Review

Traditional Uses, Phytochemistry and Pharmacological Activities of Annonaceae

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Abstract: In 1789, the Annonaceae family was catalogued by de Jussieu. It encompasses tropical and subtropical plants which are widespread in distribution across various continents such as Asia, South and Central America, Australia and Africa. The genus of Annona is one of 120 genera of the Annonaceae family and contains more than 119 species of trees and shrubs. Most species are found in tropical America, where over 105 species have been identified. Due to its edible fruits and medicinal properties, Annona is the most studied genus of Annonaceae family. To date, only a limited number of these species have economic value, including A. squamosa L. (sugar apple), A. cherimola Mill. (Cherimoya), A. muricata L. (guanabana or soursop), A. atemoya Mabb. (atemoya), a hybrid between A. cherimola and A. squamosa, A. reticulata L. (custard apple), A. glabra L. (pond-apple) and A. macrophyllata Donn. Sm. (ilama). Phytochemically, several classes of secondary metabolites, including acetogenins, essential oils, alkaloids, terpenoids and flavonoids. The pharmacological activities of Annona species leaves and seeds include antibacterial, anticancer, antidiabetic and anti-inflammatory properties.

Keywords: Annonaceae; Annona; custard apple; phytochemistry; bioactivity; ethnomedicinal pharmacological activity

1. Introduction

In 1789, the Annonaceae family was catalogued by de Jussieu [1,2]. It encompasses tropical and subtropical plants, which are widespread in distribution across various continents such as Asia, South and Central America, Australia and Africa [3]. It is one of the largest Magnoliidae families and the number of its genera and species is still debated [4–6]. Bailey and Popenoe believe that it has between 40 and 50 genera and from 500 to 600 species [6]; however, many studies have indicated that the Annonaceae family is comprised of more than 2400 species distributed in approximately 120 genera [4,5]. The family of Annonaceae involves trees, lianas and bushes arranged in four large subfamilies: Malmeoideae, Annonoideae, Ambavioideae and Anaxagoreoideae [7,8]. Economically, species of Annonaceae are important as a source of edible fruits, for instance, the pawpaw (Asimina), custard apple, sweetsop, soursop and cherimoya [1]. It has also been reported that some oils from the seeds might be used for the production of edible oils and as an ingredient in soaps, and the woods of some species have been reported for alcohol production [3]. Chemical studies of Annonaceae species have reported the isolation of a wide diversity of phytochemical components, including acetogenins, alkaloids and flavonoids from the bark, fruits, leaves, seeds and pulp of Annonaceae [9]. This review aims to provide a comprehensive summary of the botanical features, phytochemistry, pharmacological properties, and the traditional and ethnomedicinal uses of the Annonaceae family and, specifically, Annona species.
2. Botanical Features of Annonaceae Species

2.1. Distribution and Classification

Annonaceae has been listed as a diverse family of aromatic trees, bushes or shrubs, and climbers or lianas, which are predominantly found in the tropical and subtropical regions, with a limited number growing in temperate zones [1,10]. In tropical America, the Annonaceae species are usually shrubby and most grow in open grasslands [1]. In contrast, species that are climbers mostly grow in the tropical area of the old world [1]. In temperate zones like North America, the only genus reported is Asimina [1,3]. In Brazil, more than 385 species have been reported, with the majority of them reported in the Amazonian region [2]. According to the Takhtajan system of flowering plant classification, the majority of Annonaceae plants can be found in both Asia and Australasia with approximately 51 genera and more than 950 species, while 40 genera with approximately 450 species are confined to Africa and Madagascar, and about 38 genera and 740 species are native to the American continent [3]. The first classification of the Annonaceae family was described by Dunal in 1817 and was limited to only fruit morphology [11]. Subsequently, a new classification of the Annonaceae family based on flower characteristics was introduced by Diels and Alder in 1932 [11]. However, a later classification by Fries in 1959 was found to be more comprehensive and authentic, using a combination of fruit morphology and flora characteristics [11]. The Annonaceae family are characterised by the presence of a variety of primitive and archaic features, leading to them being described by Darwin as “living fossil” due to their ability to survive the mass extinction [1,11]. Under the Takhtajan system, the Annonaceae family is related to Magnoliaceae, which is one of the largest families of Magnoliiales with other families such as Degeneriaceae, Canellaceae, Himantandraceae and Myristicaceae [1,11].

2.2. Diagnostic Features

From one species to another, the botanical features of Annonaceae families vary greatly based on their origin, geography, and climate. Based on morphology and habitat, the Annonaceae family is known among the homogeneous plant families [1,4]. The aromatic flowers are commonly open before other parts are entirely developed. The flowers are terminal, axillary, hermaphrodite, singular or grouped and regular [1,11]. The stamens are typically abundant, spirally arranged and hypogenous [1,11]. The leaves are characterised by having a glaucous or metallic sheen, and they are alternate, exstipulate and regular [1,11]. The fruits are typically made up of clusters of berries with an edible fleshy receptacle, particularly in the Annona genera and they are extensively consumed due to their high nutritional value [1,11]. Finally, the seeds are enlarged and have a copious, irregular-surfaced endosperm with a minute embryo [1,11].

2.3. Traditional Uses

Annonaceae species are famous in tropical regions and used traditionally across tropical regions due to their widespread distribution. Various parts of the species are used traditionally, including leaves, seeds, bark, fruit, stem and twigs. A range of different methods for preparation is reported, such as infusions, pastes and decoctions [11]. For instance, the fresh fruit of Annona dioica is used for wound healing in Brazil [11]. The dried leaves of Annona muricata are used orally for analgesic effects in some parts of Indonesia [11]. In Burkina-Faso, the bark and roots of Annona muricata are used for dysentery and as an anthelmintic medicine, whereas the leaves are utilized for both fever and dysentery [12]. In the northwestern part of Brazil, both leaves and twigs of Duguetia chrysocarpa are ground and the extract of this mixture are utilized for treating gastrointestinal ulcers as well as a remedy for bowel disease [11]. A decoction of the stem bark of Annickia chlorantha is used orally as a remedy for the treatment of wounds and fever in Cameroon [13]. Further data on the traditional uses of the most widely used Annonaceae species are presented in Table 1.
Table 1. Uses of most commonly used Annonaceae family in traditional medicines.

| Annonaceae Species | Region | Local Name | Medicinal Uses | Part Used | Mode of Usage | References |
|--------------------|--------|------------|----------------|-----------|--------------|------------|
| Alphonsea javanica (Scheff.) | Indonesia | Aku Battu | Rheumatism and edema | Leaf | Ethanolic extract | [14] |
| Annickia chlorantha (Oliv.) | Cameroon | African yellow wood (c) | Treatment of sores, Antipyretic, Antiemic, Stimulant, Tuberculosis, Treatment of jaundice, Urinary tract infection | Bark | Powder, Crushed bark and drink extract, Decoction in baths, Decoction | [12,13] |
| Annicas affine (Exell) Versteegh & Sosef | Cameroon | African yellow wood (c) | Wound healing, Antipyretic, Antimicrobial, Antifungal | Stem bark | Decoction of stem bark | [13] |
| Annonidium floribundum Pellegr | Cameroon | Eboum, Libanga | Poison antidote, Dysentery | Roots, Bark, Leaves | Decoction taken orally | [12,15] |
| Annonidium mannii (Oliv.) | Cameroon | Ebome, Npôle, Ebome, Alan | Antipyretic | Stem bark | Decoction of stem bark | [13] |
| Boutiquea platypetala (Engl.) | Cameroon | Not reported | To treat fresh wounds | Leaves | Pounded fresh leaves | [12] |
| Cananga odorata (Lam.) Hook and Thomson | Malaysia and India | Kenanga utan, Perfume tree, Cananga oil, Ylang ylang | Rheumatism, Ophthalmic, inflammation and wound healing | Bark | Bark extract eye drops for inflammation and decoction are used to wash fresh wounds | [11] |
| Dicytisma chrysocarpa Maas | Brazil | Pindaiba-da-mata | Bowl and rheumatism inflammation | Leave and twigs | Leaves and twigs extract taken to relieve inflammation | [16] |
| Encoceannthum pulcherum (King) Heusden | Malaysia | Disepalum | Rheumatism, fever, edema and asthma | Leave | Decoction can be used for asthma and rheumatism | [17] |
| Enantia chlorantha var. soyauxii Engler and Diels | Africa | African yellow wood | Arthritis and wound healing | Bark | Powdered bark with citrus lemon used to dress | [11] |
| Friesodielsia englischiana (Diels.) Verdc | Cameroon | Lonkossa | Analgesic | Bark | Decoction of bark is taken orally | [15] |
| Friesodielsia gracilipes (Benth.) Steenis | Cameroon | Ntonda | Treatment of sores, skin infection, ulcers, and jaundice | Bark and wood | Decoction of bark and wood | [12] |
| Fissistigma oldhamii (Heinm.) Merr | Southern China | Oldhamii | Rheumatoid arthritis | Stems and roots | Powdered of stems and roots orally ingested | [11] |
| Greenwedigendron Surirensis (Engl and Diels) Verdc | Not reported | Otounga | Aphrodisiac and Vermifuge, Rheumatic pains, fevers, headache, stomach-ache | Root Leaves and bark | Chew roots, Pulverized leaves or bark and mixed with seeds of Aframomum melegueta | [15] |
| Isolona hexaloba (Pierre) Engl & Diels | Democratic Republic of Congo | Bodzungu | Malaria | Stem bark | Decoction of stem bark | [18] |
| Monodora myristica (Gaertn.) Dunal | Ivory coast | M Kpo, Abidjan district | Eye diseases and hemorrhoids, febrile pains and headache | Fruits Seed | Fruits and seeds consumed whole or ground to be used in soup and stews | [19] |
| Monodora tenifolia Benth. | Not reported | African nutmeg | Toothache | Root Bark and root | Clean the roots, boil and rinse the mouth, Prepared as a decoction and used as an enema | [12] |
| Polyalthea suaveolens Engl and Diels | Cameroon | Diels, Otungui, Ntounga | Analgesic, Antiepileptic, Antipyretic, Treatment of jaundice | Stem bark | Decoction of stem bark | [13] |
| Polyalthea longifolia (Sonn.) Thwaites | India | Ashoka | Fever | Bark | Decoction of bark | [20] |
| Xylopia ethiopica (Dunal) A. Rich | Sudan | Ethiopia or Negro pepper | Rheumatism, colic pain, headache, and neuralgia | Fruits | Ethanolic fruit extract or dried fruits are used as whole | [21] |
| Xylopia aromatic Lam. Mart | Columbia | Monkey pepper | Pulmonary inflammation and hemorrhoids | Roots Leaves | Insertion of root pieces into rectum and leaves burnt and smoke inhaled | [22] |
Table 1. Cont.

| Annonaceae Species | Region | Local Name | Medicinal Uses | Part Used | Mode of Usage | References |
|--------------------|--------|------------|----------------|-----------|--------------|------------|
| Xylopia parvifolia Hook f. and Thomson | East and Central Africa, India | Netawu/Athu ketiya | Gastrointestinal ulcers Analgesic | Roots | Decoction Finely dried powder | [23] |
| Xylopia staudtii Engl & Diels | Not reported | Ntom, Odjobi Bush pepper (c) | Cold and headache treatment | Bark | Powder | [12] |
| Monodora tenuifolia Benth | Cameroon | Ebome osso | Joint and muscle pain, promotion of breast milk production and headache | Stem bark | Decoction of stem bark powder | [13] |
| Uvaria acuminata Oliv | Cameroon | Nosoraback | Typhoid and Yellow fever Headache and epilepsy | Stem bark | Decoction of stem bark | [13] |

3. Phytochemistry of Annonaceae Family

A wide array of chemical compounds from various parts of Annonaceae plants have been discovered, isolated and characterised. The results of both phytochemical investigations and biological studies on various plants from this family have led to the identification of a wide diversity of compounds such as annonaceous acetogenins, flavonoids, alkaloids and essential oils, as summarized in (Table 2). These phytochemical constituents have been found to exhibit a broad range of biological activities such as immunosuppressive, anti-neoplastic, cytotoxic, antimicrobial, anti-inflammatory effects (Table 3). However, it is the Annona genera that are the most widely used as a food source and in traditional medicines.

