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Review Article

Phytochemical Properties and Therapeutic Applications of *Annona muricata*: A Comprehensive Review

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ABSTRACT

This review explores the diverse properties and applications of *Annona muricata*, referred to as soursop or graviola. The historical significance of medicinal herbs, particularly *Annona muricata*, was used in ancient medical practices which produce a variety of chemical compounds, including those of defense mechanisms against pests, diseases, fungi and herbivorous mammals. One of the key highlights of *A. muricata* is its role as a rich source of essential nutrients, including metals that play pivotal roles as cofactors in biochemical processes. This plant has garnered attention for its therapeutic properties in traditional medicine to address many maladies. *A. muricata's* medicinal properties include treating fever, acne, insomnia, hypertension, respiratory disorders, parasitic and bacterial infections, inflammation, diabetes and cancer. This review explores the scientific basis behind these traditional uses, focusing on the biochemical mechanisms that underlie *A. muricata's* therapeutic. Furthermore, this review discusses the global prevalence of *A. muricata*, particularly in tropical and subtropical regions and its adaptation to diverse environmental conditions, highlighting its promising role in addressing contemporary health challenges.

Keywords: *Annona muricata*, Phytoconstituents, Therapeutic activity, Soursop, Graviola.

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INTRODUCTION

Many plant species act as miniature chemical factories, producing an array of secondary metabolites, including phenolic and polyphenol compounds, terpenoids, essential oils, alkaloids, tannins, saponins and coumarins.[1] *Annona muricata* often referred to as graviola, soursop, or guanabana, displays a range of roles in the medicinal properties of plants. The tree has a thin appearance and low branches and its fruit is known for its irregular, heart-shaped appearance and contains creamy white parenchyma cells encapsulated by skin with delicate, curving spines. *A. muricata* finds extensive use in traditional medicine for various infections and diseases, including fever, acne, insomnia, hypertension, rheumatism, respiratory disorders, parasitic and bacterial infections, inflammation, diabetes, malaria, kidney and liver problems, as well as soothing and anticancer.[2] The plant's seeds treat parasitic infections; its fruits address arthritis, diarrhea and nervous disorders, while its leaves, rich in bioactive compounds, are utilized for headaches, insomnia, cystitis and cancer treatment.[3] The scientific community has recognized the significance of phytochemicals from plants in pharmaceutical discoveries, highlighting the therapeutic potential of natural products (Figure 1). However, despite scientific interest, only a restricted number of comprehensive scientific examinations of plant species are essential to fully understand the physiological impacts of these plants and their phytochemical compounds. *A. muricata*, with its rich ethnomedicinal history, presents a promising avenue for pharmaceutical exploration, as described in this review covering its botany, distribution, ethnomedicinal uses, phytochemistry, biological activities and potential mechanisms.[4] Throughout history, medicinal plants have been critical in maintaining human well-being. *A. muricata* is indigenous to Central and South America and the Caribbean region. Its rich ethnomedicinal history and extensive traditional use make it a valuable candidate for further research into its potential therapeutic applications.[5] The active ingredients of plants have garnered significant scientific interest for their potential in agriculture and medicine, leading to an exploration of their biological activities.[6] However, our understanding about the detailed scientific examination of a range of plants of some species is limited, hindering our ability to understand their inherent role treatments fully. *A. muricata* is the scientific name for a plant species also referred to as Graviola Soursop or Gunbanana and it originates from a tropical region. The plant is indigenous to Central and South America and the Caribbean region. Its rich ethnomedicinal history and extensive traditional use make it a valuable candidate for further research into its potential therapeutic applications. Understanding the biological activities and mechanisms of action of A. This review aims to provide a

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detailed analysis of the plant taxonomy, geographical range and traditional medicinal use of *A. muricata* while also summarizing its chemical composition, biological effects and potential modes of action.

SYNONYMS

Graviola-coracao (Portuguese)

Corossolier (French)

Zi guo lao (Chinese)

Guyabano (Filipino)

Toge-banreisi (Japanese)

Gang (Vietnamese)

Mullaatha (Tamil)

Mullatha (Malayalam)

Hanuman Phala (Hindi)

Ramphal (some regions of India)

Laxmanphal (certain parts of India)

Hanuman Phal (also used in some regions)

Mullachakka (Kerala)

Mullu Seetha (Tamil Nadu)

Soursop (English-speaking countries)

Graviola (Brazil and other Portuguese-speaking regions)

Guanábana (Mexico, Colombia and Puerto Rico)

Corossol (French-speaking regions like Haiti and parts of Africa)

Stachelannone (in German-speaking regions)

Jaboticaba (in some parts of South America)

Zuurzak (in Dutch-speaking areas, including Suriname and the Netherlands Antilles)

Taxonomy (family, species)

Order: Magnoliales

Family: Annonaceae Juss.-Custard-apple family

Genus: Annona L.-annona

Species: *Annona muricata* L.-soursop

Super division: Spermatophyta-Seed plants

Division: Magnoliophyta-Flowering plants

Class: Magnoliopsida-Dicotyledons

Subclass: Magnoliidae[7]

BOTANICAL DISTRIBUTION

A. muricata, sometimes called Soursop or Graviola, is a tropical shrub highly valued for its fruit. The plant offers both therapeutic advantages and possible adverse effects.[8] This plant belongs to the Annonaceae family and is categorized under the Magnoliales order and Magnoliophyta division. Annona has more than 70 species, with *A. muricata* being the most widely cultivated. Soursop trees often attain a height of 5-10 m and a diameter of 15-83 cm. They have a unique look due to their low branches. They exhibit continuous flowering and fruiting throughout the year but are altitude-dependent and seasonal fluctuations may occur. They are native to tropical climates and produce visually appealing yellow-green blooms. The fruit is an oval berry, initially having a dull green hue and holds 55 to 170 seeds. These seeds are black while fresh, turn to light brown when mature and maintain the same color when dried. The white, creamy pulp has a distinctive fragrance and flavor, making it a highly valued component in tropical gastronomy. *A. muricata*, formerly indigenous to hot tropical regions in South and North America, has spread worldwide to tropical and subtropical locations, such as India, Malaysia and Nigeria. The tree yields sizable, heart-shaped, verdant fruits, about 15 to 20 cm in diameter, with more nutritional value. Although it is widely consumed as a meal, its medicinal capabilities have garnered significant interest, especially in traditional and herbal medicines. Moreover, it is important to exercise care since excessive ingestion of certain plant components may lead to toxicological consequences.

