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Medicinal plants and animals of an important seasonal dry forest in Brazil

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ABSTRACT

Research performed in recent years indicates that efforts are still needed to understand the advances in the Caatinga, an important dry seasonal forest, and identify its potential for bioprospecting. These efforts are also important for pinpointing the challenges that should be addressed in future research focused on identifying new candidates for pharmacological studies in this complex region. Thus, in this review, we present the main advances of studies on plants and medicinal animals in the Caatinga region and their implications for ethnopharmacology, and we then discuss future challenges to promote the search for candidates with pharmacological potential. Based on an exploration of the available literature, we performed a critical reading of the available evidence to provide a good scenario on the studies in the region. We find that despite the large number of studies available, it is necessary to organize efforts to fill gaps in different areas of knowledge and optimize the search for new natural products.

Keywords: Ethnobotany; Ethnopharmacology; Ethnozoology; Phytotherapy; Zootherapy

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INTRODUCTION

Brazil possesses a rich diversity of fauna used for medicinal purposes (Alves et al. 2007, 2008a). Studies indicate that the northeast region possesses the largest volume of information on the use of medicinal fauna products (Alves and Rosa 2006 2007a, 2007b, 2007c; Alves 2009). The contribution of this information has stimulated the development of studies seeking to validate the medicinal activities of zootherapies described in ethnozoological studies in this region (Ferreira et al. 2010, Cabral et al. 2013; Oliveira et al. 2014; Sales et al. 2015).

The Caatinga of northeastern Brazil has an extensive area of 912,529 km^2 and represents an important ecological region since it shelters considerable biodiversity and is a semi-arid region that covers several human groups with different sociocultural characteristics (Silva et al. 2017a). In relation to biodiversity, recent studies have registered 4,662 species of native plants (31 endemic genera) (Queiroz et al. 2017), 371 native species of fish (203 are possibly endemic) (Lima et al. 2017), 98 species of amphibians (20 endemic) (Garda et al. 2017), 79 species of lizards (38 endemic) (Mesquita et al. 2017), 548 species of birds (67 native) (Araújo and Silva 2017) and 138 species of mammals (11 endemic species) (Carmignotto and Astúa 2017). This large diversity involves species that have adaptations to deal with low water availability environments, which is important because precipitation is concentrated in a few months and rains are irregular in the region (Silva et al. 2017b).

In addition to the diversity of environments and species, several human groups inhabit the region, such as “Maroon,” indigenous and rural communities, which interact with the Caatinga biota (Albuquerque et al. 2017). In the last decades, many studies have investigated the interactions of people with plants and animals in Caatinga areas (Albuquerque et al. 2007, 2017; Melo 2017). These resources are applied to a wide variety of uses, such as medicinal, construction, food, religious, technological, fuel, etc., thus indicating the high diversity of useful species (see Albuquerque et al. 2007, for medicinal plants).

When considering the biological and cultural diversity of the Caatinga of northeastern Brazil as well as the variety of species indicated as medicinal, this region has an important potential for ethnopharmacological studies focused on understanding the patterns of knowledge and use of medicinal resources by human populations and identifying candidates with important pharmacological activities. To evaluate the effects of bioprospecting, several research studies have been carried out in the Caatinga environment, and their findings indicate that the plants and animals in the region have pharmacological potential for a variety of diseases (Leal et al. 2009; Cabral et al. 2013; Campos et al. 2014).

Some work has gone deeper in the pursuit of patterns to identify the motives associated with the choice of medicinal resources to compose local pharmacopoeias in the Caatinga (Alencar et al. 2010; Lucena et al. 2012; Alencar et al. 2014). These works may be promising for ethnopharmacology as they investigate the formation of local medical systems. These systems involve the set of social institutions and traditions generated from the evolution of strategies that promote the health and well-being of a given locality (Dunn 1976). To understand issues related to traditional medicines, ethnopharmacology has

accessed the knowledge present in local medical systems. However, the use of local remedies is complex, and several factors can influence the use of resources for the treatment of diseases. For example, the local significance of diseases, local norms linked to the healing process, social relations and existing institutional contexts are factors that influence the choice and evaluation of treatment efficiency (Kleinman 1978).

In this article, we present an overview of the state of the art on the medicinal animals and plants in the Caatinga and highlight ethnopharmacological, phytochemical and pharmacological advances.

1. Local medical system from the Caatinga and its relevance for ethnopharmacology

The Caatinga presents a wealth of medicinal plants. Currently, the most important checklist on the medicinal plants of the Caatinga is that produced by Albuquerque et al. (2007), which reported a total of 385 species of angiosperms and four species of ferns and mosses used for medicinal purposes in 21 studies conducted in the region. We used the basis of this study (Albuquerque et al. 2017) to make some of our considerations here. Studies on medicinal plants in the Caatinga usually present a list of medicinal plants and their uses, as well as an index to highlight the most important plants (see Medeiros et al. 2011a). One of the main arguments for the use of these indices is to promote the selection of plants for future pharmacological investigations. However, fewer papers were devoted to describing and testing hypotheses about how these plants fit into the complex local medical systems of the Caatinga.

A considerable amount of evidence has been obtained from studies conducted in the Caatinga and other regions showing that the use of plants for medicinal purposes is the result of a long process of experimentation (see Medeiros et al. 2013; Ankli et al. 1999). Thus, people use certain criteria to recognize a plant as potentially effective, include it in the local pharmacopoeia, and determine the plant that will be used at the time that a disease episode occurs (see Figure 1). Organoleptic properties of plants, such as the color, shape, aroma, taste and texture, act as signs that lead to the inclusion of species in the local medicinal repertoire (Ankli et al. 1999; Casagrande 2000). An association can exist between people's perceptions of the taste and smell of plants and the diseases that they are used to treat, but not in all cases. In this sense, bitter taste may be a core organoleptic property used to treat the most popular diseases (see Medeiros et al. 2015). Only those diseases found most frequently in the lists were associated with a bitter taste, which indicates that bitter taste may be a core organoleptic property used to treat the most popular diseases.

The importance of the disease to be treated in the selection of the medical resource was highlighted in the study by Ferreira Júnior et al. (2016). This study indicates that diseases with similar symptoms have greater similarities to the set of medicinal plants used for their treatment. Considering this finding and that of Medeiros et al. (2015), people in the Caatinga choose resources with similar organoleptic characteristics for medicinal functions that are also perceived as similar. In this case, it is possible that plant characteristics are involved in the selection of medicinal resources when comparing different human groups located in different regions. The study by Saslis-Lagoudakis et al. (2012)

showed that human groups located in different regions select phylogenetically related medicinal plants to treat the same classes of diseases. The authors point out that human groups may have selected these plants independently based on their therapeutic efficacies. In another example, the study of Geck et al. (2017), which was carried out in different communities in Chiapas, Mexico, observed that the smell and taste of the plants provided important information about the humoral ("hot" or "cold") properties, thus guiding their medicinal applications. This finding may have important implications for future strategies linked to bioprospecting because it can be used to evaluate what characteristics of plants guide the construction of medical systems and determine whether these characteristics are linked to important pharmacological activities of plants.

From the characteristics of plants that can guide their selection, it is possible that redundant plants (Albuquerque and Oliveira 2007) used to treat one or more diseases share a certain set of characteristics, such as organoleptics (e.g., bitter-tasting plants targeted for certain diseases, in Medeiros et al. 2015) or chemical properties. In the case of the Caatinga, medicinal plants used for the treatment of inflammation are associated with the presence of tannins (Araújo et al. 2008). Other studies have shown that these

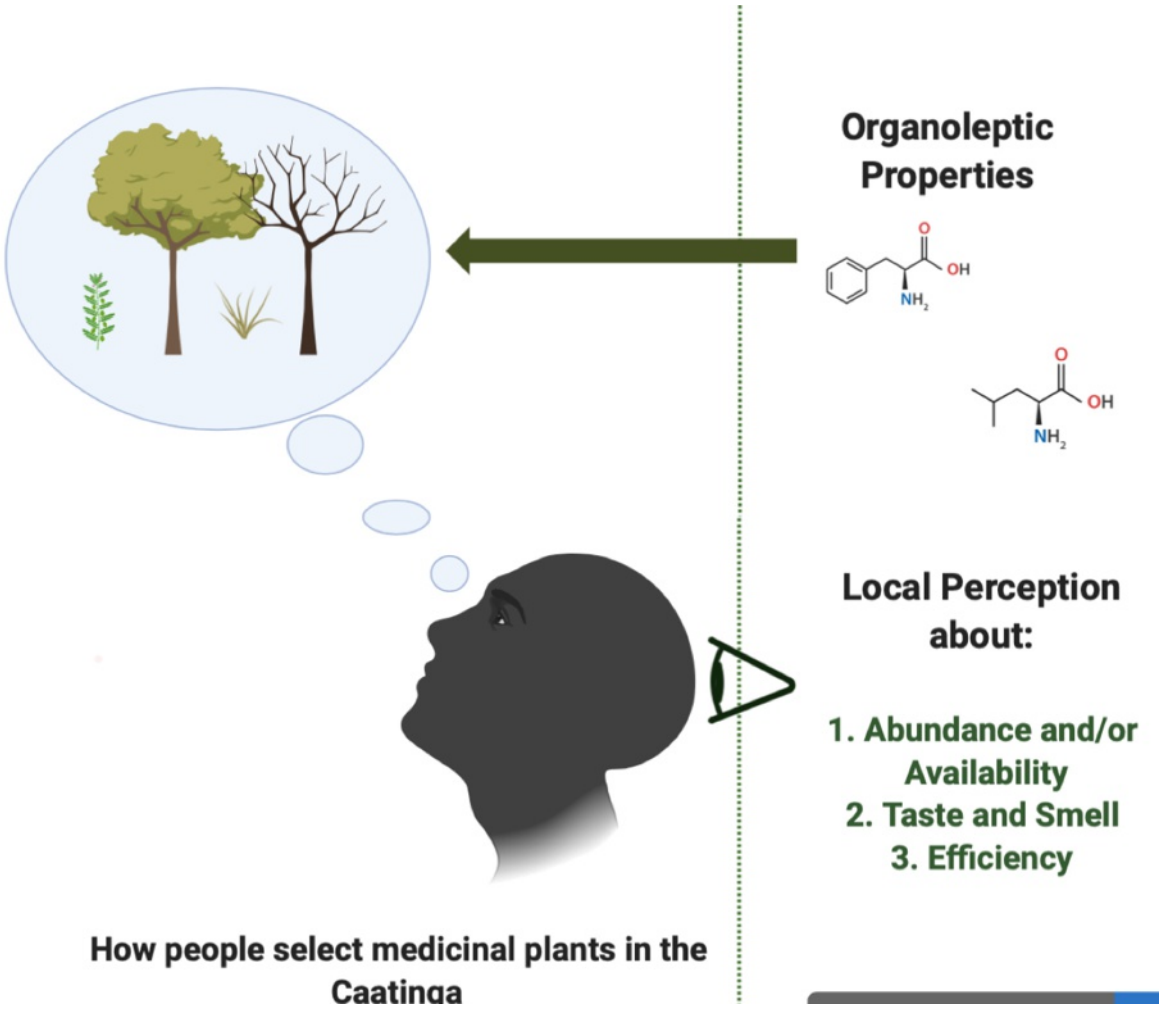

Figure 1. Some insights on how people select medicinal plants in the Caatinga.

compounds can be perceived through the astringency taste (see, for example, Dragos and Gilca 2018).

