Review

Exploring the Effects of Annona Muricata: Health Benefits and Potential Uses

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Annona muricata, commonly known as soursop or graviola, is a tropical evergreen tree belonging to the Annonaceae family, widely recognized for its diverse medicinal and nutritional properties. This plant is native to Central and South America but is now cultivated in tropical and subtropical regions worldwide. It thrives in warm, humid climates, requiring well-drained soils with moderate rainfall to grow optimally. The tree produces large, green, spiny fruits with soft white pulp, which are widely consumed as fresh fruit or used in beverages, desserts, and traditional cuisines due to their unique flavour and nutritional benefits. Traditionally, *A. muricata* has been utilized in folk medicine to treat a variety of ailments, including diabetes, hypertension, cancer, inflammation, bacterial infections, and much more. Nearly every part of the plant (leaves, bark, roots, fruit) contains bioactive compounds such as acetogenins, alkaloids, flavonoids, and phenolics, which contribute to its therapeutic effects. In vivo and *in vitro* studies have highlighted its pharmacological activities, including anti-cancer, antioxidant, antimicrobial, anti-inflammatory, anti-diabetic, and anti-hypertensive properties, etc. However, recent research has raised concerns about the potential neurotoxic effects of certain compounds in *A. muricata*, particularly annonacin, which has been associated with neurodegenerative conditions in high doses. While the plant holds promise for therapeutic applications, further research is needed to clarify its mechanisms of action, evaluate its safety profile, and determine appropriate dosage levels to balance efficacy and toxicity. This review provides a comprehensive overview of *A. muricata*, including its botanical description, growing environment, traditional and food uses, pharmacological studies, and considerations regarding potential neurotoxicity.

Keywords: *Annona muricata*, traditional medicine, bioactive compounds, neurotoxicity

1 Introduction

The use of natural additives has great potential in replacing synthetic substances in feeding animals. Dietary sustainable additives were started to find the ones with antimicrobial, antioxidant, anti-inflammatory, immunostimulant, and prebiotic functions. It is also important to identify the optimal dosage of the dietary supplementation of the natural extract to avoid problems related to the feed palatability or the overconsumption that leads to "antioxidative stress". Several studies on natural extracts from plants in animal feed have been performed to find an alternative to synthetic substances able to sustain growth performance, animal health, and product quality (Lenický et al., 2024; Knizatova et al., 2022; Vizzarri et al., 2020; Kolesar et al., 2018; Capcarova et al., 2012; Roychoudhury et al., 2009).

1.1 Characteristics of Arona muricata Plant

Annona muricata is commonly called graviola or soursop (also called guyabano and in Latin America guanábana). It is a small, evergreen, fast-growing tree in regions with a tropical climate (Datiles & Acevedo-Rodríguez, 2015). It originated in tropical regions of America but the exact origin of the tree is unknown (Moghadamtousi et al.,

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2015). It commonly grows in Central and northern South America (Büttner, 2001). Graviola is in the Annonaceae family and the genus Annona (Moghadamtousi et al., 2015). *Annona muricata* is widely known for its fruits. The fruits could be eaten on their own or juiced and mixed with water and sugar to make a refreshing beverage. The fruit pulp is often used to make various desserts such as sherbets, ice cream, and jellies (Brown, 1951). There are claims that the plant, especially the leaves can be used as alternative cancer treatment. However, there is no reliable evidence that the plant can cure cancer. On the other hand, some recent studies suggest that extracts can act against cancer cells (Pieme et al., 2014). The therapeutic potential of Graviola in combating various human tumors and disease agents has been studied extensively in *in vitro* cultures and preclinical animal models. These studies typically focus on its ability to selectively target diseased cells while minimizing harm to normal cells. Graviola extracts, derived from different parts of the plant, are known to contain over 212 identified phytochemical compounds (Rady et al., 2018).

Annona muricata, particularly the leaves, have been traditionally used in ethnomedicine by healers to treat a range of ailments, including cancer, inflammation, diabetes, liver disorders, and abscesses (Abdul Wahab et al., 2018).

