# Cactaceae antimicrobials from Seasonally Dry Tropical Forests (Caatinga) in Northeast Brazil

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Neotropical seasonally dry forest (dry forest) is a biome with a wide and fragmented distribution, found from Mexico to Argentina and throughout the Caribbean. It is one of the most threatened tropical forests in the world, with less than 10% of its original extent remaining in many countries. The dominant vegetation type in the northeastern Brazil region is a seasonally dry tropical forest (SDTF), named Caatinga, a unique biome in the world. The Caatinga vegetation is adapted to aridity of the region having exclusive plant species. Twenty-four genera and 116 taxa (88 species and 28 subspecies) are recorded to Caatinga in the northeastern Brazil. Cactaceae, which survive in the Caatinga environment, have anatomical and physiological adaptations with consequent modifications in its secondary metabolism. Therefore, several species of Cactaceae family found in the Caatinga are rich sources of phytochemicals with interesting antimicrobial properties. Thus, the present chapter addresses antimicrobials from Caatinga cactus species, since such plants face climatic conditions of the region; and some cactus are used as herbal medicines by the local population.

**Keywords**: Cactaceae; antimicrobial activity; Cactus; natural products.

## 1. Introduction

The Caatinga biome is a mosaic of thorny shrub land and dry forests located in the semiarid region of northeastern Brazil [1], and composes one of the biggest continuous complex of Seasonally Dry Tropical Forests [2]. Caatinga is highlighted as the biome most biodiverse in the world and cover 844,453 km$^2$ in northeastern Brazil [3], encompassing portions of the states of Ceará, Piauí, Bahia, Sergipe, Alagoas, Pernambuco, Paraíba and Rio Grande do Norte, as well as a small region in the north of Minas Gerais [1,4]. Similar to other tropical dry forests, the Caatinga has undergone strong human pressure and a severe loss of its original cover: data from 2009 pointed out that over 47% of the biome's vegetation have already been deforested or anthropized [3].

The biodiversity of the Caatinga has been stigmatized as being poor and with low levels of endemism, however this information has been gradually changed [5,6]. Even with many areas still unknown to science, the Caatinga has been subjected to heavy anthropic pressure, especially related to the removal of plant biomass and unbridled hunting of vertebrates [1,5,7].

Cactaceae family comprises 127 genera and about 1,438 species distributed almost exclusively in tropical and subtropical America, from Canada to Patagonia [8]. There are four centers of diversity for Cactaceae. The first area is in centre of Mexico and southwest of the United States of America. The second center, which comprises approximately 18% of the genera, is located in the Andes, including parts of Peru, Bolivia, south of Ecuador and northeast of Chile. The third center of diversity is located in the East Brazil and the fourth in southern areas of Brazil, Paraguay, Uruguay, South and Nortwest Argentina [9,10]. In the phytogeographical biome of the Caatinga, in the northeast region of Brazil, 24 genera and 116 taxa (88 species and 28 subspecies) are recorded [11]. For example, *Opuntia* is a genus of cactus that has been assigned a versatility of biotechnological applications, such as wastewater treatment and insecticidal action; the species *Opuntia ficus-indica*, in turn, is considered of great agronomic importance and human uses [12].

The aim of the present work is to discuss the phytochemical characterization made in cactus species of the Caatinga focusing on antimicrobial potential that these plants can have to serve as phytotherapic alternatives; also, to stimulate the scientific community to isolate these antimicrobial compounds from these plants.

## 2. Phytochemical Profile of Cactaceae

In relation to phytochemical profile of the cacti, among the species mentioned in Table 1, *Opuntia ficus-indica* and *Pereskia bleo* are two stand out as the most studied. *O. ficus-indica* species is considered to be a good natural source of energy, nutrients and antioxidants such as vitamin C [13]; significant values of vitamins A, B1, B6 and E also have been reported [14]. Low acidity combined with the high sugar content makes this species an adequate additive in production of various foods (sugars 88%, proteins 4.5%, fibers 1.4%, pectins 2.3%) [13,15]; and some of its compounds may be used as food dyes, among which are pigments such as betanin, reported and isolated [15-17].

