to the limited number of studies and high heterogeneity, a meta-analysis was not feasible; therefore, the findings are presented descriptively in tables and figures.

The methodological quality and potential risk of bias of the included studies were critically assessed during data extraction. Study design, sample characteristics, experimental procedures, outcome measurements, and reporting transparency were considered. Due to the methodological heterogeneity of the included studies, a formal risk-of-bias assessment tool was not applied. Potential limitations and sources of bias were considered during data interpretation and evidence synthesis.

Figure 1 - PRISMA flowchart of the results obtained during the research production process.



Source: Flowchart template available at www.prisma-statement.org/prismastatement/flowdiagram.aspx

The initial search retrieved records from multiple databases, including ScienceDirect (n = 54), PubMed (n = 38), SciELO (n = 3), Web of Science (n = 17), and Google Scholar (n = 84). After the removal of duplicate records (n = 130) and the exclusion of five records for which the full text could not be accessed, a total of 61 unique records remained for screening. These records were assessed based on their titles, abstracts, full texts, and publication dates. Following the screening and eligibility assessment process, 22 studies (n = 22) were included in the final analysis, comprising 20 journal articles, one master's dissertation, and one doctoral thesis. All selected studies met the predefined eligibility criteria and were subjected to in-depth analysis. A flow diagram illustrating the study selection process is presented in Figure 1.

2.3.BIBLIOMETRIC NETWORK CONSTRUCTION AND DATA STANDARDIZATION

The bibliometric maps and collaboration networks presented in this study were generated by the authors using data retrieved from the Scopus database. Bibliographic information, including authors' affiliations, countries, institutions, and collaboration patterns, was exported from Scopus

and analyzed using the Bibliometrix package and its Biblioshiny interface in R (Aria & Cuccurullo, 2017). Prior to analysis, institutional names were manually checked and standardized to minimize inconsistencies arising from spelling variations, abbreviations, or different naming conventions. The resulting networks and visualizations were generated directly from the processed dataset and were not reproduced from previously published sources.

3 RESULTS AND DISCUSSIONS

After applying the search strategies and selecting studies according to the previously defined inclusion and exclusion criteria, the eligible articles were systematically analyzed. Based on this analysis, Table 01 was constructed to provide a detailed overview of the main bioproducts derived from carnauba (*Copernicia prunifera*), including their names, applications, mechanisms of action, advantages, challenges, and conclusions, along with information on authorship, year of publication, and country of origin. This synthesis offers an integrated view of the current state of the art, highlighting the biotechnological, pharmaceutical, and functional potential of these.

Table 01 - Detailed exposition of carnauba (Copernicia prunifera) derived bioproducts, encompassing their names, applications, mechanisms of action, advantages, challenges, and concluding remarks.

Study design	Bioproduct	Applications/ Mechanism of action	Advantages and Challenges	Conclusions	Author Year Country
In vitro and *in vivo*	Microencapsulation of arginine in carnauba wax	Improved beef quality. Microencapsulation modulates muscle and lipid metabolism, increasing tenderness and marbling.	Improves tenderness, red color, and marbling of beef; increases intramuscular fat. Effects evaluated in the short term; biological mechanism not fully elucidated.	Arginine microencapsulated in carnauba wax improved the quality of beef by increasing intramuscular fat, showing potential as a feed additive for livestock.	(Contreras--Lopez (Silva *et al.*, 2024) Mexico
In vitro	Ethanolic extract and fractions	Potential antimicrobial. Flavonoids and tannins can damage the bacterial membrane and inhibit microbial growth.	The need to identify active compounds and confirm efficacy and safety *in vivo* studies.	Potential as a source of antimicrobial agents against *Klebsiella pneumoniae*. Amino acids and flavonoids may be related to the observed effect.	(Silva *et al.*, 2023) Brazil
In vitro	Carnauba wax nanoparticles functionalized with antibodies	Drug encapsulation in biocompatible and biodegradable lipid particles, with surface functionalization using antibodies to enable selective cellular targeting.	Targeted and controlled drug delivery, high biocompatibility, prolonged stability, and a simple surface functionalization method. Need for *in vivo* studies, standardization, and long-term safety evaluation.	Carnauba wax nanoparticles exhibited uniform size, spherical morphology, and stability, enabling efficient encapsulation of hydrophobic molecules and antibody functionalization. Their high selectivity for HER2-positive cells and long-term stability support their potential as a platform for targeted anticancer therapies.	(IYISAN *et al.*, 2022) Turkey

