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Review

Chemical Composition and Biological Activities of the *Cnidoscolus quercifolis*: A Review

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Abstract: *Cnidoscolus quercifolius*, commonly known as "favela", "faveleira", "urtiga-branca", and "cansanção", is a plant that is native to the Caatinga biome. The species is extremely tolerant to adverse weather conditions and is of great importance for the population of the semi-arid region, as it has uses in afforestation, the recovery of degraded areas, sawmills, fuels, animal feed, and food production. In addition, the species is popularly known for its medicinal uses, and it has been scientifically tested for such purposes. The objective of the research was to compile updated information about the chemical composition, biological activities, and botanical characteristics of the species, in addition to information about its use in folk medicine. It was observed that *C. quercifolius* has a strong usage among people in the Brazilian Caatinga for ophthalmic and other medical conditions, including inflammation in general, scarring, and infections. Studies involving the species have shown its effectiveness as antinociceptive, cytotoxic agent, antioxidant, and insecticide, as also thanks to its anti-inflammatory, hypoglycemic, and repellent characteristics. Other tests have indicated that the vegetable oil from the seed is promising for food consumption. This work demonstrates that further investigations are still necessary to determine the chemical composition and the toxicological characteristics of the species in order to support subsidies for the possible development of new drugs. Such future investigations may include the isolation of its substances, an analysis of its pharmacological activities, and a deepening of the understanding of the mechanisms of action of its various plant products.

Keywords: *Cnidoscolus quercifolius*; faveleira; popular use; phytochemistry; ethnopharmacology; bioactivity

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1. Introduction

Empirical knowledge about the properties of medicinal plants helps in the development of research around the world. Ethnopharmacological studies help in the scientific search for new bioactive compounds and pharmacological properties that have not yet been identified. In Brazil, the vast biodiversity of flora and cultural diversity drive the pharmacological exploration of the country's different biomes [1,2].

The Caatinga, also known as the white forest, is an exclusively Brazilian biome [3] that is considered to be the main ecosystem in the northeastern region, occupying more than 50% of that region's area [4]. Despite being the least explored and the least scientifically known Brazilian biome [5,6], the Caatinga is home to a variety of landscapes, with considerable biodiversity and a biological heritage that includes a significant number of rare and endemic plant species with various uses and strong potential for the development of scientific research [7].

The genus *Cnidoscolus* includes several species, known above all for their health properties, due to the myriad of chemical constituents. The genus includes *C. aconitifolius*, *C. chayamansa* Mc Vaugh, *C. multilobus* (Pax) Johnst., *C. quercifolius* Pohl (synonym *C. phyllacanthus* (Mull. Arg) Pax and Hoffm), *C. urens* (L.) Arthur, *C. infestus* Pax and K. Hoffman, *C. pubescens* Pohl, and *C. souzae* Mc Vaugh. Among the native species of the Caatinga biome, *Cnidoscolus quercifolius* Pohl is one of the most important from the scientific and commercial points of view [6]. It is popularly known as "favela", "faveleira", "urtiga-branca", "cansanção", "mandioca-brava", "favela-de-cachorro", or "favela-de-galinha" [7–11]. *C. quercifolius* is a species that is extremely tolerant to adverse climatic conditions and has great socioeconomic importance for the semi-arid region, as it has several uses in afforestation, the recovery of degraded areas, sawmills, fuels, and human and animal food (goats, cattle, and sheep) [12]. Traditionally, plants belonging to the *Cnidoscolus* genus are often used as fodder for the animals of the Caatinga biome, mainly in periods of low rainfall. In addition, faveleira is commonly used in traditional medicine in the treatment of hemorrhoids, kidney problems, ophthalmic infections, urinary infections, inflammation in general, genitourinary problems (uterus, ovaries, and prostate), and other diseases [13].

Although this species represents good possibilities for the development of the semi-arid region and it is widely used in traditional medicine [6], most of the studies related to faveleira are focused on its use in agriculture and livestock [12]. Accordingly, this species is still largely unexplored, with little literature investigating bioactive compounds and their potential use in biotechnological areas. The enormous diversity and the high quantity of bioactive compounds of this plant, and the challenges in identifying them, probably contribute to this absence of literature, so that even today there is only obscure knowledge of this genus. Among the main activities that have been studied are its usage as an antioxidant [14,15], an antimicrobial agent [8,16], a cytotoxic agent [17], and its hypoglycemic [18], anti-inflammatory [19], and antinociceptive properties [20–22].

This manuscript seeks to critically review the literature regarding the pharmacological properties, ethnobotanical uses, and phytochemical analyses of *C. quercifolius*, with the aim of establishing a basis for further research into the use of the products of this species.

2. Methodology

The research was carried out in the Science Direct, Pubmed, Scielo, Web of Science, PMC, DOAJ, Google Scholar, and Lilacs databases. The consulted platforms covered the literature published between the 2000 and 2023 and considered articles published in English and Portuguese. The data collection period for this research was between June 2022 and June 2023 and the searches were carried out using the following terms. in Portuguese and English: *Cnidoscolus quercifolius*, *Cnidoscolus phyllacanthus*, faveleira, biological activity, and chemical composition. The terms were targeted for titles, abstracts, and keywords, alone or in combination.

The primary search identified 2391 results, with 51 from Science Direct, 13 from PUBMED, 14 from SCIELO, 62 from Web of Science, 38 from PMC, 46 from DOAJ, and 2,159 from Google Scholar. However, among these, some articles were indexed in two or more databases; therefore, they were considered only once.

The selected articles were manually reviewed to identify and exclude works that did not meet the inclusion criteria of the study, which were as follows: the period (the last 23 years); the languages (English and Portuguese); originality; and research that

reported biological assays, chemical composition, or isolation of compounds from the species *C. quercifolius*. The exclusion criteria were as follows: works in which the content was not within the scope of the study, such as research that investigated the combination of *C. quercifolius* with other species; articles that did not report biological assays, composition chemistry, or compound isolation; and unreliable "publications" such as drafts, preprints of submitted papers, duplicate papers, and conference papers. After the initial screening of titles, abstracts, texts, and times of publication, 41 articles were selected; the rest did not meet the inclusion criteria (n = 2110).

3. Botanical Aspects of *Cnidoscolus quercifolius* Pohl

The species *Cnidoscolus quercifolius* Pohl stands out in the Caatinga biome because of its adaptation to adverse climatic conditions and its wide distribution in urban and rural areas of the Brazilian semi-arid region. It can be found in northeastern Brazil in the states of Ceará, Rio Grande do Sul, North, Paraíba, Pernambuco, Sergipe, Alagoas, Piauí, and Bahia, and in the state of Minas Gerais in the southeastern region of Brazil [23].