**Table 1** Species of the Cactaceae family from Caatinga and identified compounds.

| Species | Isolated Compounds | Tissues | References |
|---|---|---|---|
| *Opuntia ficus-indica* | Isorhamnetin 3-*O*-β-D-glucopyranoside; narcissin; benzyl-*O*-β-D-glucopyranoside; picein; androsin; 1-*O*-feruloyl-β-D-glucopyranoside. | Fruits | [18] |
| *Opuntia ficus-indica* | Isorhamnetin-glucosyl-pentoside | Cladodes | [19] |
| *Opuntia ficus-indica* | Betanin | Fruits | [16,20] |
| *Pereskia bleo* | Dihydroactinidiolide; β-sitosterol, 2,4-di-tert-butylphenol; α-tocopherol; phytol; 3,4-dimethoxy-β-phenethylamine; mescaline; vitexin; sitosterol. | Leaves | [21-24] |
| *Pereskia grandifolia* | 2,4-ditert-butylphenol | Leaves | [25] |

Butera et al. (2002) reported that bethanin is responsible for red color of fruits and when associated with polyphenolic pigments offer a yellowish color; in addition, betanin and indicaxanthin pigments were isolated and showed to be more promising than Trolox (analogue of vitamin E) in antioxidant activity [16]. Kim et al. (2016) concentrated on isolating compounds in *O. ficus-indica* (Table 1) but did not perform biological assays [18]. Hassan et al. (2011) reported that *O. ficus-indica* fruit juice has potential to restore liver, pancreas and kidneys tissues after damage. Experiments with rats showed that values of superoxide dismutase, reduced glutathione, high-density lipoprotein (HDL), protein and hepatic glycogen returned to their normal levels after treatment with this cactus. Compounds identified were generally classified as phenols, flavonoids, carotenoids, vitamins and free amino acids; however, some studies have not yet been able to prove which groups of compounds were responsible for tested biological activities [14].

Antunes-Ricardo et al. (2015) evaluated *O. ficus-indica* cladode extract and isolated compounds performing *in vitro* and *in vivo* activities. Nitric oxide production was assayed in macrophages of lineage RAW 264.7 and stimulated with lipopolysaccharide; *in vivo* studies were made by croton oil-induced ear edema model. Extract and the isolated compound named isorhametine-glucosyl-rhamonoide (IGR) suppressed the production of nitric oxide *in vitro* without affecting cell viability; moreover, IGR inhibited ear edema (77 ± 5.7%) equaling the effects of indomethacin (69 ± 5.3%), since this is an anti-inflammatory drug capable of inhibiting the formation of edema. Both IGR and extract also inhibited the production of Cox-2, TNFα and IL-6. In this way, IGR proved to be a potent anti-inflammatory compound [26].

Extract in ethyl acetate and compounds isolated from *Pereskia bleo* leaves had their cytotoxic activity analyzed against different cell lines (KB, MCF7, Caski, HCT 116, A549 and MRC-5). The 2,4-di-tert-butylphenol compound (Table 1) showed to be the most promising since it exerted low cytotoxicity against normal cells [21]. Guilhon et al. (2015) worked with *P. bleo* leaves and isolated sitosterol and vitexin; both molecules showed antinociceptive activity [24].

## 3. Lectins from Cactaceae

Lectins are proteins that may have one or more domain that binds reversibly to specific monosaccharides or oligosaccharides [27]. Carbohydrate recognition domain (CRD) in lectins provide binding of lectins to soluble carbohydrates or glycidic portions present in a glycoprotein or glycolipid; lectins can agglutinate certain animal cells and/or precipitate glycoconjugates [28,29].

Lectins are widely distributed in nature and can be found as monomers, homo- and heterodimers, as well as homo- and heterotetrameric molecules; these proteins have been isolated from viruses, bacteria, fungi, invertebrates, unicellular organisms, animals and plants [30]. Plant lectins are important proteins for their defence, since these bioactive molecules are able to recognize and interact with specific carbohydrates from invading organisms or structures of damaged plant cell wall [31]. These plant lectins have been presented as valuable tools in biomedical research, due to their ability to bind to the glycans of receptors on cell surfaces and can trigger cell signaling and biochemical responses [32].

Most plant lectins are found as storage proteins in seeds, but have also been purified from other tissues including bulb, tuber, bark, leaves and fruits [33]. Fig. 1 schematizes the process of lectin purification from a plant belonging to the Cactaceae family (Fig. 1a). In the investigation of the presence of lectins in plant extract (Fig. 1b) the hemagglutination test, known as hemagglutinating activity (HA), should be performed, as shown in Fig. 1c. Lectins interact with portions of sugar on erythrocytes surface interconnecting them (agglutination) forming a network or mesh of red blood cells. To indicate lectin specificity to favour the purification protocol, it is necessary to perform an assay named HA inhibition as shown in Fig. 1d. In this inhibition assay, carbohydrates are used at different concentrations capable of preventing agglutination and thus determining the affinity and specificity of the lectin of interest [34].

