

# Medicinal and Traditional Uses of Important *Annona* Fruits - Review Article

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**Abstract:** *Annona* species have been a valuable source of anti-infective and anticancer agents. However, only limited evaluations of their alkaloids have been carried out. This review collates and evaluates the biological data from extracts and purified isolates for their anti-infective and anti-cancer activities. An isoquinoline backbone is a major structural alkaloid moiety of the *Annona* genus, and more than 83 alkaloids have been isolated from this genus alone. Crude extracts of *Annona* genus are reported with moderate activities against *Plasmodium falciparum* showing larvicidal activities. Extract of *Annona muricata* showed apparent antimicrobial activities. The isolated alkaloids from this genus including liriodenine, anonaine, asimilobine showed sensitivity against *Staphylococcus epidermidis*. This review revealed that the alkaloids from *Annona* genus are rich in structural diversity and pharmacological activities. Further exploration of this genus and their alkaloids has potential for developing novel anti-infective and anticancer drugs. (Badrie, N. et al 2018 and 2010)

**Keywords:** *Annona*; alkaloid; anti-microbial; anti-malaria; anti-protozoa; anti-cancer

## 1. Introduction

*Annona* fruits possess major pharmacological activities like anti-carcinogenic, cytotoxic, antileishmanial, anti-microbial activity etc. There is a growing awareness particularly about the anti cancer properties of this plant among the people and the consumption of this fruit by the cancer-affected patients is on the increase. Such an important crop is seen only in neglected conditions in the farm boundaries and uncared lands. So, it has become necessary to survey the trees available in Tamil Nadu and document them. Such rich diversity is posed to dangerous threats of genetic erosion due to urbanization and other developments. Currently, seven *Annona* species and one hybrid are grown for domestic or commercial use, mostly for the edible and nutritious fruits; several others also produce edible fruits.<sup>1</sup> Syamsuhidayat<sup>81</sup> Many of the species are used in traditional medicines for the treatment of a variety of diseases, though their efficacy as a medicine has yet to be validated scientifically. Several annonaceae species have been found to contain acetogenins, a class of natural compounds with a wide variety of biological activities. (Zeng, et al 2008) *Annona* sp for edible and medicinal purpose *Annona squamosa*, *Annona muricata*, *Annona reticulata* and *Annona cherimoya*)

*Annona squamosa* is indigenous to tropical South America and the West Indies according to Wester (1912); however, Pinto *et al.* (2005) states that the sugar apple originated in lowland of Central America where it is indigenous, and from there it was distributed to Mexico and throughout tropical America. The Spaniards probably carried seeds from the New World to the Philippines and the Portuguese are assumed to have introduced the sugar apple to southern India before 1590. It was growing in Indonesia early in the 17th century and has been widely adopted in southern China, Queensland, Australia, Polynesia, Hawaii, tropical Africa, Egypt and the lowlands of Palestine. Cultivation is most extensive in India where the tree is also very common as an escape and the fruit exceedingly popular and abundant

in markets. The sugar apple is one of the most important fruits in the interior of Brazil. Morton, J. (1987) evaluated that Soursop is widely cultivated and popular in parts of Latin America, the Caribbean, Africa, Southeast Asia, and Pacific Islands, and its derivative products are consumed across the world. According to Mattietto (2011). Cherimoya (*Annona cherimola*), is an edible fruit-bearing species of the genus *Annona* from the family Annonaceae. They were believed to be native to Colombia, Ecuador, Peru, Bolivia and Chile, spreading through cultivation to the Andes and Central America. However, they are now known to originate in Central America. Cherimoya is grown in tropical regions throughout the world, as well as Spain, where it is widely consumed and grown in the southern provinces of Granada and Málaga It is in the same genus, *Australian Plant Name Index (APNI) 2008* Possibly a native of the Caribbean and Central America, *Annona reticulata* is now pantropical and can be found growing between altitudes of 0 metres (0 ft) to 1,500 metres (4,900 ft) in areas of Central America that have alternating wet and dry seasons (NRCS).2009

In India there is a very large, diverse population of this *Annona* and its commercial importance and it is so great that some botanists have considered it to be a native fruit of their country. Some of the arguments used by those who favour an Asiatic origin include the occurrence of common names for it in Sanskrit; the existence of large apparently wild populations in several parts of India. The presence of carvings and wall-paintings, maybe representing the fruit, in the ruins of ancient temples. However, according to Pinto *et al.* (2005), this is a secondary centre of diversity, created during the last 500 years. The purple-fruited form originated in India and was introduced to the Philippines from India in 1911 (Merrill, 1912 *et al.*)

*Annona* is one of the 129 genera of the Annonaceae family and contains 119 species with eight species grown for commercial uses The Plant List Version [Badrie, N. *et al* 2018 and 2010]. Most of the species grow in tropical

regions; e.g., the soursop fruit tree (*Annona muricata*) is cultivated commercially and is widespread in the West Indies, North and South Americas, Africa, the Pacific Islands, and Southeast Asia. *Annona* species have been used as medicines by indigenous people for a wide range of disorders including parasitic infections, inflammation, diabetes, and cancer (Mishera *et al* 2013).