C. quercifolius (Figures 1 and 2) is a deciduous, heliophytic, fast-growing plant with an elongated, sparse, and irregularly branched canopy. Its flowering and fruiting can occur between the months of January and March [24], and the species can reach 2 to 5 m in height. It is morphologically classified as a tree, although it presents itself as a shrub or a tree, depending on the location and environmental conditions [9,25].

Figure 1. Tree of *C. quercifolius.* Source: Núcleo de Ecologia e Monitoramento Ambiental (Nema) da Universidade Federal do Vale do São Francisco (Univasf). Espécie do mês: Faveleira, 2019.

Figure 2. Inflorescence of *C. quercifolius.* Source: Núcleo de Ecologia e Monitoramento Ambiental (Nema) da Universidade Federal do Vale do São Francisco (Univasf). Espécie do mês: Faveleira, 2019.

One of its most striking characteristics of the species is the presence of aciculiform stinging trichomes that are present in structures such as the branches, petioles, leaf blades, perianths, and fruits. These thorns act as a highly efficient defense mechanism—when in

contact with the skin, they cause allergic reactions such as intense and localized pain that can last for many days [9,26–28]. However, there are less common species, which are the result of natural mutation and which do not have spines in their structure [29,30].

The leaves of *C. quercifolius* have a size ranging from 8 to 16 cm, having a long, thick, lanceolate structure with stems on the blades and spiny endings with small pointed structures on their margins [31]. As a strategy to withstand water restriction, at the end of the rainy season, the leaves mature and fall, appearing again only in the next rainy season, right after the flowers and fruits [31,32]. The inflorescences of the *C. quercifolius* are composed of small white flowers organized in bunches, 4 cm in diameter, being dioecious, with pentamerous petals [31]. Its fruits are dry capsules, dehiscent with urticating hairs, and the dehiscence of the fruit occurs between 56 and 57 days after fertilization, with the explosive opening of the fruit throwing the seeds a distance of more than 30 m away from the mother plant, which facilitates the dissemination of this species in the region [31,32].

The oily seed of the *C. quercifolius* has recognized relevance for the people in the areas where this species is found, as it is the part that is most used for human consumption. It has a grayish-brown color with a streaky appearance; it is ovoid, rigid, and smooth, and has a considerable amount of lipids and proteins [33]. Its length varies from 1.5 to 2.0 cm and its kernel, which corresponds to 56% of its total weight, has a low-intensity yellow color [24,34]. Its roots are tuberous and have an internal viscous liquid; they can reach the deepest layers of the soil, which facilitates the use of rainwater [35]. The food reserves produced in the rainy season are stored in the roots, to be used for subsistence in the dry season [30]. In this way, due to its xerophilic character, the plant is able to grow and reproduce even in periods of prolonged drought [31].

4. Popular Uses of *C. quercifolius*

C. quercifolius is considered to be an ecologically and economically sustainable species [30] that has several forms of use. Due to its adaptation to water stress and high temperatures [23], this species is widely used in the afforestation and reforestation of degraded areas of different soil habitats in the Caatinga [12,25,36,37].

The species has a high economic value as a food source for local populations [23] because, in addition to its oilseeds being consumed in natura or used as ingredients in the preparation of food products (flour, cakes, and breads) [33], the oil extracted from the seeds is edible, having a pleasant taste and odor [29]. In addition, the seeds do not contain toxic proteins [31], and they have high quality and energy value in the production of cooking oil [38].

According to Medeiros et al. [39], the addition of oil from *C. quercifolius* to the diet of goats can increase the nutritional value of milk and of the cheese produced with this milk; therefore, it can be used as a dietary supplement [39]. Faveleira oil is also considered to be a sustainable alternative for the production of biodiesel and biomass [6,40]; however, the technological potential and industrial applications of this seed have not yet been fully explored and understood [15].

In addition to these potential uses, the use of faveleira in popular therapeutic procedures in northeastern Brazil has been reported. The species is commonly used for antimicrobial, expectorant, homeostatic [41], antiseptic, and antitumor purposes, and for the treatment of stomach infections, rheumatism [42,43], hemorrhoids, ophthalmic infections, injuries, fractures, urinary infections, inflammation in general, and genitourinary disorders (uterus, ovaries, and prostate) [13].

Its use is also indicated for toothache [44], ear pain, back pain, dysentery, appendicitis, flu, and cough [45]. The bark poultice is commonly used for healing [46] and the latex produced throughout the entire length of the plant is widely used against dermatoses and warts [45] and for cauterization and wound coagulation [45,47].

It is important to mention that most of the popularly explored therapeutic applications are passed down from generation to generation in different communities, especially in the interior of Brazil, without any scientific validation regarding their pharmacological and

toxicological properties to guarantee safety in the use of these preparations. In this sense, ethnopharmacological studies and literature reviews can help to direct the analyses of these products and, consequently, to make a scientific and social contribution by not only seeking knowledge from within the communities, but also directing the research results to them and to ensure the application appropriate and safe use of these products for the health and wellbeing of the population.

5. Chemical Study of *C. quercifolius*

Analyses of chemical constituents have been shown to be of great importance in identifying the biotechnological potential of several plant species. *C. quercifolius* is still little explored with regard to the characterization, identification, and isolation of its bioactive compounds, as well as their use in biotechnological activities. There have been few reports on these aspects, as shown in Table 1. In the paragraphs that follow, the numbers in parentheses refer to the apex numbers reported for substances in Table 1.

In the extracts of the seeds and the pressed cake, several phenolic compounds were observed, including syringic acid (1), ellagic acid (2), catechin (3), quercetin (4), vanillin (5), eugenol (6), vanillic acid (7), and, especially, gallic acid (8) [46]. Alves et al. [48] investigated the chemical composition of essential oils from various parts of *C. quercifolius* (leaves, flowers and bark) obtained by hydrodistillation and, using GC-MS, identified 31 compounds in the leaves (9–11, 39–66), 30 compounds in the flowers (10, 12, 13, 42, 43, 44, 46, 49, 52, 54, 55, 58, 60, 67–83), and 18 compounds in the stem bark (15, 41, 64, 84–98). The main constituents identified in the essential oil of the leaves were phytol (9) (42.1%), α-terpineol (10) (10.9%), and 11,12-dihydroxyvalencene (11) (7.8%). In the flowers, γ-terpinene (12) (20.5%) and β-pinene (13) (9.6%) stood out. The diterpenes dehydroabietal (14) (29.9%) and abietadiene (15) (21.4%) were already in the peels. Oliveira-Júnior et al. [49] also identified several compounds in leaves (16, 17, 99–126) and stem bark (18–23, 99–103, 105, 106, 108, 112, 115, 116, 118, 119–121, 122, 126–151), including the oxidative stress indicators β-ionone (16) and dihydroactinidiolide (17) and the triterpenes lupeol (18) and diploptene (19). In addition, the authors identified, for the first time in a species of the genus *Cnidoscolus*, the diterpenes sandaracopimaradiene (20), 13-methyl-17-norcaur-15-ene (21), kaur-16-ene (22), and dehydroabiethane (23).

