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Review Article

A Review on Botanicals, Traditional Uses, Phytochemistry, Therapeutic Potentials, Clinical Trials, and Toxicity Profile of *A. muricata*

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ABSTRACT

Annona muricata is extensively utilized in the treatment of various health conditions such as fever, malaria, bacterial infections, arthritis, diabetes, inflammation, and cancer. This study aims to provide current literature on the ethnomedicinal uses, phytochemistry, potential health benefits, clinical studies, and toxicological profile of *A. muricata*. This review contains up-to-date information on relevant literature published between 2000 and 2025. PubMed, Scopus, ScienceDirect, Springer, Wiley, and MDPI were the databases used for the material search. This study revealed numerous bioactive compounds, such as α-tocopherol, anthocyanins, α-carotene, apigenin, p-coumaric acid, myricetin, lycopene, morin, kaempferol, cinnamic acid, β-carotene, annonain, nornuciferin, annonacin, lutein, murihexocin A and corossolone. Research has shown that different parts of *A. muricata* have a variety of beneficial effects, such as antioxidant, wound-healing, antimicrobial, antiparasitic, anticancer, antiulcer, anti-inflammatory, antidiarrheal, antidiabetic, antiprotozoal, antimalarial, hepatoprotective, and antidepressant effects. This study has shown that *A. muricata* possesses therapeutic properties against several diseases, suggesting that it could be used in the pharmaceutical industry as a raw material for the development of new drugs. It can also be integrated as a functional food to add nutritive value and flavor in the preparation of different foods, such as juice and ice cream. Nevertheless, it is essential to establish quality controls and safety profiles (through chronic studies and clinical trials) and to elucidate the mechanisms of action of *A. muricata* and its bioactive compounds in the prevention and treatment of diverse health conditions.

Keywords: Bioactive compounds, *A. muricata*, ethnomedicinal uses, pharmacological activities, toxicity.

Introduction

Medicinal plants and the active compounds derived from them are used worldwide to treat and prevent numerous diseases, including various types of cancer, inflammation, ulcers, sickle cell anaemia, and stroke.[1,2] More than 80% of the world's population, especially in developing regions of Asia and Africa, currently relies on herbal medicine to treat various health problems.[3-7] This growing inclination towards the use of medicinal plants and their extracts over the last thirty years can be attributed to factors such as their accessibility, lower incidence of side effects, and cost-effectiveness.[2] For more than a decade, medicinal plants have attracted the attention of numerous scientists, not only because of their benefits in the treatment of diseases but also because they serve as novel sources for the development of pharmaceutical products such as drugs.[3,4,8,9]

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In addition, medicinal plants are important sources of natural therapeutics for healing and disease prevention, withminimal or no side effects. The tropical fruit tree *Annona muricata*, often known as soursop or graviola, is indigenous to the tropical Americas and is widely recognized for its edible fruits, which are used in both contemporary and medical contexts. Although it is currently grown in many tropical and subtropical climates worldwide, it is native to Central America and the West Indies and is a member of the *Annonaceae* family.[10] It is an amazing plant that has enormous potential for managing, preventing, and treating a wide range of illnesses in addition to being a source of medical products. The plant yields edible fruits, and different parts of *A. muricata* have varied medicinal qualities.[11] These ingredients are widely used to treat a variety of illnesses, such as cancer, diabetes, inflammation, and parasite infections.[11]

The leaves, stem bark, roots, and seeds of *A. muricata* are the primary components utilized for therapeutic purposes in tropical countries; however, other portions of the plant are also utilized in traditional medicine.[12] The leaves are especially well-known for their ability to treat ailments like cancer, headaches, sleeplessness, and cystitis, while the seeds are noted for their ability to treat parasite infections.[13] The fruit promotes breastfeeding in nursing women, reduces fever, eases diarrhoea and neuralgia, and drives out worms and parasites.[14] The primary bioactive substances found in *A. muricata* include flavonoids, alkaloids, and acetogenins. A thorough analysis of the leaf extract has identified several secondary metabolites, such as flavonoids, anthraquinones, glycosides, saponins, and tannins.[15] *In vitro* and *in vivo* pharmacological studies have demonstrated that various parts of *A. muricata* exhibit antidiarrheal,[16] anticancer,[17] antiulcer,[18]

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antiprotozoal,[19] antibacterial,[20] antiviral,[21] antihypertensive,[22] wound-healing,[23] antidiabetic,[24] and anti-inflammatory activities.[13] Figure 1a and 1b shows different parts of *A. muricata*, such as the stem and branches, leaves, fruits, pulp, and seeds. This study provided current information on the traditional applications, bioactive phytoconstituents, health benefits, and toxicity profile of *A. muricata*. In addition, prospects on the use of. *A. muricata* for therapeutic benefits is also reported in this review.

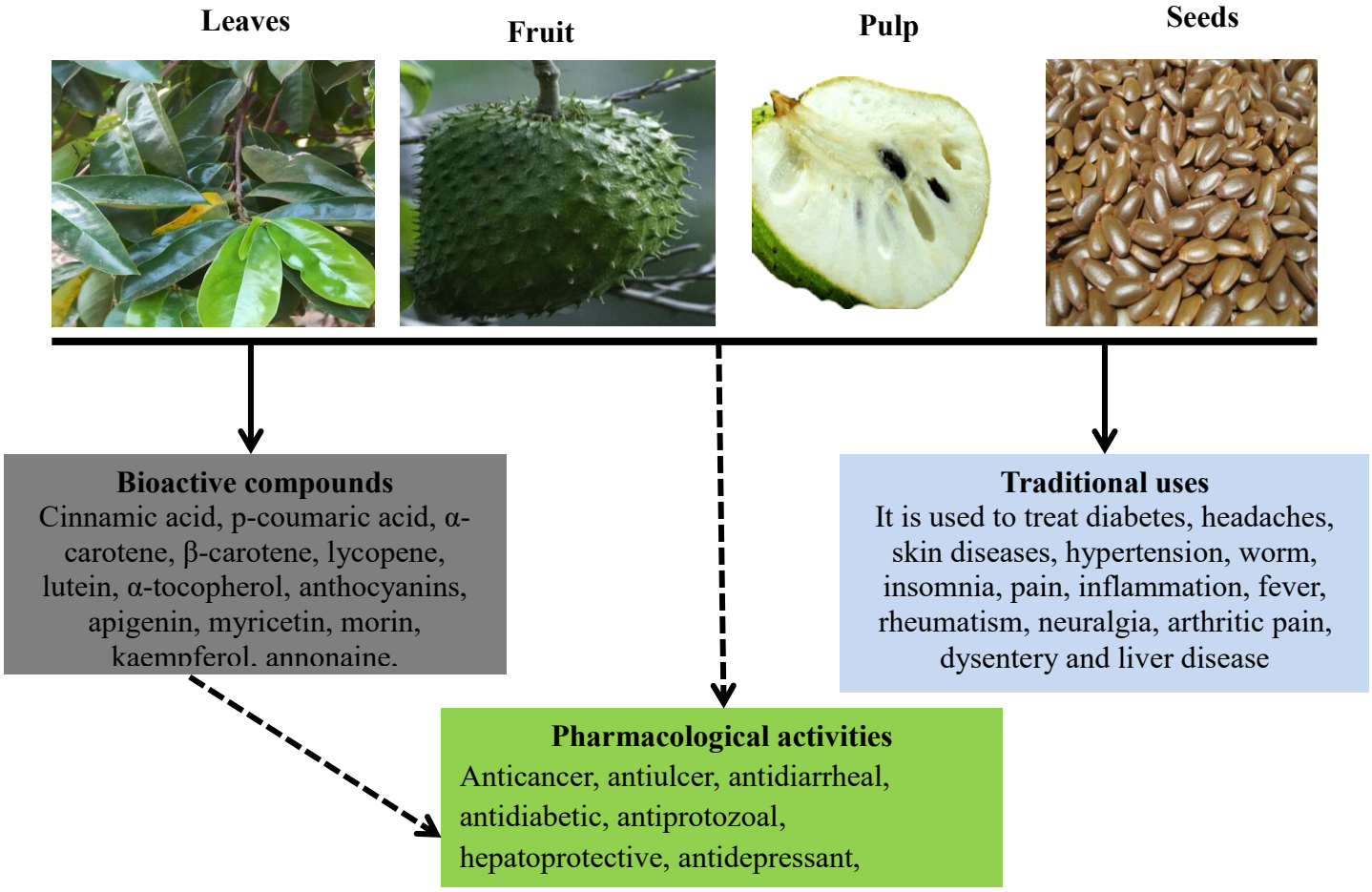

Figure 1a: Graphical Abstract showing the various parts of *A. muricata*, traditional uses, bioactive compounds, and pharmacological activities

