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REVIEW

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Comprehensive preclinical studies on the bioactivity of *Orbignya phalerata* Mart. (Babassu) and its derived products: a systematic review

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Abstract

Background Babassu (*Orbignya phalerata* Mart.) is a palm tree well distributed in Latin America, whose fruit has a mesocarp and kernel used for human feeding, and empirically related to the treatment of gastritis, vaginitis, and wound healing.

Main body of the abstract The activities attributed to babassu can guide new research on health applications and, for this reason, this study aimed to report in vitro and in vivo biological activities of *O. phalerata* constituents through a systematic review. Searches terms were applied in five world databases and the data from the publications were collected according to PICOS criteria, including the fruit component, concentration/dose, time of exposure, and comparative groups. All outcomes were reported and the most relevant outcomes were described by a narrative synthesis and a risk of bias assessment. A total of 28 in vitro ($n=15$) and in vivo ($n=11$) studies were included, and two showed both experimental designs. The studies were heterogeneous, with the predominance of metabolic analysis, wound and peptic ulcer healing, besides in vivo toxicity, among others. For in vitro analysis, antioxidant tests, cell viability and antimicrobial activity predominated. All in vivo ones used rodents. Meanwhile, tumor and non-tumor cell lines, bacteria strains, *Leishmania amazonensis*, *Artemia salina*, and antioxidant reactions were considered for in vitro protocols.

Short conclusion The most frequent applications included mesocarp and kernel in a wide range of extracts, emulsions, and concentrations. Their low in vitro lethality and cytotoxicity, and no acute toxicity in vivo open possibilities for the development of long-term toxicity assays with repeated doses in rodents and interventions in clinical trials.

Keywords Babassu, Kernel, Pharmacological activity, Mesocarp, Anti-inflammatory, Toxicity

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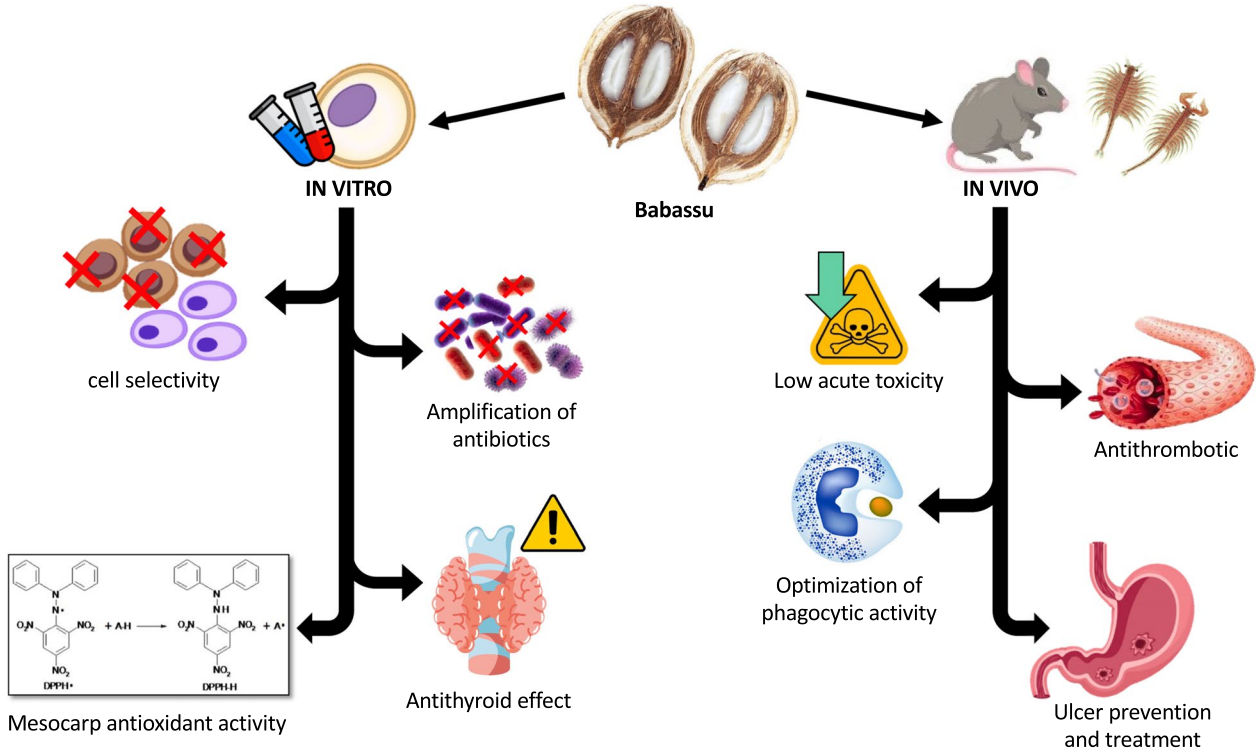
Graphic abstract



Background

Orbignya phalerata Mart. (syn. *Attalea speciosa*), belonging to the Arecaceae family, is a palm tree well distributed in different biomes in Latin America, such as Amazon rainforest, Atlantic forest, and especially in Cerrado and Caatinga, and popularly known as Babassu, uauaçu, and catolé [1]. The genus *Orbignya* has more than 20 species, but the binomial nomenclature *Orbignya phalerata* Mart. was adopted by this review because it is the most used and recent in the bibliography consulted (Fig. 1). Its fruit is generally completely used, but only its mesocarp and kernel are edible. The studies related to babassu describe about the mesocarp and/or the kernel, mainly. The first is used in cosmetics industry [2] and the mesocarp flour has been empirically consumed for the treatment of gastritis, vaginitis, and topically as wound healing [3].

Plant species are continuously studied about their potential developing new drugs and products based on the diverse biological activities and pharmaceutical properties, mainly influenced by primary and secondary plant metabolites. Primary constituents, such as fatty acids, carbohydrates, and amino acids, are crucial macromolecules aiding plant survival and structural development. Meanwhile, secondary metabolites, derived from primary metabolism, play key roles in physiological processes and act as a defense mechanism against biological or chemical agents, such as polyphenols, which are one of the most common types of bioactive compounds, including the flavonoids catechin, epicatechin, proanthocyanidin, and others, all capable of scavenging or neutralizing reactive or radical species [4], which explains, at least in part, their antioxidant, anti-inflammatory, and antimicrobial properties, to name a few [5].

Among the edible parts of babassu, the kernel stands out for its elevated concentrations of fatty acids, primarily lauric acid (12:0; 46.89%), myristic acid (C14:0; 16.95%), and oleic acid (C18:1; 13.54%) [6–8]. Conversely, the mesocarp flour is a source of energy (1375 kJ/100 g), complex carbohydrates (79.19%), potassium (3.62%), magnesium (0.39%), phosphorus (0.35%), and a small content of protein (1.41%) [9].

In human metabolism, while carbohydrates are an energy source, flavonoids act as scavenger molecules. Simultaneously, fatty acids not only contribute to caloric supply but also play specific roles such as bactericidal [10]. Regarding the total phenolic compounds in the mesocarp (558.87 mg/100 g), the most important among

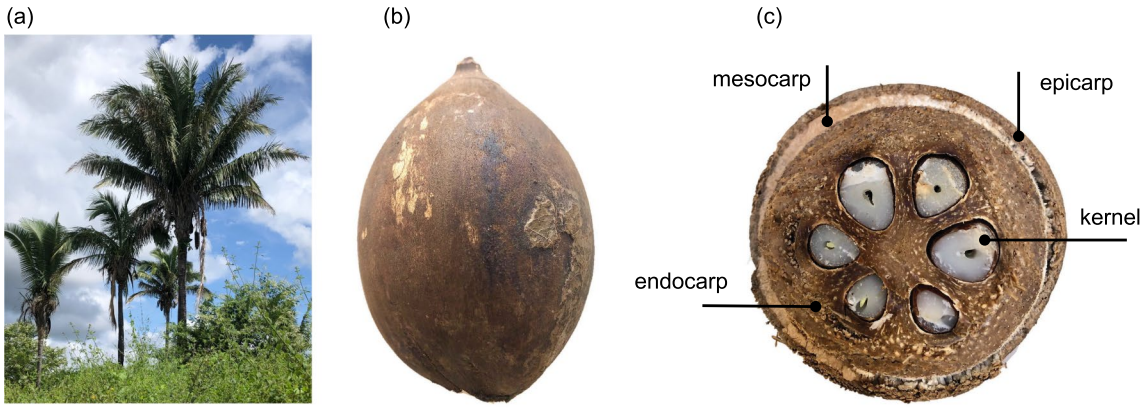


Fig. 1 Parts of *Orbignya phalerata* Mart. **a** palm; **b** whole fruit; **c** cross section. Source: personal archives

Table 1 Flavonoids from mesocarp extracted by organic solvents

Extract	Flavonoid	Content	References
Hydroethanolic	Catechin	8.02—8.22[a]	[62]
	Epicatechin	14.17—15.26[a]	
Aqueous	Catechin	0.28[b]; 0.88 µg/g[c]	[63]
	Epicatechin	na[b]; 29.61 µg/g[c]	
Ethyl acetate	Epicatechin	18.4[a]	[35]
	Dimer	17.7[a]	
	Trimer	23.8[a]	
	Tetramer	18.0[a]	
Hydroethanolic	Proanthocyanidin	421.7 mg CE/g	[35]
Ethyl acetate	Proanthocyanidin	335.6 mg CE/g	[35]

[a] Retention time in minuts (HPLC or spectrophotometry)

[b] Before in vitro digestion (spectrophotometry)

[c] After in vitro digestion (spectrophotometry)

na not available, *CE* catechin equivalents

them are the flavonoids extracted by organic solvents [9] (Table 1).

Preclinical trials have elucidated the biological effects of babassu crude components and its extracts. However, there is no evidence of compiled findings in a systematic review. Therefore, this study reported in vivo and in vitro biological activities of *O. phalerata* constituents in order to contribute to the development of original studies and applications for health care and research.

Main text

Methods

This systematic review was conducted according to PRISMA guidelines [11] (Preferred Reporting Items for Systematic Reviews and Meta-Analyzes) and registered in PROSPERO [12] (International Prospective Register of Systematic Reviews, registration nº CRD 42022302309).

