Pharmacological activities of the phenolic constituents from *Anacardium occidentale* (Anacardiaceae): A review

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ABSTRACT

The phenolic compounds present in cashew nut shell liquid (*Anacardium occidentale* L.– Anacardiaceae) present several pharmacological activities that justify the high number of research studies using these compounds. Among these molecules, we can highlight the phenolic constituents such as anacardic acid, cardanol, and cardol. This review aimed to investigate the pharmacological activities of anacardic acids, cardol, and cardanol described in scientific studies published in the literature. The PRISMA methodology was used to perform the bibliographic search applied to the LILACS, PubMed®, Scielo®, SciFinder®, and Science Direct databases, without language or region restrictions, considering articles published between the years 2014 and 2023. The results recovered 52 articles eligible for this review after applying the exclusion and selection criteria. 2 types of pharmacological activities were described, especially: antioxidant, anti-inflammatory, antibacterial, cytotoxic, and antiparasitic activity. Most of the studies involved *in vitro* (20) and *in vivo* (18) pharmacological evaluation methods. The phenolic compounds of *A. occidentale* presented a great pharmacological potential to be explored. The use of *in silico* pharmacology can additionally help in the description of physical-chemical, pharmacokinetic, and pharmacodynamic, enabling the exploration of pharmacological potential.

Keywords: Anacardic acid, Cardol, Cardanol, Phenolic Constituents, Pharmacology, *Anacardium occidentale*

INTRODUCTION

The *Anacardium occidentale* L. is an Anacardiaceae family species that is commonly known as cashew (Awakan et al. 2018). This is 81 Genera and 800 species family that is present in dry and humid environments, mainly, plain habitats in tropical and subtropical regions worldwide (Kubitzki et al. 2011). Although this species is adapted to other continents such as Asia and Africa, it is native to Brazil, as well as present in several states mainly in the Northeast region (Mota 2011).

Cashew has two main structures: the peduncle which is a pseudo fruit and corresponds to 90% of its structure, and the chestnut corresponds to 10% which is the fruit of the cashew tree (Tamiello-Rosa et al. 2019). Furthermore, the cashew nuts comprise the peel and its almond. On the other hand, even if the almond is nutritionally rich the peel is considered a residue of cashew nut production that could present a potential environmental risk if not handled correctly (Yuliana et al. 2012).

Ethnopharmacological studies have shown the use of *A. occidentale* as a medicinal plant for the treatment of diseases with an impact on public health

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(Araújo et al. 2020). The leaves, bark of the stem, bark of the cashew, and chestnuts are mainly used macerated, as well as by the method of decoction and infusion to treat the most varied clinical situations (Salihu et al. 2018). Analgesic activities (Cordaro et al. 2020), anti-inflammatory, antibacterial (Thomas et al. 2015; Sharma et al. 2017), treatment of asthma, headache, skin burn lesions, and male infertility are examples cashew medicinal uses (Silambarasan and Ayyanar 2015)India. The information was obtained through open and semi-structured face-to-face interviews with the local knowledgeable people and professional traditional healers. The statistical analysis, use value, family use value, informants' consensus factor, fidelity level, frequency of citation, relative frequency citation and informants' agreements ratio were calculated for the quantitative study of ethnomedicinal data. Results A total of 118 plant species belonging to 95 genera and 55 families dominated by the families like Leguminosae, Asteraceae and Lamiaceae were enumerated with detailed information on parts used, method of preparation, mode of administration and ailments treated. Leaves were mostly used plant part and predominantly used herbal preparations were decoction and paste. Moringa oleifera Lam. was reported by all the interviewed informants and gives the highest UV of 3.9 with 78 use reports due to its diverse medicinal uses. Conclusion The present study demonstrated the need for importance of documenting the traditional knowledge of forest dwelling people. As a result of the study, Abutilon indicum (L..

The phenolic constituents of interest are found mainly in cashew nutshell liquid (CNSL) (Morais et al. 2017). Under different extraction techniques, we can obtain different percentages of the main phenolic constituents of the CNSL (Figure 1). In solvent extraction techniques one has 60-65% anacardic acids (AA), 15-20% cardol, 10% cardanol, and traces of methyl cardanol. In thermal processes, CNSL mainly contains cardol, 15-20%, and cardanol, 60-65%. The increase in the percentage of cardanol is due to the thermal decarboxylation suffered by the AA, during the thermal extraction process (Filho et al. 2018). In addition, AA is about 90% of these constituents, which are the major compounds with the most pharmacological potential (Hemshekhar et al. 2012). The biological activities of AA have known as an antidepressant (Júnior et al. 2019), cytotoxic activity against prostate tumor cell lines (Yao et al. 2015), anti-inflammatory (de Souza et al. 2018), ovicides activity (de Carvalho et al. 2019) and antifungal (Garcia et al. 2018).