In vivo	4-methoxy-cinnamic acid diester	Functional food for the prevention and management of metabolic disorders, such as hyperglycemia, dyslipidemia, obesity, and oxidative stress.	Strong hypoglycemic, hypolipidemic, and antioxidant effects with good sensory acceptability indicate potential as a functional food. However, evidence is limited to experimental models, requiring clinical studies, standardization, and long-term safety evaluation.	The oil enriched with 4-methoxycinnamic acid diester exhibited hypoglycemic, hypolipidemic, and antioxidant effects, while preserving the physicochemical quality and sensory acceptability of the food, highlighting its potential as a functional food for the prevention of metabolic disorders.	(Silva *et al*., 2021a) Brazil
In vivo	*p*-hydroxy-cinnamic diesters	Hypoglycemic and antioxidant effect	Promising hypoglycemic and antioxidant effects comparable to metformin suggest potential as a natural bioproduct. However, evidence is still limited to preclinical studies, requiring clinical trials, standardization, and long-term safety evaluation.	The sample was properly characterized, exhibited hypoglycemic activity comparable to metformin, reduced oxidative stress, and improved antioxidant, hepatic, and renal parameters, indicating potential as an alternative treatment for diabetes.	(Silva *et al*., 2021b) Brazil
In vivo	*p*-hydroxycinnamic diesters	Hypolipidemic effect, associated with modulation of hepatic lipid metabolism.	Effective hypolipidemic effect, with reduction of total cholesterol and LDL, modulation of lipid metabolism, and a favorable preclinical safety profile. Findings are limited to animal models; clinical studies, further elucidation of mechanisms, and standardization of use are required.	Spectroscopic analyses confirmed the characterization of a p-hydroxycinnamic acid diester from carnauba wax. Pharmacological assays showed hypolipidemic effects, including reduced total cholesterol and LDL-c, increased LXR mRNA expression, and decreased nitrite metabolites, suggesting potential in attenuating dyslipidemia.	(Silva *et al*., 2021c) Brazil
In vivo	*p*-hydroxy-cinnamic diesters	Significant hypocholesterolemic activity observed in an acute Triton-induced dyslipidemia mouse model.	Natural cholesterol-lowering effect, low toxicity, potential for nutraceutical development, and abundant plant source. Limited effect on triglycerides, need for clinical studies, and optimization for bioavailability.	Reduced total cholesterol in dyslipidemic mice, showed low antioxidant activity, and no effect on triglycerides. Its crystalline structure suggests potential for pharmaceutical or phytotherapeutic applications.	(Oliveira *et al*., 2020a) Brazil
In vivo	*p*-hydroxy-cinnamic diesters	Significant hypoglycemic effect in alloxan-induced diabetic mice.	Reduced blood glucose levels, safe, and a potential natural adjuvant for diabetes treatment, with effects enhanced by physical exercise. Does not control polydipsia, and the mechanism of action remains not fully elucidated.	Demonstrated efficacy comparable to metformin in type 1 diabetes animal models, with low antioxidant activity and no impact on body weight or food intake, indicating compound safety.	(Oliveira *et al*., 2020b) Brazil
In vivo	Carnauba wax lipid microparticles.	Management of inflammatory metabolic diseases, such as obesity, type 2 diabetes, and metabolic disorders.	Significant enhancement of curcumin efficacy and bioavailability, exhibiting strong anti-inflammatory effects relevant to metabolic diseases. Evidence is currently limited to animal models; clinical trials are needed.	Carnauba wax microparticles exhibited high encapsulation efficiency, amorphous curcumin, sustained release, and superior anti-inflammatory activity compared to free curcumin, highlighting their potential as a lipid-based pharmaceutical carrier.	(Rocha *et al*., 2020) Brazil