TRADITIONAL USES

The *A. muricata* tree and other Annona species, such as A. squamosa and A. reticulata, are extensively used in traditional medicine to treat various health conditions.[9] The fruit alleviates ailments such as arthritic pain, diarrhea and fever. Tropical Africa highly regards this plant for its astringent effects and its effectiveness as an insecticide. In India, the fruit and bloom have many uses in medicinal therapies, such as anti-inflammatory and anthelmintic effects.[10] The plant's leaves, bark and roots have diverse therapeutic properties. In addition to its therapeutic use, the fruits are utilized in various culinary recipes. The plant's therapeutic properties are derived from various plant parts used traditionally for colds, influenza and malaria (Table 1).[11-20]

PHYTOCHEMISTRY

Plants produce primary metabolites for their survival and secondary metabolites in response to environmental stimuli. These secondary metabolites offer diverse medicinal properties, including alkaloids, polyphenols, terpenoids, essential oils, coumarins, saponins and tannins. *A. muricata*, are renowned for their abundance of annonaceous Acetogenin compounds (AGEs). *A. muricata* fruit contains essential minerals, including

potassium, calcium, sodium, copper, iron and magnesium, making it a valuable source of nutrients for human consumption.[21]

Alkaloids

Alkaloids extracted from the root of *A. muricata*, include coclaurine, reticuline, argentininee, atherosperminine and xylopine have garnered interest for their potential cytotoxic effects on cancer cells. These alkaloids exhibit cytotoxicity against many cancer cell lines, including HL-60 (Human Leukemia), A549 (human lung adenocarcinoma) and HepG2 (liver cancer).[22] Xylopine had the most significant cytotoxic effect, with an IC_{50} value ranging from 20 to 80 µM, suggesting it is a cytotoxic agent against cancer cells.

Phenolic Compounds

The ethyl acetate *A. muricata* leaf fraction includes kaempferol-3-O-glucoside and 1-(4-Hydroxyphenyl)-3-P henylpropan-1-one, both of which have antioxidant activity.[23] The polyphenols derived from *A. muricata*, including kaempferol, procyanidins, catechin and quercetin, exhibit cytotoxic effects on HeLa cancer cells and 3T3 fibroblast cells.

Table 1: Ethnomedicinal Uses of Graviola (*A. muricata*).[11-20]

Ethnomedicinal Uses	Plant Parts Used	Graviola Extract/ Chemical Compound
Pesticide	Seed, leaves, barks, stems, roots and flowers	Acetogenins
Anti-parasitic	Leaf	Ethanolic extract and its fractions, methanol extracts, acetogenins, ethyl acetate extract.
Hypotensive	Leaf, fruit	Aqueous extract, alkaloids (isoquinoline, coreximine, anomurine).
Fever	Leaf	Flavonoids
Respiratory illness	Leaf	Essential Oil
Sedative	Leaf	Hydroalcoholic extract
Malaria	Seed, leaf	Ethanolic extract
Gastrointestinal disorders	Leaf	Ethyl acetate extract
Liver, heart and renal disorders	Fruit, Leaf	Ethyl acetate and ethanol extracts.
Hypoglycemic	Leaf, branch	Ethanolic extract.
Cancer	Leaf, fruit, stem, bark, and branch	Annonaceous acetogenins, alkaloids, flavonoids, sterols and others.

Annonaceous Acetogenins

A. muricata includes acetogenins such as annomuricin A, B and C, muricatocin C, cis-goniothalamicin, muricatacin, arianacin, annonacin-10-one, cis-annonacin and javoricin. These compounds include hydroxyl functional groups with alpha and beta-unsaturated gamma-lactone. Reported studies indicates that 15-acetyl guanacone has significant antioxidant properties by effectively scavenging DPPH and ABTS radicals. A high concentration of 10 µg/mL caused substantial harm to the genetic material of MCF-7 cells, a specific kind of human breast cancer cells.[24] Acetogenin suppresses the growth of colon cancer cells by facilitating the movement of Apoptosis-Inducing Factor (AIF) into the nucleus, therefore beginning cell death that is reliant on AIF. The expression of Bcl-2 and Mcl-1 proteins was suppressed in both SW620 (human colorectal cancer) and RKO (poorly differentiated colon carcinoma) cell lines both in laboratory settings and in living organisms.[25] Acetogenins retards the production of ATP in mitochondria, specifically in cancer cells. This restriction on ATP production is achieved by suppressing the activity of NADH: ubiquinone oxidoreductase, often known as Complex I, is a component of the mitochondrial electron transport system seen in cancer cells.

Essential oils

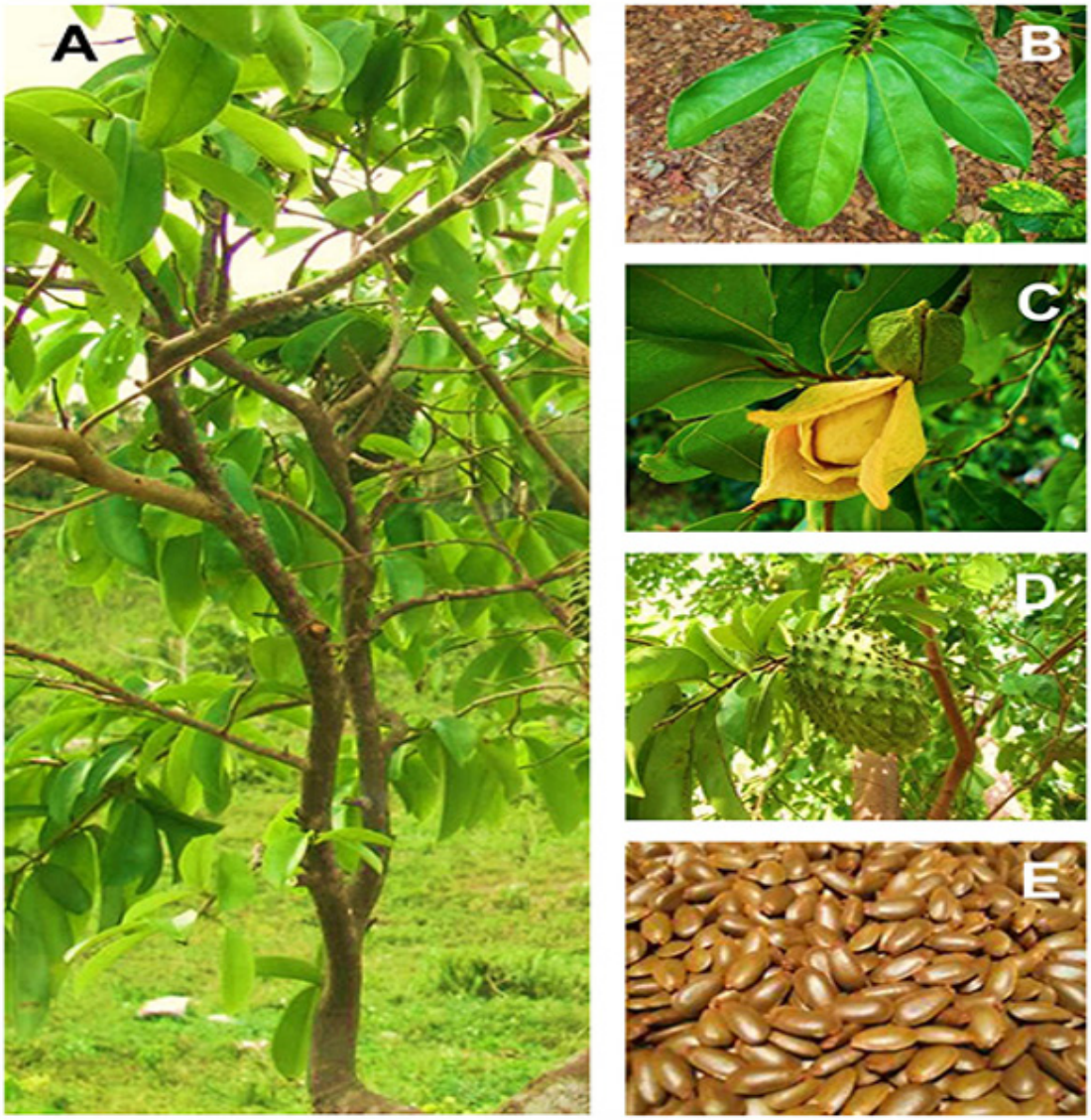
GC-MS study indicated that the oil consists mostly of sesquiterpenes, with β-caryophyllene being the predominant.[26] On the other hand, the leaf oil extracted from *A. muricata* in Vietnam includes β-pinene (20.6%), germacrene D (18.1%), ρ-mentha-2,4(8)-diene (9.8%), α-pinene (9.4%) and β-element (9.1%). The main components of the leaf oil extracts are δ-cadinene, epi-α-cadinol and α-cadinol. The primary constituents of the essential oil derived from the fruit pulp consist of esters of aliphatic acids, with 2-hexenoic acid methyl ester and 2-hexenoic acid ethyl ester. Furthermore, the fruit pulp oil contains mono- and sesquiterpenes, such as β-caryophyllene, 1,8-cineole and linalool. Advanced Glycation End products (AGEs) are a distinct category of secondary metabolites called C-35/C37 molecules. These compounds are synthesized by the polyketide pathway using long-chain fatty acids (C-32/C34) (Figures 2, 3).[27]