Publications eligibility was established based on the guiding question "Do different parts of babassu contain compounds capable of exerting biological effects in vivo and/or in vitro?" and PICOS criteria [P: Population; I: Intervention; C: Comparator; O: Outcome; S: Study] (Table 2). Only original articles from indexed journals were eligible, with no limitation of period or language. All publications from gray literature or not fully published articles were excluded.

For animal model studies, topical, intraperitoneal, parenteral, or rectal interventions were excluded. To be considered, both in vivo and in vitro designs should clearly

Table 2 Eligibility criteria according to PICOS

	In vivo	In vitro
P	Experimental strains of any sex, age, and weight	Tumor and non-tumor cell lines and/or microorganism strains, and/or chemical assays
I	Oral or gavage offering of crude or processed babassu components or isolated extracted compounds	Assays with crude or processed babassu components or isolated extracted compounds
C	Positive, negative, and/or parallel control	Positive, negative, and/or parallel control
O	Favorable or unfavorable biological effects, local or systemic, acute or chronic	Favorable or unfavorable biological effects for/against pathogenic or non-pathogenic microorganisms, cell lines, or chemical reactions
S	In vivo experimental studies	In vitro experimental studies

describe the type of substance, concentration, and intervention period, at least for the main outcome.

Data sources, searches and studies selection

Explorations in the LILACS [13], SciELO [14], Science Direct [15], Web of Science [16], and PubMed [17] databases were performed by search terms registered in MeSH, combined by AND and OR Boolean operators (Table 3) during April 1st to April 7th, 2022 and again on March 24th, 2022 to update indexes. The searches were exported to Rayyan for prior systematization and metrics [18].

Initially, the studies were screened using the title and abstract (by ND and IOC), independently. Those considered eligible were read in full (ND, IOC) and references were kept for possible inclusion if they met the criteria. Disagreements were solved by consensus and, when necessary, a third researcher (JMCS) was consulted.

Data extraction and description of results

Data extraction included authors, publication year, title, locality, and study design. For in vivo publications, characteristics of the population were collected and for in vitro assays, cell lines, strain, and/or chemical reactions were described. Interventions included fruit part and its product, concentration, time of exposure, and comparative groups. Favorable or unfavorable outcomes were reported, as well as the most relevant assessment instruments and results. The compiled data were organized into tables, facilitating a comprehensive narrative synthesis and outcomes comparison, when applicable. Values were expressed as mean and standard deviation, when available, and compared with control and/or parallel groups. Results were considered significant when $p < 0.05$.

Risk of bias assessment

The risk of bias assessment for in vivo experiments was carried out independently by ND and IOC using the SYRCLE Risk of Bias Tool and the individual results were compared between ten domains distributed in six biases (selection, performance, detection, attrition, reporting, and other bias). Each domain was defined as "yes" (low risk of bias), "no" (high risk of bias), or "unclear" (uncertain risk) [19].

For in vitro analysis, the tool developed by the World Cancer Research Fund/University of Bristol was used with adaptations [20]. Each of the six questions was answered with "yes" (low risk of bias), "no" (high risk of bias), "not clear" if details were not recorded properly, or "not applicable". Risk of bias analysis was recorded individually by study and by domain. Inter-rater reliability was determined by Cohen's kappa coefficient [21].

Results

Search results and study characteristics

Figure 2 highlights the study selection process. Initially, 424 publications were identified, of which 146 were duplicated ones and removed automatically. A total of 278 articles were eligible by the title and abstract, but only 23 were selected for full-text review and 15 of them met the inclusion criteria. On the other hand, 13 articles not included by unidentifiable reasons in the initial search were included.

According to the included reports, 39.3% ($n = 11$) refer exclusively to in vivo (Table 4) and 53.6% ($n = 15$) to in vitro assays (Table 5). Moreover, two articles showed both experimental designs and, for this reason, were described in both tables [22, 23]. Regardless of the taxonomy mentioned in the publications (*Orbignya phalerata*, *O. martiana*, *O. speciosa*, or *Attalea speciosa*), only the articles of Gaitan et al. [22] and Hovorková et al. [8] are not from Brazil, suggesting great interest about the plant and fruits in the Brazilian scenario. In preclinical interventions with animals, metabolic analysis and toxicity predominated (Fig. 3A), while in vitro assays highlight antioxidant tests (Fig. 3B).

Risk of bias assessment

Individual and for each domain in vivo

SYRCLE RoB Tool identified 130 entries distributed in ten domains for each one of the 13 studies (Table 6). It was found uncertain risk or inappropriate records in 80 entries (81.54%), low risk was present in 45 (34.61%) and high risk in five studies (3.85%). The average agreement by Cohen's kappa was 0.53 (68%), classified as intermediate to good [21].

Table 3 Search terms and Boolean operators

Search term 1		Search term 2
Orbignya phalerata OR *Attalea speciosa*	AND	*Polyphenols* OR *Phytochemicals* *Antioxidants* OR *Free Radicals* OR *Reactive Species* OR *Oxidative Stress* *Anti-inflammatory Agents* OR *Antimicrobial* OR *Antineoplasic Agents* OR *Cytotoxicity* OR *Immunomodulating Agents*

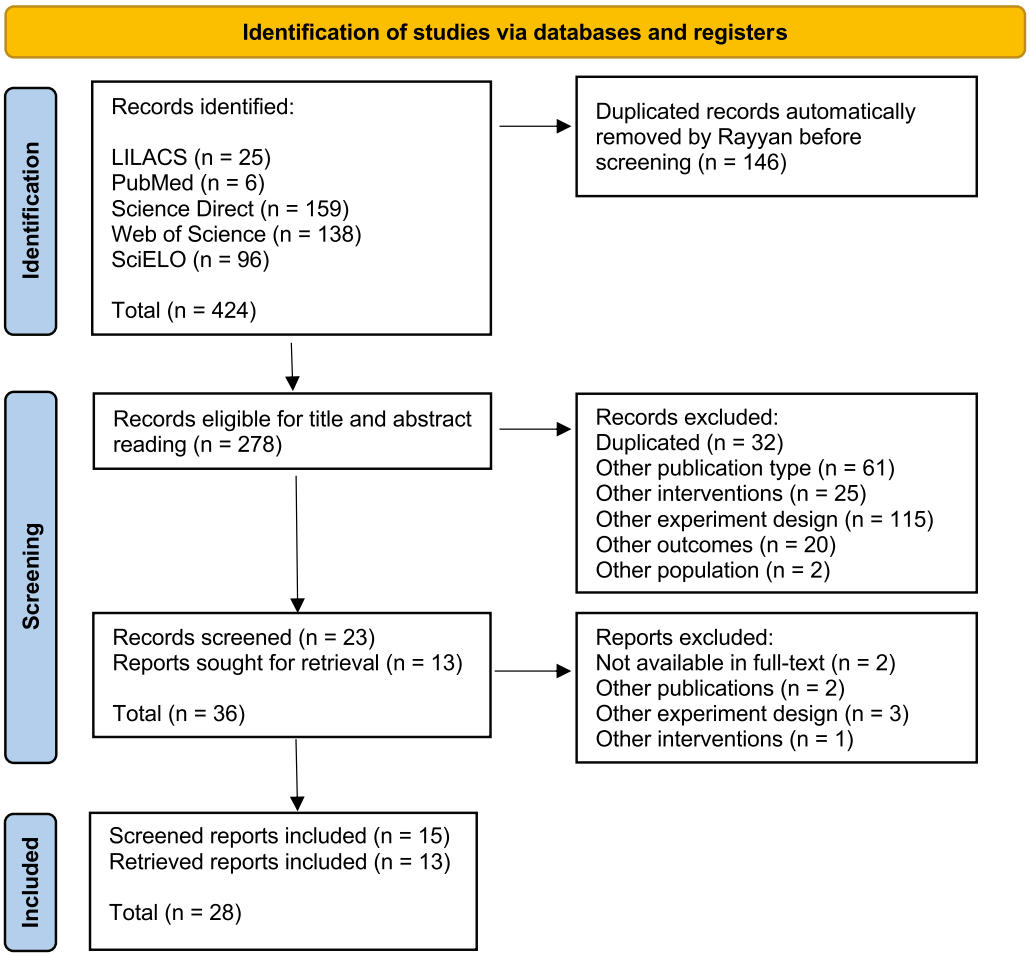


Fig. 2 Screening flow diagram based on The PRISMA 2020 Statement [11]

Uncertain risk prevailed for the domains related to sequence generation, allocation concealment, random housing, and random outcome assessment (Fig. 4). There was no record of uncertain risk related to selective outcome reporting. In the domain related to other sources of bias, only one entry was registered due to the lack of clearness if the same animals or distinct animals were submitted to the different tests and if there was no contamination by the induction of some substance used in control groups [24].

The analysis of the effective risk of bias revealed a higher frequency of low risk in baseline characteristics (92.3% of entries for the domain), selective outcome reporting, and other sources of bias (84.61% for both). Low risk was evidenced due to the appropriate description regarding the specificities of the animals. As well as for high risk of bias, specific analysis indicates that the circumstances in the intervention route were not similar in all groups [23], and there was animal loss with unknown reason, groups equalization, and randomization of the final sample [25]. Besides that, some primary outcomes were not showed [26, 27].

Individual and for each domain in vitro

The analysis of 17 studies checked 102 entries divided into six questions (Table 7). There was a predominance of low risk of bias by adequate methods reporting (65.69%), high risk in eight (7.84%), and uncertain risk in seven studies (6.86%). The average agreement by Cohen's kappa was 0.39 (51.96%), classified as low [21].

The most detailed and complete descriptions were seen in antimicrobial evaluation of hydrolyzed kernel lipid emulsion in strains of pathogenic and commensal microorganisms [8], kernel oil in pathogenic strains [10], and mesocarp with epicarp methanolic extract in viability, changes in morphology, and metabolism in different cell lines [28].