Based on these findings, we performed a review study to investigate the main pharmacological activities of phenolic constituents of the CNSL, as well as identify the main mechanisms of action of these molecules associated with their medicinal potential.

METHODS

A search of the literature was carried out according to the PRISMA methodology (Table SM1) for the selection of scientific articles related to the pharmacological activities of phenolic constituents of the CNSL, *A. occidentale* (Shamseer et al. 2015). The

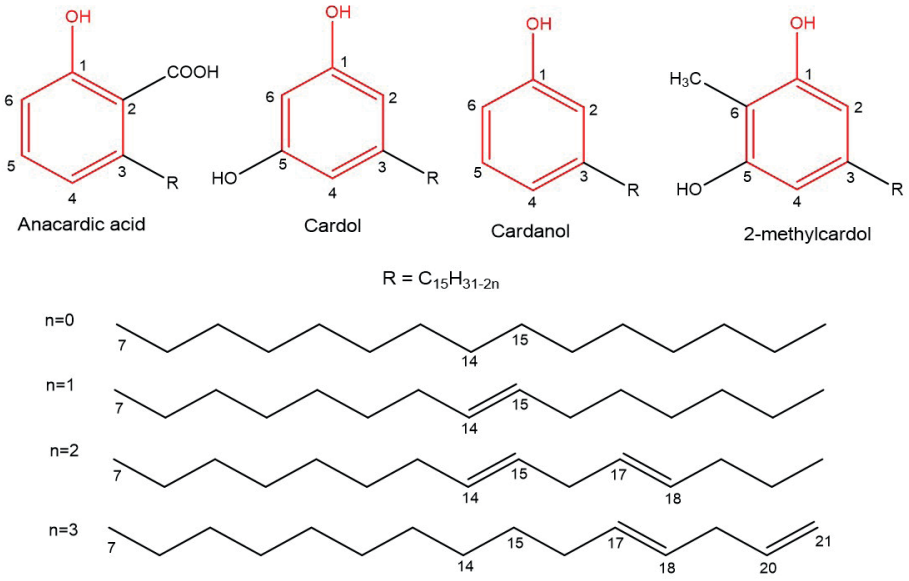

Figure 1. Chemical structures of the main phenolic constituents of the CNSL (Software ChemSketch® version 12.1).

study was conducted using international with indexed literature from the Literature Latino-Americana e do Caribe em Ciências da Saúde (LILACS) (https://lilacs.bvsalud.org), PubMed® (https://pubmed.ncbi.nlm.nih.gov), Scientific Electronic Library Online (SciELO) (https://scielo.org/en), SciFinder® (https://scifinder.cas.org) and ScienceDirect® (https://www.sciencedirect.com) databases, without language or region restrictions and publication period. Furthermore, we used the descriptors "Anacardium occidentale AND pharmacology" and "anacardic acids AND pharmacology". The year of publication was not used as an inclusion criterion. After selecting the articles, it was observed that the publications covered the years 2014 to 2023.

The reference lists obtained from the databases were evaluated by the EndNote web version X9 tool, to delete the duplicate articles. In a further step, references were made based on their title, abstract, and keywords to choose publications related to the pharmacological applications of cashew trees.

The focus of this review article is on the pharmacological activity of phenolic constituents of the CNSL from *A. occidentale*. In this context, we included exclusively pharmacological studies which used AA, cardol, and cardanol from plant extracts whose chemical structures were not produced by synthesis or semi-synthesis processes. We additionally considered commercial patterns which tested these compounds (Figure 2). Furthermore, we extracted the following information from the selected records: pharmacological application, phenolic compound, type of study, experimental model, description of the activity, authors, year of publication, and country.

