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Caatinga: barn of antioxidant and nutraceutical bio-actives

Caatinga: celeiro de antioxidantes e bioativos nutracêuticos

Caatinga: granero de antioxidantes y bioactivos nutracéuticos

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Abstract
The Caatinga, of Brazilian exclusivity, is compound by adapted plants for the climate-specific conditions present in this region. The natural resources in this phytogeography domain are used for local communities as foods source, regional economics develops, and traditional medicine. Folk medicine is applied as a local tradition through the fraction of the plants, such as roots, leaves, and fruits, to treat inflammation, tumor, metabolic or degenerative diseases. Although the technological pharmaceutical industrial process shows exponential development in benefits for human health, the search for new treatments, naturals, and alternatives linked with the significant consciousness of the populations some knowledge about folk medicine and their natural compounds are not vast. In this way, the present review aimed to realize the systematic research considering 26 species endemics in Caatinga and their most significant biological potential. As a result, it was observed that have more studies with the antioxidative and immunomodulatory activities. The previous knowledge shows the relation between the accumulation of reactive oxygen species (ROS) and the development of different immunological diseases. With this review, we propose to contribute to the biotechnological potential of the Caatinga for science health.
Keywords: Bioprospection; Inflammation; ROS; Folk medicine; Natural compounds; Cancer.

Resumo
A Caatinga, exclusivamente brasileira, é composta por plantas adaptadas às condições climáticas específicas presentes nesta região. Os recursos naturais neste domínio fitogeográfico são usados pelas comunidades locais como fonte de alimentos, desenvolvimento da economia regional e medicina tradicional. A medicina popular é aplicada como uma tradição local através da fração das plantas, como raízes, folhas e frutos, para tratar inflamações, tumores, doenças metabólicas ou degenerativas. Embora o processo tecnológico industrial farmacêutico apresente um desenvolvimento

exponencial em benefícios para a saúde humana, a busca por novos tratamentos, naturais e alternativas atreladas à significativa conscientização das populações sobre a medicina popular e seus compostos naturais não são vastas. Desta forma, a presente revisão teve como objetivo realizar a pesquisa sistemática considerando 26 espécies endêmicas da Caatinga e seu potencial biológico mais significativo. Como resultado, observou-se que há mais estudos com as atividades antioxidante e imunomoduladora. O conhecimento prévio mostra a relação entre o acúmulo de espécies reativas de oxigênio (ROS) e o desenvolvimento de diferentes doenças imunológicas. Com esta revisão, propomos contribuir com o potencial biotecnológico da Caatinga para a saúde da ciência.
Palavras-chave: Bioprospecção; Inflamação; EROs; Medicina popular; Compostos naturais; Câncer.

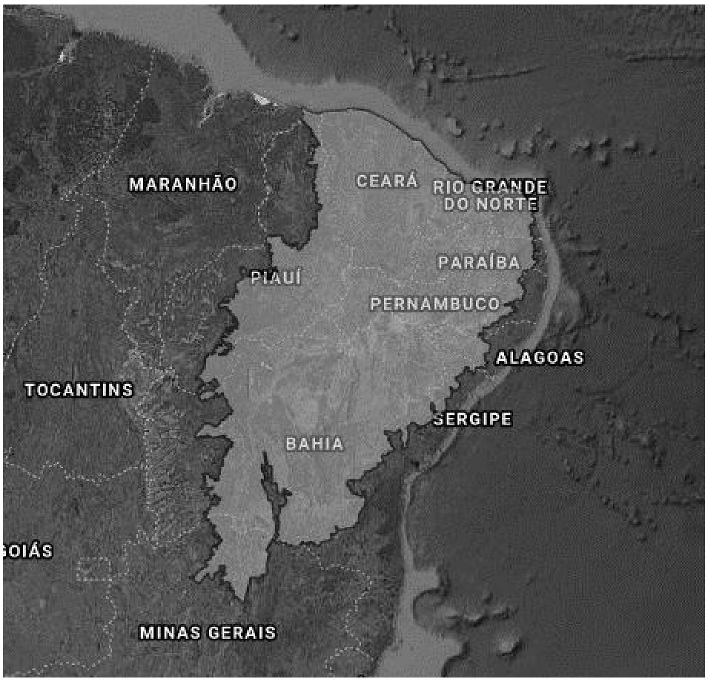
Resumen

La Caatinga, de exclusividad brasileña, está compuesta por plantas adaptadas a las condiciones climáticas específicas presentes en esta región. Los recursos naturales en este dominio de la fitogeografía se utilizan para las comunidades locales como fuente de alimentos, se desarrolla la economía regional y la medicina tradicional. La medicina popular se aplica como tradición local a través de la fracción de las plantas, como raíces, hojas y frutos, para tratar enfermedades inflamatorias, tumorales, metabólicas o degenerativas. Si bien el proceso industrial tecnológico farmacéutico muestra un desarrollo exponencial en beneficios para la salud humana, la búsqueda de nuevos tratamientos, naturales y alternativos ligada a la importante conciencia de las poblaciones sobre algunos conocimientos sobre la medicina popular y sus compuestos naturales no es muy amplia. De esta forma, la presente revisión tuvo como objetivo realizar la investigación sistemática considerando 26 especies endémicas de Caatinga y su potencial biológico más significativo. Como resultado, se observó que se tienen más estudios con las actividades antioxidante e inmunomoduladora. Los conocimientos previos muestran la relación entre la acumulación de especies reactivas de oxígeno (ROS) y el desarrollo de diferentes enfermedades inmunológicas. Con esta revisión, nos proponemos contribuir al potencial biotecnológico de la Caatinga para la ciencia de la salud.
Palabras clave: Bioprospección; Inflamación; ROS; Medicina popular; Compuestos naturales; Cáncer.

1. Introduction

Considered an exclusively Brazilian phytogeographic domain, the Caatinga occupies 11% of the entire national territory (M. V. da Silva et al., 2020) with a predominance in the country's Northeast region, between the Maranhão to Bahia states (Figure 1). Characterized by presenting a diversification in flora, the plants of this region are physiologically adapted to the sandy soil, temperature variations (14.29 ° C to 29.7 ° C) and long periods of drought (9 to 10 months) accumulating an annual rain volume of 1026 mm^3(J. M. C. da Silva & Lacher, 2020). The environmental factors on vegetation contribute to the significant variability of phytochemical agents, with bioactivities already described, capable of attenuating or blocking biological pathways involved in neurodegenerative, tumoral, and inflammatory pathophysiological processes (Costa et al., 2020; da Silva Barbosa et al., 2020a; G. C. da Silva et al., 2020; Oliveira de Veras et al., 2020; I. B. da S. Santos et al., 2020).