The high risk of bias was highlighted by the use of a single organism and the mean values of primary outcomes have not been presented [29]. Nine studies (47.05%)

Table 4 Baseline characteristics, intervention, methods, and main results of in vivo studies

References	Sex; strain; age; weight; n/group	Intervention/methods	*O. phalerata* component; dose/volume; time of exposure	Main results
Azevedo et al. [41]	Male (C57BL/6); 8–12 w.o.; 20–25 g; $n=20$	Antithrombotic effect: carrageenan-induced thrombosis, evaluation of necrosis frequency and extension; Onco BCG injection for NO induction in peritoneal cells; platelets, PT, and aPTT analysis	Mesocarp aqueous solution; 500 mg/kg/day; 240 days	↓ induced thrombosis; ↑ PT, and aPTT, no changes in platelets number; ↑ NO production by peritoneal macrophages previously activated by Onco BCG
Barbosa et al. [26]	Male (*Mesocricetus auratus*); 7–10 w.o.; 122–146 g; $n=39$	Macromolecular permeability and leukocyte adhesion in cheek pouch after ischemia induction. After reperfusion, histamine topical application. Less than 10 leaks/site accepted; IL-1, IL-6, and TNF-α analysis	Crude kernel oil; 0.02 ml, 0.06 ml, 0.18 ml twice/day; 14 days	↓ ischemia-induced leaks during reperfusion in higher doses; ↑ leaks in lowest dose; less pronounced microvascular permeability after histamine in higher doses; ↓ leukocyte adhesion in lowest dose; no significant changes in TNF-α, IL-1, and IL-6
Barroqueiro et al. [27]	Male/female (C3H/HePas); 8–12 w.o.; 25 g; $n=40$	Acute toxicity: weight, macroscopic, and histological analysis of heart, liver, spleen, kidney, and brain; glucose, urea, creatinine, ALP, TC, TG analysis	MEE; 1000 mg, 3000 mg, 5000 mg/kg; single dose	No deaths after 14 days; no significant increase in body weight; no cutaneous, neurological or behavioral changes, glucose, TC, or creatinine; ↑ ALP in 3000 and 5000 mg/kg groups; ↑ urea in all groups; ↑ TG in 1000 mg/kg
Gaitan et al. [22]	Female (Sprague–Dawley); 7 w.o.; weight (NA); $n=25$	Antithyroid effect: 14 mcg/day of iodine-rich diet; MAE and KPPS acute intake. After 1 h, i.p. Bq $Na^{125}I$; ^{125}I uptake and organification analysis by MIT + DIT coupling in thyroid tissue	MAE (16 g) and KPPS (2 g); single dose	Distinct antithyroid effects for MAE and KPPS; ↓ iodine uptake in 16 g MAE group; ↑ inorganic iodine % in MAE and KPPS; ↓ iodine % as MIT + DIT; ↑ ratio ^{125}I/MIT + DIT in MAE and KPPS
Maia and Rao [24]	Male/female (Wistar); age (NA); 180–220 g; $n=107$. Male and female (Swiss); age (NA); 25–30 g; $n=88$	Anti-inflammatory effect: carrageenan-induced inflammation in paw and edema analysis; subcutaneous cotton pellet implant-induced granuloma, pellet removal and weighing; formaldehyde-induced arthritis in paw and edema analysis; carrageenan-induced inflammatory exudate by leukocyte migration. Ulcerogenesis: gastric lesion assessment. Coagulation: bleeding time after opening the abdomen, micropuncture in a mesenteric vein, and time of hemostasis; Antipyretic: *S. cerevisiae*-induced pyrexia; Analgesia: hot-plate positive response; writhing induced by acetic acid; acute toxicity after 72 h	Mesocarp chloroformic extract; 125 mg/kg, 250 mg/kg (carrageenan, hot-plate, writhing) in a single dose; 250 mg/kg (granuloma) for 7 days; (arthritis) for 10 days; (ulcer) for 21 days; (pyrexia) in a single dose; up to 4 g/kg (toxicity); dose (NA) (exudate) 3 times/24 h; dose (NA) (bleeding) for 3 days	↓ dose-dependent acute inflammatory edema after carrageenan induction; ↓ granuloma; ↓ edema in arthritis on 7th and 8th days; absence of peptic ulcer; no influence on leukocyte migration, no effects on bleeding time and pyrexia control; no significant effect on hot-plate response; ↓ writhing; no overt acute toxicity
Pinheiro et al. [39]	Male (BALB/c, DBA/2, CBA, C3H/HePas, C57BL/6); 8–12 w.o.; 20–30 g; $n=10$	Glycolipid profile: TC and urea analysis. Immunotoxicity: medullary and splenic cell analysis	MAE; 50 mg/kg/day; 30 days	↓ splenic cells in C3H/HePas and BALB/c; no changes in medullary cells; ↑ TC in CBA and ↓ in C3H/HePas; ↓ U in all strains, except in C57BL/6

Table 4 (continued)

References	Sex; strain; age; weight; n/group	Intervention/methods	*O. phalerata* component; dose/volume; time of exposure	Main results
Scheibe et al. [43]	Male (Wistar); age (NA); 271.3 g (average); $n=54$	Wound healing: laparotomy with cecum exteriorization. Monitoring and euthanasia on 7th, 14th, and 21st day; macroscopic wound evaluation (infection, dehiscence, haematoma,and fistulae); abdominal cavity evaluation (collection, infection, fistulae, and adherence); terminal ileum air insufflation test; vascular congestion analysis, edema, presence of mono and polymorphonuclear leukocytes, angiogenesis, fibrosis, and collagen deposition	MAE; 50 mg/kg/day; 7, 14, 21 days	Adequate healing in all animals; no evidence of infection, dehiscence, haematoma, abscess; widespread adhesion, without adhering to the abdominal wall (grade III) in 1 rat on 7th day, grade II adherence on the 21st day in 100% of the animals; ↓ burst pressure over time after insufflation test; ↓ polymorphonuclear leukocytes, congestion, angiogenesis, fibroblast proliferation, and collagen deposition on the 14th day
Silva et al. [23]	Male (Swiss); 8 w.o.; 25–30 g; $n=28$	Locomotor activity: total crossings in activity cage. Motor coordination: remaining time on rotarod test (180 s at 9 RPM)	MAE; 1, 2, 3 g/kg; single dose	No significant changes in the number of crossings or in remaining time on the rotarod test
Silva et al. [44]	Male (Wistar); 7–8.5 w.o.; 275.6 g (average); $n=54$	Colonic healing: cecorrhaphy by laparotomy an exteriorization of the colon. Euthanasia on 7th, 14th, and 21st days. Animal weighing, wound analysis (infection, dehiscence, haematoma, and fistulae); abdominal cavity analysis (collection, infection, fistulae, and adhesion); terminal ileum air insufflation test; analysis of congestion, edema, presence of mono and polymorphonuclear leukocytes, angiogenesis, and fibrosis	MAE; 50 mg/kg; single dose	No dehiscence, fistulae or other complications; ↑ grade II adherence on 21st day; moderate/severe mononuclear leukocytes, congestion, and angiogenesis on the 7th day; ↓ congestion and angiogenesis on 14th day
Silva et al. [25]	Non-obese diabetic male mice (strain NA); 12 w.o.; 29–33 g; $n=25$	Onset of diabetes: individual average of extract, water, and food intake for 6 days; weighing, blood glucose analysis on 0, 30th, 90th, and 120th day; anti-insulin IgM antibodies, and total antibodies (IgG, IgM) with anti-immunoglobulin antibodies	MAE; average 66 mg/day; 120 days	Daily average intake of MAE 3.3 ± 0.9 ml; ↑ weight from 20 to 50th day and ↓ after 50th; ↓ glucose on 30th day; ↓ IgM; no significant changes in anti-insulin IgM and IgG
Silva and Parente [40]	Male (BALB/c); age (NA); 15–20 g; $n=15$	AIE and IME: Evans blue and i.p. acetic acid-induced vascular permeability. Leak analysis in the peritoneal cavity; phagocytic activity by colloidal carbon injection. Blood sample dissolved in Na_2CO_3 and absorbance determination at 660 nm	Mesocarp isolated α-glucan; 100 mg/Kg (AIE) single dose; 50 mg/kg/day (IME) for 5 days	↓ vascular permeability; ↑ phagocytic activity

Table 4 (continued)

References	Sex; strain; age; weight; n/group	Intervention/methods	*O. phalerata* component; dose/volume; time of exposure	Main results
Soares et al. [6]	Male (Swiss); 8.5 w.o.; 35–40 g; $n=32$	Lipid profile and IME: pre and post-euthanasia weighing; macroscopic and histological analysis of heart, liver, kidneys, spleen, gastrocnemius muscle, and retroperitoneal fat. AST, ALT, TC, LDL, HDL, TG, glucose, urea, creatinine, IL-6, and TNF-α analysis; immunophenotyping of splenic cells; RT: stair climbing with load adjustment in daily sessions, 5 days a week for 8 weeks	MAE; 5 mg/kg/day; 5 days/week for 8 weeks	MAE: ↓ total weight; ↓ fat tissue; ↓ TG; ↓ TC; ↑ AST; ↑ medullary cells; ↑ B lymphocytes; ↓ activated macrophages; ↓ IL-6; ↑ TNF-α MAE/RT: ↓ total weight; ↑ kidneys weight but no histological changes; ↓ fat tissue; ↓ TG; ↓ TC; ↑ AST/ALT; ↓ splenic or medullary cells; ↓ activated Th; ↑ activated B lymphocytes; ↑ macrophages; ↓ activated macrophages; ↓ IL-6; ↑ TNF-α
Torres et al. [42]	Male (Wistar); 6 w.o.; 180–240 g; $n=40$	Prevention and treatment of peptic ulcer: macroscopic analysis (ulceration, mucosal hyperemia, loss of fold, and/or bleeding; histopathological analysis (inflammation, necrosis, fibroblasts, fibrosis, reepithelialization, neocapillar generation)	MAE; 2 g/kg/day; 3 days	Prophylaxis: ↓ peptic ulcer, mucosal hyperemia, loss of fold, and bleeding; treatment: ↓ necrosis, fibrosis, reepithelialization, and neocapillar generation; marked inflammation and mucosal ulceration

↑ increase; ↓ decrease; *AIE* anti-inflammatory effect, *ALP* alkaline phosphatase, *ALT* alanine aminotransferase, *aPTT* activated partial thromboplastin time, *AST* aspartate aminotransferase, *BCG* bacillus Calmette–Guérin, *DIT* diiodotyrosine, *HDL* high-density lipoprotein, *IgG* immunoglobulin G, *IgM* immunoglobulin M, *IL* interleukin, *IME* immunomodulatory effects, *i.p.* intraperitoneal, *KPPS* kernel pressed paste with skin, *LDL* low-density lipoprotein, *MAE* mesocarp aqueous extract, *MAE/RT* mesocarp aqueous extract combined with resistance training, *MIT* monoiodotyrosine, *NA* data not available, *NO* nitric oxide, *PT* prothrombin time, *RPM* rotations per minute, *TC* total cholesterol, *TG* triglycerides, *Th* T helper lymphocytes, *TNF-α* tumoral necrosis factor, *w.o.* weeks old