Table 2. Representative phytochemicals isolated from plants of Annonaceae.

| Species | Part | Compounds | Class | References |
|---------|------|-----------|-------|------------|
| Anaxagoma dolichocarpa Sprague and Sandwith | Fruits | $p$-Cymene Spathulenol Caryophyllene oxide Guaiene | ESO | [5] |
| Anomianthus dulcis (Dunal) J. Sinclair | Stem | $(-)$-Anolobine $(-)$-Anonaine | ALK | [24] |
| Artabotrys pierreanus Engl. & Diels | Stem bark | Cyperene Caryophyllene oxide Cyperermone Cadalene | ESO | [5] |
| Artabotrys hexapetalus (L.f.) Bhandari | Aerial parts | 9-Oxo-asimicinone Artapetalin-A Artapetalin-B | ACT | [25,26] |
| Goniolhalamus giganteus Hook f. & Thomson | Bark | Pyranicin Pyragoncin Goniotronin | ACT | [27] |
| Miliusa balansae Finet & Gagnep | Leaves and branches | Ombuine Chrysosplenol Pachypodol Chrysosplenol C | FLA | [28] |

ALK (Alkaloids), ACT (Acetogenins), ESO (Essential oils) and FLA (Flavonoids).
### Table 3. Pharmacological activities of some isolated compounds from Annonaceae species.

| Species                     | Part Used             | Isolated Compounds          | Pharmacological Activity | Mechanism of Action                                                                 | References |
|-----------------------------|-----------------------|-----------------------------|--------------------------|-------------------------------------------------------------------------------------|------------|
| *Alphonsea javanica* Scheff | Leaves                | (+)-Altholactone            | Anti-inflammatory         | Inhibited lipopolysaccharide (LPS) induced NO production in RAW 264.7 macrophages with IC<sub>50</sub> = 0.8 µM. | [14]       |
| *Artabotrys hexapetalus* (L.f.) Bhandari | Roots, stems, and leaves | Artabonatine B, Squamolone | Anticancer               | Exhibited activity against 2,2,15 and Hep G2 cell lines with IC<sub>50</sub> 11.0 and 9.1 µg/mL. Displayed activity against Hep G2 cell lines with IC<sub>50</sub> 2.8 µg/mL. | [29]       |
| *Cananga odorata* (Lam.) Hook.f. & Thomson | Fruits                | Cleistopholine              | Cytotoxic                | Exhibited cytotoxicity against both Hep 2,2,15 and Hep G2 cell lines with IC<sub>50</sub> 0.54 and 0.22 µg/mL, respectively. | [30]       |
| *Goniothalamus tamirensis* Pierre ex Finet & Gagnep | Stem bark             | Dielsiquinone               | Cytotoxic                | Displayed cytotoxic activity against U251, RPMI, MCF7, HT029 and A549, with ED<sub>50</sub> 0.37, 0.11, 0.11 1.12 and 0.11, respectively. | [31]       |
| *Guatteria blepharophylla* Mart | Bark                  | Isocoreximine              | Anti-proliferative activity | Exhibited activity against UACC-62, NCI-H460, HT-29 and MCF-7 with TGI > 764.52 µM. | [32]       |
| *Rollinia sylvatica* A.St.-Hil | Leaves               | Hinesol, z-Caryophyllene beta-Maaliene | Anti-inflammatory | Leukocytes migration was significantly reduced at concentrations of 36.04–45.37 µg/mL. | [33]       |

### 4. *Annona* Genera

The genus of *Annona* is one of the 120 genera of the Annonaceae family and contains more than 119 species of trees and shrubs, most of them distributed in tropical areas of the Americas and Africa [6]. The majority of these species are found in tropical America, with more than 105 species (26 of them are endemic) and 10 species distributed in tropical Africa [10,34]. It has been reported that this genus is the second or the third largest genus in the Annonaceae family [35]. Its generic name derives from the Latin Hispaniolan Taino “annual harvest” [6,35]. Due to its edible fruits and medicinal properties, *Annona* is the most important genus of Annonaceae family [2]. Numerous *Annona* species furnish edible fruits like *Annona muricata* (“graviola”), *Annona crassiflora* (“araticum”) and *Annona squamosa* (“fruta do conde”) [2]. Most of the fruits are consumed either in fresh form or used in desserts, juices and ice cream preparations [34]. Despite *Annona* having many species, only limited species of this family are economically important such as *A. squamosa* L. (sugar apple), *A. cherimola* Mill. (Cherimoya), *A. muricata* L. (guanabana or sourpuff), *A. atemoya* Mabb. (atemoya), a hybrid between *A. cherimola* and *A. squamosa*, *A. reticulata* L. (custard apple), *A. glabra* L. (pond-apple) and *A. macrophyllata* Donn. Sm. (ilama) [6]. Phytochemically, several classes of secondary metabolites such as acetogenins,
essential oils, alkaloids, terpenoids and flavonoids have been described in this genus [34,36]. A variety of pharmacological activities have been reported from various parts of Annona species specially leaves and seeds including applications against antibacterial [37], antinociceptive [38], anticancer [39], anticonvulsant [40], anti diarrheic [41], antidiabetic [42], antimalarial [39], anti-inflammatory [43], antioxidant [44], antileishmanial [45], anti ulcer [46] and antidepressant [47].

4.1. Botanical Features

Generally, Annona species are small trees or shrubs with a height from 5 to 11 m depending on various factors including soil, climate, species, and crop management [2]. In relation to the botanical characteristics of Annona species, the majority of them are moderately erect with brown bark that is frequently furrowed (Table 4) [10]. The stems are rust-coloured (ferruginous) and covered with densely matted hairs (tomentose) when young, becoming smooth and hairless (glabrous) as they mature [6,10]. It has thin lateral roots and a taproot that is not generally pronounced [2]. With regard to the flowers, they are hermaphrodites, solitary or fascicle containing from two to four flowers. The flowers are usually fragrant, with six petals and three green sepals, in a circular arrangement of two verticils [6]. Flowering of the plant usually starts at 3 to 4 years and flower opening usually occurs by separation of the apex of external petals [6,10]. Finally, the leaves may be shiny or hairy and have an impressed vein on the upper side, and the fruits are syncarpous and comprised of seeds and many carpels [6,10].

Table 4. Botanical information of some Annona species.

| Species          | Synonyms                               | Local Names       | Geographic Distribution                              | References   |
|------------------|----------------------------------------|-------------------|------------------------------------------------------|--------------|
| A. cherimola     | A. tripetala Aiton                     | Chirimoya         | South Africa, China, Egypt, Eritrea, Myanmar, Philippines, India, France, Italy, Mexico, Ecuador, Portugal, Peru | [6,48]       |
|                  | A. pubescens Salisb                     | Chirimolía        |                                                       |              |
|                  |                                        | Cherimoya Momona  |                                                       |              |
| A. coriacea      | A. coriacea var. amplexicaulis S.Moore, A. coriacea var. cuneate, A. coriacea var. pygmaea Warm | Marolo Araticum Marolino | Brazil (Cerrado, Caatinga) | [10,49]       |
|                  | A. c. var. cuneate                      |                   |                                                       |              |
|                  | A. c. var. pygmaea Warm                 |                   |                                                       |              |
| A. cornifolia    | A. walkeri S. Moore                    | Araticum-mirim    | Brazil                                               | [50]         |
| A. crassiflora   | A. macrocarpa Barb A. rodriguesii Barb | Araticum Pinha-docerrado Cerrado pinecone Marolo | Brazil                                               | [51]         |
|                  | A. m. Barb                              | Cabeça de negro   |                                                       |              |
| A. macrophylata  | A. diversifolia Saff                   | Ilama, Papauce Anona blanca | Mexico China India                                   | [52,53]       |
| A. montana Macfad| A. Montana f. marcgravii (Mart.) Porto | Mountain soursoap False graviola jãci do Fará Azaticum grande Shan di fan li zhi | Southern Asia, South America Amazon Rainforest and Atlantic Forest | [10]         |
| A. muricata      | A. macrocarpa Barb A. muricata Guanahanus A. cearensis Morales | Brazilian pawpaw Soursop, ci guo fan li zhi, Graviola Araticum grande Mullu Raama Phala, Corossol Catuche | Tropical regions of Americas Malaysia, Myanmar, Pakistan, India, Indonesia, China | [6,10]       |
Table 4. Cont.

| Species | Synonyms | Local Names | Geographic Distribution | References |
|---------|----------|-------------|-------------------------|------------|
| A. reticulata | A. excelsa Kunt | Custard apple | Indonesia, West Indies, Bangladesh, China, India | [54] |
| A. excelsa Kunt | A. laevis Kunth | Bullock’s heart | | |
| A. longifolia Moc | A. riparia Kunth | | | |
| A. longifolia Moc | A. riparia Kunth | | | |
| A. reticulata | A. excelsa Kunt | Custard apple | Indonesia, West Indies, Bangladesh, China, India | [54] |
| A. excelsa Kunt | A. laevis Kunth | Bullock’s heart | | |
| A. longifolia Moc | A. riparia Kunth | | | |
| A. reticulata | A. excelsa Kunt | Custard apple | Indonesia, West Indies, Bangladesh, China, India | [54] |
| A. excelsa Kunt | A. laevis Kunth | Bullock’s heart | | |
| A. longifolia Moc | A. riparia Kunth | | | |
| A. reticulata | A. excelsa Kunt | Custard apple | Indonesia, West Indies, Bangladesh, China, India | [54] |
| A. excelsa Kunt | A. laevis Kunth | Bullock’s heart | | |
| A. longifolia Moc | A. riparia Kunth | | | |
| A. reticulata | A. excelsa Kunt | Custard apple | Indonesia, West Indies, Bangladesh, China, India | [54] |
| A. excelsa Kunt | A. laevis Kunth | Bullock’s heart | | |
| A. longifolia Moc | A. riparia Kunth | | | |
| A. reticulata | A. excelsa Kunt | Custard apple | Indonesia, West Indies, Bangladesh, China, India | [54] |
| A. excelsa Kunt | A. laevis Kunth | Bullock’s heart | | |
| A. longifolia Moc | A. riparia Kunth | | | |