Figure 1: Phytogeographic domain of the Caatinga in Brazilian territory (Source: Caatinga | SiBBr)



Source: Authors.

Plant fractions, such as roots, stems, leaves, fruits, and seeds, are traditionally applied by popular medicine as a therapeutic resource for preventing and controlling circulatory, respiratory, dermatological, metabolic, endocrine, digestive disorders, among others. (Sile et al., 2020). Currently, the growing search for traditional folk medicine stimulates the use of natural products as a resource in the intervention of the health-disease process, bringing new concepts and the need for further research regarding the safety and efficacy of use. Because of this new scenario, some authors argue that any extract or isolated phytochemical agent capable of preventing pathologies or mitigating the pathological condition is considered a nutraceutical element aimed at rebalancing the normal physiological state (López-Gutiérrez et al., 2015).

In this context, this article aims to discuss the nutraceutical potential of some plant species found in the Caatinga, addressing the main biological actions documented as antihypertensive (*Myrciaria floribunda*), hypoglycemic (*Cnidoscolus quercifolius*), regulation of the lipid profile (*Eugenia dysenterica*), cachexia inhibition (*Euphorbia tirucalli*) and anti-obesity (*Hancornia speciosa*)

2. Methodology

This is a narrative review, where the 26 species endemics in the Caatinga bases were select on the "Species of Sociobiodiversity for Economics Interesting" list published by the Brazilian government in the Portaria Interministerial N° 284, March 30th, 2018. Species confirmation and inclusion of others not mentioned in the list were obtained from the website Reflora– Plants of Brazil (www.reflora.jbrj.gov.br). Articles between 2016 to 2020 were researched in Pubmed and ScienceDirect using the keywords "biological activities" and "bioactivity" associated with species' scientific names.

Articles with methodologies *in vitro, in vivo,* and clinical trials using extracts or molecules isolated from the vegetable fraction of the plant were selected. Review articles or studies not directed from human health were not included. The process of selection is representing in Figure 2. Based on the studies, the species with more articles were selected for being discussed. The relative rate of mainly biological activities in the total of the articles was performed in GraphPad Prism 6®.

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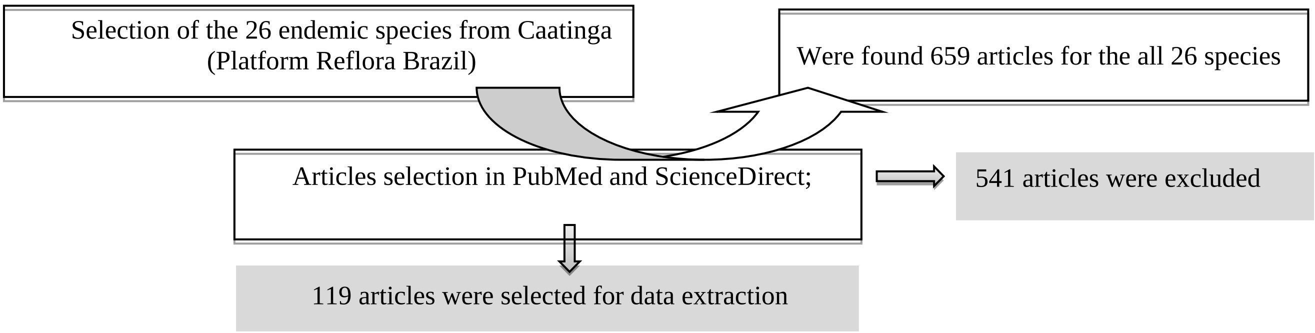
Figure 2: Methodological flowchart for the selection and analysis of articles.



Source: Authors.

3. Results and Discussion

Considering all species researched were selected 119 articles (Table 1). The significant studies analyzed the antioxidative and immunomodulatory activity in hydroalcoholic extracts from different parts of the plants. The antioxidant assay represents 41.17% of all analyses and the immunomodulatory potential in the study in 24.16% of the articles. Both investigations correlate with diseases like neurodegenerative, anticancer properties, and metabolic dysfunction in many articles. The distribution of bioactivities present in the papers is shown in Figure 3.

Table 1: The all 26 species endemics in Caatinga with the respectives compounds, source of extractions and biological activity.

Species	Biological activity	Compounds	Sources	References
Anacardium occidentale	Antihypertensive	Peptides	Cashwe Nut	(Amorim et al., 2018)
	Anti-inflammatory, Bronchodilator	Oleamid	Leaves	(Awakan et al., 2018)
	Anticancer	Polysaccharide, Cardonol Derivative, Zoapatanoloid, Agastiflavone, Anacardicin, Methyl gallate	Fruit residue, Chestnut, Leaves	(Barros et al., 2020; Braga et al., 2021a; de Oliveira Silva Ribeiro et al., 2020; M Ashraf & Rathinasamy, 2018a; J. M. Santos et al., 2019; Sunderam et al., 2019; Taiwo et al., 2017)
	Glycemic metabolic regulation and liver markers	Fibers	Fruit residue	(Carvalho et al., 2018)
	Antimicrobian activity	Phenolics and Flavonoids	Bark Stalk, Leaves and Seeds	(J. S. C. de Araújo et al., 2018; G. H. F. dos Santos et al., 2018; M Ashraf & Rathinasamy, 2018a; Morvin Yabesh et al., 2019; Sunderam et al., 2019)
	Anti-inflammatory	Anacardic acid, cardol, cardanol and methylcardo, Gallic acid, Ellagic, Shikimic, phosphoric and benzoic and Polysaccharides	Chestnut, Fruit, Flowers	(M. Q. de Souza et al., 2018a; Ferreira-Fernandes et al., 2019; Goulart da Silva et al., 2021a; A. S. Oliveira et al., 2019; Souza Filho et al., 2018a)
	Gastoprotection and Motility	Carotenoids and anarcadic acid, Oleic acid, 11-Octadecanoic acid methyl ester, Anacardol	Fruit residue and Bark Stalk	(Goulart da Silva et al., 2021a; Omolaso et al., 2020a)
	Anxiolytic, Anticonvulsant, Neuroprotective	Anacardic Acid, Agastiflavone, Phenolics and Flavonoids	Leaves and Chestnut	(Gomes Júnior et al., 2018a; Junsathian et al., 2018; Luiz Gomes et al., 2018a; Velagapudi et al., 2018a)
Arachis hypogaea	Cell protection	Phenolic compounds (catechin, epicatechin, procyanidin and proanthocyanidin and quercetin dimers)	Grain skin	(Rossi et al., 2020b)
	Antihemolytic activity	Luteolin	Bark	(M. Peng et al., 2021)
	Anti-bacterial	Stilbene (trans-arachidine-1 and trans-arachidine-3	Roots	(Eungsuwan et al., 2021a)
	Antioxidant / anti-inflammatory	Flavonoids, Stybenes, Anthocyanins	Integument, roots and black peanut shells; Leaves; Sprouted grain	(Cossetin et al., 2019; Fernandes et al., 2020; Limmongkon et al., 2018, 2019; J. Peng et al., 2019b)
	Differentiation of osteoblasts	Concentrated aqueous extract	Peanut sprouts	(Kim et al., 2019b)
Byrsonima verbascifolia	Antioxidant, antidiarrheal,	Ethanol extract, ethyl acetate extract, hexane extract	Leaves	(de Araújo Rodrigues et al., 2019)