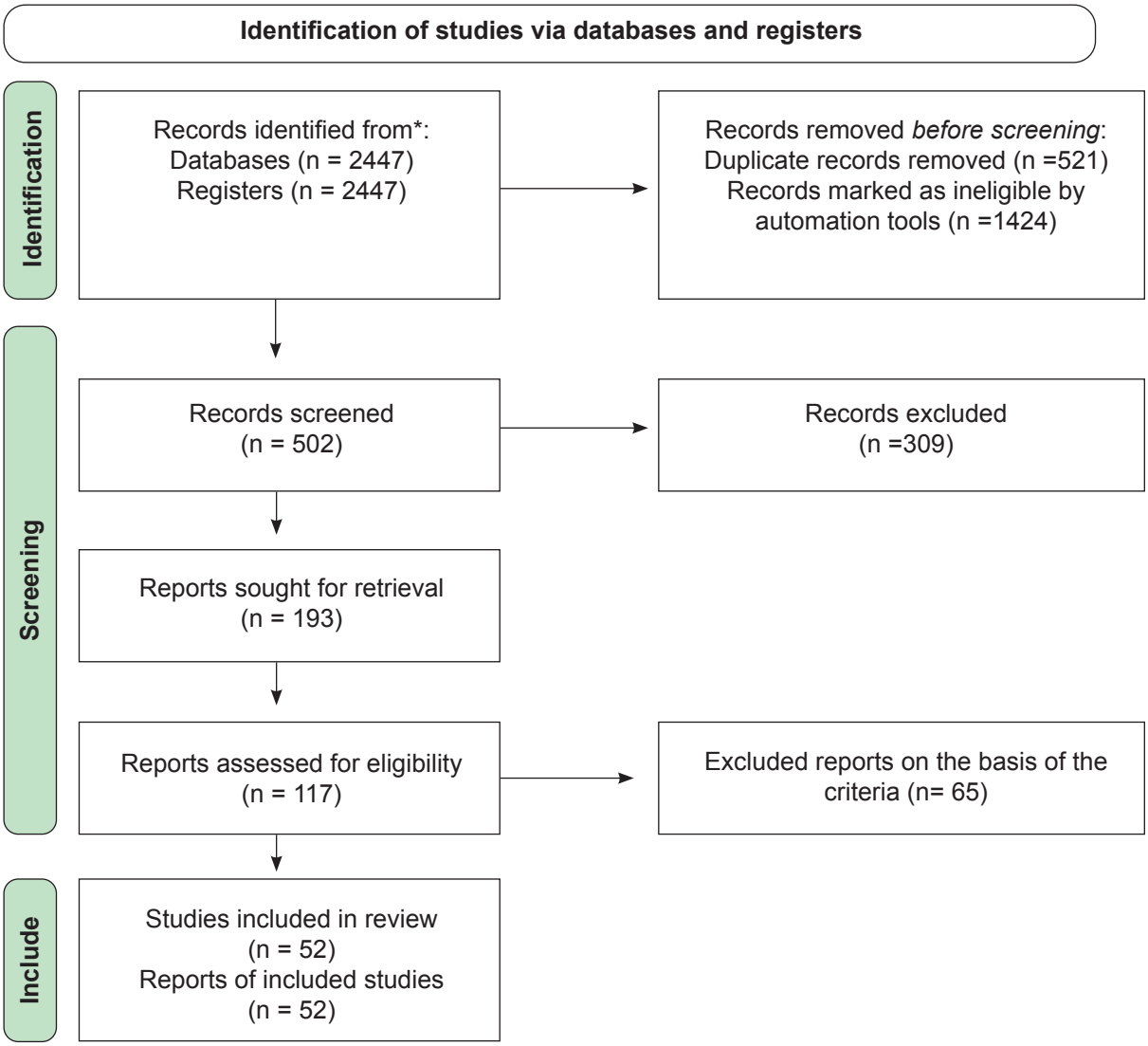

Figure 2. Research protocol for a review with data selection and recovery criteria.

RESULTS

A review of indexed articles

From the 2,447 publications recovered from the initial bibliographic search, only 52 articles were eligible for this review after the application of the exclusion and selection criteria. The impact factor of these articles ranged from 1,1 to 4,554. Furthermore, from the studies included in this review 22 pharmacological activities were identified involving the phenolic constituents of the CNSL (AA, cardol, and cardanol), which are described in Table 1. Cytotoxic activity, antiparasitic and antibacterial activities were the most cited.

In general, the pharmacological activities were described as antibacterial and antifungal, larvicidal and pupicidal, antioxidant, anti-inflammatory and healing, anxiolytic, anticonvulsant and antiparkinsonian, and antihypertensive. In addition, enzymatic inhibition for enzymes of biomedical interest such as acetylcholinesterase and histone acetylase was found. Other associated activities describe dental action as a dentin modifier.

The word cloud based on the top 100 terms in the titles of all included articles shows that the words Anacardium, occidentale, acid, anarcardic, cashew, effect, and activities are among the most frequent words. The time analysis graph of the years of publication shows that the selected studies were published in 2014 and 2023, and the number of studies on the pharmacological activity of the phenolic constituents of *Anacardium occidentale* was published in greater numbers from 2018 to 2020 (Figure 3).