4.1.1. Annona Cherimola

*Annona cherimola* Mill (Cherimoya) belongs to the genus *Annona* in the Annonaceae family in magnolias order, which means “cold seeds”, and is a small tree that produces heart-shaped and conical edible fruit [55]. It is a steep, semi-momentary and a low bunched tree that is widespread in Ecuador and Peru and distributed throughout Asia, South Europe, America and Africa [56]. In Mexican traditional medicine, this plant has been used to treat various diseases such as diabetes, cough, fever, headache, worms and inflammation either alone or in combination with other plant species [48,57–60]. Recently, various parts of *A. cherimola* have been phytochemically profiled and contain various polyphenols and alkaloids. The leaves were found to be a source of bioactive compounds with potential for use as treatments for skin and eye diseases and gastric, cardiovascular and intestinal disorders [55].

4.1.2. Annona Squamosa

*Annona squamosa* L., commonly known as custard apple, is a tropical, endemic species of the West Indies, Ecuador, Peru, Brazil, South and Central America, Mexico, Bahamas, Bermuda, and Egypt [61]. This plant is extensively cultivated in various states of India, including Maharashtra, Gujarat, Madhya Pradesh, Chhattisgarh, Assam, Uttar Pradesh, Bihar, Rajasthan, Andhra Pradesh, and Tamil Nadu. The total area of cultivation has been reported by the Indian Council of Agricultural Research (ICAR) as 40,000 ha [62]. Its tree grows as a small sapling from 3 m to 8 m, with large branches having brownish or light brownish bark and it has thin leaves and is known for its edible fruit [61]. In the Aligarh district village in Uttar Pradesh, *A. squamosa* is well-known for its antidiabetic properties [63]. Its seeds, bark and leaves possess various pharmacological properties, mainly anti-tumour properties [64].

4.1.3. Annona Muricata

*Annona muricata* L. is commonly known as soursop and graviola and is native to Central and South America. It is a small tree 5–10 m tall and 15–83 cm in diameter; it has low branches and edible fruit that are used commercially for the production of candy, juice and
scherbets [65]. Traditionally, the aerial parts of this plant have been used to treat various diseases like diabetes and malaria and nowadays, it is widely used by people diagnosed with cancer [66]. Moreover, this species possesses several pharmacological properties, including vasodilator, cardio-depressive, antispasmodic, antimutagen, anticonvulsant, antiviral, antidiabetic and antihypertensive effects [67]. Both the leaves and seeds of A. muricata have been evaluated for their constituents resulting in the identification and isolation of more than 50 mono-THF acetogenins, alkaloids, terpenoids, saponins, flavonoids, coumarins, cardiac glycosides, phenols, tannins and anthraquinones [67].

4.1.4. Annona Reticulata

Annona reticulata Linn is a traditionally important plant utilized in traditional medicines [68]. It is indigenous to the West Indies and widely distributed in tropical and subtropical regions of the world [54]. It is a small tree with a height between 6 and 7.5 m and contains numerous lateral branches [54]. It has a cylindrical stem that contains lenticels and very short coffee-colored hairs [54]. The leaves of A. reticulata are lanceolate, membranous, oblong, and rounded or curate at the base. Fruits are edible, rough, somewhat heart-shaped and yellow in color that shifts to yellowish-red on ripening, and the seed is smooth and blackish in color [69]. Traditionally, A. reticulata has been utilized for the treatment of epilepsy, dysentery, cardiac problem, constipation, haemorrhage, bacterial infection, parasite and worm infestations, fever, ulcers and as an insecticide [68,69]. Its leaves are used for helminthisis treatment while bark is a powerful astringent and used as a tonic [68,69].

4.1.5. Annona Coriacea

Annona coriacea Mart. is a species belonging to the Annona genera, commonly known as “marolo”, “araticum” and “araticum-liso” [70]. This plant is distributed across Paraguay and Brazil, with little available information about its ethnomedicinal uses [71]. It is a small tree (3–6 m) and its edible fruit consist of an ovoid-obtuse syncarp and weighing up to 1.5 kg [72]. The leaves are glabrous on the ventral surface, obovate, and the base is frequently cordate and margin undulate [73]. The flowers are terminal, thick, solitary and having fleshy petals with colors shifting between orange and pink [73]. The leaves are traditionally used as carminatives, anthelmintics, antirheumatics and in the treatment of stomatitis, headaches, abscesses, neuralgia, rheumatism, ulcers and dermatitis [74,75]. Both seeds and fruits are toxic when crushed and exhibited effects against ectoparasites like lice [75].

4.1.6. Annona Senegalensis

Annona senegalensis is a small tree 2–6 m tall that is commonly known as wild custard apple and wild soursop [76]. This plant is native to tropical east and northeast, west and west-central, and southern Africa and islands in the western Indian Ocean [76]. Its leaves are simple, alternate, oblong, green to bluish-green, ovate or elliptic, and mainly lack hairs on the upper surface and brownish hairs on the lower surface [77]. This plant has been used in traditional medicine as a pain reliever, antioxidant, antidiarrheal, antitrypanosomal, antimalarial, anti-inflammatory, antimicrobial, antiparasitic, anticonvulsant and as an antishock venom [78]. It has been reported that the leaves of A. senegalensis are used for the treatment of tuberculosis, yellow fever and smallpox, whereas stem bark is reported for the treatment of injury from venomous animals [79]. The root was also reported for treating erectile dysfunction, tuberculosis, gastritis, reproductive deficiency and in the management of malaria and diabetes [80].

4.1.7. Annona Vepretorum Mart

Annona vepretorum is commonly recognized as ‘bruteira’, is a small tree of 2.5–10 m high native to the Brazilian biome Caatinga [81]. The fruits of A. vepretorum can be consumed either raw or as juice for nutritional purposes [82]. Traditionally, a decoction of the leaves have been used to bathe in for the treatment of allergies, yeast, skin diseases
and microbial infections, whereas the root is traditionally used to treat snake and bee bites, inflammatory conditions and heart pain [81].

4.1.8. *Annona Salzmannii*

*Annona salzmannii* is a tree of 6–20 m high that known as “araticum-da-mata” and “araticum”apé” [83]. It is commonly cultivated in Brazil especially in the States of Bahia, Pernambuco, and Paraíba [83]. Its root, seeds and leaves are used in folk medicine for treating several illnesses like ulcers, dysentery and inflammatory conditions [83]. The leaves and bark of *A. salzmannii* are utilized for the treatment of tumors, diabetes and inflammatory conditions [84].

4.1.9. *Annona Crassiflor*

*Annona crassiflor* is known as araticum of cerrado or cerrado [85]. It is a small tree that bears a typical fruit known as araticum of cerrado or cerrado [86]. The fruits are highly consumed “in natura” by native people and can be used to make juice, jelly and ice-cream [85,86]. In folk medicine, the seeds are used to treat scalp infections, and infusions of the leaves and seeds are utilized for their antidiarrheal and antitumor properties [85]. For more details about the botanical characteristics and traditional uses of *Annona* species, see Tables 4 and 5.

**Table 5. Traditional uses of common *Annona* species.**

| Species               | Region                  | Local Name                | Medicinal Uses                  | Part Used     | Mode of Usage                  | References |
|-----------------------|-------------------------|---------------------------|---------------------------------|---------------|------------------------------|------------|
| *A. ambotay* Aubl     | French Guiana           | Not reported              | Treating fever                  | Leaves and bark crushed and rubbed on body | [18]       |
| *A. cherimola* Mill.  | Tropical America Gabon  | Cherimola Cherimoya       | Abortion                        | Aerial parts  | Fruit Root Seed Stem          | [87,88]   |
|                       | Cultivated in Spain and Australia | Custard apple Mao ye fan li zhi | Anti-anxiety Cough Diarrhea Hypercholesterolemia Infections Painful inflammations Parasitic Sedative | | | |
| *A. coriacea* Mart.   | Brazilian (Cerrado, Caatinga) | Araticum Marolino Marolo | Anthelmintic Chronic diarrhea Inflammation Leishmaniasis Malaria Rheuma | Leaves Root Seeds | Not reported | [89]       |
| *A. cornifolia* St-Hil| Bolivian and Brazilian savannah | Not reported              | Antiulcerative (green fruit)    | Seeds         | Not reported                 | [90]       |
| *A. crassiflora* Mart. | Brazil (Cerrado)         | Araticum of the Cerrado Araticum-mirim Marolo Pana | Analgesic Antimicrobial Antirheumatic Carminative Rheumatism, Anti-inflammatoryWound healing | Leaves Root bark Root wood Seeds Fruit | Not reported | [43,91,92] |
| *A. cuneata* (Oliv.) R.E. Fr | Congo                   | Not reported              | Asthenia Female sterility Hernia Parasitic infections Venereal diseases | Root bark Stem bark | Not reported                 | [93]       |
| *A. dioica* A. St.-Hil. | Brazil (Cerrado, Pantanal) | Ceraticum and ariticum    | Diarrhea Rheumatism             | Fruits Leaves Dried leave paste and fresh fruit decoction | [11,33]   |
Table 5. Cont.