PHARMACOLOGICAL ACTIVITIES

The Table 2 provides a comprehensive overview of the pharmacological activities associated with various parts of *Annona muricata* and its extract. Each part of the plant, including leaves, fruits, seeds, bark and roots, exhibits unique therapeutic activities, ranging from anticancer and antimicrobial to anti-inflammatory and antioxidant effects. This compilation highlights the potential of *Annona muricata* as a valuable resource in natural medicine

Table 2: Pharmacological Activities of Various Plant Parts.[28-43]

Pharmacological activity	Parts used	Model	Method	Mechanism of action	Extract
Anti-cancer	Leaves	*In vitro* (cancer cell lines)	MTT assay, cell proliferation assays.	Induction of apoptosis, cell cycle arrest.	Ethanolic extract.
Anti-microbial	Leaves, fruit	*In vitro* (bacteria, fungi)	Disk diffusion, MIC/MBC.	Inhibition of microbial growth.	Ethanolic, aqueous.
Antioxidant	Leaves	*In vitro* (DPPH, FRAP assays)	Free radical scavenging assays.	Free radical scavenging, antioxidant enzymes.	Methanolic extract.
Anti-inflammatory	Leaves	*In vivo* (animal models)	Carrageenan-induced paw edema.	Inhibition of inflammatory mediators.	Ethanolic extract.
Anti-diabetic	Leaves	*In vivo* (animal models)	Blood glucose level measurements.	Increased insulin sensitivity, reduced glucose production.	Aqueous, ethanolic.
Anti-parasitic	Leaves, seeds	*In vitro* (protozoa), *in vivo* (animal models)	Parasite viability assays, observation of parasitic load.	Disruption of parasitic cell membranes.	
Anti-depressant	Leaves	*In vivo* (animal models)	Forced swim test, tail suspension test.	Modulation of serotonin and dopamine levels.	
Anti-hypertensive	Leaves	*In vivo* (animal models)	Blood pressure measurements.	Vasodilation, calcium channel blocking.	
Hepatoprotective	Leaves	*In vivo* (animal models)	Liver enzyme assays, histopathological studies.	Reduction in liver damage, antioxidant activity.	
Neuroprotective	Leaves, fruit	*In vivo* (animal models)	Neurological tests, oxidative stress measurements.	Antioxidant activity, neuroinflammation reduction.	
Anti-ulcer	Leaves	*In vivo* (animal models)	Gastric ulceration tests.	Reduction in gastric acid secretion, mucosal protection.	
Anti-parasitic	Leaves, seeds	*In vitro* (protozoa), *in vivo* (animal models)	Parasite viability assays, observation of parasitic load.	Disruption of parasitic cell membranes.	
Anti-depressant	Leaves	*In vivo* (animal models)	Forced swim test, tail suspension test.	Modulation of serotonin and dopamine levels.	
Anti-hypertensive	Leaves	*In vivo* (animal models)	Blood pressure measurements.	Vasodilation, calcium channel blocking.	
Hepatoprotective	Leaves	*In vivo* (animal models)	Liver enzyme assays, histopathological studies.	Reduction in liver damage, antioxidant activity.	
Neuroprotective	Leaves, fruit	*In vivo* (animal models)	Neurological tests, oxidative stress measurements.	Antioxidant activity, neuroinflammation reduction.	
Anti-ulcer	Leaves	*In vivo* (animal models)	Gastric ulceration tests.	Reduction in gastric acid secretion, mucosal protection.	



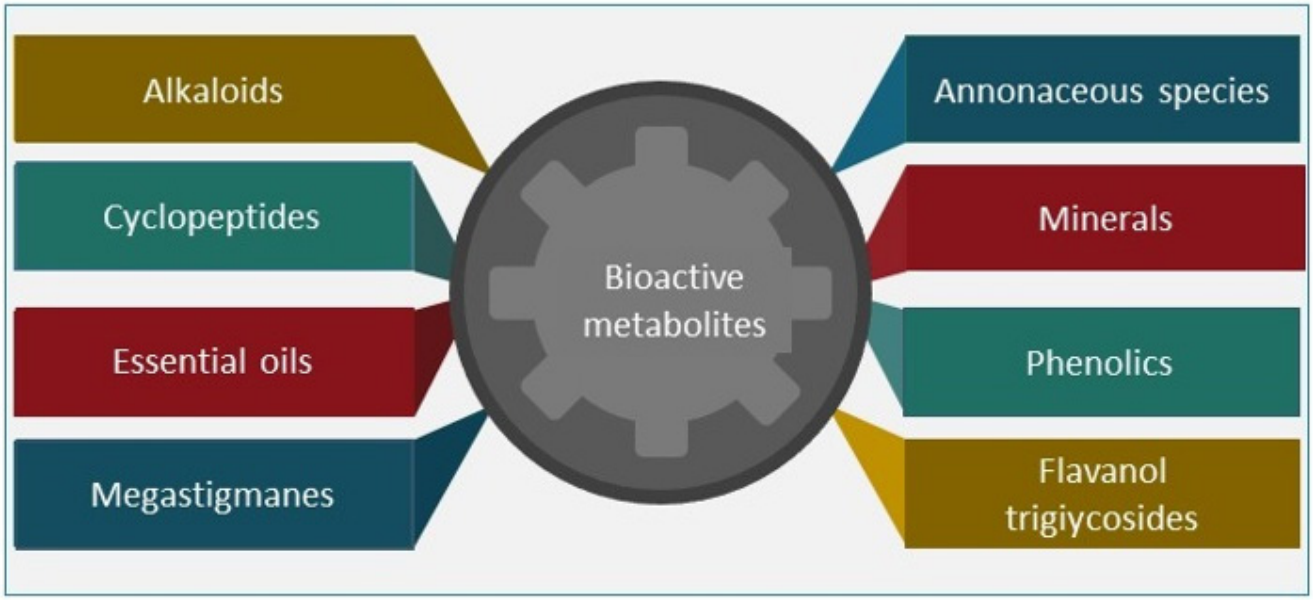
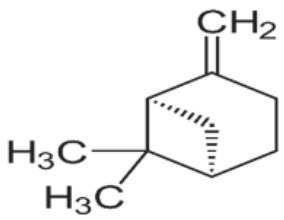


Figure 1: *A. muricata* tree, leaves, flower, fruit, seed.[6]



structure of β-pinene

Figure 2: Bioactive metabolites present in *A. Muricata.*

and pharmaceutical research. Specific pharmacological activities are detailed below.