Literature data report the isolation of some chemical constituents for the species. Paredes et al. [50] isolated favelin (24), *O*-methyl favelin (25), deoxofavelin (26), and neofavelanone (27) from the root bark, but they also extracted linamarin (28), *trans*-cinnamic acid (29), a mixture of the steroids β-sitosterol (30) and stigmasterol (31). A mixture of the triterpenes lupeol-3β-*O*-cinnamate (32) and lupeol-3β-*O*-dihydrocinnamate (33) were isolated from the leaves [51] and phylacantone (34) from the stem bark [49].

Paula et al. [52] carried out a phytochemical investigation of the hexanic extract of faveleira stem bark, resulting in the isolation of the compounds 3-β-*O*-nanoyl lupeol (35), a mixture of the triterpenes of 3-β-*O*-cinnamoyl lupeol (37) and 3-β-*O*-dihydrocinnamoyl lupeol (38), lupeol (18), and a mixture of β-sitosterol (30) and stigmasterol (31). In the ethanolic extract, bis-nor-diterpenes deoxofaveline (26) and methyl faveline (36) were isolated.

Other authors also analyzed the chemical composition of various plant parts of this species [18,25,53–55] and identified the presence of several metabolites, including xanthones, steroids, triterpenoids, tannins, coumarins, lignans, monoterpenes/diterpenes, naphthoquinones, flavonoids (flavonols, flavones, catechins, and anthocyanins), and phenolic acids (gallic acid). The presence of anthracene derivatives, anthraquinones, xanthines, and saponins was also observed [11]. In this sense, it can be emphasized that the main representatives of the classes of secondary metabolites found in *C. quercifolius* are flavonoids and terpenes (triterpenes and diterpenes) [17,51]. A compilation of all chemical compounds reported for the species is provided in Table 1, and their respective structural formulas are shown in the Supplementary Materials, Figure S1.

The physicochemical characteristics of the oil from the seeds of *C. quercifolius* were also analyzed in some studies [17,27,33,36,39,54–56]. In a study carried out with 100 Caatinga species belonging to the Euphorbiaceae family, Silva et al. [57] reported that faveleira was the species with the highest oil content (22.6 and 33.5% *w*/*w*). The oil obtained from this species has low acidity, low peroxide index [15,58,59], low moisture [15], good thermo-oxidative stability, and low content of carotenoids, β-carotene and chlorophyll [19]. In addition, it has a yellow color [29] or a green color [58], with a density of 0.9122 ± 0.00 g/cm^3 or 912.20 ± 0.00 kg/m^3, viscosity of 0.0525 ± 0.0001 Pa/s [19], and a high saponification index, with a pleasant flavor and aroma [38].

However, the composition of the faveleira seed can undergo some variations. According to Medeiros et al. [35], during the dry season, there is a reduction in humidity that causes a concentration of nutrients, except for lipids. In addition, the composition of the faveleira seed can also be affected by the presence or absence of thorns. Cavalcanti et al. [29] compared the physicochemical characteristics of the oil from the seeds of *C. quercifolius* and observed some differences in its composition with and without thorns. The seed oil of the thorny variation showed higher values than the seed oil without thorns, in terms of density and viscosity, and lower values in terms of refraction, acidity, and saponification. The iodine and peroxide indices did not show significant differences.

A variety of techniques have been applied for the extraction of faveleira seed oil, including mechanical pressing [35,60], solvent extraction [59], extraction assisted by ultrasound [61], and supercritical carbon dioxide extraction [62]. Santos et al. [30] investigated the existence of differences in the composition of faveleira oil extracted by the conventional Soxhlet method with alternative solvents (ethyl acetate, isopropanol, and ethanol) and by the non-conventional pressurized liquid-extraction method. The results of that study showed that extraction with pressurized ethanol at 10 MPa (40 °C, 60 °C, and 80 °C) showed high oil yields (up to 92% efficiency) with lower solvent consumption (58 g versus ~160 g) and shorter extraction time (19 min versus 360 min); however, there was no significant difference in oil quality compared to the quality obtained by the conventional method.

Table 1. Chemical compounds identified and/or isolated in the species *C. quercifolius*. The numbers reported at the apex of following substances are related to molecule numbers reported in Figure S1.

Substance	Part of the Plant	Identification/Isolation Technique	Type of Extract/Fraction	Ref.
Syringic acid [1]	Seed and press cake	UHPLC-DAD	Acetone/water extract	[51]
Ellagic acid [2]	Seed and press cake	UHPLC-DAD	Acetone/water extract	[51]
Catechin [3]	Seed and press cake	UHPLC-DAD	Acetone/water extract	[51]
Quercetin [4]	Seed and press cake	UHPLC-DAD	Acetone/water extract	[51]
Vanillin [5]	Seed and press cake	UHPLC-DAD	Acetone/water extract	[51]
Eugenol [6]	Seed and press cake	UHPLC-DAD	Acetone/water extract	[51]
Vanillic acid [7]	Seed and press cake	UHPLC-DAD	Acetone/water extract	[51]
Gallic acid [8]	Seed and press cake	UHPLC-DAD	Acetone/water extract	[51]
Phytol [9]	Leaves	GC-MS	Essential oil	[48]
α-Terpineol [10]	Leaves, flowers	GC-MS	Essential oil	[48]
11,12-dihydroxyvalencene [11]	Leaves	GC-MS	Essential oil	[48]
γ-Terpinene [12]	Flowers	GC-MS	Essential oil	[48]
β-Pinene [13]	Flowers	GC-MS	Essential oil	[48]
Dehydroabietal [14]	Stem bark	GC-MS	Essential oil	[48]
Abietadiene [15]	Stem bark	GC-MS	Essential oil	[48]
β-Ionone [16]	Leaves	GC-MS	Hexane fraction	[49]
Dihydroactinidiolide [17]	Leaves	GC-MS	Hexane fraction	[49]