The recurrence of a disease event appears to be an important factor for structuring local medical systems. Some studies have shown that diseases considered frequent tend to be associated with a large number of medicinal plants (Santoro et al. 2015; Nascimento et al. 2016). Sousa et al. (2016) found that the species cited first in lists of medicinal plants are those that have been used to treat diseases that have occurred in the last year, and these plants are also considered as more important, but new studies need to be conducted to confirm or not this finding.

All of these data suggest that most studies in the Caatinga have accessed and inferred patterns concerning diseases that are most common in the local medical system. Apparently, the most relevant medical information for people is how to deal with recent and/or recurring illness events, which is interesting because it is widespread within the discourse of many authors working with medicinal plants, who consider that the most popular plants are the most relevant for bioprospecting.

In addition to the application of plants for the treatment of frequent diseases, different therapeutic modalities can also be used for these diseases. The study by Nascimento et al. (2018) found that the combined use of plants with medicinal products of biomedical origin can be favored in diseases with high frequency of occurrence according to local perception. An interesting example is the case of the Fulni-ô Indians, whose strategies for health management include the use of plants, visits to practitioners (local specialists), and the use of biomedical drugs (see also Soldati and Albuquerque 2012; Zamudio and Hilgert 2011). However, such combined use can have negative consequences for people from a pharmacological point of view. Several studies have observed adverse effects when medicinal plants are given in conjunction with conventional drugs (Staines 2011; Larson et al. 2014; Murray et al. 2016). For example, plant extracts of different species may affect the expression of the CYP2D6 gene, which produces an important drug-metabolizing enzyme that may cause toxic reactions with or inhibit therapeutic effects when the extracts are administered along with conventional drugs (Feltrin et al. 2019). Therefore, future studies should focus on the interactions between medicinal plants native to the Caatinga and conventional drugs.

In addition to plant-drug interactions, the accumulation of distinct treatments (plants and drugs of biomedical origin) in diseases with a higher frequency of occurrence can increase the probability of maladapted information in local medical systems, i.e., the inclusion of plants that are not effective in the treatment of these diseases (Tanaka et al. 2009; Santoro et al. 2018). For example, according to the model proposed by Tanaka et al. (2009), diseases with higher frequencies of occurrence can increase the chance of non-effective plants being copied among pairs of people in a human group. Santoro et al. (2015) also explained that a greater number of species used for frequent diseases can be related to information transmission errors.

Therefore, future investigations could assess how much non-effective plants are present in local medical systems and the factors that increase the probability of insertion of these plants over time. If these transmission errors are frequent in local medical systems in the Caatinga, then caution should be exercised in the selection of medicinal plants in future studies on

bioprospecting because some of these plants cited for different uses may not be effective in the treatment of certain diseases. Moreover, future research should exercise caution when selecting plants for pharmacological evaluation by including plants prescribed for diseases that are highly frequent in a given region as a criterion.

Another important factor is that not all species known for medicinal purposes or even for a given disease are actually used by a community (Albuquerque 2006), and one plant is often used more frequently than others. Several factors may be involved in the differential use of medicinal plants (see Medeiros et al. 2015); therefore, different criteria have been associated with the prioritization of a medicinal plant in human groups in the Caatinga. For example, Ferreira Júnior et al. (2011) found that the most cited criterion for prioritizing a plant was its perceived therapeutic efficacy. In this case, a plant that is widely cited as preferred because of its perceived efficacy for a large set of diseases may be of interest for future pharmacological investigations aimed at bioprospecting (Ferreira Júnior et al. 2011; Albuquerque et al. 2014).

However, in addition to the perceived efficiency, other criteria are important in the prioritization of medicinal plants. In addition, factors such as accessibility to the resource can promote greater experimentation and learning (Molares and Ladio 2008), thus leading to greater use of these species. Cost-benefit relationships can guide the exploration of medicinal resources, in which a shorter time spent during collection demonstrates weight in the choices of human populations (Soldati and Albuquerque 2012). In environments with marked seasonality, such as the Caatinga, the temporal availability of the species may be another factor that leads to the differential use of medicinal plants; for example, the study of Albuquerque (2006) reports the greater use of the bark of arboreal species in this region because they are found in the environment during the whole year. These environmental factors need to be taken into account since people may come to use more of a medicinal feature not for its efficiency but for its ease of collection. Many medicinal plants are transported by people to the backyards of their homes, for example, to avoid the costs associated with their collection.

In addition to plant resources, products of animal origin are frequent in Caatinga folk medicine. There is an expressive richness of species of medicinal animals used by human populations that live in the region, and these species encompass several groups of invertebrates and vertebrates (Alves et al. 2016a,b; Alves et al. 2012; Bezerra et al. 2013; Mendonça et al. 2014). Ethnozoological reviews indicate that at least 24 reptile species (Alves et al. 2012) and 38 mammal species (Alves et al. 2016a,b) are used for medicinal purposes in the region. Other groups, such as birds, amphibians and fish, are also registered as a source of medicine in the region's folk medicine (Bezerra et al. 2013; Santos and Alves 2016). Among invertebrates, insects stand out (Alves 2009). Curiously, medicinal species of marine origin are used in the region, and they are obtained in public markets in urban areas and are usually obtained from clandestine commercialization (Alves et al. 2009b). Zootherapy is also a practice employed in ethnoveterinary medicine in the region (Souto et al. 2011), and at least 39 animal species have been reported as source of remedies used in local ethnoveterinary medicine for the production of medicines used to treat diseases of domestic animals.

Animals are used in whole or in part, such as the feather, leg, hair, leather, tooth, lard (fat), flesh, spur, horn, scales, nail, blood, penis, bones, liver, heart, head, testicle, marrow, eye, ear, etc. Products of their metabolism, such as excreta (feces, urine) and honey, as well as materials built by animals, such as nests and cocoons, are also medicinally usable resources. Milk, blood and eggs are also part of the therapeutic arsenal. In most cases, the products are extracted after the animal's death since such raw materials are primarily obtained mainly through fishing and hunting activities, a common practice in the region (Alves et al. 2009a; Fernandes-Ferreira and Alves 2017). It is emphasized that slaughter is not always directly related to the medicinal use of animals. For example, in the municipality of Pocinhos, Paraíba, tejuaçú (*Tupinambis merianae*) is hunted mainly for food purposes, and the by-products thereof, such as lard and tongue, are used in the elaboration of popular remedies. Another example is the rattlesnake (*Crotalus durissus*), which is an animal that poses a risk to humans and domestic "creations;" therefore, it is usually slaughtered only under precaution or control (Alves 2009), and its by-products are used in zoos. Thus, the use of medicinal products optimizes the use of slaughtered animal resources. Moura and Marques (2008) point out that a common feature in fractions of animals or even whole animals used as medicines is their uselessness for other purposes. These authors also point out that although studies on Brazilian popular zootherapy have not yet turned to the quantitative analysis of the use of leftovers or animal by-products, the practice is well documented in the lists of zootherapies used in different Brazilian states (Alves et al. 1990) as well as in the literature (Martínez 2013).

It is also worth noting that live animals are used in zootherapeutic practices. For example, *jabutis* (*Chelonoidis* sp.) are usually raised as pets because this practice is believed to prevent bronchitis and erysipelas among the residents of the breeder's home (Alves et al. 2012). Another example is recorded in the semi-arid states of Paraíba and Pernambuco, where the live song (*Cyanocorax cyanopogon*) is used in popular "sympathy" treatments for asthmatic processes in which the bird is fed with the patient's food remains (Alves et al. 2009b). Raw animal materials are also used in the form of amulets and in "sympathies" to prevent and treat diseases associated with unnatural causes (Alves and Rosa 2006). The interrelation between popular beliefs and zootherapy has been recorded in different localities of Brazil (Alves et al. 2007).

The application of remedies prepared from animal substances varies according to the nature of the disease, the purpose of use and the ingredients used. Thus, different modes of preparation and administration of zootherapeutic resources are reported (Alves 2009). Hard parts of animals, such as shells, are usually sun dried, then trodden or grated, resulting in a powder, which is then used for tea preparation or ingested along with food. Some biotherapeutic products can be used in association with medicinal plants in "*garrafadas*," a therapeutic drink that may have products derived from animals and plants that are usually soaked in cachaça (sugarcane brandy) or white wine and stored in bottles (hence the name ‘bottled’).

A significant portion of the fauna with medicinal value is marketed by sellers in markets and free fairs throughout the Caatinga region (Alves et al. 2008a,b; Alves et al. 2010; Alves et al. 2009b; Costa-Neto 1999). Trade in zootherapies involves a wide

variety of species, including whole animals (when small), although the commercialization of parts (derived from animals of medium and large size) is more common.

It is important to emphasize that some natural products (derived from plants, animals and minerals) used in traditional medicine can cause serious adverse effects and transmit zoonoses (Van Vliet et al. 2017), especially when considering the sanitary conditions associated with the maintenance and storage of the products (Alves et al. 2009b). This study, there was a significant increase in the prevalence of this disease in the Brazilian semi-arid region, which indicates the possibility of microbiological contamination and represents a potential risk to the users' health (Alves et al. 2007). A good example of this is "armadillos," which are hunted and used for food and medicinal purposes (Alves et al. 2009a; Barboza et al. 2016).

2. Major compounds identified in Caatinga plants

Several studies point to the great variety of secondary metabolites found in Caatinga species (see, for example, Almeida et al. 2011). It is believed that the synthesis of the secondary metabolites in this type of vegetation is favored by the adverse environmental conditions typical of this ecosystem that can influence the biosynthesis routes of compounds associated with plant defenses against biotic and abiotic factors (Montanari and Bolzani 2001; Almeida et al. 2011). Some of the key metabolites identified to date are described below and summarized in Table 1.

2.1. Alkaloids

Alkaloids are a group of heterogeneous nitrogenous secondary metabolites widely recognized for their therapeutic effects, especially on their action on the nervous system, as well as their analgesic, hallucinogenic and antitumor effects (Makkar et al. 2007). Several studies point to the presence of these metabolites in Caatinga plants (Almeida et al. 2005, Nascimento-Silva et al. 2011, Brandão et al. 2017), particularly in Apocynaceae, Erythroxylaceae and Fabaceae (Nogueira et al. 2014; Negreiros Neto et al. 2016; Ceravolo et al. 2018; Macedo Pereira et al. 2018). *Aspidosperma pyrifolium* Mart., for example, may be among the most studied species of the Caatinga in relation to their alkaloidal profile (Gilbert et al. 1962; Craveiro et al. 1983; Araújo et al. 2007). In *Erythroxylum pungens* O.E.Schulz (Erythroxylaceae), were identified twelve alkaloids in which one 3-(2-methylbutyryloxy)tropan-6,7-diol, showed 50% cell viability reduction against HeLa (Macedo Pereira et al. 2018). According to these author, edaphoclimatic features of Caatinga biome could stimulate the biosynthesis of the unusual alkaloids, e.g. tropane alkaloids.