In vivo (Doctoral thesis)	*p*-Methoxycinnamic diesters	Liver protection and control of oxidative stress.	Safe, antioxidant, hepatoprotective, and with potential preventive effects in metabolic diseases. Clinical studies and evaluation of anti-inflammatory effects are required.	Demonstrated safety, with no mutagenicity or toxicity, exhibiting strong antioxidant effects by restoring Erk 1/2 and increasing GPX3 and catalase, without altering Nrf2 and SOD, indicating low risk and potential applicability in metabolic diseases.	(Canabrava, 2020) Brazil
In vivo	*p*-Methoxycinnamic Acid Diesters	Control of dyslipidemia and liver protection in high-fat diets.	Reduces total cholesterol and LDL, increases HDL, provides hepatoprotective effects, prevents weight gain, and demonstrates safety *in vitro* and *in vivo*; Further clinical trials and long-term efficacy evaluations are required.	Shows no cytotoxic or genotoxic effects and presents hypolipidemic activity (reducing total cholesterol and LDL-C while increasing HDL-C), along with hepatic antioxidant protection and lipid metabolism modulation via LCAT, indicating potential for preventing and managing dyslipidemia.	(Paim *et al.*, 2020) Brazil
Phytochemical characterization (Master's Dissertation)	Extracts from the seeds and bark of the carnauba palm.	Demonstrates significant antioxidant potential, including the presence of tannins and tocopherols, particularly **α**-tocopherol.	Natural source of bioactive compounds with antioxidant potential and applications in food and pharmaceuticals; supercritical CO_2 extraction preserves sensitive compounds. Limitations include low antioxidant activity in certain fractions and the high cost and complexity of supercritical extraction.	Supercritical CO_2 extraction enhanced oil yield and antioxidant compound concentration, influenced by processing conditions. Seed extracts showed stronger antioxidant activity than peel, and bioactive compounds (e.g., fatty acids and tocopherols) may help protect against metabolic diseases by reducing oxidative stress and regulating lipid metabolism.	(Buriti, 2020) Brazil
In vivo	*p*-hydroxycinnamic diesters	Hypoglycemic effect by reducing blood glucose levels in diabetic mice.	It reduces blood sugar, protects the liver and kidneys, and controls weight. Pre-clinical studies and safety assessments are needed.	Protected liver and kidneys, aided in weight control, and attenuated water and food intake in diabetic mice.	(Moura *et al.*, 2020) Brazil
Phytochemical characterization	Carnauba fruit extract	Significant antioxidant activity attributed to the content of anthocyanins, phenolic compounds, and vitamin C.	Natural antioxidant, protects against oxidative stress, and may help prevent metabolic disorders. Requires *in vivo* studies and assessment of bioavailability.	They contain natural antioxidants that help protect against oxidative stress and may contribute to the prevention of metabolic diseases.	(Moreira-Araújo *et al.*, 2019) Brazil
In vivo	Carnauba wax palm fruit	Modulated the expression of genes related to lipogenesis and cholesterol, suggesting a potential hypolipidemic effect and improvement in meat quality.	Improvement in meat quality (more tender, lower cholesterol), favorable genetic modulation, without altering physical parameters or growth. Minor changes in the lipid profile were observed, indicating the need for further studies to confirm practical and long-term effects.	Dietary inclusion of carnauba fruit in goats did not affect growth or physical parameters but modulated genes associated with lipogenesis and cholesterol metabolism, suggesting hypolipidemic effects and improved meat quality. These findings support its potential as a functional feed additive.	(Silva *et al.*, 2019) Brazil
Phytochemical characterization and *in vitro* study	Carnauba wax extracts	Antioxidant activity, reducing oxidative stress.	Strong natural antioxidant activity, presence of bioactive compounds, and potential applications in functional foods and pharmaceutical products. Requires *in vivo* studies, standardization, and long-term safety evaluation.	Carnaúba wax extracts show antioxidant and antifungal activity due to bioactive compounds, especially in mature leaves, indicating potential for pharmaceutical and food applications.	(Andrade *et al.*, 2018) Brazil

In vivo	*p*-methoxy-cinnamic diester	Hypolipidemic and hepatoprotective effect	Strong hypolipidemic effect, reducing cholesterol and triglycerides, with hepatoprotective action and efficacy comparable to conventional drugs. Clinical studies and standardization are required.	Significant hypolipidemic potential, especially at 100 mg/kg, reducing cholesterol and triglycerides, with effects comparable or superior to simvastatin and hepatoprotective action. May modulate lipoprotein lipase, suggesting potential in cardiovascular disease prevention.	(Filho *et al.*, 2017) Brazil
Phyto-chemical characterization	Hexane and ethanolic extracts from the carnauba fruit	Antioxidant activity	Rich in bioactive compounds (phenols, flavonoids, tannins, anthocyanins), with significant antioxidant activity and nutritional value, showing potential for functional foods and animal nutrition. Requires determination of safe and effective doses in *in vivo* models.	Is nutritious and rich in bioactive compounds such as phenols, tannins, and flavonoids, exhibiting high antioxidant activity, particularly in ethanolic extracts. It shows potential for functional use in human and animal nutrition and promotes sustainable utilization of the biome.	(Aline *et al.*, 2017) Brazil
Technological application	Mini-tablets for sustained-release soluble drugs	Carnauba wax forms lipid matrices that slow drug dissolution, extending release time and enabling prolonged therapeutic action.	Sustained drug release, improved powder flow and tabletability, good mechanical strength, suitable for highly soluble drugs, and potential for combination therapies. Need for clinical studies.	Enhanced flowability, compressibility, and mechanical strength of captopril and metformin mini-tablets, enabling sustained drug release for over 450 minutes. The excipient proved safe, effective, and promising for multiparticulate formulations and fixed-dose systems.	(Nart *et al.*, 2017) Brazil
In vivo	Aqueous Extract	Reduction of dyslipidemia and metabolic protection.	Reduces lipids, helps control body weight, protects the liver and kidneys, and is safe with natural activity. Clinical trials and long-term efficacy evaluations are still required.	The aqueous extract reduces total cholesterol, LDL, and triglycerides, increases HDL, regulates weight gain, and protects the liver and kidneys. Its mechanism of action involves bile acid sequestration, increased intestinal viscosity, and modulation of lipid absorption.	(Paim *et al.*, 2017) Brazil
In vitro	*p*-methoxy-cinnamic diesters	Management of metabolic diseases associated with oxidative stress, such as dyslipidemia, diabetes, and cardiovascular disorders.	Strong antioxidant activity, good bioaccessibility, and high stability indicate potential for functional foods and pharmaceuticals. However, evidence is limited to *in vitro* studies, requiring in vivo validation, standardization, and long-term safety assessment.	Exhibits high purity, crystalline structure, thermal stability, and strong UV absorption, along with significant antioxidant activity even after simulated digestion, highlighting its potential for food and pharmaceutical applications.	(Freitas *et al.*, 2016) Brazil
In vivo	*p*-methoxy-cinnamic diester	The potential hypoglycemic effect is associated with modulation of glucose metabolism.	Safe, natural, with potential hypoglycemic activity and sustainable. Mechanism not fully elucidated and lacking clinical studies.	Exhibited low acute toxicity in mice, with no mortality or significant changes in behavior or vital organ weights, indicating safety for therapeutic use and potential as a hypoglycemic agent.	(Rodrigues *et al.*, 2015) Brazil