1.2 Description of the Plant

Annona muricata is a relatively small (7.5 to 9 m tall), non-deciduous, evergreen, fast-growing tree that may be tall, upright, and narrow or a bush with low branching habit (Janick & Paull 2008). Leaves are 6.5–20 cm long, 2.5–6.5 wides, petiolate, trichomes are absent, blade is narrowly obovate or elliptic or obovate-elliptic. The base of the leaf is acute to rounded and the apex is pointy (Moghadamtousi et al., 2015). Inflorescences grow directly on the trunk or large branches in bundles or solitary and leaf opposed. The flower consists of 3 sepals, 3 inner and outer petals. Sepals are triangular 3–4 mm long and 5–6 mm wide. Inner petals are 20–22 long and 10–15 mm wide, thick, fleshy with greenish-yellow colour. Outer petals are 30 mm long and 22 mm wide, ovate, apex acuminate. The ovary is 5 mm long and 8 mm wide, broadly conical. Stamens are 4 mm long and 1 mm in diameter, numerous (Moghadamtousi et al., 2015).

The fruit is large (up to 30 cm) conical with curved spines 2 to 3 mm long (Figure 1). Flesh is white, juicy with lots of fibres surrounding numerous seeds which are dark brown 13–17 mm long and 9–10 mm wide, ellipsoid (Moghadamtousi et al., 2015).

Figure 1 *Annona muricata* plant
Source: Moghadamtousi et al., 2015

1.3 Annona muricata Natural Habitat

Annona muricata is of tropical American origin (Moghadamtousi et al., 2015). It is native to Central America and northern South Africa (Büttner, 2001). Graviola is cultivated in Africa, especially in warm lowlands of eastern and western parts, temperate and tropical Asia, Australasia, North America, the south-central Pacific Islands, the Caribbean, and Mesoamerica (Datiles and Acevedo-Rodríguez, 2015).

1.4 Climate Requirements

Annona muricata requires a warm and humid climate. It grows up to an altitude of 1000 m and as far as 25° south in Asia (Verheij & Coronel, 1991). It is one of the least hardy species of the genus Annona. Cold severely affects the growth and fruiting and only a light frost can kill the tree. A dry season leads to leaf drop from lack of humidity, so a sheltered site is recommended to limit transpiration. Season with a lack of rainfall also synchronizes extension growth and flowering to some degree and the plant prefers well-drained, loose, deep loamy, rich in organic matter soil with a pH of 5 to 6.5 and cannot tolerate water-logged soils (Verheij & Coronel, 1991).

1.5 Uses of Annona muricata

Every part of the plant has its own uses. The fruit, leaves, seeds, and bark are used as food or to cure various diseases and illnesses (Moghadamtousi et al., 2015; Adewole & Ojewole, 2009).

The sweetest and least fibrous fruits are cut into sections and eaten with a spoon. The pulp without seeds may be cut into pieces and served in salads, fruit cups, or chilled and served as desserts. In Mexican restaurants in New York and other north-located cities, the canned Gaviola pulp has been served for years (Morton, 1987). Soursop drinks are popular throughout the tropics. They are called champola in Brazil and carato in Puerto Rico. To make a refreshing soursop drink the pulp must be seeded and then extracted using a sieve or cheesecloth. The rich, creamy juice is then mixed with milk or water and sweetened. Another way to make juice is to use a blender. Before using a blender, the pulp must be seeded because the seeds are somewhat toxic, and nobody should grind them up in juice. Then the seeded pulp is blended with equal amounts of boiling water and then sweetened (Morton 1987). In Puerto Rico hand peeled and cored fruits are processed in factories. In Guatemala, the juice is prepared as a carbonated bottled beverage and in the West Indies, the juice is fermented to make a cider-like drink. In the Philippines, vacuum-concentrated juice is canned commercially. In the Dominican Republic soursop pulp is cooked in syrup with cinnamon to make custard or ice cream is made in ice-cube trays. In the Bahamas, soursop drink is simply made by pressing the pulp in water, letting it stand for a while, and then straining it to remove the juice from seeds and fiber material. In Indonesia, immature fruits are used to make soup or cooked as vegetables. In Northern Brazil, the immature fruit is roasted or fried (Morton, 1987).

