

Full Length Research Paper

Therapeutic applications of *Caryocar brasiliense*: Systematic review

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The interest and search for natural active principles with therapeutic properties from plants are growing, given their potential for use by the cosmetic and pharmaceutical industries. Thus, the objective of this review was to carry out a systematic analysis of scientific productions that have explored some therapeutic potential of *Caryocar brasiliense*. The methodology of the preferred reporting items was adopted for systematic review and meta-analysis protocols (PRISMA). Articles published in the period from 2009 to 2019 in the Web of Science and Bireme were selected and evaluated. The descriptors used were *C. brasiliense*, extract, and therapeutic. After applying the exclusion criteria, 25 studies were selected, elucidating a miscellany of therapeutic potentials for pequi, such as antioxidant, antifungal, antibiotic, antineoplastic, neuroprotective, regulation of blood pressure as well as analysis of the toxicity of different parts of the plant. It was verified that the pulp extract was the most used for therapeutic purposes, mainly orally. Toxicological studies have shown low toxicity for all parts of the plant, in high doses. The therapeutic benefits observed consisted mainly of antioxidant, anti-inflammatory, antimicrobial, antineoplastic, antiparasitic, and blood pressure control activities.

Key words: *Caryocar brasiliense*, extracts, systematic review, therapeutic potential.

INTRODUCTION

The therapeutic action of plants comes from active ingredients that are produced by their metabolism and

that have some medicinal properties and are then used to treat lung affections, cough, bronchitis, skin wounds,

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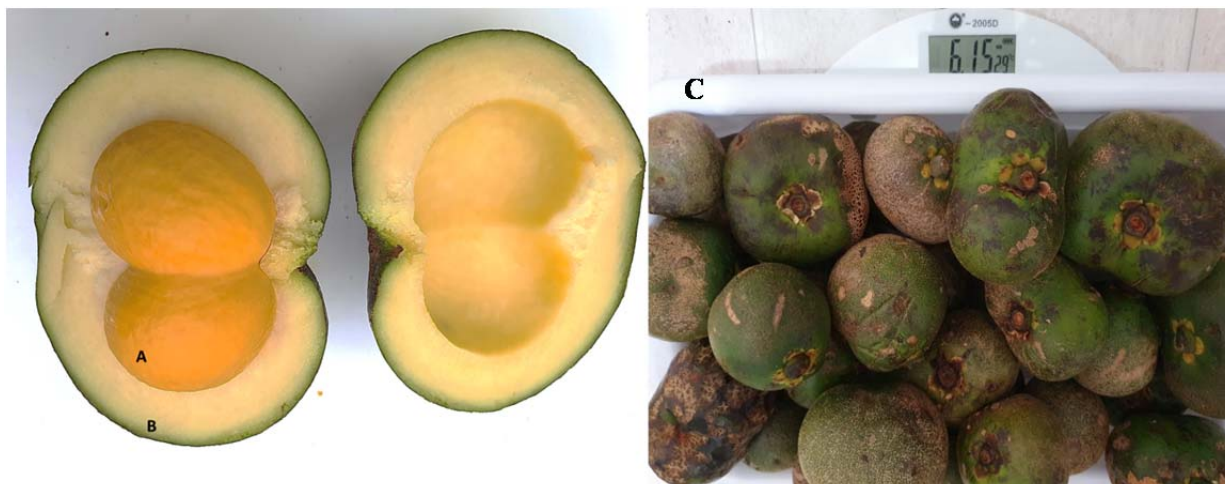


Figure 1. *C. brasiliense* fruit sectioned, showing the almond with the yellow oleaginous pulp (A) and the peel (B); closed ripe fruits (C).

worms, headache, colic, constipation, diarrhea, pharyngitis, anemia, pruritus, kidney stones, bladder stones, bacterial infections, fungal infections and neoplasms (França et al., 2008; Gupta and Gupta, 2020). Historically, plant products have been used since prehistory for medicinal purposes and have passed through time being used until today (Souza and Rodrigues, 2016). In the last decades, important discoveries have been made about new phytotherapeutic properties of various plants, so that the interest and search for natural active principles with potential for use by the cosmetic and pharmaceutical industries are growing (Amaral et al., 2014).

