Screening of antidiabetic and antioxidant potential along with phytochemicals of Annona genus: a review

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Abstract

Background: Annona species can be found in the subtropical and tropical parts of the world. Because of their medicinal capabilities and highly exotic edible fruits, they are one of the most important members of the Annonaceae family. Isoquinolines, pyrimidine-β-carboline alkaloids, lectins, acetogenins, and volatile oils are among the active metabolites found in this genus, all of which have been shown to have anti-diabetic and antioxidant activities.

Main body: The fundamental objective of this review was to summarize the antidiabetic and antioxidant activity based on reported secondary data from different plants of the genus Annona. These species include Annona cherimola, Annona squamosa, Annona macrophyllata, Annona muricata, Annona reticulata, Annona carcans, Annona coriacea, Annona coriifolia, and Annona senegalensis. The Annona species investigated had significant antihyperglycemic and antioxidant properties.

Conclusion: The available evidence, both in vitro and in vivo, confirms the ability of Annona species to treat diabetes in addition to producing oxidative damage.

Keywords: Annona, Antioxidants, Medicinal plants, Antidiabetic

Background

The Annona genus is named after the Latin phrase “annual harvest.” Among the Annonaceae families, this genus provides the most food. It contains approximately 162 species of trees and shrubs. These species are thin, 5 to 11 m tall, upright or slightly disseminated, and sometimes rough, with gray to brown bark [1]. With around 2400 species in 108 genera, Annonaceae are mainly pantropical, are a larger family than any other Magnoliidae group. The botanist Jussieu published his classification of the Annonaceae family in 1789 [2, 3]. Different analytical methods have documented terpenoids (mainly diterpenes) and alkaloids (isoquinoline alkaloids) in this family species [4]. The family has several plant species of economic value as they are edible worldwide, including tropical America, Australia, Africa, India, Europe, and the Mediterranean [5], which makes this genus economically the most important because of its foodstuffs and medicinal properties. The fruits of a number of Annona species are edible, including Annona crassiflora (araticum), Annona squamosa (Fruita do conde), and Annona muricata (Graviola). In Brazil, several of the Annonas’ fruits are highly prized. It is frequently consumed “naturally” or in the form of juice, cake, or ice cream [6]. Earlier molecular and medicinal studies of the species have shown substantial biological activities, such as cytotoxicity to various cell lines, anti-platelet, antiparasitic, antibiotics, and antimicrobial properties. The existence and reason for these activities is due to the presence of alkaloids, acetogens, and terpenes [7]. As a result, the purpose of this study was to examine the Annona genus...
species that have anti-diabetic and anti-oxidant capabilities.

**Methods**

We reviewed scientific articles published in journals by electronic databases (Google Scholar, PubMed, Medline, Web of Science, DOAJ, and Scopus) using specific keywords such as “Annona”; “Diabetes mellitus”; “Antioxidants”; “Medicinal plants”; “Antidiabetic”. We reviewed 76 articles that provided data on the use of Annona species to treat diabetes and oxidative damage. The synonyms, taxonomy, and several other botanical distribution and descriptions were retrieved from “The Plant List” (http://www.theplantlist.org/), “Flora of Bangladesh” (http://bnh-flora.gov.bd/species-list/), and “CABI” (https://www.cabi.org/isc/).

**Main text**

**Botanical distribution**

Nine species of the Annona genus were characterized in this study, whose botanical representation is summarized in Table 1.

**Annona cherimola**

*Annona cherimola* Miller belongs to the genus Annona in the Annonaceae family in magnolias order, which is also provides edible fruit species. It is a steep, semi momentary but low bunched tree. The plant, highly prevalent in Ecuador and Peru is widely distributed throughout the tropics and subtropics of America, Africa, Asia, and even South Europe [8, 9]. Alone or in combination with others, it has been used in Mexican Traditional medicine to treat several diseases like fever, cough, worms, headache, and inflammation. Currently, this is utilized in the treatment of diabetes [10–12].

**Annona squamosa**

*Annona squamosa* L., known as custard apple, generally is an endemic of the West Indies, and throughout India, it is well grown. Annona squamosa is renowned for its anti-diabetic properties among tribal men in and around Aligarh district’s village in Uttar Pradesh [13]. There, native people make a mixture of 4–5 newly emerged leaves with five grains of black pepper early in the morning to treat diabetes. Continuing the therapy ensured up to 80% positive results [13].