Table 5 Baseline characteristics, intervention, methods, and main results of studies

References	Species/cell lines/strains/reactions	Intervention/methods	*O. phalerata* component; concentration	Main results
Barroqueiro et al. [46]	*E. coli* (ATCC 25922), *P. aeruginosa* (ATCC 27853), *E. faecalis* (ATCC 29212), *S. aureus* (ATCC 25923), *S. aureus* (MRSA)	AMA: disk diffusion method by analyzing zones of inhibition; MIC: growth absence or presence after inoculation in tubes	MEE; 500 and 250 mg/mL (disk diffusion); 500 to 0.9 mg/mL (MIC)	Disk diffusion: inhibition > 7 mm on *S. aureus*, MRSA, and *E. faecalis*; no inhibition on *E. coli* and *P. aeruginosa*. Complete inhibition on *S. aureus*, MRSA, and *E.* faecalis by the highest concentration. MIC: 7.8 mg/mL (*E. faecalis*)
Bezerra et al. [38]	Promastigote forms of *L. amazonensis*	Leishmanicidal activity: promastigotes incubated during 24 h with extract. Count of living protozoa after 24 h by flagellar motility. CL_{50}	MAE; serial concentrations 500 to 31.25 µg/mL	CL_{50} > 500 µg/mL. Deaths about 20% in all concentrations
Caetano et al. [37]	*S. aureus* (ATCC6538, ATCC9144), *S. aureus* MRSA (2 nosocomial strains), *S. aureus* MSSA (3 nosocomial strains)	AMA: disk diffusion method by analyzing zones of inhibition	Mesocarp hydroalcoholic extract; 30 mg/mL	Growth inhibition on all strains (14 to 18 mm zones)
Ferreira et al. [45]	AMA: *S. epidermidis* (ATCC12228), *S. aureus* (ATCC25923), *E. coli* (ATTC11229), *P. aeruginosa* (ATTC27853); DPPH•; *A. salina*	AMA disk diffusion method by analyzing zones of inhibition; AA: DPPH• scavenging. EC_{50}; Lethality: *A. salina* assay for 24 h. CL_{50}	Kernel oil; 10 mg/mL (AMA); 300, 250, 200, 150, and 100 mg/mL (DPPH•); 50 to 0.05 mg/mL (lethality)	AMA: no inhibition; DPPH•: EC_{50} 70.57 mg/mL; CL_{50} > 1000 µg/mL
Gaitan et al. [22]	Porcine thyroid slices; TPO	Antithyroid effect: thyroid hormone synthesis assessed by measuring total accumulated iodine and iodine organification in MIT + DIT, and $T_3 + T_4$; TPO: spectrophotometry by oxidation of I^- to I^{3-}. Inhibition of TPO-catalyzed iodination, compared to PTU concentration. I_{50}	MAE, MME, kernel skin, KPPS, kernel oil; cellular assays: 1×10^5 µg/5 mL (MAE, skin); 5×10^4 µg/5 mL (KPPS, oil); TPO: 100 to 200 µg/mL	Cellular: antithyroid effect in all extracts by ↑ ^{125}I/MIT + DIT ratio, ↓ % ^{125}I demonstrated as $T_3 + T_4$ (NA). Kernel oil 1/5 from KPPS I/MIT + DIT ratio (I/MIT + DIT = 15). Higher ratio for mesocarp; TPO: ↑ inhibition % by MME and kernel skin
Hovorková et al. [8]	*E. cecorum* (CCM3659, CCM4285), *C. perfringens* (CIP105178, CNCTC5454, UGent 56), *Listeria monocytogenes* (ATCC7644), *S. aureus* (ATCC25923), *Bifidobacterium animalis* (CCM4988, MA5), *Bifidobacterium longum* (TP1, CCM4990), *Lactobacillus fermentum* (CCM91), *Lactobacillus acidophilus* (CCM4833)	AMA: previous kernel oil hydrolysis with porcine pancreatic lipase. Inoculation of each strain with emulsion. Growth assessment by the culture turbidity read at 405 nm. MIC_{80}	Kernel hydrolyzed lipid emulsion; 4.5 mg/mL	MIC_{80}: 0.56 mg/mL on *C. perfringens,* 1.13 mg/mL on *S. aureus,* and 2.25 mg/mL on *E. cecorum.* No effect on pathogenic strains before hydrolysis or on commensal strains

Table 5 (continued)

References	Species/cell lines/strains/reactions	Intervention/methods	*O. phalerata* component; concentration	Main results
Nobre et al. [30]	TBARS, deoxyribose degradation, DPPH•, iron chelation, FRAP	AA: TBARS: phospholipids diluted in the extract with or without iron to induce peroxidation and absorbance with MDA; Deoxyribose degradation: induction of sugar decomposition by Fe/H_2O_2 added to the extract to produce MDA; DPPH•: scavenging, read at 518 nm; Iron chelation: chelation potential by extract (plus Fe^{2+}, Tris–HCl, and phenanthroline), absorbance read at 510 nm; FRAP: ability to reduce the equivalent of 1 mM $FeSO_4{\cdot}7H_2O$. IC_{50}, EC_{50}, EC	Kernel methanolic extract; 1000 to 100 µg/mL (TBARS, deoxyribose, DPPH•, iron chelation); 50 to 5 µg/mL (FRAP)	No TBARS inhibition; deoxyribose $IC_{50} > 1000$ µg/mL; DPPH• EC_{50} 3517.01 ± 77.07 µg/mL; iron chelation: < 20%, $IC_{50} > 1000$ µg/mL; FRAP EC: 1560.2 ± 18.30 µmol.L^{-1}/g
Nobre et al. [10]	*S. aureus* (ATCC12692), *P. aeruginosa* (ATCC15442), *E. coli* (ATCC25922), *E. coli* (Ec27), *S. aureus* (Sa358)	Antibacterial activity: growth evidence after inoculating extract with resazurin solution into tubes. MIC	Fixed kernel oil: 512 to 8 µg/mL	Higher inhibition on *E. coli* 27 (MIC 23 µg/mL); ↓ MIC in the association between oil and amicacin on *S. aureus* 358 and *P. aeruginosa*, as well as neomycin on *S. aureus* 358, *P. aeruginosa*, and *E. coli* 27 (NA)
Pessoa et al. [31]	Enteropathogenic *E. coli*, mononuclear phagocytes	Cellular viability: slides fixed by acridine orange method; viability index by counting dead and alive cells in a total of 100. Functional activity by phagocytic index: number of cells that ingested at least 3 bacteria in a pool of 100 cells. Bactericidal index: dead/alive bacteria ratio by acridine orange	Kernel microemulsion and oil; 20 µL	↑ viability index and ↑ phagocytic index by microemulsion; ↑ bactericidal index by oil
Rennó et al. [28]	Leukaemic cell lines (HL-60, K562), K562-Lucena 1 MDR counterpart, lymphocytes, mouse fibroblast cell line (3T3-L1), human breast cancer cell line (MCF-7)	Cellular viability: erythroleukemic cells evaluated by permeability to trypan blue up to 24 h. Inhibition of cell proliferation calculated by comparing treated/untreated cells. Morphology: non-viable stained cells were separated in retained shape and lysed; lymphocytes evaluated with trypan blue after 24 h; MCF-7 and 3T3-L1 trypsinized and evaluated with trypan blue. Metabolism: 6-phosphofructo-1-kinase activity to convert into fructose-1,6-bisphosphate in HL-60. ID_{50}	Mesocarp with epicarp ethanolic extract; 2000, 1500, 1200, 600, 300, and 150 µg/mL	ID_{50} more effective on HL-60; moderate sensitivity on K562, K562-Lucena 1, and MCF-7; Resistance on 3T3-L1 and lymphocytes; morphological changes by 1200 µg/mL on HL-60; ↑ 6-phosphofructo-1-kinase on HL-60

Table 5 (continued)