Antioxidant Activity

An overabundance of Reactive Oxygen Species (ROS) inside the cells may result in oxidative stress, which disrupts metabolic processes and causes cell death due to biochemical and physiological harm.[44] Padma and her colleagues conducted a further experiment and found that the ethanolic extract derived from the stem bark of *A. muricata* showed adaptogenic characteristics. It decreased lipid peroxidation induced by cold immobilization stress in the brains and livers of rats.

Anti-viral Activity

A. muricata extracts possess antiviral activity against Herpes Simplex Virus (HSV), Human Immunodeficiency Virus (HIV) and influenza virus, which is attributed to acetogenins, alkaloids and flavonoids.[45] The antiviral mechanism involves inhibiting viral replication and attachment to host cells. Studies have shown that *A. muricata* extracts can disrupt viral entry and replication, thus preventing viral spread and infection.[46] Compounds isolated from *A. muricata*, such as annonacin, annonamine and quercetin, exhibit potent antiviral activity, targeting various stages of the viral life cycle. These compounds, including acetogenins, alkaloids and flavonoids, demonstrate broad-spectrum antiviral effects against HSV, HIV and influenza viruses. The results emphasize the capacity of *A. muricata* to serve as a reservoir of innovative antiviral substances.

Anti-convulsant Activity

The leaves of *A. muricata* are traditionally used in decoction form in numerous African regions to manage fever and convulsive seizures. This traditional practice has garnered interest in scientific research to substantiate its efficacy. The anticonvulsant effect of *A. muricata* leaves was reported for its ethanolic extract to counteract tonic-clonic seizures produced by pentylenetetrazol convulsions in rats.

Anti-diabetic Activity

Extensive *in vivo* studies have explored *A. muricata*'s traditional use in treating diabetes. There was a significant decrease in blood glucose levels from 21.64 to 4.22 mmol/L in an early reported study.[47] Similarly, research conducted in Cameroon examined the ethno pharmacological use of *A. muricata* leaves in diabetic rats induced by streptozotocin and revealed the encouraging antidiabetic benefits of the extract, which were related to its antioxidant and hypolipidemic activities. The histopathological study provided further confirmation for these observations, demonstrating the leaf extract had stimulated the regrowth of pancreatic β-cells.[48]

Anti-arthritic activity

A. muricata is also known for its traditional medicine, which alleviates arthritis. The plant extract was administered at various dosages (3, 10, 30 and 100 mg/kg) to Complete Freund's Adjuvant (CFA) induced arthritic rats, which revealed a significant correlation between the dose of the extract and the amount of decrease in swelling within two weeks.[49] *A. muricata* leaves also inhibited the production of pro-inflammatory cytokines, such as TNF-α and IL-1β, crucial for joint destruction in arthritis which suggests that *A. muricata* leaves have anti-arthritic properties by suppressing these cytokines. The dose-dependent reduction in swelling and cytokine suppression indicates *A. muricata*'s potential as a natural remedy for arthritis.

Anti-Inflammatory Activity

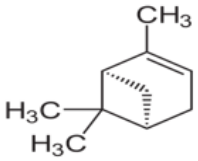
When given orally at doses of 10, 30, 100 and 300 mg/kg, the leaf extracts of *A. muricata* in ethanol showed anti-inflammatory effects.[50] This intervention markedly decreased the inflammation caused by carrageenan in the paws of rats by 79%, with a direct correlation to the amount administered. This was associated with reductions in leukocyte movement and fluid secretion. The observed effect was linked to a reduction in the production of TNF-α and IL-1β in mice with arthritis caused by CFA and ear edema produced by xylene.

Anti-parasitic Activity

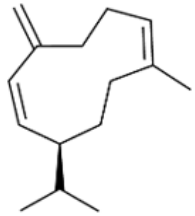
Protozoal diseases like leishmaniasis and trypanosomiasis are of global health concerns, posing significant treatment challenges due to increasing medication resistance and toxicity. In a study examining *A. muricata*, researchers found that the seeds contained two active compounds, annonacinone and corossolone, demonstrated significant efficacy against leishmania species. The anti-parasitic effects of these compounds were dose-dependent, indicating proper dosage is critical for maximizing efficacy while minimizing potential toxicity.[51] The researchers noted that annonacinone and corossolone inhibited the growth of leishmania species, suggesting a potential mechanism involving the disruption of mitochondrial function.

Anti-cancer Activity

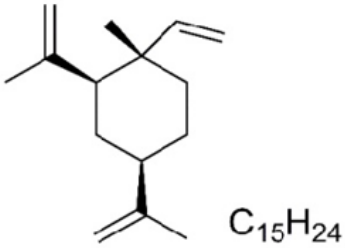
Multiple studies have shown the inhibitory effects of different plant extracts on tumor cell development. Furthermore, scientific