**Annona macroprophyllata**

*Annona macroprophyllata* Donn. Sm. is yet another species that is known to be classified under the genus Annona. It is referred to as “ilama,” a common tree in central Mexico. It is familiar by “papauce” or “anona blanca” in the Southeast [14, 15]. Its fruits are consumed as food, but its leaves are used as anticonvulsants [16]. In traditional medicine, it is also prescribed as an analgesic and anti-inflammatory agent [17].

**Annona muricata**

*Annona muricata* is a well-known member of the Annonaceae family and the Annona genus. It is commonly known as sour-sop. It is employed for treating diabetes, hypertension, fever, pain, and against worms and vomiting [18]. Several pharmacological studies showed that *Annona muricata* possess vasodilator, cardio-depressive, antispasmodic, antihypertensive, antimutagen, anticonvulsant antiviral, antidiabetic, and antioxidant properties [26–30].

**Annona reticulata**

*Annona reticulata* in India is typically known as “custard apple” or “heart bullock.” It is locally useful in the treatment of epilepsy, dysentery, cardiac problem, parasite and worm infection, constipation, and bacterial infection [19].

**Annona carcas**

*Annona carcas* is a member of the Annonaceae family, which comprises woody, arbustive, or arborist plants and many fruits [21, 31] and also known as *Annona amambayensis* Hassl. It is commonly known as “araticum-caga - reso” or “cortic - a reso.” It is used as purgative in folk medicine, and found in the Brazil [21].

**Annona coriacea**

Annona coriacea is a fruit tree native to Brazil. The ecoregions of Cerrado, Caatinga, and Pantanal are part of their original habitat. Buildings and toys are made from the wood. Synonyms of this plant are *Annona coriacea* var. cuneata R.E. Fr and *Annona geraensis* Barb. Rodr [32].

**Annona cornifolia**

*Annona cornifolia* is part of the family of Annonaceae and *Annona walkeri* S.Moore is used as a synonym of this plant. It is commonly referred to as “aratian-mirim.” The fruit pulp is mature, orange, and sweet and aromatic. The green fruit is well-known for its ability to treat ulcers [24].

**Annona senegalensis**

*Annona senegalensis*, referred to as sour soup (English), abo (Yoruba, Western Nigeria), and uburuocha (Igbo, Eastern Nigeria), is commonly found in Nigeria [25]. The bark of the stem is silvery gray or gray-brown. The leaves are simple, alternate, and oblong, and they’re hairless on top with brownish hair on the underside. Leaves are used to treat diarrhea, joint disease, respiratory disease, conjunctivitis, burns, snakebite sores, trypanosomiasis, jaundice, bleeding, female barrenness, seizures, asthenia, and fever [26].
Phytochemicals

Nine species of the Annona genus were characterized in this study, whose phytochemical study is summarized in Table 2.

**Annona cherimola**

From the ethanol leaf extract of *Annona cherimola*, four flavonoid compounds: kaempferol, quercetin, nicotinflorin, and rutin and phenolic compound caffeic acid was also identified using the TLC method [33]. Chen et al identified Aromin-A; squamocin from the stem extract of *A. cherimola*, along with Cherimolin; dihydrocherimolin; molvizarin;motrilin; itrabin; jetein; cherimolin-2; almunequin from the seeds [34]. In the ethanol extract of the *Annona cherimola* seeds, two new cytotoxic addictive acetogenins, anomolin and annonocherimolin, were identified [35].

**Annona squamosa**

*Annona squamosa* is proven to have glycosides, alkaloids, saponins, flavonoids, tannins, carbohydrates, proteins, phytosterols, amino acids, and phenolic compounds. Different chemical components have been identified from the plant’s leaves, stems, and roots, including 15 alkaloids, 10 cyclopeptides, 39 acetogenins, and 8 diterpenoids [36].

**Annona macrophyllata**

Seed extract of *Annona macrophyllata* constitutes 3 compounds namely, Laherradurin (acetogenin), rolliniastin-2, and cherimolin-2 [47, 48].