Figure 1b: Various parts of *A. muricata* showing the leaves, branches, fruit (pulp and seed)

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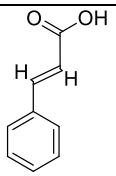
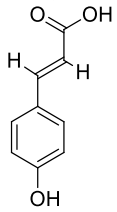
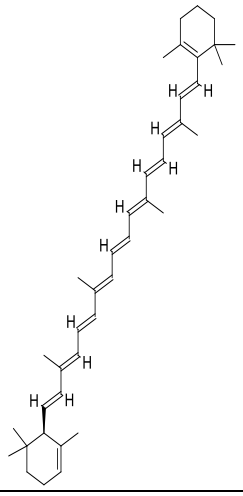
Materials and Methods

This review employed a comprehensive search strategy to identify relevant articles published between January 2000 and March 2025, which were used for the study. The articles were retrieved from databases such as Springer, Scopus, Multidisciplinary Digital Publishing Institute (MDPI), ScienceDirect, PubMed, and Wiley. Relevant keywords and their combinations were used, such as "*A. muricata*," "*A. muricata* AND phytochemistry," "pharmacological effects of *A. muricata"*, "antidiabetic effect, anticancer effect, antidiarrheal effect, antioxidant effect, hepatoprotective effect, antimicrobial effect, antiulcer effect, anti-inflammatory effect of *A. muricata"*, and other related terms. The Boolean operators "AND" and "OR" were used to combine these keywords. In addition, the reference lists of the identified articles were further screened for relevant literature that can be included in the review.

The titles and abstracts of the identified articles were first imported into a reference manager to identify possible duplication for removal. The articles were then screened using titles and abstracts to identify their suitability for full article review, followed by full article screening for relevant articles within the scope of the review that were published in English between 2000 and 2025. The included studies were peer-reviewed, full-text articles that focused on the *A. muricata* in terms of their traditional and medicinal uses, geographical distribution, phytochemistry, pharmacological benefits, clinical trials, and toxicity profile. However, the exclusion criteria include articles without full-text access, non-English literature, and articles that were not related to *A. muricata.*

Data were extracted using tables in a well-structured format. Table 1 provides a description of important bioactive components of *A. muricata*, their structures, method of extraction, plant part used, and their biological activity. The chemical structures were depicted via ChemDraw (version 12.0.2). Table 2 provides a description of the pharmacological activities of *A. muricata*, including doses, experimental models, observations, and effects. Table 3 describes clinical trials of *A. muricata*. The study employed a narrative synthesis due to the heterogeneity of the collected data in terms of study design, methodology, treatments, and outcomes. The collected data were organized into the following thematic categories: botanical description, geographical distribution, traditional uses, bioactive compounds, health-promoting effects, toxicity, and clinical trials of *A. muricata.*

Table 1: Names, structures, methods of extraction, and pharmacological activities of the major bioactive compounds of *Annona muricata*

Compound	Structure	Method of extraction	Plant part	Biological activity
Cinnamic acid		UV detection and HPLC	Leaf	Antioxidant, antibacterial, anticancer, anti-inflammatory, antidiabetic properties.[67,68]
p-Coumaric acid		HPLC	Fruits	Antioxidant, anti-inflammatory properties.[69]
α-Carotene		The high-pressure fluid chromatography (FC)	Pulp	Antioxidant, anti-carcinogenic properties.[70]

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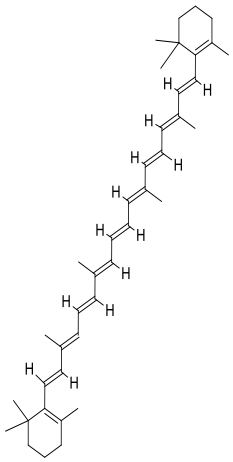
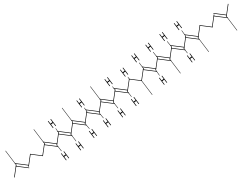
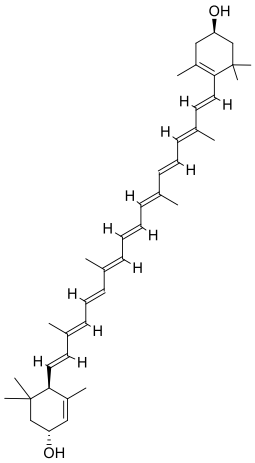
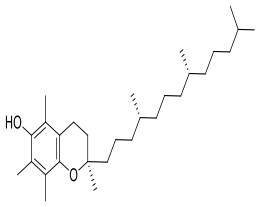
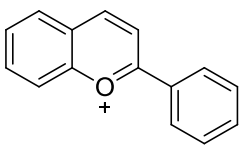
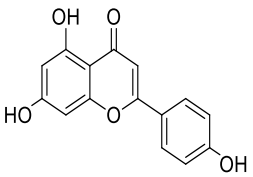
β-Carotene		Spectrophotometry	Pulp	Anti-inflammatory, anticancer and antioxidant effects.[71,72]
Lycopene		TLC and colorimetric technique.	Pulp	Antioxidant and anticancer effects.[73]
Lutein		Matching of the Lutein sample retention time (RT) using lutein standard.	Pulp	Hepatoprotective, anticancer and antioxidant effects.[74,75]
α-Tocopherol		Ultra-high -pressure fluid chromatography combines with Quadrupole time-of-flight mass spectrometry.	Leaf	Antioxidant activity[76]
Anthocyanins		TLC and UV–visible spectroscopy.	Leaf	Antioxidant, anti-inflammatory, antitumour activities.[77,78]
Apigenin		HPLC	Leaf	Antioxidant, antimutagenic, anticancer, antiinflammatory, and antiproliferative properties.[79]