Based on the information presented in Table 1, the studies investigating carnauba-derived bioproducts employed diverse methodological approaches, including chemical and phytochemical characterization (n = 3), *in vitro* assays (n = 5), and predominantly *in vivo* experimental models (n = 14). One study specifically evaluated pharmaceutical applications involving the use of carnauba-derived

materials as functional excipients. No clinical trials were identified, indicating that the available evidence remains largely preclinical and technology-oriented.

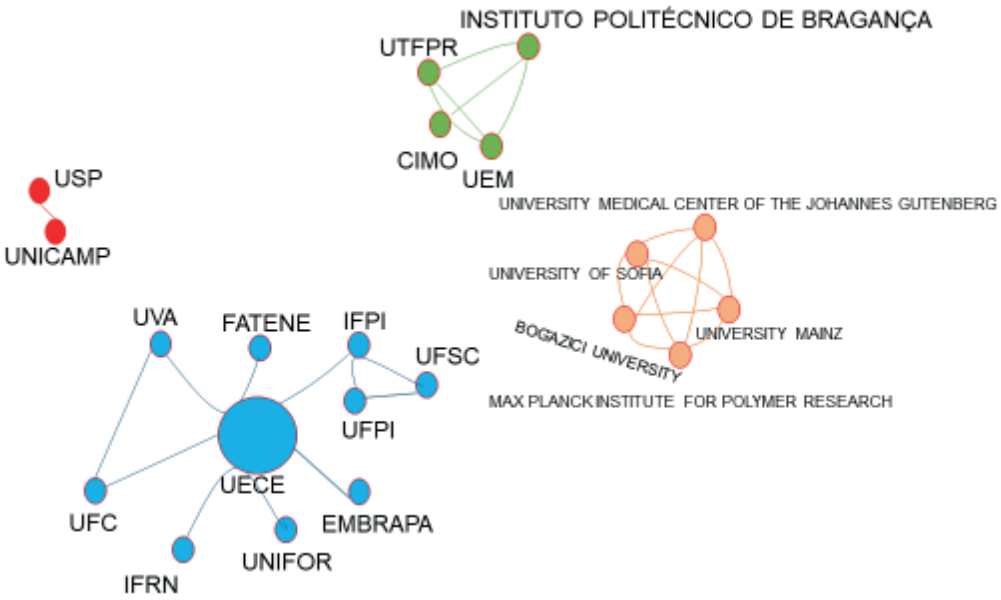
The studies highlight the versatility of carnauba-derived bioproducts, with applications in drug delivery and metabolic disorder management. Carnauba wax nanoparticles and microparticles act as biocompatible carriers for bioactive compounds, such as cinnamic esters, with hypoglycemic, hypolipidemic, and antioxidant effects. Additionally, plant extracts show strong antioxidant activity, reinforcing carnauba's potential for pharmaceutical, nutraceutical, and technological applications, especially in metabolic disease prevention.

Carnauba-derived bioproducts show high biocompatibility, safety, stability, and multiple biological activities (e.g., hypoglycemic, hypolipidemic, antibacterial, antioxidant, and anti-inflammatory), with potential in drug delivery, functional foods, and pharmaceuticals. However, evidence is mostly preclinical, highlighting the need for clinical trials, standardization, mechanistic studies, and long-term safety evaluation.