| Species                  | Region                        | Local Name                      | Medicinal Uses                          | Part Used | Mode of Usage         | References |
|--------------------------|-------------------------------|---------------------------------|-----------------------------------------|-----------|-----------------------|------------|
| A. diversifolia Saff     | Tropical forest of Central America China | Ilama Papausa White anona, Yi ye fan li zhi | Arthritic pain Anti-spasmodic          | Leaves    | Not reported          | [40,53]    |
| A. foetida Mart          | Brazil                        | Araticum-da-coatinga            | Malaria                                | Bark and leaves | Decoction of bark and leaf | [94]       |
| A. glabra L              | Caribbean                     | Mamain                          | Fever                                  | Leaves    | Not reported          | [95]       |
| A. glauca Schumach. & Thonn | West Tropical Africa (Senegal, Ghana, Suriname) | Dangan Mampilhege, Mandé sunsun Tangasu | Arachnicides Bienmorhhoa Diuretics Fish-poisons Insecticides | Roots    | Not reported          | [96]       |
| A. haematantha Miq       | French Guiana                  | Not reported                     | Fever                                  | Leaves    | Bark                  | Leaves and bark crushed rubbed on body | [18,97]       |
| A. montana Macfad.       | South America                 | Mountain soursop Shan Di fan li zhi false Graviola Araticum grande Jacá do Pará | Against snake bite Against obesity | Leaf Bark Stem | Seed Twig          | Not reported | [98,99]       |
| A. mucicata Linn         | Brazil                        | Araticum Condessa Graviola       | Anthelmintic Analgesic, neuralgia, rheumatism, arthritis pain | Fruit, juice, and crushed seeds Fruit and leaves | Juice of fruit Water extraction of the leaf | [66]       |
| A. pickelii (Diels) H. Rainer | Mexico Central America Venezuela Colombia Belize, Central America South America Southern Asia Africa Madagascar | Sincollo Soncoyo Bullock's-heart Custard apple Anona blanca Anona Niuu xin fan li zhi | Contraceptive Blood dysentery Cold Stomachache Fainting spinal disorders Fever Hysteria Influenza Mental depression Skin diseases Unhealthy ulcers Wounds | Leaf Leaf Root Stem Aerial parts | Bark Fruit Leaf Seed Root Seed Stem bark | Not reported | [100,101]       |
| A. reticulata Linn       | West Indies                   | Ramphal                          | Bronchitis Asthma Bowel inflammation  | Fruit Seeds | Leaves Decoction of fruit Oral ingestion of powdered seeds Oral ingestion of the leaf powder | [102]       |
| A. senegalensis Persoon  | Nigeria                       | Ukopko (Idoma)                  | Anti-inflammatory Analgesic Anthelmintic Cancer Diarrhea Epilepsy Infectious diseases Inflammations Sleeping sickness Snakebite Cardiovascular diseases Diabetes Febrile seizures Gout Mental disorders Painful | Leaves Seed Stem | Bark Root bark | Roots and bark are ground together and their decoction is used | [103]       |
| A. squamosa Linn         | Cameroon                      | Sugar apple (English), Kedahan (Yambetta) | Vomiting, abscesses, muscle aches, fever, and skin disease | Leaves    | Decoction of leaves   | [13]       |
| A. vepretorum Mart        | Brazil                        | Araticum Bruteira               | Analgesic and anti-inflammatory         | Leaves    | Methanolic leaf extract | [104]       |
4.2. Traditional and Ethnomedicinal Uses of Annona Genus

Traditionally, the Annona species have been used widely. For instance, antidiarrheal effects have been reported for *A. reticulata*, *A. muricata* and *A. salzmannii*, whereas *A. cherimola*, *A. squamosa* and *A. reticulata* have been reported for their antiparasitic effects (Table 5) [10]. Moreover, both *A. vepretorum* and *A. salzmannii* have been also reported for anti-inflammatory effects [10]. Furthermore, both *A. vepretorum* and *A. salzmannii* have been also reported for anti-inflammatory effects [10]. *A. purpurea* and *A. reticulata* have been used to treat fever, while anticancer effects have been reported for *A. senegalensis* and *A. muricata* [105,106]. Furthermore, *A. foetida*, *A. muricata* and *A. glabra* have been traditionally used to treat rheumatism [107], while *A. reticulata*, *A. salzmannii*, *A. foetida* and *A. squamosa* have been described for treating ulcers [4]. In Indonesia, the fruit juice of *A. muricata* has used as a diuretic and to treat liver ailments and leprosy [108], whereas leaves was used to treat spasms, boils and as an aphrodisiac [36]. The leaves of *A. diversifolia* have been used as anti-inflammatory, anticonvulsant and analgesic agents [52]. Ethnobotanically, despite reports of the toxicity of *A. muricata* seeds, the powder of toasted seeds has been reported to be used as an emetic and cathartic in the traditional Mexican pharmacopeia [36]. To Southeast Asian people, the immature fruit of *A. reticulata* was used to treat both dysentery and diarrhea, and a decoction of roots was used to cure toothache and as an antipyretic [109]. Additionally, a decoction of leaves has been used internally against worms and topically to treat abscesses and boils [109]. Finally, the leaves of *A. squamosi* have been used as tonic and cold remedy in tropical America and systemically to cure dysentery in India [108].

5. Phytochemistry of Annona Species

A wide range of secondary metabolites, including acetogenins, flavonoids, alkaloids and essential oils (Figure 1), from nearly every part of Annona plants, have been discovered, isolated and characterised (Table 6). The plants of the Annona genera are also found to be rich in minerals and vitamins, for instance, calcium, potassium, magnesium, sodium, copper, zinc, selenium, phosphorus, iron, vitamin C, pantothenic acid B₅, thiamine and riboflavin [6].

**Alkaloids**

![Structure of selected compounds identified in Annona species.](image)

- Annonaine
- Lysicamin
- Cleistopholine
- Cassythicine
- Nornuciferine
- Stepharine
- Asimilobine
- Thalicsimidine

**Flavonoids**

- Isorhamnetin-3-O-glucoside
- Nicotiflorin
- Rutin
- Isoquercitrin

**Terpenoids**

- Bicyclogermacrene
- Spathulenol
- Caryophyllene oxide
- Ledol
- Sabinene

Figure 1. Cont.
Figure 1. Structure of selected compounds identified in Annona species.

Table 6. Compounds isolated from plants of Annona genus.

| Species          | Part        | Isolated Compounds                                                                 | References |
|------------------|-------------|------------------------------------------------------------------------------------|------------|
| A. amazonica R.E. Fries | Stems       | Cassythicine                                                                       | [110]      |
|                  | Root        | Corytrenchine, Isocoreximine (ALK)                                                 |            |
|                  | Fruit       | α-Pinene, α-Thujene, Terpinen-4-ol, Germacrene D (ESO)                              |            |
| A. cherimola     | Seed        | 2,4-cis-Annonerionones, Annocherin, 2,4-trans-Isoannonacins, Annocherimolin, Annomolin, Annomocherin, Annomontacin, Annonacin, Asimicin, Tucumanin, 2,4-trans-Annonerionones, 2,4-cis-Isoannonacins, cis-Annonacin, Annonagalene, Annesenegalolin, Annmonol A, Annmonol B, Cherimalacyclopeptide C (ACT) | [111–116] |
|                  | Stem        | Annocherine A and B, Artabonatine B, Romucosine H, Cherianoine (ALK)               |            |
|                  | Bulb        | Crolechinic acid, Crolechinic acid (methyl ester), Annonenone, Annonalide (ESO)     |            |
|                  | Seed        | Gigantecin, Coriapentocin A and B, Bullacin (ACT)                                  |            |
| A. coriacea Mart. | Leaf        | Quercetin-3-O-β-(6′′-O-β-glucosyl)-glucoside, Quercetin-3-O-β-(6′′-O-α-rhamnosyl)-galactoside, Trigonelline, Rutin, Hyperin, Hyperin, Isohamnetin-3-O-β-glucoside, Isohamnetin-3-O-β-galactoside, Isoqueretin, Isoqueretin, Nicotiflorin, Biorobin, Ketoside, Caeticin, Isohamnetin-3-O-β-glucoside, Narcissin, Rutin (FLA) | [117–123] |
|                  | Root        | Coriacin, Coriadienin, Coriheptocin A and B, Coriacyclodienin, Coriacycloenin, 4-Deoxycoriacin, Annoheptocin A and B (ACT) |            |
| A. crassiflora   | Leaf        | Kaempferol-3-O-β-diglucoside, Kaempferol-3-O-β-glucoside, Quercetin-3-O-β-D-galactopyranoside, Epicatechin, Quercetin-3-O-β-L-arabinopiranoside (FLA) | [124]      |
### Table 6. Cont.

| Species                  | Part                           | Isolated Compounds                                                                 | References               |
|--------------------------|--------------------------------|------------------------------------------------------------------------------------|--------------------------|
| *Annona foetida* (R.E.Fr.) H. Rainer | Bark                           | Annomontine, N-Hydroxyannomontine, Liriodenine, O-methylmoschatoline (ALK)         | [125–127]                |
|                          | Leaf                           | (E)-caryophyllene, Bicyclogermacrane, α-Copaene (ESO)                               |                          |
|                          | Branch                         | Atherospermidine (ALK)                                                             |                          |
| *Annona glabra*          | Fruit                          | Annonoglbasin A, B, C, D, E and F, (−)-Anonaine, (−)-Asimilobine, (−)-N-Anomuciferine, (+)-Stepharine, Blumenol A, Liriodenine, N-p-Coumaroyltyramine, (−)-N-Formylalanoin, (−)-Nordomesticine, Annobraine, Dehydrocorydalmine, Lycisamine, N-trans-Feruloyltyramine (ALK), 6-O-Palmitoyl-β-sitosteryl-D-glucoside, β-Sitosteryl-glucoside, Stigmasteryl-D-glucoside, β-Sitosteryl, Stigmastanol (STE) | [128–132]                |
|                          | Fruit & stem                   | Bullatanocin, Glabracins A and B, Javoricin, Glacins A and B (ACT), 3-O-α-L-Arabinopyranoside, 3-O-β-D-Glucopyranoside (GLU), (−)-Actinodaphnine, (−)-Asimilobine, (−)-Anolobine, (−)-N-Methylactinodaphnine, (−)-Paulemonil, (+)Boldine, (+)-Nortisodomesticine, (+)-Stepharine, Liriodenine, (−)-Pallidine, (+)-Itor-β-t verte N-oxide, (+)-Magnoflorine, (+)-Reticuline (ALK), Quercetin, Quercetin-3-O-β-D-galactopyranoside (FLA) |                          |
| *Annona leptopetala* (R.E.Fr.) H. Rainer | Leaves and branches             | Laurotenanine, Nornuciferine, Corypalmine, Norannuradhapurine Anonaine (ALK)       | [133]                    |
| *A. montana*             | Leaf                           | Annolatine, Annoretine, Liriodenine, Argentinine (ALK), β-Sitosterol-β-D-glucoside, β-Sitosterol (STE), Montanacin-K, L, C, D, B and E, Annonacin-10-one, Annonacin-A, cis-Annonacin-10-one, Annonacin, cis-Annonacin (ACT) | [134–137]                |
|                          | Seeds                          | Montalicins G, Montalicins H Monlicins A & B, Murisolin, 4-Deoxynontomontacan, Muricatacin (ACT) |                          |
|                          | Stem                           | N-trans-Feruloyltyramine, N-p-Coumaroyltyramine, N-trans-Caffeoyltyramine (PHE)    |                          |
|                          | Seed                           | 2,4-cis-Gigantetrocinone, 2,4-trans-Isaionacin, 2,4-trans-Gigantetrocinone, 2,4-trans-Isaionacin-10-one, Gigantetrocin-A, Muricatol, Annomontacin, Gigantoteronin, Annornacin A, Annoreticicum-9-one, cis-Annonactin, Murisolin, Muricin H, Xylomaticin, Muricin L, cis-Annonacin, cis-Gonothalamicin, cis-Annonacin-10-one, Arianacin, Javoricin, Donhexocin, Murhexocin, Cohibins C, Cohibins D, Gigantetrocin B, Longifolincin, Muricin A, B, C, D, E, F and G, Annomucinaricin B and C (ACT) |                          |
|                          | Stem bark                      | Muricatin A, B and C (ACT)                                                         |                          |
|                          | Fruit                          | Epomuricenins-A and B, Epomurinins-A and B, Epomusenins-A and B, Muricin J, K and L (ACT)  Asimilobine, Nornuciferine, Annonaine (ALK) |                          |
|                          | Fruit & root                   | Sabadelin (ACT)                                                                    |                          |
| *A. muricata*            | Leaf                           | Annonacin, Annomuricin C, Muricatocin C, (2,4-cis)-10R-anonannin-A-one, Annuxocin, Annomucatin, Annopentocin A, B and C, Annornucine, Murcapentocin, Annomuricin C, B and A, A, Annomuricin, trans-anomuricin-D-ones, trans-anomuricin-D-ones, Muricatocins A and B, Muricatin A and B, Muricatonin, Murhexocin C (ACT) | [138–146]                |
|                          | Leaf                           | (R)-4-O-methylcoclaurine, (R)-O, O-dimethylcoclaurine, (R)-Anonine, Annomone, (S)-N-stigmatyrine, Anonaine, Isoalureline, Xyloline (ALK) |                          |
|                          | Leaf & seed                    | Annonacin, Annocactin A and B, Annocactinone, Annoncalitin, cis-Corosololose, Gonothalamicin, Annosacalin, Corossolone (ACT) |                          |
|                          | Pericarp                       | Annnonacin, Annonacin A, Annornucin A (ACT)                                       |                          |
|                          | Root                           | Annnonacin, Muriuineins-1, 2,3 and 4, Chatenaytrieneins-1, 2 and 3, Mucadienin, Monticristin, cis-Panatellin, cis-Reticulatin-10-one, cis-Uvariamcin IV, Coronin, cis-retulcatalin, cis-Solamin, Cohibins A and B (ACT) |                          |
Table 6. Cont.