References	Species/cell lines/strains/reactions	Intervention/methods	*O. phalerata* component; concentration	Main results
Santos et al. [33]	Mouse fibroblasts (L929) and peritoneal macrophages	Cellular viability: MTT assay up to 72 h; absorbance read at 560 nm; macrophages stimulated by LPS from *E. coli* for 1 h and treated with kernel oil. NO and cytokines measured after 24 h; Scratch assay: fibroblasts migration in monolayers, production of 1.2001.500 µm width wounded area. Cellular migration measured each 6 h	Kernel oil; 100 to 1.56 µg/mL	No toxicity up to 100 µg/mL; cell proliferation with MTT metabolism ↑ above 25 µg/mL on L929; dose-related ↓ NO; ↑ IFN-γ, IL-6, and ↑TNF-α by 3.12 µg/mL; ↑ fibroblasts migration in scratch assay by 6.25 and 12.5 µg/mL
Santos et al. [32]	DPPH$^{\bullet}$, mouse fibroblasts (NIH/3T3, ATCCR, CRL-1658)	AA: DPPH$^{\bullet}$ scavenging, read by electron spin resonance; EC_{50}; Cellular viability: MTT assay with nanoemulsion up to 72 h, IC_{50}	Kernel oil, lipidic nanoemulsion; 4.0; 24.9; 49.9; 74.8, and 99.8 mM (DPPH$^{\bullet}$); 2500 to 39.06 µg.mL^{-1} of nanoemulsion (MTT)	DPPH$^{\bullet}$ EC_{50}: nanoemulsion: 0.4329 mg mL^{-1}; oil: 0.5488 mg mL^{-1}; cytotoxicity by nanoemulsion ≥ 78.12 µg.mL^{-1}
Silva et al. [34]	DPPH$^{\bullet}$, *S. cerevisiae* (BY4741)	AA: DPPH$^{\bullet}$ scavenging, read at 518 nm; IC_{50}. *S. cerevisiae*: incubation of 0.1 mg mL^{-1} cells with 3 mM TBH and 5 mg ml^{-1} extracts; microorganism viability assessed after 72 h	Endocarp, flowers, and leaves ethanolic extract; 1.0 mg ml^{-1}	DPPH$^{\bullet}$ IC_{50}: 4104.3 ± 6.7 µg.ml^{-1} (endocarp); 427.4 ± 1.8 µg.ml^{-1} (flowers), and 895.9 ± 2.3 µg.ml^{-1} (leaves); no yeast survival
Silva et al. [23]	NO, TBARS, deoxyribose degradation	AA: nitrite measured by Griess reaction after NO generated in sodium nitroprusside decomposition. Absorbance read at 540 nm. TBARS: phospholipids diluted in the extract with AAPH as peroxidation inducing agent, absorbance read at 532 nm; OH$^{\bullet}$ production by MDA synthesis, a product of deoxyribose degradation induced by Fe/H_2O_2 added to the extract, absorbance read at 532 nm	MAE; 1000, 100, 10, and 1 µg/mL	No effect on NO and OH$^{\bullet}$ removal or over lipid peroxidation
Silva et al. [35]	DPPH$^{\bullet}$, ABTS$^{\bullet+}$, FRAP, tyrosinase	AA: DPPH$^{\bullet}$ scavenging, absorbance read at 517 nm; ABTS$^{\bullet+}$ scavenging absorbance read at 734 nm; FRAP: analysis of ability to reduce Fe^{3+} into Fe^{2+} with, read at 593 nm; Tyrosinase inhibition: L-tyrosine for monophenolase reaction and 3,4-dihydroxyphenylalanine for diphenolase reaction. Absorbance read at 492 nm	Mesocarp hydroalcoholic extract and fractions (hexane, chloroform, ethyl acetate, hydroalcoholic); 100 to 5 µg/mL (DPPH$^{\bullet}$), 6 to 1 µg/mL (ABTS$^{\bullet+}$), 100 to 1 µg/mL (FRAP), 200 to 50 µg/mL (tyrosinase)	↑ AA by ethyl acetate fraction in DPPH$^{\bullet}$ IC_{50}: 3.38 ± 0.05 µg/mL, ABTS$^{\bullet+}$ IC_{50}: 2.04 ± 0.03 µg/mL and FRAP: 15.41 ± 0.18 mmol Fe^{2+}/g; IC_{50} for tyrosinase: 48.43 ± 29.51 µg/mL (monophenolase) and 132.63 ± 5.71 (diphenolase)
Silva et al. [29]	Promastigote forms of *L. amazonensis* (IFLA/BR/67/PH8)	Leishmanicidal activity: promastigotes incubated with the isolated extract and mesocarp-loaded microparticles. Protozoa counting after 48 h by flagellar motility. CL_{50}	MAE; 500 to 62.5 µg/mL and mesocarp-loaded microparticles; 100 to 3.125 µg/mL	Lethality: pentamidine > microparticles > extract in solution. CL_{50} microparticles: 12 pg/mL

Table 5 (continued)

References	Species/cell lines/strains/reactions	Intervention/methods	*O. phalerata* component; concentration	Main results
Souza et al. [36]	Benign prostate hyperplasic cells	Cellular viability: MTT assay, absorbance read at 570 nm up to 72 h; cytotoxicity by LDH release: damage estimated after from 4 up to 48 h, absorbance read at 490 nm; Immunohistochemistry: cultures treated for 24 h, PCNA immunostained; Apoptosis: TUNEL test by blocking endogenous peroxidase. DNA fragmentation assessment; Histomorphometry: nuclei counting with PCNA or TUNEL stained, distribution and intensity of staining assessment inside the glandular epithelium or stroma; Morphology: indirect assessment using phalloidin after 4, 6 and 12 h	Kernel crude oil, oily extract, nanocomposite with lipophilic extract; 300 to 100 µg/mL (MTT), 300 µg/mL (LDH, Immunohistochemistry, histomorphometry, apoptosis)	Viability: ↑ dose-related inhibition by nanocomposite; time-dependent disorganization of the actin cytoskeleton; ↑ time-dependent LDH release; immunohistochemistry: preserved glandular architecture; ↓ cell proliferation in 24 h; diffuse apoptosis and ↑ in apoptotic index after 24 h

↑ increase; ↓ decrease; *AA* antioxidant activity, *AMA* antimicrobial activity, *AAPH* 2,2′-azobis(2-methylpropionamidine) dihydrochloride, *ABTS*$^{\bullet+}$ 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid), CL_{50} lethal concentration, *DIT* diiodotyrosine, *DPPH*$^{\bullet}$ 2,2-diphenyl-2-picryl-hydrazine, *EC* equivalent concentration, EC_{50} effective concentration, *FRAP* ferric-reducing antioxidant power, I_{50}/IC_{50} inhibitory concentration, *IFN-γ* interferon-γ, *IL-6* interleukin-6, *KPPS* kernel pressed paste with skin, *LDH* lactate dehydrogenase, *LPS* lipopolysaccharide, *MAE* mesocarp aqueous extract, *MDA* malondialdehyde, *MEE* mesocarp ethanolic extract, *MDR* multidrug resistant, MIC/MIC_{80} minimum inhibitory concentration, *MIT* monoiodotyrosine, *MME* mesocarp methanolic extract, *MRSA* methicillin-resistant *Staphylococcus aureus*, *MSSA* methicillin-sensitive *Staphylococcus aureus*, *MTT* (3-[4,5-dimethylthiazol-2y]-2,5-diphenyltertrazolium bromide), *NA* data not available, *NO* nitric oxide; $O_2^{\bullet}$ superoxide anion, $OH^{\bullet}$ hydroxyl radical, *PCNA* proliferation cell nuclear antigen, *PTU* propyl-2-thiouracil, *TBARS* thiobarbituric acid reactive substances, *TBH tert*-butylhydroperoxide, T_3 triiodothyronine, T_4 thyroxine, *TNF-α* tumor necrosis factor-α, *TPO* thyroperoxidase

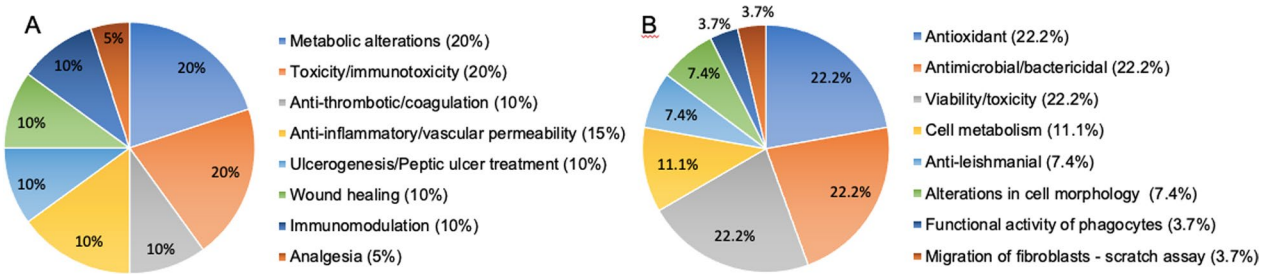


Fig. 3 Assessed outcomes from in vivo (**A**) and in vitro (**B**). Some publications have more than one outcome

demonstrated the non-application of two questions, most frequently for the impossibility of comparing cell lines/strains or culture conditions between groups, as they were assays with a single microorganism, strain or distinct chemical reactions (Q4, Q6) [23, 29–36].

When analyzing the methodological quality by domain (Fig. 5), the selective result was avoided in 94.11% of the studies and the low risk of bias was in 76.47%, regarding the validation of cells and strains repository and the use of a control group (Q1, Q2). Less frequently, there were some doubts about the cell line origin (Q1, 5.88%) and technical repeats (Q2, 17.65%) [22, 29, 30, 37].

The most frequent classification for 'high risk' was based on the use of a single cell line/strain in 41.17% of the investigations [22, 29, 31–33, 38] and, less frequently, for the reason of the impossibility in comparing reactions due to different outcomes [23], and again, due to selective report when the result was presented by a single sample [29].

In vivo interventions and main results

Animals' interventions and related results are described in Table 4. The antithyroid effect was evaluated by offering acutely mesocarp aqueous extract (MAE) and kernel pressed paste with skin (KPPS) after a previous iodine-rich diet. This effect was observed by thyroid uptake reduction of ^{125}I and by the ratio between ^{125}I and monoiodotyrosine (MIT) coupled to diiodotyrosine (DIT). As a result, ^{125}I uptake was suppressed by MAE, but not significantly by KPPS. However, the ratio ^{125}I/MIT + DIT was high for both MAE and KPPS, suggesting a thionamide-like antithyroid effect [22].

Concerning the effect on lipid metabolism, urea and the development of type 1 diabetes, three studies offering MAE evaluated the intake of 50 mg/kg for 30 days in five mouse strains and found a significant increase in total cholesterol (TC) levels only in CBA strain (27 vs. 9 mg/dL) and a decrease only in C3H/HePas (18 vs. 47 mg/dL). There was a significant decrease in urea levels, except for C57BL/6 (49 vs. 67 mg/dL). Despite the glycolipid profile outcome mentioned, levels of lipoproteins, triglycerides (TG) or glucose were not demonstrated [39]. Another intervention offered a dose ten times lower than the previous study for 40 non-consecutive days, associated or not with resistance training (RT). They verified weight of loss after an 8-week supplementation period and, associated with RT, after 4 weeks. In addition, animals supplemented combined or not with RT had retroperitoneal fat reduction up to 73%, a decrease in TC levels (MAE: 79 mg/dL; MAE/RT: 70 vs. 97 mg/dL) and TG (MAE: 90 mg/dL; MAE/RT: 82 mg/dL vs. 166 mg/dL). There was a reduction in glucose only in RT animals (131 vs. 145 mg/dL). Animals trained without supplementation showed greater Delta force, suggesting a possible ergolytic effect of the substance [6].

On the other hand, Silva et al. [25] observed weight gain with intake of 3.3 mL/day of a suspension of MAE 20 mg/mL. In this study, the animals were not subjected to any type of physical labor and weight gain occurred between the 20th and 50th days, but with an abrupt drop afterwards. There was blood glucose fluctuation with lower levels on the 30th day and returning to baseline on the 60th. They did not observe significant changes in immunoglobulin IgG levels, possibly due to the low effect of MAE on T lymphocyte activation and cytokine production.