Table 1. *Cont.*

Substance	Part of the Plant	Identification/Isolation Technique	Type of Extract/Fraction	Ref.
Lupeol [18]	Stem bark	GC-MS; CLAE-UV-Vis	Hexane fraction; Hexane:AcOEt fraction	[49,52]
Diploptene [19]	Stem bark	GC-MS	Hexane fraction	[49]
Sandaracopimaradiene [20]	Stem bark	GC-MS	Hexane fraction	[49]
13-methyl-17-norkaur-15-ene [21]	Stem bark	GC-MS	Hexane fraction	[49]
Kaur-16-ene [22]	Stem bark	GC-MS	Hexane fraction	[49]
Dehydroabietano [23]	Stem bark	GC-MS	Hexane fraction	[49]
Faveline [24]	Root bark	HPLC–DAD, 1H- and 13C-NMR	Chloroform fraction	[50]
O-Methyl faveline [25]	Root bark	HPLC–DAD, 1H- and 13C-NMR	Chloroform fraction	[50]
Deoxofaveline [26]	Stem bark, root bark	CLAE- UV-Vis; HPLC–DAD, 1H- and 13C-NMR	Hexane:AcOEt fraction; Chloroform fraction	[50,52]
Neofavelanone [27]	Root bark	HPLC–DAD, 1H- and 13C-NMR	Chloroform fraction	[50]
Linamarin [28]	Leaves	IV, MS and NMR	Ethanolic extract	[63]
trans-cinnamic acid [29]	Leaves	IV, MS and NMR	Ethanolic extract	[63]
β-Sitosterol [30]	Leaves, stem bark	IV, MS and NMR; CLAE- UV-Vis	Hexane:AcOEt fraction	[52,63]
Stigmasterol [31]	Leaves, stem bark	IV, MS and NMR; CLAE- UV-Vis	Ethanolic extract; Hexane:AcOEt fraction	[52,63]
Lupeol-3*β*-*O*-cinnamate [32]	Leaves, stem bark	IV, MS and NMR; GC-MS	Ethanolic extract; Hexano:AcOEt fraction	[49,63]
Lupeol-3*β*-*O*-dihydrocinnamate [33]	Leaves, stem bark	IV, MS and NMR; GC-MS	Ethanolic extract; Hexane fraction	[49,63]
Phyllcanthon [34]	Stem bark	GC-MS	Hexano:AcOEt fraction	[49]
3-*β*-*O*-nanoyl-lupeol [35]	Stem bark	CLAE-UV-Vis	Hexane:CH2Cl2 fraction	[52]
Methyl favelin [36]	Stem bark	CLAE-UV-Vis	Hexane:AcOEt fraction	[52]
3-*β*-*O*-cinnamoyl-lupeol [37]	Stem bark	CLAE-UV-Vis	Hexane:CH2Cl2 fraction	[52]
3-*β*-*O*-dihydrocinnamoyl-lupeol [38]	Stem bark	CLAE-UV-Vis	Hexane:CH2Cl2 fraction	[52]
1,4-cineole [39]	Leaves	GC-MS	Essential oil	[48]
cis-arbusculone [40]	Leaves	GC-MS	Essential oil	[48]
trans-pinene hydrate [41]	Leaves, flowers, stem bark	GC-MS	Essential oil	[48]
Dihydrolinalool [42]	Leaves, flowers	GC-MS	Essential oil	[48]
Menthone [43]	Leaves, flowers	GC-MS	Essential oil	[48]
Tetrahydrolavandulol [44]	Leaves, flowers	GC-MS	Essential oil	[48]
Neo-dihydrocarveol [45]	Leaves	GC-MS	Essential oil	[48]
Shisofuran [46]	Leaves, flowers	GC-MS	Essential oil	[48]
cis-4-caranone [47]	Leaves	GC-MS	Essential oil	[48]
Citronellol [48]	Leaves	GC-MS	Essential oil	[48]
Thymol [49]	Leaves, flowers	GC-MS	Essential oil	[48]
trans-verbenyl acetate [50]	Leaves	GC-MS	Essential oil	[48]
Silfiperfol-4,7(14)-diene [51]	Leaves	GC-MS	Essential oil	[48]
(*Z*)-*β*-Damascone [52]	Leaves, flowers	GC-MS	Essential oil	[48]
α-Funebrene [53]	Leaves	GC-MS	Essential oil	[48]
Sesquithujene [54]	Leaves, flowers	GC-MS	Essential oil	[48]

Table 1. *Cont.*

Substance	Part of the Plant	Identification/Isolation Technique	Type of Extract/Fraction	Ref.
(*E*)-*β*-farnesene [55]	Leaves, flowers	GC-MS	Essential oil	[48]
Methyl-*β*-(*E*)-ionol [56]	Leaves	GC-MS	Essential oil	[48]
(*E*)-*β*-Ionene [57]	Leaves	GC-MS	Essential oil	[48]
Biciclogermacrene [58]	Leaves, flowers	GC-MS	Essential oil	[48]
β-Bisabolene [59]	Leaves	GC-MS	Essential oil	[48]
α-Cadinene [60]	Leaves, flowers	GC-MS	Essential oil	[48]
(*E*)-nerolidol [61]	Leaves	GC-MS	Essential oil	[48]
Curcumenol [62]	Leaves	GC-MS	Essential oil	[48]
Vetivenic acid [63]	Leaves	GC-MS	Essential oil	[48]
Cryptomeridiol [64]	Leaves, stem bark	GC-MS	Essential oil	[48]
β-Vetivone [65]	Leaves	GC-MS	Essential oil	[48]
Isophytol [66]	Leaves	GC-MS	Essential oil	[48]
α-Pinene [67]	Flowers	GC-MS	Essential oil	[48]
Sabinene [68]	Flowers	GC-MS	Essential oil	[48]
Myrcene [69]	Flowers	GC-MS	Essential oil	[48]
Dehydroxy-trans-Linalool oxide [70]	Flowers	GC-MS	Essential oil	[48]
Meta-mentha 1-(7),8-diene [71]	Flowers	GC-MS	Essential oil	[48]
δ-2-Carene [72]	Flowers	GC-MS	Essential oil	[48]
α-Phellandrene [73]	Flowers	GC-MS	Essential oil	[48]
o-Cresol methyl ether [74]	Flowers	GC-MS	Essential oil	[48]
iso-sylvestrene [75]	Flowers	GC-MS	Essential oil	[48]
δ-3-Carene [76]	Flowers	GC-MS	Essential oil	[48]
α-Terpinene [77]	Flowers,	GC-MS	Essential oil	[48]
Limonene [78]	Flowers	GC-MS	Essential oil	[48]
Dihydrolinalool [79]	Flowers	GC-MS	Essential oil	[48]
cis-verbenol [80]	Flowers	GC-MS	Essential oil	[48]
cis-*β*-Terpineol [81]	Flowers	GC-MS	Essential oil	[48]
neo-3-Thujanol [82]	Flowers	GC-MS	Essential oil	[48]
cis-Di-hidro-*β*-terpineol [83]	Flowers	GC-MS	Essential oil	[48]
(8*S*),14-cedranediol [84]	Stem bark	GC-MS	Essential oil	[48]
Isopimara-9(11),15-diene [85]	Stem bark	GC-MS	Essential oil	[48]
Beyerene [86]	Stem bark	GC-MS	Essential oil	[48]
Isohibaene [87]	Stem bark	GC-MS	Essential oil	[48]
Palmitic acid [88]	Stem bark	GC-MS	Essential oil	[48]
Cembrene [89]	Stem bark	GC-MS	Essential oil	[48]
13-*epi*-Dolabadiene [90]	Stem bark	GC-MS	Essential oil	[48]
Polygodial [91]	Stem bark	GC-MS	Essential oil	[48]
Phyllocladene [92]	Stem bark	GC-MS	Essential oil	[48]
Manool [93]	Stem bark	GC-MS	Essential oil	[48]
Linoleic acid [94]	Stem bark	GC-MS	Essential oil	[48]
Oleic acid [95]	Stem bark	GC-MS	Essential oil	[48]
Sandaracopimanal [96]	Stem bark	GC-MS	Essential oil	[48]
Phyllocladanol [97]	Stem bark	GC-MS	Essential oil	[48]
Dehydro-abietal [98]	Stem bark	GC-MS	Essential oil	[48]