Byrsonima crassifólia	gastroprotective	Phenolic compounds	Leaves	(R. O. de Souza et al., 2018)
Byrsonima cydoniifolia	Photochemical protection	flavonoids and stilbenes	Fruits	(V. S. dos Santos et al., 2017)
Campomanesia guazumifolia	Antioxidant, antimicrobial	Antioxidant activity monoterpenes terpinolene, sabinense, β-mycrene, α-terpinene, γ-terpinene and the farnesol and guaiol sesquiterpenes Antimicrobian activity: Bicyclogermacrene, β-pinene and karyophylene	Leaves	(A. L. dos Santos et al., 2019)
	Anti-inflammatory, antiedematogenic	Glycosylated flavonoids and cyclohexanecarboxylic acid quercetin pentose, quercetin deoxyhexoside, myricetin deoxyhexoside and quinic acid	Leaves	(Catelan et al., 2018)
Cnidoscolus quercifolius	Hypoglycemic	Phenols, flavones, flavonols, xanthones, catechins, triterpenes and tannins.	Leaves	(Lira et al., 2017)
	Antibacterial	Lupeol-3β-O-cinnamate and lupeol-3β-O-dihydrocinamate, bis-nor-diterpene filacantona	Bark Stalk	(de Oliveira-Júnior et al., 2018)
	Antioxidant, anti-inflammatory and antinociceptive	Phenolics (vanillin, eugenol and quercetin)	Seeds	(Ribeiro et al., 2021)
	Antioxidant	Phenolics and Flavonoids	Seed, oil and residual cake	(Ribeiro et al., 2017)
Croton argyrophyllus	Antioxidant, antimicrobial, antifungal	Bicyclogermacrene, β-pinene and spatulenol Total phenols and flavonols	Leaves and Stalk	(da Silva Brito et al., 2018)
Eugenia brejoensis	Trypanocidal	δ-cadineno, trans-cariofileno e α-Muurolol	Leaves	(Oliveira de Souza et al., 2017); (Bezerra Filho et al., 2020)
	Antioxidant, anti-inflammatory	hydroxybenzoic acids, vanylic acid-O-hexoside, Hexoside ellagic acid / hydroxycinnamic acids and their derivatives Catechin and Epicatechin Quercetin (dihydro quercetin glycoside), Flavanones of the flavanone class (naringin. Hydrate, eriodicthiol) eriodictiol-7-O-glucoside, Tellimagrandin II / pterocaryanin C, two Di-HHDP-galloyl-glucose (casuarictine / potentiline) isomers and five Di-HHDP-galloyl-glucose (casuarictine / potentiline) ellagic acid derivatives)	Pulp	(Soares et al., 2019); (F. F. de Araújo et al., 2021)
	Antinociceptive, anti-inflammatory, Antipyretic	Guaiol, trans-karyophylene and β-eudesmol and γ-eudesmol	Leave	(Costa et al., 2020)
Eugenia dysenterica	Neuroprotective, Antioxidant	N/D	Leaves	(Thomaz et al., 2018a)
	Prevent hypertriglyceridemia, antioxidant	N/D	Leaves	(A. B. Lima et al., 2017)

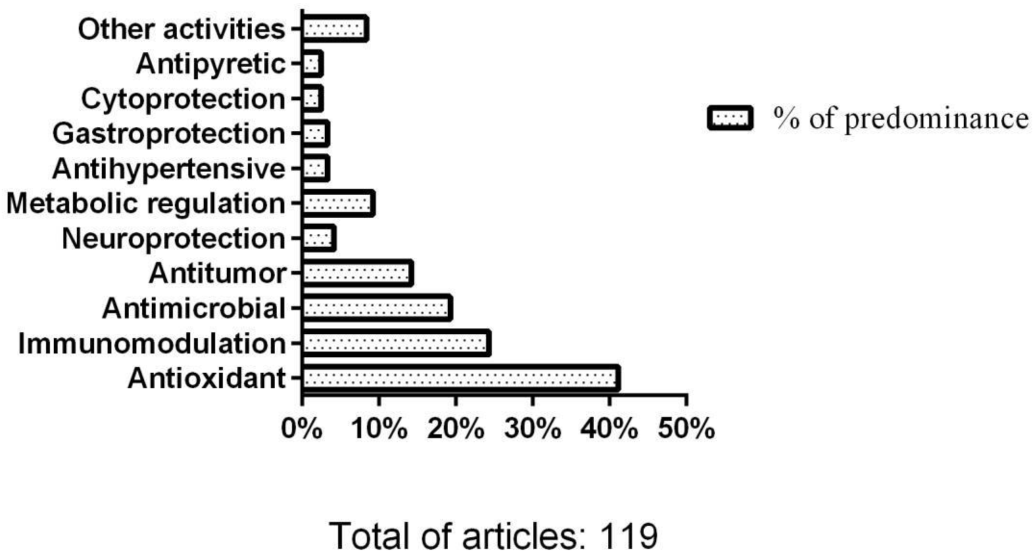
	Regulation of the lipid profile, fasting hyperglycemia and glucose intolerance	Polyphenols	Pulp	(Donado-Pestana et al., 2018b)
	Anti-inflammatory, Angiogenic	α-humuleno, β-cariofileno	Leaves	(S. M. M. Da Silva et al., 2019a)
	Hypotensive	Proanthocyanidins	Leaves	(Fidelis-de-Oliveira et al., 2020)
	Antioxidant and chelator	Polyphenols	Leaves	(Ávila et al., 2016a)
	Moderate cytotoxic against SH-SY5Y	Flavonoids, quercetin and catechin	Leaves	(Gasca et al., 2017)
	Antioxidant and anti-glycation	Ferulic and gallic acids, myricetin, quercetin and kaempferol-pentosides	Pulp	(Justino et al., 2020a)
Euphorbia tirucalli	Antimicrobial	Phenolics: myricetin, 3,3'-dimethoxy-4-O-a-rhamnopyranoside-ellagic acid, 4 O-methyl-gallicacid and ampelopsin.	Root	(M. de F. R. de Lima et al., 2021)
	Antioxidant, Anticancer	Steroidal groups: Pregn-4-ene-3,20-dione, 11-Hydroxyl , 9,19-Cyclo-9.beta.-lanostane-3.beta.,25-diol, Lanosterol, Phenolics: Galic, Ferulic, Sinapic, Rutin, Quercetin	Stems	(Abdel-Aty et al., 2019)
	Anticancer	Euphol, and tirucallol, myristic, palmitic, linoleic, oleic and stearic acids,	Stems	(L. S. de Souza et al., 2019)
	Anticancer	Tirucadalenone, Euphorol L	Stems	(Duong et al., 2019)
	Nociceptive, anti inflammatory	Tannin, Lupeol, b-Sitosterol	Root	(Palit et al., 2018)
	Anticancer, immunomodulation and cachexia inhibition	Euphorol	Stems	(Martins et al., 2020)
	immunomodulation	Triterpenes	Leaves	(Ibrahim et al., 2019)
	Anticancer	Euphol	Stems	(V. A. O. Silva et al., 2019)
Eryngium foetidum	Antimicrobial	Alkaloids, flavonoids, phenolics, anthraquinones, steroid	Methanol extract from leaves	(Kouitcheu Mabeku et al., 2016)
	Antioxidant	(E)-2-Dodecenal, 13-tetradecenal, dodecanal, 2,4,5-trimethylbenzaldehyde	Essential oil from roots, stem and leaves	(Thomas et al., 2017)
Hancornia speciosa	Angiogenic, antibacterial, antioxidant	Flavones, flavonols, flavanones, and tannins	Latex fractions	(D'abadia et al., 2020)
	Antioxidant, antimutagenic, enzymatic inhibition (acetylcholinesterase, butyrylcholinesterase, tyrosinase, hyaluronidase, lipase, *α*-amylase, and *α*-glycosidase), antiobesity, antihyperglycemic	Carotenoids and polyunsaturated fatty acids	Ethanolic extract of leaves	(U. P. Dos Santos et al., 2018a)
	Anti-inflammatory	Rutin and chlorogenic acid	Aqueous extract from the fruits	(Bitencourt et al., 2019; Torres-Rêgo et al., 2016a)
	Antihypertisive	Cyclitol bornesitol	Leaves	(Moreira et al., 2019a)