Acute toxicity effects were observed with high doses of mesocarp extracts and measured by organ relative weight and histological and biochemical analysis. No deaths were registered after a single dose up to 5000 mg/kg of mesocarp ethanolic extract (MEE) [27], as well as significant physical and or behavioral changes were not found. The same investigation also evidenced a reduction in urea levels at 5000 mg/kg (26 vs. 40 mg/dL) and increased TG at 1000 mg/kg (104 vs. 54 mg/dL) in a dose-dependent way. Alkaline phosphatase (ALP) increased after 3000 and 5000 mg/kg intake (23 and 21 U/L, respectively, vs. 6 U/L). No toxic effects were observed with gradual doses up to 4000 mg/kg [24]. MAE, mainly associated with RT, increased both aspartate (AST) and alanine aminotransferase (ALT) [6]. Alterations in locomotor activity and motor coordination can also be a sign of toxicity. Thus, a single dose of up to 3 g/kg of MAE did not affect these outcomes [23].

Table 6 In vivo individual risk of bias

Reference	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10
Azevedo et al [41]	?	+	?	?	?	?	?	?	+	+
Barbosa et al [26]	?	+	?	?	?	?	?	?	-	+
Barroqueiro et al [27]	?	+	?	?	?	?	?	+	-	+
Gaitan et al [22]	?	+	?	?	?	?	?	?	+	+
Maia and Rao [24]	?	+	?	?	?	?	?	?	+	?
Pinheiro et al [39]	?	+	?	?	?	?	?	+	+	+
Scheibe et al [43]	?	+	?	?	+	?	+	+	+	-
Silva et al [23]	?	+	?	?	-	?	?	+	+	+
Silva and Parente [40]	?	?	?	?	?	?	?	+	+	+
Silva et al [44]	?	+	?	?	?	?	?	+	+	+
Silva et al [25]	?	+	?	?	?	?	?	-	+	+
Soares et al [6]	?	+	?	?	?	?	?	+	+	+
Torres et al [42]	?	+	?	?	?	?	+	+	+	+

Domains: D1—sequence generation; D2—baseline characteristics; D3—allocation concealment; D4—random housing; D5—blinding (performance bias); D6—random outcome assessment; D7—blinding (detection bias); D8—incomplete outcome data; D9—selective outcome reporting; D10—other sources of bias. Total: 130 (100%); (+) Yes: 45 (34.61%); (–) No: 5 (3.85%); (?) Unclear: 80 (61.54%) [19]

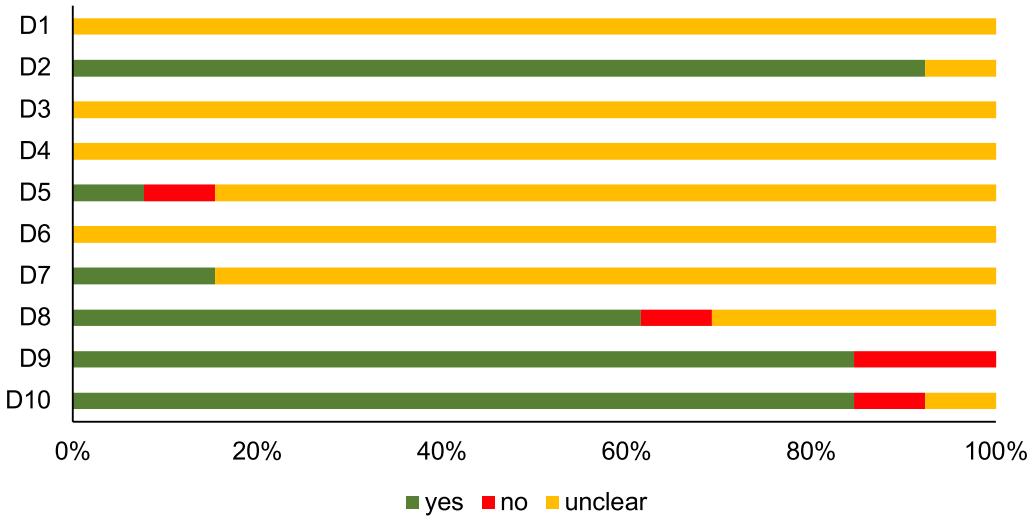


Fig. 4 In vivo risk of bias assessment by domain. (legend) Domains: D1—sequence generation; D2—baseline characteristics; D3—allocation concealment; D4—random housing; D5—blinding (performance bias); D6—random outcome assessment; D7—blinding (detection bias); D8—incomplete outcome data; D9—selective outcome reporting; D10—other sources of bias. Yes: low risk; No: high risk; Unclear: uncertain risk [19]

Table 7 In vitro individual risk of bias

Reference	Q1	Q2	Q3	Q4	Q5	Q6
Barroqueiro et al [46]	+	+	+	+	+	?
Bezerra et al [38]	+	+	-	?	+	∅
Caetano et al [37]	+	?	+	+	+	+
Ferreira et al [45]	+	+	+	+	+	?
Gaitan et al [22]	?	+	-	+	+	∅
Hovorková et al [8]	+	+	+	+	+	+
Nobre et al [30]	∅	?	+	∅	+	+
Nobre et al [10]	+	+	+	+	+	+
Pessoa et al [31]	+	+	-	∅	+	∅
Rennó et al [28]	+	+	+	+	+	+
Santos et al [33]	+	+	-	∅	+	∅
Santos et al [32]	+	+	-	∅	+	∅
Silva et al [34]	∅	+	+	-	+	∅
Silva et al [23]	+	+	+	∅	+	∅
Silva et al [35]	+	?	-	∅	-	∅
Silva et al [29]	∅	+	+	∅	+	+
Souza et al [36]	+	∅	+	∅	+	+

Questions: Q1—cells/strains from validated repository or appropriately verified; Q2—technical repeats and controls inclusion; Q3—use of different cell lines/strains/reactions; Q4—comparable conditions between groups/assays; Q5—selective outcome reporting; Q6—comparison of different cell lines/strains/substances. Total: 102 (100%); (+) Yes: 67 (65.69%); (–) No: 8 (7.84%); (?) Unclear: 7 (6.86%); (∅) Not applicable: 20 (19.61%). Questions adapted from Lewis et al. [20]

Low toxicity was observed since no changes in the number of medullary cells and a decrease of splenic cells only in BALB/c and C3H/HePas (both 3×10^7 vs. 5×10^7) was noted. Weight loss in organs was reported for HePas after 30 days exposure at 50 mg/kg of MAE [39]. On the other hand, MAE 5 mg/kg was able to increase the number of medullary cells in the absence of RT in Swiss mice (30×10^6 vs. 13×10^6), but in the scenario of splenocyte levels' preservation (41×10^6). When associated with RT, splenic cells were reduced (30×10^6) [6].

After different doses and periods, Maia and Rao [24] evaluated the effect of mesocarp chloroform extract intake on the inflammatory process. Analyzing the carrageenan-induced inflammation in edema paw, it decreased up to 32% with progressive doses. The edema reduction caused by formaldehyde-induced arthritis was also observed on the 7th and 8th days of treatment. In this same study, seven-day intake at 250 mg/kg inhibited subcutaneous granuloma, measured by the weight of the cotton pellet introduced (112 vs. 192 mg) and it reduce leukocyte migration (24.19 vs. 23.62 cells/mm^3) and inflammatory exudate after a subcutaneous sponge implant impregnated with carrageenan.

In a stage before exudate induction, Silva and Parente [40] verified a significant inhibition in vascular permeability progression following a single dose of an isolated polysaccharide from mesocarp composed of alpha-(1 → 4) linked D-glucopyranose residues. Meanwhile, Barbosa et al. [26] observed the same effect in microvessels after volumes greater than 0.06 mL of the crude kernel oil twice a day. This study also reported attenuation in leukocyte adhesion with intake of 0.02 mL.

When analyzing proinflammatory cytokines, MAE intervention decreased interleukin-6 (IL-6) and increased tumoral necrosis factor-alpha (TNF-α) levels [6]. However, kernel oil was not able to cause significant changes in IL-1, IL-6, and TNF-α [26].

Leukocyte-specific activity is closely related to inflammatory stages. In this regard, five days of α-glucan from mesocarp increased zymosan-like phagocytic activity induced by colloidal carbon [40]. However, MAE associated with RT increased total splenic macrophages, but reduced activated macrophages, without changes in monocytes [6]. There was an activated T helper decrease and an increase of B cells, suggesting an immunomodulatory effect well [6].

Other outcomes, similar or antagonistic, were also evaluated. Although the antithrombotic effect of the aqueous mesocarp suspension was indicated by the prothrombin time increase (11.2 vs. 10 s) and activated partial thromboplastin time (33.6 vs. 29.5 s) [41], on the other hand, the chloroform extract of mesocarp given for three days did not extend the hemostasis time (98.0 vs. 90.3 min) [23].

Regarding peptic ulcer induction, prevention, or treatment, Maia and Rao induced ulceration with phenylbutazone and observed an average score of 1.03 for the lesion in five of six animals treated with phenylbutazone, on a 0–4 scale [24]. In opposition, animals treated with mesocarp chloroformic extract for 21 days did not exhibit lesions. In a different study, the prophylactic and therapeutic effect of MAE was compared to omeprazole, before or after ethanol-induced ulcers. In the preventive treatment, the effect was similar to omeprazole in the absence of lesions (60% of the animals), but superior to the drug in the absence of hyperemia, bleeding, and preservation of folds (100% vs. 60% on all outcomes). Despite

