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A review on a miracle fruits of *Annona muricata*

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Abstract
Annona muricata is a member of the Annonaceae family and is a fruit tree with a long history of traditional use. *A. muricata*, also known as soursop, graviola and guanabana, is an evergreen plant that is mostly distributed in tropical and subtropical regions of the world. The fruits of *A. muricata* are extensively used to prepare syrups, candies, beverages, ice creams and shakes. A wide array of ethnomedicinal activities is contributed to different parts of *A. muricata*, and indigenous communities in Africa and South America extensively use this plant in their folk medicine. This article summarizes external morphology of the plant including leaves, fruit and seeds. Numerous investigations have substantiated these activities, including anticancer, anticonvulsant, anti-arthritic, antiparasitic, antimalarial, hepatoprotective and antidiabetic, analgesic hypotensive, antiinflammatory, and immune enhancing effects. Phytochemical studies reveal that annonaceous acetogenins are the major constituents of *A. muricata*. More than 100 annonaceous acetogenins have been isolated from leaves, barks, seeds, roots and fruits of *A. muricata*. In view of the immense studies on *A. muricata*, this review strives to unite available information regarding its phytochemistry, traditional uses and biological activities.

Keywords: *Annona muricata*, Annonaceae, acetogenins, natural products, biological activity, bioactive compounds, fruit tree

1. Introduction
Natural products, especially those derived from plants, have been used to help mankind sustain its health since the dawn of medicine. Over the past century, the phytochemicals in plants have been a pivotal pipeline for pharmaceutical discovery. The importance of the active ingredients of plants in agriculture and medicine has stimulated significant scientific interest in the biological activities of these substances [1]. Despite these studies, a restricted range of plant species has experienced detailed scientific inspection, and our knowledge is comparatively insufficient concerning their potential role in nature. Hence, the attainment of a reasonable perception of natural products necessitates comprehensive investigations on the biological activities of these plants and their key phytochemicals [2]. In a pharmaceutical landscape, plants with a long history of use in ethno medicine are a rich source of active phytoconstituents that provide medicinal or health benefits against various ailments and diseases. *Annona muricata* Linn. is a lowland tropical fruit-bearing tree in the Annonaceae family. *Annona muricata* is also commonly known as Graviola or Soursop or Gunbanana. The name soursop is due to sour and sweet flavour of its large fruit. Related species include cherimoya (A. cherimola) and sugar-apple (A. squamosa); paw paw (Asimina triloba) is also in the family. The soursop is native to tropical Central and South America and the Caribbean, but is now widely cultivated in tropical areas worldwide, including southern Florida and Southeast Asia, from sea level to altitudes of around 1150 meters. Soursop is one of most commonly used medicinal plants in Caribbean. Pulp of the fruit is eaten and used as an ingredient in many foods and beverages. Tea is drunk daily and often mixed with other herbal decoctions. Soursop is a slender, small, and cold-intolerant tree, generally reaching heights of 4-6 meters. The soursop is adapted to areas of high humidity and relatively warm winters; temperatures below 5 °C (41°F) will cause damage to leaves and small branches, and temperatures below 3 °C (37°F) can be fatal. Plants became the basis of traditional medicine system throughout the world for thousands of years and continue to provide mankind with new remedies. Here, an attempt is made to review on medicinal plant, *Annona muricata* (soursop or graviola). It has a wide potent anticancerous agents coined as Acetogenins which play a key role towards many varieties of cancer, Acetogenins are potent inhibitors of NADH oxidase

(nicotinamide adenine dinucleotide phosphate-oxidase) of the plasma membranes of cancer cells. The fruit is of economic value and hence cultivated and used widely as an edible food. The plant possess the major pharmacological activities includes cytotoxic, antileishmanial, wound healing, anti-microbial activity. It also has the anticarcinogenic and genotoxic effect. Phytochemical analysis of the plant revealed the presence of tannins, steroids and cardiac glycosides which are the major phytochemical compounds [3].

2. Botanical Description and Distribution

A. muricata L., commonly known as soursop, graviola, guanabana, paw-paw and sirsak, is a member of the Annonaceae family comprising approximately 130 genera and 2300 species [4, 5].