| Species          | Part     | Isolated Compounds                                                                 | References       |
|------------------|----------|------------------------------------------------------------------------------------|------------------|
| *A. purpurea*    | Leaf     | Lirinidine, 7-Formyl-dehydrothalicsimidine, 7-Hydroxy-dehydrothalicsimidine, N-Methylasimilobine, N-Methylaurotetanine, Thalicsimidine, Norpurpureine (ALK) | [105,147]        |
|                  | Root     | Annomontine (ALK)                                                                  |                  |
|                  | Leaf     | Dopamine, Salsolinol, Spathenol, Muurolene, Cochlaurine, Copaene, Eudesmol (ESO), Squamone, Solamin, Rolliniastatin 2, Annoreticuin-9-one, Annomoninic, Annonaretin A (ACT) |                  |
|                  | Stem     | Dopamine, Salsolinol (ESO), Reticullacinone, Rolliniastatin-2, (ACT)              |                  |
|                  | Bark     | Reticulatacin, Liriodenine, Norushinsunine, Neoannonin, Reticuline (ALK)           |                  |
|                  | Root     | Spathenol, Copaene, Eudesmol, Muurolene (ESO)                                      |                  |
| *A. reticulata*  | Bark     | Reticulatacin, Liriodenine, Norushinsunine, Neoannonin, Reticuline (ALK)           | [54,148–152]     |
|                  | Root     | Dopamine, Salsolinol (ESO), Reticullacinone, Rolliniastatin-2, (ACT)              |                  |
| *A. senegalensis* | Leaf   | (−)-Roemerine, α-Humuleine, γ-Cadinene, Germacrene D, β-Caryophyllene (ESO)        | [153,154]        |
|                  | Aerial parts | (−)-Anonaine, (−)-Asimilobine, (+)-Normantenine (ALK) (+)-Catechin (FLA)       |                  |
| *Annona sericea* Dunal | Leaf | Normantine, Norcuciferine, Isoboldine, Lycicaine, Hydroxynornuciferine (ALK)      | [155]            |
|                  | Leaf     | (−)-Anonaine, O-Methylarmpavine, β-Caryophyllene, Germacrene D, Bicyclogermacrene, Quercetin-3-O-glucoside (ESO) |                  |
| *A. squamosa*    | Stem     | 11 ent-Kauranes, 10-nor-ent-Kaurane-4α,16β,17-triol, 16α,17-Dihydroxy-ent-kauran-17,19- dioic acid, 17,19-Dihydroxy-16β-ent-kauran-19- oic acid, en-Kaur-16-en-19-oic acid, 16α,17-Dihydroxy-ent-kauran-19-al, 16α-Hydro-19-al-ent-kauran-17,19 -oic acid, 16β-Hydroxy-17-ent-kauren-19-oic acid, 4α-Hydroxy-19-nor-ent-kauran-17-oic acid | [156,157]        |
|                  | Stem     | Neoannonin-B, Annosquamins A, B and C, Annosquamin-I, Annosquamin A, B and C, Annosquatin A and B, Annotemoyin-1 and 2, Chemoroln-1 and 2, Diepomuricanin A and B, Dieporeticenin, Dieposabadelin, Squadiolin A, B and C, D, E, F, G, H, I, J, K, L, M and N, Squamostatin A, B, C, D, E and F, Cyclosquamosin A, B, C, D, E, F, G, H, I, J, K, L, M and N, Squamostatin A, B, C, D, E and F, Cyclosquamosin A, B, C, D, E, F, G, H, I, J, K, L, M and N, Squamostatin A, B, C, D, E and F, Cyclosquamosin A, B, C, D, E, F, G, H, I, J, K, L, M and N, Squamostatin A, B, C, D, E and F, Cyclosquamosin A, B, C, D, E, F, G, H, I, J, K, L, M and N, Squamostatin A, B, C, D, E and F, Cyclosquamosin A, B, C, D, E, F, G, H, I, J, K, L, M and N, Squamostatin A, B, C, D, E and F, Cyclosquamosin A, B, C, D, E, F, G, H, I, J, K, L, M and N, Squamostatin A, B, C, D, E and F, Cyclosquamosin A, B, C, D, E, F, G, H, I, J, K, L, M and N, Squamostatin A, B, C, D, E and F, Cyclosquamosin A, B, C, D, E, F, G, H, I, J, K, L, M and N, Squamostatin A, B, C, D, E and F, Cyclosquamosin A, B, C, D, E, F, G, H, I, J, K, L, M and N, Squamostatin A, B, C, D, E and F, Cyclosquamosin A, B, C, D, E, F, G, H, I, J, K, L, M and N, Squamostatin A, B, C, D, E and F, Cyclosquamosin A, B, C, D, E, F, G, H, I, J, K, L, M and N, Squamostatin A, B, C, D, E and F, Cyclosquamosin A, B, C, D, E, F, G, H, I, J, K, L, M and N, Squamostatin A, B, C, D, E and F, Cyclosquamosin | [159] |
| *A. cepretorum*  | Leaf     | Spathulenol, Bicyclogermacrene, α-Phellandrene (ESO)                               | [116,158]        |

6. Pharmacological Properties of *Annona* Species

The species of the *Annona* genera have been reported to elicit a diversity of biological activities such as antitumor, anti-inflammatory, antioxidant, antinociceptive, antiprotozoal, antipyretic, antiulcer, antihyperglycemic, anthelmintic, antileishmanial, antimalarial, antidiarrheal, antifungal and antimicrobial promoted by whole extracts, fractions, or pure compounds (Table 7).
Table 7. Pharmacological activities of *Annona* species.

| Species          | Biogeographical Distribution          | Used Part | Traditional Use | Pharmacological Activities | Extract/Compound Evaluated | References |
|------------------|---------------------------------------|-----------|----------------|---------------------------|----------------------------|------------|
| *A. ambloy*      | South American tropical rainforest    | Trunkwood | Antipyretic    | Antimicrobial              | Alkaloids                  | [159]      |
| *A. bullata*     | Endemic of Cuba                       | Bark      | Not reported   | Antitumoral               | 32-Hydroxybullatacinone    | [160]      |
| *A. cherimola*   | Tropical America, Asia, Spain, Gabon  | Aerial parts/Fruit | Abortion, Anti-anxiety, Cough, Diarrhea, Hypercholesterolemia Infections, Painful inflamations, Parasitic Sedative | Antiinflammatory, Antitumoral, Antimicrobial | Acetogenins: Molvizarin, Squamocin, Cherimolín – J., Motrilín, Atheradurin, Tucumanin Annomocherin, Annonasin, Annomontacin, Alkaloids: Roemerine, Annonaine, Dehydromeronine | [37,161] |
| *A. coriacea*    | Brazilia (Cerrado and Caatinga)       | Leaf      | Leschmaniasis, Malaria, Rheuma Anhemnætic Chronic diarrheaa Inflammation | Antifungal, Antinflammatory, Antitumoral, Antimicrobial | Acanthoheptocins A-B, Coriadin, 4-Decyoxycoracin, Coriadiheptocins A-B, Coriadien, Gigantecin | [10]       |
| *A. muricata*    | America, Asia, Africa                 | Bark      | Anthelmintic, Antibacterial, Ascorbutic, Asthma, Cancer, Cough, Cystitis, Diabetes, Diuretic | Antiarthritic, Antihypercholesterolemia, Antidialetic, Antidiabetic | Acanthoheptocins A-B, Muricin A, Muriacin B, Muriacin C, Muriacoracin, Muriapatocin, Muriheptocins A-B, Annopentocins A-C | [162,163] |
| *A. salzmannii*  | Brazil                               | Bark      | Not reported   | Antioxidant, Antimicrobial | Antioxidant, Antimicrobial | Alkaloids: Reticuline, Anomaine, Laurellitine, Isoboldine | [101]      |
| *A. senegalemis* | Madagascar, Comornos, Cape Verde, Tropical Africa | Leaves | Anti-inflammatory and Analgesic, Anthelmintic, Cancer, Diarrhea, Eplepsy, Infectious diseases, Inflammations, Leishmaniasis, Sleeping sickness, Snakebite | Anticonvulsant, Antidiabetic, Antitumoral | Aqueous extract, Ethanolic extract, Terpenoids, coumarins, flavonoids, tannins, alkaloids, quinones, Methanolic extract containing Annosenegealin, Annogalene | [10,164] |
| *A. squamosa*    | Tropical America, Asia Australia      | Seed      | Analgesic, Antitumoral, Antineumatic Cancer, Digestive, Headache, Anti-inflammatory, Antimicrobial, Carminative | Antibacterial, Antidiabetic, Antifungal, Antiparasitic | Acetogenins: Squaicosin A and B, Squaicosin B, Bullatacinona, Squamona, Tetrahydroxysquamous Monoterpenes: Limonene, β-Cubebene, β-Caryophyllene, Spathuleol, Caryophyline oxide | [10]       |