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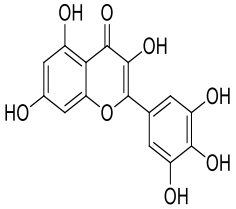
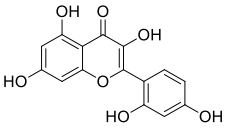
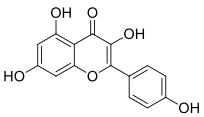
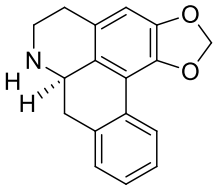
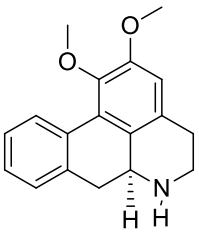
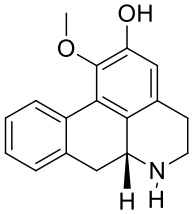
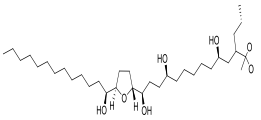
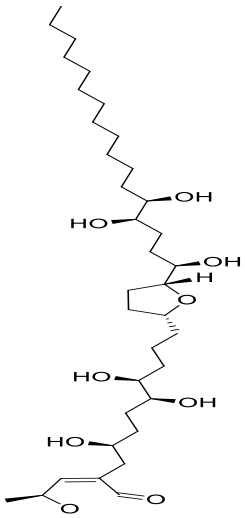
Myricetin		HPLC	Pulp	Antidiabetic, anticancer, anti-inflammatory and antioxidant effects.[80]
Morin		HPLC	Pulp	Antioxidant, anti-inflammatory, antidiabetic, antimicrobial activities.[81]
Kaempferol		HPLC	Leaf	Antioxidant, anti-inflammatory, anti-diabetic and anticancer effects.[82-84]
Annonaine		TLC	Fruits	Anti-depressants, anti-plasmodial, antibacterial, anti-fungal, antioxidative, anticancer.[85-87]
Nornuciferine		High pressure fluid chromatography and photodiode arrays.	Fruits	Antiobesity, and anti-hyperlipidemia effects.[88-90]
Asimilobine		Spectroscopic methods	Fruits, leaves	Antimalarial and anticancer effects.[91]
Annonacin		TLC	Seeds, leaves, pericarp	Antitumour, antioxidants effects[92]
Murihexocin A		LC–MS	Leaves, pulp	Antidiarrheal, anti-inflammatory, antiparasitic, analgesic effects[11,93]

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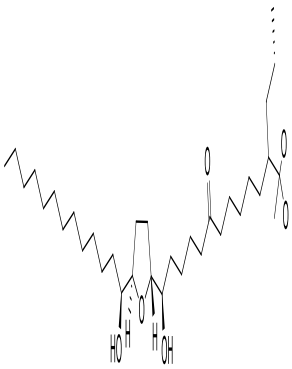
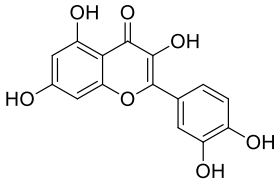
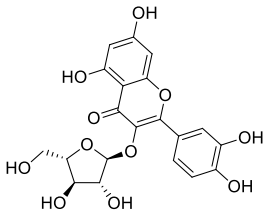
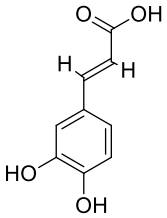
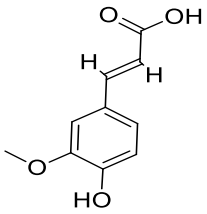
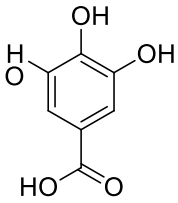
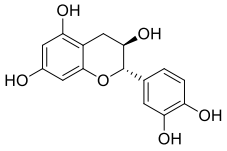
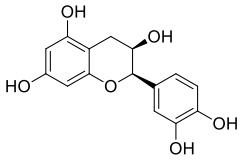
Corossolone		HPLC	Leaves, seeds	Anti-hypertensive, anti-inflammatory, and antitumour effects.[30,31]
Quercetin		HPLC	Leaves	Antidiabetic, inflammatory, antibacterial, anticancer, antioxidant, anti-hypertensive activities.[94]
Rutin		HPLC	Leaves	Anti-diabetic, antioxidant, antiinflamatory and anticancer.[95]
Caffeic acid		HPLC	Leaves	Anticancer, and anti-diabetes[96]
Ferulic acid		HPLC	Leaf	Antioxidant, and anti-inflammatory[97]
Gallic acid		HPLC	Leaf	Anti-inflammatory, antioxidant, antitumour, and antimicrobial[98]
Catechin		Identified using DPPH center dot scavenging capacity and phosphomolybdenum method	Leaf	Antioxidant activity[99]
Epicatechin		Identified using DPPH center dot scavenging capacity and phosphomolybdenum method	Leaf	Antioxidant activity[99]

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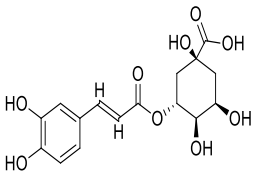
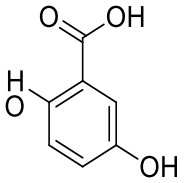
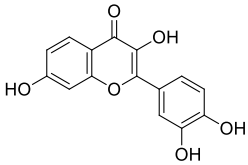
Chlorogenic acid		HPLC	Leaf	Antioxidant activity[99]
Gentisic acid		HPLC	Leaf	Antiinflammatory, antimicrobial, hepatoprotective, and antioxidant effect[100]
Fisetin		HPLC	Pulp	Anti-inflammatory[101]

Table 2: Pharmacological activities of *A. muricata*

Doses	Experimental model	Observations	Effects	References
One capsule/ day of *A. muricata* extract for 8 weeks	Colorectal cancer patients	Cytotoxic activities on colorectal cancer	Anticancer	[17]
250 and 500 mg/kg of *A. muricata* leaf extract	Mice	Reduced tumor volume in Dba/2 (P815) mice	Antitumour	[104]
200 mg/kg ethanolic extract of *A. muricata* leaves	Rats	Decreased mortality, tumour occurrence, tumour volume in DMBA exposed rats	Antitumour	[105]
0.468 - 30 µg ml/L of either ethanolic or water extract of *A. muricata* leaves	Human breast cancer MCF-7 cell line	Cytotoxic activities on MCF-7 cell line	Anticancer	[102]
0.97- 250 µg/mL of either n-hexane, ethyl acetate or water fractions of *A. muricata* leaf extracts	Human breast cancer MCF7 cells	Cytotoxic activities on MCF-7 cell line	Anticancer	[109]
0-500 µg/mL of purified graviola pericarp fraction	Cell line	Decreased cell viability	Anticancer	[158]
50-400 mg/kg of *A. muricata* leaves.	Rats	Decreased abdominal pain	Antiulcer	[20]
200- 400 mg/kg ethyl acetate extract of *A. muricata* leaves	Rats	Protected against ethanol-induced gastric injury	Antiulcer	[107]
0.125-100 mg/ml of *A. muricata* leaf extract	*H.pylori*	Inhibited *H.pylori*	Antiulcer	[119]
150, 300 and 600 mg/kg of hydroethanol extracts of *A. muricata* fruit pulp	Rats	Decreased the fecal count in castor oil diarrhea-induced rats	AntidiarrheaL	[121]
100, 200 and 400 mg/kg of fruit extract	Mice	Inhibited loose stools caused by castor oil	Antidiarrheal	[122]
25 mg/kg (hexanefraction) or 25, 50 and 100 mg/kg of methanol pulp extract	Rats	Inhibited castor oil-induced stooling	Antidiarrheal	[159]
100-800 mg/kg of fruit-pulp and rootbark methanolic extracts	Rats	Inhibited α-amylase and α-glucosidase activities	Antidiabetic	[126]