Generally, crude extract containing the lectin undergoes preliminary fractionation, for example, by precipitation with ammonium sulphate, in order to obtain a protein fraction devoid of undesirable components like polysaccharides. Final purification is carried out by a method of chromatography (Fig. 1e), and affinity chromatography is usually applied in adsorbents composed of polymeric systems; the most usual are polysaccharides such as Sephadex [35]. Then a specific eluent is added to obtain the pure lectin (Fig. 1f).

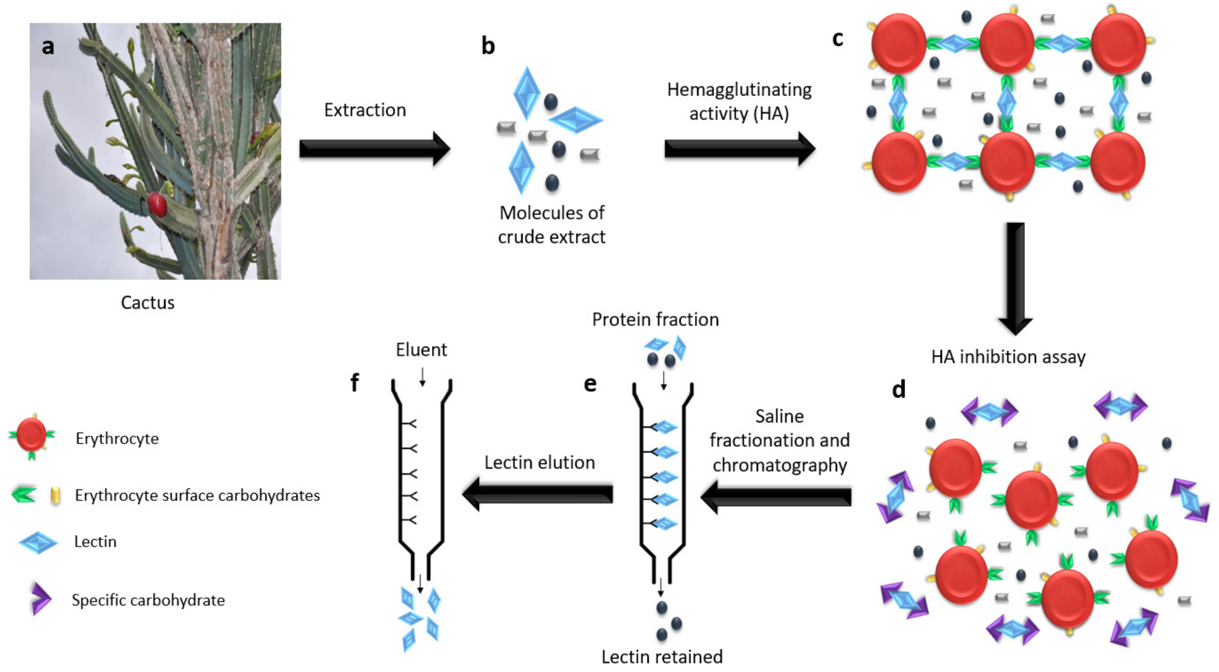


**Fig. 1** Stages of lectin purification from a cactus. Process begins with the plant tissue (a) that goes through the extraction process until obtaining a crude extract containing the lectin along with other molecules (b). HA assay is performed for the identification of lectin in the extract that is able to bind to the carbohydrates on erythrocyte surface promoting the interconnection of these cells (c). Inhibition of HA occurs when a specific carbohydrate binds to the lectin and desorbs the binding site in the erythrocytes (d). Final purification generally occurs after fractionation of crude extract, when protein fraction is submitted to chromatographic column (e) and then the pure lectin is eluted from the column through a specific eluent (f).

Few lectins have been extracted from Cactaceae; the first two isolectins obtained from the *Machaerocereus eruca* stem, called MEAI and MEAII, through mucin-Sepharose 4B affinity chromatography, both with high specificity to galactose and affinity by O-glycans [36,37]. Combination of hydrophobic interaction chromatography with affinity chromatography on a column with immobilized human erythrocytes led to the isolation and purification of four isolectins (ME-C2, -D2, -E2 and -F2) from *M. eruca* stem, which promoted a suppression of the murine humoral immune response in response to particulate antigens [38].

