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Therapeutic effects of *Anacardium occidentale*: an integrative review

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Abstract

Anacardium occidentale Linn is a medicinal plant, member of the family Anacardiaceae. Several parts of the plant have therapeutic properties, enabling its use as an herbal medicine. Thus, this review identified the available literature data on the herbal properties of *A. occidentale*, considering articles published in the last twelve years. This is an integrative literature review using descriptors of the Virtual Health Library (VHL), considering the PubMed and SciELO databases. The search resulted in 694 articles and, after employing the inclusion and exclusion criteria, totaled 66 publications for full analysis. We found 98 different properties of *A. occidentale*: anti-inflammatory; antioxidant; antimicrobial; antidiabetic; healing; analgesic; effects on the digestive tract and on the autonomic nervous, respiratory, and blood systems; hypotensive and cardioinhibitory effects; protective against male sexual dysfunction; antimutagenic, antimetastatic, and clastogenic; odontological use; toxic and nontoxic effects; and others. The main effects were antioxidant and antimicrobial. However, the phytotherapeutic use of *A. occidentale* is wide, requiring further contributions to herbal medicine research and development for promoting and integrating traditional medicine.

Keywords: Anacardiaceae, pharmacology, medicinal plant, phytotherapeutic properties.

Efeitos terapêuticos de *Anacardium occidentale*: uma revisão da literatura

Resumo

Anacardium occidentale Linn é caracterizada como uma planta medicinal, membro da família Anacardiaceae. Diversas partes da planta possuem propriedades terapêuticas, o que propicia seu uso como fitoterápico. Assim, o objetivo desta revisão foi identificar dados disponíveis na literatura sobre as propriedades fitoterápicas de *A. occidentale* em artigos publicados nos últimos doze anos. Trata-se de uma revisão integrativa da literatura com uso de descritores presentes na Biblioteca Virtual em Saúde (BVS) empregados nos bancos de dados do PubMed e SciELO. Com isso, a pesquisa resultou em 694 artigos e, após aplicar os critérios de inclusão e exclusão, totalizou 66 publicações para a análise na íntegra. Encontrou-se 98 propriedades diferentes de *A. occidentale*, foram elas: anti-inflamatória; antioxidante; antimicrobiana; antidiabética; cicatrizante; analgésica; efeitos no aparelho digestório; no sistema nervoso autônomo, respiratório e sanguíneo; efeitos hipotensivos e cardio-inibitórios; protetor contra a disfunção sexual masculina; antimutagênico, antimetastático e clastogênico; uso odontológico; efeito tóxico e não tóxico e outros. Tanto o efeito antioxidante quanto o antimicrobiano foram os principais relatados, possuindo aplicabilidade vasta na fitoterapia, sendo necessário uma contribuição no desenvolvimento e pesquisa de medicamentos fitoterápicos, valorizando assim, o conhecimento e a medicina tradicional.

Palavras-chave: Anacardiaceae, farmacologia, planta medicinal e propriedades fitoterápicas.

Introduction

Medicinal plants consist of cultivated or wild plant species with therapeutic uses. They can serve as material for research and production of modern medicine drugs, being also present in popular practices such as homemade medications and folk remedies (traditional medicine) (WHO, 2013).

Brazil is one of the countries with the highest biodiversity in the world, having a lot of different ethnic groups. These groups have a wealth of traditional knowledge accumulated over centuries and an easy, direct access to nature in its various biomes. This leads to a vast and valuable popular wisdom for discovering the pharmacological activities of various plant-derived agents, enabling analyses of the potential of phytotherapeutic medicines (Silva, Melo, Vasconcelos, Carvalho, & Sousa, 2012).

This scenario includes *Anacardium occidentale* Linn, a medicinal plant belonging to the family Anacardiaceae. It is one of the species in the National List of Medicinal Plants of Interest to SUS (Brazilian Unified Health System), RENISUS, which contains plants of therapeutic interest that need further investigation and research to provide a safe and rational use by the Brazilian population (BRASIL, 2016).

Cultivation of *A. occidentale* takes place in various regions of the world. The plant is native to northeastern Brazil, where it is commonly known as "cajueiro" (cashew tree). It produces a fruit, the cashew nut, and a peduncle or accessory fruit, the cashew apple. The various parts of the plant, such as stem bark, fruits, and leaf extract, have multiple pharmaceutical properties, the main ones being: anti-inflammatory (Souza *et al*., 2018), antioxidant (Adriano-Anaya, Trejo-Roblero, Rosas-Quijano, Velázquez-Ovalle, & Vázquez-Ovando, 2017), antibacterial (Montanari *et al*., 2012), and antidiarrheal (Silva *et al*., 2012), among others. These effects stem from high levels of secondary metabolites such as tannins, flavonoids, phenols, saponins, and alkaloids, as well as derivatives such as anacardic acid, which are used as raw material for the formulation of herbal medicines (Okpashi, Bayim, & Obi-Abang, 2014; Santos, Silva, Silva, Sena, & Lima, 2011).