### Table 1: Botanical Information of the species

| Scientific name | Local name | Synonym | Local uses | Distribution | References |
|-----------------|------------|---------|------------|--------------|------------|
| Annona cherimola | Chirimoya, Atemoya, Chirimonia, Cerimoya, cherimoyer, momona | Not reported | Insecticide, fever, cough, worms, anti-inflammatory, headache | Egypt, Eritrea, Somalia, South Africa, China, India, Israel, Myanmar, Philippines, France, Italy, Portugal, Spain, Mexico, Ecuador, Peru | [8–12] |
| Annona squamosa | Custard apple, chirimoya fruta do conde, tiep baay, amrtaphala | Annona asiatica L. | Antidiabetic | Egypt, Sudan, China, India, Israel, Pakistan, Thailand, Costa rica | [13] |
| Annona macrophyllata | Ilama, Papauce, Annona blanca | Annona diversifolia Saff. | Anticonvulsant, analgesic, anti-inflammatory | Mexico, China, India | [14–17] |
| Annona muricata | ci guo fan li zhi nangka seberang durian belanda | Annona macrocarpa Barb.; Annona muricata L.; Annona muricata L. | diabetes, hypertension, fever, pain and against worms and vomiting | China, India, Indonesia, Malaysia, Myanmar, Pakistan | [18] |
| Annona reticulata | Bullock’s heart | Annona excelsa Kurt; Annona laevis Kunth; Annona longifolia Moc.; Annona longifolia Sesse.; Annona riparia kunth. | Epilepsy, dysentery, cardiac problem, parasite and worm infection, constipation, and bacterial infection | India, Bangladesh, China, Indonesia, West indies | [19] |
| Annona crassiflora | Araticum, marolo, pinha-docerrado (cerrado pine-cone), cabeza de negro, etc | Annona macrocarpa Barb., Annona rodighuesi Barb. | Astringent, antidiarrheal, rheumatism, treating wounds, snake bites and pediculosis. | Brazil | [20] |
| Annona carcin | ‘araticum-caga - reso” or “cortic - a reso,” | Annona amambayensis Hassl. ex R.E.Fr., Annona cacans var. glabriuscula R.E.Fr., Annona cacans subsp. glabriuscula (R.E.Fr.) H.Rainer | Purgative | Minas Gerais, Mato Grosso do Sul, Espírito Santo, Parana’, Rio de Janeiro, Rio Grande do Sul, Santa Catarina, and Sao Paulo | [21] |
| Annona coriacea | Marolo, araticum | Annona coriacea var. amplexicaulis S.Moore, Annona coriacea var. cuneate, Annona coriacea var. pygmaea Warm. | Chronic diarrhea, antimalarial, antihelmintic | Brazil | [22, 23] |
| Annona cornifolia | araticum-minim | Annona walkeri S.Moore | – | Brazil | [24] |
| Annona senegalensis | Sour soup, abo, uburoochaud gwanwar | Annona senegalensis var. arenaria Sillans, Annona senegalensis var. cuneata Oliv, Annona senegalensis var. glabrescens Oliv. | Diarrhea, disease of the joints, conjunctivitis, wounds, snakebites, trypanosomiasis, jaundice, hemorrhoids, feminine barrenness, convulsions, fever, and asthenia | Nigeria | [25] |
| Scientific name | Parts used                  | Compounds                                                                 | Reference |
|-----------------|-----------------------------|---------------------------------------------------------------------------|-----------|
| Annona cherimola| Leaf, Stem, Seed            | kaempferol, quercetin, nicotinflorin, rutin, caffeic acid, Aromin-A, squamocin, cherimolin, dihydrocherimolin, molvizarin, motrilin, itrabin, jetein, cherimolin-2, almuquequin, acetoegenin, anomolin, annocincholin | [33–35]  |