2.2. Phenolics and Flavonoids

Flavonoids are secondary phenolic metabolites that are mainly found in high-quality vegetables, and they are responsible for conferring color to flowers and fruits and protection against UV and pathogens. In human foods, flavonoids contribute to several health benefits mainly because of their antioxidant effect (Buckingham and Munasinghe 2015). They are also known for their pharmacological importance because of their anti-inflammatory, antioxidant,

antifungal and antitumor properties, among others (Cordeiro et al. 2018).

Most studies on species occurring in the Caatinga have concentrated on quantifying the total flavonoid content. However, refined methods of identifying flavonoids have also been employed, such as direct flow injection-electrospray-ion trap tandem mass spectrometry (DFI-ESI-IT-MS) or even high-performance liquid chromatography with a diode-array detector (HPLC-DAD). Some studies, for example, have led to the isolation of isoquercetin, quercetin and rutin in Caryocar coriaceum Wittm. - Caryocaceae (Alves et al. 2017), gallic acid, rutin, ellagic acid, catechin, quercetin, kaempferol and caffeic acid were identified in *Terminalia argentea* Mart. - Combretaceae (Beserra et al. 2018), gallic acid and hyperoside in Spondias tuberosa Arruda - Anacardiaceae (Cordeiro et al. 2018) and amentoflavone and agathisflavone in *Poincianella pyramidalis* (Tul.) LP Queiroz - Fabaceae (Pereira Gomes-Copeland et al. 2018). Recently, kaempferol, quercetin, isorhamnetin and myricetin were identified in *Ziziphus joazeiro* Mart. - Rhamnaceae (Andrade et al., 2019).

2.3 Tannins

Tannins are phenolic compounds known especially for their astringency and ability to chemically bind to proteins, sugars and alkaloids. They present an important ecological function and are used by plants as a defense strategy against herbivores (Monteiro et al. 2005). Economically, they are used in the manufacture of leather products. Tannin-rich species are used in folk medicine mainly for their antidiarrheal, antiseptic, antifungal, antimicrobial, anti-inflammatory and healing effects (Mello and Santos 2001; Monteiro et al. 2005).

According to Almeida et al. (2011), tannins are one of the most investigated and most frequent compounds in the medicinal plants of the Caatinga. Species such as *Anacardium occidentale* L. (Anacardiaceae), *Anadenanthera colubrina* (Vell.) Brenan (Fabaceae), *A. falcata* (Benth.) Speg. (Fabaceae), *Caesalpinia ferrea* Mart. ex Tul. (Fabaceae), *Casearia sylvestris* var. *angustifolia* Uittien (Flacourtiaceae), *Cnidoscolus urens* (L.) Arthur and *C. infestus* Pax & K. Hoffm. (Euphorbiaceae), *Lafoensia replicata* Pohl. (Lythraceae), *Myracrodruon urundeuva* Allemão (Anacardiaceae), and *Terminalia brasiliensis* (Cambess.) Eichler (Combretaceae) are referred to as having a high amount of tannins (Araújo et al. 2008; Peixoto Sobrinho et al. 2011; Monteiro et al. 2014). Despite the high number of species, most tannin studies were limited to quantifying their levels in sought to correlate their presence with their therapeutic effects and their use value by local communities (Araújo et al. 2008; Monteiro et al. 2005; Siqueira et al. 2012; Monteiro et al. 2014). An exception is the study of Beserra et al. (2018), which have identified terminalin, corilagin, punicalin and punicalagin in the leaves of the T. argentea.

2.4 Volatile oils and diterpenes

Volatile oils (mono-10C and sesquiterpenes-15C) consist of a mixture of aliphatic and cyclic compounds derived from isoprene (5C). Volatile or essential oils have different functional groups in their structure, such as hydrocarbons, alcohols, aldehydes, esters, ethers and ketones, and they are mainly responsible for the odor of plants, the main function of which is to attract and/or repel herbivorous insects.

Several aromatic species are observed in Caatinga flora, and the main studies on

essential oils in this environment have focused on the chemical composition of the oils, seasonal effects on the chemical profile of the oil and the biological activity of the oil. Euphorbiaceae family, especially the genus *Croton* (Dourado et al. 2005; Neves and Camara 2012; Ramos et al. 2013; Almeida et al. 2014a; Carvalho et al. 2016; Souza et al. 2017; Anjos et al. 2018; Ribeiro et al. 2018), Annonaceae (Meira et al. 2015; Araújo et al. 2015a; Diniz et al. 2019), Verbenaceae (Neves et al. 2008; Souza et al. 2018) and Lamiaceae (Pereira et al. 2018) contains the largest number of studies.

Diterpenes are terpenoids with 20 carbon atoms originating biosynthetically from geranylgeranyl diphosphate (GGPP) and are classified as linear, bicyclic, tricyclic, tetracyclic, pentacyclic and macrocyclic. Diterpenes have attracted increasing attention because of their numerous biological and pharmacological activities (Lanzotti 2013). Compared with studies on volatile oils, work with diterpenes in Caatinga species is scarce and has concentrated on a few species such as *Calliandra depauperata* Benth. - Fabaceae (Pires et al. 2011), *Croton grewioides* Baill. - Euphorbiaceae - (Medeiros et al. 2011b), *Erythroxylum revolutum* Mart. - Erythroxylaceae (Oliveira 2012), and *Cnidoscolus quercifolius* Pohl -Euphorbiaceae (Oliveira-Júnior et al. 2018).

2.5 Triterpenes and allied compounds

The triterpenes are terpenoids with 30 squalene-derived carbon atoms, generally with five ring systems. They differ from phytosteroids because they have less than 30 carbons and are usually tetracyclic. Some studies have interrogated triterpenes in Caatinga species (Silva et al. 2010; Barbosa et al. 2014; Araújo Gómez et al. 2014; Vieira et al. 2016). Acids triterpenes such as betulinic, oleanolic and ursolic acids, besides lupeol, α-amyrin, β-amyrin, cycloeucalenol, friedelin and derivatives were identified from Caatinga species (Barbosa-Filho et al. 1985; Silva et al. 2010; Vieira et al. 2016; Oliveira-Júnior et al. 2018). For phytosteroids, most of the studies have performed phytochemical screening (Peixoto et al. 2016; Pereira et al. 2017). To the best of our knowledge, phytosteroids were isolated and identified in only two studies: *Senna spectabilis* var. *excelsa* (Schrad.) H.S.Irwin & Barneby - Fabaceae (Silva et al. 2010) and *Pilosocereus pachycladus* F. Ritter – Cactaceae (Brito-Filho et al. 2017).

Saponins are glycosides which provide sugars and aglycones (sapogenins) under hydrolysis, which may be triterpene or steroidal. Studies on saponins in Caatinga species are limited, with the majority of studies only indicating the presence and absence of these metabolites (Peixoto Sobrinho et al. 2012; Pereira et al. 2016; Pereira et al. 2017; Cordeiro et al. 2018). Studies on the structural properties of saponins in the Caatinga have primarily focused on *Z. joazeiro*, a tree with stem bark rich in saponins (2-10%) that is used by local communities as detergent and phytotherapic (Higuchi et al. 1984; Ribeiro et al. 2013; Ribeiro et al. 2014) and *Manilkara rufula* (Miq.) H.J.Lam (Sapotaceae), which presents antitrichomonal activity (Vieira et al. 2017).

To the best of our knowledge, there are no studies focused on isolation, purification and structural elucidation of cardenolides in Caatinga species, although families such as Apocynaceae are very representative in this ecosystem.

2.6 Fatty acids and other lipids

Several Caatinga species are rich sources of fatty acids and other lipids of economic interest. Fatty acids consist of straight chain carboxylic acids found primarily in seeds in the form of triglycerides, and they are often associated with antioxidant compounds such as carotenoids, tocopherols, and tocotrienols (Gunstone 1996; Barbosa et al. 2019). In the Caatinga, the Euphorbiaceae, Sapindaceae and Malvaceae families stands out because of the large number of potentially oleaginous species (Pinho et al. 2009; Barros et al. 2015; Coutinho et al. 2015; Coutinho et al. 2016; Silva et al. 2010; Silva et al. 2014).

Another group of lipids studied in Caatinga plant species are those that constitute cuticular waxes, which are formed of aliphatic and cyclic constituents and cover the primary aerial surface of plants. The primary function of these waxes is to reduce water loss, especially under water stress situations, which are common in the Caatinga. Several aliphatic compounds (n-alkanes, fatty acids, primary and secondary alcohols and ketones) have been identified as well as triterpenes such as α-amyrin, β-amyrin, betulin, lupeol, epifriedelinol, ursolic acid, oleanolic acid, and betulinic acid (Oliveira et al. 2000; Costa Filho et al. 2012; Medeiros et al. 2017; Pereira et al. 2019).

3. Biological activity of medicinal plants from the Caatinga

Many of the Caatinga's plant are widely used in Brazilian traditional medicine and as phytomedicine products, and they include *Myracrodruon urundeuva* All., *Amburana cearensis* (Arr. Cam.) A.C. Sm., *Erythrina velutina* Willd., *Anadenanthera colubrina* (Vell.) Brenan (Magalhães et al. 2019). The number of medicinal plants indicates the importance of this environment, and experimental approaches focused on such species have improved. To rationally explore the possible uses of this biome, its potential needs to be demonstrated scientifically. Considering the Caatinga biome, improving our knowledge about medicinal flora can provide alternatives to treating common diseases and will also serve preserve the genetic, biological and cultural diversity. We will present below some of the main studies that have accumulated data on plants of great cultural importance in the region (see Albuquerque et al. 2007).

3.1 *Amburana cearensis* (Allemão) A.C. Smith

A. cearensis is a native tree commonly found in the Brazilian semi-arid region and the Caatinga biome, where it is popularly known as *'cumaru,' 'amburana-de-cheiro'* or *'umburana'* (Albuquerque et al. 2007; Leal et al. 2005, 2009). Its trunk bark and seeds are widely used in folk medicine for the treatment of respiratory disease, pain, worm infections, sore throat, and inflammation and as antitussive and antispasmodic agents (Bitu et al. 2015).

The anti-inflammatory and bronchodilator activities of *A. cearensis* were promoted by carrageenan and N-formyl-methyl-leucyl-phenylalanine (fMLP)-induced migration in rat peritoneal cavities (Leal et al. 2003). The crude ethanolic extract of *A. cearensis* leaves was shown to have a positive effect on ovarian cell cultures, and the antioxidant compounds could protect ovarian follicles from Reactive Oxygen Species (ROS) during in vitro culture (Barberino et al. 2016; Gouveia et al. 2016). The *A. cearensis* extract increased the rate of antrum

Table 1. Major compounds identified in Caatinga plants.