The geographical distribution of studies on pharmacological applications of *A. occidentale* shows that the research production occurred in five continents: South America, North America, Europe, Africa, and Asia. South America was the most representative in the number of studies and type of applications, in particular Brazil. In addition to Brazil, other countries in the world also have studies developed in this area, such as China, Nigeria, India, and the United States of America (USA). Among the pharmacological applications found, antioxidants and anti-inflammatories were the most studied and presented the highest predominance in Brazil, Italy, and Nigeria. In Brazil, the applications that have been mostly addressed are anti-inflammatories, cytotoxic, antiparasitic, and antioxidants (Fig. 4).

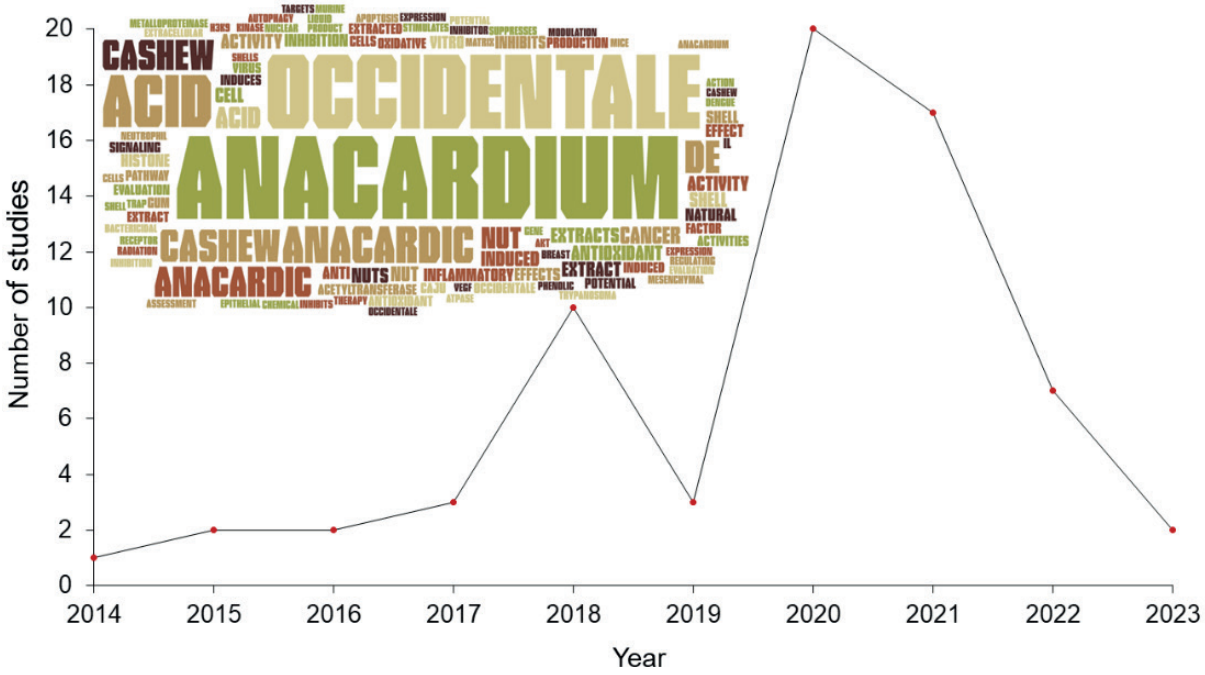

Figure 3. Word cloud based on the titles of the included publications and graph of years of publication of these studies.