All parts of plants of the genus Annona other than *Annona muricata* including *Annona squamosa* and *Annona reticulata* are used in traditional medicine to treat various human ailments and diseases, more importantly cancer and parasitic infections (Moghadamtousi et al., 2015).

The fruit is used to treat arthritic pain, neuralgia, arthritis diarrhea, dysentery, fever, malaria, parasites, rheumatism, skin rushes, worms and it is used to raise human milk production during lactation after childbirth (Moghadamtousi et al., 2015). The leaves are used to treat cystitis, diabetes, headaches, and insomnia. Tea made from leaves is believed to have anti-rheumatic and neuralgic effects The cooked leaves are used topically to treat abscesses and rheumatism (Moghadamtousi et al., 2015). Supposedly the crushed seeds have antihelmintic effects against external and internal worms and parasites and in tropical Africa are used to treat coughs, pain, skin diseases and it is used as an insecticide and piscicide agent. In India, the flower and fruit are used to treat catarrh and the leaves and root are used to treat inflammation and parasites (Adewole & Ojewole, 2009; Watt & Breyer-Brandwijk, 1962).

In Malaysia, the mix of macerated leaves of *Annona muricata*, *Annona squamosa*, and *Hibiscus rosa sinensis* is made into juice and used on the head to prevent and protect from fainting (Ong & Norzalina, 1999). In South America, tropical Africa, and Nigeria the leaves of *Annona muricata* are used as medicine to cure tumors and cancer (Adewole & Ojewole, 2009). The leaves, bark, and roots of *Annona muricata* are attributed to additional effects such as anti-inflammatory, hypoglycaemic, sedative, smooth muscle relaxant, hypotensive, and antispasmodic effects (Moghadamtousi et al., 2015).

2 Phytochemistry

The key bioactive compounds contributing to graviola's anticancer, antioxidant, anti-inflammatory, antimicrobial, and other health benefits include various types of annonaceous acetogenins (products of the polyketide pathway), along with alkaloids, flavonoids, sterols, and other phytochemicals (Rady et al., 2018) including megastigmanes, flavonol triglycosides, phenolics, cyclopeptides, and essential oils (Moghadamtousi et al., 2015).

2.1 Essentials Oils

The leaf oil present in *A. muricata* leaves collected from Cameron has shown the presence of sesquiterpenes, the major compound being β-caryophyllene (Fekam et al., 1996). Another set of analyses of *Annona muricata* oil collected from leaves from Vietnam identified volatile oil compounds as β-pinene (20.6%), germacrene D (18.1%), *p*-mentha-2,4(8)-diene (9.8%), α-pinene (9.4) and β-elemene (9.1%) (Thang et al., 2013). Other major compounds found in leaf oil extract are also δ-cadinene, epi-α-cadinol, and α-cadinol (Kossouoh et al., 2007). The essential oil from fruit pulp contains esters of aliphatic acids with major compounds of 2-hexenoic acid methyl ester and 2-hexenoic acid ethyl ester. Also, high concentrations of sesquiterpenes, including β-caryophyllene, 1,8-cineole, and linalool were isolated from fruit pulp (Alali et al., 1999; Zafra-Polo et al., 1998).