A. muricata is native to the warmest tropical areas in South and North America and is now widely distributed throughout tropical and subtropical parts of the world, including India, Malaysia and Nigeria, Australia, Africa, [6]. *A. muricata* is an evergreen, terrestrial, erect tree reaching 5–8 m in height and features an open, roundish canopy with large, glossy, dark green leaves. The tree has larger individual yellow flowers on woody stalks (pedicels). Flowers are large and solitary, yellowish or greenish-yellow in colour. Three outer petals are broadly ovate with heart-shaped base, inner 3 also large, elliptical and rounded. The edible fruits of the tree are large, oval or heart-shaped and green in color, and frequently irregular lopsided composite soursop fruit is derived from the fusion of many fruit lets and can weigh more than 4 kg. and the diameter varies between 15 and 20 cm The fruit pulp consists of white fibrous juicy segments surrounding an elongated receptacle. In each fertile segment there is a single oval, smooth hard, black seed {1/2}–{3/4} in (1.25–2 cm) long. A fruit may contain as few as 5 or up to 200 or more seeds. (Figure 1) [7]. The reticulated leathery looking skin has short spines. Its inner surface is cream-colored and granular and separates easily from the mass of white, fibrous juicy segments which surround the central soft pithy core [9].

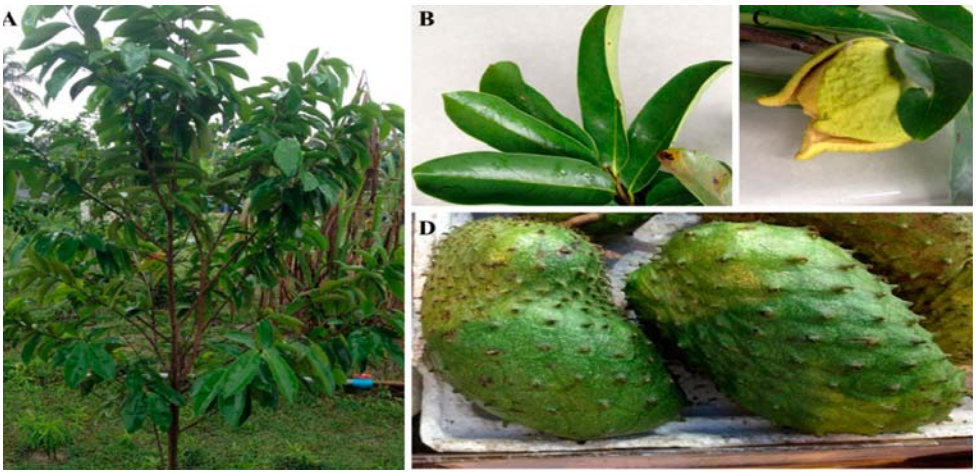

Fig 1: (A) *Annona muricata* L.; the appearance of the (B) leaves; (C) flowers and (D) fruits

3. Ethnomedicinal Uses

All portions of the *A. muricata* tree, similar to other *Annona* species, including *A. squamosa* and A. *reticulata* are extensively used as traditional medicines against an array of human ailments and diseases, especially cancer and parasitic infections

Table 1: Worldwide Ethnomedical uses of *Annona muricata* [10]

Worldwide Ethnomedical Uses	
Brazil	for abscesses, bronchitis, chest problems, cough, diabetes, diarrhoea, dysentery, edema, fever, intestinal colic, intestinal parasites, liver problems, neuralgia, nervousness, pain, parasites, rheumatism, spasms, worms
Caribbean	for chills, fever, flu, indigestion, nervousness, palpitations, rash, spasms, skin disease, and as a sedative
Curaçao	for childbirth, gallbladder problems, nervousness, and as a sedative and tranquilizer
Haiti	for digestive sluggishness, coughs, diarrhoea, fever, flu, heart conditions, lactation aid, lice, nerves, parasites, pain, pellagra, sores, spasms, weakness, wounds, and as a sedative
Jamaica	for asthma, fevers, heart conditions, hypertension, lactation aid, nervousness, parasites, spasms, water retention, weakness, worms, and as a sedative
Malaysia	for boils, coughs, diarrhoea, dermatosis, hypertension, rheumatism, and to reduce bleeding
Mexico	for diarrhoea, dysentery, fever, chest colds, ringworm, scurvy, and to reduce bleeding
Panama	for diarrhoea, dyspepsia, kidney, stomach ulcers, worms
Peru	for diabetes, diarrhoea, dysentery, fever, hypertension, indigestion, inflammation, lice, liver disorders, parasites, spasms, tumours, ulcers (internal), and as a sedative
Trinidad	for blood cleansing, fainting, flu, high blood pressure, insomnia, lactation aid, palpitations, ringworms
U.S.A.	for cancer, depression, fungal infections, hypertension, intestinal parasites, tumours
West Indies	for asthma, childbirth, diarrhoea, hypertension, lactation aid, parasites, worms
Elsewhere	for arthritis, asthma, bile insufficiency, childbirth, cancer, diarrhoea, dysentery, fever, heart problems, kidney problems, lactation aid, lice, liver disorders, malaria, pain, ringworm, scurvy, stomach problems, and as a sedative

4. Phytochemistry

Extensive phytochemical evaluations on different parts of the *A. muricata* plant have shown the presence of various phytoconstituents and compounds, including alkaloids (ALKs) [5, 16], megastigmanes (MGs) [17] flavonol triglycosides (FTGs) [18], phenolics (PLs) [19], cyclopeptides (CPs) and essential oils (Table 1, Figure 2) [20, 21]. However, *Annona* species, including *A. muricata*, have been shown to be a generally rich source of annonaceous acetogenin compounds (AGEs) [22]. The presence of different major minerals such as K, Ca, Na, Cu, Fe and Mg suggest that regular consumption of the *A. muricata* fruit can help provide essential nutrients and elements to the human body [23].