Brazil has a rich, diverse, and abundant flora (Flora do Brasil, 2020). In addition to the biological value, they represent in the ecosystem, several native plants play a socioeconomic and cultural role in certain regions. In the Midwest region of Brazil, *Caryocar brasiliense* Cambess. (Figure 1), a typical fruiting plant from the Cerrado, popularly known as *pequi*, *piquei*, or *amêndoa-de-espinho*, has great socio-economic value. The pequi belongs to the family Caryocaraceae, its tree reaches about 10 m in height and has twisted-looking branches (Figure 2). The tree blooms between the months of September and November while the fruits reach the point of maturity between November and February. *C. brasiliense* (*C. brasiliense*) has leaves with opposite decussate phyllotaxy and they are composite with three densely hairy surface and crenate margin leaflets (Figure 3) (Lorenzi, 1992; Castro et al., 2012). The voucher material is registered in the Herbarium Jatiense (HJ) under the numbers HJ 1156, HJ 5736 and HJ 8456.

The pequi fruit is widely used in the cuisine of the State of Goiás, while the pequi oil has also been used in the cosmetics industry. Due to its chemical composition rich in micronutrients and fatty acids such as oleic, palmitic,

and linoleic acid, *C. brasiliense* oil has good characteristics that justify its use in cosmetic formulations and for popular medicine (Mimura et al., 2016). It is known that linoleic fatty acid present in pequi is, for example, beneficial in the treatment of skin wounds. Its use accelerates the healing process, decreasing local inflammation and increasing collagen synthesis, which results in a more resistant tissue (Nascimento et al., 2015).

Studies suggest that the intake of *C. brasiliense* oil as a food supplement can be an important ally against oxidative stress related to aging, thus helping to prevent chronic degenerative diseases. The results showed that the use of this substance improves anemic conditions and reduces inflammatory processes (Roll et al., 2018). Pequi oil also acts against free radicals, has hepatoprotective activity (Vale et al., 2019), performs leishmanicidal and antimicrobial activity against enteric bacteria isolated from humans (Paula-Junior et al., 2006).

Research has demonstrated that *C. brasiliense* oil was able to accelerate the wound regression process, reduce the number of inflammatory cells and contribute to neovascularization, in addition to the increase in fibroblasts and collagen in the tissue, crucial factors in the process of healing (Bezerra et al., 2015). Batista et al. (2010) also pointed out promising results regarding the anti-inflammatory potential when using *Caryocar coriaceum* Wittm oil, a species of the same genus, in dermal lesions in rats. The pequi fruit, in addition to oils, has vitamin A, being useful in protecting the skin against ultraviolet rays and extremely efficient in skin hydration and treatment of senile marks (Faria et al., 2014).

Due to the high associated cost, about 66% of the Brazilian population does not have access to commercial medications, traditional folk medicine being an alternative used. Despite the benefits, the mistaken or exacerbated



Figure 2. *C. brasiliense* tree, in a private area in the Midwest region of Brazil.

use of plant compounds can present toxicity and be harmful to health (Souza and Rodrigues, 2016). The objective of this work was to carry out a systematic study of scientific productions that explored the therapeutic potential of *C. brasiliense*, in order to summarize and harmonize the results of research in the last ten years, which sought to validate its medicinal use.

MATERIALS AND METHODS

The bibliographic survey was carried out in the Web of Science and Bireme (Latin American and Caribbean Center for Health Sciences Information) databases. The terms used as search descriptors were

"*Caryocar brasiliense* extract" and "*Caryocar brasiliense* therapeutic" on both platforms.

For the definition of the sample, the one recommended by the flowchart Prisma 2009 was followed. The inclusion criteria for composing the sample of this study were: complete articles, published from January 2009 to December 2019, in national and international journals; peer-reviewed, published in Portuguese, English, and Spanish; and that they were articles of experimental research that presented contributions regarding the therapeutic applicability of *C. brasiliense*.

The exclusion criteria consisted of scientific productions that did not correspond to the format of a complete research article (theses, dissertations, and abstracts) or that it was a review article. After careful reading of the selected works, those who did not research and presented therapeutic actions of *C. brasiliense* were also excluded. Two reviewers independently assessed abstracts and titles for eligibility and retrieved potentially relevant articles, with differences resolved by a third reviewer where necessary. In an attempt to identify further papers not identified through electronic searching, we examined the reference lists of included papers, applying the same inclusion and exclusion criteria mentioned.