People are becoming more interested in the use of medicinal plants due to the benefits from the substantially easier access in comparison to synthetic options, providing low cost treatment and satisfactory therapeutic results. Thus, this review identifies available literature data on the herbal properties of *A. occidentale*, considering articles published in the last twelve years, from 2009 to 2020.

Materials and Methods

The present article is an integrative review, which allows critical analysis of literature data in a broad and systematic way. This type of review consists of the fulfillment of the following steps: identification of the theme and selection of the research question; establishment of eligibility criteria; identification of studies on scientific databases; evaluation of selected studies and critical analysis; categorization of studies; evaluation and interpretation of results; and presentation of data in the integrative review framework (Botelho, Cunha, & Macedo, 2011).

Initially, we used Health Sciences Descriptors (DeCS) through the Virtual Health Library (VHL) to find universal descriptors. Then, we applied the following descriptors: "*Anacardium occidentale*" and "cajueiro " (or "cashew tree").

Subsequently, we defined the following inclusion criteria: available articles, fully published in 2009-2020, electronically accessible in any language, and addressing the phytotherapic effects of *A. occidentale*. Exclusion criteria were the following: publications outside the previously defined time period; publications not fully accessible online; publications that did not address the chosen theme; short communication papers.

We performed the bibliographic search in an orderly manner from December 2018 to June 2020. The search took place in two databases: SciELO and PubMed, leading to the selection of 694 articles. We excluded 52 studies that were indexed in both databases. After reading the titles and abstracts and applying the established inclusion and exclusion criteria, we selected 66 articles, 41 from PubMed and 25 from SciELO. The second stage consisted of the full reading of articles to systematically list the following information: objectives, research results, plant part analyzed, secondary metabolites/plant-derived compounds, and therapeutic effect.

Results and Discussion

Table 1 presents an overview of the 66 selected publications, highlighting phytotherapic aspects (plant part used, secondary metabolites/plant-derived compounds, and therapeutic effect obtained). Many of these studies on plants that have disease-modifying compounds took place in northeastern Brazil (Chaves & Barros, 2012). It is noteworthy that the public health system in Brazil does not have a pharmaceutical assistance policy capable of meeting the medical needs of the population, especially in this region (Souza *et al*., 2013).

Depending on the extract obtained, *A. occidentale* has several therapeutic effects. Among them is the anti-inflammatory action (n = 15) of the fruit and its rind (cashew nuts); cashew gum; leaves; accessory fruit (cashew apple); and stem bark. The active compounds consist of phenolic derivatives, like the anacardic acid, having properties that decrease oxidative stress and the expression of TNF-α, COX-2, malondialdehyde, and myeloperoxidase. These properties also protect against inflammations by reducing the production of nitric oxide, IL-1β, IL-6, ICAM-1, and P-selectin expression (Siracusa *et al*., 2020; Miranda *et al*., 2019; Souza *et al*., 2018; Hemshekhar, Sebastian, Kemparaju, & Girish, 2012) in a fast and effective way (Silva *et al*., 2018; Souza *et al*., 2018; Vilar *et al*., 2016), and by inhibiting lipoxygenase (Okpashi *et al*., 2014; Hemshekhar *et al*., 2012).

Furthermore, *A. occidentale* leaf extract blocked the lipopolysaccharide-mediated inflammatory effect on macrophage cells in both lipid peroxidation and protein carbonylation (Oyedemi *et al*., 2017). Aguilar, Yero, Arias, Rodríguez, & Navarro (2012) also reported good anti-inflammatory action in the gastrointestinal mucosa due to the properties of tannin and phenolic compounds, improving the treatment of intestinal mucositis and colitis (Siracusa *et al*., 2020; Miranda *et al*., 2019).

Researchers also paired these substances with other bioactive compounds (anthocyanins and ketone) to decrease edemas (Silveira Vasconcelos *et al*., 2015; Okpashi *et al*., 2014; Vanderlinde *et al*., 2009). Aguilar *et al*. (2012) states that anthocyanins also increase lymphocyte production Cashew fruit, in turn, acted as a neutralizing agent in osteoarthritis inflammation, reducing not only pain, but also proinflammatory cytokines, metalloproteinases, and mast cell recruitment (Fusco *et al*., 2020).

Table 1: Phytotherapic aspects of *Anacardium occidentale* Linn.