| Annona squamosa | Leaves, tender stem, Bark, Seeds, Stem bark | Annonaine-Anolobine,Aphorpine,Corydine/soycordine,Norcorydine,Norisocorydine, Glaucine,Lirodine,Norlaureline,Reticuline,Roemerine,Samoquasine A, Annoquatilin,Cyclosqamosin A, Cyclosqamosin B, Cyclosqamosin C, Cyclosqamosin D, Cyclosqamosin E, Cyclosqamosin F, Cyclosqamosin G, Cyclosqamosin H, Cyclosqamosin I, Squamtin A, Annosquamocin A, Annonacin, AnnonacinA, Annonatatin, Squamocin, Squamocin-OI, Squamocin-O2, Bullatacin, Bullataticine, 4-deoxyannocerin, cis-4-deoxyannoceratocin(2,4 cis and trans)-squamoxinone, (2,4 cis and trans)-Mosinone A, Mosin B, Mosin C, Squamotacin, Molvizarin, (2,4 cis and trans)-squamolinone, (2,4 cis and trans)-9-oxoasimicrinone, Bullacin B, Squamostatin D, (2,4 cis and trans)-bullatacine, Squamostatin C, Annonin I, Annonin VI, Squamostene-A, Reticulacin-1, Squamosinin-A, Annotemoyin-1, Annotemoyin-2, Annonosin A, Annosquisins A, Annosquisins B, Annosquamosin C, Annosquamosin D, Annosquamosin E, Annosquamosin F, Annosquamosin G. | [36]     |
| Annona macrophylaltta | Seeds                      | Laherradurin, Rottolinastatin-2, cherimolin-2                                | [37]      |
| Annona muricata  |                             | Annonaine, normuciferine, asimilobine, epomusenin-A, epomusenin-B, epomurinin-A, epomurinin-B, cis-anocarecin, muricin J, muricin K, muricin L, cinnamic acid derivative, coumaric acid hexose, 5-caffeoylquinic acid, dihydrokaempferol-hexoside, p-coumaric acid, caffeic acid derivative, e, dicaffeoylquinic acid, feruloylglycoside, 4-feruloyl-5-cafeoylquinic acid, p-coumaric acid methyl ester, annonacin A, annonacin B, annonacin C, annonacin E, annonacin A-one, (2,4-cis)-10B-annonacin-A-one, (2,4-trans)-10B-annonacin-A-one, annocinexin, muniperacotin, (2,4-cis)-isoannonacin, (2,4-trans)-ionononacin, muricatin A, muricatocin B, muricatocin C, gigantepteronenin, annocinalcin, annocinalcin B, annocinalcin C, annocatalin, (2,4-trans)-10R-annonacin-A-one, squamocin-O1, Squamocin-O2, Bullatacin, Bullataticine, 4-deoxyannocerin, cis-4-deoxyannoceratocin(2,4 cis and trans)-squamoxinone, (2,4 cis and trans)-Mosinone A, Mosin B, Mosin C, Squamotacin, Molvizarin, (2,4 cis and trans)-squamolinone, (2,4 cis and trans)-9-oxoasimicrinone, Bullacin B, Squamostatin D, (2,4 cis and trans)-bullatacine, Squamostatin C, Annonin I, Annonin VI, Squamostene-A, Reticulacin-1, Squamosinin-A, Annotemoyin-1, Annotemoyin-2, Annonosin A, Annosquisins A, Annosquisins B, Annosquamosin C, Annosquamosin D, Annosquamosin E, Annosquamosin F, Annosquamosin G. | [38]      |
| Annona reticulata | Leaf, Bark, Stem bark, Root bark, Seed, Fruit | Dopamine, Salololin, Coquarine, Sesquiterpenes mainly Spathenelol, Muurolene, Copaene, Eudesmol, Acetogenin – Squamone, Solamin, Annomonicin, Rottlinastatin 2, Annonreticulin-9-one. Triterpenoid – annonaretin A, Monotetrahydrofuran acetogenin, Reticulatocin, Diterpenes: (--) kau-M-en-19-19-cid acid and methyl 1β, 17-dihydro(--)-kauran-19-oate, Alkaloids: Lirodine, Copaene, Patchouline and 1H-cycloprop (e) azulene, (--)Kau-16-en-19-oic acid, Bisetrahydrofrone acetogenin, Bullataticine. Dopamine, Salololin, Coquarine, Diterpenes: (--) kaur-16-en-19-oic acid, 16 α-hydroxy(--)-kauran-19oic acid, Methyl-17-hydroxy-16 β-(-)-kauran-19-oate, Reticulatocin, Rolliniastatin-2 (= bullatacin = annomolin-V), Molvizarin, Aporphine alkaloids, Lirodine, Norushinsunine. Reticuline, Acetogenin neoannoretin, Sesquiterpenes mainly Spathenelol, Muurolene, Copaene, Eudesmol, Annonine, Michelalbine, Oxoushinsunine, Reticuline, Unknown phenolic comp, Series of N-fatty acyl tryptamine where acyl portion ranged from hexadecanoyl to hexacosanoyl. Cytotoxic acetogenins as Squamocin, cis-trans-isomurisolein, Annoreticin, Annoreticin-9-one, Bullatacin, cis-trans-bullatacin, cis-trans-murisalalione, Solamin, Annomonicin, Rolliniastatin-1, 2 squamone and isoannonareticin. Volatile oil constituents like α-pine, β-pine, Myrcene, Limonene, Terpinen-4-ol, and | [19, 39]  |
Annona muricata