6.1. Antibacterial Activity

The antibacterial activities of *Annona* species have been reported in many studies, for example, both methanolic and Ethanolic leaf extracts of *A. muricata* exhibited antimicrobial activity against *Staphylococcus aureus*, and this activity was attributed due to the presence of flavonoids, alkaloids and steroids in the extract [165,166]. In contrast, an aqueous extract of the peel of *A. muricata* did not show any activity [165,166]. The root of *A. reticulata* has also been investigated for its antibacterial activity against Gram-positive *Staphylococcus aureus, Bacillus cereus and Bacillus subtilis*, and Gram-negative *Pseudomonas aeruginosa, Escherichia coli* and *Salmonella typhi* [54]. The root extract was found to possess pronounced activity against *Bacillus cereus* as well as notable inhibition against all tested strains [54]. Moreover, the leaves of *A. cherimola* have been reported for antibacterial activity against *Staphylococcus aureus* and *Bacillus subtilis* with growth inhibition zone diameters of 11 mm and 14 mm, respectively [37]. The aqueous and methanolic seed extracts of *A. squamosa* have reported activity against *Staphylococcus aureus with Minimum Inhibitory Concentrations (MIC) of 50 mg/mL and Minimum Bactericidal Concentrations (MBC) of 100 mg/mL [167]. The activity of the isolated compounds from *Annona* species has been reported in various studies; for instance, the fatty alcohol 11-hydroxy-16-hentriacontanone...
isolated from leaves of *A. squamosa* has a reported activity against Gram-positive and Gram-negative bacterial strains, with MIC values of 25–50 µg/mL [168]. Additionally, the alkaloids liriodenine, annonaine, asimilobine, reticuline and cleistopholine isolated from *A. salzmannii* demonstrated activity against a range of Gram-positive bacteria, including *Kocuria rhizophila, Staphylococcus aureus, Staphylococcus epidermidis* and *Enterococcus faecalis* with MIC values from 25 to 500 µg/mL [36]. Notably, annonaine and asimilobine had activity equal to or better than the control chloramphenicol (MIC 50 µg/mL) against many of the species tested [36].

6.2. Anticancer and Antiproliferative Activity

Various studies have reported the anticancer activity of either crude extracts or isolated compounds from *Annona* species. For example, the leaves extract of both *A. squamosa* and *A. reticulata* exhibited potent antiproliferative effects against two human T-lymphotropic virus type = 1 infected cell lines (MT-1 and MT-2) with EC50 values from 0.1 to 1 µg/mL [169]. In in vitro studies, the ethanolic extract of *A. muricata* leaves was reported for its cytotoxicity against promonocytic leukemic cells (U-937) with an LC50 = 7.8 µg/mL [170]. Isocoreximine isolated from *A. cherimola* demonstrated cytotoxicity against multiple cancer cell lines. At a concentration of 50 µg/mL, isocoreximine inhibited cell viability of the breast cancer cell line (MCF-7) by 85.76%, human colorectal carcinoma cell line (HCT-15) by 63.05%, human prostate tumor cell line (PC-3) by 78.71%, human astrocytoma cell line (U-251) by 65.23% and human leukemia cell line (K-562) by 94.15% [112].

The antiproliferative activity of methanolic extracts from the leaves and seeds of *A. coriacea* was tested in vitro against a range of human tumor cell lines; including melanoma (UACC-62), non-small cell lung cancer cells (NCI-H460), colon cancer cell line (HT29), breast cancer (MCF-7) and leukemia (K-562). The seed extracts displayed potent antitumor activity with GI50 values between 0.02 and 3.83 µg/mL, and the leaf extracts exhibited anticancer activity at concentrations ranging from 0.02 to 0.08 µg/mL [35,171]. The cytotoxicity of annonacin, found in many *Annona* species, has been reported against various cell lines derived from cervical cancer (HeLa and HeLa S3) with IC50 0.219 and 0.426 µg/mL, and ovarian cancer (PA-1 and SKOV3) with IC50s of 0.452 and 0.411 µg/mL [172]. The cytotoxicity of annonacin has also been demonstrated against bladder cancer (T24), breast cancer (MCH7) and skin cancer (BCC-1) with IC50s 0.324, 0.433 and 0.427 µg/mL, respectively [172]. The cytotoxicity of five other acetogenins (squamocin M, annofolin, isolongimicin B, glucanisin, and annotacin) isolated from *A. cornifolia* against human breast cancer (MCF-7) was reported, with IC50s of approximately 0.3 µM [173]. In an in vitro study, the annonaceous acetogenins laherradurin and cherimolin-2 isolated from *A. diversifolia* were shown to have ED50s of 0.015 and 0.05 µg/mL, respectively, against the cervical cancer cell line (HeLa) [174].

In clinical studies, the anticancer activity of *A. muricata* has been reported in a small number of studies. A patient diagnosed with breast cancer has maintained stable disease activity with no reported side effects after using an aqueous extract of *A. muricata* leaves for more than five years [175]. Another patient with metastatic ovarian cancer experienced disease stability after starting to take a complementary medication containing *A. muricata* as a tablet [176]. Finally, the effect of *A. muricata* leaves extract revealed higher cytotoxicity in the supplemented group with colorectal cancer compared with the placebo group in a randomized controlled trial [177].

6.3. Antidabetic and Antilipidemic Activity

Multiple studies have investigated the antidiabetic activity of various extracts from *Annona* plants such as *A. cherimola, A. squamosa, A. muricata* and *A. reticulata*. The ethanolic leaf extract of *A. cherimola* (300 mg/kg) was administered to alloxan-induced type 2 diabetic rats, and four hours later, blood glucose level had decreased from 331.5 mg/dL to 149.2 mg/dL [58]. The young leaves of *A. squamosa*, often in combination with black pepper (*Piper nigrum*), have been used in northern Indian traditional medicine as an anti-diabetic, and are
still in use today. Administration of aqueous A. squamosa leaf extract to streptozotocin-nicotinamide type-2 diabetic rats resulted in decreased blood glucose and increased levels of serum insulin [178]. Another traditional Indian medicine used as an antidiabetic and anti-lipidemic is a polyherbal formulation of A. squamosa fruits and Nigella sativa seeds. The polyherbal formulation administered over a one-month period, dose-dependently decreased blood glucose and increased insulin in streptozotocin-induced diabetic rats, with a dose of 200 mg/kg showing similar to the effects of a dose of 250 mg/kg tolbutamide [179]. A single dose of 100 or 200 mg/kg of aqueous leaf extract of A. muricata did not inhibit blood glucose levels in normal rats; however, the same doses administered to the diabetic rats effectively lowered blood glucose levels by 31.77% and 45.77%, respectively [180]. Finally, a dose of 100 mg/kg of both methanolic extract and the residual fractions of A. reticulata leaves decreased blood glucose levels from 432.33 to 371.67 mg/dL and 417.83 to 402.50 mg/dL, respectively, in streptozotocin-induced diabetic rats [181]. A. cherimola leaf extract was also found to decrease HbA1c by 7% and lead to a significant decrease in urine glucose over a 28-day subchronic study in streptozotocin-induced diabetic mice [182]. These studies support the traditional use of Annona species as antidiabetics, suggesting that further identification of the active constituent(s) with antidiabetic properties and clinical studies of a longer duration are warranted.

Limited studies have also investigated the antilipidemic activity of some Annona species. The polyherbal formulation of A. squamosa fruits and Nigella sativa seeds (200 mg/kg) administered to streptozotocin-induced diabetic rats for one month also resulted in significant inhibition of the formation of both lipid peroxide and tissue lipids [179]. Administration of an extract of A. muricata leaves resulted in reductions in the serum total cholesterol, low-density lipoprotein cholesterol and triglycerides in diabetic rats [183]. The tea infusion of leaves from A. cherimola (1.5 g) also elicited a reduction in the total cholesterol, triglycerides, and low-density lipoprotein by 15.4, 21.9 and 63.2%, respectively, in streptozotocin-induced diabetic rats [182].

6.4. Anti-Inflammatory Activity

The anti-inflammatory effects of Annona plants have been reported in many studies; for instance, after one day of orally administered doses of 200 and 400 mg/kg of A. squamosa root extract in an acute carrageenan-induced rat paw edema model, significant inhibition was produced with 24% and 47% inhibition respectively compared to diclofenac sodium inhibiting inflammation by 72% [184]. In an in vitro study, the chloroform extract of A. muricata leaves significantly inhibited activity of phospholipase A₂ [185]. With doses of 0.2–0.6 mg/mL, the enzyme activity was inhibited by 23.91%–43.48% [185]. In the same study, the chloroform extract of A. muricata leaves at 0.5 and 1.0 mg/mL also inhibited prostaglandin synthase activity by 87.46% and 82.92%, respectively, compared to the positive control indomethacin at 1 mg/mL which reduced enzyme activity by 87.46% [185].

Extracts of A. senegalensis roots were assessed for anti-inflammatory activity through in vitro inhibition of protein denaturation, hyaluronidase and xanthine oxidase. The ethyl acetate fraction was found to have the greatest activity inhibiting protein denaturation (70.6%), hyaluronidase (72.2%) and xanthine oxidase (78.7%) at a concentration of 100 µg/mL [186]. The ethanolic extract of A. muricata leaves exhibited anti-inflammatory effects in the carrageenan-induced rat paw acute edema model. Paw edema was reduced after orally administered doses of 200 and 400 mg/kg with (23.16% and 29.33%) and (29.50% and 37.33%), respectively, after 60 and 90 min of treatment [187]. Additionally, A. muricata fruit has been shown to exert an anti-inflammatory effect in a xylene-induced ear edema test [188]. Additional information regards pharmacological activities of Annona species, see (Table 7).