1.0 mL/kg oral administration of *A. muricata* seed oil	Mice	Reduced blood glucose level in streptozotocin-induced mice	Antidiabetic	128
100 mg/kg of *A. muricata*	Rats	Reduced blood sugar levels	Antidiabetic	24
100, 200, and 300 mg/kg of ethanolic leaf extract of *A. muricata*	Mice	Decreased parasitemia levels in *Plasmodium berghei* NK-65 infected mice	Antimalarial	160
A. muricata stem-bark extract of 50, 150 and 300 mg/kg.	Rats	Reduced swim time and safety time in rats in the Porsolt test.	Antidepressant activity	161
6.6% of *A. muricata* leaf extract.	*Candida albicans*	Reduced fungal growth and cell density by 58% and 65%, respectively.	Antifungal activity	143
96% ethanol of *A. muricata* leaf extract.	*Candida albicans*	Biofilms were greatly reduced, as were fungal weight and inflammation.	Antifungal activity	144
20 mg/ml ethyl acetate extract of soursop	Rats	Increased antioxidant levels and decreased MDA levels	Wound healing	107
150, 300, and 600 mg/kg of ethanolic extracts of soursop leaves, roots, and bark	Rats	Decreased levels of paracetamol-induced AST and ALT	Hepatoprotective activity	133
150, 300, and 600 mg/kg ethanol stem bark extract of *A. muricata* doses	Rats	Reduced paracetamol-induced increase in AST and ALT levels	Hepatoprotective activity	162
150, 300 and 600 mg/kg of hydroethanolic extract of soursop pulp	Rats	Reduced size of edematous paws.	Anti-inflammatory activity	121
200 mg/kg of ethanolic of *A. muricat*a leaves extract	Rats	Increased GSH, SOD, and CAT, decreased MDA in DMBA induced rats	Antioxidant	105
200 mg/kg of Graviola	Rats	Increased CAT, SOD, GST, and GSH	Antioxidant	141
200 mg/kg of ethanol leaf *A. muricata* extracts	Rats	Increased SOD, CAT and GSH in doxorubicin-induced toxicity	Antioxidant	148
1.5% of *A. muricata* leaf kombucha extract	*Escherichia coli* and *Staphylococcus aureus*.	Inhibited the microorganisms	Antimicrobial activity	146

Table 3: Clinical trial studies of *A. muricata*[165]

S/N	NCT Number	Conditions	Intervention	Status
1.	NCT03909945	Hypertension	One tablet of 796 mg aqueous extracts of *A. muricata* leaves daily for 60 days	Completed
2.	NCT02439580	Colorectal cancer	*A. muricata* ethanol-soluble fraction of water extract capsule, 300 mg/day, for 8 weeks	Completed
3.	NCT02263378	HPV infection	Ellagic acid + *A. muricata*	Completed
4.	NCT03531203	Blood pressure, prehypertension, uric acid	Soursop supplementation (2 times a day for 100 g each for 3 months)	Completed

Botanical description

A. muricata is classified within the genus *Annona*, which belongs to the family *Annonaceae*, the order *Magnoliales*, and the phylum *Magnoliophyta*. Of more than 70 species of the genus *Annona*, *A. muricata* is the most widespread. The fruit-bearing branches of this species typically reach a height of 5 to 10 meters and can be between 15 and 83 centimetres in width.[25] It flowers almost every year, although the seasons vary according to altitude.[26] In South and Central America, Western Africa, and Southeast Asia,[26] the annual rainfall is more than 1500 mm, the relative humidity ranges from 60 to 80%, and the temperature ranges from 25 to 28 degrees Celsius. The natural soursop product is a tasty, completely oval, dark green berry.[26] *A. muricata* has a unique taste and smell, and its flesh is creamy and white in colour. According to [27], each fruit contains 55-170 dark seeds when freshly harvested, which change to chocolate colour when dried.

Geographical distribution

A. muricata is native to Bolivia, Nicaragua, Ecuador, Colombia, Honduras, Costa Rica, Mexico, Peru, and Venezuela. This is represented by the green legend as presented in Figure 2 of the geographical distribution of *A. muricata*. In contrast, *A. muricata* was introduced to countries such as Gabon, Bangladesh, Nigeria, Cameroon,

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El Salvador, Guinea, Benin, China, Cuba, Taiwan, Thailand, Ghana, Mexico, Taiwan, Gambia, Brazil, Thailand, Guinea-Bissau, Trinidad-Tobago, Haiti, India, Jamaica, Puerto Rico, Senegal, the Caribbean, and Vietnam,[163] as illustrated by the purple legend in the map showing the distribution of *A. muricata* in Figure 2.

Traditional uses of A. muricata

A. muricata plant is used to cure cancer, diabetes, inflammation, parasite infections, and malaria in several tropical sub-Saharan African nations. The seeds of *A. muricata* are frequently employed as an antiparasitic and anthelmintic. Additionally, it contains analgesic, antidiabetic, antihypertensive, sedative, and antispasmodic properties.[13,28] Its regenerated leaves cure liver problems, diabetes, headaches, hypertension, cystitis, and insomnia. They also have antidysenteric and anti-inflammatory effects. The leaves are used to make an ointment for abscesses.[29] The pulp helps to cure various diseases, including arthritis, arteriosclerosis, and liver and kidney diseases, and it can improve milk production in nursing mothers.

Reports from Uganda by [30] and [31] show that *A. muricata* treats digestive problems, cancer, diabetes, parasites, malaria, and other diseases. In Nigeria, people have traditionally used the plant to treat skin problems.[28] Reports of its effectiveness in curing diseases have also been published in some parts of Indonesia by [32], who reported that oral ingestion of dried leaves of *A. muricata* relieves discomfort. According to,[33] who worked with previous reports on the effectiveness of *A. muricata*, state that the plant's flower and fruit are used to treat catarrh, while its roots, bark, and leaves are utilized for their anti-inflammatory and worm-killing qualities. In Malaysia, the scalp is treated using a juice produced from a combination of *A. muricata*, *H. rosa-sinensis*, and *A. squamosa* leaves.[34] Tropical Africa and South America employ the leaves of *A. muricata* in traditional medicine to treat tumours and cancer.[28] In Ghana, *A. muricata* is brewed together with several other plants to make a concoction that pregnant women use for their pregnancy baths.[35] In regions such as New Guinea[36] and Ecuador[37], the leaves are applied topically to relieve localized pain. In Brazil, the consumption of a leaf decoction serves as an analgesic,[38] while similar practices are observed in Martinique, Mexico, and Nicaragua.[38] Furthermore, this decoction is also used in several countries, including Cuba, the Caribbean, and Benin, to treat cold, flu, and asthma symptoms.[39] In addition to its culinary use, its juice is also used in South America to treat intestinal parasites, diarrhoea, and liver and heart damage.[12,40]

A. muricata has several advantages in healthcare compared to conventional pharmaceutical drugs. They have been reported to be natural and environmentally friendly, safe, easily accessible, with little or no side effects, and cheap compared to pharmaceutical drugs.[33,85,90] Furthermore, in anticancer studies, *A. muricata* has been demonstrated to show greater efficacy as a cytotoxic agent compared to pharmacological drugs in *in vitro* studies.[14,17] Nevertheless, additional research and clinical trials are required to assess their long-term safety and efficacy. *A. muricata*'s toxicity has arguably been the subject of multiple investigations, as this review discusses, indicating the need for more thorough research to clarify the plant's safety and effectiveness in traditional medicine.