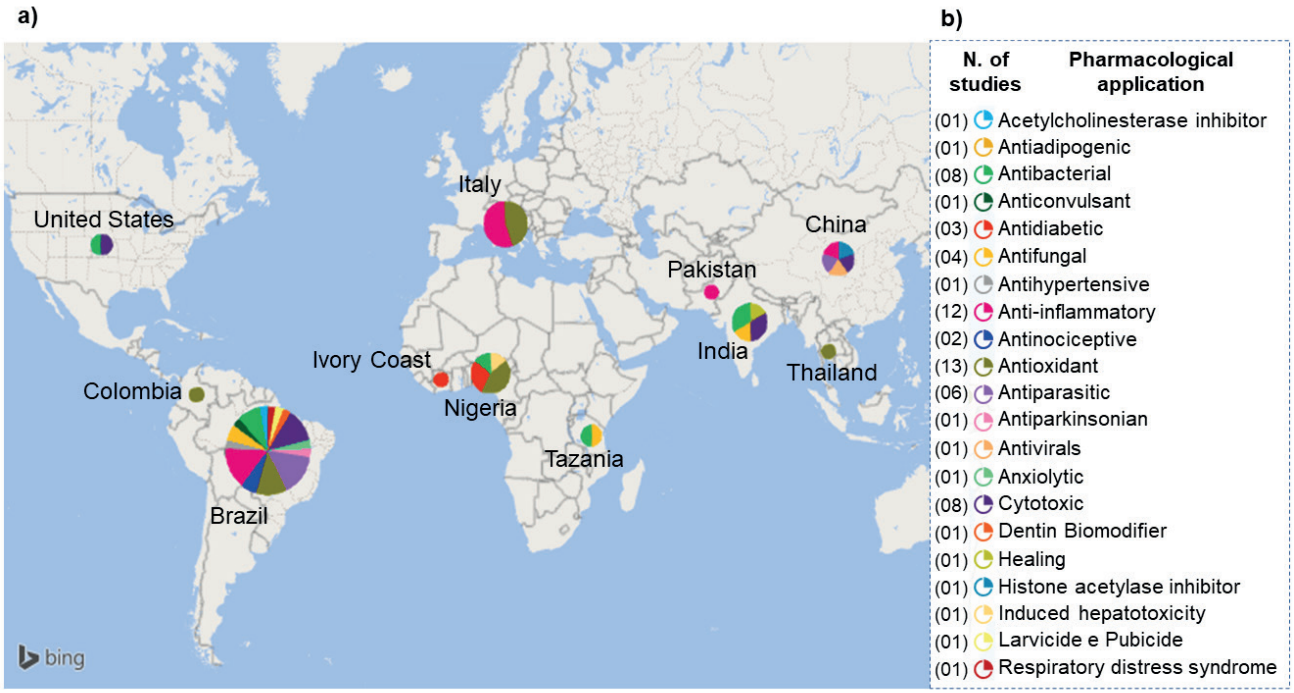

Figure 4. Distribution of selected publications according to (A) geographic location, (B) number of publications by pharmacological applications.

Regarding the types of experimental trials of the studies involving *A. occidentale* as potential pharmacological agents, the results showed that 20 (47%) of the studies were *in vitro*, 18 (42%) *in vivo*, 04 (9%) *in vivo*/*in vitro* and 1 (2%) *in vivo*/*in silico* studies (Fig. 5).

The *in vitro* assays revealed the use of several mammalian strains, mainly Hela cells, human hepatoma HepG2, and human cell lineages of pancreatic cancer: BxPC3, CAPAN-2, and PANC-1. From the *in vivo* experimental trials, we observed the use of male/female albino mice of the DBA/1J, as well as non-isogenic mice and adult rats.

In studies that considered *in vivo*/*in vitro* approaches, the use of Mekada fish (*Oryzias latipes*) and *Staphylococcus aureus* (SA113) was reported. Furthermore, there was a work associating *in vitro* and *in silico* (computational experiments) reporting antifungal activity against *Candida albicans* and molecular docking.

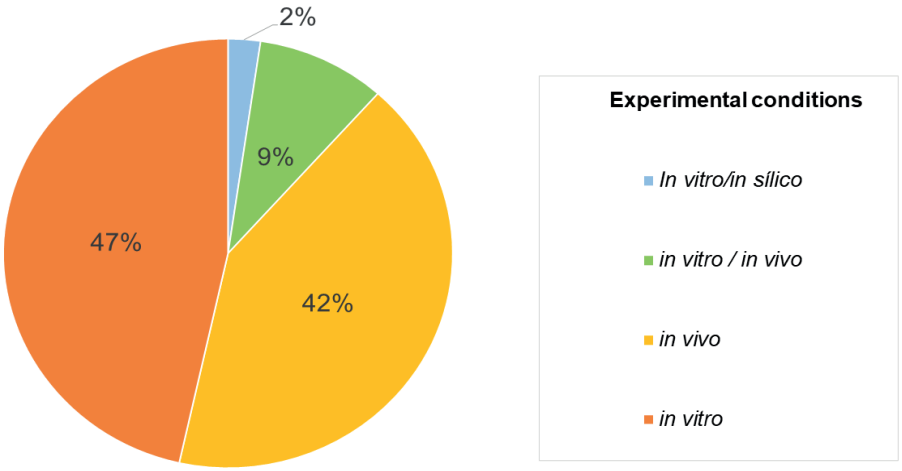

Figure 5. Experimental test models related to the pharmacological activities of phenolic constituents from *Anacardium occidentale*.

Table 1. Pharmacological applications from *Anacardium occidentale* as a research substance and the number of articles selected for each application.