Table 1. *Cont.*

Substance	Part of the Plant	Identification/Isolation Technique	Type of Extract/Fraction	Ref.
Tetradecane [99]	Leaves, stem bark	GC-MS	Hexane fraction	[49]
Pentadecane [100]	Leaves, stem bark	GC-MS	Hexane fraction	[49]
3-methylpentadecane [101]	Leaves, stem bark	GC-MS	Hexane fraction	[49]
Hexadecane [102]	Leaves, stem bark	GC-MS	Hexane fraction	[49]
2,6,10-trimethyl-pentadecane [103]	Leaves, stem bark	GC-MS	Hexane fraction	[49]
1-cyclohexyl decane [104]	Leaves	GC-MS	Hexane fraction	[49]
Heptadecane [105]	Leaves, stem bark	GC-MS	Hexane fraction	[49]
2,6,10,14-tetramethylpentadecane [106]	Leaves, stem bark	GC-MS	Hexane fraction	[49]
4-ethylheptadecane [107]	Leaves	GC-MS	Hexane fraction	[49]
3-methylheptadecane [108]	Leaves, stem bark	GC-MS	Hexane fraction	[49]
2,6,10,14-tetramethylhexadecane [109]	Leaves	GC-MS	Hexane fraction	[49]
4-cyclohexyl-tridecane [110]	Leaves	GC-MS	Hexane fraction	[49]
Hexadecane-1-ol [111]	Leaves	GC-MS	Hexane fraction	[49]
Nonadecan [112]	Leaves, stem bark	GC-MS	Hexane fraction	[49]
Octasane [113]	Leaves	GC-MS	Hexane fraction	[49]
3-methyl-nonadecane [114]	Leaves	GC-MS	Hexane fraction	[49]
1-tricosene [115]	Leaves, stem bark	GC-MS	Hexane fraction	[49]
Eicosane [116]	Leaves, stem bark	GC-MS	Hexane fraction	[49]
Octadecan-1-ol [117]	Leaves	GC-MS	Hexane fraction	[49]
Heneicosan [118]	Leaves, stem bark	GC-MS	Hexane fraction	[49]
Docosan [119]	Leaves, stem bark	GC-MS	Hexane fraction	[49]
Pentacosan [120]	Leaves, stem bark	GC-MS	Hexane fraction	[49]
Nonacosane [121]	Leaves	GC-MS	Hexane fraction	[49]
Hexacosane [122]	Leaves, stem bark	GC-MS	Hexane fraction	[49]
Heptacosan-1-ol [123]	Leaves	GC-MS	Hexane fraction	[49]
Tetracontane [124]	Leaves	GC-MS	Hexane fraction	[49]
Tetratetracontane [125]	Leaves	GC-MS	Hexane fraction	[49]
Squalene [126]	Leaves, stem bark	GC-MS	Hexane fraction	[49]
1-tridecene [127]	Stem bark	GC-MS	Hexane fraction	[49]
2,3,7-trimethyl-decane [128]	Stem bark	GC-MS	Hexane fraction	[49]
2-methyl-tetradecane [129]	Stem bark	GC-MS	Hexane fraction	[49]
3-methyl-tetradecane [130]	Stem bark	GC-MS	Hexane fraction	[49]
2-methylhexadecane-1-ol [131]	Stem bark	GC-MS	Hexane fraction	[49]
5-methylpentadecane [132]	Stem bark	GC-MS	Hexane fraction	[49]
2-methylpentadecane [133]	Stem bark	GC-MS	Hexane fraction	[49]
3-methylpentadecane [134]	Stem bark	GC-MS	Hexane fraction	[49]
3- hexadecene [135]	Stem bark	GC-MS	Hexane fraction	[49]
1-hexadecene [136]	Stem bark	GC-MS	Hexane fraction	[49]
3-hexyl-1,1,2-trimethyl-cyclobutane [137]	Stem bark	GC-MS	Hexane fraction	[49]
1-decyl-cyclopentane [138]	Stem bark	GC-MS	Hexane fraction	[49]
2-methylhexadecane [139]	Stem bark	GC-MS	Hexane fraction	[49]

Table 1. *Cont.*

Substance	Part of the Plant	Identification/Isolation Technique	Type of Extract/Fraction	Ref.
2-methylheptadecane [140]	Stem bark	GC-MS	Hexane fraction	[49]
2-phenyldodecane [141]	Stem bark	GC-MS	Hexane fraction	[49]
7-methylhexadecane [142]	Stem bark	GC-MS	Hexane fraction	[49]
1-octadecene [143]	Stem bark	GC-MS	Hexane fraction	[49]
Octadecane [144]	Stem bark	GC-MS	Hexane fraction	[49]
2-methyl-eicosane [145]	Stem bark	GC-MS	Hexane fraction	[49]
1-nonadecene [146]	Stem bark	GC-MS	Hexane fraction	[49]
Heneicosan-1-ol [147]	Stem bark	GC-MS	Hexane fraction	[49]
7-hexil-eicosano [148]	Stem bark	GC-MS	Hexane fraction	[49]
7-hexyl-docosane [149]	Stem bark	GC-MS	Hexane fraction	[49]
Heptacosan-1-ol [150]	Stem bark	GC-MS	Hexane fraction	[49]
Tetracontane [151]	Stem bark	GC-MS	Hexane fraction	[49]

UHPLC—ultra-high performance liquid chromatography; GC—gas chromatography; MS—mass spectrometry; UV-Vis—ultraviolet-visible; HPLC—high performance liquid chromatography; DAD—diode array detection; 1H- and 13C-NMR—1H and 13C nuclear magnetic resonance spectroscopy; IV—infra-red.