Therapeutic effect/References	Plant part	Secondary metabolites/derivatives/extracts
Anti-inflammatory [3, 21, 25, 31, 38, 47, 51-53, 55, 57, 58, 62, 64, 65]	Fruit, fruit rind, fruit shell, leaves, stem bark, accessory fruit (cashew apple juice), and cashew gum	Phenols, anacardic acid, anthocyanins, tannins, reactive species to thiobarbituric acid, carbonyl, thiol,acetone extracts, and hydroalcoholic extracts
Antioxidant [1, 3, 9, 11, 13, 16, 20, 21, 28-30,33, 38, 41, 43, 44, 46, 51, 53, 55, 63]	Stem bark, fruit, fruit rind, leaves, buds, and accessory fruit (cashew apple juice,pulp,and fiber)	Phenols, tannins, flavonoids, anthocyanins, anacardic acid, ascorbic acid, carotenoids, tocopherol, cardol, cardanol, xanthones, triterpenes, catechins, sterols, and antioxidant enzymes
Antimicrobial [2, 3, 8-11, 22-25, 30, 32, 36, 42, 45, 46, 48, 51, 56, 60, 64]	Leaves, stem bark, fruit, fruit rind, flowers, accessory fruit, accessory fruit peel, cashew gum, and buds	Flavonoids, tannins, anthocyanins, coumarins, anacardic acid, alkaloids, saponins, phenols, alkylphenols, cardol, cardanol, anacardol, methylcardol, hydroalcoholic and aqueous extracts, and leaf oil ((caryophyllene, D-germacrene, α-copaene, α-cadinene, bicyclogermacrene and germacrene-B)
Interaction with blood glucose levels [4, 6, 17, 19, 26, 38, 39, 41, 51, 54]	Leaves, stem bark, buds, leaf powder, fruit, accessory fruit (cashew apple juice), and accessory fruit peel	Alkaloids, saponins, flavonoids, tannins, phenols, catechin, anacardic acid, triterpenes, anthocyanidins, and ethanolic extracts and fractions (ethyl acetate, dichloromethane, and butanol)
Interaction with lipid profile and body fat [17, 18, 19]	Fruit	Anacardic acid, flavonoids, phenols, and catechin
Wound healing [6, 12, 47, 49, 51, 53, 64]	Stem bark, leaves, fruit rind, accessory fruit (cashew apple juice), and accessory fruit peel	Tannins, anacardic acid, flavonoids, phenols, anthocyanins, and hydroalcoholic extracts
Analgesic [21, 52, 62, 64]	Cashew gum, stem bark, leaves, fruit, and fruit rind	Anacardic acid, tannins, and acetone extracts
Effects on the digestive tract[a] [4, 6, 12, 36, 51, 64]	Leaves, fruit shell, fruit, stem bark, accessory fruit, accessory fruit peel, and leaf powder	Flavonoids, anacardic acid, tannins, and hydroalcoholic extracts
Effects on the autonomic nervous system (Anticholinesterase) [7, 33, 59]	Fruit rind, accessory fruit peel	Anacardic acid, allylphenol, cardol, cardanol, methylcardol, and resorcinolic lipids
Effects on the respiratory system[b] [6, 12, 51]	Fruit, stem bark, and leaves	Anacardic acid and tannins
Effects on the blood system[c] [14, 15, 27, 40]	Fruit, leaves, accessory fruit, and accessory fruit peel	Coumarin, tannins, aqueous extracts, and pseudofruit peel oil
Hypotensive and cardioinhibitory effects [61]	Stem bark	Phenols, lignans, flavonoids, sterols, and tannins
Protects against sexual dysfunction [66]	Leaves	Phenols
Anticancer, antimutagenic, antimetastatic, clastogenic [25, 40, 50, 51, 60]	Leaves, fruit rind, accessory fruit (cashew apple juice)	Anacardic acid and aqueous extract
Causes acute nephropathy [5, 34]	Leaves and accessory fruit	Ascorbic acid
Non-hepatotoxic effect [37]	Stem bark	Tannins, oxalates, saponins, phytate, and cyanide
Effects on oral pathologies[d] [64]	Fruit shell	Hydroalcoholic extracts
Effects on the skin[e] [35, 40, 51]	Fruit, stem bark, leaves,and accessory fruit peel	Anacardic acid, tannins, linoleic oil, and pseudofruit peel oil

[a] Antidiarrheal, antihemorrhoidal, treats abdominal discomfort, dyspepsia, intestinal hypersensitivity, and oral and peptic ulcers; [b] Treats asthma, bronchitis, sore throat, flu, and pneumonia; [c] Thrombolytic, sickle cell membrane destabilization, and formation of micronucleus of polychromatic erythrocytes; [d] Treats gingivitis, dental pain, dental plaque, mouth ulcers, and gingival bleeding; [e] Antiwrinkle, disruption of skin cell integrity, and treats Leishmania ulcers.