Several plant phytochemicals, such as alkaloids, flavonol, phenols, and essential oils, were evaluated from the A. muricata plant. However, acetogenin was found to be a rich source in A. muricata. The existence of several key minerals, including Potassium (K), Calcium (Ca), Sodium (Na), Copper (Cu), Iron (Fe), and Magnesium (Mg), demonstrate that the frequent intake of A. muricata fruit may assist in providing the human body with essential nutrients and elements [19, 47, 49–55]. According to research findings, Annona muricata reported 17 Alkaloids, 100 Annonaceae acetogenin, 10 phenolics, 13 flavonol triglycerides, 17 megastigmane, and 2 cyclopeptides from its fruits, leaves, seeds, and pericarp, respectively [38].

Annona reticulata

Various phytoconstituents from various parts of the A. reticulate have been described through identification of tannins, alkaloids, and phenolic compounds from the stem bark. Leaves are abundant in chemical constituents such as alkaloids, amino acids, carbohydrates, hormones, flavonoids, protein, tannins, glycosides, and phenolics. The root has been discovered to include acids, alkaloids, carbohydrates, proteins, flavonoids, and tannins. This species has also proven rich in Ca, Phosphorus (P), Na, Chlorine (Cl), Sulfur (S), Manganese (Mn), Zinc (Zn), Fe, Cu, Selenium (Se), Cobalt (Co), Nickel (Ni), and Chromium (Cr) [56–58].

Annona coriacea

Gomes et al. 2019 reported, leaves extract of Annona coriacea has been found to contain palmitic acid, oleic acid, asitrocinone, annonacin, trilobalnicin, annomuricin E, asimicin, bullatacin, annomuricin, murihexocin, goniotriocin, bullatacinone, annoglaucin, ginsenoside Rh5, salzmanolin, annophoetocin A, annophoetocin B, squamocin glycosilated using analysis of the electrospray ionization Fourier transform ion cyclotron resonance mass spectrometry [40].

Annona ceratocarpa

The assessment of phytochemicals from various plant parts led to numerous bioactive constituents being found among different Annona species. Acetogenins, alkaloids, essential oils, phenolic compounds, cyclopeptides, amino acids, pigments, and vitamins are among the principal phytochemical components [48]. The study found acetogenins namely 9-Hydroxyfolianain, annofolin, folianin B, 4-desoxylongimicin, folianin A, squamocin M, squamocin L from seed extract of Annona ceratocarpa [41].

Annona senegalensis

The study identified acetogenin and annosenegalin from the seed extract of Annona senegalansis and annogalene; gigantetronenine; squamocine; glaucanisine; glaucanetine; gonoithalamicine, Roemerine; annonaine; normuciferine; liroidenine; coclaurine; isoboldine from the leave extract of Annona senegalensis [42–46].

Biological activity

Antidiabetic activity

Annona cherimola

Ethanol extract of Annona cherimola was tested in alloxan-induced type-2 diabetic rats to study the antidiabetic effect of the leaves of Annona cherimola. Plant extract administered at dose 300 mg/kg on alloxan-induced anti-hyperglycemic rats decreased blood glucose level 331.5 mg/dl to 149.2 mg/dl 4 h after
the administration \((P < 0.05)\) compared to the acarbose (151.3 mg/dl), an alpha glucosidase inhibitor. The above study proved that rutin, a flavonal glucoside present at the ethanol extract, acts as an alpha glucosidase inhibitor like acarbose, which contributes significantly to the decrease of blood glucose level \([59]\) (Table 3).

**Annona squamosa** A research study was conducted using the aqueous extract of *Annona squamosa* in streptozotocin-nicotinamide type 2 diabetic rats where symptomatic decrease in plasma glucose level was seen for oral glucose tolerance test from 30 min onwards compared to 250 mg/kg and 500 mg/kg doses administered in normal rats. The result ensured that, aqueous extract of *A. squamosa* has significant potential of antihyperglycemic effect. In that study, the anti-hyperglycemic effect of that aqueous extract was independent of the dose since no significant difference in results were observed between 250 and 500 mg/kg extract \([61]\).

**Annona macropropyllata** A study in Mexico stated that *Annona muricata*, *Annona glabra*, and *Annona cherimola* are used as antidiabetic plants. Based on their research, another study is carried out on *Annona macropropyllata* as it is a similar species of the *Annona* genus.

Kamalakkannan, N., & Prince, P. S. M. (2006) isolated a flavonal compound rutin from *Annona micropropyllata* extract which was tested on hyperglycemic rats, and was found to inhibit fasting plasma glucose level, while the insulin and the antioxidant levels were increased \([70, 71]\). Rutin also reduced the alpha-glucosidase activity in both in vivo and in vitro studies \([72]\). They demonstrated the same yeast alpha-glucosidase behavior as