2.2 Annonaceous Acetogenins

Acetogenin compounds (AGEs) are distinctive C-35/C-37 secondary metabolites formed from long-chain fatty acids (C-32/C-34) through the polyketide pathway. They typically consist of fatty acids linked to a 2-propanol unit at the C-2 position, resulting in a methyl-substituted α,β-unsaturated γ-lactone structure (Alali et al., 1999). Since uvaricin was first identified from *Uvaria accuminata* in 1982, over 500 acetogenins (AGEs) have been discovered in various parts of plants belonging to the Annonaceae family (Tempesta et al., 1982; McLaughlin, 2008). The unique structures and diverse biological properties of AGEs have garnered considerable scientific attention in recent years. These compounds have been reported to exhibit a range of biological activities, including antimalarial, antiparasitic, and pesticidal effects (Alali et al., 1999; Zafra-Polo et al., 1998). Annonaceous acetogenins were extracted six from a 95% ethanol leaf extract of *Annona muricata*. They achieved this by repeatedly purifying the active fraction using flash chromatography and high-performance liquid chromatography (HPLC), resulting in the isolation of compounds such as annomuricin A, annomuricin B, annomuricin C, muricatocin A, muricatocin B, and muricatocin C (Abdul Wahab et al., 2018). The biological activities of AGEs are mainly defined by their toxicity toward cancer cells and their ability to inhibit mitochondrial complex I (mitochondrial NADH: ubiquinone oxidoreductase) (Chih et al., 2001; Zafra-Polo et al., 1996).

3 *In vivo* Studies

Malaria, a parasitic disease prevalent in tropical regions, is among the most significant infectious diseases globally. It is caused by *Plasmodium* species and transmitted through the bite of female *Anopheles* mosquitoes. A study evaluated the *in vivo* antimalarial activity of aqueous leaf extract from *Annona muricata* against *Plasmodium berghei* in infected mice. Experimental infections were induced via intraperitoneal injection of approximately 107 parasitized erythrocytes. The *A. muricata* leaf extract demonstrated a dose-dependent antimalarial effect, significantly inhibiting *P. berghei* infection compared to the untreated group. The highest level of inhibition was observed with a dose of 1,000 mg·kg^{-1}. However, complete parasite clearance was not achieved at any dose, although all treatments notably extended the mean survival time of the mice (Somsak et al., 2016). Another study examined the blood pressure-lowering effects of the aqueous extract from its leaves. *A. muricata* caused a significant dose-dependent reduction in blood pressure without affecting the heart rates (Nwokocha et al., 2012). A study was conducted to determine the *in vivo* bilirubin-lowering potential of the aqueous extract of *A. muricata* leaves. The study focused on phenylhydrazine-induced jaundice in adult rats, measuring direct and total bilirubin levels in rats orally administered 50 and 400 mg·kg^{-1} of the extract. The aqueous leaf extract demonstrated hepatoprotective properties against liver damage caused by carbon tetrachloride and acetaminophen. Pretreatment with various concentrations of the extract before inducing liver injury helped restore liver function to normal homeostasis, as evidenced by biochemical and histological analyses (Arthur et al., 2012).

3.1 Antinociceptive, Anti-inflammatory, and Anti-ulcerogenic Activities of the Ethanolic Extract of Annona muricata Leaf

The ethanolic extract of *Annona muricata* L. (Annonaceae) leaves (AML) was evaluated for its antinociceptive and anti-ulcerogenic properties and the antinociceptive activity of the AML extract was assessed using the acetic acid-induced abdominal writhing test in mice, the formalin test in rats, and the hot plate test in mice. The anti-ulcerogenic effect of the AML extract was evaluated using an ethanol-induced ulcer model in rats, as well as ethanol-induced gastric lesion models in rats pre-treated with L-NAME and NEM, to investigate its underlying mechanism (Hamid et al., 2012). AML was also used to investigate its anti-inflammatory activities by using the carrageenan-induced edema model and acetic acid-induced writhing test. Finally, AML demonstrated notable, dose-dependent antinociceptive activity and significantly reduced ethanol-induced ulcerative lesions in rats in a dose-dependent fashion (Hamid et al., 2012).