Asare, G.A *et al* (2014) , Asare, *et al*(2015) explained about the phytochemical investigation of this plant genus revealing the presence of acetogenins, alkaloids, essential oils, flavonoids, terpenoids, and other chemical classes Oliver *et al* (2014)and, Barbalho(2013) reported that Acetogenins (ACGs) are the major constituents of the *Annona* genera and examples were found to possess a variety of pharmacological properties including antitumor, immunosuppressive, pesticidal, antiprotozoal, antimicrobial, antimalarial, anthelmintic, and antiviral agents, with some being commercially developed for the treatment of oral herpes and treating infestations of head lice, fleas, and ticks. ( Magadula *et al* (2008) reported that *Annona* species is limited and scattered. Badrie, N. *et al* (2010)., They explained the ethnopharmacological uses, alkaloid constituents, and the anti-infective properties of constituents contained within the genus *Annona*.

The *Annona* species are moderately erect shrubs or small trees that grow to 5–11 m in height depending upon species and the region they inhabit, and are ferruginous to greyish, and tomentose when young, but later becoming glabrous Coria-Téllez *et al* (2018 ). Ethnobotanically, the plants from this genus play significant role as food products and medicinal agents. A recent review on *A. muricata* showed that it is widely used in traditional decoctions in as many as 35 different countries for treating numerous diseases [Coria-Téllez *et al* 2018] traditional Mexican pharmacopeia uses powdered toasted seed as a potent emetic and cathartic. The seed was also used as an insecticidal agent and seed powder was used as a lotion when mixed with grease to treat parasitic skin disorders. A decoction of the fruit skin was used to treat pneumonia

Traditionally, *Annona* plants have been prepared for use against infection related diseases, such as ulcer, dysentery, and boils, and therefore became a driving force for conducting anti-microbial studies against common bacteria; preliminary results on the crude extracts. Most of the studies were based on the anti-microbial activity of crude extracts with no separate non-polar to polar fractions tested or individual constituents isolated. Therefore, further investigations are required to substantiate the traditional claims for these *Annona* plants by the isolation and identification of individual constituents. *A. muricata*, *A. squamosa*, *A. cherimola*, showed reasonable antimicrobial activities, whereas *A. reticulata* did not present antimicrobial activity, The chemical constituents benzoquinoline alkaloid, anonaine. (Coria-Téllez *et al* 2018, ) indicated comparable anti-microbial activities with positive control, with the exception against *Staphylococcus aureus*. Another study reported annoquinone A, isolated from *A. Montana*, possessed anti-microbial activity against *Bacillus subtilis* and *Micrococcus luteus* i. Anticancer Alkaloids Present in the Genus *Annona* In addition to the above antiprotozoal and

antimicrobial activities, both the crude extracts from *annona* plants and the individual alkaloids have shown potent anticancer/antitumour activities. Many crude extracts of *Annona* species showed significant anti-cancer activities, but most of the bioactive constituents present in those crude extracts were acetogenins, fatty acids, and peptides [Quílez *et al* 20047].

The leaves of *Annona muricata* also showed potency to reduce gastric lesion, to expel parasitic worms and, moreover, the crude extract from the bark possessed antiviral activity against herpes simplex virus type 1. The extracts and compounds also showed anticancer activities against breast cancer (Rupprecht,*et al* 1990).