References: [1] Adriano-Anaya *et al*., 2017; [2] Aguilar *et al*., 2012; [3] Aguilar *et al*., 2012; [4] Aguilar *et al*., 2012; [5] Akpan & Ekrikpo, 2015; [6] Albertasse *et al*., 2010; [7] Almeida *et al*., 2019; [8] Anand *et al*., 2015; [9] Baptista, Gonçalve, Bressan, & Pelúzio, 2018; [10] Bastos *et al*., 2019; [11] Carrenho *et al*., 2019; [12] Chaves & Barros, 2012; [13] Chaves *et al*., 2010; [14] Chikezie & Uwakwe, 2011; [15] Chikezie, 2011; [16] Chotphruethipong *et al*., 2019; [17] Chung *et al*., 2020; [18] Costa *et al*., 2020; [19] Dias *et al*., 2019; [20] Duangjan *et al*., 2019; [21] Fusco *et al*., 2020; [22] Gimenez *et al*., 2019; [23] Gomes *et al*., 2016; [24] Gonçalves & Gobbo, 2012; [25] Hemshekhar *et al*., 2012; [26] Jaiswal, Tatke, Gabhe, & Vaidya, 2016; [27] Khan *et al*., 2011; [28] Lima *et al*., 2014; [29] Lopes *et al*., 2012; [30] Mendes *et al*., 2019; [31] Miranda *et al*., 2019; [32] Montanari *et al*., 2012; [33] Morais *et al*., 2017; [34] Moyses-Neto *et al*., 2018; [35] Mujica *et al*., 2010; [36] Neiva *et al*., 2014; [37] Okonkwo *et al*., 2010; [38] Okpashi *et al*., 2014; [39] Romero *et al*., 2012; [40] Owumi *et al*., 2015; [41] Oyedemi *et al*., 2017; [42] Quelemes *et al*., 2013; [43] Rabelo *et al*., 2016; [44] Rico *et al*., 2015; [45] Roumy *et al*., 2015; [46] Salehi *et al*., 2019; [47] Santos *et al*., 2009; [48] Santos *et al*., 2011; [49] Santos, Araujo, Sousa, & Lemos, 2016; [50] Shilpa *et al*., 2015; [51] Silva *et al*., 2012; [52] Silva *et al*., 2018; [53] Silveira Vasconcelos *et al*., 2015; [54] Singh, 2009; [55] Siracusa *et al*., 2020; [56] Souza *et al*., 2013; [57] Souza *et al*., 2017; [58] Souza *et al*., 2018; [59] Stasiuk *et al*., 2014; [60] Sunderam *et al*., 2019; [61] Tchikaya *et al*., 2011; [62] Vanderlinde *et al*., 2009; [63] Vieira *et al*., 2011; [64] Vieira *et al*., 2014; [65] Vilar *et al*., 2016; [66] Wattanathorn *et al*., 2018.

Other studies report the use of *A. occidentale* in dentistry for gingival inflammation (gingivitis) (Gomes, Cavalcante, Girão Filho, Costa, & Pereira, 2016; Vieira, Amaral, Maciel, Nascimento, & Libério, 2014; Santos, Dantas, Santos, Diniz, & Sampaio, 2009), which can take place through the decoction of fruits and leaves (Vieira *et al*., 2014).

The following parts showed antioxidant action (n = 21): leaves, accessory fruit and its peel, stem bark, buds, fruit and its rind, as well as cashew apple juice and pulp. Ripe cashew apple juice showed higher antioxidant activity than green cashew apple juice (Silveira Vasconcelos *et al*., 2015), and cashew apple fiber showed low bioaccessibility (Lima *et al*., 2014).

The isolated compounds include vitamins such as ascorbic acid and tocopherol, carotenoids, flavonoids, anthocyanins, tannins, and phenols. Extracts showed potent free radical scavenging activity (Chotphruethipong, Benjakul, & Kijroongrojana, 2019; Adriano-Anaya, Trejo-Roblero, Rosas-Quijano, Velázquez-Ovalle, & Vázquez-Ovando, 2017; Chaves *et al*., 2010) and efficient reducing power in relation to other plant samples (Oyedemi *et al*., 2017). Researchers attribute the antioxidant activity of *Anacardium occidentale* mainly to polyphenol compounds (Carrenho, Silva, Uebel, & Agostini, 2019; Lopes, Miranda, Moura, & Enéas Filho, 2012; Vieira, Sousa, Mancini-Filho, & Lima, 2011). Besides these compounds, triterpenes, xanthones, cardol, and cardanol also showed antioxidant activity (Salehi *et al*., 2019).