	Antioxidant, antimicrobial, cytotoxic	Quinic acid, chlorogenic acid, catechin, rutin, isoquercitrin, kaempferol-rutinoside, and catechin-pentoside.	ethanolic extract of leaves	(U. P. Santos, Campos, Torquato, Paredes-Gamero, Carollo, Estevinho, De Picoli Souza, et al., 2016)
	Anti-inflammatory, antioxidant	Bornesitol, quinic acid, ascorbic acid, chlorogenic acid, isochlorogenic acid, 3-feruloylquinic acid, rutin, 5-feruloylquinic acid, quercetin-3-*O*-hexoside, kaempferol-rutinoside, kaempferol-hexoside, isorhamnetin-3-*O*-rutinoside, and quercetin	Fruit juice	(de Oliveira Yamashita et al., 2020)
	Antioxidant, *In vitro* gastrointestinal digestion	Protocatechuic acid, *p*-Coumaric acid, Salicylic acid, Syringic acid, *trans*-Cinnamic acid, Gentisic acid, Vanillic acid, Ferulic acid, Elagic acid, Gallic acid, Rutin, Myricetin, Quercetin, Catechin, Hesperetin, Kaempferol	Pulp of fruits	(Dutra et al., 2017a)
Hymenaea cangaceira	Antinociceptive, antioxidant, antimicrobial	Hydrocarbon sesquiterpenes (SH): α-Copaene, β-Elemene, (E)-Caryophyllene, α-Guaiene, α-Humulene, Germacrene D	Essential oil from leaves	(Oliveira de Veras et al., 2020)
Hymenaea stignocarpa	Enzymatic inhibition (α-amylase and α-glucosidase), nutritional quality, glycemic index	caffeic acid, kaempferol, quercetin-3-rutinoside and quercetin-3-rhamnoside	N/D	(C. P. da Silva et al., 2019)
Myrciaria floribunda	Antitumor, antioxidant	Phenolics, flavonoids and tannin	Ethyl acetate extract from the leaves	(de Azevedo et al., 2019; Tietbohl et al., 2017)
	Enzymatic inhibition of acetylcholinesterase	Sesquiterpenes: *δ*-Cadinene, γ-Cadinene, γ-Muurolene, α-Selinene, α-Muurolene (*E*)-Caryophyllene	Essential oil from the fruit peel	(da Silva Barbosa et al., 2020b)
	Antimicrobial, antioxidant	Nor-lupane triterpenoids platanic acid and messagenic I acid; triterpenoids (betulinic aldehyde, ursolic acid acetate, betulinic acid, 2α,6α,30-trihydroxybetulinic acid); flavonoids (catechin, quercetrin and mirycitrin)	Methanol extract from the leaves	(de Azevedo et al., 2019)
Oocotea glomerata	Antifungal	cinnamic acid derivatives and flavonoids	Hydro alcoholic extracts from the leaves	(Anjos et al., 2020)
Psidium guineense	antioxidant, anti-inflammatory, antiproliferative and antimycobacterial	Monoterpenes, oxygenated monoterpene, sesquiterpene, oxygenated sesquiterpene	Essential oil from the leaves	(do Nascimento et al., 2018)
	Antinociceptive and anti-inflammatory	Spathulenol	Essential oil from the leaves	(E. Dos Santos et al., 2020)
Passiflora cincinnata	Atimicrobial	N/D	hydroalcoholic extracts of leaves, stems, bark, pulp and seeds	(Siebra et al., 2018)