### Table 3 Result and methods of antidiabetic and antioxidant activity

| Scientific name     | Parts                                                                 | Result                                                                                     | Method                                                                                   | References |
|---------------------|----------------------------------------------------------------------|-------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|------------|
| **Annona cherimola**| Leaves                                                               | Aqueous extract at 300 mg/kg displayed substantial decrease the level of glucose in blood. | Alloxan induced male albinos Sprague-Dawley rats.                                         | \([59, 60]\) |
|                     | Juice, Skin, Flesh                                                   | Flesh extract at 98,085 Trolox Equivalents per 100 g dose showed maximum scavenging activity. | Oxygen radical absorbance capacity (ORAC) assay                                          | \([60]\)   |
| **Annona squamosa** | Leaves                                                               | Aqueous leaf extract revealed significant Antihyperglycemic effect                           | Streptozotocin-nicotinamide type 2 diabetic rats (250 and 500 mg/kg)                     | \([61]\)   |
|                     | 
|                     | • \(IC_{50} = 40 \mu g/ml\)                                         |                                            | • ABTS                                                                                  | \([62]\)   |
|                     | • \(IC_{50} = 60 \mu g/ml\)                                         |                                            | • Nitric oxide                                                                          | \([63]\)   |
|                     | • \(IC_{50} = 110 \mu g/ml\)                                        |                                            | • DPPH                                                                                  | \([64]\)   |
|                     | • \(IC_{50} = 115 \mu g/ml\)                                        |                                            | • Superoxide                                                                            | \([65]\)   |
| **Annona macropropyllata** | Leave                                                              | With a low \(IC_{50}\) (1.18 \mu g/ml) repressed the activity of yeast alpha-glucosidase and reduce blood glucose level. | Streptozotocin induced diabetic male Wistar rats.                                         | \([66]\)   |
| **Annona muricata**  | Leaves                                                               | The aqueous extract showed significant blood glucose lowering effect at dose 100 and 200 mg/kg. | Streptozotocin induced diabetic albino Wistar rats.                                       | \([67]\)   |
|                     | Ethanol extract of *Annona muricata* showed significant antioxidant activity in in vitro model. |                                            |                                            | \([68]\)   |
| **Annona reticulata** | Leaves                                                              | Ethyl acetate fraction from hydroalcoholic extract of *Annona reticulata* at dose 100 mg/kg reduced blood glucose level significantly. | Streptozotocin induced hyperglycemic Wistar albino rats                                   | \([69]\)   |
|                     | –                                                                  | Antioxidant activity not reported.                                                         |                                            | \([70]\)   |
| **Annona crassifora** | Peel, Seeds, Pulp                                                   | Ethanol and aqueous extract express in vitro antioxidant potential.                         | DPPH and lipid peroxidation assay.                                                       | \([71]\)   |
|                     | –                                                                  | Not reported Antidiabetic activity.                                                        |                                            | \([72]\)   |
| **Annona coriacea**  | Seeds, Pulp                                                         | \(\bullet\) DPPH and beta carotene bleaching test showed free radical scavenging activity of 31.53%, 51.59% respectively in in vitro model. | DPPH, Beta-carotene bleaching and ABTS radical cation.                                    | \([73]\)   |
| **Annona carcans**   | Pulp, Seeds, Leaves                                                 | Potent in vitro antioxidant activity was shown by pulp, leaves and seeds extract and fractions. | DPPH, ABTS, and beta-carotene/linoleic acid methods.                                     | \([74]\)   |
|                     | –                                                                  | Antidiabetic activity not reported.                                                        |                                            | \([75]\)   |
| **Annona senegalensis** | Leaves                                                             | Aqueous leave extract showed potent antioxidant activity in in vitro model                 | DPPH, \(H_2O_2\), superoxide ion, ABTS and ferric ion models                             | \([76]\)   |
|                     | –                                                                  | Antidiabetic activity not reported.                                                        |                                            | \([77]\)   |
Annona macrophyllata, whereas a low IC$_{50}$ (1.18 μg/ml) was observed [63].

**Annona muricata** Research has shown that a single dose of 100 mg/kg and 200 mg/kg of an aqueous extract of *Annona muricata* did not significantly affect blood glucose levels in regular rats. The extract administration of single dosing effectively lowered the blood glucose levels in hyperglycemic rats after 2 h of dosing. Plant extracts at 100 mg/kg and 200 mg/kg reduced blood glucose levels by 31.77% and 45.77% after injection of streptozotocin for 14 days, respectively. Repetitive administering of *Annona muricata* aqueous extract at all doses led to a substantial decline of near-normal blood glucose levels on day 7. Also, 76.56% and 58.3% reductions were shown at doses 100 mg/kg and 200 mg/kg, respectively, compared to the initial value. The result also showed that before streptozotocin injection, plant extract’s daily administration did not inhibit streptozotocin-induced hyperglycemia during 3 days. However, a significant drop in blood glucose levels during 14 days without treatment has shown that plant extract can work long. The findings also indicate decreased bodyweight loss, fluid and water intake in streptozotocin-induced rats, and blood glucose levels decreased during the four weeks of daily extract administration within one week. The presence of tannins and flavonoids in the phytochemistry of *Annona muricata* confirmed their hypoglycemic activity [64].