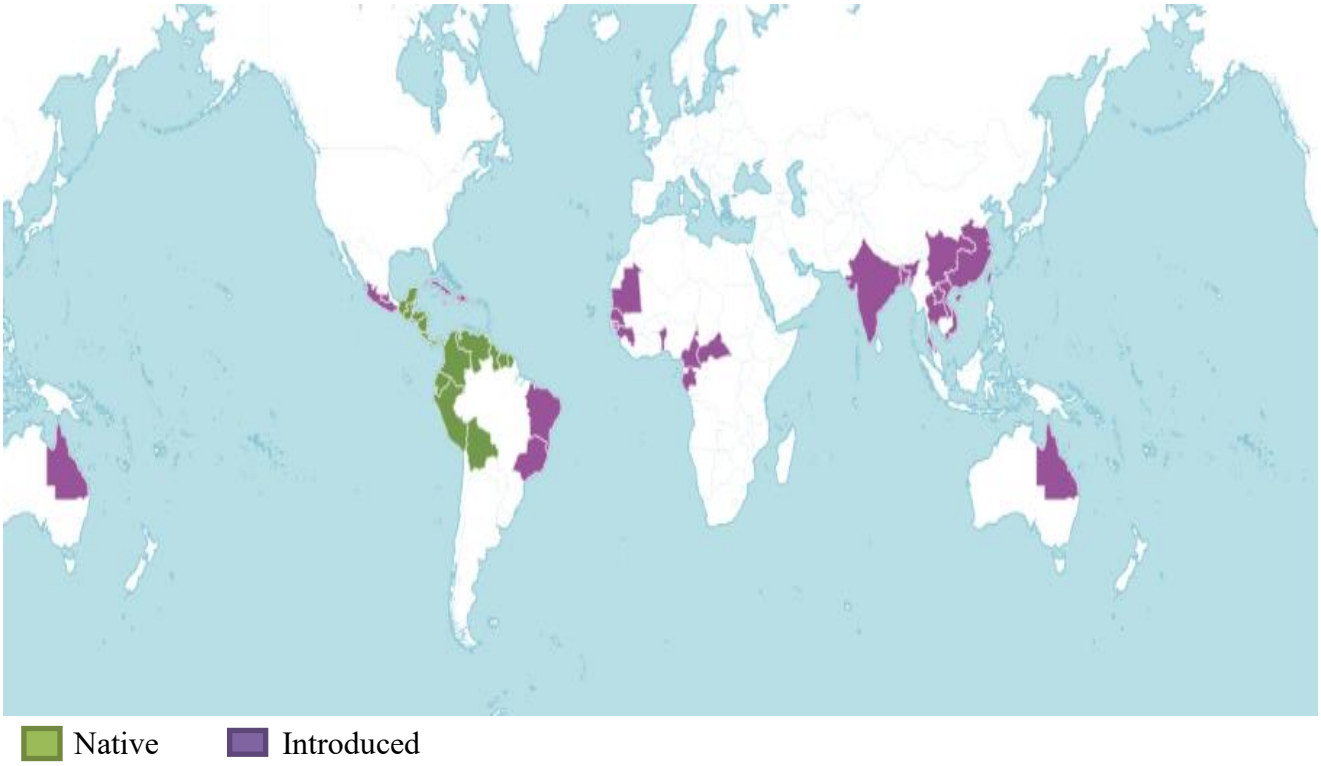

Figure 2: Geographical distribution of *A. muricata*[163]

Bioactive compounds in A. muricata

A. muricata is a rich source of bioactive phytochemicals that have attracted considerable interest due to their potential pharmacological effects and health benefits for humans.[41] (Table 2). A range of qualitative and quantitative analytical techniques have been used to characterize the phytochemical constituents present in soursop fruits, including phenolic compounds,[42-44] flavonoids,[43,45-49] carotenes,[48,50] alkaloids,[51-53] saponins,[54,] and acetogenins.[55-58]

Polyphenols, carotenoids, and flavonoids

Flavonoids, carotenoids, and phenols are beneficial to humans due to their different functional properties.[59] The various chemical constituents identified in natural products from soursop plants include epicatechin, kaempferol, quercetin, tocotrienols, lutein, and tocopherols, as well as protocatechuic acid, gallic acid, 4-hydroxybenzoic acid, ellagic acid, syringic acid, and chlorogenic acid.[42,43,45,48,50] Research suggests that the natural compounds of *A. muricata* are rich in antioxidants, and antioxidant-containing diets are associated with reduced risk of diseases.[60] This suggests that the consumption of *A. muricata* provides

antioxidants that can scavenge free radicals and reduce the risk of diseases in humans. Consequently, regular consumption of *A. muricata* fruits can improve human health and prevent degenerative diseases.[61]

Alkaloids

Alkaloids, which are secondary metabolites with nitrogen atoms that are produced and stored in the leaves of the plant, are contained in the natural products of *A. muricata*.[52] Alkaloids, mostly isoquinoline compounds, such as reticulin, annonain, nornuciferin, asimilobin, and N-methylcoculaurine, are present in the organic products of *A. muricata*.[62,63] Alkaloids can be used as antidepressants even though they cause toxicity to SH-SY5Y neuroblastoma cells by disrupting the chondrosome-blastoma complex.[55,62,63]

Acetogenins

Acetogenins originate from the *Annonaceae* family and are classified as secondary metabolites characterized by elongated aliphatic chains that include oxygen and end in γ-methyl-γ-lactone. Most of these lactones exhibit α, β-unsaturation, with a minor presence of tetrahydrofuran within the hydrocarbon structure.[55] These compounds are regarded as essential members of the *Annonaceae* family; about 120 distinct acetogenins have been identified from various parts of *A. muricata*, including leaves, pulp, roots, stems, and strips.[64] The skin of the fruit, in particular, contains about 20 different acetogenins, of which annonacin is the most widely distributed.[55-58] Acetogenins have different therapeutic effects, with the anti-inflammatory effect being one of the best researched.[55-58] To extract acetogenins from *A. muricata* natural products, [65] evaluated several extraction methods, including Soxhlet extraction, ultrasonication, and toaster ovens, as well as several solvents, including methanol, chloroform, water, and ethyl acetate derivatives. They explained how acetogenins could be rapidly and inexpensively isolated from *A. muricata* using microwave sonication (ethyl acetate and chloroform derivatization). Furthermore, the goal for the manifestation of acetogenins in food products, such as *A. muricata* dairy products (38 ng/g) and *A. muricata* preserved delicacy (15 ng/g), was reported by [66.] The three bioactive components of acetogenins shown are annonacin, murihexocin A, and corossolone.

Health-promoting effects of A. muricata

Anticancer

A. muricata leaf extract was studied by [102] with an emphasis on its value in breast cancer treatment. Following 24 and 48 hours of incubation, their findings demonstrated that the ethanolic extract of *A. muricata* leaves exhibited cytotoxicity in response to the MCF-7 cell line, yielding IC_{50} values of 88.788 µg and 14.678 µg, respectively. Moreover, [103] showed that an IC_{50} value of 33.43 µg indicated a notable cytotoxic effect of silica nanoparticles and *A. muricata* (referred to as AM/SNP) on the breast cancer cell line MCF-7. This effect was obtained by incorporating 20 ml of the extract from the leaves of *A. muricata* into 100 mL of sodium silicate solution. This suggests strong toxicity at low dosages, potentially lowering the possibility of side effects while administering the medication. Furthermore, AM/SNP was shown to cause cell death in the MCF-7 model, indicating that it may be a viable option for customized cancer treatments. According to [104], oral dosing of 250 and 500 mg/kg for 30 days resulted in a decrease in tumor volume in Dba/2 (P815) mice, indicating that the leaf extract of *A. muricata* has anticancer proliferative qualities. Rats exposed to DMBA for 20 weeks were given daily dosages of 200 mg/kg of either aqueous or ethanolic extracts of *A. muricata* fruit or leaves, along with 3.3 mg/kg of tamoxifen in a different study by [105]. The results indicated a remarkable decrease in tumour volume and weight, total protein concentration, CA15-3 concentration, mortality rate, and tumour incidence compared with the control group of rats that did not undergo the experimental treatment.