Furthermore, carnauba-derived bioproducts display well-defined physicochemical properties, preclinical safety, and relevant biological activity. The evidence supports their potential use in controlled drug delivery systems, targeted therapies, functional foods, and strategies for the prevention and management of metabolic disorders. The encapsulation capacity and stability of carnauba wax-based lipid matrices, the effectiveness of cinnamic esters in modulating lipid and glucose metabolism, and the high bioactive compound content in plant extracts further reinforce the value of carnauba as a promising source of bioproducts for pharmaceutical, nutraceutical, food, and veterinary applications. However, the consolidation of these applications depends on the advancement of clinical studies, process standardization, and the validation of long-term efficacy and safety.

The 22 articles included, published between 2015 and 2024, demonstrate a clear predominance of Brazilian scientific production on bioproducts derived from carnauba (*Copernicia prunifera*). This pattern reflects the species' endemic origin and Brazil's leading role in this field of research. International contributions are limited, represented by a single study conducted in Turkey, indicating that despite growing global interest, Brazil remains the primary center of investigation, with considerable potential to expand international collaborations.

Figure 2 - Network of institutional interaction and collaboration in research on carnauba bioproducts.

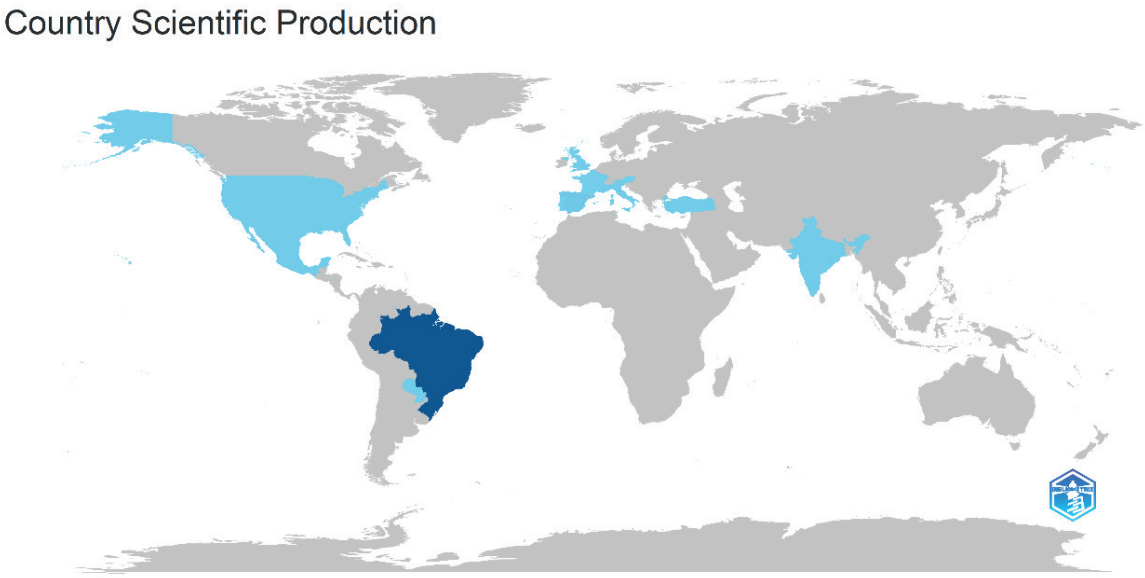


Source: Prepared by the authors based on data retrieved from Scopus and analyzed using the Bibliometrix package and the Biblioshiny interface in R (Aria; Cuccurullo, 2017).

The figure illustrates the network of interactions and collaborative relationships among national and international institutions involved in studies on bioproducts derived from carnauba (*Copernicia prunifera*). Distinct collaboration clusters can be identified, with Brazilian institutions emerging as the principal hubs of scientific connectivity. Among these, the State University of Ceará (UECE) exhibits a prominent central position within the network, maintaining collaborative links with several federal universities, technological institutes, and research organizations, including UFC, UFSC, EMBRAPA, and UNIFOR. This pattern highlights the institution's strategic role in fostering scientific cooperation and advancing knowledge related to carnauba-derived bioproducts.

In parallel, international clusters are identified, especially in Europe, involving universities and centers of excellence such as the University of Mainz, the Max Planck Institute for Polymer Research, and the University Medical Center of Johannes Gutenberg University. These collaborations are primarily focused on advanced studies, compound characterization, and technological applications. The presence of connections between national and international groups demonstrates the internationalization of research on carnauba-derived bioproducts, reinforcing their scientific, technological, and economic potential and underscoring the global relevance of this species native to northeastern Brazil within the context of sustainable innovation.