The lyophilized fruit extract at 50 mg/kg and 100 mg/kg inhibited the xylene-induced ear edema by 82.35% and 76.47%, respectively, compared to prednisolone, which reduced ear edema by 47.06% [188]. At intraperitoneal doses of 25, 50 and 100 mg/kg, the ethanolic extract of A. vepretorum leaves, inhibited carrageenan-induced leukocyte migration to the
peritoneal cavity by 62%, 76% and 98%, compared to dexamethasone (2 mg/kg, i.p.), which reduced leukocyte migration by 89% [104]. The flavonoids, quercetin and kaempferol isolated from leaves of *A. dioica* exhibited potent dose- and time-dependent anti-inflammatory activity in a carrageenan-induced paw oedema model with IC$_{50}$s of 8.53 and 10.57 µg/mL, respectively. The crude methanolic extract of *A. dioica* also reduced myeloperoxidase activity 6 h after the induction of paw oedema with a maximal inhibition of 51% at a dose of 300 mg/kg. [189]. Finally, hinesol, β-caryophyllene and beta-maaliene isolated from leaves of *A. sylvatica* also inhibited leukocyte migration at concentrations from 36.04 to 45.37 µg/mL in both carrageenan- and complete Freund’s adjuvant-induced mouse paw edema [33].

### 6.5. Antioxidant Activity

An extract of *A. coriacea* seeds was investigated for its antioxidant activity using free radical 2,2-diphenyl-1-picrilhidrazil (DPPH) and bleaching of β-carotene, and a moderate antioxidant effect was reported of 31.53% in the DPPH test and 51.59% for the β-carotene bleaching test [190]. The pulp of *A. coriacea* fruit displayed a weaker antioxidant activity compared to the seeds, with 13.49% for the DPPH test and 32.32% for the β-carotene assay [190]. Additionally, various parts of *A. muricata*, including bark, leaves and stem, exhibited antioxidant activity using DPPH assay and the EC$_{50}$ value was recorded as 90 mg/g for bark, 290 mg/g for leaves, and 116 mg/g for the stem, compared to ascorbic acid with 157.5 mg/g [44]. Finally, an ethanolic extract of *A. squamosa* leaves was also reported as having antioxidant activity when evaluating DPPH, nitric oxide and superoxide radical assays. The activity was reported as 75.12%, 34.69% and 10.29%, respectively, at a concentration of 100 µg/mL [191].

### 6.6. Antileishmanial Activity

Many extracts and pure compounds from *Annona* plants have been tested against *Leishmania*, such as methanolic seed and leaf extracts of *A. squamosa*, for activity against *L. amazonensis*, with resulting showing IC$_{50}$s of 46.54 µg/mL and 28.32 µg/mL, respectively [192]. Alkaloids and acetogenins isolated from both leaves and seeds of *A. squamosa* were also reported for their activity against promastigote forms of *L. chagasi*, with the EC$_{50}$ value reported as 23.3 µg/mL for alkaloids and from 25.9–37.6 µg/mL for acetogenins [192]. Alkaloids like liriodenin isolated from the leaves of *A. mucosa* exhibited antileishmanial activity against promastigote forms of *L. braziliensis*, *L. guyanensis* and *L. amazonensis* with IC$_{50}$s of 55.92 µg/mL, 0.84 µg/mL 1.43 µg/mL respectively [193]. Finally, O-methylarmepavine isolated from leaves *A. squamosa* displayed antileishmanial activity against both promastigote and amastigote forms of *L. chagasi* with EC$_{50}$s of 23.3 µg/mL and 25.3 µg/mL, respectively [45].

### 6.7. Antiviral Activity

The antiviral activity of various *Annona* species was reported in several studies using either whole extract or pure compounds. For instance, 16β,17-dihydroxy-ent-kauran-19-oic acid was isolated from the fruits of *A. squamosa* and showed significant activity against human immunodeficiency virus (HIV) replication using H9 lymphocyte cell assay with EC$_{50}$ value of 0.8 µg/mL [194]. The ethanolic extract of *A. squamosa* seeds at 0.15 µg/mL, 0.25 µg/mL and 0.35 µg/mL also exhibited dose-dependent antiviral activity against the Avian influenza virus with the percentage of antiviral activity at 33.33%, 43.06% and 59.72%, respectively [195]. The leaves of *A. squamosa* extract were also tested against dengue virus type-2 (DENV-2) in Vero cells using Viral ToxGLo™ assay. At a concentration of 6.25 µg/mL, DENV-2 replication was reduced with IC$_{50}$ 73.78 µg/mL in Vero cells [196]. The methanolic extracts from the peels of *A. squamosa* and *A. reticulata* demonstrated antiviral activity against human immunodeficiency virus 1 (HIV-1) using a non-radioactive immune/colorimetric assay. Both *A. squamosa* and *A. reticulata* revealed high antiviral activity by inhibition of HIV-1 reverse transcriptase with values of 96.45% and 78.63% [197].
Moreover, *A. cherimola* was also evaluated for its antiviral activity against herpes simplex virus type 2 (HSV-2) using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay. The leaf extract inhibited HSV-2 replication and showed antitherapeutic activity with a therapeutic index 8.40 [198]. Finally, the ethanolic stem extraction of *A. muricata* demonstrated antiviral activity against herpes simplex virus type 1 (HSV-1) with a minimum inhibitory concentration (MIC) of 1 mg/mL [199].

### 7. Pharmacological Activity of Isolated Compounds from *Annona* Species and their Mechanism of Action

The in vitro and in vivo biological activity of compounds that have been isolated from various parts of *Annona* plants will be discussed. Squamins C–F were isolated from the seeds of *A. globifora* and tested in vitro against trophozoites of *Acanthamoeba* spp. strains such as *A. castellanii* Neff, *A. polyphaga*, *A. griffinii* and *A. quina* (Table 8) [200]. All tested compounds exhibited antiamoeboid activity against the strains by inducing programmed cell death [200]. The same compounds were also tested for their cytotoxicity against murine macrophage cell line J774A.1 (ATCCCTIB-67) and showed no cytotoxicity effect with CC$_{50}$ values greater than 200 µM [200].

**Table 8. Antiamoebic activity of squamins C-F versus *Acanthamoeba* spp. Strains.**

| Compounds   | *A. castellanii* Neff IC$_{50}$ (µM) | *A. polyphaga* IC$_{50}$ (µM) | *A. griffin* IC$_{50}$ (µM) | *A. quina* IC$_{50}$ (µM) |
|-------------|-------------------------------------|-------------------------------|-----------------------------|---------------------------|
| Squamin C   | 20.77 ± 3.48                        | 71.78 ± 0.41                  | 38.81 ± 7.34                | 24.28 ± 0.64              |
| Squamin D   | 18.38 ± 1.14                        | 71.57 ± 0.14                  | 39.53 ± 5.90                | 26.52 ± 0.87              |
| Squamin E   | 21.00 ± 0.86                        | 62.19 ± 15.52                 | 44.75 ± 2.06                | 25.82 ± 0.99              |
| Squamin F   | 18.02 ± 3.28                        | 64.08 ± 12.42                 | 50.49 ± 6.92                | 30.32 ± 0.27              |

Rollinicin and rolliniastatin-1 isolated from the seed of *A. mucosa* were also reported for their larvicial effect against *Aedes aegypti* and *Aedes albopictus* larvae [201]. Rolliniastatin-1 exhibited the best larvicial effect against both *Aedes aegypti* and *Aedes albopictus* with LC$_{50}$ of 0.43 and 0.20 µg/mL$^{-1}$, respectively. Rollinicin displayed similar activity against *Aedes aegypti* and *Aedes albopictus* with LC$_{50}$ of 0.78 µg/mL and 1.128 µg/mL, respectively [201]. However, the larvicidal mechanism action of these compounds was not reported. Annonacin isolated from the seed of *A. muricata* was evaluated for its larvicial activity on *Aedes aegypti* and *Aedes albopictus* larvae [202]. The greater larvicial activity was reported against *Aedes aegypti* with a LC$_{50}$ of 2.65 µg/mL compared to *Aedes albopictus* with LC$_{50}$ of 8.34 µg/mL. The mechanism of action was reported as being inhibition of their metabolic enzymes, particularly proteases and amylases that are important for the development of *Aedes* spp. larvae [202]. Twelve acetogenins isolated from the seed of *A. cornifolia* were tested for their antioxidant activity against DPPH [90]. These acetogenins were identified as 9-hydroxyfolianain, 4-desoxylongimicin, squamocin M, squamocin L, folianin A, folianin B, amnofolin, isolongimicina B, bullatacin, asimicin, cornofolin and anotacin, and showed a strong DPPH radical scavenging with IC$_{50}$ ranging from 0.99 ± 0.18 to 1.95 ± 0.34 µg/mL compared to ascobic acid with an IC$_{50}$ 1.62 ± 0.35 µg/mL [90]. It has been suggested that the antiradical activity of acetogenins may be related to the α,β-unsaturated lactone ring moiety, which is also present in ascobic acid [90]. Furthermore, the antioxidant activity of pure compounds from the bark of *A. salzmanni* after isolation of five alkaloids identified as lirodineine, annonaine, asimilobine, reticuline and cleistopholine [203]. The antioxidant activity was assessed through the Oxygen Radical Absorbance Capacity (ORAC) assay and asimilobine was found to be the most active alkaloid with ORAC value of 2.09 [203]. The rest of the compounds exhibited antioxidant activity with ORAC values ranging from 0.25 to 0.85 [203]. These same compounds were also examined for their antimicrobial activity against *Kocuria rhizophila*, *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Enterococcus faecalis* with MIC values from 25 to 100 µg/mL [203]. In an in vitro study, the antimicrobial activity of isolated alkaloids from aerial parts of *A. senegalensis* was assessed in a microdilution assay [154].
These alkaloids were identified as anonaine and asimilobine, and demonstrated against Streptococcus mutans with MIC values of 0.12 and 0.25 mg/mL, respectively [154]. For trypanocidal activity, three alkaloids liriodenine, annomontine, and O-methylmoschatoline were isolated from the branch of A. foetida and tested against both epimastigote and trypanomastigote forms of Trypanosoma cruzi [101]. A potent trypanocidal effect was demonstrated against epimastigote forms with IC₅₀ ranging from 92.0 ± 18.4 to 198.0 ± 4.2 µg/mL, and from 3.8 ± 1.8 to 4.2 ± 1.9 µg/mL for trypanomastigote forms [101]. Additionally, N-hydroxyannomontine isolated from the bark of A. foetida, demonstrated antileishmanial activity versus Leishmania braziliensis and L. guyanensis with IC₅₀ values of 252.7 ± 2.2 and 437.5 ± 2.5 µM, respectively [204].