Moreover, consumption of natural antioxidants protects against cancer, aging, and cardiovascular and neurodegenerative diseases (Duangjan, Rangsinth, Gu, Wink, & Tencomnao, 2019; Baptista, Gonçalve, Bressan, & Pelúzio, 2018; Rico, Bulló, & Salas-Salvadó, 2015; Okpashi *et al*., 2014). Studies on *A. occidentale* also point to the presence of antioxidant enzymes such as superoxide dismutase, catalase, ascorbate peroxidase, guaiacol peroxidase, polyphenol oxidase, pectin methylesterase, and polygalacturonase in these plants. All these enzymes showed good heat resistance, especially at 75 °C for 30 minutes, with pectin methylesterase being the most resistant enzyme (Rabelo, Brito, Moura, Oliveira, & Miranda, 2016).

These plants also have sterols with similar protective action against cellular oxidative stress (Aguilar *et al*., 2012), as well as anacardic acids (Souza *et al*., 2017) that showed potential to inhibit xanthine oxidase, an enzymatic form that produces reactive oxygen species (ROS) (Hemshekhar *et al*., 2012). The carotenoids present in cashew extract are also potent ROS scavengers, decreasing oxidative stress (Mendes *et al*., 2019).

Oral administration of cashew nuts decreased the levels of malondialdehyde (MDA) and nitrotyrosine in mice (Siracusa *et al*., 2020). The same type of administration restored the serum biochemical parameters of glutathione and catalase activity (CAT), glutathione peroxidase (GPx), and lipid peroxidation in an experimental model of painful degenerative joint disease (Fusco *et al*., 2020).

The following plant parts showed antimicrobial action (n = 21): leaves, cashew apple and its peel, stem bark, flowers, leaf oil, cashew gum, and cashew nut rind. Regarding the spectrum of action, stem bark showed greater activity against enterobacteria, Gram-negative nonenterobacteria, Gram-positive cocci, *Lactobacillus casei*, *Bacillus subtilis*, and other types of strains, with therapeutic indication mainly for urinary infection (Anand, Ravinanthan, Basaviah, & Shetty, 2015; Quelemes *et al*., 2013; Aguilar, Rodríguez, Saavedra, Espinosa, & Yero, 2012). The leaves, in turn, showed greater activity against *Enterococcus faecalis*, Gram-negative nonenterobacteria, *Staphylococcus aureus*, *Streptococcus mutans*, *Escherichia coli*, *Candida albicans*, *Giardia lamblia*, and *Bacillus subtilis* (Sunderam *et al*., 2019; Anand *et al*., 2015; Roumy *et al*., 2015; Neiva *et al*., 2014; Aguilar *et al*., 2012). Ripe cashew peel showed good results against *Staphylococcus epidermidis* and *Staphylococcus aureus* (Gonçalves & Gobbo, 2012). Cashew gum affected mainly Gram-negative bacteria (Souza *et al*., 2013). The other plant parts had general antimicrobial activity without species specificity.

Secondary metabolites and/or derivatives consisted of flavonoids, anthocyanins, cardol, anacardol, alkaloids, saponins, alkylphenols, phenols, among others. Anacardic acid, for example, present in cashew nut rind and cashew apple juice, revealed various effects such as parasiticide, fungicide, anti-*Staphylococcus aureus*, anti-*Propionibacterium acnes*, anti-*Corynebacterium xerosis*, and anti-*Helicobacter pylori* (Okpashi *et al*., 2014; Hemshekhar *et al*., 2012). The secondary metabolites present in the leaves and cashew nut oil showed, in addition to the above effects, action against *Brevibacterium ammoniagenes*, *Streptococcus mutans*, *Enterococcus faecium*, and *Acinetobacter anitratus* (Salehi *et al*., 2019). Furthermore, these metabolites act on dental plaque-causing bacteria (*Streptococcus mutans*, *S. mitis*, *S. sanguis*, *S. sobrinus, and L. casei*), being potent biofilm reducers when in the form of a mouthwash containing 10% *Anacardium occidentale*, acting similarly to 0.12% chlorhexidine digluconate. Consequently, they had a broad antigingivitis effect (Gomes *et al*., 2016).

Another study reported that the anacardic acid present in the crude ethanol extract of cashew showed significant antiplasmodial activity, demonstrating good antimalarial action against *Plasmodium falciparum* (Gimenez *et al*., 2019).