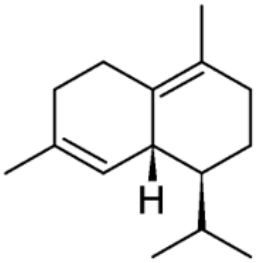
structure of α -pinene



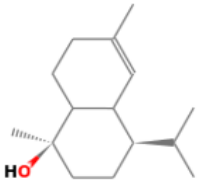
Structure of germacrene D



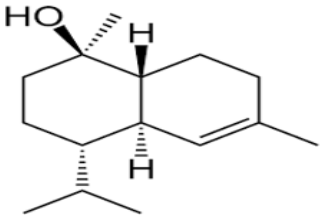
structure of β-elemene



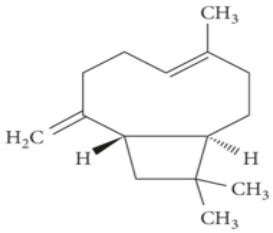
structure of δ-cadinene



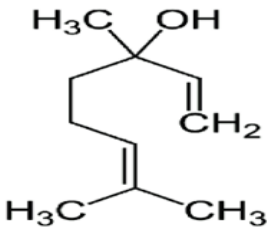
structure of epi-α-cardinal



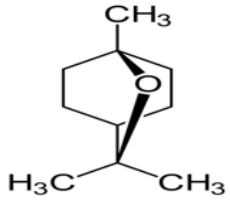
structure of α-cadinol



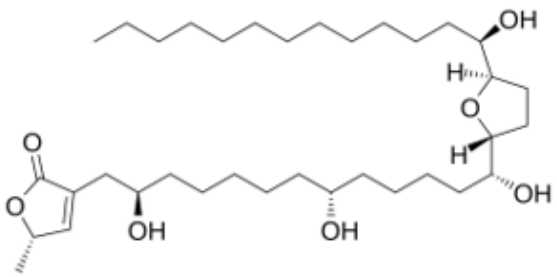
structure of β-caryophyllene



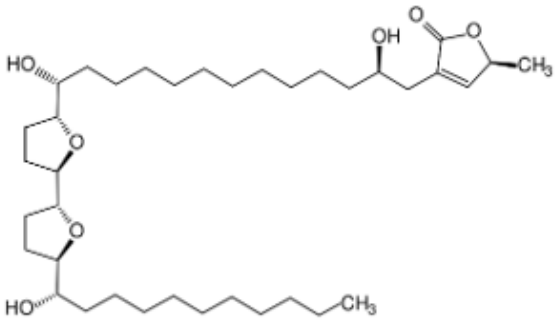
structure of linalool



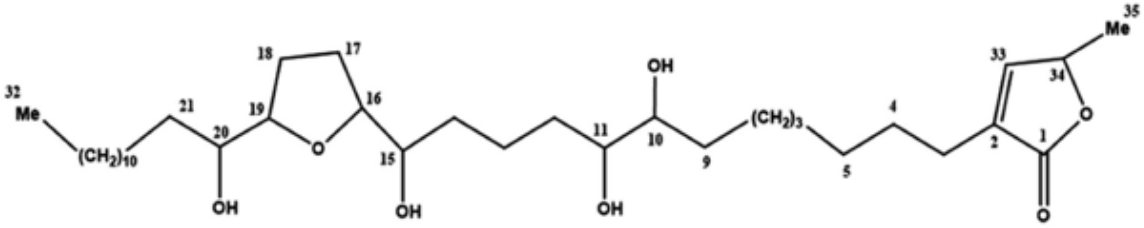
structure of 1,8-cineole



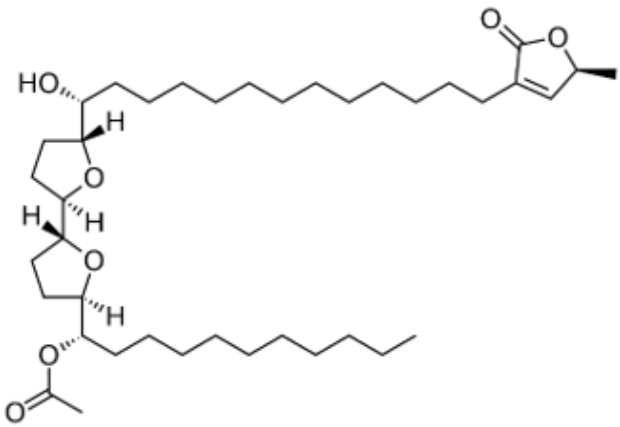
Structure of Annonacin



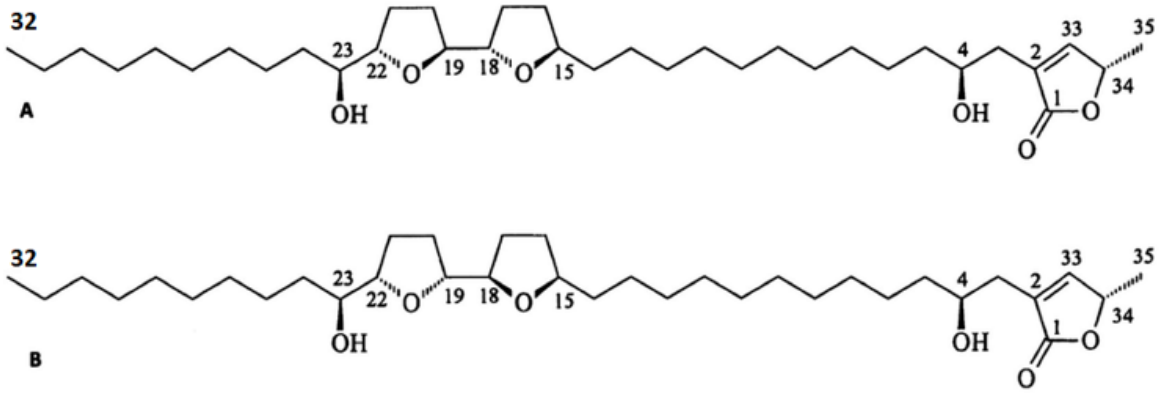
Structure of Bullatacin



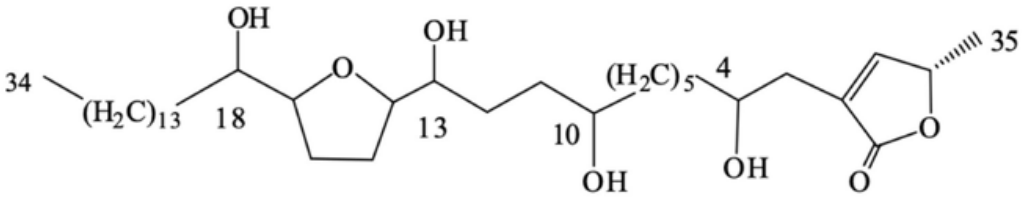
Structure of Annomuricin E



Structure of Uvaricin



Structure of Annocatacin A (A) and Annocatacin B (B)



Structure of Longicin

Figure 3: Structure of Phytoconstituents.

studies have examined the impact of isolated Advanced Glycation End products (AGEs) on several cancer cell lines.[52] Only a limited number of researches have investigated the fundamental biochemical processes. The effects of an ethyl acetate extract of *A. muricata* on colon cancer cells (HT-29 and HCT-116) and lung cancer cells (A549) were examined. This extract triggered programmed cell death (apoptosis) and halted the progression of the cell cycle, mainly in the G1 phase. An aqueous extract inhibited BPH-1 cells and reduced rat prostate size.

Pancreatic cancer

The incidence of pancreatic cancer is on the rise, largely because of the absence of first clinical signs. The powder derived from the leaves and stem extract of *A. muricata* has inhibitory effects on cell proliferation and tumor growth in subcutaneous xenograft models and pancreatic cancer cell lines. These effects result in the cessation of cell division, the initiation of programmed cell death" and the start of programmed cell death. *A. muricata* triggers metabolic catastrophe, modulates glucose metabolism to induce cell death and down-regulates MUC4 (mucin).[53]

Lung carcinoma

Lung cancer is a major contributor to global mortality from cancer. Studies have shown that the ethyl acetate extract is derived from the foliage of *A. muricata*. Exhibits cytotoxic effects on the A549 cell line, a human lung cancer variant. This extract induces cell cycle arrest, specifically in the G0/G1 phase and enhances apoptosis.[54]

Prostate cancer

Multiple studies have demonstrated that extracts from the fruit pulp of *A. muricata* have antiproliferative properties in many cell lines, such as 22Rv1, LNCaP and PC-3. These extracts also inhibit NOX activity, a mechanism linked to downregulating HIF-1 expression.[55]

Breast cancer

Among women, breast cancer is the most widespread cancer. While early stages are treatable, advanced cases pose challenges. Recent studies demonstrate *A. muricata's* potent antiproliferative and anticancer effects. Cancer cells exposed to *A. muricata's* ethyl acetate extract exhibit apoptosis-like changes, including cell membrane rupture.[56]