A complete analysis of their respective texts was carried out. For the analysis of the selected articles, the following were considered: year of publication, plant material used in the extracts and method of manufacturing the compounds; experimental model used, therapeutic activity evaluated, and main results found. The data were organized in Excel tables for descriptive analysis and displayed in Graph Prisma 2009. Data were extracted by one reviewer, and a second reviewer subsequently checked for consistency.

RESULTS AND DISCUSSION

The search for the descriptors "*Caryocar brasiliense* extract" and "*Caryocar brasiliense* therapeutic" resulted in 231 records (Figure 4), of which 33 (14.3%) were duplicated on the platforms, the replica being excluded from the sample, leaving, at this stage, 198 works. Twenty-five additional records were identified by analyzing the references of the selected articles. After analyzing the title and summary, 77.7% of the works were eliminated from the sample because they did not address any phytotherapeutic potential using pequi. Of the remaining amount, 16 papers were removed because they were not presented in the original research article format or because they were review articles. Thus, 27 articles were selected for a complete evaluation of the text. Then, two papers were excluded due to the lack of access to the full text. Therefore, 25 studies made up the sample and were included in the qualitative synthesis.

More than half of the evaluated works (52%) used the pequi fruit as a product for prospecting the extracts, while the extracts corresponding to the use of the leaf and peel of the fruit represented 20% of the works, each. Only two studies (8%) evaluated the action of the extract from the leaves of the pequi tree (pequizeiro) and the fruit peel within the same work.

Different medicinal properties were elucidated in the studies evaluated, with 40% pointing to the antioxidant action of *C. brasiliense*. Of these, 60% used the fruit and/or its respective oil to manufacture the extract.



Figure 3. *C. brasiliense* tree top section showing branches with leaves and unripe fruits (A); branch detail with trifoliolate composite leaf and crenate margin leaflets, and open flowers with many stamens (B); details *C. brasiliense* flower buds (C).

According to Ferreira et al. (2011), the main fatty acids present in pequi oil are oleic, palmitic, gallic and quinine

acids. Responsible for sequestering chelating metals and free radicals, antioxidants are also present in the pequi