Regarding the lipid profile of this seed oil, some authors have claimed that *C. quercifolius* has a large amount of unsaturated fatty acids, especially polyunsaturated ones, and that the predominant fatty acid is linoleic acid, followed by oleic acid [15,34,57]. Although it is necessary to carry out a more detailed bioprospecting of the compounds present in the chemical constitution, it is possible to state that the seed oil of *C. quercifolius* has several physicochemical characteristics that make it suitable for use as an edible oil [40].

6. Biological Activities of *C. quercifolius*

6.1. Antinociceptive and Anti-Inflammatory Activities

The study by Ribeiro et al. [19] investigated the anti-inflammatory capacity of *C. quercifolius* seed oil. At a concentration of 500 mg/kg, the oil inhibited paw edema better than indomethacin (20 mg/kg); moreover, the oral administration of the oil significantly reduced the sensation of pain in mice, demonstrating its antinociceptive potential. It was also observed that the oil significantly reduced the pro-inflammatory mediator TNF-α in the plasma of mice.

The authors indicated that quercetin, found in the oil, may be related to anti-inflammatory properties, in view of its already established action in inhibiting the metabolism of arachidonic acid and in the production of eucosanoids, which are important inflammatory mediators.

Some other in vivo methods using models of peritonitis and myeloperoxidase, can help to verify the extent of the anti-inflammatory potential of the oil, In addition, the determination and quantification of cytokines and mediators can help to direct the inhibition pathways and elucidate the oil's mechanisms of action.

It was established by Gomes et al. [20] that the ethanolic extract of the bark and leaves of *C. quercifolius* has an antinociceptive capacity, using established models such as writhing induced by acetic acid, hot plate testing, and formalin testing. In all trials, an effect was observed when using doses that ranged from 100 to 400 mg/kg.

According to Ribeiro et al. [19], the extract could inhibit the production of prostaglandins, which is an important mediator of nociceptive processes. The tests also demonstrated that the extract possibly acts at a central level of pain control, possibly by interacting with opioid receptors. In this sense, the verification of these hypotheses and the elucidation of the antinociceptive mechanisms of the extract can be carried out using tests with opioid receptor antagonists and through the quantification of inflammatory mediators.

6.2. Cytostatic Activity

An investigation into the antiproliferative activity of four species of *Cnidoscolus* referenced in ethnopharmacological surveys in the Caatinga was carried out by Peixoto-Sobrinho et al. [64]. *C. quercifolius* was among the four species that wee studied. The authors found that faveleira bark extract was active against HT-29 (human colon adenocarcinoma) and Hep-2 (human laryngeal squamous cell carcinoma) strains. Paredes et al. [50] evaluated the cytotoxic activity of five extract fractions of the root bark of *C. quercifolius* (hexane, chloroform, ethyl acetate, methanol, and water) against several cell lines. Among the tested extracts, only the chloroform fraction showed good cytotoxic activity against different cancer cell lines—colon carcinoma (HCT-116), ovarian carcinoma (OVCAR-8), and human glioblastoma (SF-295). Better results were achieved for the cell lines HCT-116 and OVCAR-8. These findings were in agreement with the study by Alves et al. [45], who also found that *C. quercifolius* has cytostatic activity against tumor cells.

Furthermore, Oliveira-Júnior et al. [17] reported that the ethyl acetate fraction obtained from the leaves of *C. quercifolius* demonstrated strong cytotoxicity against prostate cancer cell lines (PC3 and PC3-M) and breast cancer (MCF-7), presenting IC_{50} values between 15.75 and 46.97 μg/mL. It was also observed that the ethyl acetate fraction had the highest flavonoid content; according to the authors, these compounds may be related to the cytotoxic activity of the species.

It was found in other studies that compounds isolated from parts of this plant also have this biological activity. The anti-melanoma potential of a terpenoid filacantone (34) obtained from *C. quercifolius* was investigated by Oliveira-Júnior et al. [65] and showed promising cytotoxic activity (IC_{50} 40.9 μM) against chemoresistant human melanoma cells. The antiproliferative activity of linamarin (28) and lupeol derivatives (lupeol-3*β*-*O*-cinnamate (32) and lupeol-3*β*-*O*-dihydrocinnamate (33)) were evaluated in human tumor cells; however, the compounds did not show significant inhibition of cell growth when compared to the antitumor used as a control (doxorubicin) [63,66].

Other compounds isolated from faveleira stem bark, such as deoxofaveline (26), 3-*β*-*O*-nanoyl-lupeol (35), 3-*β*-*O*-cinnamoyl-lupeol (37), the *β*-sitosterol mixture (30), and 3-*β*-*O*-dihydrocinnamoyl-lupeol (38) were also evaluated for their cytotoxic potential against tumor cell lines HL60 (promyelocytic leukemia), MCF-7 (breast carcinoma), and NCIH292 (lung cancer). It was observed in that study that the compound deoxofaveline was considered the most active, with IC_{50} values ranging from 2.7 to 8.9 μg/mL. Faveline methyl was selective for leukemia cells (IC_{50} 1.6μg/mL), showing weak activity in other cells [63].

Some authors indicated that the antiproliferative activity of *C. quercifolius* can be attributed to the presence of cytotoxic substances identified in the species, such as faveline methyl ether, deoxofaveline, favelanone, and neofavelanone, as well as the terpenoids filacantone, 3*β*-*O*-cinamoyl -lupeol, and 3*β*-*O*-dihydrocinnamoyl-lupeol. The results of these studies showed that the species has very promising activity for the treatment of neoplastic conditions and may guide the discovery of bioactive compounds for the development of new anti-cancer drugs. However, more specific investigations are needed to determine the mechanism of action of the extracts and their isolated substances.

6.3. Hypoglycemic Effect

C. quercifolius also seems to be promising for the development of new drugs in the treatment of diabetes. It was demonstrated by Lira et al. [54] that the aqueous extract of the leaves of *C. quercifolius* at a dose of 200 mg/kg of body weight has a hypoglycemic effect in diabetic mice, without the presence of oral toxicity. Brito et al. [67], when analyzing the hypoglycemic effect of the aqueous and methanolic extracts of the leaves of *C. quercifolius* in the treatment of diabetic mice, observed that after 30 days all the mice that were treated with the extracts presented a higher percentage of decrease in glycemia than the mice who were treated with metformin (28.67%) at a dose of 200 mg/kg. The percentage of reduction of the aqueous extract was 42.77% and the percentage of reduction of the methanolic extract was 40.25%. This activity was attributed to the presence of gallic acid in both extracts, identified

by HPLC. This phenolic compound had already established hypoglycemic activity, by reducing insulin resistance [67].