Many compounds isolated from various Annona species have demonstrated cytotoxicity against different cancer cell lines (Table 9). Three alkaloids were isolated from leaves of A. crassiflora identified as crassiflorine, xylopine and stephalagine and tested for their activity against colon carcinoma cells (HCT-116) using MTT assay [204]. The cytotoxicity activity for the tested compounds was reported with IC₅₀ values of 143.4 µM, 30.2 µM and 48.5 µM, respectively [204]. Muricin J–K isolated from the fruit of A. muricata exhibited anticancer activity against human prostate cancer cell lines (PC-3) through inhibition of the mitochondrial complex I in an in vitro study [205]. The anticancer activity was also reported for the alkaloid coclaurin isolated from aerial parts of A. squamosa. Cytotoxicity studies against human breast cancer cells (MCF-7), human colon cancer cells (HCT116) and human liver cancer cells (HEPG-2) reported IC₅₀ values of 15.345 µg/mL, 8.233 µg/mL and 1.674 µg/mL, respectively [206]. Bullatacin isolated from A. cherimola demonstrated inhibition of tumor growth at a dose of 15 µg/kg in mice bearing HepS and S180 xenografts and tumor growth was reduced by 63.4% and 65.8%, respectively [207]. Muricin J–K exhibited antiproliferative activity against human breast cancer cell lines (PC-3) through inhibition of the mitochondrial complex I in an in vitro study [205]. The anticancer activity was also reported for the alkaloid coclaurin isolated from aerial parts of A. squamosa. Cytotoxicity studies against human breast cancer cells (MCF-7), human colon cancer cells (HCT116) and human liver cancer cells (HEPG-2) reported IC₅₀ values of 15.345 µg/mL, 8.233 µg/mL and 1.674 µg/mL, respectively [206]. Bullatacin isolated from A. cherimola demonstrated inhibition of tumor growth at a dose of 15 µg/kg in mice bearing HepS and S180 xenografts and tumor growth was reduced by 63.4% and 65.8%, respectively [207]. In the same study, annonacin administrated orally (10 mg/kg) to hybrid mice (BDF-1) models significantly reduced lung cancer by 57.9% [207]. However, the mechanism of action of these acetogenins was not described in this study. Finally, stephalagin, an alkaloid isolated from the peel of A. crassiflora fruit, was reported as pancreatic lipase inhibitor with an IC₅₀ of 8.35 µM−1 in vitro study [208].

Table 9. Anticancer activity of isolated compounds from Annona species and their mode of action.

| Annona Species | Plant Part | Isolated Components | Cell Line or Animal Model | Mechanism of Action | References |
|---------------|------------|---------------------|--------------------------|---------------------|------------|
| A. cherimola  | Seeds      | Annomolin and Annocerinolin | Prostate tumor cell line (PC-3), breast (MCF-7) and colon (HT-29) cancer cell lines | Exhibited potent cytotoxicity | [209] |
|               | Leaves     | Asimilobine         | Acute myeloid leukemia cell line | Ureplgulation of Bax, downregulation of Bcl2, and cleavage of PARP | [210] |
| A. crassiflora| Crude extract | Catechin         | Cervical cancer cell | Apoptosis via intrinsic pathway | [211] |
|               | Fruits     | Annoglabin H       | Lung adenocarcinoma cell line (LU-1), human breast carcinoma (MCF-7), human melanoma (SK-Mel2) | Exhibited significant cytotoxicity | [212] |
|               |            | Annoglabin H       | Human liver cancer cell line (Hep G2) | Apoptosis via mitochondrial pathway | [132] |
| A. glabra     | Fruits     | Cunabic acid and ent-kauran-19-al-17-oic acid | Liver cancer (HLC) cell line SMMC-7721 | Apoptosis via down-regulation of BCL-2 gene and upregulation of bax gene | [213] |
|               | Leaves     | Asinicin           | Human monocytic leukemia cells (CRL-12253) | Mitochondria mediated anticancer and antiproliferative effects | [214] |
|               |            | Annoglacin A and B | Human breast carcinoma (MCF-7) and Pancreatic carcinoma (PACA-2) cell lines | Suppressed proliferation | [215] |
|               |            | Icariside D2       | Human leukemia cell line (HL-60) | Induced apoptosis and decreased phosphorylation of AKT in cells | [216] |
Table 9. Cont.

| Annona Species | Plant Part | Isolated Components | Cell Line or Animal Model | Mechanism of Action | References |
|----------------|------------|---------------------|---------------------------|---------------------|------------|
| **A. muricata** | Leaves     | Annomuricin, Muricoreacin, Muricapentocin, Muricatoxins A and B | Colon cancer cell (HT-29, HCT-116) Pancreatic carcinoma (PACA-2) and colon adenocarcinoma (HT-29) Lung tumor cell line (A-549) | Suppressed breast cancer proliferation and induced apoptosis Up-regulation of Bax, downregulation of Bcl-2 proteins and activated initiator and executioner caspases | [217], [218], [219] |
| Fruits         | Muricorneacin, Murihexocin | (HT-29, HCT-116) | Colon cancer cell (HT-29, HCT-116) | Enzyme-cleaved procaspases caspase-dependent apoptosis | [218] |
| **A. purpurea** | Roots      | Annopurpuricins A–D | HeLa and HepG2 cells | Mitochondrial membrane depolarization and apoptosis | [220] |
| Fruits         | Catechin   | Breast cancer cell line (MCF-7) | Exhibited cytotoxic effect | | [222] |
| Fruits         | Annonacin  | T24 bladder cancer cells | Bax expression was induced, caspase-3 activity enhanced and caused apoptosis | | [172] |
| Fruits         | Bullatacin | Leukemia cell line (K562) and breast cancer cell line (MCF-7) | Cell death via apoptosis | | [223] |
| **A. reticulata** | Leaves     | Annomonicin, Rolliniastatin | Colon cancer (HCT15), human lung cancer (HOp65) and human hepatoma (HEPG2) cell lines | Exhibited cytotoxic effect | [224] |
| **A. senegalensis** | Leaves | Roemerine | Breast cancer MDA-MB-231 cells | Exhibited dose-dependent cytotoxicity via targeting the ribosomal protein eL42 and arresting the crosslinking reaction with tRNAox | [226] |
| Bark           | Kaurenoc acid | Pancreatic tumor (PANC-1) cell lines and Henrietta Lacks' cervical cancer cell line (HeLa) | Exhibited significant cytotoxic activity | | [227] |
| Stem           | Ent-kaurenoids | Breast cancer (MCF-7) cells, prostate cancer (PC-3) cells | Exhibited significant cytotoxic activity | | [228] |
| Leaves         | Annoreticuin | Breast cancer cell (MCF-7) | Induced Apoptosis | | [229] |
| Fruits         | Diepotetecin B, Squamocin, Annosquatin III, Asimilobine | Nasopharyngeal cancer (KB) cell lines, breast cancer (MCF-7) cell lines | Exerted inhibitory activity | | [230] |
| **A. squamosa** | Seeds      | Annosquatin A, B | Human colon cancer cell (WiDr) Human leukemia cell line (K-562), human colon carcinoma (COLO-205) | Increased expression of caspase-3 Reduced intracellular glutathione levels and regulation of Bcl-2 and PS externalization | [231], [232] |
| Fruits         | Annosquacins A-D, Annosquatin A, B | Human breast cancer cell line (MCF-7), human lung adenocarcinoma cell line (A-549) | Exhibited cytotoxic activity | | [233] |
| Bark           | Coclaurine | DMBA painted hamsters | Enhanced lipid peroxidation | | [235] |
| Fruits         | (−)-Ent-kaur-16-en-19-oic acid, 16α,17 dihydroxy-ent-kauran-19-oic acid | Dalton's lymphoma cells, HeLa cells | Exhibited cytotoxic activity | | [236] |
| **A. sulcata** | Leaves     | Quercetin | Anti-inflammatory | Leukocytes migration was significantly reduced at IC50 8.53 and 10.57 µg/mL, respectively. | [189] |
| **A. vepretorum** | Leaves | Bicyclogermaene | Antimicrobial | Against Candida tropicalis with a MIC value of 100 µg ·mL⁻¹. | [237] |
8. Toxicity and Interactions

Generally, the safety of natural medicines can be assessed according to their effects and drug-drug interactions. An epidemiological study has reported that consumption of fruits of Annonaceae led to the prevalence of atypical parkinsonism in Guadeloupe due to the presence of acetogenins in the plant fruits [238]. According to Champy et al. 2005, the amount of annonacin per a single fruit is approximately 15 mg, and an adult who consumes a daily intake of one fruit for one year is equivalent to the amount of annonacin injected into rats, which induced the brain lesions [239]. It has been suggested that the toxicity might be related to the capacity of the tetrahydrofuran ring to chelate calcium ions [35]. Moreover, the fruit of *A. squamosa* has been analysed for its quantity of squamocin using HPLC-MS and reported 13.5–36.4 mg of squamocin for each fruit, and that long-term consumption of *A. squamosa* fruit may be a risk factor in the development of neurodegenerative disorders [240]. Additionally, the use of a dietary supplement sold in the USA containing an extract of *A. muricata* has been found to exhibit neurotoxic effects in human neuron cultures [241].

The interactions of *Annona* species with other drugs have been reported in other studies; for instance, administration of capsules of *A. muricata* leaves in combination with glibenclamide resulted in improved glycaemic control compared to patients who received only glibenclamide [242]. An additional study reported that a combination of aqueous custard apple leaf extract and glipizide enabled a decrease in the dose of glipizide by up to half in rats with type-2 diabetes and reduced the risk of requiring insulin therapy [243]. These outcomes suggest the potential use of certain *Annona* species in conjunction with antidiabetic medications to maximize the efficacy of a lower therapeutic dose.

9. Conclusions

This review provides a comprehensive summary of the botanical features, ethnomedical uses, pharmacology and phytochemistry of the main species of Annonaceae family and, in particular, the *Annona* genera used in traditional medicine practices. Of the many members of the Annonaceae family, the *Annona* species is heavily used in traditional medicines across the world. Among the 30 reviewed *Annona* species, six species *A. squamosa, A. muricata, A. cherimola, A. senegalensis, A. reticulata* and *A. coriacea* are the most widely studied for their pharmacological activities and phytochemical profiles of their bark, leaves, fruits and seeds. Various pharmacological properties have been reported, including antidiabetic, hepatoprotective, anti-inflammatory, antiprotozoal, antitumor, antioxidant, antimicrobial and anticonvulsant activity.

With regard to the phytochemistry of *Annona* species, the main classes of constituents identified to date are acetogenins, alkaloids, phenols and essential oils. The alkaloids are mainly present in the leaves, whereas acetogenins are present in the seeds and found in smaller quantities in the pulp and leaves of *Annona* species. The chemical profiles of the acetogenins present in different species have been extensively studied and their anticancer activity investigated, with low concentrations exhibiting chemotoxicity against several cancer cell lines. These preclinical results, along with the reported case studies, suggest that further clinical studies evaluating the role of acetogenins in the treatment of various types of cancers are warranted. Importantly, formulations, including the parts of the *Annona* species used, agricultural practices and the extraction methods vary considerably, leading to likely variations in the phytochemical and pharmacological profiles. In this respect, further characterization of standardized formulations of *Annona* species is required to predict likely clinical effects. Additional interesting results on the antidiabetic effects of fruits from *Annona* species also warrant further investigation as nutraceuticals to assist in the therapy of diabetes.
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