	antinociceptive and anti-inflammatory	Flavonoids	Ethanolic extract of the aerial parts	(de Lavor et al., 2018)
	Antioxidant	Phenolics: isoquercetin, caftaric acid and rutin; β-carotene, flavonoids	Pulp	(de Souza Silva et al., 2020)
	Antioxidant	Phenolic compounds, flavonoids	Ethanol extracts of leaves, seeds, steam, flowers, fruit peel	(Leal et al., 2020)
Schinus terebinthifolius	Antioxidant	doxorubicin, polysaccharides α-pinene and α-felandrene, oleic acid, α-felandrene, δ-cadynene, oleic and palmitic.	Fruits and Leaves	(Aumeeruddy-Elalfi et al., 2015; P. D. S. da Rocha et al., 2020a; dos Santos da Rocha et al., 2019b; Feriani et al., 2020a, 2021; M. D. C. L. Lima et al., 2020a; P. dos S. da Rocha et al., 2018a; Salem et al., 2018b; Todirascu-Ciornea et al., 2019)
	Atimicrobial	ácido gálico, galotaninos e flavonóis glicosilados, α-pineno e α-felandreno	Fruits	(P. dos S. da Rocha et al., 2018b; Salem et al., 2018b)
	Antidiabetic Activity	gallic acid, galotanins and glycosylated flavonols	Fruits	(Feriani et al., 2020a)
	Antinociceptiva	Flavonoids	Fruits	(Feriani et al., 2020a)
	Endodontic treatment	Flavonoids	N/D	(Pinto et al., 2020a)
	Anti-inflammatory	Polysaccharides and flavanones	Fruits	(Estevão et al., 2017)
	Angiogenics	α-pinene and α-felandrene	Leaves	(Estevão et al., 2017)
	Keratitis	α-pinene and α-felandrene	Leaves	(M. D. C. L. Lima et al., 2020a)
	Atinviral	Phenolic compounds (resveratrol, catechin and epicatechin)	Peel and fruits	(M. B. S. Oliveira et al., 2020)
Spondias tuberosa	Regulation in lipid metabolism	N/D	Bark	(de Moura Barbosa et al., 2018)
	Antifungal	N/D	Folhas	(Cordeiro et al., 2020)
Syagrus Coronata	Antibacterial and antibiofilm, Antifungal, anti-inflammatory and healing	Fatty acids (octanoic acid, dodecanoic acid, decanoic acid and γ-eudesmol)	Seeds	(Souza dos Santos et al., 2019)
Verbesina macrophylla	Hemolytic, antimicrobial, anti-inflammatory and antipyretic activity	Sesquiterpenos e hidrocarbonetos	Essential oil of the leaves	(de Veras et al., 2021)
Xanthosoma sagittifolium	Significant effects on the intestinal microbiota.	Starch, amylose and milopectin	Fruits	(Graf et al., 2018)

Source: Authors.

Figure 3: Distribution of biological activity study in the select articles.



Source: Authors.

3.1 Chemical composition of plants observed in the Caatinga

Environmental conditions such as soil, climate, and interaction between fauna and flora determine factors for structuring the phytochemical composition of bioactive compounds (Teixeira et al., 2010). The Caatinga domain, when compared to the other biomes found in Brazil, presents as main characteristics the predominance of regions with dry soil between 9 to 10 months of drought, and irregular distribution of rainfall during 2 to 3 months, accumulating in some regions approximately 1.026 mm³ (J. M. C. da Silva & Lacher, 2020). Irregularities in the region's climate favor the development of vegetation adapted to low rainfall, requiring the production of primary and secondary metabolites for the maintenance and survival of the species, changes in the environmental conditions affect directly in the metabolic production of the plant (Jia et al., 2014). The metabolities mainly the secondaries metabolities as phenolics and flavonoids are necessaries for the plant survive, including activities in growth regulation, enzyme inhibition, antioxidant activity and ultraviolet light (UV) (Jia et al., 2014; Räisänen et al., 2008).

Considering what was observed in Table 1, the bioactive obtained from different fractions between roots, leaves, stems, fruits, and residues, are included among the classes of Flavanoids: Agathisflavone (*Anacardium occidentale*), Luteolin (*Arachis hypogaea*), and kaempferol (*Hancornia speciosa)*; Phenolics: Stilbene (*Byrsonima cydoniifolia)* among others, and Terpenes: α-Muurolol (*Eugenia brejoensis*), Zoapatanol (*Anacardium occidentale*) and Bicyclogermacrene (*Campomanesia guazumifolia* and *Croton argyrophyllus*).

The phenolic compounds and flavonoids are the major groups referred to with antioxidant activity in hydrophilic or lipophilic systems, such as cardanol, comprised among the phenolic lipids found in *Anacardium occidentale*, with anti-inflammatory action (Cossetin et al., 2019; Souza Filho et al., 2018a). Under stressful environmental conditions, as observed in the Caatinga, there is a natural increase in the concentration of phenolic compounds as a self-defense mechanism (Sharma et al., 2019). Chemically, phenolic compounds have in their molecular structure a hydroxyl radical (-OH) linked to an aromatic ring (Figure 4). The antioxidant activity of phenolic compounds comprises the structuring of the chemically active molecule; changes in the hydroxyl radical can positively or negatively compromise the antioxidant action of the compound (Regueira et al., 2017; Teixeira et al., 2010). The group of phenolics can be divided into flavonoid compounds (Ex. Anthocyanins) and nonflavonoids (Ex. Stilbenes and Lignins). Both groups are present in the plants cataloged in this study, with specific biological activities, such as antibacterial and anti-inflammatory activity (*Arachis hypogaea*), photoprotection (*Byrsonima cydoniifolia*), hypotensive activity (*Eugenia dysenterica*), and hypoglycemic (*Cnidoscolus quercifolius*) (Eungsuwan et al., 2021a; Fidelis-de-Oliveira et al., 2020; Lira et al., 2017).

Terpenes are the second most observed class in bioactive compounds extracted from the plant fractions presented in this paper. Terpenoid groups are included within the secondary compounds of plant metabolism. Made up of sequences of isoprenes with five carbon units (C5), terpenes are chemically classified as monoterpenes (C10), sesquiterpenes (C15), and diterpenes (C20) according to the number of isoprenes associated with the final molecule (Yang et al., 2016). Terpenes comprise the most abundant secondary metabolites, with approximately more than 36,000 being recognized and acting as a crucial element in the interaction of the plant species with the environment in which it is inserted (Gershenzon & Dudareva, 2007).

Among the activities described were reported the antioxidant, antimicrobial, and antifungal potential of the compound bicyclogermacrene isolated from *Campomanesia guazumifolia* and *Croton argyrophyllus* species. The Spathulenol obtained by extracting the leaves of *Psidium guineense* demonstrates antinociceptive and anti-inflammatory activity, similar to the terpene caryophyllene from *Eugenia brejoensis* leaves.

3.2 Correlation of antioxidant potential and immunomodulatory capacity

Antioxidant compounds are reducing agents with the ability to regulate the concentration of reactive oxygen species (ROS) (e.g., OH ·, NO ·, HOO ·) that are naturally produced by mitochondrial cellular respiratory metabolism or NADPH oxidase (NOX) activity, present in phagocytes and epithelial cells. Under normal physiological conditions, ROS plays an essential role in molecular signaling, cell differentiation, and activation of apoptotic mechanisms in tumor cells (Mittal et al., 2014).