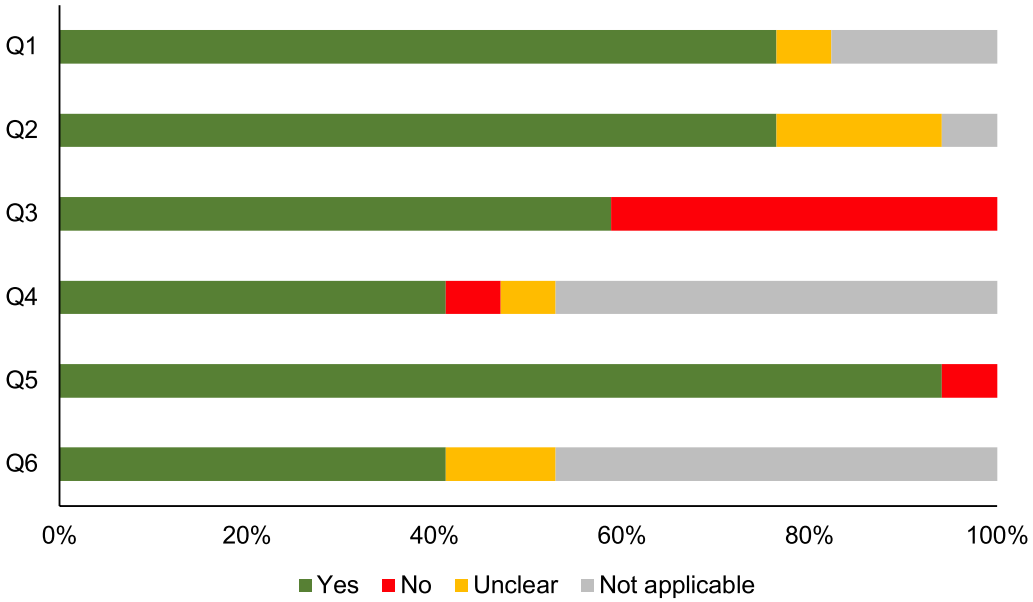


Fig. 5 In vitro risk of bias assessment by domain. (legend) Q1—cells/strains from a validated repository or appropriately verified; Q2—technical repeats and controls inclusion; Q3—use of different cell lines/strains/reactions; Q4—comparable conditions between groups/assays; Q5—selective outcome reporting; Q6—comparison of different cell lines/strains/substances. Yes: low risk; Não: high risk; Unclear: uncertain risk. Questions adapted from Lewis et al. [20]

the accentuated related-inflammatory lesions, such damage reached only the mucosa in MAE-treated animals, while there was deeper damage up to the submucosa in those ones receiving vehicle. Moreover, microscopic analysis showed MAE prevented necrosis in 80% of animals [42].

Scheibe et al. [43] evaluated 21-day MAE intake for healing. After this period, the animals underwent laparotomy with cecum exteriorization. Significantly, they identified a grade II adhesion (two adhesions between organs or between an organ and abdominal wall) in 100% of the animals on the 21st postoperative day compared to the negative control. Morphological evaluations did not identify polymorphonuclear leukocytes (vs. moderate presence), and mild congestion and angiogenesis (vs. severe) and moderate fibroblasts (vs. severe) were detected in MAE-exposed animals. Collagen production was also more intense than in the control group. Silva et al. [44] used the same procedures, but offered a MAE single dose. They found similar results, except for collagen production.

Finally, antipyretic and analgesic properties of mesocarp chloroform extract were analyzed [24]. After pyrexia induced by *Saccharomyces cerevisiae*, no time-related decrease in body temperature was observed (1 h: 39.18 vs. 39.18 °C; 2 h: 39.1 vs. 39.3 °C; 3 h: 39.18 vs. 39.31 °C). The analgesic effect was compared to morphine after exposure to a hot-plate at 55 °C. After 30 min of 250 mg/kg intake, the extract was not able to promote analgesia. Reaction time was similar to negative control and shorter than morphine (extract: 3.5 s; control: 2.83 s; morphine: 14.0 s). In contrast, the same dose was able to reduce acetic acid-induced writhing around 62% [24].

In vitro assays and main results

In vitro studies are useful for preliminary testing of substances in a controlled environment. The studies included are described in Table 5. Six studies evaluating antimicrobial and phagocytic activities on pathogenic or commensal strains [8, 10, 27, 31, 37, 45] and two investigations against protozoa [29, 38] were identified. Cellular assays were carried out with tumor or non-tumor cell lines to study viability or cytotoxicity, morphological or metabolic changes [22, 28, 31–33, 36]. Lethality assays were carried out in microcrustaceans (*Artemia salina* Leach.) [45].

Assays using chemical reactions or yeasts can also be developed to measure preliminary effective concentrations (EC_{50}) for achieving half desirable effects. This review included six studies which evaluated the antioxidant activity of babassu [23, 30, 32, 34, 35, 45].

The most common component of *O. phalerata* was the kernel (52.9% of the studies) [8, 10, 22, 30–33, 36, 45]. MAE and mesocarp alcoholic extracts were tested in 47% and one publication associated mesocarp with epicarp [22, 23, 28, 29, 35, 37, 38, 46]. Only Silva et al. [34] used

endocarp, flowers, and leaf extracts. The concentrations ranged a lot from 500 mg/mL of MEE [46] to assess the antimicrobial effect to 1 µg/mL of MAE for the antioxidant activity [23].

The disk diffusion assay was used to evaluate the effect of mesocarp on pathogenic bacteria strains. At 250 and 500 mg/mL, MEE promoted concentration-dependent inhibition zones on *Staphylococcus aureus* (18.5 mm), methicillin-resistant *S. aureus* (17.4 mm), and *Enterococcus faecalis* (14.4 mm). The most relevant minimum inhibitory concentration was observed for *E. faecalis*, while 500 mg/mL inhibited the growth of them completely. In contrast, there was no inhibition of *Escherichia coli* and *Pseudomonas aeruginosa* [46]. Similar levels of inhibition on methicillin-resistant or sensitive *S. aureus* were observed with lower concentrations of the hydroalcoholic extract [37].

Kernel oil also did not demonstrate efficacy on Gram-positive and negative strains [45], but after hydrolysis, it inhibited 80% of *Clostridium perfringens*, *S. aureus,* and *Enterococcus cecorum* [8]. Furthermore, the fixed oil increased the effectiveness of antibiotics over *S. aureus*, *P. aeruginosa,* and *E. coli* [10].

After evaluating mononuclear phagocyte activity and bactericidal potential, Pessoa et al. [31] found a higher rate of phagocytosis by lipid microemulsion (69.1 vs. 47%), and the bactericidal activity was higher by isolated oil (47.9%). When testing the leishmanicidal effect of MAE, it was observed a low activity when compared to Glucantime® (LC_{50} > 500 vs. 440.3 µg/mL) [38]. On the other hand, microparticles loaded with the same extract demonstrated upper effectivess, but lower than pentamidine (IC_{50} 12 vs. 0.8 pg/mL) [29].

In a study developed by Rennó et al. [28] using the trypan blue method, leukemic promyelocytes (HL-60) were more sensitive to the crude ethanolic extract from mesocarp combined with epicarp when compared to negative control (ID_{50} 9.3 vs. 125 µg/mL), whose activity was time dependent (150 µg/mL: 8.6 h; 2 mg/mL: 0.4 h). The concentration of 1.2 mg/mL promoted changes in HL-60 morphology, with decrease in size and cytoplasmic/nuclear condensation. Interestingly, there was an increase in levels of 6-phosphofructo-1-kinase (PFK) enzyme at 300 µg/mL were tested, 6.6 times greater than the negative control. In this study, non-tumor cells showed greater resistance, such as L929 (127 vs. 88.7 µg/mL) and human lymphocytes (141.2 vs. 84.4 µg/mL). It is important to highlight that both erythroleukaemic sensitive to chemotherapy line and its multidrug-resistant counterpart were equally affected.

Regarding cytotoxicity, Santos et al. [32] tested a lipid nanoemulsion from kernel oil droplets in L929 cells and it was found a time and concentration-dependent IC_{50} after 24 h of exposure (396.1 µg mL^{-1}), 48 h (363.3 µg mL^{-1}) and 72 h (333.1 µg mL^{-1}). Santos et al. did not find kernel oil toxic effects on L929 after MTT (3–4,5-dimethylthiazol-2-yl-2,5-diphenyltetrazolium bromide) assay. Conversely, the same effect was not verified on peritoneal macrophages. Furthermore, they reported an increased migration of L929 cells in the scratch assay, concentration-dependent nitric oxide attenuation (0.31 to 0.29 vs. 1.15 µM), and higher levels of INF-γ (interferon-γ) production with 6.25 µg/mL of the nanoemulsion (2214.2 vs. 980.4 pg/mL), TNF-α (107.7 vs. < 0.9 pg/mL) and IL-6 with 3.12 µg/mL (1286.1 vs. 584.4 pg/mL) by macrophages, suggesting a modulation of inflammatory response in wound healing situations.

Concerning phagocyte viability, a higher viability index similar to culture medium was found for lipid microemulsion when compared to isolated oil (98 vs. 94.3%) [31]. Another study using benign prostatic hyperplasic cells observed viability inhibition up to 75% after 24–72 h of exposure to a 300 µg/mL of nanocomposite with lipophilic extract. Even after the addition of fetal bovine serum, the inhibition was sustained. There was also induction of disorganization (disassembly) or disruption in the structure of actin microfilaments in a time-progressive manner, and a progressive lactate dehydrogenase (LDH) release. For this enzyme, there was a release of up to 75% after 48 h. Immunoreactivity for proliferation cell nuclear antigen (PCNA) was also tested and proved to be 50% lower when compared to the negative control in association of apoptosis induction [36]. The single report about multicellular organisms observed no toxicity on *A. salina* (LC_{50} > 1000 µg/mL) after testing concentrations up to 50 mg/mL of kernel oil [45].

The antithyroid effect in porcine thyroid slices was tested by Gaitan et al. [22] with different babassu components. The study verified that, although ^{125}I absorption by thyroid tissue was similar between the substances, the extracts showed a higher incorporation of ^{125}I/MIT + DIT, mostly after MME (mesocarp methanolic extract) exposure indicating iodine organification inhibition. Concerning thyroperoxidase activity, the MME and kernel peel evidenced an EC_{50} of 140 and 160 µg/mL, respectively, for thyroperoxidase-catalyzed iodination. Tyrosinase inhibition was also tested and a higher IC_{50} was found for the mesocarp ethyl acetate in comparison with extract or hydroalcoholic fraction for both monophenolase and diphenolase activity [35].

The antioxidant potentiality of babassu is detailed in Table 5. EC_{50} required for DPPH• (2,2-diphenyl-1-picrylhydrazyl) scavenging was described for kernel oil [37, 45] and for a nanoemulsion [32]. Nobre et al. [30] did not find thiobarbituric acid reactive substances (TBARS) inhibition and evidenced a low effect on deoxyribose

degradation, DPPH•, and iron chelation by kernel methanolic extract. In this study, the expected effect occurred only for FRAP (ferric-reducing antioxidant power), but required higher concentrations than quercetin (1560 vs. 155.2 μmol $L^{-1}Fe^{2+}$). Likewise, no antioxidant effect of MAE up to 1000 μg/mL was detected. Endocarp, flower, and leaf alcoholic extracts also did not demonstrate antioxidant potential based on reaction with DPPH•. Furthermore, there was no yeast survival when the same extracts were associated with tert-butylhydroperoxide [23]. A positive result was verified only by Silva et al. [35] for mesocarp ethyl acetate fraction on DPPH• (IC_{50} of 3.38 μg/mL), $ABTS^{•+}$ (2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) scavenging (2.04 μg/mL), and FRAP (15.41 mmol Fe^{2+}).