Compounds isolated from cashew nuts showed anti-*Trypanosoma cruzi* activity, attacking metabolism enzymes of this protozoan. Anacardic acid inhibited the enzymes TcSir2rp1 and TcSir2rp3, while the cardol compound inhibited only TcSir2rp1 (Bastos *et al*., 2019).

Coumarin, present in cashew leaves and derived from ethanolic and aqueous extracts, had an effect only against *Staphylococcus aureus*, at a concentration of 200 mg/mL (Aguilar *et al*., 2012). Hydroalcoholic extracts moderately inhibited the growth of *Giardia lamblia* trophozoites (Neiva *et al*., 2014), also acting against *S. mitis*, *S. mutans*, and *S. sanguis*, with expressive minimum bactericidal concentration values (Vieira *et al*., 2014).

Tannins, extracted from stem bark and leaves, affected Gram-positive bacteria, acid-fast bacteria, and yeast, also decreasing biofilm development (Anand *et al*., 2015; Santos *et al*., 2011). In other studies, cashew extract added to yogurt as well as phenols present in cashew pulp processing not only reduced yeasts and molds, but also acted against *Salmonella* spp. and fecal coliforms (Carrenho *et al*., 2019; Mendes *et al*., 2019).

Other compounds were caryophyllene and germacrene D, both derived from leaf oil. These compounds were responsible for antimicrobial action through cell wall degradation; damage to the cytoplasmic membrane and its proteins; leakage of cellular content; and depletion of the proton force. The oil from *A. occidentale* showed worse results in comparison to the oil of other species such as *Astronium fraxinifolium* and *Schinus terebinthifolius* (Montanari *et al*., 2012).

Leaves, accessory fruit, stem bark, and buds interacted with blood glucose levels (n = 10). Secondary metabolites were alkaloids, saponins, flavonoids, and tannins, which significantly reduced the complications of type 2 diabetes mellitus, and better controlled serum glucose in comparison to the drug glibenclamide (Silva *et al*., 2012). In rat experiments, the use of triterpenes, anthocyanidins, ethanolic extracts and fractions (ethyl acetate, dichloromethane, and butanol), and leaf derivatives reduced fasting serum glucose levels, except for the butanol fraction. The effects were comparable to treatment with pioglitazone (Jaiswal, Tatke, Gabhe, & Vaidya, 2016; Singh, 2009). Moreover, anacardic acid reduced insulin resistance in mice fed diets high in fat and sucrose (Chung, Shin, Choi, Park, & Hwang, 2020).

Studies show alpha-amylase enzyme inhibition around 26.39% from the use of crude methanol extracts, which is an important therapeutic target for postprandial glucose reduction in diabetic patients. However, the authors observed a low Pearson coefficient between alpha-amylase inhibition and total phenolic content (r = 0.25), as well as a negative correlation regarding total flavonoid content (Oyedemi *et al*., 2017). The aqueous extract of leaves, in turn, protected against streptozotocin-induced type 2 diabetes mellitus in rats (Okpashi *et al*., 2014).

Adding *A. occidentale* leaf powder to bird diets reduced glucose levels ($p \leq 0.001$), requiring lower blood insulin concentration (Aguilar, Martínez, Olmos, Siza, & Betancur, 2012). Equivalently, studies have shown the cashew apple juice to be hypoglycemic, decreasing postprandial glycemic response due to a possible stimulation of pancreatic cells for greater insulin secretion (Romero, Bravo, Maury, & Esteva, 2012). Cashew nut, however, has a reverse effect on glycemic metabolism (n = 1) since other data pointed to an increase in serum glucose levels through the analysis of fasting glucose and the oral glucose tolerance test in dyslipidemic animals. This increase was due to high concentration of phenols, flavonoids, and catechins (Dias *et al*., 2019).

From the fruit interaction with lipid profile and body fat (n = 3), the use of anacardic acid significantly reduced hepatic steatosis in mice by inhibiting lipid accumulation in cells (Chung *et al*., 2020). Phenols and flavonoids, in turn, reduced visceral and retroperitoneal fat deposition, increasing fecal excretion of fat. These compounds also reversed the damage from diminished HDL levels in dyslipidemic animals, and increased fat deposition in the liver tissue (Dias *et al*., 2020). Moreover, adding cashew nut to the diet of moderately malnourished children decreased LDL and increased HDL levels (Costa *et al*., 2020).

Cashew apple juice, stem bark, leaves, fruit, and fruit rind showed wound healing action (n = 7). Studies also showed a considerable wound healing activity from tannins in the aqueous extract (Okpashi *et al*., 2014; Albertasse, Thomaz, & Andrade, 2010; Santos, Dantas, Santos, Diniz, & Sampaio, 2009). Other researchers reported a significant use of *A. occidentale* for wound healing (Santos, Araujo, Sousa, & Lemos, 2017) and a discrepancy between green and ripe cashew juice, with the former having better wound contraction (86.31%) than the second (67.54%) (Shilpa, Kaveri, & Salimath, 2015). Vieira *et al*. (2014) also report the decoction of leaves for healing after tooth extraction.