3.2 Anti-hyperglycemic and Anti-lipidemic Activities of Annona muricata

A study aimed to evaluate the effects of methanolic extracts of *Annona muricata* on blood glucose levels in streptozotocin-induced diabetic Wistar rats. Hyperglycemia was induced by administering a single intraperitoneal injection of 80 mg·kg^{-1} streptozotocin dissolved in 0.1 M citrate buffer. The treated group received a daily intraperitoneal injection of 100 mg·kg^{-1} *A. muricata*. The blood glucose levels in the treated group gradually decreased with the administration of *A. muricata* extracts (Aderibigbe et al., 2010). A significant difference was observed between the blood glucose levels of the treated and untreated hyperglycemic rat groups, indicating that *A. muricata* extracts exhibit strong antihyperglycemic activity. Furthermore, the extract at the same dose significantly reduced serum levels of total cholesterol, low-density lipoprotein, triglycerides, and very low-density lipoprotein cholesterol (Aderibigbe et al., 2010).

3.3 Insecticidal Activity

Plants from the Annonaceae family, including *A. mucosa* and *A. sylvatica*, have demonstrated potential as effective biopesticides among tropical species (Ribeiro et al., 2014). Various extracts from *A. muricata* seeds exhibited activity against *Sitophilus zeamais*, a harmful pest of stored grains. Both ingestion and topical application of hexane and ethyl acetate extracts were effective, with this activity attributed to the presence of AGEs in the less polar fractions (Hincapié-Llanos et al., 2008). The seed extracts revealed high weevil mortality against *S. zeamais* by dipping and surface-protectant methods (Asmanizar et al., 2012). Aqueous and oil extracts from *A. muricata* seeds showed significant bioactivity against the larvae and adults of *Aedes albopictus* and *Culex quinquefasciatus*, with lethal concentration 50 (LC_{50}) values ranging from 0.5% to 1% for larvae and 1% to 5% for adults (Ravaomanarivo et al., 2014). The leaf extract of *A. muricata* exhibits time-dependent toxicity against the larvae of *Anastrepha ludens* (Mexican fruit fly), causing mortality rates between 63% and 74% (González-Esquinca et al. 2012). The ethanolic leaf extract (1.0 g·L^{-1}) caused 40%, 80%, and 98% mortality in *Callosobruchus maculatus* (*Fabricius*) at 24-, 48-, and 72-hours post-treatment, respectively. At the same concentration, the extract significantly reduced oviposition in *C. maculatus*, suggesting its potential as an effective protectant for stored cowpea (Adeoye & Ewete, 2010).

3.4 Moluscicidal Activity

To develop plant-based molluscicides for controlling schistosomiasis vectors, various parts of *Annona* species were evaluated for their effectiveness against *Biomphalaria glabrata* in both egg masses and adult stages. The leaves of *A. muricata* exhibit notable toxicity against adult worms, with an LD90 value of 8.75 ppm. Furthermore, *A. muricata* leaves demonstrate pronounced toxicity against snail egg masses compared to other *Annona* species (Dos Santos & Sant'Ana, 2001).

3.5 Wound Healing Ability

The wound-healing potential of the ethyl acetate extract from *A. muricata* leaves (at concentrations of 5% w/w and 10% w/w) was evaluated using an excisional wound model in rats. Topical administration of the extract for 15 days demonstrated significant wound healing potential assessed by macroscopic and microscopic analyses (Moghadamtousi et al., 2015).

3.6 Anticancer Activity in vitro

Over 47% of anticancer drugs available today are derived from natural products, their modified forms, or synthetic mimics. Additionally, more than 25,000 identified phytochemicals have demonstrated significant anticancer properties (Rady et al., 2018). Extensive research has been conducted on numerous natural products, revealing many compounds with anticancer and other health-promoting effects in well-controlled modern studies. Most anticancer natural products exert their effects by influencing key processes involved in cancer initiation, development, and progression, such as cellular proliferation, differentiation, apoptosis, angiogenesis, and metastasis (Gupta et al., 2010). Numerous studies also highlight the strong antiproliferative effects of various plant extracts and isolated AGEs against different cancer cell lines (Mohamed Abdoul-Latif et al., 2023).