Study by Moura et al. [8], showed that a protein isolated from the seed of *C. quercifolius* called Cq-IMP (*Cnidoscolus quercifolius*—insulin mimetic protein) has cross-reactivity of the anti-insulin antibody with hypoglycemic potential. This is considered to be an insulin mimetic protein with potent hypoglycemic activity. Moreover, it was able to reduce glycemia in vitro, using the glucose-responsive cell line RIN-5f. Protein toxicity was also evaluated and, according to the authors, Cq-IMP did not show cytotoxicity even at the highest concentration tested (1 mg/mL). The authors also showed that the protein has primary structural characteristics similar to those of sucrose-binding proteins, requiring further investigation to assess the mechanisms involved in the activity.

6.4. Antimicrobial Activity

Through the minimum inhibitory concentration (MIC) and the minimum bactericidal concentration (MBC), Oliveira-Junior et al. [6] verified that three terpenoids (lupeol-3β-*O*-cinnamate (32), lupeol-3β-*O*-dihydrocinnamate (33), and filacantone (34)) isolated from the stem bark of *C. quercifolius* showed significant antibacterial action—especially filacantone (0.25 mg/mL^{-1}), which was considered to be more effective than the standard drug (gentamicin) (0.40 mg/mL^{-1}) against *Enterococcus faecalis* and *E.coli*. The hexanic and methanolic extracts, on the other hand, showed low antibacterial capacity compared to the isolated compounds, both in MIC (5.0 mg/mL^{-1}, both extracts) and in MBC (>10 mg/mL^{-1}, both extracts). Carvalho et al. [68] investigated the hydroalcoholic extract of leaves against 18 bacteria isolated from the teats of goat; however, among the strains analyzed, the extract was effective only on *Staphylococcus* sp. negative coagulase.

The methanolic extract of the bark and the leaves was evaluated by Sobrinho et al. [9], and only the bark extract showed antibacterial activity. It was active against strains of *Staphylococcus aureus*, with MIC between 250 and 500 µg/mL. Its dichloromethane fraction was the most active among the tested samples, with MIC values ranging from 62.5 to 250 µg/mL. Fernandes et al. [51] carried out antimicrobial activity tests with the ethanolic extract of the leaves and with compounds obtained from the extract (linamarin, trans-cinnamic acid, a mixture of two steroids, and a mixture of triterpenes) and observed that linamarin acted as a moderate inhibitor of strains of *E.coli* but was a weak inhibitor of *S. aureus* and *P. aeruginosa*. Thus, the authors stated that the antimicrobial potential of *C. quercifolius* may be partially related to these compounds.

Methanolic extracts of the leaves, roots, and root bark of *C. quercifolius* were evaluated using Gram-positive and Gram-negative bacteria and fungi. Extracts from the leaves and root bark showed similar activity, inhibiting the growth of *Enterococcus faecium*, *E. faecalis*, *Staphylococcus epidermidis*, and *Pseudomonas aeruginosa*, while the extract from the roots inhibited only the *S. epidermidis* strain. According to the authors, the methanolic extracts of *C. quercifolius* showed better inhibition against Gram-positive bacterial strains, as none of the extracts tested managed to inhibit the growth of *E. coli* and *Klebsiella pneumoniae*. Regarding the inhibition of fungal growth, it was observed that the leaf extract showed inhibition against *Lasiodiplodia theobromae* LF11, *L. theobromae* LF124, and *Colletotrichum gloeosporioides* LF50, while root and root bark extracts showed inhibition only against *Colletotrichum gloeosporioides* LF50.

Other authors who investigated the antimicrobial activity of extracts or oils from *C. quercifolius* did not obtain the same results. According to de Souza Eller et al. [69], the crude hydroalcoholic extract of faveleira bark did not show antimicrobial activity, nor did the ethanolic extract of the leaves [43]. Furthermore, Ribeiro et al. [19] found that the seed of *C. quercifolius* does not have antimicrobial activity, as it is not able to inhibit the growth of *S. aureus*, *Listeria monocytogenes*, *Bacillus cereus*, *E. faecalis*, *P. aeroginosa*, *Enterobacter cloacae*, *E. coli*, *Salmonella typhimurium*, or *Enterobacter aerogenescultures*.

These studies suggested that *C. quercifolius* can be considered a source of new antibacterial agents; however, further investigations against different microorganisms and drugs

are necessary, as well as other more specific methods of analysis aimed at determining the effectiveness of this species and identifying its mechanism of action in bacterial inhibition.

6.5. Antioxidant Potential

The antioxidant potential of *C. quercifolius* seeds was investigated in some studies [19,28,32,58,59]. The methanolic extract of the leaves, roots, and root bark was evaluated. The root bark extract showed the best antioxidant results, with an IC_{50} of 21.56 ± 0.71 g·mL^{-1}, followed by the extract from the leaf (IC_{50} 133.30 ± 0.73 g·mL^{-1}) and the extract from the root (IC_{50} 171.82 ± 0.69 g·mL^{-1}) [10].

Ribeiro et al. [19] stated that the seed oil, its fractions, and the *C. quercifolius* press cake have antioxidant activity, with the press cake presenting higher potential in the test of ferric reducing antioxidant power (FRAP) (p = 0.0000008), oxygen radical absorbance capacity (ORAC) (p = 0.0015), free radical scavenging DPPH• (p = 0.0011), and total antioxidant activity (p = 0.0023). The antioxidant activity was evaluated using the phosphomolybdenum method. When analyzing the antioxidant activity of seed and pressed cake extracts, Ribeiro et al. [46] also observed similar behavior. The percentage of DPPH• inhibition in the seed and press cake extract was 81.53 ± 1.80% and 96.63 ± 1.62%, respectively.

According to the authors, the greater inhibition found in the pressed cake may have been related to the lower lipid content of the press cake, which was capable of interfering with the analysis of antioxidant activity. Although interferences may occur, chemical investigation using GC/MS or LC/MS is necessary in order to elucidate which compounds are present in these extracts. In general, hexane extracts are rich in fatty materials and are generally cited as important interferences in the most diverse types of analyses. However, depending on the method applied and the type of compound present in the extract, it is possible that some of these have activity.

This condition was observed in studies by Morais et al. [55], who investigated the antioxidant action of leaves, branches, and roots extracted in hexane, ethanol, and water using the free radical scavenging method, DPPH•. The extracts showed relatively low antioxidant capacity, with a significant potential identified only in the hexane extract of the leaves (IC_{50} of 58.3 ppm).

In most studies, phenolic compounds such asflavonoids were identified as responsible for antioxidant action of *C. quercifolius*, [39,46]. Torres et al. **[60]** suggested that higher antioxidant activity occurs when conditions that favor the extraction of the flavonoid rutin are employed, indicating that this may be partly related to the antioxidant potential of the species.