Table 2: Chemical compounds isolated from *Annona muricata*. ALK: alkaloid; AGE: annonaceous acetogenin; MG: megastigmane; FTG: flavonol triglycoside; PL: phenolic; CP: cyclopeptide

Plant Part	Compound	Class	Biological Activity	References
Fruits	annonaine	ALK	anti-depressive	[24, 25]
Fruits	nornuciferine	ALK	anti-depressive	[24, 25]
Fruits	asimilobine	ALK	anti-depressive	[24, 25]
Fruits	epomusenin-A	AGE	-	[26]
Fruits	epomusenin-B	AGE	-	[26]
Fruits	epomurinin-A	AGE	-	[26]
Fruits	epomurinin-B	AGE	-	[26]
Fruits	*cis*-annoreticuin	AGE	-	[27]
Fruits	muricin J	AGE	toxicity against prostate PC-3 cancer cells	[28]
Fruits	muricin K	AGE	toxicity against prostate PC-3 cancer cells	[28]
Fruits	muricin L	AGE	toxicity against prostate PC-3 cancer cells	[28]
Fruits	cinnamic acid derivative	PL	-	[19]
Fruits	coumaric acid hexose	PL	-	[19]
Fruits	5-caffeoylquinic acid	PL	-	[19]
Fruits	dihydrokaempferol-hexoside	PL	-	[19]
Fruits	*p*-coumaric acid	PL	-	[19]
Fruits	caffeic acid derivative	PL		[19]
Fruits	dicaffeoylquinic acid	PL	-	[19]
Fruits	feruloyl glucoside	PL	-	[19]
Fruits	4-feruloyl-5-caffeoylquinic acid	PL	-	[19]
Fruits	*p*-coumaric acid methyl ester	PL	-	[19]
Leaves, Pericarp	annomuricin A	AGE	toxicity against brine shrimp, lung A549, breast MCF-7 and colon HT-29 cancer cells	[15, 29]
Leaves	annomuricin B	AGE	toxicity against brine shrimp, lung A549, breast MCF-7 and colon HT-29 cancer cells	[15]
Leaves	annomuricin C	AGE	toxicity against brine shrimp, lung A549, breast MCF-7 and colon HT-29 cancer cells	[30]
Leaves	annomuricin E	AGE	toxicity against pancreatic MIA PaCa-2 and colon HT-29 cancer cells	[31]
Leaves	annomutacin	AGE	toxicity against lung A549 cancer cells	[32]
Leaves	(2,4-*cis*)-10*R*-annonacin-A-one	AGE	toxicity against lung A549 cancer cells	[32]
Leaves	(2,4-*trans*)-10*R*-annonacin-A-one	AGE	toxicity against lung A549 cancer cells	[32]
Leaves	annohexocin	AGE	toxicity against brine shrimp and different cancer cells	[33]
Leaves	muricapentocin	AGE	toxicity against pancreatic MIA PaCa-2 and colon HT-29 cancer cells	[31]
Leaves	(2,4-*cis*)-isoannonacin	AGE	-	[34]
Leaves, Seeds	(2,4-*trans*)-isoannonacin	AGE	-	[34, 35]
Leaves	muricatocin A	AGE	toxicity against lung A549 cancer cells	[34]
Leaves	muricatocin B	AGE	toxicity against lung A549 cancer cells	[34]
Leaves	muricatocin C	AGE	toxicity against brine shrimp, lung A549, breast MCF-7 and colon HT-29 cancer cells	[30]
Leaves, Seeds	gigantetronenin	gigantetronenin	-	[30, 35]
Leaves, Seed Pericarp	annonacin A	AGE	-	[29, 34, 36]
Leaves	annopentocin A	AGE	toxicity against pancreatic MIA PaCa-2 cancer cells	[37]
Leaves	annopentocin B	AGE	toxicity against lung A549 cancer cells	[37]
Leaves	annopentocin C	AGE	toxicity against lung A549 cancer cells	[37]
Leaves	*cis*-annomuricin-D-one	AGE	toxicity against lung A549, colon HT-29and pancreatic MIA PaCa-2 cancer cells	[37]
Leaves	*trans*-annomuricin-D-one	AGE	toxicity against lung A549, colon HT-29	[37]