3.7 Ethanol and Aqueous Extracts

The cytotoxic effects of ethanol and aqueous extracts of *Annona muricata* leaves were evaluated on EACC, MDA, and SKBR3 tumor cell lines. The ethanol extract exhibited IC_{50} values of 335.85 µg·mL^{-1}, 248.77 µg·mL^{-1}, and 202.33 µg·mL^{-1} for the EACC, MDA, and SKBR3 cell lines, respectively, while showing no cytotoxicity towards normal spleen cells. In contrast, the aqueous extract demonstrated no anticancer activity at any of the tested concentrations (Gavamukulya et al., 2014). In addition to leaves, the fruit stems, and seeds of *Annona muricata* have also shown notable anticancer properties. An *in vitro* study on *A. muricata* fruit demonstrated significant inhibition of breast cancer cell growth (MDA-MB-468) and selective suppression of the epidermal growth factor receptor (EGFR), which is often overexpressed in breast cancer, with an IC_{50} of 4.8 µg·mL^{-1}. Notably, no effects were observed on non-tumorigenic human

breast epithelial cells (MCF-10A) (Dai et al., 2011). Another study successfully isolated and identified three new annonaceous acetogenins – muricin J, muricin K, and muricin L – from the fruit of *Annona muricata* using chromatographic methods and HPLC purification. These compounds demonstrated antiproliferative effects against human prostate cancer PC-3 cells (Sulistyoningrum et al., 2017). In addition to the leaves and fruits of *Annona muricata*, the stem also exhibited cytotoxic activity against various cell lines, including U937 histiocytic lymphoma cells. The ethyl acetate, hexane, and methanol extracts of the stem showed IC_{50} values of 10.5 μg·mL^{-1}, 18.2 μg·mL^{-1}, and 60.9 μg·mL^{-1}, respectively (Valencia et al., 2011). The stems also exhibited cytotoxic effects by inhibiting the expression of molecules related to hypoxia and glycolysis in CD18/HPAF pancreatic cancer cells, with an IC_{50} value of 73.0 μg·mL^{-1} (Torres et al., 2012). Additionally, the ethanol extract of *Annona muricata* seeds demonstrated cytotoxic activity against MDBK and HEp-2 cells, with IC_{50} values of 34.5 mg·mL^{-1} and 55 mg·mL^{-1}, respectively, at 24 hours. After 72 hours, the IC_{50} for HEp-2 cells was 49.6×10^{-3} mg·mL^{-1} (Betancur-Galvis et al., 1999).

3.8 Hexane Extracts

The hexane extract of *Annona muricata* leaves exhibited a concentration-dependent inhibitory effect on cell proliferation in Capan-1 pancreatic cancer cells (Abdul et al., 2018). A total of 19 *Annona muricata* samples from various locations were tested against breast cancer cell lines MCF-7, MDA-MB-231, and 4T1. Among them, the aqueous leaf extract from Selangor, Malaysia, demonstrated the strongest activity, showing the lowest IC_{50} values of 220 μg·mL^{-1}, 350 μg·mL^{-1}, and 250 μg·mL^{-1} for the MCF-7, MDA-MB-231, and 4T1 cell lines, respectively (Syed Najmuddin et al., 2016). The extract significantly reduced tumor size and weight exhibited anti-metastatic properties, and induced apoptosis in 4T1 cells both *in vitro* and *in vivo*. It also suppressed nitric oxide (NO) and malondialdehyde (MDA) levels in tumors while boosting white blood cell counts, as well as T-cell and natural killer cell populations. Additionally, another study found that the chloroform, n-hexane, and ethyl acetate extracts of *Annona muricata* leaves showed cytotoxic effects on Raji cells, with IC_{50} values of 90.6 μg·mL^{-1}, 407.2 μg·mL^{-1}, and 260.2 μg·mL^{-1}, respectively. For HeLa cells, the chloroform and *n*-hexane extracts exhibited IC_{50} values of 127.3 μg·mL^{-1} and 169.2 μg·mL^{-1}, respectively (Artanti et al., 2016).