Pharmacological applications	Citation
Acetylcholinesterase inhibitor	1
Antiadipogenic	1
Antibacterial	8
Anticonvulsant	1
Antidiabetic	3
Antifungal	4
Antihypertensive	1
Anti-inflammatory	12
Antinociceptive	2
Antioxidant	13
Antiparasitic	6
Antiparkinsonian	1
Antivirals	1
Anxiolytic	1
Cytotoxic	8
Dentin modifier	1
Healing	1
Histone acetylase inhibitor	1
Induced hepatotoxicity	1
Larvicide and Pupicide	1
Respiratory Distress Syndrome	1
Acetylcholinesterase inhibitor	1

DISCUSSION

Publications evaluating cytotoxic activity, antiparasitic, antibacterial, antioxidant, larvicidal and pupicidal, antifungal, and anti-inflammatory activities were the most frequently observed in the scientific literature. In this way, these activities will be discussed in separate topics and the least mentioned will be addressed in a single point classified here as other activities.

Pharmacological activities of *A. occidentale*

Cytotoxic activity

The discovery of new agents with cytotoxic activity from natural sources has grown and acquired important space in cancer prevention and treatment (Ashraf and Rathinasamy 2018). In this topic, AA, cardol, and cardanol have already been reported by researchers involving breast cancer cells, brain tumor cells (Shilpa et al. 2015), inhibition of cancer cell proliferation (Huang et al. 2014), and more recently pancreatic cancer cell inhibitors (Park et al. 2014).

Purified CNSL containing AA, cardol, and methyl cardol inhibited the proliferation of HeLa cells in a dose-dependent manner with a CI_{50} of 0.004% after 24 hours of treatment (Ashraf and Rathinasamy 2018). These compounds induced a moderate mitotic block causing the depolymerization of the microtubules of the mitotic spindle leaving them abnormal with more misaligned chromosomes and thus affecting cell division. Additionally, another suggested way is to induce cell death by apoptosis (Muzaffar et al. 2016; Zhao et al. 2018).

AA showed cytotoxic activity in non-metastatic breast cancer MCF-7 lineage and glioma (Melo et al. 2011; Shilpa et al. 2015; Galot-Linaldi et al. 2021). Additionally, AA and cardanol suppressed the expression of the Twist and Snail genes, which are metastatic oncogenesis responsible for the Mesenchymal-Epithelium Transition (MET), as well as increased transcription of E-cadherin which is an epithelial marker usually decreased when MET is occurring. Furthermore, AA could be associated with inhibiting the translocation of the transcription factor Sp1 which regulates many genes involved in the promotion of tumor, angiogenesis, and metastasis (Shilpa et al. 2015).

Human hepatocellular carcinoma (HepG2), myeloma (U266) bronchial epithelial cell lines (16HBE) (Huang et al. 2014) and prostate cancer cells (Tan et al. 2017) were submitted to different concentrations of AA and the results showed that induced apoptosis in the lines of HepG2, U266 (Melo et al. 2011; Shilpa et al. 2015). The mechanisms of action proposed for these results are related to the activation of caspases, increased expression of pro-apoptotic proteins (Bim), and decrease in antiapoptotic (Bcl-2) through the activation of the intrinsic and extrinsic pathways of apoptosis fundamental in its cytotoxicity induced in tumor cells (Ashraf and Rathinasamy 2018). In prostate cancer cells, AA acts by inducing apoptosis by inhibiting the androgen receptor and activating signaling p53 (Tan et al. 2012).

The cytotoxicity effect of cashew gum was performed by MTT assay, and the B16-F10 melanoma model was used to evaluate the antitumor effect. Although it has no cytotoxic effect in vitro, demonstrated antitumor activity in melanoma B16-F10 in vivo model. Furthermore, CG did not induce toxicity to organs, with few hematological changes (Barros et al. 2020).

The inhibition effects of AA, cardol, and cardanol against pancreatic cancer cells were reported to be dependent on the stage of the disease, the number of cells treated, and the concentration administered, which could be related to the increase of chromatin 1st modifier protein (Chmp1A) followed

by the activation of Telangiectasia Mutated (ATM) and p53 which are DNA-bind proteins and act as tumor suppressors (Park et al. 2014).

Anti-parasitic activity

Leishmania braziliensis

An effective and less toxic treatment of cutaneous Leishmaniasis is desirable, given its impact on human health and the emergence of resistant parasites. Silver nanoparticles synthesized with CNSL, main constituents: anacardic acid and cardol, showed in vitro antileishmanial activity. Such in vitro antileishmanial tests indicate that silver nanoparticles with cardol show greater potential to be exploited as a promising non-toxic treatment for cutaneous Leishmaniasis (Bezerra et al. 2022).

Schistosoma mansoni

Promising results of the schistosomicidal capacity of phenolic constituents of the CNSL in adult worms have been found. In one study, adult *S. mansoni* worms were treated with the compound 2-methyl cardol diene in a concentration of 25 µM. After 24 h of treatment, adult worms were severely damaged with flaking and decreased number of tubers (Alvarenga et al. 2016).