The maintenance of physiological ROS concentrations is performed by organic molecules such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR), glutathione S-transferase (GST), and glutathione (GSH) (Ansari et al., 2020; Fukui & Zhu, 2010; Rhee et al., 2012). The imbalance between these organic molecules and the generation of ROS, marked by an increase in the [antioxidant] / [ROS] ratio, contributes to the deleterious effects of ROS on proteins, lipids, and DNA / RNA molecules, such as the activation of cellular immune response with a pro-inflammatory profile mediated initially by T-helper 1 (Th-1) and Th-17 cells, with activation of macrophages, neutrophils and local release of cytokines and chemokines (Agita & Thaha, 2017). The phagocytic system is an essential source of peroxidases responsible for combating pathogens. Neutrophils comprise significant concentrations of myeloperoxidases (MPO), and their activation in inflammatory conditions contributes to the elevation of ROS (Goulart da Silva et al., 2021a; Souza Filho et al., 2018a; Zhang et al., 2020), increasing the imbalance in the [antioxidant] / [ROS] ratio.

The inflammatory process mediated by ROS initially involves the transcription factor-kappa B / activating protein 1 (NF-kβ), found in connection with the molecule IkBα in the cell cytoplasm. The IkBα / NF-kβ complex inhibits the translocation of NF-kβ from the cytoplasm to the nucleus, thereby controlling the expression of genes encoding cytokines chemokines that act in the inflammatory process (Prasad et al., 2017). Antioxidant therapies have been a step towards the alternative treatment of inflammatory disorders that result in pathologies such as cancer, diabetes, and neurodegenerative diseases (Belcaro et al., 2018; Seyyedebrahimi et al., 2018).

The antioxidant action of phytochemicals can occur by (i) increasing SOD, CAT, GPx, GR, GST, or GSH (ii) as direct reducing agents when interacting with ROS, and (iii) inhibiting Toll-like receptor (TLR). Palitt et al. (2018) demonstrated the action of terpene groups of aqueous extracts of *Euphorbia tirucalli* (Alvelós) in the inhibition of TLR-4 in macrophage cells treated and exposed to lipopolysaccharide (LPS). The endotoxin LPS is recognized by the TLR-4, which presents as one of the intracellular domains TRIF, an inducer of INF-1 gene transcription (Chen et al., 2018). The authors found a decrease in inflammatory markers IL-6, IL-12, TNF-α, and INF-γ cytokines (Palit et al., 2018), proving the involvement of terpene antioxidants in inhibiting the inflammatory pathway. Other studies point to a positive correlation between antioxidant phytochemicals and anti-inflammatory potential in different pathologies, which are better discussed below.

Arachis hypogaea

Peanut (*Arachis hypogaea L.*) is an herbaceous plant belonging to the Fabaceae family and grown worldwide. The genus *Arachis* is native to South America and includes 80 species. More than 50% of the world's production of peanuts is used to make peanut butter and oil, their primary forms of consumption. In addition, it is also ingested in the form of flour and candy (Limmongkon et al., 2018; Treuter et al., 2017). It is a legume with an abundance of nutrients and chemical constituents, such as proteins, carbohydrates, fibers, fats, niacin, folate, thiamine, arachidic acid, flavonoids, magnesium, phosphorus, polyphenols, and bioactive components (Limmongkon et al., 2018; Menis Candela et al., 2020).

Among the selected articles, the analysis of the compounds of the roots, leaves, seed shoots, and byproducts of peanut processing, such as skin and shell, were the study targets. Among the activities identified are antioxidants and anti-inflammatory drugs in a significant way, as well as a display of anti-hemolytic activity, inhibition of prostatic, antibacterial, and anti-adipogenic hyperplasia (Cossetin et al., 2019; Eungsuwan et al., 2021b; Fernandes et al., 2020; Kim et al., 2019a; Limmongkon et al., 2018; J. Peng et al., 2019a; Rossi et al., 2020a).

The industrial manufacturing process is usually done by blanching or roasting the peanuts without the skin of the seeds, where they are destined for animal feed (resulting in about 7.5 × 10 5 tons of shell each year (J. Peng et al., 2019a; Rossi et al., 2020a). However, it is known that these byproducts are sources of phenolic acids, flavonoids, stilbenes, and various procyanidin and proanthocyanidin oligomers, which configures them as bioactive and nutraceutical compounds, mainly due to their properties of elimination against reactive oxygen species (ROS) in biological systems (Bodoira et al., 2017; Larrauri et al., 2016). The general phenolic profiles vary according to the peanut cultivar, germination stage, growing season, and growing conditions storage (Rossi et al., 2020a). Studies have also reported that such biological activities can be enhanced through peanut sprouts (Kim et al., 2019a; Limmongkon et al., 2019).

It has been established that increased ROS production could lead to tissue damage and the mediation of chronic and inflammatory diseases, such as diabetes, cardiovascular diseases, neurodegenerative diseases, and osteoarthritis (Lepetsos et al., 2019; Locatelli et al., 2018). The stilbene compounds, abundantly found in peanuts, belong to a polyphenolic group and are characterized by a 1,2-diphenylethylene-based phytoalexin with trans-resveratrol acting by inhibiting pro-inflammatory mediators, such as prostaglandins, thromboxanes, and leukotrienes (Limmongkon et al., 2018).

Through the germination of the peanut seed, Kim et al. (2019) demonstrated that the aqueous extract and its phytochemicals, the yasaponin Bb, potentiate the differentiation of osteoblasts mediated by bone morphogenetic protein - 2, leading to the expression of factors necessary for bone formation.

In addition to these properties, Peng et al. (2021) found that the anthocyanins in black peanut shells have an anti-adipogenic function, inhibiting lipids' accumulation depending on the concentration used. This function is based on the partial inhibition of digestion enzymes: α-glucosidase, α-amylase, and lipase, by decreasing the digestion of fat and carbohydrate in fatty acids and glucose, acting as a strategy to regulate body weight.

Anacardium occidentale

Comprised in the Anacardiaceae family, *Anacardium occidentale* L. is geographically distributed throughout the Brazilian territory, with high occurrence in the Northeast region (Borges, 2021). According to data from the Brazilian Institute of Geography and Statistics- IBGE (https://sidra.ibge.gov.br/), the fruits, popularly known as cashew, are an important economic source for local agriculture that concentrates approximately 98% of the country's cultivars.