Discussion

In vivo studies

The fruit of babassu has shown favorable biological activities. However, the absence of results or undesirable outcomes were also observed, such as the antithyroid effects.

In animal models, the sex, age, weight, and metabolic condition are essential to optimize the relevance of the results [47]. Despite the analysis of beneficial effects, the in vivo trials seem to be useful for acute, subacute, or chronic toxicity tests, since even natural substances cannot be considered completely safe. Notably, widely studied nutrients also exhibit upper limits and restrictions [48]. In this context, investigations subjected animals to varied experimental conditions, including a single dose [23, 27], short or moderate durations throughout their lifetime [6, 39], or progressive dose regiments [24], but not always waiting for long latency periods [23], which limits the outcomes.

One of the alterations found that could indicate possible toxicity suggests that even after 14 days of latency, ALP increase was not followed by changes in liver and kidney functions. The hypothesis suggests that young animals are susceptible to alterations in this enzyme according to their diet [27]. In turn, increasing levels in aminotransferases should be evidence of oxidative stress due to lipid peroxidation, notably when there is a greater oxygen demand, as the rodents submitted to RT [6]. In terms of immunotoxicity, the decrease of splenic cells and spleen weight were both selective. The authors suggest sparse effects due to the divergence of results in strains with distinct haplotypes [39]. In short, despite the cited changes, all publications suggest low toxicity of the kernel and the mesocarp, not only with a single dose intervention up to 5 g/kg [23, 24, 27], but also with low doses up to 40 days [6, 39].

Results on metabolic effects show discrepant changes in serum TG. This marker increase could suggest an increment in lipogenesis due to the high carbohydrate content in the mesocarp (79.2%) [6], but it did not worse with doses above 1000 g/kg [27]. The presence of fibers in the mesocarp (17.9%) could also be associated with TC and LDL (low-density lipoprotein) decrease by reducing lipids absorption when they interact with lipase and/or colipase and limit the enzymatic activity [6, 49].

The reason for urea level reduction lies in the fact that foods with a high carbohydrate content, mostly resistant types, are not absorbed and remain available for gut microbiota fermentation. In this condition, endogenous proteins and plasma nitrogen would be recruited to ensure microorganism growth, reducing plasma urea levels, especially when dietary protein intake is deficient [50].

Investigations have also displayed weight gain and glycemic fluctuation after intervention with MAE, which would contraindicate mesocarp intake, mainly for type II diabetes patients, in which weight loss is the most common aim, or when the risk of developing diabetes is increased [25]. However, the glycemic load of foods with a high content of digestible carbohydrates can be attenuated in association with proteins, lipids, and dietary fiber, constituting an essential strategy for maintaining adequate glycemic levels [51]. In opposition, the absence of weight gain and retroperitoneal adiposity reduction was demonstrated by Soares et al. [6] after MAE intake associated or not with RT, indicating a possible adjuvant effect of mesocarp in fat loss and weight control.

The anti-inflammatory activity of mesocarp chloroform extract suggests its application in subacute situations due to the inhibition of granuloma, a proliferative phase of inflammation. However, as the chloroform extract had no effect on pyrexia or leukocyte migration, arachidonate metabolism is not possibly involved in the mechanism [24].

Despite the high content of saturated fatty acids in crude kernel oil, the hypothesis is that vascular permeability decrease and leukocyte adhesion observed by Barbosa et al. [26] may have attributed to the anti-inflammatory action of oleic acid and the antioxidant effect of α-tocopherol.

Other positive effects on inflammation processes demonstrated by α-glucan propose that the residual chains of 1 → 3 bonds not hydrolyzed by amylase may be long enough to contribute to phagocytic amplification and vascular protection [40].

In vitro studies

The selective antibacterial effect of MEE, mainly on *E. faecalis* and *S. aureus*, has likely clinical effects because these strains are associated with nosocomial infections and usually resistant to antibiotics. Its mechanism of

action probably involves the generation of complexes between phenolic acids, proteins, and polysaccharides capable of breaking cell wall and inhibiting microorganisms' enzymes [37, 46]. In turn, the synergistic effect between mesocarp and antibiotics may occur by different pathways, including changes in drug receptors [10, 52]. The microparticle encapsulation system can delay compound cytoplasm release, which improves the effect [29]. Applications with crude kernel oil on gram-positive or negative strains were not effective [45]. After its hydrolysis, it showed a selective effect against pathogenic bacteria, but not commensal strains [8]. This effectiveness is related to the free lauric acid, which can cross cell membranes, acidify the intracellular medium, and block bacterial growth, besides the oxidative effect after phagocyte activation [31, 53].

The results observed against tumor cells only demonstrated relative selectivity of mesocarp with epicarp ethanolic extract, including over chemoresistant cell lines, a phenomenon that represents the main failure of antineoplastic treatments. However, the absence of PFK inhibition on HL-60 suggests that the remaining tumor cells may have increased metabolic activity in face of extract toxicity [28, 36].

Fibroblasts have been employed because they are abundant cells in the human body and one of the first to come into contact with substances during absorptive processes. Thus, nanoemulsions based on kernel oil extracts showing low toxic effects against fibroblasts in vitro can predict in vivo studies, as well as the low toxicity against *A. salina* by a wide number of plant species [32, 45, 54].

Experimental evidence demonstrated the antithyroid effect of mesocarp flours, imputing its intake for the persistence of endemic goiter in Maranhão (Brazil) in the mid-1990s [22]. Nonetheless, since the sodium chloride iodination strategy was implemented in the 1950s, the prevalence of iodine deficiency disorders in Brazil has reduced from 20.7% in 1955 to 1.4% in 2000 [55].

The inhibition of tyrosinase activity promoted by the mesocarp ethyl acetate fraction was justified by the high concentration of proanthocyanidins (453.7 mg CE/g) in the inhibitory steps of monophenolase and diphenolase activity [35]. This enzymatic inhibition is one of the key mechanisms for alterations in melanogenesis, responsible for some characteristics of malignant melanoma [56]. The mechanism of this phytochemical consists of blocking L-tyrosine oxidation, depressing L-dopa oxidation products, and preventing pigment synthesis [57].

Given the importance of controlling oxidative stress and its pathological consequences, some tests identified the antioxidant potential of babassu to neutralize free radicals and prevent lipid peroxidation. After finding a total phenolic content of 288 mg/g in kernel oil, the antioxidant activity did not overcome the ascorbic acid, there may not be a direct correlation between high levels of phytochemicals and better effects though [45]. It is also suggested that specific flavonoids may act in the intermediate process of lipid peroxidation, but they do not neutralize specific radicals [30]. Some concerns about the interference of kernel oil pigments in antioxidant assays have some grade of plausibility, such as DPPH$^{\bullet}$, because they can affect the optical density, which can lead to misinterpretations [58]. Therefore, the use of electronic spin resonance may be useful to bypass this interference [32].

The low affinity between MAE and lipids in TBARS can be answered by the lack of interaction with specific lipids, or hydrophilic portions of amphipathic lipids, as they are more sensitive to radical activity [23], even using polar solvents which can extract flavonoids that provide hydroxyl radicals to neutralize reactive species. However, different solvents can optimize the extraction of polyphenols [59, 60]. With the use of ethyl acetate to prepare samples from mesocarp, it was possible to identify monomers and tetramers of catechins. While the monomer is capable of reacting with a single free radical, its polymer can neutralize three radicals simultaneously [61]. On the other hand, the lack of effect by the endocarp, leaf, and flower ethanolic extracts on radicals and protection against tert-butylhydroperoxide, can be explained by low flavonoid content [34].

Conclusion

This review highlights the prevalent use of mesocarp and kernel in alcoholic extracts and emulsions, emphasizing their low lethality and weak cytotoxicity in vitro, along with the absence of acute toxicity in vivo. This opens perspectives for advancing to in vivo toxicity assays with repeated doses. The empirical intake of both mesocarp flour and kernel oil provides a basis for considering an extension to clinical trials to comprehensively understand the potential applications and effects of these substances.

Abbreviations

ABTS	2,2′-Azino-bis(3- ethylbenzothiazoline-6-sulfonic acid)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
DIT	Diiodotyrosine
DPPH	2,2-Diphenyl-1-picryl-hydrazyl
FRAP	Ferric-reducing antioxidant power
EC_{50}	Effective concentration
IC_{50}	Inhibitory concentration
ID_{50}	Inhibitory dose
IFN-γ	Interferon-γ
Ig	Immunoglobulin
IL	Interleukin
KPPS	Kernel pressed paste with skin
LC_{50}	Lethal concentration
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein

MAE	Mesocarp aqueous extract
MEE	Mesocarp ethanolic extract
MIT	Monoiodotyrosine
MME	Mesocarp methanolic extract
MTT	3-4,5-Dimethyl-thiazol-2-yl-2,5-diphenyltetrazolium bromide
PCNA	Proliferation cell nuclear antigen
PFK	6-Phosphofructo-1-kinase
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyzes
PROSPERO	International Prospective Register of Systematic Reviews
RT	Resistance training
SYRCLE	SYstematic Review Center for Laboratory Animal Experimentation
TBARS	Thiobarbituric acid reactive substances
TC	Total cholesterol
TG	Triglycerides
TNF-α	Tumoral necrosis factor-alpha

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Author contributions
ND conceived the review idea, conducted the literature review, database searches, data extraction, risk of bias assessment and edited drafts as well as the final version. IOC performed the database searches, data extraction, risk of bias assessment and provided intellectual input into draft versions. ABSS contributed to the review, edited drafts, provided intellectual input into draft versions. VAO edited drafts, provided intellectual input into draft versions. HAN developed the graphic abstract and provided intellectual input into draft versions. PMPF provided intellectual input into draft and final versions. JMCS contributed to the review idea, conducted the risk of bias conflicts, edited drafts and provided intellectual input into draft versions as well as the final version. All authors read and approved the final manuscript.

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Declarations

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Not applicable.

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