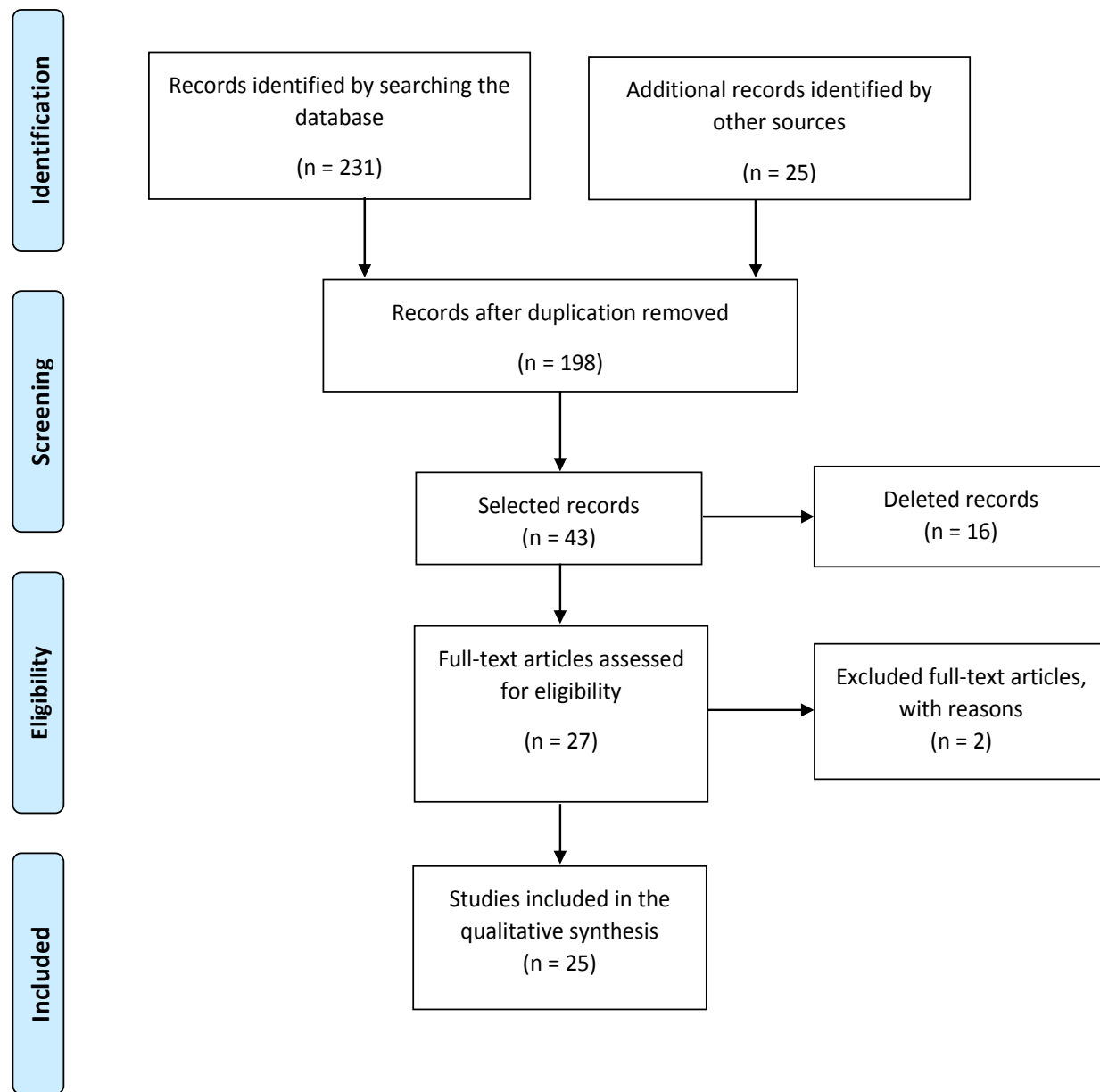


Figure 4. Flow diagram with the relationship between the records found and included.

peel. The peel is rich in gallic acid, with the potential to eliminate reactive oxygen species and act in the prevention of diseases (Rocha et al., 2015), but commonly discarded. The relationship between the part of *C. brasiliense* used and the action studied is shown in Table 1.

Toxicity assessment

Toxicity assessment studies are extremely important for the transformation of the plant into a medicine. The toxicity of *C. brasiliense* was verified in three studies.

Amaral et al. (2014) evaluated the cytotoxicity of the supercritical carbon dioxide extract extracted from the leaves of the pequi tree on rodent fibroblast cells using a colorimetric method. The results showed that the extract, tested at concentrations of 0.0001 to 50%, did not show cytotoxic potential on the cells evaluated since it did not reduce their viability. This finding suggests the prospect of applying the extract for pharmacological and cosmetic purposes.

The effects of acute exposure, on the oral ingestion of the pulp oil of the fruit of *C. brasiliense*, were evaluated by Traesel et al. (2016) when submitting Wistar rats to the consumption of 2,000 mg/kg in a single dose.

Table 1. Relationship between the part of *C. brasiliense* used and the action studied.

Action studied	Part of plant used	References
Blood pressure control	Leaf	Oliveira et al. (2012)
	Fruit	Miranda-Vilela et al. (2009b)
Antifungal	Leaf and peel	Breda et al. (2016)
	Leaf	Naruzawa and Papa (2011)
Antiparasitic	Peel	Nogueira et al. (2012)
		Pinho et al. (2012)
Antimicrobial	Leaf	Ribeiro et al. (2018)
Antioxidant and Anti-inflammatory	Leaf and peel	Gusman et al. (2015)
	Peel	Moura et al. (2017)
Rocha et al. (2015)		
Miranda-Vilela et al. (2014)		
Miranda-Vilela et al. (2010)		
Vale et al. (2018)		
Antioxidant	Fruit	Miranda-Vilela et al. (2009a)
		Miranda-Vilela et al. (2016)
		Montalvão et al. (2016)
Antineoplastic	Leaf	Oliveira et al. (2018)
	Fruit	Colombo et al. (2015)
Toxicity		Leaf
	Amaral et al. (2014)	
Healing	Fruit	Traesel et al. (2016)
		Traesel et al. (2017)
Digestibility		Bezerra et al. (2015)
Activity in the reproductive system	Peel	Freitas et al. (2018)
		Souza et al. (2019)