An ethanol extract from *A. muricata* leaves was shown by [106] to trigger apoptosis in liver cancer cells through the endoplasmic reticulum stress pathway. In their investigation into the anti-cancer properties of soursop pulp extracts, [14] proposed that soursop seed, twig, and root extracts reduce inflammation in the human blood cancer cell line HL-60 by interacting with matrix metalloproteinases (MMPs), producing free radicals, and stopping the cell cycle in the G0/G1 phase, which lowers the risk of malignancy. In addition, a link was established between apoptosis induced by the ethyl ethanoate extract of soursop leaves and apoptosis in the G0/G1 phase.[107] According to [108], leaf extracts caused the COLO-205 colon cancer cell line to produce more caspase-3, which in turn caused apoptosis. Ethyl acetate and ethanol extracts from soursop leaves efficiently triggered apoptosis in MCF-7 cells by upregulating the expression of Bcl2 and upregulating the synthesis of caspase-9 and caspase-3, as shown by [109]. These findings suggest the crucial role of the bioactive components, which are responsible for the anticancer properties of *A. muricata*. In addition, [110] found that various compounds from *A. muricata* exhibited antitumor properties. In particular, the aqueous leaf extract of *A. muricata* selectively targets colorectal tumor cells without inhibiting their proliferation.[17] The mechanism of acetogenin within the electron transport chain of mitochondrial complex I inhibits the growth of cancer cells by hindering ATP production, which is essential for cell proliferation.[17]. Research suggests that people diagnosed with colorectal cancer who incorporate 5 g of *A. muricata* seeds and powdered leaf extract into their daily routine three times a day, along with implementing lifestyle changes, may see an improvement in their prognosis.[17 111] demonstrated how annonachrimoline, a particular acetogenin from *A. muricata*, may cause HT-29 colon cancer cells to undergo apoptosis. The anti-cancer properties of *A. muricata* have been validated by numerous investigations. For instance, it was discovered that leaf extracts could increase the amount of cervical cancer cells *in vitro* by preventing HeLa cells from proliferating. Additionally, it was demonstrated that extracts containing dimethyl sulfoxide (DMSO) HT-1080 shielded HMEC-1 endothelial cells and fibrosarcoma cells from oxidative stress. The phytoconstituents in the extract of *A. muricata* leaves, which are well-known for their anti-cancer qualities, are most likely responsible for this protective action.[112-118]

Antiulcer

A. muricata has proven its potential in the relief of gastric lesions, as shown in the study by [20.] Their study showed that in rats suffering from gastritis induced by anhydrous or acidified indomethacin, treatment with the hydroalcoholic leaf extract of *A. muricata* caused the inhibition of invasive changes in the gastric mucosa. This extract also appears to activate the protective mechanisms of the stomach associated with prostaglandin synthesis, thereby delaying the onset of gastric ulcers and the ulcerative process. In addition, [107] found that an ethyl ethanoate extract of soursop exhibited anti-ulcer properties in rats by effectively scavenging reactive oxygen species and protecting the gastric mucosa from ethanol-induced damage. Additional hypothesized pathways for *A. muricata*'s anti-ulcer actions include downregulating Bax and upregulating heat shock protein 70 (Hsp70), both of which are linked to intestinal damage repair. Furthermore, [119] discovered that the minimum inhibitory concentration of soursop leaf extract against *Helicobacter pylori* is 20 mg/mL. [120] also discovered that *A. muricata* possesses anti-ulcer benefits by lowering Bax levels, lowering malondialdehyde (MDA), and boosting the activity of antioxidant enzymes such nitric oxide (NO), prostaglandin E2 (PGE2), glycogen production, and Hsp70.

Antidiarrhea

[121] demonstrated that hydroethanol extracts from the pulp of *A. muricata* administered at doses of 150, 300, and 600 mg/kg were effective in reducing fecal counts in rats with castor oil-induced diarrhea. Similarly,.[122] found that mice suffering from loose stools due to castor oil responded positively to a soursop product at a dosage of 400 mg/kg body weight. The antidiarrheal effects of soursop are probably due to its saponins, flavonoids, and triterpenoids, which are known to inhibit the secretions responsible for diarrhea and modulate intestinal motility. A study by [123] investigated the effects of *A. muricata* on intestinal motility and enteropooling induced by castor oil. In addition, the results of [124] suggest that *A. muricata* improves intestinal motility in a concentration-dependent manner. Specifically, soursop extract at doses of 150 and 650 mg/kg body weight resulted in a 50% and 58.98% reduction in the distance travelled by charcoal-fed diets, respectively. In comparison, the negative and positive control

groups showed a reduction of 14.69% and 67.34%, respectively.[124] The observed reduction in gastric muscle movement may prolong the retention time of substances in the digestive tract and thus increase the potential for fluid retention. [124] suggested that the reduced transport distance of charcoal flour could be due to the presence of antimotile compounds in the extract. The antimotile properties of certain phytochemicals, including flavonoids and tannins, have been shown to have antidiarrheal properties.[124] The authors pointed out that the main factor contributing to the antidiarrheal effects observed in *A. muricata* is likely the influence of tannins and flavonoids on intestinal motility. Specifically, *A. muricata* at a dosage of 650 mg/kg showed an inhibition rate of 90.3%, in contrast to loperamide hydrochloride, which showed an inhibition rate of 83.67%. The antidiarrheal properties of soursop are thought to be due to its ability to inhibit the spontaneous formation of prostaglandins. This is particularly important as castor oil is known to promote the biosynthesis of prostaglandins, which contribute to diarrhoea.[124]

Antidiabetic

A. muricata has demonstrated its safety and potential efficacy in the treatment of adult-onset diabetes in combination with various biochemicals. The antidiabetic effect of soursop may also be attributed to the presence of flavonoids that hydroxylate and modify the B-ring, thereby inhibiting the activity of α-glucosidase.[125] This inhibition serves as a barrier for the hydrolysis of starch, the storage of glucose, and the conversion of carbohydrates into glucose. [124] demonstrated that tart cherry pulp extract has antidiabetic properties by inhibiting key enzymes associated with adult-onset diabetes, including maltase and ptyalin, in *in vitro* studies. [126] found that the leaf extract not only inhibited ptyalin and maltase but also improved glucose uptake in the bloodstream postprandially, making it superior to conventional drugs. [28] also found that *A. muricata* decreased lipid peroxidation, a sign of oxidative stress, in streptozotocin-induced diabetic rats, which directly affects insulin synthesis. Because treated samples had lower blood glucose levels than controls and a higher protected islet percentage. [127] hypothesized that *A. muricata* seed oil could prevent streptozotocin-induced insulin-dependent diabetic mellitus. Furthermore, *A. muricata* was found to be successful in reducing blood glucose levels in diabetic rats in a study by [24.] After receiving daily intraperitoneal injections of 100 mg/kg body weight of *A. muricata* for 15 days, diabetic rats improved their glycaemic control by increasing their body weight, even though they consumed less food and water. This evidence strongly supports the utilization of active ingredients in *A. muricata* in pharmaceutical products for their antidiabetic properties; however, safe doses and toxicity measures need to be further explored by future studies.