Accorded to Jansen *et al* (1991) decocted leaves of *Annona reticulata* (Bulls heart) was used internally against worms, and poultice, leaves were applied externally to treat abscesses, boils, and ulcers. Unripe fruit was used to treat diarrhea and dysentery, and decocted root was used as febrifuge and to treat toothache, [Morton *et al* ,1991 , Karou *et al* 2011] represented that in India, *Annona squamosa* (“sugar apple”) leaves are crushed and applied to wounds, ulcers, and is sniffed to relieve hysteria and fainting spells. Decocted leaves are used systemically to treat dysentery (India), and as a tonic, febrifuge, and cold remedy (tropical America). Crushed ripe fruit was applied to surface tumors (India), whereas the unripe fruit was used to treat dysentery. The stem bark and root were used to treat diarrhea and dysentery Karou *et al* (2011). Decocted leaves were used as an analgesic, antispasmodic agents in Ecuador, whereas it is used as a remedy for cough, catarrhal inflammation, diarrhea, dysentery, bladder problems, and inflammation in the West Indies. Mashed leaves were also used as a poultice to relief eczema, rheumatism, and skin eruptions [Morton *et al* 1991]. Traditional medicine in Indonesia has used the leaves as a treatment for boils, spasms, and as an aphrodisiac [Syamsuhidayat 1991, and Hutapea,1998]. The fruit juice was used as a diuretic agent and to treat leprosy and liver ailments [Morton *et al* 1991]. Currently, in Indonesia, the fruit is commonly used traditionally to treat breast cancer. A decoction of the seeds was used as a strong emetic agent, and the flower was used to treat catarrhal inflammation. In Materia Medica of British Guiana, a tincture of the powdered seeds and bay rum serves as a strong emetic. Soursop flowers are believed to alleviate catarrhal inflammation. The roots have been used as a vermifuge and an antidote for poisoning [Morton *et al* 1991]. The roots are commonly used in Guinea as anti-parasitic and pesticidal agents. In Indonesia, currently, the stem and root bark are used as an alternative medication to treat malarial fever.. A tea made of the stem and leaf of *A. glabra* L. was consumed to eliminate flatworm and nematodes in Guyana. A decoction of the bark of *Annona haematantha* Miq. was used as a bath to treat skin ulcers, while its syrup was used to relieve cough. The bark infusion of *Annona sericea* Dunal was used to treat cramps [DeFilipps, and Main. 2004]. In Mexico, the leaf of *Annona diversifolia* Safford Syamsuhidayat, (“Ilama”) was commonly used as an anticonvulsant, anti-inflammatory, and analgesic a (González-Trujano *et al* 1998]. An infusion of the leaves of *A. senegalensis* (“wild custard apple”) was used to treat diarrhea and pulmonary complaints. Decocted stem bark was

used to treat stomachache, toothache, dysentery, and worm infection. The root was used to treat venereal diseases and intestinal problems, snake bites, and as cancer therapy (Nigeria). Its green fruits was used to treat Guinea worm sores, diarrhea, dysentery [Mortan *et al* 1991]. The juicy pulp of the fruit is often a good source of sugar, vitamins, minerals, and phenolic intake. For example, the dried pulp of *Annona muricata* contains 68% sugars for every 100 g containing 1.0 g protein, 0.97 g fat, 1.28 niacin, and 29 mg ascorbic acid. Moreover, it could supply 3 g of phenolic substances for every 100 g of pulp. This was quoted by, Quílez *et al* 2018.

According to Linn Churchill *et al* (1980) *Annona muricata* Fruit and fruit juice are taken for worms and parasites, to cool fevers, to increase mother's milk after childbirth, as an astringent for diarrhea and dysentery. The crushed seeds are used against internal and external parasites, head lice. The bark, leaves, and roots are considered as sedative, ulcer treatment, hypotensive, and nervine, and a tea is made for various disorders towards those effects. Coria-Téllez *et al* (2018) explained that in fruits and Roots of *Annona muricata* contains acetogenins proved to have anticarcinogenic effect. In *Annona squamosa* Asare *et al* (2015) explained that Leaves are used to treat hysteria, fainting spells. Leaf decoction is used in the treatment of cold, cough, intestinal infections and acidity condition Nehey pandya (2011) reported in *Annona cherimola* Seeds are used in folk medicine for their insecticidal activity, parasitic activity. Roots are reported to take alkaloids like apomorphine Reomerine, Annonine and Dehydro reomerine for producing skeletal muscle relaxant effect. It was found that Yellow resin extracted from seeds exhibits sympathetic action such as dilatation of pupil, dryness of mouth, decreases secretions. *A. squamosa* is usually grown as a backyard fruit tree and as a component of agroforestry systems. Its fruit is a source of food and the flowers are used for apiculture. In some instances, *A. squamosa* is planted in parks or places as a shade and ornamental tree due to its attractive fruit colour Its fruit is a source of food and the flowers are used for apiculture. This was in accordance with the findings of Current name: *Annona cherimola* (2009)