Trypanosoma cruzi

The parasite *T. cruzi* is also considered a target of phenolic constituents of the CNSL. Recent studies have shown that the administration of the anacardic acids diene and mono ethene in the specific *T. cruzi* sirtuins TcSir2rp1 and TcSir2rp3 stopped the growth of amastigotes with EC_{50} of 40 µM (Bastos et al. 2019). In addition, another study demonstrated that natural and synthetic derivatives of anacardic acid such as 6-n-pentadactyl-(1) and 6-n-dodecylicylic acids (10e) are potential inhibitors against the target enzyme glyceraldehyde-3-phosphate dehydrogenase of *T. cruzi* with IC_{50} values of 28 and 55 µM, respectively (Pereira et al. 2008).

***Echinococcus* spp.**

Commercial AA scans have also presented promising results ore when tested *in vitro* against protoscoleces of *Echinococcus multilocularis* and *Echinococcus granulosus.* In a study conducted with 0.5 and 20 µM of AA, mortality of these parasites was observed after 24 h of treatment (Yuan et al. 2019). Although initial research has demonstrated the antiparasitic potential of these compounds, the action of AA against echinococcosis remains unknown.

Plasmodium falciparum

The phenolic constituents of the CNSL were investigated as potential antimalarial agents *in vitro*, and the results showed that the compounds cardol triene and 2-methylcardoltriene presented good antiparasitic activity that may be related to the existence of a double bond between C-14 and C-15, and C-11 and C-12 in these compounds (Gimenez et al. 2019). However, the mechanism of target-receptor interaction has not been elucidated and specific medicinal chemistry studies are necessary to obtain these responses.

Antibacterial activity

The rapid increase in multidrug-resistant bacterial strains is a problem of great concern, both in medical communities and in the field of public health, so currently the emergence of antibiotic resistance strains surpasses the development of new drugs capable of destroying these microorganisms (Hollands et al. 2016). In addition, catheter biofilm infection is considered one of the main causes of morbidity and mortality in patients requiring catheterization, and this is mainly caused by *Staphylococcus aureus* (Galot-Linaldi et al. 2021).

Phenolic constituents of the CNSL when evaluated for antibacterial potential revealed effectiveness against strains of *Bacillus subtilis* (Ashraf and Rathinasamy 2018), *Streptococcus pyogenes*, Methicillin-Resistant *Staphylococcus aureus* (MRSA), *Streptococcus agalactiae*, *Escherichia coli* and *S.aureus* (Moreira et al. 2017). In addition, these compounds acted against bacterial targets by selectively stimulating the pro-inflammatory pathways of neutrophils resulting in the mortality of *S. pyogenes* and *S. agalactiae* (Hollands et al. 2016). The antimicrobial effect of zein nanoparticles containing CNSL on the in vitro formation of *S. mutans* biofilm has been reported (Lima, et al. 2020). The anacardic acid and cardol have the potential to be used as an oral antibacterial agent, they showed antibacterial activity in planktonic cells against oral bacteria and antibiotic effect on *S. mutans* and *C. Albicans* dual-species biofilm model when incorporated into a universal adhesive system (Souza et al. 2022). Another research on bactericidal activity using purified CNSL showed that phenolic constituents acted against *B. subtilis* reducing the number of colonies in samples treated with 0.6% purified CNSL and 0.34% CI_{50} (Ashraf and Rathinasamy 2018).

A study conducted in two experiments (*in vitro* and *in vivo*) with the use of phenolic constituents of the CNSL demonstrated antibacterial activity against *S. aureus* and inhibition of biofilm formation using catheters impregnated with CNSL which were implanted in the fish *Oryzias latipes* (Sajeevan et al. 2018). This also demonstrates the need for other research techniques that validate the *in vivo* antibacterial capacity of the pharmacological activity

of phenolic constituents.

Larvicidal and pupicidal action

AA, cardols, and cardanols are also potential candidates for insecticide activity. In a study with CNSL from *A. occidentale*, samples with the presence of these compounds demonstrated effective ovicidal activity against *Musca domestica* and *Chrysomya megacephala* and exhibited insecticide activity in *Anticarsia gemmatalis* and larvae of *Spodoptera frugiperda* (Torres et al. 2017; de Carvalho et al. 2019).

Antioxidant activity

A study using phenolic constituents from *A. occidentale* on *Saccharomyces cerevisiae* culture showed antioxidant activities in strains with mutated superoxide dismutase (SOD) (Gomes et al. 2018), which mono, di, and tri-saturated AA were evaluated. These compounds by the free radical inhibition method 1,1-diphenyl-2-picrilhydrazil (DPPH) showed antioxidant action, and triene AA presented the best capacity for antioxidant action and enzymatic inhibition that can be attributed to the presence of three double bonds in the lateral alkyl chain of this compound (Morais et al. 2017; Salehi et al. 2020).