Subchronic exposure to pequi oil was also evaluated, offering it in doses of 125, 250, 500, and 1000 mg/kg to different groups. Both acute and subchronic administration of the oil orally was unable to cause death, signs of toxicity, or change in the animals' health status. However, the authors came across some hematological changes and suggested further studies to verify whether such findings were in fact due to the use of pequi oil or other factors. In view of the results, it was determined that the LD₅₀ of *C. brasiliense* oil is greater than 2,000 mg/kg for acute exposure and greater than 1,000 mg/kg for subchronic exposure.

In continuation, Traesel et al. (2017) tested the same oil for teratogenic and embryotoxic effects on pregnant rodent females, administering the oil orally in concentrations of 250, 500, or 1000 mg/kg in each group until the 15th day of gestation. The doses used were unable to produce significant effects in relation to teratogeny, fetal toxicity, maternal behavior, or any other fetal or maternal variable, thus suggesting that the use of pequi oil during pregnancy is safe for both the female and the fetus.

Souza et al. (2019) evaluated the effects of subchronic

exposure to the ethanolic extract of the peel of *C. brasiliense* on the reproductive system of male rats, offering by gavage the extract in the doses of 75, 150, and 300 mg/kg for a period of 28 days. Such exposure was not able to exert a significant influence on serum testosterone levels as well as on sperm fertility, production, and morphology. However, there was a reduction in sperm transit in the epididymis and changes in the dynamism of spermatogenesis at a dose of 300 mg/kg.

Antioxidant activity

The therapeutic benefits of pequi's antioxidant activity were investigated in ten scientific articles (Table 1), among which studies of anti-inflammatory effects were observed. In the study by Miranda-Vilela et al. (2010), 400 mg of pulp extract was provided daily, for 14 days, to 74 men and 45 women, in order to assess exercise-induced anisocytosis. The results showed that pequi oil helped improve exercise-induced anisocytosis in runners, as well as the ability to carry oxygen in the blood.

However, it was emphasized that the best response to treatment with pequi oil was presented by individuals with the MnSOD Val/Val genotype, CAT AA or AT genotype, and GPX1 Pro allele.

In addition to the previous study and using a similar methodology, the influence of the IL-6-174 G/C polymorphism on tissue damage and markers of inflammation, lipid peroxidation, blood count, and lipid profile of runners was evaluated (Miranda-Vilela et al., 2016). The authors concluded that there was a protective effect of pequi, as they did not observe a positive correlation between triglyceride and C-reactive protein levels after supplementation. They also drew attention to the need for further studies, especially with regard to the role of IL-6. Still, Miranda-Vilela et al. (2009a) showed that supplementation of runners with 400 mg of pequi oil prior to physical activity was able to reduce oxidative damage to the DNA of athletes and decrease tissue damage caused by exercise, assessed through serum levels of liver enzymes and creatine.

Another study, carried out by Vale et al. (2018), verified the effect of *C. brasiliense* pulp extract, orally (400 mg, five times a week, for 4 weeks) on the liver of Wistar rats submitted to strenuous swimming sessions. It was observed that pequi oil acted as an antioxidant, reducing tissue damage caused by free radicals during strenuous exercise, acting as a liver protector, forming a barrier against other harmful metabolic processes, such as necrosis, fibrosis, steatosis, and cirrhosis. The antioxidant and anti-inflammatory effects of *C. brasiliense* have been studied in human patients with systemic lupus erythematosus between 18 and 60 years old, with Disease Activity Index (SLEDAI) below 10 (Montalvão et al., 2016), treated with 400 mg of pulp extract daily, orally, for 60 days. It was observed that supplementation did not significantly decrease the DNA damage index, but significantly reduced the levels of US-CRP in patients, indicating a decrease in inflammation with the use of *C. brasiliense*.