From the cashew processing, four byproducts sources of bioactive compounds can be obtained, i) raw nuts, ii) cashew grains, iii) apple-shaped stems (cashew apples) and the residue after juice extraction, and iv) the cashew nut shell liquid (CNSL) (Braga et al., 2021a). The identification and isolation of phytochemicals from these sources can be therapeutic alternatives for pathologies such as cancer (de Oliveira Silva Ribeiro et al., 2020), periodontitis (Souza Filho et al., 2018b), diarrheal conditions (Omolaso et al., 2020a), neurodegenerative diseases (Junsathian et al., 2018; Velagapudi et al., 2018a) and enzyme inhibitor (Amorim et al., 2018).

The anacardic acid, cardol, cardanol, and methylcardo, mainly isolated from nuts and CNSL, are among the primary compounds with the biological activities mentioned (Braga et al., 2021b; M. Q. de Souza et al., 2018a; Gomes Júnior et al., 2018a; Goulart da Silva et al., 2021b; Luiz Gomes et al., 2018a; M Ashraf & Rathinasamy, 2018a; Omolaso et al., 2020b; Taiwo et al., 2017). Compounds like Gallic acid, Ellagic acid, Shikimic acid, phosphoric acid, and benzoic acid, known for their potential antioxidants, are found preferentially in the leaves and flowers of cashew trees (A. S. Oliveira et al., 2019; J. M. Santos et al., 2019; Sunderam et al., 2019).

The imbalance between natural antioxidant molecules, such as natural antioxidants GSH, CAT, and SOD at the neuronal level, compromises neuronal functionality by accumulating ROS with activation of the local inflammatory response inducing the neurodegenerative process with consequent cell death. The accumulation of ROS is one of the factors involved in the pathophysiology of anxiety, depression, seizures, and aggravation in neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's (PD) (Simpson & Oliver, 2020).

In neuronal cells, anacardic acid has anxiolytic action, via GABA receptor, by increasing the concentration of GSH, SOD, and CAT that result in the inhibition of lipid peroxidation in the hippocampus and frontal cortex, without suppression of the neuromotor response observed in traditional anxiolytics (Gomes Júnior et al., 2018b; Luiz Gomes et al., 2018b). Contrary to anacardic acid, the neuroprotective action, in microglia cells, of the isolate Agastiflavone obtained from the cashew leaves inhibits the elevation of the ROS concentration. It is possible by modulation in the inflammatory process by blocking the NF-kβ pathway, decreasing the expression of the COX-2 genes (81%), iNOS (100%), IL-1β (93%), IL-6 (88%), and TNF-α (88%) (M. Q. de Souza et al., 2018b; Velagapudi et al., 2018b). The 100% inhibition of the iNOS gene activity is confirmed by the reduction in the generation of nitric oxide (NO), an essential molecule in the oxidative stress process and produced by the action of the enzyme nitric oxide synthase expressed by the transcription of iNOS (Abdolahi et al., 2019).

IL-1 β and TNF-α play a central role in the innate immune system, being inducers in the differentiation of monocytic-phagocytic system with increased dendritic cells (DC), macrophages of type M1, activation of neutrophils, and natural clonal cell expansion killer (NK)(Bent et al., 2018). In addition to the immunomodulatory action of phytochemicals in cashews, the compounds contribute to increased SIRT 1 protein in microglial cells. Proteins are weakly expressed in AD inducing oligomerization of Aβ peptides, a ROS-generating phenotype and recognized by the pathophysiological neurotoxicity of the disease (Velagapudi et al., 2018b).

At the tumor level, the mechanism of anticancer action of phytochemicals is still not well understood. However, some hypotheses point to dysregulation in the signaling of proteins involved in the migration, proliferation, maturation, and colonization of tumor cells by activating apoptotic flags (Ex. Caspase-8) to reduce metastasis and tumor mass (Blanco-Vaca et al., 2018). *A. occidentale* compounds demonstrate the antitumor activity by inducing the apoptotic mechanism via caspase-3 activation (Luiz Gomes et al., 2018b) and mitotic block, with depolymerization of the microtubules in the phase of the interphase, compromising the alignment and chromosomal division (Barros et al., 2020; M Ashraf & Rathinasamy, 2018b) that results in the disruption of cell proliferation.

In Hela cells treated with extracts of *A. occidentale*, morphological changes are observed with loss of 40 and 73% of tumor cell viability at concentrations below 0.01% (M Ashraf & Rathinasamy, 2018b). In composite tumor cells derived from Cardonol, it presented activity in IC50 in 0.12 to 42 µg / mL, with more significant action in renal tumor cells (Braga et al., 2021b). According to the American National Cancer Institute, compounds with anticancer activity, in pre-clinical trials, must have an IC50 <30µg / mL to be considered a promising herbal medicine in palliative cancer treatment (Aini et al., 2008).

Eugenia dysenterica

Eugenia dysenterica (Mart.) DC, belonging to the Myrtaceae family, is a tree found in the Atlantic Forest, Cerrado and Caatinga, popularly known as "cagaita" or "cagaiteira"(Cardoso et al., 2011). Compared to other species in the Cerrado, the use of fresh fruit is limited, with losses as it is highly perishable. It is necessary to encourage the use of the fruit in new technological processes for its use (de Sousa et al., 2018).

The fruits and leaves have various bioactive compounds, such as polyphenols, proanthocyanidins, flavonoids, quercetin, and catechins, guaranteeing different biological activities as shown in Table 1. The extracts obtained from the pulp stand out for improving glucose homeostasis with the α–glucosidase enzyme inhibition mechanism (Donado-Pestana et al., 2018a; Justino et al., 2020b), promoting slower absorption of dietary carbohydrates and minimizing glycemic pikes (Dornas et al., 2009).

Studies that evaluate leaf extracts emphasize antioxidant activity, as in work carried out by [56], which aimed to evaluate the neuroprotective potential of the hydroalcoholic extract of *E. dysenterica* leaves, *in vitro* and *in vivo,* and found that the extract could protect the brain against damage induced by oxidation.

Another study, also using the hydroalcoholic extract of the leaves, attested the *in vitro* antioxidant activity capable of reducing reactive oxygen species and the chelating action that prevented damage induced by toxic metals. In the *in vivo* test, animals exposed to chromium and pretreated with the extract showed a reduction in liver and kidney damage and lower concentrations of the metal in these organs and the plasma (Ávila et al., 2016b).

In addition to the activities presented, the essential oil obtained from the leaves of *E. dysenterica* had an anti-inflammatory effect by inhibiting the production of excess nitric oxide within the cell (S. M. M. Da Silva et al., 2019b). Nitric oxide is a fundamental mediator, but when in excess, they form free radicals, such as superoxide, causing peroxynitrite synthesis, a reactive species with great oxidative potential and related to various inflammatory diseases (Eming et al., 2017).