Figure 3 - Geographic Distribution of Scientific Publications on *Copernicia prunifera* Bioproducts



Source: Prepared by the authors based on data retrieved from Scopus and analyzed using the Bibliometrix package and the Biblioshiny interface in R (Aria; Cuccurullo, 2017).

Figure 3 shows that Brazil leads global scientific production on bioproducts from carnauba (*Copernicia prunifera*), despite its endemic origin. Other countries, especially in Europe, such as Germany, Turkey, Bulgaria, and Portugal, also contribute, reflecting growing international interest. This highlights the global relevance of carnauba research and its potential to drive international collaboration and sustainable innovation.

3.1 ANTIDIABETIC ACTIVITY AND GLYCEMIC CONTROL

The diester of *p*-hydroxycinnamic acid is widely found in fruits and beverages and belongs to the cinnamic acid family. It is a chemical compound present in carnauba leaf powder (*Copernicia prunifera*) and exhibits promising pharmacological properties for the management of chronic non-communicable diseases. In this context, (Silva *et al.*, 2021b) characterized a p-hydroxycinnamic acid diester from carnauba and evaluated its effects in diabetic mice. Treatment at doses of 200 and 400 mg/kg demonstrated strong antioxidant activity and significantly reduced blood glucose levels, oxidative stress markers, body weight, and water intake, indicating beneficial effects against diet-induced diabetes.

Treatment with olive oil enriched with PCO-C (4-methoxycinnamic acid diester) markedly reduced blood glucose levels, restoring them to values close to baseline and producing a reduction of more than 40% compared with the control group, with efficacy comparable to that of metformin. PCO-C administered alone also promoted a significant decrease in glycemia, whereas olive oil alone did not exhibit hypoglycemic effects. These findings highlight the potential of PCO-C, alone or in

combination, as a promising natural alternative for controlling and preventing obesity-associated hyperglycemia (Silva *et al.*, 2021a).

In an experimental model of alloxan-induced diabetes, *p*-hydroxycinnamic diesters also demonstrated significant antihyperglycemic activity, as evidenced by significant reductions in blood glucose levels. The study was conducted with 50 female Swiss mice, allocated into five groups (n = 10): negative control (healthy animals treated with water), positive control (diabetic animals treated with water), *p*-hydroxycinnamic diester-treated groups at doses of 25 and 50 mg/kg, and a metformin-treated group (200 mg/kg) used as the standard drug. After 28 days of treatment, a significant hypoglycemic effect was observed in animals treated with the carnauba-derived bioproduct at the lowest tested dose (25 mg/kg), reinforcing the therapeutic potential of these compounds for glycemic control (Moura *et al.*, 2020).

Oliveira *et al.* (2020b) evaluated p-methoxycinnamic acid (PCO-C) with and without physical exercise in diabetic mice. Diabetes was induced by alloxan, and treatments included PCO-C (200 mg/kg), exercise, and metformin. After 21 days, PCO-C, alone or combined with exercise, significantly reduced blood glucose levels, with effects comparable to metformin, indicating similar efficacy to the standard therapy.

3.2 ANTI-HYPERLIPIDEMIC ACTIVITY

Dyslipidemia is increasingly prevalent worldwide, and although statins are effective, they may be associated with adverse effects and elevated treatment costs, highlighting the need for alternatives. In this context, p-hydroxycinnamic diesters (HCE) from carnauba wax were evaluated in mice fed a high-fat diet. Treatment with HCE (200 and 400 mg/kg) significantly reduced total cholesterol and LDL levels, increased LXR expression, and did not induce relevant inflammatory responses. Overall, HCE was safe and attenuated dyslipidemia induced by a Western-style diet (SILVA *et al.*, 2021c).

Another dyslipidemia treatment involving a carnauba-derived bioproduct was reported by Oliveira *et al.* (2020a), evaluated a carnauba-derived bioproduct in an acute dyslipidemia model induced by Triton WR-1339. Animals were divided into control, gemfibrozil-treated, and p-hydroxycinnamic acid diester groups (200 and 400 mg/kg). Treatments were administered before and after induction. Both doses significantly reduced total cholesterol ($p < 0.05$), indicating promising pharmacological activity.

In another study, the hypolipidemic effects of *p*-methoxycinnamic acid diesters (PCO-C) extracted from *Copernicia prunifera* were evaluated in murine models of acute and chronic dyslipidemia. Administration of PCO-C at 100 mg/kg significantly reduced plasma total cholesterol and triglyceride levels in both experimental models. Histological analyses demonstrated that PCO-C did not induce hepatotoxicity and effectively reduced hepatic steatosis in animals fed a hyperlipidemic diet. These findings

indicate that PCO-C isolated from *Copernicia prunifera* is effective in lowering total cholesterol and triglyceride levels across different dyslipidemia induction models, suggesting its potential as a therapeutic agent for the management of hyperlipidemia and atherosclerosis (Filho *et al.*, 2017).