**Annona reticulata** Various fractions of 100 mg/kg of ethyl acetate, methanol, and residual fractions were obtained from *Annona reticulata* leaves hydro-alcoholic extract and was examined to determine its reduction of blood glucose level potential in streptozotocin-induced diabetic rats. After 14 days of treatment, fasting blood glucose levels decreased in hyperglycemic rats. Fasting blood glucose level decreased by 3.67%, 14.03%, 47.69%, and 50.93% for treatment with residual fraction, methanol fraction, ethyl acetate fraction, and standard drug. The study exhibited a significant ($P < 0.001$) decreased blood glucose level in comparison to the diabetic control group.

The blood glucose levels decreased by a residual fraction and methanol fraction from 417.83 to 402.50 mg/dl and 432.33 to 371.67 mg/dl. Compared to diabetic control groups, these levels were not substantial and the fraction of ethyl acetate was capable of controlling the increase in blood glucose and also attenuating secondary variables with hyperglycemia due to streptozotocin [73].

**Antioxidant activity**

**Annona cherimola** The cherimoya skin, flesh, and juice were isolated from *Annona cherimola* and analyzed for antioxidant content using the oxygen radical absorbance capacity (ORAC) assay. The juice showed the highest antioxidant activity, while the flesh exhibited the lowest [60]. Gupta-Elera et al. stated that the cherimoya juice extract enhanced the antioxidant uptake against the burkitt’s lymphoma and colon cancer cell lines [60].

**Annona crassiflora** Ethanol and aqueous extract of *Annona crassiflora* peel, seed, and pulp were screened for in vitro antioxidant activity, whereas antioxidants were measured using DPPH and lipid peroxidation assay. The ethanol extract exhibited substantial and concentration-based scavenging activity in DPPH, together with lipid peroxidation activity inhibition in mice’s model. Furthermore, the in-vitro antioxidant activity of peel, seed, and pulp exposed noticeable total phenolic content (TPC), whereas the ethanol peel extract contains the maximum TPC [67].

**Annona muricata, A. squamosa, A. reticulata** Using different in vitro models (DPPH, ABTS, nitric oxide, superoxide, hydroxyl radical, and lipid peroxidation), the antioxidant potential of leaves of three other species of *Annona (Annona muricata, Annona squamosa, Annona reticulata)* were studied. *Annona muricata* ethanol extract displayed a maximum scavenging activity (90.05%) at 500 μg/ml for ABTS, followed by hydroxyl radical scavenging (85.88%) and nitric oxide scavenging (72.60%), whereas a moderate action observed for lipid peroxidation assay. *Annona squamosa* extract showed the least inhibition in all in vitro antioxidant models. The ethanol extract of *Annona reticulata* showed maximum inhibition of 89.37% in DPPH, 89.05% in ABTS, 71.10% in nitric oxide, 77.72% in hydroxyl radical, 80.88% in superoxide radical, and 35.54% in lipid peroxidation at 500 μg/ml. The ethanol extract of *Annona squamosa* showed maximum inhibition of 88.77% in DPPH, 88.06% in ABTS, 68.03% in nitric oxide, 79.79% in hydroxyl radical, 77.21% in superoxide radical, and 50.83% in lipid peroxidation at 500 μg/ml. These findings indicate that *Annona muricata* extracts have strong in-vitro antioxidants efficacy compared to *Annona squamosa* and *Annona reticulata* leaves, which show the function as an effective, free radical scavenger, increasing its therapeutic value [62, 65].

**Annona coriacea** Seeds and pulp extracts of fruit *Annona coriacea* and *Annona sylvatica* were tested for antioxidant potential. DPPH, Beta-carotene bleaching, and ABTS methods were applied to determine the antioxidant activity. The pulp and seeds of the fruits were extracted by using methanol/water (8:2) for maceration. An excellent extraction yield was shown in the seeds and pulp extracts of fruit *Annona coriacea* (14.5 and
20.5%) and *Annona sylvatica* (8.7 and 5.2%). A moderate antioxidant effect and exhibited free radical scavenging activity of 31.53% by DPPH test was demonstrated by the seed extracts of *Annona coriacea*. By the Beta-carotene bleaching test, the seed further showed 51.59% antioxidant activity. Besides, the ABTS assay afforded 159.50 μM Trolox/g antioxidant activity. Seed extracts of *Annona coriacea* showed significant antioxidant activity. On the other hand, the antioxidant activity of seeds and pulp extract of *Annona sylvatica* was not significant [68].