Class compounds	Species	Plant organ	Biological activity	Reference
Alkaloids				
2-Methyl-9H-*β*-carboline-2-ion and 2´,6´-Dihydroxy-4´-methoxyacetophenone-2´-O-*β*-glucoside	*Harrisia adscendens* (Cactaceae)	Root	Antimicrobial	Santos et al. (2018)
3-Benzoyloxytropane; 3-(3′,5′-Dimethoxy-4′-hydroxy)benzoyloxytropane; 3-(4′-Methoxy)benzoyloxytropane; 3-Phenylacetoxytropane; 3-Phenylacetoxynortropane; 3-(2-Methylbutyryloxy)tropan-6-propionyl-7-ol; 3-(2-Methylbutyryloxy)tropan-6-propionyl-7-ol; 3-(2-Methylbutyryloxy)tropan-6,7-diol; 3-(2-Methylbutyryloxy)nortropan-6,7-diol; 3-Isovaleryloxytropan-6-ol; 3-Phenyltropan-6-ol and N,N-Dimethyl-1-H-indole-3-ethanamine	*Erythroxylum pungens* (Erythroxylaceae)	Bark, root and leaf	Cytotoxicity	Macedo Pereira et al. (2018)
Usaramine and Monocrotaline	*Crotalaria pallida* and *Crotalaria retusa* (Fabaceae)	Seed	Antimicrobial	Negreiros Neto et al. (2016)
(+)-Pyrifoline; 6-Demethoxypyrifoline; (-)-Aspidofiline; (+)-Aspidospermine; Pyrifolidine; 15-Demethoxypyrifoline; Aspidofractinine and N-Formylaspidofractinine	*Aspidosperma pyrifolium* (Apocynaceae)	Stem, root and leaf	-	Araújo et al. (2007); Gilbert et al. (1962); Craveiro et al. (1983)

Anonaine; Asimilobine; Lanuginosine; Liriodenine; Lysicamine; Pronuciferine and Stepharine	*Annona cherimola* and *Annona squamosa* (Annonaceae)	Leaf	-	Rabêlo et al. (2015).
Phenolics and Flavonoids				
Kaempferol; Quercetin; Isorhamnetin and Myricetin	*Ziziphus joazeiro* (Rhamnaceae)	Leaf	Antimicrobial	Andrade et al. (2019)
Gallic acid; Rutin; Ellagic acid; Catechin; Quercetin; Kaempferol; Caffeic acid; Quinic acid; Galloylmucic acid; Quercetin xyloside; Quercetin rhamnoside; Quercetin glucoside; Caffeoyl ellagic acid; Quercetin galloyl xyloside; Quercetin galloyl glucose; Quercetin digalloyl xyloside and Quercetin digalloyl glucoside	*Terminalia argentea* (Combretaceae)	Leaf	Cytotoxicity, genotoxic and sub-chronic toxicity	Beserra et al. (2018)
Gallic acid and Hyperoside	*Spondias tuberosa* (Anacardiaceae)	Leaf	Antioxidant, antimicrobial and hemolytic	Cordeiro et al. (2018)
Amentoflavone and Agathisflavone	*Poincianella pyramidalis* (Fabaceae)	Leaf (calluses)	-	Pereira Gomes-Copeland et al. (2018)
oquercetin; Quercetin and Rutin	*Caryocar coriaceum* (Caryocaceae)	Fruit	Antioxidant, antimicrobial and antileishmanial	Alves et al. (2017)

Tannins				
Terminalin; Corilagin; Punicalin and Punicalagin	*Terminalia argentea* (Combretaceae)	Leaf	Cytotoxicity	Beserra et al. (2018)
Volatile oils and diterpenes				
Spathulenol; Limonene; Caryophyllene oxide; *α*-Pinene, (E)-*β*-Ocimene, Germacrene D and Bicyclogermacrene	*Annona vepretorum* (Annonaceae)	Leaf (essential oil)	Anxiolytic, sedative, antiepileptic and antidepressant	Diniz et al. (2019); Araújo et al. (2015a)
Phyllacanthone	*Croton quercifolius* (Euphorbiaceae)	Stem bark	Antimicrobial	Oliveira-Júnior et al. (2018)
Ent-kauran-16-ene; 13-Hydroxy-8 (17); 14-Labdialiene; *Ent*-kaur-16-en-3*β*-ol; 3-Oxo- hydroxy-8(17); 14-Labdiene; 3,13,19-Trihydroxy-8(17); 14-Labdiene and *Ent*-kauran-16*β*, 17-diol	*Erythroxylum revolutum* (Erythroxylaceae)	Aerial parts	Antimicrobial	Oliveira (2012)
7*β*,17-Dihydroxy-12-oxo-cassan-13,15-diene; Depauperatin and 15,16-Bisnor-7*β*,17-dihydroxy-12-oxo-cassan-13-ene	*Calliandra depauperata* (Fabaceae)	Root	-	Pires et al. (2011).
Ent-15,16-epoxy-2-oxo-3,13(16); 14-Clerodatriene and Ent-15,16-epoxy-20-acetoxy-2-oxo-3,13(16),14-clerodatriene	*Croton grewioides* (Euphorbiaceae)	Aerial parts	-	Medeiros et al. (2011b)

Fatty acids and other lipids				
Oleic and Paullinic acids; *β*-Carotene; *α*-Tocopherol and *γ*-Tocopherol	*Guarea guidonia* (Meliaceae), *Allophylus puberulus* and *Paullinia elegans* (Sapindaceae)	Seed	-	Barbosa et al. (2019)
Oleic and Eicosenoic acids	*Cupania racemose*, *Paullinia pinatta* and *Serjania* spp. (Sapindaceae)	Seed	-	Coutinho et al. (2015)
Palmitic; Oleic and Linoleic acids	*Herissantia tiubae* and *Sida* spp. (Malvaceae)	Seed	-	Silva et al. (2010)
Palmitic and Oleic acids	*Anemopaegma leave*, *Pyrostegia venusta* and *Tabebuia impetiginosa* (Bignoniaceae), *Hippocratea volubilis* (Celastraceae)	Seed	-	Pinho et al. (2009)
Lupeol and Betulin	*Cynophalla flexuosa* (Capparaceae)	Leaf (cuticle)	-	Pereira et al. (2019)
Lupeol	*Aspidosperma pyrifolium* (Apocynaceae)	Leaf (cuticle)	-	Medeiros et al. (2017)
Ursolic Acid; *n*-Alkanes; Epifriedelinol and Lupeol	*Tocoyena formosa*, *Maytenus rigida* and *Didymopanax vinosum*	Leaf (cuticle)	-	Oliveira and Salatino (2000)

- not reported

formation, which was higher in follicles cultured with plant extract than the control, and it also improved the cell viability, maturation and functionality (Barberino et al. 2016). Several culture media have been used to improve the rate of follicular viability and growth, although ovarian culture is too expensive. The use of *A. cearensis* is an interesting economic alternative that may make in vitro culture studies cheaper and more feasible for ovine and caprine animals (Barberino et al. 2016; Gouveia et al. 2016). *A. cearensis* may represent a very important biotechnology tool.

The extract of *A. cearensis* seeds was shown to have neuroprotective and antioxidant effects in cerebellar culture cells exposed to excitotoxic damage induced by glutamate. In addition, this species attenuated oxidative stress, reducing swelling, membrane potential dissipation, ROS production and calcium influx in isolated rat brains. Moreover, it induced the preservation of astrocytes, neurons and microglia in damaged rat brains (Lima Pereira et al. 2017). Parkinson's disease (PD) is reproduced in animal models via the injection of 6-hydroxydopamine (6-OHDA), a hydroxylated derivative of dopamine (Blum et al. 2001). Its neurotoxic action leads to oxidative stress (Tiffany-Castiglioni et al. 1982), catecholaminergic cell line apoptosis and activates nuclear factor-kappaB (NFkB) (Oh et al. 1995; Blum et al. 2001). Amburoside A, a phenol glucoside derived from *A. cearensis*, acts as an antioxidant molecule and protects mesencephalic cells against 6-OHDA neurotoxicity (Leal et al. 2005).

Compounds isolated from *A. cearensis*, such as afromorsin, kaempferol, isokaempferide, amburoside A, and protocatechuic have important biological effects, (Costa-Lotufo et al. 2003; Lopes et al. 2013; Leal et al. 2008). Specifically, afromorsin isolated from the extract of *A. cearensis* bark (EBAC) inhibited neutrophil degranulation, myeloperoxidase activity, TNF-α secretion, and ROS generation (Lopes et al. 2013). Amburoside A and isokaempferide, a flavonol, showed anti-inflammatory activity and reduced the accumulation of inflammatory cells, myeloperoxidase activity and TNF-α production without cytotoxicity (Leal et al. 2009). These results show that *A. cearensis* is a good source of interesting molecules for the treatment of several diseases.

3.2 *Anadenanthera colubrina* (Vell) Brenan

A. colubrina, also known as *"angico,"* is a tree belonging to the subfamily Mimosoideae (Leguminosae), and it occurs in different biomes and predominantly in seasonal forests and riparian galleries (Mota et al. 2017). *A. colubrina* is an important species to local communities in the Caatinga, and it is used for timber, charcoal and firewood as well as in popular medicine (Monteiro et al. 2006a,b). Its products are employed to treat respiratory and lung infections, ulcerative external lesions, inflammation, diarrhea, cough, bronchitis, influenza, and toothache (Agra et al. 2008, 2007; Almeida et al. 2005; Araújo et al. 2008).

β-Sitosterol and β-sitosteryl linoleate were also isolated from the hexane-soluble fraction of *A. colubrina* fruits and exhibits intense antifungal effects against Alternaria alternata (Campos et al. 2014). Moreover, bufotenine, a well-studied alkaloid, has been isolated from *A. colubrina* seeds and is able to block rabies virus infection in BHK-21 cells (Vigerelli et al. 2014). In addition, tannins isolated from stem-bark extract from *A. colubrina* is able to impair Pseudomonas

aeruginosa adhesion and biofilm formation (Trentin et al. 2013), and strong antifungal effects were demonstrated against Candida albicans. This extract also demonstrated the capacity to inhibit the formation of hyphae and blastospores, thus demonstrating the susceptibility of *C. albicans* biofilm to this plant. Although *A. colubrina* did not have a strong antiproliferative effect, it was capable of diminishing tumor growth in all cell lines (Lima et al. 2014). The antimicrobial effects of *A. colubrina* demonstrate the possibility of developing novel antifungal and antimicrobial agents from this plant. In addition, Barbosa et al. (2014) evaluated several extracts of native plants from Caatinga against Aedes aegypti and demonstrated that an extract from the seed of *A. colubrina* was adulticidal for insects (96% died) but did not show toxicity in mammal cells.

Anti-inflammatory and antinociceptive effects of the aqueous extract of *A. colubrina* bark was demonstrated using rodent in vivo models. Mice subjected to acetic acid-induced writhing tests showed an improved peritoneal nociceptive response, which was partially because of the reduction of algogenic/hypernociceptive endogenous mediators, such as prostaglandins (PG), bradykinin (BK), serotonin (5-HT), and histamine (Le Bars et al. 2001; Santos et al. 2013). In addition, the hot plate test, a classical test used to evaluate the central pain process, revealed no effect of *A. colubrina* on central nociceptive pathways in mice. However, the anti-inflammatory effect of this plant was clearly demonstrated in carrageenan-induced paw edema and carrageenan peritonitis (Santos et al. 2013) because of a reduction in microvascular permeability and leukocyte influx and possibly because of a reduction in the formation and release of inflammatory mediators, such as histamine, BK,5-HT, PG, and others. The anti-inflammatory and peripheral antinociceptive effects of *A. colubrina* are consistently exerted across different pathways; however, the underlying mechanisms still need to be elucidated.