Colon carcinoma

A. muricata leaf extract demonstrates anticancer properties, particularly in Colorectal Carcinoma (CRC). It increases the protein caspase-3, which promotes programmed cell death (apoptosis), inhibits the movement and infiltration of HT-29 and HCT-116 cell lines, the initiation of cell cycle arrest and cell death results in the destabilization of the mitochondrial membrane, affecting the function of Bax and Bcl-2 proteins.[57]

Head and Neck cancers

Most tumors that impact the head and neck area region, often called head and neck squamous cell carcinomas; occur in the mouth and throat. *A. muricata* leaf extract demonstrates antiproliferative effects and arrests cell cycle during the G2/M phase. Combining *A. muricata* extracts with cisplatin may enhance effectiveness due to their apoptosis-inducing properties.[58]

Hematological malignancies

The ethanol and methanol extracts obtained from *A. muricata* leaves have been found to trigger apoptosis, a process of programmed cell death, in different forms of leukemia, including the cell lines of human myelogenous leukemia (K562), human T-cell leukemia (CCRF-CEM), multidrug-resistant leukemia (CEM/ADR5000), B-cell chronic lymphocytic leukemia, myeloid leukemia and multiple myeloma.[59]

Cervical cancer

Methanol, extract derived from the foliage of *Annona muricata*, has inhibitory effects on the rapid increase in the number of Hep-2 (laryngeal carcinoma) cell lines.[60]

CONCLUSION

In conclusion, *A. muricata* is valued for its rich composition of essential vitamins such as thiamine, niacin and Vitamin C, as well as minerals including calcium, magnesium, potassium, iron, phosphorus and zinc. Its abundance of acetogenins, which are long-chain fatty acid moieties, has been detected in many plant components, with the highest concentrations found in the seeds. Moreover, the leaves of *A. muricata* contain corossolone, p-coumaric acid, epicatechin, epicatechin gallate and ferulic acid, among other phytoconstituents which contribute to the plant's diverse medicinal applications, including antioxidant, anti-inflammatory, antiparasitic, antidiabetic, antibacterial, anticancer, wound healing, antiulcer, anti-malarial, antihypertensive and gastroprotective activities.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AGEs: Annonaceous Acetogenins; ***A. muricata:*** *Annona muricata:* **ROS:** Reactive Oxygen Species; **IC_{50}:** Half-Maximal Inhibitory Concentration; **TNF-α:** Tumor Necrosis Factor-alpha.

REFERENCES

1. Kaur P, Pandey DK, Gupta RC, Kumar V, Dwivedi P, Sanyal R, *et al.* Biotechnological interventions and genetic diversity assessment in Swertia sp.: a myriad source of valuable secondary metabolites. Appl Microbiol Biotechnol. 2021;105(11):4427-51. doi: 10.1007/s00253-021-11345-4, PMID 34037841.
2. Coria-Téllez AV, Montalvo-Gónzalez E, Yahia EM, Obledo-Vázquez EN. *Annona muricata*: A comprehensive review of its traditional medicinal uses, phytochemicals, pharmacological activities, mechanisms of action and toxicity. Arab J Chem. 2018;11(5):662-91. doi: 10.1016/j.arabjc.2016.01.004.
3. Nolasco-González Y, Chacón-López MA, Ortiz-Basurto RI, Aguilera-Aguirre S, González-Aguilar GA, Rodríguez-Aguayo C, et al. *Annona muricata* leaves as a source of bioactive compounds: extraction and quantification using ultrasound. Horticulturae. 2022;8(7):560. doi: 10.3390/horticulturae8070560.
4. Zubaidi SN, Mohd Nani H, Ahmad Kamal MS, Abdul Qayyum T, Maarof S, Afzan A, et al. *Annona muricata*: comprehensive review on the ethnomedicinal, phytochemistry and pharmacological aspects focusing on antidiabetic properties. Life (Basel). 2023;13(2):353. doi: 10.3390/life13020353, PMID 36836708.
5. Moghadamtousi SZ, Fadaeinasab M, Nikzad S, Mohan G, Ali HM, Kadir HA. *Annona muricata* (Annonaceae): a review of its traditional uses, isolated acetogenins and biological activities. Int J Mol Sci. 2015;16(7):15625-58. doi: 10.3390/ijms160715625, PMID 26184167.
6. Abdul Wahab SM, Jantan I, Haque MdA, Arshad L. Exploring the leaves of *Annona muricata* L. as a source of potential anti-inflammatory and anticancer agents. Front Pharmacol. 2018;9:661. doi: 10.3389/fphar.2018.00661, PMID 29973884.
7. Plants US. Database [Internet]. Available from: plants.usda.gov. Available from: https://plants.usda.gov/home/classification/71478.
8. Rady I, Bloch MB, Chamcheu RN, Banang Mbeumi S, Anwar MR, Mohamed H, *et al.* Anticancer properties of Graviola (*Annona muricata*): a comprehensive mechanistic review. Oxid Med Cell Longev. 2018; 2018:1826170. doi: 10.1155/2018/1826170, PMID 30151067.
9. Thang TD, Dai DN, Hoi TM, Ogunwande IA. Study the volatile oil contents of *Annona glabra* L., *Annona squamosa* L., *Annona muricata* L. and *Annona reticulata* L. from Vietnam. Nat Prod Res. 2013;27(13):1232-6. doi: 10.1080/14786419.2012.724413, PMID 22989376.
10. Ferreira LE, Castro PM, Chagas AC, França SC, Beleboni RO. *In vitro* anthelmintic activity of aqueous leaf extract of *Annona muricata* L. (Annonaceae) against *Haemonchus contortus* from sheep. Exp Parasitol. 2013;134(3):327-32. doi: 10.1016/j.exppara.2013.03.032, PMID 23583362.
11. Arroyo J, Prashad M, Vásquez Y, Li E, Tomás G. Actividad citotóxica *in vitro* de la mezcla de *Annona muricata* y *Krameria lappacea* sobre células cancerosas de glándula mamaria, pulmón y sistema nervioso central (in Spanish). Rev Peru Med Exp Salud Publ. 2005;22:247-53.
12. Gavamukulya Y, Abou-Elella F, Wamunyokoli F, AEl-Shemy H. Phytochemical screening, anti-oxidant activity and *in vitro* anticancer potential of ethanolic and water leaves extracts of *Annona muricata* (Graviola). Asian Pac J Trop Med. 2014;7S1:S355-63. doi: 10.1016/S1995-7645(14)60258-3, PMID 25312150.
13. Asare GA, Afriyie D, Ngala RA, Abutiate H, Doku D, Mahmood SA, *et al.* Antiproliferative activity of aqueous leaf extract of *Annona muricata* L. On the prostate, BPH-1 cells and some target genes. Integr Cancer Ther. 2015;14(1):65-74. doi: 10.1177/1534735414550198, PMID 25411208.
14. Cortes D, Hla Myint S, Laurens A, Hocquemiller R, Davoust D, Davoust D. Murisolin: A new cytotoxic mono-tetrahydrofuran-γ-lactone from *Annona muricata*. Heterocycles. 1990;31(5):861-7. doi: 10.3987/COM-90-5338.
15. Minari JB, Okeke U. Chemopreventive effect of *Annona muricata* on DMBA-induced cell proliferation in the breast tissues of female albino mice. Egypt J Med Hum Genet. 2014;15(4):327-34. doi: 10.1016/j.ejmhg.2014.05.001.
16. Hamizah S, Roslida AH, Fezah O, Tan KL, Tor YS, Tan CI. Chemopreventive potential of *Annona muricata* L. leaves on chemically induced skin papilloma genesis in mice. Asian Pac J Cancer Prev. 2012;13(6):2533-9. doi: 10.7314/apjcp.2012.13.6.2533, PMID 22938417.
17. Eggadi V, Gundamedi S, Sheshagiri SB, Revoori SK, Jupally VR, Kulandaivelu U. Evaluation of anticancer activity of *Annona muricata* in 1,2-dimethyl hydrazine induced colon cancer. World Appl Sci J. 2014;32:444-50.
18. N'gouemo P, Koudogbo B, Tchivounda HP, Akono-Nguema C, Etoua MM. Effects of ethanol extract of *Annona muricata* on pentylenetetrazol-induced convulsive seizures in mice. Phytother Res. 1997;11(3):243-5. doi: 10.1002/(SICI)1099-1573(199705)11: 3<243::AID-PTR66>3.0.CO;2-A.
19. Adeyemi DO, Komolafe OA, Adewole SO, Obuotor EM. Anti hyperlipidemic activities of *Annona muricata* (Linn). Internet J Altern Med. 2008;7:1.