Cashew gum, in turn, showed analgesic effect (n = 4), with anacardic acid as the predominant derivative, being partly responsible for the antinociceptive action and for reducing prostaglandin E2 (PGE2) (Silva *et al*., 2018). Furthermore, acetone extracts from stem bark showed positive pain control in mouse experiments (Vanderlinde *et al*., 2009). Oral administration of cashew nuts significantly reduced allodynia associated with osteoarthritis, showing an antinociceptive effect (Fusco *et al*., 2020). Some authors also reported the popular use of stem bark, leaves, fruit, and fruit rind for treating toothache (Vieira *et al*., 2014).

Regarding *A. occidentale* effects on the digestive tract, leaf preparations had an antidiarrheal effect (n = 2), being widely used in folk medicine (Neiva *et al*., 2014; Chaves & Barros, 2012). Furthermore, Albertasse *et al*. (2010) reported the popular use of sitz baths applying stem bark or accessory fruit to obtain an antihemorrhoidal action (n = 1). In this context, a study reported decreased abdominal discomfort (n = 3) with the addition of leaf powder to the diet of birds. The procedure reduced intestinal hypersensitivity, also improving nutrient digestion and body function due to the presence of flavonoids (Aguilar *et al*., 2012). In folk medicine, leaf infusions are important in the treatment of abdominal pain (Chaves & Barros, 2012).

Moreover, fruit, stem bark, and leaf extract preparations stood out in the treatment of dyspepsia (upper abdominal discomfort), intestinal disorders, and oral and peptic ulcers (Okpashi *et al*., 2014).

Regarding the action of *A. occidentale* on the autonomic nervous system, we found anticholinesterase effect (n = 3) from resorcinolic lipids and allylphenol with the use of fruit rind and accessory fruit peel (Stasiuk, Janiszewska, & Kozubek, 2014). In addition, cardol hydrolyzes acetylcholine and prevents neural excitation in *Aedes aegypti* larvae (Almeida *et al*., 2019). Triene anacardic acid in the fruit rind could partially inhibit acetylcholinesterase (AChE); increasing the unsaturation of the side chain of this acid also increases inhibition. This event revealed therapeutic benefits for the treatment of Alzheimer's disease. Thus, anacardic acid showed better results than cardanol and cardol. Among its double bonds in the side chain, triene showed better inhibition, followed by diene and monoene in comparison to physostigmine (Morais *et al*., 2017).

As for the respiratory system, studies show the use of fruit, stem bark, and leaf extract for protective effect. Manipulation of these plant parts focused on fighting flu (n = 2), bronchitis (n = 2), asthma (n = 1), pneumonia (n = 1), and throat inflammation (n = 1), with reports of administration through infusion baths (Okpashi *et al*., 2014; Chaves & Barros, 2012; Albertasse *et al*., 2010).

For the blood system, using accessory fruit peel oil led to significant formation of polychromatic erythrocyte micronucleus (n = 1) in the bone marrow of rats ($p<0.05$). Other important effects were: anticoagulant (from leaf powder), with coumarin (Aguilar *et al*., 2012) as a compound; thrombolytic (n = 1) (from the aqueous extract of fruit and accessory fruit), with a relevant percentage difference in clot lysis in comparison to the control group ($p<0.0001$) (Khan *et al*., 2011); and destabilization of the sickle cell erythrocyte membrane (n = 2), which underwent hemolysis in the presence of 800 mg/dL of aqueous extract of leaves. This latter event may be due to the presence of tannins, considered as chaotropic agents (Chikezie & Uwakwe, 2011). A study found that the ability of *A. occidentale* to inhibit the polymerization of deoxygenated sickle hemoglobin molecules diminishes over time, varying according to the aqueous extract concentration (Chikezie *et al*., 2011).

The aqueous extract of stem bark, rich in polyterpenes and phenolic compounds such as phenols, lignans, and flavonoids, showed hypotensive and cardioinhibitory effects (n = 1). These secondary metabolites contributed to a dose-dependent blood pressure reduction in previously normotensive rats, producing negative inotropic and chronotropic effects, not reversed by the use of atropine (Tchikaya *et al*., 2011).