Rocha et al. (2015) evaluated the antioxidant action of the hydroethanolic extract of the pequi peel, observing the extract's ability to eliminate free radicals. His research showed that the extract showed significant antioxidant activity. When separating the extract in fractions, the authors concluded that gallic acid is the metabolite in greater quantity in the fruit peel and responsible for most of the antioxidant action. Using a similar methodology, Oliveira et al. (2018) also studied the antioxidant action of hydroalcoholic extract from the leaves of *C. brasiliense* and its different fractions. In addition to providing radical reduction, this effect being related to the presence of phenolic compounds, the extract in concentrations between 10 and 300 mg/kg also played a neuroprotective function and prevented the experimentally induced memory loss in rats. Such results, linked to the blockade of cerebral lipid peroxidation, suggest the use of pequi in the prevention and/or treatment of neurodegenerative

diseases such as Alzheimer's.

In addition to corroborating the antioxidant effects of other studies with alcoholic extract of the peel and leaves of *C. brasiliense* observing the ability to reduce radicals 2,2-diphenyl-1-picrylhydrazyl (DPPH), Gusman et al. (2015) also verified the anti-inflammatory action of the extracts when faced with the ability to inhibit tumor necrosis factor-alpha generated by the use of the extracts, relating such effect to the presence of polyphenols.

Antineoplastic activity

Antineoplastic activities were mainly attributed to the antioxidant effects of *C. brasiliense*. Doxorubicin is a chemotherapy used in the treatment of cancer; however, this pharmacological asset causes oxidative damage to the body. Miranda-Vilela et al. (2014) pointed out in their study that the use of pequi oil reduced the damage caused by oxidative stress, improved immunity, and reduced tumor growth when compared with other study groups that used different antioxidants, in rats with Ehrlich tumor. The findings indicate that the use of pequi oil can make up the diet of cancer patients, due to its antioxidant potential. Another effect caused by the administration of doxorubicin is cardiotoxicity. Moura et al. (2017) indicated in their study that the use of an ethanolic extract from the peel of *C. brasiliense* by gavage at a dose of 600 mg/kg was able to minimize the cardiotoxicity resulting from this chemotherapy.

Data published by Palmeira et al. (2016), showed that pequi oil has hepatoprotective potential against neoplasia. Using a model of hepatocarcinogenesis induced in rats, the authors observed that the administration of 400 mg/kg of the oil, twice daily for 25 days, orally, reduced by more than half the volume of adenomas and liver lesions, as well as to preventing the development of neoplasia in part of the individuals who received such treatment.

In a similar work, Colombo et al. (2015) used an experimental model of lung carcinogenesis induced in mice. At the time, different groups received an ethanolic extract from the fruit pulp by gavage. The work showed that pequi was able to increase the expression of antioxidant enzymes and consequently reduce oxidative stress, restore DNA changes, and prevent the development of neoplasia. Such activities are related to the antioxidant potential of *C. brasiliense*.

Antimicrobial activity

Over time, bacteria have become resistant to commercial antimicrobials. Faced with this problem, new products have been sought and plants represent an alternative in the demand for active ingredients with bactericidal action (Ribeiro et al., 2018).

According to Ferreira et al. (2011), *C. brasiliense* oil at a concentration of 10 mg/ml showed bacteriostatic action against strains of *Pseudomonas aeruginosa* but did not perform antibacterial activity against *Staphylococcus epidermidis*, *Staphylococcus aureus*, and *Escherichia coli* through the solid medium diffusion test. On the other hand, Ribeiro et al. (2018) showed that the ethanolic and aqueous extract of the leaves of *C. brasiliense* showed antimicrobial activity by the agar diffusion method against strains of *Staphylococcus* spp. and *E. coli* isolated from sick cattle. The authors pointed out tannin as the main antimicrobial compound. The minimum inhibitory concentration of the ethanolic and aqueous extract of *C. brasiliense* was determined, corresponding to 0.27 and 0.71 mg/mL, respectively.

Despite being rich in compounds with known antimicrobial activity such as tannins and flavonoids, Pinho et al. (2012) showed in their study that the hydroalcoholic extract of bran from pequi peel did not perform an antimicrobial activity *in vitro* on *S. aureus* and *E. coli* in concentrations between 200 and 500 mg/ml through the agar diffusion test. However, the authors pointed out that the studied concentration and variation in the quality of the raw material due to changes in seasonality are factors that may have influenced the performance of the extract.