The leaves, bark, roots, seeds and fruit of *A. squamosa* have various important medicinal uses. The green fruit and seed have effective vermifugal and insecticidal properties and are used as astringents in diarrhoea and dysentery. The seeds contain 45% of a yellow, non-drying oil which is an irritant poison for lice. Crushed leaves are applied as an effective cure for ulcers and malignant sores. A poultice from fresh leaves is used for dyspepsia and when mixed with oil is used for diseases of the scalp. Crushed fresh leaves are applied to the nasal area in cases of fainting spells. A decoction of roots is used as a drastic purgative Coronel, 1983). *A. squamosa* is usually grown as a backyard fruit tree and as a component of agroforestry systems. He also explained (Coronel, 1983) that the leaves, bark, roots, seeds and fruit of *A. squamosa* have various important medicinal uses. The green fruit and seed have effective vermifugal and insecticidal properties and are used as astringents in diarrhoea and dysentery. The seeds contain 45% of a yellow, non-drying oil which is an irritant poison for lice. Crushed leaves are applied as an effective cure for ulcers and

malignant sores. A poultice from fresh leaves is used for dyspepsia and when mixed with oil is used for diseases of the scalp. Crushed fresh leaves are applied to the nasal area in cases of fainting spells. A decoction of roots is used as a drastic purgative (Coronel, 1983). The astringent bark, leaves, unripe fruit and seed can be used as a source of the alkaloid anonaine (Troup, 1975). *A. squamosa* is planted in parks or plazas as a shade and ornamental tree due to its attractive fruit colour (Coronel, 1983).

The 20th century reported preliminary examinations of the *Annona* plants of the leaves, fruits, and seeds. Since the 1980s, with the advent of pursuing anti-cancer drug leads from medicinal plants, acetogenin was isolated from the *Annona* genus based on its promising anti-cancer activity. For example, a recent acetogenin, squamocin P, isolated from *A. squamosa*, possessed significant anticancer activity. Marta *et al* (2008) reported that *Annona* plants have been used in traditional medication for the treatment of both infectious and non-infectious diseases led to the pharmacological and chemical screening of numerous species to confirm these pharmacological claims and to isolate the compounds which might be responsible for these activities. The *Annona* genus has been studied for activity against parasites, cancer, and as anti-oxidant agents. Antiprotozoal activities Ethnopharmacological studies have revealed the *Annona* species *A. muricata*, *A. squamosa* were prescribed in malarial fever therapy Another study of Marta *et al* using the crude methanol extract of *A. squamosa* indicated moderate activity against *Plasmodium falciparum* 3D7 with an IC50 value of 30 µg/mL compared to the chloroquine control, which gave an IC50 value of 0.021 µg/m giving a moderate effect.

Although there was a limited record regarding traditional uses of *Annona* plants to treat other parasitic protozoal infections, e.g., leishmaniasis and trypanosomiasis, several crude extracts of *Annona* plant (*A. muricata*) were also tested against *L. amazonensis*, *L. braziliensis*, *L. Donovanii*, and *T. cruzi*. A different strategy to control malarial infection involves controlling its vector. Annonaceous acetogenins are a group of constituents obtained from plants belonging to Annonaceae, having potentials of anti-neoplastic agents. Acetogenins are potent cytotoxic inhibitors of the mitochondrial NADH:ubiquinone oxidoreductase (complex I of the respiratory chain). A study of Mravec. Salsolinol (2006) shows that main five annonaceous acetogenins which are solamin, annoreticulin-9-one, annomonicin, squamone, and rolliniastatin are having cytotoxic activities. Acetogenins isolated from the seeds of *A. reticulata* are bullatacin, cis-/trans-isomurisolenin, cis-/trans-bullatacinone, annoreticulin, annoreticulin-9-one, cis-/trans-murisolinone and squamocin

## 2. Conclusions

This review presents the ethnomedicinal, alkaloidal and biological, properties of *Annona* species with respect to reported anti-infective and anti-cancer activities. The *Annona* species: *A. muricata* (soursop), *A. squamosa* (custard apple), and *A. cherimola* (cherimola) are renowned traditionally for their anti-tumor properties. Among these, *A. muricata* is widely studied and has shown broad range of



biological activities including anti-protozoal, anti-cancer, anti-tumour, antimicrobial, and antiparasitic properties. Simeon *etal*(1998 ) reported that this species has also produced several patents and commercial products. Investigations into extracts from the leaves, bark, fruit, and seeds of this plant genus have found terpenoids, steroids, flavonoids, cardiac glycosides, tannins, phenols, sugars, fatty acids, acetogenins, and alkaloids. As many as 200 phytochemicals belonging to these chemotypes have been identified and isolated from this *Annona muricata* species alone. So the most important being acetogenins, phenols and anonaine alkaloids, Anonaine and its structurally related alkaloids were the most abundant and commonly available alkaloids in Annonaceae family. The oxoaporphine alkaloid, liriodenine, was found in at least in twenty different species, ranging across flowering plants but mostly in annonaceae family. However, wherever studied, *Annona* alkaloids have been reported to possess anti-inflammatory, anti-cancer, antitumor, anti-HIV, antiprotozoal, antiparasitic, antidiabetic, analgesics, gastroprotective, antihypertensive, hepatoprotective, nephroprotective, and neuroprotective properties. ( <sup>^</sup> *University of Southampton* (March 2002)

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