Another lectin that was also isolated from a species belonging to the family Cactaceae is OfiL, purified from cladodes of *O. ficus-indica* by chromatography of chitin column and Sephadex G-25, being a single polypeptide with molecular weight of 8.4 KDa. OfiL presented antifungal activity against *Colletotrichum gloeosporioides*, *Candida albicans*, *Fusarium decomcelulare, F. lateritium*, *F. moniliforme*, *F. oxysporum* and *F. solani* [39]. OfiL also presented termiticidal activity against workers and soldiers *Nasutitermes corniger*, showing itself as a new tool for the control of this termite species [40].

A great diversity of biological applications is attributed to plant lectins, such as mediators of inflammatory and immune response; possessing cicatrizant, antimicrobial and antitumor actions; acting as histochemical markers and in disease biosensors [41]. This class of proteins has gained prominence over its possible antimicrobial action besides being able to interfere with microbial biofilm formation, which is responsible for biomaterial infections, mainly caused by *Staphylococcus aureus* and *Staphylococcus epidermidis* [42,43]. In view of this range of applications and the small number of investigations on Cactaceae lectins, further research is needed to try to identify and isolate these bioactive proteins in cactus species that may have potential biotechnological uses.

## 4. Cactus from Caatinga: antimicrobial actions

Among methodologies used to screen antimicrobial activity of a compound and/or extract containing various molecules, the diffusion test in agar is highlighted, since it is simple to perform and low cost. This method consists of impregnating small filter paper disks in the investigated solution containing the active principle, which are placed on solid culture medium previously inoculated in Petri dishes with different microbial charges. In order to analyze the antimicrobial activity in plant extracts, the Minimum Inhibitory Concentration (MIC) is determined, which is defined by lowest concentration of the test substance required to inhibit the growth of a microorganism. In addition, it is also possible to determine the Minimum Bactericidal Concentration (MBC), defined as the minimum concentration of the compound that causes microbial death. These methods present high sensitivity and demand a minimum amount of substance, allowing a greater number of replicates and, therefore, an increase in the reliability of results [44]. There are several studies that show the antimicrobial efficacy of the Cactaceae family. Table 2 shows the studies carried out with these plants and their action against pathogenic microorganisms.

**Table 2** Species of the Cactaceae family with their identified antimicrobial activity.

| Cactaceae | Microorganisms | References |
|---|---|---|
| *Opuntia ficus-indica* | *Staphylococcus aureus; Staphylococcus epidermidis; Bacillus cereus*; *Pseudomonas aeruginosa; Escherichia coli; Salmonella* sp.; *Candida albicans; Listeria monocytogenes*; *Saccharomyces cerevisiae.* | [45,46] |
| *Opuntia albicarpa* | *C. albicans; E. coli*; *S. aureus, L. monocytogenes*; *P. aeruginosa*; *S. cerevisiae.* | [46] |
| *Opuntia dillenii* | *Bacillus licheniformis; Brevibacterium luteum; E. coli*; *Flavobacterium devorans; Klebsiella pneumoniae; Micrococcus flavum; Micrococcus luteus; Rhodococcus terrae*; *Salmonella typhi; Shigella boydii*; *Shigella flexneri*; *Shigella sonnei; S. aureus.* | [47] |
| *Opuntia stricta* | *S. aureus*; *E. Coli*; *C. albicans; Bacillus cereus; Bacillus licheniformis; P. aeruginosa.* | [48,49] |
| *Opuntia matudae* | *E. coli.* | [50] |
| *Cereus jamacaru* | *S. epidermidis*; *S. aureus; P. aeruginosa*; *E. coli.* | [51] |
| *Epiphyllum oxypetalum* | *E. coli*; *S. aureus; K. pneumoniae; Bacillus subtilis.* | [52] |
| *Hylocereus* sp. | *E. coli*; *S. aureus;S. epidermidis*; *Salmonella enterica*; *K. pneumoniae*; *C. albicans, Aspergillus niger*; *P. aeruginosa.* | [53] |
| *Hylocereus polyrhizus*<br>*Hylocereus undatus* | *B. cereus; S. aureus*; L. *monocytogenes; E. faecalis; Salmonella typhimurium, E. coli*; *K. pneumoniae*; *Yersinia enterocolitica*; *Campylobacter jejuni.* | [54] |
| *Nopalea cochenillifera* | *E. coli*; *S. enterica; C. albicans*; *S. aureus; S. epidermidis; K. pneumoniae; P. aeruginosa; S. cerevisiae*; *S. typhi*; *Micrococcus* sp.; *Candida glabrata*; *Prototheca zopffi*; *Cryptococcus neoformans; Malassezia furfur.* | [55-57] |