The positive effect of the hydroalcoholic extract of *A. colubrina* bark on the healing process of the skin of rats has been demonstrated. Wound treatment with this extract showed more organized granulation tissue, a higher concentration of typical fibroblasts, and greater collagen fiber and blood vessel contents (angiogenesis) at the 7th and 14th day after surgery when compared to the untreated group (Pessoa et al. 2012, 2015).

An interesting polysaccharide isolated from *A. colubrina* has been characterized as an immunomodulatory and antitumor molecule. A complex acidic heteropolysaccharide primarily containing galactose and arabinose (ARAGAL) was able to activate mice peritoneal macrophages in a time- and dose-dependent manner and promoted phagocytic ability and anion superoxide production (Moretão et al. 2003). The same research group subsequently reported that ARAGAL increased alpha tumor necrosis factor (α-TNF) levels, which is an important antitumor molecule, and killed sarcoma 180 cells both in vitro and in vivo (Moretão et al. 2004). Therefore, A. colubrina has a promising antitumor effect.

3.3 *Annona vepretorum* Mart.

A. vepretorum, which is popularly known in Brazil as *"araticum," "bruteira"* and *"pinha da Caatinga,"* is a shrub or tree native to the Caatinga (Bomfim et al. 2016) that is widely used for human nutrition and medicinal purposes (Bomfim et al. 2016; Dutra et al.

2014). The leaves are used in a decoction to treat allergies, skin diseases, yeast and bacterial infections, while its roots are indicated for the treatment of bee stings and snakes bites and as a sedative, antioxidant, antimicrobial, anti-inflammatory and pain treatment (Almeida et al. 2014b; Bomfim et al. 2016; Diniz et al. 2013; Dutra et al. 2014; Silva et al. 2015).

In addition, the crude ethanolic extract of *A. vepretorum* exerts antinociceptive and anti-inflammatory action in vivo under a chemically or thermally noxious stimulus. Mice treated with *A. vepretorum* show reduced acetic acid-induced writhing (Silva et al. 2015). A similar positive effect was detected in a formalin test, hot plate test and tail flick test. In general, these tests assess the central and peripheral nociceptive pathways (Le Bars et al. 2001), and the effects were blocked by naloxone, which might indicate that the antinociceptive effects are related to opioid receptor activation by the extract. Moreover, animals treated with *A. vepretorum* had better results in histamine and carrageenan hind paw edema models and showed reduced leucocyte migration in carrageenan-induced edema than untreated mice.

Several reports have shown that the *Amona* genus is a source of antitumor molecules (Formagio et al. 2015; Tundis et al. 2017; Zorofchian Moghadamtousi et al. 2014). The antitumoral activity of *A. vepretorum* has been associated with the essential oil (EO) from the leaves, especially spathulenol. The cytotoxic effect was also evaluated in peripheral blood mononuclear cells and B16-F10 melanoma cells with promising results. Spathulenol has been reported to be active against gastric adenocarcinoma cells (Areche et al. 2009), and it is a good candidate as an adjuvant chemotherapy. In addition, C57BL/6 mice inoculated with B16-F10 melanoma cells were treated consecutively for 11 days with the EO of spathulenol; *in vivo* tumor growth was inhibited by the treatment, and no toxic effects or hematological or peripheral blood biochemistry parameter changes were observed in mice (Bomfim et al. 2016).

Additionally, the leaf EO shows antioxidant, trypanocidal, antimalarial, antifungal properties. The antioxidant property of the EO from *A. vepretorum* (EOAV) was evaluated by two *in vitro* models, i.e., radical scavenging activity using the 1,1-diphenyl-2-picrylhydrazyl radical (DPPH) method and the β-carotene-linoleate model system, and it showed weak activity (Araújo et al. 2015a; Costa et al. 2012).

The EOAV demonstrated potent antimalarial activity against the erythrocytic stage of *Plasmodium falciparum* and a trypanocidal effect against *Trypanosoma cruzi* epimastigotes and trypomastigotes. In addition, an in vitro model of mouse macrophages infected with intracellular amastigotes, the chronic clinically relevant forms of *T. cruzi* showed that EOAV both significantly reduced the number of infected macrophages and the relative number of amastigotes per 100 macrophages (Meira et al. 2015). Trypanocidal action is mediated by plasma membrane alterations (sterol biosynthesis inhibition), severe mitochondrial swelling with a large loss of electron density from its matrix and induced necrosis (Meira et al. 2015). The intense trypanocidal activity could be attributed to the high concentration of bicyclogermacrene. Thus, EOAV had interesting results with low toxicity.

3.4 *Aspidosperma pyrifolium* Mart.

A. pyrifolium, which is popularly known as *“pereiro,” “pereiro preto”* or *“pereiro do*

sertão" (Araújo et al. 2007), has been used in folk medicine, such as for the relief of benign prostatic hyperplasia, diabetes, erectile dysfunction, would healing, dizziness and inflammation (Almeida et al. 2019; Souza Lima and Soto-Blanco 2010; Souza Lima et al. 2017).

The anti-inflammatory effects of the aqueous extract of *A. pyrifolium* leaves were evaluated in carrageenan-induced and Tityus serralutus scorpion venom-induced peritonitis models. This extract was able to prevent inflammation and reduce leukocyte migration (Souza Lima et al. 2017). The mechanisms involved in envenomation by *T. serralutus* involved local leucocyte migration, sodium and potassium ions in excitable cells, nitric oxide and cytokine mediators (Martin-Eauclaire et al. 2018; Pucca et al. 2015). Thus, *A. pyrifolium* may modulate ion channels and pro-inflammatory mediator synthesis. The phytochemical profile revealed the presence of a large amount of flavonoids and phenolic derivatives in the hydroalcoholic extract of *A. pyrifolium.* Recently, the neuroprotective and antioxidant properties of this extract were demonstrated in rats (Araújo et al. 2018). The extract of *A. pyrifolium* seeds blocked the behavioral changes in a rat model of PD, such as apomorphine-induced rotation, motor incoordination and degeneration of dopaminergic tonus (Araújo et al. 2018). Araújo et al. (2018) showed that rats treated with *A. pyrifolium* extract presented reduced nitrite levels and lipid peroxidation in lesioned striatum. These authors also showed the reduction of TNF-alpha content in the striatum, thus confirming the anti-inflammatory effect of this species.

Malaria is a major parasitic infection in many tropical and subtropical regions, and it still remains one of the leading causes of death worldwide (WHO 2017, 2018). *Plasmodium vivax* is the most common cause of malaria in Latin American, and it has developed resistance to the antimalarial drug Chloroquine (Rahman et al. 2019). Several plants have been used to treat malaria. The ethanolic crude stem-bark extract of *A. pyrifolium* showed high antimalarial activity with low in vitro toxicity (Ceravolo et al. 2018). The beneficial biological effects have been associated with the presence of monoterpenoid indole alkaloids, such as aspidofractinine and 15-demethoxypyrifoline (Araújo et al. 2007), and another report showed that the ethanolic extract of *A. pyrifolium* leaves caused hemolysis, lethality to 1-day-old Artemia salina larvae, and abortion, low fetal birth weight and high toxicity in Wistar pregnant rats (de Souza Lima and Soto-Blanco 2010). Previous reports showed that embryonic death, abortion and premature birth were induced by *A. pyrifolium* in farm animals (de Souza Lima and Soto-Blanco 2010; Riet-Correa et al. 2012).

3.5 *Cnidoscolus quercifolius* Pohl

C. quercifolius, which is popularly named *"favela" or "faveleira,"* is a native forage species of the Caatinga that produces latex, can be used to recover degraded areas; provide food for animal and human consumption; and as medicine, timber, and energy (de Araújo Gomes et al. 2014; Paredes et al. 2016). Considering folk medicine, *C. quercifolius* is also used to treat inflammation (Lorenzi and Matos 2002; Maia-Silva et al. 2012). Reports about the pharmacological effects of this species are scarce. The genus *Cnidoscolus* is used for several medicinal purposes, including as an anti-inflammatory, an antitumor agent for the genitourinary system, an antiseptic and to treat kidney infections, dermatological and

ophthalmic lesions, bruises, fractures, wounds, warts, dysentery, hemorrhage, appendicitis and rheumatism (Albuquerque et al. 2007; Almeida et al. 2005; José et al. 2012).

The popular use of *C. quercifolius* extract to treat inflammation is supported by its anti-inflammatory activity as demonstrated in carrageenan-induced paw edema and peritonitis inflammation models in mice. The anti-inflammatory effect of the ethanolic extract of *C. quercifolius* is at least partially because of the inhibited synthesis of inflammatory mediators including prostaglandins, histamine and neutrophils (de Araújo Gomes et al. 2014). The crude extract from the bark of *C. quercifolius* is efficient against *Staphylococcus epidermidis* (AM235), an important bacteria involved in severe infection, including endocarditis and sepsis, as well as routine clinical procedures, such as catheter implantation (José et al. 2012). However, this extract inactive against gram-negative bacteria.

The aqueous extract of *C. quercifolius* did not present an acute toxic effect because physical, behavioral or motor changes were not observed, none of the treated animals died, and the organ weight of the treated mice did not change. However, this extract exerts a hypoglycemic effect in diabetic streptozotocin-induced mice (Lira et al. 2017) and has antioxidant properties (Ribeiro et al. 2017).

3.6 *Erythrina velutina* Willd

E. velutina is an endemic tree to the plains and riverbanks of Northeast Brazil, and it is popularly called *"mulungu."* This tree is well known for its effects on the central neural system, such as sedation, insomnia, convulsions (Dantas et al. 2004).

The antinociceptive effect of the hydroalcoholic extract of *E. veluntina* stem bark was demonstrated by the reduction of abdominal pain induced by acetic acid independent of the opioid system in mice, and this effect was primarily caused by anti-inflammatory action (Vasconcelos et al. 2003). Curiously, Marchioro et al. (2005) showed that the ethanolic extract of *E. veluntina* leaves had antinociceptive effects and was dependent on the opioid system.

The use of *E. velutina* to treat others central nervous system (CNS) disturbances has been demonstrated. The hydroalcoholic extract of *E. velutina* stem bark exerts anxiolytic-like effects in rats (Raupp et al. 2008; Ribeiro et al. 2006), anticonvulsant activity (Vasconcelos et al. 2007), attenuation of schizophrenia-like behavior (Dias KCF et al. 2019; Ximenes et al. 2018), antioxidant effects (Dias KCF et al. 2019; Silva et al. 2016) and neuroprotective effects against 5-6-hydroxydopaimine-induced neurotoxicity (Silva et al. 2016) and acute cerebral ischemia (Rodrigues et al. 2017). In addition, the indole alkaloid hypaphorine isolated from *E. velutina* induces sleep in normal mice. Taken together, these results confirm the effect of this species on the CNS, which is reflected in the traditional knowledge of this species.