20. Hemalatha G, Sivakumar K, Rajesh S, Shyamala Devi K. Phytochemical profiling, the anticancer and apoptotic activity of Graviola (*Annona muricata*) fruit extract against human hepatocellular carcinoma (HepG-2) cells. Int J Zool Appl Biosci. 2020;5(1):32-47.
21. Muhammad NA, Elbeltagy RS, Diab MS, Gardouh AR, Ola H. *Annona muricata* L. leaves extract loaded on chitosan nanoparticles combined with methotrexate induce Cytotoxicity in A549 cancer cell line.
22. Jaramillo MC, Arango GJ, González MC, Robledo SM, Velez ID. Cytotoxicity and antileishmanial activity of *Annona muricata* pericarp. Fitoterapia. 2000;71(2):183-6. doi: 10.1016/s0367-326x(99)00138-0, PMID 10727816.
23. Qorina F, Arsianti A, Fithrotunnisa Q, Tejaputri N, Azizah NN, Putrianingsih R. Cytotoxicity of soursop leaves (*Annona muricata*) against cervical HeLa cancer cells. Pharmacogn J. 2020;12(1):20-4. doi: 10.5530/pj.2020.12.4.
24. Soini Y, Kinnula V, Kaarteenaho-Wiik R, Kurttila E, Linnainmaa K, Pääkkö P. Apoptosis and expression of apoptosis regulating proteins bcl-2, mcl-1, bcl-X and bax in malignant mesothelioma. Clin Cancer Res. 1999;5(11):3508-15. PMID 10589765.
25. Warenius HM. Selectively depleting the energy of cancer cells: A new therapeutic paradigm. J Cancer Biol. 2024;5(1):1-10. doi: 10.46439/cancerbiology.5.057.
26. Kelechi OE, James AF, Ajah OI. Characterization of *Annona muricata* stem methanol extract by gas chromatography-mass spectrometry analysis. Res J Pharmacogn Phytochem. 2016;8(3):165-71. doi: 10.5958/0975-4385.2016.00028.5.
27. Prabhakaran K, Ramasamy G, Doraisamy U, Mannu J, K R, Murugesan JR. Polyketide natural products, acetogenins from Graviola (*Annona muricata* L.), its biochemical, cytotoxic activity and various analyses through computational and bio-programming methods. Curr Pharm Des. 2016;22(34):5204-10. doi: 10.2174/1381612822666160531163144, PMID 27262333.
28. Rosdi MN, Daud NN, Zulkifli RM, Yaakob H. Cytotoxic effect of *Annona muricata* Linn. leaves extract on Capan-1 cells. J App Pharm Sci. 2015;5(5):45-8. doi: 10.7324/JAPS.2015.50508.
29. Silva RM, Silva IM, Estevinho MM, Estevinho LM. Anti-bacterial activity of *Annona muricata* Linnaeus extracts: a systematic review. Food Sci Technol. 2021;42. doi: 10.1590/fst.13021.
30. Balderrama-Carmona AP, Silva-Beltrán NP, Gálvez-Ruiz JC, Ruíz-Cruz S, Chaidez-Quiroz C, Morán-Palacio EF. Antiviral, antioxidant and antihemolytic effect of *Annona muricata* L. leaves extracts. Plants (Basel). 2020;9(12):1650. doi: 10.3390/plants9121650, PMID 33256023.
31. Ziyan L, Yongmei Z, Nan Z, Ning T, Baolin L. Evaluation of the anti-inflammatory activity of luteolin in experimental animal models. Planta Med. 2007;73(3):221-6. doi: 10.1055/s-2007-967122, PMID 17354164.
32. Alwan IA, Lim V, Samad NA, Widyawati T, Yusoff NA. Effect of *Annona muricata* L. on metabolic parameters in diabetes mellitus: a systematic review. Curr Res Nutr Food Sci J. 2020;8(1):1-11. doi: 10.12944/CRNFSJ.8.1.01.
33. Mutakin M, Fauziati R, Fadhilah FN, Zuhrotun A, Amalia R, Hadisaputri YE. Pharmacological activities of soursop (*Annona muricata* Lin.). Molecules. 2022;27(4):1201. doi: 10.3390/molecules27041201, PMID 35208993.
34. Bikomo EO, Ebuehi OA, Magbagbeola O. Antidepressant activity of ethanol leaf extract of *Annona muricata* L., in Sprague-Dawley rats. Am J Biochem. 2017;7(1):1-5.
35. Candra A, Prasetyo BE, Darge HF. Honey utilization in soursop leaves (*Annona muricata*) kombucha: physicochemical, cytotoxicity and antimicrobial activity. Biocatal Agric Biotechnol. 2023;52:102815. doi: 10.1016/j.bcab.2023.102815.
36. Sokpe A, Mensah ML, Koffuor GA, Thomford KP, Arthur R, Jibira Y, *et al.* Hypotensive and antihypertensive properties and safety for use of *Annona muricata* and *Persea americana* and their combination products. Evid Based Complement Alternat Med. 2020; 2020:8833828. doi: 10.1155/2020/8833828, PMID 33488751.
37. Nwokocha CR, Owu DU, Gordon A, Thaxter K, McCalla G, Ozolua RI, *et al.* Possible mechanisms of action of the hypotensive effect of *Annona muricata* (soursop) in normotensive Sprague-Dawley rats. Pharm Biol. 2012;50(11):1436-41. doi: 10.3109/13880209.2012.684690, PMID 22950673.
38. Larbie C, Arthur FN, Woode E, Terlabi E. Evaluation of hepatoprotective effect of aqueous extract of *Annona muricata* (Linn.) leaf against carbon tetrachloride and acetaminophen-induced liver damage. J Nat Pharm. 2012;3(1):25-. doi: 10.4103/2229-5119.96957.
39. Nirmala M, Girija K, Lakshman K, Divya T. Hepatoprotective activity of *Musa paradisiaca* on experimental animal models. Asian Pac J Trop Biomed. 2012;2(1):11-5. doi: 10.1016/S2221-1691(11)60181-0, PMID 23569826.
40. Keskin E, Elmas O, Keser Sahin HH, Tonge C, Gunaydin A. The neuroprotective and anti-inflammatory effects of *Annona muricata* (Graviola) on radiation-induced rat sciatic nerve injury. Marmara Med J. 2022;35(2):211-8. doi: 10.5472/marumj.1121375.
41. Al Omairi NE, Al-Brakati AY, Kassab RB, Lokman MS, Elmahallawy EK, Amin HK, *et al.* Soursop fruit extract mitigates scopolamine-induced amnesia and oxidative stress via activating cholinergic and Nrf2/HO-1 pathways. Metab Brain Dis. 2019;34(3):853-64. doi: 10.1007/s11011-019-00407-2, PMID 30919246.