Natural antioxidants for the food industry have become an important focus. CNSL is composed of compounds that can act as natural antioxidants in food systems. The protective effects of CNSL, cardol, cardanol, and anacardic acid were tested in terms of the peroxide value of bulk soybean oil in accelerated assays and were compared against controls with and without synthetic antioxidants. Pointing out that, cardols and cardanols can be used as natural antioxidants in soybean oil (Gaitán-Jiménez et al. 2022).

Antifungal activity

When the action of monoene, diene, and triene AA in *Trichophyton rubrum* strains was evaluated, the result revealed that monoene AA showed higher antifungal activity. The authors' explanation for this feat was that the monoene AA is the molecule more lipophilic when compared to the di and tri-unsaturated AA. Lipophilicity is an important feature for penetration into the cell membranes of microorganisms (Morais et al. 2017). The antifungal activity analyzed with *S. cerevisiae* yeasts showed that AA at concentrations of 0.1, 0.2, 0.4, and 0.8 mM present antagonistic activity against this microorganism.

The results of the analyses in the yeasts *S. cerevisiae* showed that plates incubated for 6h containing AA at concentrations 0.2 mM showed antifungal activity against this microorganism with 99% inhibition of cell growth when compared to the control plate where there was positive growth of the colonies (Muzaffar and Chattoo 2017).

Anti-inflammatory action

A. occidentale has been traditionally used for curing many inflammatory diseases. Studies have shown the anti-inflammatory effects of CNSL in different models of inflammation. The anti-inflammatory action of CNSL was tested *in vivo* using a mouse model of FCA-induced rheumatic arthritis treated with CNSL. In conclusion, *A. occidentale* has significant anti-arthritic potential, which can be attributed to the suppression of lysosomal enzymes and collagenase levels (Naz 2020). In rodent species with induced edema, the inhibiting action of the synthesis of chemical mediators involved in inflammation was observed when treated with polysaccharide-free cashew gum (da Silva et al. 2018). In another experiment, the gravity of arthritis in mice exposed to collagen was significantly decreased when submitted to a concentration of 5mg/kg of phenolic constituents, which was able to supply the proliferation of fibroblast-like synoviocytes in the joint cavity-blocking pro-inflammatory mediators such as TNF-α and IL-1β (Yang et al. 2018).

Other activities

Besides other potential pharmacological applications, AA, cardol, and cardanol are considered promising candidates for the treatment of anxiety and oxidative stress (Júnior et al. 2018), inhibition of pentylenetetrazol-induced seizures (PTZ) in guinea pig mice (Gomes et al. 2018), antihypertensive properties such as the ability to inhibit the angiotensin-converter enzyme I (ACE) (Trevisan et al. 2018), antiparkinsonian activities as reversing ten times more lipoperoxidation damage in rat and promoting significant recovery of locomotor capacity in tested guinea pigs (Linard et al. 2018), as well as acting as dentin modifiers (Moreira et al. 2017). Furthermore, the compounds AA, cardol, and methyl cardol have healing properties of wounds by inducing the proliferation of fibroblast (Ashraf and Rathinasamy 2018) and mono, di, and triene are also able to perform the inhibition of the enzyme acetylcholinesterase (AchE) (Moreira et al. 2017). Finally, phenolic constituents of the CNSL also to be able to inhibit the histone acetyltransferase enzyme (HAT) showing a cardioprotective effect against alcohol-induced cardiac hypertrophy (Peng et al. 2015).

CONCLUSION

Phenolic constituents of the CNSL have an extensive list of pharmacological activities and are

promising chemical structures for the development of various inhibitors and pharmacological modulators. Furthermore, due to its variety of natural structures, phytoprototypes can be configured for the discovery of new compounds with pharmacological action applied to several areas. The phenolic compounds of *A. occidentale* presented a great pharmacological potential to be explored. Despite the large number of studies on the extracts of *A. occidentale*, works with pharmacodynamic and pharmacokinetic characterization, are still promising fields of studies, which guide future clinical trials.

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AUTHORS' CONTRIBUTION

All authors contributed to the study. Conceptualization, methodology, formal analysis, investigation, VDMS, VSJ and MXS; writing - original draft, VDMS, NOS and RSB; visualization, RMA, RSB and WRAS; writing - review and editing, BSA and RMA; supervision and project administration, RMA and WRAS; All authors read and approved the final manuscript.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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