Additionally, olive oil enriched with PCO-C exhibited a significant hypolipidemic effect in adult zebrafish with dyslipidemia induced by an obesogenic diet. This treatment resulted in a marked reduction in total cholesterol levels, reaching approximately 50% compared with the control group, with results comparable to those observed with simvastatin. Furthermore, PCO-C administered alone significantly reduced non-HDL cholesterol levels, contributed to decreased triacylglycerol concentrations, and exerted antioxidant effects, protecting the liver against oxidative stress without inducing hepatic or renal toxicity. Collectively, these findings indicate that PCO-C, either alone or in combination with olive oil, represents a promising therapeutic strategy for the management of dyslipidemia and metabolic disorders, even after a short treatment period (Silva *et al.*, 2021a).

Oral treatment with *p*-methoxycinnamic acid diesters demonstrated a significant hypolipidemic effect in Swiss mice fed a high-fat diet. After 30 days of treatment, *p*-methoxycinnamic acid significantly reduced total serum cholesterol levels (−18.84%) compared with the HFD group, showing efficacy comparable to that of simvastatin. This effect was sustained for 90 days, resulting in an approximate 19% reduction, in addition to preventing the progressive increase in cholesterol observed in untreated animals. Regarding LDL-C, a significant reduction was already observed at 30 days (−26.7%), with *p*-methoxycinnamic acid being the only treatment to produce this effect at that time point (Paim *et al.*, 2020).

The aqueous extract of *Copernicia prunifera* fruit pulp (APE) exhibited marked anti-hypercholesterolemic activity in mice subjected to a hypercholesterolemic diet. Oral administration of APE (150 and 300 mg/kg/day) for up to 90 days significantly reduced total cholesterol and LDL-C levels, increased HDL-C, and maintained triglycerides at reduced levels, in addition to reversing excessive diet-induced weight gain. These effects were dose- and time-dependent and, for some parameters, were superior to those observed with simvastatin. Overall, the results indicate that carnauba APE has preventive and therapeutic potential against hypercholesterolemia and cardiovascular diseases, with no evidence of treatment-related adverse effects (Paim *et al.*, 2017).

3.3 ANTIOXIDANT, OXIDATIVE STRESS-MODULATING, AND ANTI-INFLAMMATORY ACTIVITIES

Cinnamic acid esters isolated from carnauba (*Copernicia prunifera*) exhibit a wide range of biological activities, particularly antioxidant effects. Studies have shown that esterification enhances this activity, making the esters more effective than free cinnamic acid. Antioxidant assays (FRAP, ABTS, and cellular antioxidant activity) confirmed that the *p*-methoxycinnamic acid diester (PCO-C)

possesses marked antioxidant capacity, good bioaccessibility, thermal stability, and UV absorption. In cellular models, PCO-C significantly reduced reactive oxygen species production. These findings indicate the potential of PCO-C as an antioxidant for pharmaceutical and food applications, including functional foods and active packaging (Freitas *et al*., 2016).

Olive oil enriched with PCO-C exhibited relevant antioxidant effects without promoting fatty acid oxidation or compromising the oil's natural antioxidants, such as tocopherols and polyphenols, while also its technological and sensory characteristics were preserved. In an obesogenic diet-induced model in adult zebrafish, treatment with PCO-C, either alone or in combination with olive oil, significantly reduced hepatic reactive oxygen species levels, an effect not observed with simvastatin, indicating protection against hepatic oxidative stress (Silva *et al*., 2021a).

A study evaluating *p*-methoxycinnamic acid diesters demonstrated a significant antioxidant effect in an *in vivo* high-fat diet model. In mice fed a high-fat diet, oral treatment with PCO-C significantly reduced hepatic lipid peroxidation, as evidenced by decreased levels of malondialdehyde (MDA), a classical marker of oxidative stress. While untreated animals showed a marked increase in MDA levels, the *p*-methoxycinnamic acid-treated group exhibited values close to those of the control group, indicating a hepatoprotective effect. These results confirm the role of PCO-C in attenuating diet-induced oxidative stress without inducing hepatic or renal toxicity, reinforcing its potential as a natural antioxidant compound (Paim *et al*., 2020).