There are few reports on antiviral activity among the Cactaceae present in the Brazilian semi-arid region; the *Opuntia* genus presented positive assays. Ahmad et al. (1996) found antiviral effect initially through the crude extract of *O. streptacantha* [58]. A protein from *O. ficus-indica* cladodes was isolated, which in turn inhibited cucumber mosaic virus (CMV), zucchini yellow mosaic virus and tobacco mosaic virus. This protein promoted interaction with viral nucleic acid as identified by Western blot analysis [59]. This work was of great interest to the scientific community since it showed the inhibitory effect of *O. ficus-indica* crude extract against several viruses: *Tobamovirus*, *Potyvirus* and *Cucumovirus*. *O. ficus-indica* has antiviral activity and the encouragement for new research to be done not only with the genus *Opuntia* but also with all Cactaceae is of great relevance.

Different diseases caused by parasitic protozoa and helminth worms afflict humans. Remarkable number of species that can infect the human is about 300 helminths and 100 protozoa. Not all of these organisms are pathogenic, but some are responsible for the world's most important diseases, especially in the tropics [60]. According to the World Health Organization, nearly half of the world's population is at risk of serious parasitic infections, such as malaria, with hundreds of millions of people being infected each year. In 2016, an estimated 216 million malaria cases worldwide and 445,000 deaths, mainly children in the African Region were estimated [61].

Natural products provide an efficient alternative for the treatment of parasite infection. Local communities of the Caatinga use *Melocactus zehntneri*, *M. bahiensis* and *Opuntia palmadora* to treat helminthiasis and amebiasis [62-64]. However, there is a huge gap in the antiparasitic activity of plants from Cactaceae family. Few studies have been found in the literature with these plants; in addition, some have shown antiparasitic activity of crude extracts, without identification of the compounds responsible for the action.

A study by Vatta et al. (2011) demonstrated the effect of *Cereus jamacaru* against *Haemonchus contortus* and *Trichostrongylus colubriformis* and cattle helminths. In this research, an infection was made in ewes with third stage larvae (L3) from a population of *H. contortus* and *T. colubriformis* susceptible to anthelmintic. After administration of *C. jamacaru*, the samples were submitted to a fecal experimental counting method using a modified McMaster technique.

Based on this *in vivo* assay, *C. jamacaru* was effective in reducing the egg count by 18% to 65% for 49 days of experimentation [65].

In another study, 281 plants were tested for *in vitro* anti-schistosomical activity. Several parts of the plants of *C. jamacaru*, *O. leucotricha*, *O. tomentosa* and *Pereskia aculeata* were used. The leaves of *C. jamacaru* had IC 50 and IC 90 activity were 45 and 70 ppm, respectively [66]. In addition, Singh et al. (2011) demonstrated that the extract of *O. dillenii* affected the proliferation of *Leishmania donovani* promastigotes, showing the potential of this plant as leishmanicide.

Plants of the family Cactaceae present alkaloids and sterols and/or triterpenes in their composition. These compounds have activity against *Trichomonas vaginalis* [67,68], the etiologic agent of trichomoniasis, a non-viral sexually transmitted disease of high prevalence in the population. Alkaloids of *Melocactus zehntneri* were active against *T. vaginalis*, however, in this study, the alkaloid responsible for the antiparasitic activity was not identified [69]. β-Sitosterol is a compound that has been identified in *O. ficus-indica* (Park and Chun, 2001), which has important activity against *Leishmania* sp., *P. falciparum Trypanosoma brucei rhodesiense*, *Trypanosoma cruzi* and *Leishmania donovani* [70,71].

## 5. Conclusions

The Cactaceae family has an abundant number of species, especially in the Caatinga. However, few antimicrobial activities against viruses, bacteria, fungi and parasites were performed with the Cactaceae of this biome. The isolation of compounds with antimicrobial activities and the elucidation of their chemical structure may be of great importance for the pharmaceutical industry. Lectins and another compounds with different biotechnological properties can be purified from cactus. The Cactaceae has a small number of studies that revealed biological applications and at the same time is a family rich in species of cactus in the Caatinga. This paradox demonstrates the need to do more research using cactus plants for possible medicinal use. It is necessary also, scientific evidence to the popular knowledge besides the possibility of discovering new biomolecules with biomedical applicability.

**Acknowledgements** The Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) is acknowledged for fellowships (TT, LCBBC and MTSC) and grants. Authors are grateful to the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), and to the Fundação de Amparo à Ciência e Tecnologia do Estado de Pernambuco (FACEPE) for financial supports. The Instituto Nacional do Semiárido (INSA) is also recognized.

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