Antiprotozoal

The cytotoxic effect of *A. muricata* against different pathogenic parasites has been reported by previous studies.[128,129] [19] identified several protozoan diseases associated with these parasites, including malaria, trypanosomiasis, leishmaniasis, and toxoplasmosis. According to [128] an ethanolic soursop leaf extract given at 500 mg/kg showed a substantial decrease in Toxoplasma gondii's impact, with an IC_{50} value of 113.3 µg/mL. This result demonstrates that *A. muricata* leaves have antiprotozoal properties. In addition, [129] discovered that several compounds extracted from *A. muricata*, such as anonacinone, corosolone, and two acetogenins isolated from the seeds, possess antiprotozoal properties. The compounds in question had IC_{50} values ranging from 13.5 to 37.6 µg/mL, indicating antileishmanial activity. Furthermore, at an IC_{50} value of 46.1 µg/mL, [128] discovered that an ethanol extract from soursop leaves demonstrated antiprotozoal action against *Plasmodium falciparum*. In addition, extracts from the soursop root and its subfractions, as well as the bark, showed antiprotozoal effects against *Plasmodium falciparum*, with IC_{50} values between 0.07 and 3.46 µg/mL. [130] also reported that a gallic acid compound extracted from the bark and roots of soursop was effective against *P. falciparum*, yielding an IC_{50} value of 3.32 µg/mL.

Hepatoprotective

[131] have highlighted the hepatoprotective effects of an aqueous extract of soursop leaves, which has demonstrated efficacy in preventing jaundice and has comparable effects to silymarin (*Silybum marianum*). This extract serves to protect the physiological functions of the liver from hepatotoxins, including paracetamol, a widely used painkiller that carries the risk of liver damage if consumed in excess. The authors found that the glycosidic fraction of *A. muricata* extract is converted to glucuronic acid, which subsequently conjugates with bilirubin, facilitating its excretion and possibly reducing bilirubin levels. [132] investigated the antihepatotoxic properties of soursop leaves, focusing on their effects on extracellular matrix (ECM) deposition, lysosomal membrane stability, and liver injury in rats exposed to dimethylnitrosamine (DMN)-induced fibrosis. Their results indicated that *A. muricata* leaf extract effectively reversed liver damage, restored synthesis capacity, stabilized lysosomal membranes, and improved ECM functionality. In addition, [133] reported that extracts from *A. muricata* leaves can attenuate fibrogenic arthritis by reducing ECM accumulation, improving the integrity of lysosomal membranes, and enhancing the synthetic capabilities of the liver. In addition,.[133] examined the impact of acetaminophen-induced toxicity on the anticholestatic and anti-sinusoidal congestion properties of aqueous extracts from the root bark of *A. muricata*. Their biochemical analyses and liver microscopy showed that these extracts exhibited significant anticholestatic, anti-sinusoidal congestion, and hepatoprotective effects. Ethanolic extracts of soursop leaves, roots, and bark, given at 150, 300, and 600 mg/kg body weight, successfully decreased paracetamol-induced aspartate aminotransferase (AST) and alanine transaminase (ALT) in all experimental settings.[13]

Antidepressant

[134] investigated the antidepressant and communicative activities of *A. muricata*, commonly known as soursop, grown in Nigeria, using Wistar rats as an experimental model. The researchers used the despair test together with the Porsolt swim test to assess the effect of the plant extract. Over the course of 14 days, subjects were given varying doses of *A. muricata* leaf extract at 50, 150, and 300 mg/kg body weight. Additionally, some groups received imipramine at a level of 10 mg/kg body weight as part of a combination treatment. In the open field test, the extract reduced the rats' attractiveness, according to the data, but it did not affect their forced swimming behavior. Instead, the extract increased the duration of swimming and decreased the time they spent immobile. Furthermore, at the higher concentrations of 150 and 300 mg/kg body weight, the combination of soursop extract and imipramine at a dose of 150 mg/kg body weight led to a reduction in both calling preference and attenuation time. These findings point to the possible application of *A. muricata*'s ethanolic extract in ethnomedicine for the treatment of depression by suggesting that it possesses sedative and antidepressant qualities.[134]

Antiviral

A research study on a cohort of women undergoing a standard Pap smear revealed that an extract of *A. muricata*, administered at a dosage of 200 mg/kg in conjunction with an ellagic acid complex, exhibited significant antiviral properties against human papillomavirus (HPV). This extract was found to induce apoptosis, facilitate DNA repair, and promote cell death during the G1 phase in squamous cell carcinomas.[135] In addition, [136] highlighted the antiviral efficacy of the fermented ethanol leaf extract of *A. muricata* and attributed its effect to a high concentration of rutin. The entire acetogenin family showed pronounced inhibitory effects against SARS-CoV-2.[137] Among them, cis-annacin proved to be the most effective acetogenin, characterized by its increased ability to form hydrogen bonds and its reduced activation energy. Although the potential of acetogenins from the *Anonaceae* family as agents against SARS-CoV-2 is promising, further *in vitro* and *in vivo* studies are needed.[137]

Antihypertensive

[138] reported that *A. muricata* extract exerts a blood pressure-lowering effect in NaCl-induced hypertension. [139] found that natural compounds from *A. muricata* at a dosage of 200 mg/kg exhibited *in vitro*

antihypertensive effects by converting the enzyme angiotensin 1. [140] indicated that soursop extract contributes to lowering blood pressure by inhibiting the activation of calcium ion channels. In addition, other herbs, including *A. muricata* and *P. americana*, are effective and safe combinations for the treatment and prevention of hypertension, as noted by [22]

Anti-inflammatory

[141] demonstrated that administration of 200 mg/kg graviola to rats exposed to DMBA-induced toxicity resulted in a remarkable decrease in the mRNA expression levels of cytochrome P450, subfamily e, family 2, tumor necrosis factor-alpha (TNF-α), polypeptide 1 (CYP2E1), and interleukin 1 beta (IL-1β). In addition, [13] reported that oral administration of soursop leaf extract at doses of 10, 30, 100, and 300 mg/kg resulted in a 79% reduction in carrageenan-induced edema in rats. This reduction in leukocyte migration is thought to contribute to its anti-inflammatory effect. In addition, the reduced production of interleukin-1β and tumor necrosis factor-α associated with xylene-induced ear edema in rats suggests the leaf's potential to alleviate significant and chronic discomfort. Different studies have confirmed the anti-inflammatory properties of soursop.[13,121]

Antimicrobial

A. muricata methanol and aqueous extracts at a dosage of 2000 mg/kg have shown promising antibacterial properties against various bacterial strains. Soursop leaf extract has potential therapeutic applications for a range of microbial-related diseases, including dermatological problems, urinary tract infections, febrile illnesses, pneumonia, liver disease, and diarrhoea.[142] In addition, several studies have confirmed the antifungal activity of *A. muricata*.[143-146] These studies indicated that soursop leaf extract could lead to a 65% reduction in cell mass and a 58% reduction in the progression of mycosis.

Wound healing

Soursop is widely known for its wound-healing properties. A study conducted by [13] showed that two doses of ethyl acetate extract of soursop significantly improved wound healing, as determined by both macroscopic and microscopic evaluations. The study showed that the application of a cream containing 20 mg/ml soursop ethyl acetate extract resulted in increased antioxidant levels and reduced malondialdehyde (MDA) levels in the affected tissues compared to the vehicle control.[13] In addition, extracts from the soursop plant have been shown to support wound healing more effectively than untreated extracts.[23] Additionally, the wound healing effect of *A. muricata* was observed mainly in the fruit and leaves of the plant.[164] This effect can be attributed to the presence of health-promoting phytochemicals in the plant, such as phenols, flavonoids, and alkaloids in the plant. Despite these benefits, future studies must examine safe therapeutic doses to prevent toxicity in the body.