Aqueous and ethanolic extracts of carnauba wax powder (*Copernicia prunifera*) demonstrated high antioxidant activity, particularly the ethanolic extracts of type B wax, which were associated with elevated levels of phenolic compounds, flavonoids, and flavanols, such as gallic acid, catechin, and chlorogenic acid. Considering that oxidative stress is closely linked to inflammatory processes, the ability of these extracts to scavenge free radicals (DPPH and ABTS assays) suggests a potential indirect anti-inflammatory effect. Thus, carnauba wax stands out as a promising source of bioactive compounds with capable of modulating inflammation through antioxidant mechanisms mediated by the reduction of reactive species and antioxidant protection (Andrade *et al*., 2018).

The carnauba fruit (*Copernicia prunifera*) exhibits a relevant composition of bioactive compounds and notable antioxidant activity. Total phenolic content of 314.44 ± 9.50 mg GAE/100 g was reported, along with a high anthocyanin content (9.35 ± 0.00 mg cyanidin-3-glucoside/100 g). Carnauba fruit also stood out for its vitamin C levels (≈78.1 mg/100 g), exceeding the recommended daily intake. Antioxidant activity was determined using the DPPH radical scavenging assay and expressed as Trolox equivalent antioxidant capacity (TEAC), confirming the fruit's antioxidant potential. These data highlight the nutritional and functional value of carnauba as a natural antioxidant source from the Brazilian Cerrado (Moreira-Araújo *et al*., 2019).

Solid lipid microparticles based on carnauba wax were prepared for curcumin encapsulation via hot homogenization. Anti-inflammatory activity was evaluated in a carrageenan-induced paw

edema model in rats by measuring edema volume, myeloperoxidase activity, and nitric oxide levels in plantar tissue. Overall, carnauba wax-based solid lipid microparticles demonstrated high encapsulation efficiency and enhanced curcumin's anti-inflammatory activity by up to 16-fold, highlighting this system as a promising strategy to improve the therapeutic performance of bioactive molecules (Rocha *et al*., 2020).

Taken together, these findings support the potential of *Copernicia prunifera,* derived bioproducts as promising sources of bioactive compounds capable of modulating oxidative stress and inflammatory responses, two key mechanisms involved in the pathogenesis of metabolic disorders. According to Stromsnes *et al.* (2021), chronic low-grade inflammation and increased oxidative stress contribute directly to the development of insulin resistance, dyslipidemia, obesity, and cardiovascular complications, making them important therapeutic targets. In this context, natural products rich in phenolic compounds and other antioxidant molecules have attracted considerable attention due to their ability to regulate redox balance and inflammatory pathways. The antioxidant, hepatoprotective, hypoglycemic, and hypolipidemic effects reported for carnauba-derived compounds are consistent with this broader body of evidence and suggest that *Copernicia prunifera* may represent a valuable natural resource for the development of innovative strategies aimed at preventing and managing metabolic disorders and related disorders.

Although the available evidence suggests promising pharmacological and technological applications for *C. prunifera*, derived bioproducts, important limitations should be acknowledged. Most studies were preclinical, with no clinical trials identified, limiting the direct translation of findings to humans. In addition, several studies used small sample sizes and heterogeneous experimental models, making comparisons difficult. Variability in extraction methods, formulations, and chemical composition also limits reproducibility and standardization. Furthermore, information regarding randomization, blinding, and other measures to reduce bias was often insufficiently reported. Therefore, larger, standardized, and well-designed studies, particularly clinical trials, are needed to strengthen the current evidence base.

4 CONCLUSIONS

To the best of our knowledge, this study provides the first comprehensive synthesis of the scientific evidence on bioproducts derived from *Copernicia prunifera*. The available literature demonstrates that carnauba-derived compounds, particularly p-hydroxycinnamic and p-methoxycinnamic acid diesters, as well as extracts obtained from different plant parts, exhibit promising hypoglycemic, hypolipidemic, antioxidant, anti-inflammatory, and hepatoprotective activities in preclinical models. In addition, carnauba wax has shown considerable potential as a biocompatible and biodegradable material for controlled drug delivery systems, expanding its pharmaceutical and technological applications.

The findings highlight the relevance of *C. prunifera* as a valuable resource for the development of pharmaceutical, nutraceutical, food, and veterinary products, while reinforcing the strategic role of Brazilian research and the growing international interest in this species. However, the current evidence remains largely restricted to *in vitro* studies and animal models, limiting the direct translation of these findings to human health.

Future research should prioritize the standardization of extraction methods and formulations, pharmacokinetic and bioavailability studies, long-term safety assessments, and the elucidation of molecular mechanisms underlying the observed biological effects. Furthermore, well-designed clinical trials are needed to establish safe and effective dosing regimens and to evaluate clinically relevant outcomes related to glycemic control, lipid metabolism, inflammation, and cardiovascular risk. Such advances will be essential to validate the therapeutic potential of carnauba-derived bioproducts and support their future clinical and industrial applications.

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