3.7 *Lippia origanoides* Kunth

L. origanoides is an aromatic shrub popularly known as *"erva-do-marajó," "alecrim-angola," "alecrim pimenta," "orégano," "orégano do monte,"* or *"salva-do-marajó"* (Brito FCR et al. 2018; Menezes et al. 2018; Raman et al. 2017). The leaves are used as seasoning, and its tea is used as a sedative and to treat gastrointestinal disease; infections of the throat, skin, and scalp; pain; and asthma (Menezes et al. 2018; Oliveira et al. 2014).

The ethanolic extract of *L. origanoides* leaves demonstrate an acaricidal effect against *Tetranychus cinnabarinus* and the potential for the biological control of pests (Sivira et al. 2011). In addition, an extract of *L. origanoides* leaves was able to inhibit the progression of aggressive breast cancer cells (Raman et al. 2017), which was partially associated with its ability to trigger the rapid irreversible apoptosis of cancer cells by reducing mitochondrial oxidative metabolism and ATP levels (Raman et al. 2018). The biological effect of this species is associated with its EO. In fact, the EO of *L. origanoides* (EOLO) has antimicrobial (Hernandes et al. 2017), trypanocidal (Baldissera et al. 2017) and insecticidal activity (Vera et al. 2014) because of its chemical composition, which is predominantly terpenoids compounds, including monoterpenes, such as carvacrol, p-cymene, linalool, thymol, and carvophyllene (Menezes et al. 2018).

In addition, EOLO has a relaxant effect on trachea smooth muscle, which is related to its ability to modulate potassium channels and soluble guanylyl cyclase (Menezes et al. 2018). The secondary metabolite profile of EOLO showed at least 91 different compounds of *L. origanoides* such as limonene, β-myrcene, naringenin, luteolin, quercetin, trans-β-ocimene and linalool, which are common in EO (Stashenko et al. 2013). In addition, this profile included well-known antimicrobial and antioxidant molecules and promoted adipose tissue proliferation (Brito FN et al. 2018; Stashenko et al. 2013). Carvracol and thymol have been associated with the genoprotective effect of *L. origanoides* (Vicuña et al. 2010).

3.8 *Myracrodruon urundeuva* Allemão

M. urundeuva is a tree widely distributed in the Caatinga in the semi-arid region of Northeast Brazil. It is popularly named *"aroeira"* or *"aroeira do sertão"* and is used in folk medicine to treat gynecological infections and as an anti-inflammatory agent (Oliveira et al. 2017; Viana et al. 2003). Unfortunately, this species is threatened with extinction and has been highly exploited as a timber source and fuel (Soares et al. 2018).

The anti-inflammatory effect of *M. urundeuva* has been proved in several models. Enemas of *M. urundeuva* reduce the number of inflammatory cells and increased the reepithelization of tissue without fibrosis in a colitis model induced by acetic acid (Rodrigues et al. 2002). The aqueous extract of *M. urundeuva* leaves reduced *Streptococcus mutans* accumulation and prevented enamel demineralization and caries in rats (Crivelaro de Menezes et al. 2010). Matos et al. (2019) showed that the *M. urundeuva* extract modulates mineral bone metabolism. In addition, the ethanolic, ethyl acetate and hydroalcoholic extracts of *M. urundeuva* bark and leaves showed no hemolytic, genotoxic, mutagenic or toxic effects in rats. In addition, the *M. urundeuva* bark extract has a potential effect against *C. albicans*. These effects are associated with the presence of flavonoids and tannins (Oliveira et al. 2017). In addition, the chalcone-enriched fraction had a beneficial effect on periodontal disease in rats (Botelho et al. 2008).

Neuroprotection is another important beneficial effect of *M. urundeuva*, and this activity is associated with the antioxidant and anti-inflammatory effect of the extract, thus indicating its potential use as a tool to prevent or treat neurodegenerative states, such as PD (Calou et al. 2014). The chalcone-enriched fraction isolated from the *M. urundeuva* stem bark had a protective

effect on the CNS, including reduced oxidative stress and apoptotic injury induced by 6-hydroxydopamine in mesencephalic cells (Nobre-Júnior et al. 2009). In this context, the dimeric chalcones derived from of *M. urundeuva* presents inhibitory activity against cathepsins V, which is important because this enzyme is involved in several physiological and pathological processes, including the development of neurological disorders (Niwa et al. 2012; Sarria et al. 2018).

The tannin-enriched fraction derived from the stem bark of *M. urundeuva* has both anti-inflammatory and antiulcer gastric action in mice, which is because of its antioxidant properties and presence of polyphenols (Souza et al. 2007). These results were confirmed in several experimental models, such as ethanol-induced gastric lesions and croton oil-induced ear edema in rats (Aguiar Galvão et al. 2018). The antinociceptive and anti-inflammatory effects of the dimeric chalcone-enriched fraction derived from the stem-bark ethyl acetate extract of *M. urundeuva* was reported in a mouse model (Viana et al. 2003). Taken together, these data confirmed the traditional uses of this species.

The anthelmintic and insecticidal effects of *M. urundeuva* have been demonstrated. Recently, Soares et al. (2018) showed the anthelmintic activity of the extract of *M. urundeuva* seeds against *Haemonchus contortus*. An extract of the leaf and stem of *M. urundeuva* also efficiently inhibited egg hatching and larval exsheathment of *H. contortus* (de Oliveira et al. 2011). Moreover, lectins isolated from this species had larvicidal effects (Sá et al. 2009), and pentadecadienyl-phenol had insecticidal effects against *Aedes aegypti* (Souza et al. 2012). Taken together, the data show that M. urundeuva is a source of beneficial molecules with therapeutic potential.

3.9 *Spondias tuberosa* Arruda

S. tuberosa, which is popularly known as *"umbu"* or *"imbu,"* is an endemic species to the Caatinga that is widely used as a medicinal plant for the treatment of colic, diarrhea, diabetes mellitus, menstrual disturbances, placental delivery, inflammation, renal infection, and throat afflictions, and it is also used as an antiemetic and tonic (Silva et al. 2012a; de Albuquerque et al. 2007; de Freitas Lins-Neto et al. 2010; Araújo et al. 2012). The occurrence of phenols, hydrolysable tannins, flavones, flavonoids, leucoanthocyanidins in the Spondias genus has been well described. Phenols, tannins, triterpenes and quinones were detected in an ethanolic extract of the inner bark (Almeida et al. 2005), and the flavonoid and tannin content has been quantified in a methanolic extract of the bark (Araújo et al. 2008). HPLC analysis of a methanolic extract of S. tuberosa leaves performed by Silva et al. (2012a) showed the occurrence of high amounts of rutin, quercetin, and ellagic acid. The chlorogenic acid, caffeic acid, rutin and isoquercitrin contents were quantified in a hydroethanolic extract of leaves from *S. tuberosa*. Although *S. tuberosa* has been extensively used in folk medicine, pharmacological studies on this species are scarce in the literature.

The anti-inflammatory activity of *S. tuberosa* extract has been demonstrated via different experimental protocols using a carrageenan-induced paw edema model as well as a peritonitis animal models (Silva Siqueira et al. 2016). *S. tuberosa* extract reduces the influx of neutrophils in mice paw tissues and decreases myeloperoxidase (MPO) activity and leukocyte counts in the

peritoneal fluid after carrageenan challenge (Siqueira et al. 2016). These effects were similar to that of dexamethasone treatment, which is a standard anti-inflammatory drug. The antibacterial activities of *S. tuberosa* extract were assayed against eight gram-negative bacteria in vitro by the agar well diffusion method (Silva et al. 2012a). In general, the data showed a weakly antibacterial effect of *S. tuberosa* via determination of the minimum inhibitory concentration (MIC). Although the activities of *S. tuberosa* were reduced compared with that of ciprofloxacin, a standard antibiotic, the increased resistance of microorganisms to antibiotics must be considered to promote the search for new drugs. Interestingly, the hexane extract of *S. tuberosa* leaves had a potent antifungal effect (low value of MIC50) via the mitochondrial overproduction of anion superoxide and hyperpolarization of the mitochondrial membrane (da Costa Cordeiro et al. 2018). Recently, the antidiabetic effect of *S. tuberosa* was detailed (Barbosa et al. 2018). A hydroethanolic extract of the inner stem bark of S. tuberosa attenuated hyperglycemia and glucose oral tolerance and improved insulin sensitivity in diabetic streptozotocin-induced rats. In addition, *S. tuberosa* had important antioxidant and hepatoprotective effects in diabetic models (Barbosa et al. 2018).

The antioxidant activity of *S. tuberosa* has been shown in vitro (Silva et al. 2012a; Cordeiro et al. 2018) and in vivo (Barbosa et al. 2018). The antioxidant activity was evaluated by scavenging the radicals DPPH and 2,2-azino-bis (3-ethylbenzthiazoline-6-sulfonic acid) (ABTS•+), which demonstrated a weak and moderate effect (Cordeiro et al. 2018). In addition, *S. tuberosa* exerted a potent in vivo antioxidant effect, reduced lipid peroxidation, improved enzymatic defense and increased the antioxidant status in diabetic rats (Barbosa et al. 2018). These effects are consistent with phytochemical constitution of *S. tuberosa.*

An acute toxicity and cytotoxicity evaluation of *S. tuberosa* inner bark extract showed the absence of poisonous effects (Barbosa et al. 2016), which demonstrates that this species may be safely used as therapeutic alternative in the treatment of several diseases.

3.10 *Ximenia americana* L.

X. americana is a bushy or small tree popularly known as *"ameixa,"* and it is distributed in Africa, Asia and tropical America. In traditional medicine, the leaves and bark of *X. americana* are used in a tea to treat pain, obesity, dysmenorrhea, inflammation, wound healing, diabetes, cough, hoarseness, constipation, venereal disease, leprotic ulcer, skin diseases, malaria and osteoporosis (Diallo et al. 2002; Grønhaug et al. 2008; Le et al. 2012; Ogunleye and Ibitoye 2003; Bitu et al. 2015).

X. americana has antiviral activity against HIV-1 (Asres et al. 2001). In addition, this species has been used as an herbal medicine by persons living with HIV/AIDS in Africa to ameliorate HIV/AIDS-related symptoms and HIV/AIDS infection (Nagata et al. 2011).

The potent anticancer activity of *X. americana* aqueous extracts has also been observed (Voss et al. 2006b). In addition, riproximin, a type II ribosome-inactivating protein, was isolated from *X. americana* fruits and seeds and shows high selectivity for tumor cell lines (Bayer et al. 2012). Riproximin (RPX) was able to inhibit protein synthesis in a cell-free system and is toxic to HeLa cells. This antineoplastic effect was confirmed in vivo in a CC531 colorectal cancer rat model and in humans (Pervaiz et

al. 2015; Voss et al. 2006a). In addition, RPX induced important cytotoxic effects in the selected human breast cancer cell lines MDA-MB-231 and MCF-7 by modulating cytostatic and apoptotic pathways (Pervaiz et al. 2016). RPX was able to inhibit pancreatic cancer metastasis to the liver in rats bearing intraportal implanted Suit2–007 cells (Adwan et al. 2014).