3.9 Anticancer Activity in vivo

The leaf extract of *Annona muricata* was found to inhibit DMBA/TPA-induced skin tumorigenesis in ICR male mice by modulating antioxidant enzyme activity (Roduan et al., 2017). Studies also revealed that the hexane and dichloromethane extracts of *Annona muricata* leaves effectively inhibited tumor incidence and reduced tumor volume, whereas the methanol extract showed moderate suppressive effects compared to the carcinogen control group. In contrast, the ethanol extract of *Annona muricata* leaves demonstrated a chemoprotective effect against DMBA-induced cell proliferation in the breast tissues of female albino mice (Minari, 2014). Additionally, *Annona muricata* leaves exhibited chemopreventive potential in rats against colonic aberrant crypt foci induced by azoxymethane (Moghadamtousi et al., 2015). Another study revealed that the ethanol extract of *Annona muricata* leaves triggered apoptosis in HepG2 liver cancer cells via the endoplasmic reticulum stress pathway (Liu et al., 2016). Proteomic analysis identified 14 proteins involved in the extract's role in inducing apoptosis, including the upregulation of HSP70, GRP94, and DPI-related protein 5, confirming the involvement of the endoplasmic reticulum stress pathway. This study highlighted the potential of *Annona muricata* leaf extract as a promising anticancer agent. Furthermore, the extract was shown to inhibit the proliferation of HL-60 cells by causing morphological changes, arresting cells in the G0/G1 phase, reducing cell viability, and disrupting mitochondrial membrane potential (Pieme et al., 2014). The findings above establish *Annona muricata* as a highly promising chemotherapeutic agent for cancer treatment. These results demonstrate that not just the leaves, but all parts of the *A. muricata* plant possess versatile anticancer properties.

3.10 Anticancer Activity of Different Bioactive Isolates

In addition to the results obtained from crude extracts, further research has focused on the isolated bioactive compounds from the leaves of *A. muricata* to gain a deeper understanding of their mechanisms of action. However, only a limited number of these isolates have been studied for their biological and pharmacological properties, particularly their anti-inflammatory and anticancer activities (Abdul Wahab et al., 2018).

Presented below are the anticancer activities of the primary bioactive compounds isolated from the leaves of *A. muricata*. Annonacin induced the cell cycle arrest in T24 bladder cancer cells and caused cytotoxicity in a Bax and caspase-3-related pathway. Annonacin also exhibited strong antitumor activity and induced growth arrest and apoptosis in ER-related pathways in MCF-7 cells (Yuan et al., 2003). Annomuricin E on HT-29 cells showed IC_{50} values of 5.72 ±0.41, 3.49 ±0.22 and 1.62 ±0.24 μg·mL^{-1} after 12, 24 and 48 h of treatments. Annomuricin E also induced LDH leakage in cells at 1 and 2 μg·mL^{-1}

and exhibited significant LDH release at the concentration from 4 to 16 μg·mL^{-1} and induced the cell cycle arrest at G1, the phosphatidylserine externalization, the caspase activation, the mitochondria-initiated events, as well as Bax up- regulation and Bcl-2 down-regulation (Moghadamtousi et al., 2015). Muricoreacin was found to be selectively cytotoxic against the PC-3 cell line with five times higher activity compared to the positive antitumor control Adriamycin (Kim et al., 1998). Murihexocin C showed selective cytotoxicity against the PACA-2 as well as the PC-3 cell lines (Kim et al., 1998).