**Annona car kans** A research study was done to evaluate the antioxidant effect of the hydro-methanol extract of the leaves, pulp, and seeds of *Annona car kans*. Antioxidant activity was determined by a different model (DPPH, ABTS, and beta-carotene/linoleic acid methods). These three different extracts demonstrated that all of them possess prominent free radical scavenging activity with IC$_{50}$ estimating between 89.67 μg and 26.25 μg/ml, especially the pulp extract with IC$_{50}$ 44.08 μg/ml (DPPH) and 39.32 μg/ml (ABTS). The pulp fraction displayed promising activity in multiple assays with IC$_{50}$ = 47.11 μg/ml (DPPH) and IC$_{50}$ = 26.25 μg/ml (ABTS), relatable to the positive control ascorbic acid. The lipid peroxidation assay also revealed good antioxidant effects of both hydro methanol (51.51 μg/ml) and ethyl acetate (34.34 μg/ml) fractions of pulp. It is observed that due to the presence of quercetin and kaempferol derivative, the pulp extract of *Annona car kans* probably showed antioxidant effects [21].

**Annona cornifolia** *Annona cornifolia* has been tested for its antioxidant potential against DPPH using seed ethanol extract fractions containing acetogenins, and these compounds exhibited a robust antioxidant activity at 10–100 μg/ml in DPPH assay with a lower IC$_{50}$ [41].

**Annona senegalensis** The aqueous extract of the *Annona senegalensis* leaves were assessed for in-vitro antioxidant activities using DPPH, H$_2$O$_2$, superoxide, 2, 2′-azo-(3-ethylbenzthiazoline-6-sulfonate), and ferric ion models, while the in vivo antioxidant activities were evaluated at the doses of 100 mg/kg, 200 mg/kg, and 400 mg/kg by enzymes and ion levels. In vitro antioxidant activity of the aqueous plant extract of *Annona senegalensis* demonstrated concentration-dependent activity (0.2–1 mg/ml) in 2,2 diphenyl-1 picrylhydrazyl (DPPH), H$_2$O$_2$, superoxide ion, 2, 2′-azo-(3-ethylbenzthiazoline-6-sulfonate), and ferric ion models. The extract produced maximum inhibitory scavenging activity of DPPH and H$_2$O$_2$ which was 96.9% and 77.54% at higher concentration, respectively, while superoxide ion inhibitory activity was 97.4%. Furthermore, the in-vitro antioxidant activity of leaves extract exhibited noticeable total phenolic content (TPC), total flavonoids contents, and proanthocyanidins [69].

**Conclusion** This review involves nine of the Annonaceae species and highlights the antidiabetic and antioxidant ability of *Annona* plants. *Annona* species are widely distributed worldwide, while many species are used for both medicinal and food use. As the global scenario is now heading toward non-toxic herbal products with therapeutic applications, comprehensive research into this gold mine of centuries-old expertise should be emphasized. The majority of the plants in this study demonstrated that their antidiabetic and antioxidant activity was potent. Five species were reviewed as having antidiabetic activity, and they demonstrated potent antihyperglycemic effect. Furthermore, antioxidant activity was reviewed from ten species, and they showed potent antioxidant activity with different in vitro models. Though several in vitro studies have confirmed the antioxidant and antidiabetic potential of the species of the *Annona* genus, still only a few in vivo and clinical trials were performed to date to validate the in vitro outcomes. So their potential in animal and human models should be assessed in the future. Furthermore, the mechanism of action by which they confer antidiabetic and antioxidant activities is still not developed elaborately. This should also be developed in further studies. Moreover, it can be concluded that, since natural medicines have the least side effects and are considered safe for human health, they can substantially substitute synthetic drugs in the future.

**Abbreviations**
- DPPH: 2,2-Diphenyl-1-picryl hydrazyl
- ABTS: 2,2′-Azino-Bis(3-ethyl benzothiazoline-6-sulfonic acid); IC$_{50}$: Half maximal inhibitory concentration; H$_2$O$_2$: Hydrogen peroxide; TPC: Total phenolic content; ORAC: Oxygen radical absorbance capacity

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**Authors’ contributions**
SSC and AMT planned and designed the research. SSC and SF conducted the complementary literature searches and reviews. SSC, AMT, and SF wrote the initial draft. SMT and MAS edited and revised the final draft. All authors have read and approved the manuscript.

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**Availability of data and materials**
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**Declarations**

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