Furthermore, a rat experiment using *A. occidentale* leaf powder extracted with 95% ethanol protected against male sexual dysfunction and stress-induced infertility, showing a sexual enhancing effect (n = 1). Such actions took place by improved dopaminergic function, suppression of monoamine oxidase B (MAO-B) in the nucleus accumbens, and phosphodiesterase type 5 in the penis. The extract also improved interstitial spaces between Leydig cells in the testes (Wattanathorn *et al*., 2018).

Regarding the carcinogenic and mutagenic action of *A. occidentale* (n = 5), reports on cashew apple juice point to several antimutagenic and antitumor properties, without specifying the relative biochemical compound (Silva *et al*., 2012).

One study has shown that cashew nut shell ether and acetone extract were not mutagenic up to a concentration of 0.003% and 10%, respectively. In addition, the aqueous extract of cashew leaves showed anticancer activity, with a selective toxicity to cancer cells. The anacardic acid has also shown anticancer activity through several mechanisms, such as: surfactant activity; direct interaction with the estrogen receptor; induction of cellular apoptosis; histone acetyltransferase inhibition (n = 1) through noncompetitive inhibition of p300 p300/CBP associated factor, thus affecting DNA transcription; and suppression of the enzyme NF-κBα, which is activated by carcinogens, by growth factors, and by inflammatory stimuli (Hemshekhar *et al*., 2012).

The anacardic acid also potentiates TNF-α-induced apoptosis and chemotherapeutic agents, with significant potential as an anticancer agent (Hemshekhar *et al*., 2012). Experiments with rats have shown that anacardic acids isolated from cashew leaves present antimetastatic action by increasing the epithelial expression of E-cadherins (Shilpa *et al*., 2015). However, a study involving rats showed that exposure to cashew oil led to clastogenic activity (n = 1), promoting dose-dependent hepatocyte proliferation and thus affecting carcinogenesis (Owumi, Fatoki, Gbadegesin, & Odunola, 2015).

The use of folk medicine is widespread in the field of dentistry. In addition to the abovementioned uses for gingivitis, dental pain, and dental plaque, reports include its use for treating mouth ulcers (n = 1), from stem bark infusion or decoction, and gingival bleeding (n = 1), also from stem bark preparations (Vieira *et al*., 2014).

Studies also show cases of acute nephropathy (n = 2) due to excessive intake of accessory fruit. This condition relates to low renal function because the accessory fruit is rich in vitamin C, which the kidneys excrete in the form of oxalate (Moyses-Neto *et al*., 2018). Another case reported complaints of hematuria and reduced urinary output from the use of *A. occidentale* tea (Akpan & Ekrikpo, 2015). In contrast, subchronic administration of stem bark extracts rich in tannin, oxalate, saponin, phytate, cyanide, and iron led to a non-hepatotoxic effect in rats (n = 2) (Okonkwo, Okorie, Okonta, & Okonkwo, 2010). Moreover, administration of cashew nut oil to rats did not lead to a significant toxicity; the authors observed a dose-dependent increase in the number of hepatocytes in some subgroups (Owumi *et al*., 2015).

Other phytotherapeutic effects of *A. occidentale* concern the use of fruits, stem bark, and leaf extracts for treating *Leishmania braziliensis* ulcers (n = 1) (Okpashi *et al*., 2014). Mujica *et al*. (2010) reported the use of cashew nut oil in the preparation of an antiwrinkle cosmetic (n = 1) that, after purification, was able to enhance cell regeneration and mitigate the appearance of wrinkles. When exploring this characteristic, 78.4% state that there was an improvement in the appearance and / or attenuation of wrinkles in the areas of the face. In addition, some authors report the use of vitamin preparations in the form of juice or decoction of the accessory fruit and its peel (Albertasse *et al*., 2010). Cashew nut rind, rich in anacardic acids, inhibited the activity of tyrosinase and urease (n = 1) (Hemshekhar *et al*., 2012). Furthermore, research with rats has shown that exposure to cashew oil has compromised skin integrity and caused trauma to the exposed skin region (n = 1) (Owumi *et al*., 2015).

Despite the variety of therapeutic effects reported for *A. occidentale*, some studies evidenced the popular use of the plant, without clinical trials. Most research involving clinical trials to identify pharmacological activities are still in the preclinical phase.

Conclusion

Species *A. occidentale*, popularly known as cashew tree, has several uses in herbal medicine. The main reported therapeutic effects are its antimicrobial action against bacteria, fungi, protozoa, and other parasites, and its antioxidant activity, both mentioned 21 times. Other effects are also widespread in the literature, such as its anti-inflammatory action. This shows the importance of further research on the therapeutic properties of this plant, so as to contribute with data that attest to its safety and effectiveness. Research and development of herbal medicines requires funding and resources to enable its mass production and distribution through the Brazilian Unified Health System (SUS), thus promoting and integrating traditional medicine.

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