Antioxidant

Extracts from the leaves of *A. muricata*, particularly ethyl acetate and n-butanol, show antioxidant qualities and lessen lipid peroxidation in liver tissue.[147] Rats subjected to DMBA for 20 weeks had excellent antioxidant properties when given an ethanolic extract of the leaves or an aqueous extract of the fruits of *A. muricata* at a dosage of 200 mg/kg daily.[105] Increased glutathione (GSH), superoxide dismutase (SOD), and catalase levels, as well as a drop in malondialdehyde (MDA) concentrations in comparison to the control group that received DMBA alone, demonstrated this. Also, pro-inflammatory cytokine levels like TNF-α, IL-6, and INF-γ were shown to decrease after receiving *A. muricata* treatment. In rats subjected to DMBA, [141] showed that a dose of 200 mg/kg of graviola significantly reduced MDA levels and significantly increased the activities of catalase (CAT), SOD, glutathione S-transferase (GST), and GSH. Furthermore, [148] discovered that giving male rats with doxorubicin-induced tissue damage 200 mg/kg ethanol leaf extracts of *A. muricata* orally once daily for two weeks markedly raised their levels of SOD, CAT, and GSH. Based on these findings, *A. muricata* can be considered a rich source of plant-based antioxidants that contribute to its several medicinal properties and disease prevention. Future studies can investigate the key bioactive compounds responsible for the antioxidant properties of *A. muricata* and utilize them for their pharmaceutical benefits.

Anti-Alzheimer activities of A. muricata

A recent study by [149] has reported on the anti-Alzheimer activity of *A. muricata* and a possible neuroprotective effect of the plant. Alzheimer-like symptoms were used in wistar rats to mimic the neural and inflammatory damage linked to the disease using aluminium chloride. The treatment of the induced wistar rats using soursop seed extract led to improvements in neural tissue, most especially the optic chiasm, where oligodendrocytes and astrocytes are regenerated, indicating a neuroprotective effect after treatments with soursop. This is also evident in the biochemical analyses, which showed a significant reduction in the pro-inflammatory cytokine TNF-α, which is linked with the disease condition. The experimental group treated with soursop showed a comparable effect to the group treated with donepezil, a standard medication used to treat Alzheimer's. Another study by Tasi'u.[150] also reported that *A. muricata* shows a dose-dependent anticholinesterase effect in the treatment of Alzheimer's.

Toxicity of A. muricata

Investigating the toxicity of *A. muricata* is crucial in establishing safe and effective doses in the use of *A. muricata* for both medicinal and modern applications. Understanding the toxicity of *A. muricata* is important in minimizing risks and harnessing the plant's therapeutic potential at safe and effective doses. Despite the plant's pharmacological benefits, different phytoconstituents in *A. muricata*, such as acetogenins, annonacin, and crocetin, have been reported to induce toxicity based on experimental studies.[151-153] This informs the need to evaluate the toxicity profile of *A. muricata* to understand toxic phytoconstituents and their mechanism of action and establish safe and effective doses for therapeutic purposes. [29] stated that the toxicity threshold for the aqueous extract of *A. muricata* reaches up to 5 g/kg body weight, while the ethanolic extract has a threshold of over 2 g/kg. [154] conducted an acute toxicity assessment of the ethanolic leaf extract of *A. muricata* and determined a median lethal dose (LD_{50}) of 3807.89 mg/kg. In addition, [29] found that the LD_{50} for the aqueous extract of *A. muricata* leaves exceeded 211 mg/kg body weight, a value that exceeds the recommended daily intake for humans. [155] discovered that the aqueous extract of soursop can induce hypoglycemia at doses greater than 1 g/kg and can cause kidney damage at doses greater than 5 g/kg. [151] identified acetogenin in *A. muricata* as a neurotoxic agent possibly associated with neurodegenerative diseases. [152] observed that acetogenin enhances phosphorylation, a process associated with neurodegenerative diseases. In addition, various alkaloids found in *A. muricata* are thought to affect the nervous system.[13]

Annonacin, the predominant acetogenin in soursop, as well as other alkaloids such as coreximin, reticulin, and solamine, are known to affect the mechanisms of energy production of dopaminergic neurons.[64 153] reported that crocetin can cross the blood-brain barrier, leading to a decrease in adenosine triphosphate (ATP) levels in brain regions, causing damage to the basal nuclei in rats. [151] also found that annonacin decreases adenosine triphosphate levels in the striatal nucleus and interferes with mitochondrial ATP synthesis, leading to cell destruction and manifestations of neurodegenerative diseases. Despite the association of certain compounds in *A. muricata* with neurological disorders, the toxic levels are comparable to eating one fruit daily over the course of a year.[156] [141] found that administration of 200 mg/kg graviola to rats exposed to DMBA-induced toxicity resulted in a significant improvement in renal function, as evidenced by a reduction in levels of urea, creatinine, and uric acid. In another study, [157] reported that female rats receiving 300 mg/kg of graviola leaf extract daily for nine days showed a protective effect against brain injury caused by ionizing radiation. Studies on the neurotoxicity of annonacin have shown that neurodegenerative diseases associated with these compounds occur with prolonged exposure or consumption. To reduce the risk of neurological problems associated with *A. muricata*, it is advisable to limit excessive intake.[27]

Clinical trial studies of A. muricata

The clinical trials on *A. muricata* are presented in Table 3. According to ClinicalTrials.gov[165] only four completed clinical trials with *A. muricata* have been documented. These studies focus on conditions such as hypertension, colorectal cancer, HPV infection, and prehypertension. At the time of writing this review, none of the results from these clinical trials have been posted, even though the studies were said to be completed on ClinicalTrials.gov.[165] On the other hand, no clinical trials have been reported on other pharmacological effects of *A. muricata*. Furthermore, there are no clinical studies on the isolated phytochemicals from *A. muricata*.

Conclusion

In conclusion, *A. muricata* is used in traditional medicine to treat various diseases, including fever, malaria, respiratory diseases, diabetes, inflammation, and cancer. Pharmacological studies conducted *in vitro* and *in vivo* have demonstrated the efficacy of *A. muricata* against ulcers, diarrhoea, inflammation, oxidative stress, hypertension, viral infections, malaria, hepatitis, diabetes, and cancer. These pharmacological benefits are attributed to the various phytochemicals contained in the different parts of the plant, which can be integrated in the preparation of novel pharmaceutical drugs for the treatment of different diseases in humans. Despite these pharmacological benefits, the integration of *A. muricata* has been faced with different limitations, such as a lack of clinical trials on the plant, toxicity concerns, risk of side effects, safe dosage, standardization issues, understanding its exact mechanism of action, and possible drug interactions. There is variation in the part of the plant used as well as their extraction method, which can affect phytochemical yield and bioactivity. Future studies need to examine individual components of the plant, phytochemical yield, pharmacological benefits, and their exact mechanism of action. Toxicity remains a major concern in the utilization of the plant and its bioactive components as pharmaceutical products and functional foods. Consequently, there is an urgent need for future studies to conduct more in-depth studies on chronic toxicity to determine the efficacy, potency, and optimal dosage of the different constituents of *A. muricata* in the treatment of diseases while minimizing possible adverse effects. The study also has potential limitations that might affect the interpretation and generalizability of the findings reported. There are no published results on the human clinical trials conducted, which made the review rely mostly on data from preclinical studies, both *in vitro and in vivo* experiments. Additionally, more clinical trials need to be investigated on other pharmacological properties of the plant apart from those already completed on ClinicalTrials.gov, whose results are yet to be reported. This will provide in-depth information on the pharmacological benefits of the plants and integration of the plants as pharmaceutical agents. *A. muricata* can be integrated as a functional food in the preparation of different foods such as ice cream and juices, adding nutritive value and flavour to these foods. Furthermore, there is a lack of standardization on safe dosage for administration and toxicological analyses of the plant's phytoconstituents, which may affect the generalizability of the findings. Therefore, further studies are needed to standardize and validate the therapeutic properties of the different components of *A. muricata*, which will be essential for their integration into pharmaceutical products and functional foods.

Conflict of interest

The authors declare no conflicts of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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