42. Bento EB, Júnior FE, de Oliveira DR, Fernandes CN, de Araújo Delmondes G, Cesário FR, *et al.* Antiulcerogenic activity of the hydroalcoholic extract of leaves of *Annona muricata* Linnaeus in mice. Saudi J Biol Sci. 2018;25(4):609-21. doi: 10.1016/j.sjbs.2016.01.024, PMID 29736140.
43. Mutakin M, Fauziati R, Fadhilah FN, Zuhrotun A, Amalia R, Hadisaputri YE. Pharmacological activities of soursop (*Annona muricata* Lin.). Molecules. 2022;27(4):1201. doi: 10.3390/molecules27041201, PMID 35208993.
44. Apel K, Hirt H. Reactive oxygen species: metabolism, oxidative stress and signal transduction. Annu Rev Plant Biol. 2004;55:373-99. doi: 10.1146/annurev.arplant.55.031903.141701, PMID 15377225.
45. Wahab NZ, Ibrahim N, Kamarudin MK, Lananan F, Juahir H, Ghazali A, *et al.* Cytotoxicity and antiviral activity of *Annona muricata* aqueous leaves extract against dengue virus type 2. J Fundam Appl Sci. 2018; 10(1S):580-9.
46. La Vignera S, Basile L, Aversa A, Calogero AE, Grillo A, Cannarella R, *et al.* The use of ellagic acid and *Annona muricata* improves semen quality in men with high-risk Papillomavirus infection. J Clin Med. 2022;11(16):4691. doi: 10.3390/jcm11164691, PMID 36012935.
47. Aderibigbe K, Komolafe O, Adewole O, Obuotor E, Adenowo T. Anti-hyperglycemic activities of *Annona muricata* (Linn). Afr J Tradit Complement Altern Med. 2010;6(1):6-10. doi: 10.4314/ajtcam.v6i1.57075.
48. Ojo OA, Grant S, Amanze JC, Oni AI, Ojo AB, Elebiyo TC, et al. *Annona muricata* L. peel extract inhibits carbohydrate metabolizing enzymes and reduces pancreatic β-cells, inflammation and apoptosis via upregulation of PI3K/AKT genes. PLOS ONE. 2022;17(10):e0276984. doi: 10.1371/journal.pone.0276984, PMID 36301972.
49. Chan P, Ah R. Mh K. Antiarthritic activities of *Annona muricata* L. leaves extract on complete Freund's adjuvant (CFA)-induced arthritis in rats. Planta Med. 2010;76(12). doi: 10.1055/s-0030-1264464.
50. Foong CP, Hamid RA. Evaluation of anti-inflammatory activities of ethanolic extract of *Annona muricata* leaves. Rev Bras Farmacogn. 2012;22(6):1301-7. doi: 10.1590/S0102-695X2012005000096.
51. Miranda NC, Araujo EC, Justino AB, Cariaco Y, Mota CM, Costa-Nascimento LA, *et al.* Anti-parasitic activity of *Annona muricata* L. leaf ethanolic extract and its fractions against *Toxoplasma gondii in vitro* and *in vivo*. J Ethnopharmacol. 2021;273:114019. doi: 10.1016/j.jep.2021.114019, PMID 33716084.
52. Usunobun U. A review of some African medicinal Plants. Int J Pharm Biol Sci. 2012;3(1):104-10.
53. Lawal AZ, Abdulrahim HA, Iyanda YA, Munirudeen I, Adekunle AS. Effects of ethyl acetate leaf extract of *Annona muricata* on some enzymes of carbohydrate metabolism in streptozotocin-induced diabetic Wistar rats. Niger J Biochem Mol Biol. 2022;37(1):87-92.
54. Zorofchian Moghadamtousi S, Karimian H, Rouhollahi E, Paydar M, Fadaeinasab M, Abdul Kadir H. *Annona muricata* leaves induce G1 cell cycle arrest and apoptosis through mitochondria-mediated pathways in human HCT-116 and HT-29 colon cancer cells. J Ethnopharmacol. 2014;156:277-89. doi: 10.1016/j.jep.2014.08.011.
55. Handayani SI, Rahmadi L, Prasasty VD. Molecular docking and drug-likeness for identifying the inhibitory action of acetogenins from *Annona muricata* as potential anticancer against hypoxia-inducible factor 1 alpha. Biomed Pharmacother J. 2018;11(3):1301-7.
56. Minarni IM, Artika IM, Julistiono H, Bermawie N, Riyanti EI, Hasim, *et al.* Anticancer activity test of ethyl acetate extract of endophytic fungi isolated from soursop leaf (*Annona muricata* L.). Asian Pac J Trop Med. 2017;10(6):566-71. doi: 10.1016/j.apjtm.2017.06.004, PMID 28756920.
57. Zorofchian Moghadamtousi S, Rouhollahi E, Karimian H, Fadaeinasab M, Firoozinia M, Ameen Abdulla M, *et al.* The chemopotential effect of *Annona muricata* leaves against azoxymethane-induced colonic aberrant crypt foci in rats and the apoptotic effect of acetogenin annomuricin E in HT-29 cells: a bioassay-guided approach. PLOS ONE. 2015;10(4):e0122288. doi: 10.1371/journal.pone.0122288, PMID 25860620.
58. Han JM, Song HY, Kim KI, Park WY, Park SH, Byun EB, *et al.* Polysaccharides from *Annona muricata* leaves protect against cisplatin-induced cytotoxicity in macrophages by alleviating mitochondrial dysfunction. Mol Med Rep. 2023;27(1):1-8. doi: 10.3892/mmr.2022.12903, PMID 36453199.
59. Ezirim AU, Okachi VI, James AB, Adebeshi OA, Ogunnowo S, Odeghe OB. Induction of apoptosis in myelogenous leukemic K562 cells by ethanolic leaf extract of *Annona muricata*. Indian J Drugs Dis. 2013:241-7.
60. Jepkorir M, Ambundo T, Ngule CM, Ndung'u JW, Njuguna DK, Mbugua RW, *et al.* Phytochemical screening and *in vitro* antiproliferative activity of the fruit of *Annona muricata* and *Abelmoschus esculentus* pods against selected cancer cell lines. Asian Pac J Trop Biomed. 2019 28;9(2): 53-9.

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