Antifungal activity

Breda et al. (2016) elucidated that the ethanolic extract of the peel of *C. brasiliense* represents an alternative as a natural antifungal since in concentrations between 350 and 1000 µg/ml the extract was effective *in vitro* on *Venturia pirinacom*, *Alternaria alternata*, and *A. solani*. On the other hand, the hydroethanolic extract from the leaves of *C. brasiliense* had no significant effect on *Colletotrichum gloeosporioides* and *Corynespora cassiicola*, phytopathogenic fungi, at a concentration of 50% (Naruzawa and Papa, 2011).

Antiparasitic activity

The development of resistance to the pharmacological bases of available antiparasitic drugs is a problem faced in sheep production. Nogueira et al. (2012) in their work evaluated the *in vitro* action of the pequi peel aqueous extract on gastrointestinal sheep nematodes and showed that the concentrations equivalent to 15 and 7.5 mg/ml of the extract showed efficacy close to 100% in the inhibition test hatching eggs. On the other hand, the inhibition of larval development of 90% of the larvae of different nematodes was achieved at a concentration of 53.19 mg/ml (LC90). Still, the action of the extract was evaluated *in vivo*, administering 2 g/kg of the extract by means of an esophageal probe in lambs, observing the average count of eggs present in the feces of these

animals, in which it was verified equivalent efficiency 32.2% two weeks after treatment with the extract. There is considerable anthelmintic action of *C. brasiliense*, although research with other ruminants, rabbits, birds, swine, horses, dogs and cats is still needed.

Blood pressure control

Oliveira et al. (2012) tested the *in vivo* and *in vitro* action of the hydroalcoholic extract of the leaves of *C. brasiliense* on rings of the thoracic aorta of Wistar rats as well as on blood pressure. In this study, it was shown that the extract provided the modulation of vascular effects in both experimental models, thus pointing out the potential to be used in pressure regulation since it was able to decrease it and cause relaxation of the aortic rings previously contracted with the use of phenylephrine.

In another study, Miranda-Vilela et al. (2009b) offered daily doses of 400 mg of pequi oil orally for 14 days to male and female athletes aged 15 to 67 years. At the time, it was noted that the intake of such a compound was able to reduce the blood pressure of athletes, regardless of gender. The authors relate such a hypotensive effect to the presence of monounsaturated fatty acids contained in *C. brasiliense* oil since other studies point to the inversely proportional relationship between fatty acid intake and blood pressure.

Other effects

The use of plants topically in the treatment of wounds is widely used in folk medicine and satisfactory results are reported. Bezerra et al. (2015) evaluated the action of commercial pequi oil on the healing process of dermal lesions in rats. The groups treated with the oil showed a significant reduction in healing time when compared to the control group. It was noted that at the histological level, pequi oil was also able to attenuate the inflammatory process during tissue repair.

Brazil is among the largest meat producers in the world. As a result, it has a large number of ruminants. It is known that these animals contribute significantly to the emission of methane into the atmosphere, directly influencing the greenhouse effect. In view of the environmental impact they represent, it is of worldwide interest to reduce the methanogenesis of these animals without causing a drop in production. Freitas et al. (2018) showed that *C. brasiliense* oil significantly reduced the percentage of methane in 24 h when tested *in vitro*. In the *in vivo* experiment, sheep received 75 g of oil per day for 21 days and was suitable for reducing CH₄ production from ruminants, with no negative effects on intake and digestibility.

Conclusion

The main extracts extracted from *C. brasiliense*, for

therapeutic purposes, are the pulp or peel. The main form of treatment used is orally. The toxicological studies already carried out showed low toxicity of the pulp, skin, and leaves. The therapeutic benefits verified in this study consisted mainly of antioxidant, anti-inflammatory, antimicrobial, antineoplastic, antiparasitic, and blood pressure control activities.

In view of the multiple therapeutic actions pointed out in this systematic review, the continued use of *C. brasiliense* in research with pharmacological, toxicological purposes, pre-clinical trials, and obtaining therapeutic formulations is justified.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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