The aqueous extract of *X. americana* elicited a potent analgesic effect on inflammatory pain but possessed a weak effect on central nociceptive pathways (Soro et al. 2016). These effects are related to the anti-edematogenic effect of the hydroalcoholic extract of *X. americana* on acute and chronic inflammation, which likely inhibits inflammatory mediators (Silva et al. 2018). Moreover, the hydroalcoholic extract of *X. americana* showed angiogenic effects and stimulated collagen synthesis to accelerate wound healing in rats (Souza Neto Júnior et al. 2019) and antidiabetic activity (Siddaiah et al. 2019). The tannin-rich extract of *X. americana* has hepatoprotective and antidiabetic properties (Sobeh et al. 2017). The gastroprotective effect has been confirmed in other gastric ulcer models, and this protection is mediated by sulfhydryl, nitric oxide and antisecretory activity, which is correlated with its major constituents, procyanidins B and C and catechin/epicatechin (Aragao et al. 2018).

In addition, the heteropolysaccharide-enriched fraction of *X. americana* bark had anti-inflammatory and analgesic effects in an experimental model of caerulein-induced acute pancreatitis, and they involved type 2 carabinoid receptors (Silva-Leite et al. 2018). Moreover, a polysaccharide-rich tea of *X. americana* bark protected against indomethacin-induced gastric injury mice, which was likely associated with a reduction of neutrophil infiltration (Silva Pantoja et al. 2018).

It is noteworthy that pharmaceutical technology has been used to improve natural products for treatment purposes; for example, a tablet of *X. americana* was developed from mucoadhesive polymers for the oral treatment of fungal infection (Almeida et al. 2019).

3.11 *Ziziphus joazeiro* Mart.

Z. joazeiro (Rhamnaceae) is a native tree widely distributed in northeastern Brazil (Lucena et al. 2008) and the Caatinga biome, where it is named *"juazeiro."* It is used traditionally in folk medicine for treating fever, bacterial infection, general pain, gingivitis, and respiratory diseases; for topical healing; and as a hepatic and cardiac tonic; as a diuretic; and for other purposes (Brito et al. 2015).

The antipyretic effect of *Z. joazeiro* was demonstrated in endotoxemic rabbits (Nunes et al. 1987), and a low antioxidant effect was also reported based on the scavenging of the radical DPPH (Silva et al. 2011; Brito et al. 2015) and ferric reducing ability of plasma assay (Brito et al. 2015).

3.12 Antimicrobial activity

A great number of papers on the antimicrobial activity of plants in the Caatinga are being accumulated. Most of them are studies with crude extracts and show activities that can be considered irrelevant, since they are carried out with extracts in high concentrations. In Table 2, we present 18 plant species that showed antimicrobial activity ≤1000 µg/mL against the microorganisms tested. Based on these data, most of the results were obtained with extracts at high concentrations and thus are not very interesting for future

pharmacological studies (according to Ríos and Recio 2005).

The strains that were most susceptible to extracts at ≤1000 µg/mL concentrations were the Gram-positive *Staphylococcus aureus*, which was susceptible to extracts of 11 plant species; *Micrococcus luteus,* which was inhibited by the extracts of seven species; and the gram-negative *P. aeruginosa*, which was inhibited by four extracts (see Table 2). The bacteria reported as being more susceptible to extracts were also the most registered in the studies (>20 publications), with the exception of the bacteria *M. luteus*. *Escherichia coli* was the most commonly used in laboratories to test the sensitivity of plant extracts (25 publications). However, only extracts from *A. vepretorum* and *S. brasiliensis* presented good activity (≤1000) (Almeida et al. 2014b; Saraiva et al. 2011).

The extracts of the species that presented activities at very low concentrations (MICs≤100 µg/mL) were the methanolic extract of the leaf of *Shinopsis brasiliensis*, which presented an effect on the strains of *P. aeruginosa* and *S. aureus* at a very low concentration (31 µg/mL) (Saraiva et al. 2011). Additionally, the methanolic extract of *C. quercifolius* inhibited the growth of *Enterococcus faecalis*, *Enterococcus faecium, Lasiodiplodia theobromae, P. aeruginosa, S. epidermidis* and the fungus *Colletotrichum gloeosporioides* at concentrations of 7–62 µg/mL (Paredes et al. 2016) (Table 2). Plant extracts that showed a broad spectrum of activity (≤1000) were those of *Buchenavia tetraphylla* (Aubl.) R.A. Howard, *Poincianella pyramidalis* (Tul) L.P. Queiroz, *Senna macranthera* (Collad.) H.S. Irwin & Barneby, and *Shinopsis brasiliensis* Engl. (Table 2).

Only a few extracts (2% of all tested extracts [n = 174]) inhibited fungal growth. For this group, the most recorded species in the studies was *C. albicans*, which was more susceptible to the plant extracts (Cruz et al. 2007; Silva et al. 2011, 2012b). An aqueous extract of the leaf of *C. pyramidalis*, an aqueous extract of the bark *Z. joazeiro* and an ethanolic extract of the leaf and bark of *Z. joazeiro* presented antimicrobial action at low concentrations ranging from 6-25 µg/mL, and they also presented broad spectra of action against the fungi *C. albicans, Candida guilliermondii, Cryptococcus neoformans, Fonsecaea pedrosoi,* and *Trichophyton rubrum* (Cruz et al. 2007).

The low number of active extracts against fungi may reflect the difficulty of finding active extracts for this group. Owing to the complexity of fungal cells, finding substances that are both selective against a specific target and provide a safe antifungal effect is difficult. This limitation coupled with the limited research on plants for antifungal activity compared to antibacterial activity has been a barrier in the search for new natural antifungal products. Thus, the results indicate the need for in vitro studies to discover new alternatives for fighting fungi.

Newman and Cragg (2016) surveyed antimicrobial sources and observed the lack of new antifungal agents obtained from natural products from 1981 to 2014. This study found that compared with antibacterial agents, antifungal agents were predominantly of synthetic origin, with 73% of the antibacterial agents obtained from natural products, while only 10% of the antifungals are from natural products. These data are of concern because of the urgent need to obtain new products since many have lost their effectiveness.

In general, in the tests evaluated by the disc-diffusion method in agar, the concentrations were very high when compared to those of the microdilution

Table 2. Native Caatinga plants with antimicrobial activity at concentrations of ≤1000 µg/ml.

Family/Species	Part used	Type of extract	Microorganism	Reference
Anacardiaceae				
Schinopsis brasiliensis Engl.	Bark	Ethanol/water 10%, 20%, 30%, 50%, 70%	*P. aeruginosa, S. aureus, Streptococcus oralis*	Silva et al. (2012c)
	Bark	Ethanol/water 30%, 50%	*E. faecalis*	Silva et al. (2012c)
	Leaf	Methanolic	*E. faecalis, E. coli, Klebsiella pneumoniae, P. aeruginosa, S. aureus, Staphylococcus epidermidis, Staphylococcus saprophyticus, Staphylococcus* sp.	Saraiva et al. (2011)
Annonaceae				
Annona vepretorum Mart.	Leaf	Chloroform, ethanolic 95%	*E. coli*	Almeida et al. (2014b)
	Leaf	Hexane	*E. coli, Salmonella enterica, Serratia marcescens, S. aureus*	Almeida et al. (2014b)
Burseraceae				
Commiphora leptophloeos (Mart.) J. B. Gillett	Bark	Aqueous	*P. aeruginosa*	Trentin et al. (2013)
Caesalpiniaceae				
Poincianella pyramidalis (Tul.) L.P.Queiroz	Leaf	Aqueous	*C. albicans, Candida guilliermondii, C. neoformans, F. pedrosoi, Trichophyton rubrum*	Cruz et al. (2007)
	Leaf	Aqueous	*Fusobacterium nucleatum, Porphyromonas gingivalis, Prevotella intermedia*	Alviano et al. (2008)

Combretaceae				
Buchenavia tetraphylla (Aubl.) R.A. Howard	Leaf	Ethanolic 70%	*S. aureus, Mycobacterium smegmatis, Bacillus subtilis, M. luteus, Salmonella enteritidis, P. aeruginosa, Proteus vulgaris*	Oliveira et al. (2012)
Euphorbiaceae				
Cnidoscolus pubescens Pohl	Root	Methanolic 80%	*S. aureus*	Peixoto Sobrinho et al. (2012)
Cnidoscolus quercifolius Pohl.	Leaf, Root	Methanolic	*S. epidermidis, E. faecium, Lasiodiplodia theobromae, P. aeruginosa, E. faecalis, Colletotrichum gloeosporioides.*	Paredes et al. (2016)
	Bark	Methanolic 80%	*S. aureus, Staphylococcus coagulase.*	Peixoto Sobrinho et al. (2012)
Jatropha mutabilis (Pohl) Baill.	Root	Hydroalcoholic	*M. luteus*	Silva et al. (2012b)
Fabaceae				
Anadenanthera colubrina (Vell.) Brenan var. colubrina	Leaf	Hydroalcoholic	*S. aureus*	Silva et al. (2012b)
Bauhinia acuruana Moric.	Leaf	Ethanolic	*M. luteus*	Silva et al. (2012b)
Libidibia ferrea (Mart. exTul.) L.P. Queiroz	Fruit	Ethanolic	*M. luteus*	Silva et al. (2012b)
	Fruit	Hydroalcoholic	*M. luteus, S. aureus*	Silva et al. (2012b)
Pityrocarpa moniliformis (Benth.) Luckow & R. W. Jobson	Leaf	Hydroalcoholic	*M. luteus*	Silva et al. (2012b)

Senna macranthera (Collad.) H.S. Irwin & Barneby	Flower	Ethanolic	*S. aureus*	Diaz et al. (2010)
	Root	Dichloromethane, ethanol	*S. aureus, Streptococcus agalactiae, Streptococcus bovis*	Andrade et al. (2015)
Stylosanthes viscosa Sw.	Leaf	Hydroalcoholic	*B. subtilis*	Silva et al. (2012b)
Malpighiaceae				
Stigmaphyllon paralias A. Juss.	Leaf	Hydroalcoholic	*S. aureus*	Silva et al. (2012b)
Myrtaceae				
Eugenia brejoensis Mazine	Leaf	Hydroalcoholic	*C. albicans, M. luteus*	Silva et al. (2012b)
Olacaceae				
Ximenia americana L.	Bark	Ethanol/water 10%, 20%, 30%, 50%	*S. aureus*	Silva et al. (2012c)
	Bark	Ethanol/water 30%	*E. faecalis*	Silva et al. (2012c)
	Bark	Ethanol/water 70%	*S. oralis*	Silva et al. (2012c)
Rhamnaceae				
Ziziphus joazeiro Mart.	Bark	Ethanolic	*B. subtilis, C. albicans, Enterobacter aerogenes, E. faecalis, K. pneumoniae, M. luteus, M. smegmatis, Proteus mirabilis, P. vulgaris, S. marcescens, S. aureus, Streptococcus pyogenes*	Silva et al. (2011)
	Inner bark	Aqueous	*P. gingivalis*	Alviano et al. (2008)

	Leaf	Ethanolic	*E. aerogenes, K. pneumoniae, M. luteus, M. smegmatis, P. vulgaris, P. aeruginosa, S. pyogenes*	Silva et al. (2011)
	Stem	Aqueous	*C. albicans, C. guilliermondii, C. neoformans, F. pedrosoi, T. rubrum*	Cruz et al. (2007)

method, which is common in such studies (Braga 2016). It is reasonable that there are differences in the concentrations used for both tests, since they employed different techniques. However, excessively high amounts should be avoided to optimize the search for extracts with better activities for more detailed future studies. The extremely high doses applied in the trials have shown that there is a need to relativize the findings since they do not determine the activity of a plant. Therefore, it is suggested that new microdilution assays should be performed for the extracts that were evaluated only by diffusion, since this technique is the most recommended for determining antimicrobial activity (Alves GA et al. 2008).