Naturally, this factor is not an absolute rule. For example, the ethanolic extract of stem bark has been investigated for its antioxidant potential by Nunes et al. [70], using the free radical scavenging methods DPPH• (radical 1,1-diphenyl-2-picrylhydrazil) and $ABTS^{+}$ (radical 2,2'azinobis-(3-ethylbenzthiazoline-6-sulfonic acid)). This extract showed no detectable antioxidant activity, such as the ethanolic extract of the leaves [19] and the methanolic extract of the bark and leaves [26]. It is important to emphasize that, generally, a higher content of phenolic compounds and flavonoids is found in these types of extracts.

Despite these results, several classes of compounds can exert antioxidant activity, and it is essential to verify different methods that evaluate other types of mechanisms. It can be seen that most of the mentioned studies analyzed their products through free radical scavenging assays; however, other methods, such as deoxyribose protection assays and β-carotene/linoleic acid co-oxidation, can verify the real extent of the antioxidant potential of these products and all their mechanisms of action.

6.6. Insecticidal and Repellent Potential

The insecticidal potential of the seed oil and crude extract of the bark of *C. quercifolius* on the pupae and larvae (late L3 and early L4 stages) of *Aedes aegypti* was investigated by Candido et al. [20]. The authors observed that the studied concentrations were not toxic for the L3 larvae; however, they were lethal for the pupae of this vector, demonstrating that

the insecticide potential of *C. quercifolius* may vary according to the period of development of this insect's life cycle. In addition, it was verified that there was similarity between the pupal mortality of the extract and the oil after 24 h. The authors also verified that the seed oil has a repellent action against the oviposition of *A. aegypti* [71] and that the bark extract has an insecticide action, showing efficacy in the control of *Neoleucinodes elegantalis* and *Bemisia* sp. in tomato cultivation [64].

Despite promising results in controlling pests and vectors, the application of these products as natural insecticides requires further evaluation, considering two main factors. The first factor concerns the efficiency of these products, because establishing their active components and their concentration is essential for the proper use of a product that requires constant application. The second factor is related to the inhibition mechanism of the product, especially when it comes to a complex mixture of substances that act synergistically and can cause unwanted effects. Some mechanisms are already established and can be explored in terms of investigations in this direction, either by inhibiting the process of nutrition, development, or reproduction, or by acting directly on specific targets [72]. It is essential to establish its mode of action in order to guarantee effectiveness and safety in the use of these products.

6.7. Hepatoprotective Activity

Hepatoprotective and antioxidant activity in D-galactosamine-induced hepatitis in rats was investigated by Kolli et al. [73]. Using doses of 200 and 400 mg/kg of ethanolic extract of *C. phyllacanthus* (syn. *C. quercifolius* Pohl) leaves, the authors found that the treatment at both doses had a hepatoprotective effect against liver damage, reducing the amount of enzymes and serum markers of liver damage. Such treatments also demonstrated antioxidant activity, with the dose of 400 mg/kg/body weight proving to be more promising and presenting results similar to those with the standard medication (Vitamin-E).

A similar study was carried out by Sharma et al. [74], in which it was observed that the ethanolic extract of the leaves at dosages of 200 mg/kg and 400 mg/kg attenuated the increase in the serum levels of liver enzymes. The reduction of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) to normal values indicated that the repair of damaged tissues had occurred. In addition, the histopathological study showed liver repair, demonstrating that the extract has a hepatoprotective effect.

In these studies, the authors suggested that the ethanolic extract of the leaves of *C. quercifolius* acts by preserving the structural integrity of the hepatocyte membrane and, possibly, in regenerating the cell parenchyma; however, histological analyses and a deeper biochemical evaluation are necessary in order to determine how this process occurs. It was also demonstrated that the ability to eliminate free radicals is directly related to the hepatoprotection presented by the extract, which proved to be capable of helping to maintain the function of enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, which are fundamental in the antioxidant defense system.

6.8. Toxicity

In some regions, during periodic droughts, farmers use *C. quercifolius* to feed their animals. However, in a study carried out by Oliveira et al. [24], intoxication in goats due to the ingestion of leaves of *C. phyllacanthus* was reported. Toxicity was caused in proportion to the amount of leaves consumed and their degree of maturation. High doses of the fresh plant caused more intense signs of intoxication, even leading to the death of some animals. According to the authors, this intoxication was caused by the presence of compounds that contain hydrocyanic acid (HCN) in their structures.

The toxicity of the methanolic extract of leaves, roots, and root bark was evaluated by testing against *Artemia* sp. [10]. The results revealed that the leaf extracts (LC_{50} = 1079.78 g·mL^{-1}) and the root bark extracts (LC_{50} = 341.45 g·mL^{-1}) showed low toxicity, while the root extracts showed significant toxicity with LC_{50} = 84.76 g·mL^{-1} [10]. The hydroalcoholic extract of the

barks was also evaluated in rodents and presented relatively low acute oral toxicity, with an LD_{50} greater than 2 g/kg [69].

The first study on the toxicity of faveleira seed oil in vitro and in vivo was carried out by Ribeiro et al. [59]. According to the authors, the oil does not have cytotoxic potential against non-tumor cells at a maximum concentration of 5000 µg/mL. Furthermore, in the acute oral toxicity test, no deaths or behavioral changes that would indicate toxicity were observed in any of the mice treated with doses ranging from 10 to 5000 mg/kg. However, further research is needed to analyze the toxicity of the species.

Most of the studies presented in this section bring important toxicological analyses to ensure the adequate evolution of research, through effective and safe concentrations and doses, especially in in vivo studies. It is important to mention that different methods can be applied to investigate the toxicity of natural products. Recently, our research group has been working with models using zebrafish [75], as an alternative with high reproducibility and good efficacy in the analyses.

7. Conclusions

C. quercifoliusis is a species of high value for the populations of the semi-arid region, mainly because of its therapeutic uses in the treatment of diseases and its potential use as a source of food. However, despite being traditionally used in several communities in northeastern Brazil, few of its properties have been scientifically evaluated and determined by pharmacological studies. In addition, there are few studies that address the potential of faveleira for human consumption. Therefore, it is necessary to deepen the scientific investigations involving the chemical composition, biological properties, and nutritional effects of the species, and to isolate and characterize the substances responsible for the claimed effects of the species. Such studies are extremely important, not only in proving the efficacy and promoting the safe use of this species, but also to elucidate its various bioactivities and to support subsidies for the development of new drugs with therapeutic properties.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/pr11072203/s1, Figure S1: Structural formulas of chemical compounds identified and/or isolated in the species *C. quercifolius*.

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