3.11 Neurotoxicity

Previous studies on rats (Lannuzel et al., 2003; Hendawy et al., 2019; Ekweaga et al., 2025), mice (Rottscholl et al., 2016) reported that the dietary supplements containing twigs or leaves from Annonaceous species are toxic to neuronal cells similarly as fruit pulp extracts from Annonaceae that are known to have a high amount of neurotoxic acetogenins. A study reports a possible link between atypical parkinsonism in the French West Indies and the consumption of tropical fruits, including *Annona muricata*. The study proposed a connection between the consumption of herbal tea and fruits from the Annonaceae family (*Annona muricata* and *Annona squamosa*), which contain neurotoxic benzyl-tetrahydro-isoquinoline alkaloids. However, as the research was based on a small case study of 87 human patients, a larger epidemiological study is needed to confirm the association between these fruits, atypical parkinsonism, and supranuclear palsy (Caparros-Lefebvre & Elbaz, 1999). It was suggested that chronic exposure to these neurotoxic alkaloids might play a significant role in the development of the disease, as these compounds have been shown to induce parkinsonism. This correlation has also been noted among patients from New Caledonia and the Caribbean living in London (Shaw & Höglinger, 2008). Another study found a strong link between the consumption of annonaceous acetogenins and the etiology of neurodegenerative disease on Guadeloupe Island. The primary compound, annonacin, was shown to deplete ATP levels in rat striatal neurons and disrupt the transport of mitochondria to the cell soma. This disruption caused cellular disturbances in the tau protein, resulting in several features resembling those observed in neurodegenerative diseases (Escobar-Khondiker et al., 2007).

3.12 Quantification of Acetogenins

Analysis of acetogenins in *Annona muricata* extracts using reversed-phase HPLC and matrix-assisted laser desorption-ionization mass spectrometry (MALDI MS) found that an average fruit contains around 15 mg of annonacin, a can of commercial nectar contains 36 mg, and a cup of infusion or decoction contains 140 μg (Champy et al., 2005). The neurotoxic effects of annonacin were evaluated by administering it intravenously to rats at doses of 3.8 and 7.6 mg per kg per day over a 28-day period (Champy et al., 2004). Annonacin penetrated the brain parenchyma, reducing brain ATP levels by 44% and inducing neuropathological changes in the basal ganglia and brainstem nuclei. It caused a significant loss of dopaminergic neurons in the substantia nigra, as well as cholinergic and DARPP-32-immunoreactive GABAergic neurons in the striatum. These effects were accompanied by a marked increase in astrocyte and microglial cell populations, as determined through stereological cell counts (Champy et al., 2004).

4 Conclusion

In conclusion, *Annona muricata* is a versatile plant with significant medicinal, nutritional, and pharmacological value. *Annona muricata* is widely utilized in traditional medicine to address a range of ailments. Research has highlighted that this plant contains various bioactive compounds, such as acetogenins, flavonoids, phenols, alkaloids, and megastigmanes. Both *in vivo* and *in vitro* studies have demonstrated its potential in treating conditions such as wound healing, ulcers, inflammation, cancer, diabetes, and hypertension. This is largely due to the rich array of biologically active compounds in natural products, which can exert diverse effects, particularly on cancer cells, by inhibiting growth, inducing apoptosis, suppressing angiogenesis, and modulating immune responses. This review summarizes the traditional applications, medicinal properties, chemical components and pharmacological activities of *A. muricata*. While previous studies have primarily focused on the biological activity of the plant's extracts, further research is required to investigate the biochemical and physiological roles of its active compounds and the mechanisms underlying their effects. Additionally, reports suggest that annonacin, an important constituent, may have neurotoxic effects. Thus, distinguishing between chemical constituents, their doses, and associated toxicities is essential. Future studies and clinical trials should prioritize understanding the compounds linked to toxicity, their dosage thresholds, and their impact on the body. This article aims to provide researchers with valuable insights and encourage continued exploration of this plant.

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Conflict of Interest

The authors declare that there is no conflict of interest.

Author Contributions

Conceptualization, R.R., M.L., L.D., M.H.Jr., T.S. and P.M.; Methodology, R.R., M.L., L.D., M.H.Jr., T.S., F.T. and P.M.; Validation, R.R., and P.M.; writing – Original Draft Preparation, R.R. and P.M.; writing – Review & Editing, R.R., M.H.Jr. and P.M.; Visualization, R.R., Project Administration, S.R., R.S., E.R.S. and P.M.; Funding Acquisition, S.R., R.S., E.R.S. and P.M.

AI and AI-assisted technologies use declaration

No generative AI tools/AI-assisted technologies were used during the preparation of the manuscript.

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