4. Zoopharmacognosy and Zoopharmacology in the Caatinga

A study by Ferreira et al. (2010) indicated that research describing the chemical composition and pharmacological effects of remedies obtained from animal parts are still scarce. In the Northeast Brazil, bioprospecting has contributed to the identification and elucidation of the therapeutic effects of chemical compounds that may be present in zootherapies, which are frequently used for the empirical treatment of different health conditions (Alves and Rosa 2005, 2006, 2007a, 2007b, 2007c; Alves et al. 2007; Cabral et al. 2013; Dias et al. 2013; Oliveira et al. 2014; Sales et al. 2015).

Reptiles and amphibians are among the most frequently studied wild species in the Caatinga in terms of their chemical compositions, especially in studies that aim to identify and/or isolate compounds present in extracts obtained from body fat and secretions (such as saliva and venom). Moreover, ethnozoology surveys have shown that reptiles are among the most commonly used animal species in folk medicine (Zhou and Jiang 2004; Mahawar and Jaroli 2006, 2008; Alves and Pereira-Filho 2007; Alves et al. 2008a, 2008b) and show that body fat stands out as one of the most commonly used products (Costa-Neto and Alves 2010; Alves and Alves 2011).

Studies performed with reptiles from the Caatinga a predominantly investigate the chemical composition and pharmacological properties of secretions obtained from venomous snakes. A new bradykinin-potentiating peptide was identified and isolated (Pro-Asn-Leu-Pro-Asn-Tyr-Leu-Gly-Ile-Pro-Pro) from the venom extracted from *Crotalus durissus* cascavella. When investigated for its pharmacological

potential, the effects of this peptide were compared to that of the potentiated bradykinin peptide (BBP9a) isolated from *Bothrops jararaca* and the antihypertensive drug captopril® (Lopes et al. 2014). Studies with the *Crotalus durissus collilineatus* species have identified and isolated factors with potent central analgesic activity that possibly act on the opioid system. Gomes (2007) isolated an analgesic factor called crotamine from *C. durissus* poison; in this study, the author observed that crotamine in natura or after heat treatment (boiling at 100ºC for 8 minutes) was effective at reducing algic stimuli in mice and exhibited a potency greater than morphine with a longer lasting effect. Olinda (2010) isolated an analgesic factor (Cdc factor) from *C. durissus* and observed that this substance possesses central and peripheral analgesic actions in mice, with this effect being 108% more potent than that of morphine.

Fixed oils obtained from the body fat of reptiles have shown a predominance of unsaturated fatty acids when compared to saturated fatty acids (Ferreira et al. 2010; Cabral et al. 2013). Dias et al. (2013) verified that the body fat of *Phrynops geoffroanus* is composed of 84.63% and 13.38% unsaturated and saturated methyl esters, respectively. Among the constituents identified in the *P. geoffroanus* fixed oil, palmitoleic and oleic acids were present in greater amounts and accounted for 58.39% and 15.7% of the extract's composition, respectively. This species displayed antifungal modifying activity against *C. albicans* strains. For lizards used as a zootherapy, fat from *Tupinambis merianae* was evaluated for its anti-inflammatory activity (Ferreira et al. 2010), and it demonstrated a reduction in inflammation in mouse ear edema models; however, analyses of the antibacterial activity of *T. merianae* fat (Ferreira et al. 2009) and skin (Ferreira et al. 2018) did not identify antibacterial action. The fat from *Tropidurus hispidus* lizards also showed antibiotic modifying activity (Santos et al. 2015). Bioprospecting of reptile fat to determine the antibacterial and antibiotic activity modifying effects also showed that fat from *Boa constrictor, Spilotes pullatus* and *Crotalus durissus* snakes exhibited a synergistic effect when combined with aminoglycosides (Ferreira et al. 2009; Oliveira et al. 2014).

Oliveira et al. (2014) analyzed the chemical composition of the oil obtained from the body fat of the *Spilotes pullatus* snake and revealed the presence of 10 fatty acids that accounted for 94.97% of the extract's chemical composition. The authors observed a higher concentration of unsaturated fatty acids than saturated fatty acids (61.38% and 33.59, respectively), with the unsaturated fatty acids elaidic acid (37.26%) and linoleic acid (17.28%) and the saturated fatty acids palmitic acid (19.01%) and stearic acid (10.58%) predominating.

Extracts and decoctions of *Tropidurus hispidus, Tropidurus semitaeniatus, Ameiva ameiva, Tupinambis merianae, Iguana, B. constrictor* and *C. durissus* reptiles were also examined as potential antibacterial agents (Santos et al. 2012a, b; Ferreira et al. 2018.). However, modifying activity was only validated for *T. hispidus, T. semitaeniatus* and *A. ameiva* (Santos et al. 2012a, b). In anti-inflammatory activity validation studies using paw and ear edema models, skin decoctions from *C. durissus, I. iguana,* and *B. constrictor* reduced inflammation (Ferreira et al. 2014).

The *Leptodactylus* and *Rhinella* genera are among the Caatinga amphibians used in popular medicine. Cabral et al. (1926) investigated the chemical composition of fixed oils obtained from the body fat of two

species belonging to the *Leptodactylus* genus, *Leptodactylus macrosternum* Miranda-Ribeiro (1926) and *Leptodactylus vastus* Adolf Lutz (1930) and observed that the oil obtained from *L. macrosternum* contained 40% saturated fatty acids and 60% unsaturated fatty acids while the oil obtained from *L. vastus* contained 58.33% saturated fatty acids and 41.67% unsaturated fatty acids. In the aforementioned study, both species possessed common constituents, including methyl myristate, methyl pentadeacanoate, methyl palmitoleate, methyl linoleate, methyl estereate and methyl 5,8,11,14-eicosatetraenoate. The authors stated that the presence of large amounts of unsaturated fatty acids in the *L. macrosternum* and *L. vastus* fixed oils was unexpected and indicated that the animals' diets potentially influencing this result since essential fatty acids are not synthesized by animals.

In the study by Sousa et al. (2009), the authors identified and isolated a new neutral peptide rich in glycine/leucine called leptoglycine from *Leptodactylus pentadactylus* Laurenti skin secretions. The authors observed that this peptide displayed a significant antimicrobial effect and could inhibit the growth of different gram-negative bacteria, such as *P. aeruginosa, E. coli* and *Citrobacter freundii*. Limaverde et al. (2009) isolated the protein toxin leptoxin and investigated its toxicological properties in a study performed with *L. pentadactylus* skin secretions, observing that leptoxin promotes death in mice because of acute lung edema because of an increase in lung microvascular pressure arising from direct vasoconstriction induced by this substance.

Studies with species belonging to the *Rhinella* genus have identified the presence of different saturated fatty acids, including lauric acid, myristic acid, pentadecanoic acid, stearic acid, palmitic acid and heptadecanoic acid, and of unsaturated fatty acids, including arachidonic acid, linoleic acid, oleic acid and palmitolytic acid, in fixed oils obtained from the body fat of *Rhinella jimi* frogs (Stevaux 2002) (Sales et al. 2015). Moreover, the study by Sales et al. (2017) analyzed secretions obtained from the parotid glands of the aforementioned species and identified the presence of bufotenin, dehydro-bufotenin, marinobufagine, telocinobufagine, and bufaline. Similar constituents were also identified in venom extracted from Bufo schneideri Werner, namely, marinobufagine, telocinobufagine and bufaline (Freitas 2003).

Regarding wild mammals, Ferreira et al. (2018) evaluated the antibacterial activity of fat from *Euphractus sexcinctus* and spines from *Coendou prehensilis*, although the antibacterial action of its components was not validated. Fats from mammals and domestic fowl are also described as zootherapies used in the Caatinga biome for diseases affecting domestic animals and humans (Ferreira et al. 2012; Dias et al. 2018, Dias et al. 2019a, 2019b). In the study by Dias et al. (2019a), the antibacterial and antibiotic modifying action of fats from the mammals *Bos taurus, Capra hircus,* and *Ovis aries* domestic against bacteria of veterinary interest were analyzed, and these fats showed antibiotic modifying activity for terramycin, norfloxacin, amikacin, and amoxicillin. This same modifying activity was also found for fat from *Sus scrofa* domesticus (Dias et al. 2019b), *Gallus gallus* birds, and *Meleagris gallopavo* (Dias et al. 2018). For invertebrates, the modifying activity of aminoglycoside antibiotics associated with products derived from the termite Nasutitermes corniger was also observed (Coutinho et al. 2009; Coutinho et

al. 2010).

5. Perspectives and gaps

Although hundreds of plants occurring in the Caatinga have been identified, studies on their secondary metabolites are still limited with respect to the isolation and identification of bioactive molecules. As listed above, a large proportion of the studies are only aimed at verifying the presence of metabolites and quantifying them. Because the Caatinga is a unique ecosystem, greater partnerships with universities and research centers can provide greater insights into the phytochemistry of species occurring in the Caatinga, especially the endemic species. This collaborative effort may be important to investigate a set of questions that require the interaction of different lines of research. For example, these investigations could assess what the perceived characteristics of the medicinal plants by people (smell, taste) would be more associated with their pharmacological potential. These studies will be interesting in the future as they may benefit bioprospecting by highlighting a set of important plant characteristics from local knowledge that may be essential in finding new candidates for disease treatment. In addition, future efforts could also be directed to verify if the pharmacological potential of plants varies in response to the marked climatic seasonality of the Caatinga (see, for example, Monteiro et al. 2006a) and/or to the diversity of climatic conditions present in the region.

The ethnopharmacological data on zootherapeutics enable the discovery of new drugs and may also serve as a guide for the rational and sustainable use of exploited species (Alves 2009; Ferreira et al. 2012). Research has shown that the animal species used for traditional medicine are threatened with extinction, and information on the biological activity of these resources may not be available (Alves and Rosa 2005, 2007c).

The treatment of human and animal diseases using animal derivatives constitute the basis of many traditional therapeutic systems and is considered relevant to science, thus necessitating a better understanding of the biological, social, cultural and economic aspects of these resources (Lev 2003; Alves and Albuquerque 2013).

Bioprospecting studies investigating the activities of fats from domestic animals that are also used as zootherapeutics were reviewed here (Dias et al. 2018, Dias et al. 2019a, 2019b). These studies have shown that fats from domestic species present the same ability to modulate antibiotic activity as the fats from wild species, which indicates that possible substitutes may be available for products from endangered species.

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