Hancornia speciosa

Popularly known as "magabeira", *Hancornia speciosa* Gomes is a Brazilian native tree belonging to the Apocynaceae family. It is distributed in different Brazilian regions comprising some phytogeographic domains, including the Caatinga. Mangaba fruits can be consumed fresh or processed in jams, sweets, ice cream, juices, syrups, and others. In addition to the fruits, this tree can provide byproducts with pharmacological potential extracted from different parts such as stem and leaves (De Almeida et al., 2016).

The leaf extract composition can vary according to climatic conditions and the form of extraction, but some constituents are familiar, such as carotenoids, polyunsaturated fatty acids, phenolic compounds, and flavonoids (Table 1) which can act as bioactive compounds. Bornesitol, a cyclitol isolated from an ethanolic extract of the *H. speciosa* leaves, was used by Moreira et al. (2019) in normotensive Wistar rats to investigate the ability of this compound to reduce blood pressure.

Results demonstrated that the administration of bornesitol reduced blood arterial pressure in normotensive rats, increased the plasma level of nitrite, and decreased the angiotensin-converting enzyme activity while in the aorta, the cyclitol induced endothelium-dependent dilatation (Moreira et al., 2019b). The results described by the authors corroborate the traditional use of *H. speciosa* to reduce blood pressure, thus demonstrating the antihypertensive potential of this plant.

The ethanolic extract also demonstrated antioxidant activity, which occurred by the scavenging of free radicals, hemolysis inhibition, and lipid peroxidation inhibition in human erythrocytes; it can be explained by the presence of a high concentration of phenolic compounds found in the extract of the leaves, such as rutin, a flavonoid identified as a major compound by the authors (U. P. Dos Santos et al., 2018b; U. P. Santos, et al., 2016). The leaves of *H. speciosa* were considered safe according to microbiological quality parameters, indicating the safety of their use as a pharmacological potential (U. P. Dos Santos et al., 2018a).

A study using the frozen pulps of *H. speciosa* fruits also showed the antioxidant activity by free phenolic compounds and their bioaccessibility after exposure to simulated gastrointestinal conditions. The activity was demonstrated by the high iron reduction capacity, and rutin was the free phenolic compound that demonstrated an increase in their bioaccessible amount after exposure to simulated gastric conditions; rutin is generated from quercetin by breaking the bond with sugar when exposed to acidic conditions, which may justify its increase after simulating gastric conditions (Dutra et al., 2017b).

In addition, the aqueous extract from the fruits of *H. speciosa* presented the rutin and chlorogenic acid as the main secondary metabolites, molecules that can be in part responsible for the anti-inflammatory activity described by the authors. The aqueous extract administered at various concentrations was able to reduce the cell recruitment into the peritoneal cavity of mice and inhibited the production of cytokines; it also was capable of reducing the ear edema, indicating a possible anti-phlogistic effect suggesting their use as an alternative option for treating inflammatory disorders (Torres-Rêgo et al., 2016b).

Schinus terebinthifolius

The red mastic (*Schinus terebinthifolius* Raddi) is a native Brazilian plant with a high association with alternative, socio-cultural and botanical therapies. According to popular knowledge, mastic fractions are applied to the treatment of urinary and respiratory infections, wounds and skin ulcers, tumors, diarrhea and arthritis (P. D. S. da Rocha et al., 2020b), antidiabetic, antinociceptive, and anti-inflammatory (Feriani et al., 2020b), endodontic treatment (Pinto et al., 2020b), angiogenic and keratitis (M. D. C. L. Lima et al., 2020b). The compounds demonstrated high antioxidant activity in vivo and in vitro models, with α-pinene and α-phellandrene being reported with high bioactivity (Salem et al., 2018a).

The methanolic extract of the leaves of *S. terebinthifolius* obtained high concentrations of antioxidant compounds, evaluated by DPPH assay, in an animal model; results point to reducing oxidative stress and inhibiting cardiotoxicity induced by the drug doxorubicin (P. D. S. da Rocha et al., 2020b). In another study, the leaves methanolic extracts inhibited the action of α-glucosidase, an enzyme responsible for the rapid breakdown of polysaccharides in the intestinal wall and consequently its rapid ingestion (dos Santos da Rocha et al., 2019a). The extract also had greater functionality with the reference drug for the treatment of diabetes, metformin, at the concentrations tested in the work; with reduced postprandial glycemia after glucose overload in diabetic mice, decreased liver weight, blood glucose, and reduced serum glycated hemoglobin, aspartate transaminase, and alanine transaminase levels. (dos Santos da Rocha et al., 2019a).

In metabolic conditions such as type 2 diabetes, the levels of natural enzymatic and non-enzymatic antioxidants (vitamin E and C) are reduced, compromising the physiological balance of ROS production antioxidants, significantly increasing biomarkers related to oxidative stress. This state is possibly inhibited by the presence of phenolic groups (Ciocoiu et al., 2009).

Hyperglycemia is a favorable condition for increasing the generation of ROS. The chronic exposure of β cells to a high glucose rate and low content of antioxidant enzymes results in a significant increase in H_2O_2, causing damage to β cells most susceptible to the deleterious effects of ROS, with the involvement of self-oxidation, oxidative phosphorylation, and glycosylation (Rehman & Akash, 2017). In patients with type 1 diabetes, insulin resistance is correlated with TNF-α (Farinha et al., 2018). As previously discussed, TNF-α transcription is regulated by translocating the NF / Kβ from the cytoplasm to the nucleus by accumulating ROS.

4. Final Considerations

This work aimed to survey the biological potential of some species in the Caatinga domain without initially considering a specific biological activity. The results showed a greater propensity to search for antioxidant and anti-inflammatory activity extracts from various materials, such as leaves, fruits, stems, and roots. It is known that innumerable pathological dysfunctions present at the core of the aggravation of diseases and the imbalance in the immunological condition. Many studies point to the correlation of antioxidant actives in the control of pathologies such as diabetes, neurodegenerative diseases, and metabolic disorders, aiming to control the immune response of these diseases by reducing the concentration of ROS and the consequent reduction in the pro-inflammatory stimulus. As noted, the Caatinga biome is a source of antioxidative and functional bioactive capable of regulating biological dysfunctions, being recognized as a potential nutraceutical resource.

In this way, we highlight the importance of defending the Caatinga and encouraging new experimental research to evaluate dosages and duration of use to obtain health benefits and elucidate the knowledge of folk medicine in this uniquely Brazilian biome.

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