			and pancreatic MIA PaCa-2 cancer cells	
Leaves	murihexocin A	AGE	toxicity against different cancer cells	[38]
Leaves	murihexocin B	AGE	toxicity against different cancer cells	[38]
Leaves	murihexocin C	AGE	toxicity against different cancer cells	[39]
Leaves	muricoreacin	AGE	toxicity against different cancer cells	[39]
Leaves	*cis*-corossolone	AGE	toxicity against human hepatoma cells	[40]
Leaves	annocatalin	AGE	toxicity against human hepatoma cells	[40]
Leaves	annocatacin B	AGE	toxicity against human hepatoma cells	[41]
Leaves	anonaine	ALK	Neurotoxic	[42, 43]
Leaves	isolaureline	ALK	-	[42]
Leaves	xylopine	ALK	-	[42]
Leaves	Quercetin 3-*O*-α-rhamnosyl-(1→6)-β-sophoroside	FTG	-	[18]
Leaves	gallic acid	FTG	-	[18]
Leaves	epicatechin	FTG	-	[18]
Leaves	quercetin 3-*O*-rutinosid	FTG	-	[18]
Leaves	quercetin 3-*O*-neohispredoside	FTG	-	[18]
Leaves	quercetin 3-*O*-robinoside	FTG	-	[18]
Leaves	catechin	FTG	-	[18]
Leaves	chlorogenic acid	FTG	-	[18]
Leaves	argentine (1-*N*,*N*dimethylethanyl-4,6-dimethoxy-3,8-dihydroxy-phenanthrene)	FTG	-	[18]
Leaves	kaempferol 3-*O*-rutinoside	FTG	-	[18]
Leaves	quercetin 3-*O*-glucoside	FTG	-	[18]
Leaves	quercetin	FTG	-	[18]
Leaves	kaempferol	FTG	-	[18]
Leaves	annonamine	ALK	-	[43]
Leaves	(*S*)-norcorydine	ALK	-	[43]
Leaves	(*R*)-4′-*O*-methylcoclaurine	ALK	-	[43]
Leaves	(*R*)-*O*,*O*-dimethylcoclaurine	ALK	-	[43]
Leaves	annoionol A	MG	-	[17]
Leaves	annoionol B	MG	-	[17]
Leaves	annoionol C	MG	-	[17]
Leaves	annoionoside	MG	-	[17]
Leaves	vomifoliol	MG	-	[17]
Leaves	roseoside	MG	-	[17]
Leaves	turpinionoside A	MG	-	[17]
Leaves	citroside A	MG	-	[17]
Leaves	blumenol C	MG	-	[17]
Leaves	(+)-epiloliolide	MG	-	[17]
Leaves	loliolide	MG	-	[17]
Leaves	(1*S*,2*S*,4*R*)-*trans*-2-hydroxy-1,8-cineole β-D-glucopyranoside	MG	-	[17]
Leaves	(*Z*)-3-hexenyl β-glucopyranoside	MG	-	[17]
Leaves	rutin	MG	-	[17]
Leaves	kaempferol 3-*O*-rutinoside	MG	-	[17]
Leaves	kaempferol 3-*O*-robinobioside	MG	-	[17]
Leaves	kaempferol 3-*O*-β-D-(2″-*O*-β-glucopyranosyl, 6″-*O*-α-L'Rhamnopyranosyl) glucopyranoside	MG	-	[17]
Roots	montecristin	AGE	-	[44]
Roots	cohibin A	AGE	-	[45]
Roots	cohibin B	AGE	-	[45]
Roots	*cis*-solamin	AGE		[46]
Roots	*cis*-panatellin	AGE	-	[46]
Roots	*cis*-uvariamicin IV	AGE	-	[46]
Roots	*cis*-uvariamicin I	AGE	-	[46]
Roots	*cis*-reticulatacin	AGE	-	[46]
Roots	*cis*-reticulatacin-10-one	AGE	-	[46]
Roots	chatenaytrienin 1	AGE	-	[47]
Roots	chatenaytrienin 2	AGE	-	[47]

Roots	chatenaytrienin 3	AGE	-	[47]
Roots	muridienin 3	AGE	-	[47]
Roots	muridienin 4	AGE	-	[47]
Roots	muricadienin	AGE	-	[47]
Roots	coronin	AGE	-	[48]
Roots, Fruits	sabadelin	AGE	-	[27, 49]
Seeds	murisolin	AGE	-	[50]
Seeds	muricatacin	AGE	toxicity against lung A549, breast MCF7, colon HT-29 cancer cells	[51]
Seeds, Leaves, Pericarp	annonacin	AGE	neurotoxic, molluscicidal, inhibitor of mitochondrial complex I	[15, 29, 51–54]
Seeds, Leaves	corossolone	AGE	toxicity against oral KB cancer cells and brine shrimp larva, antileishmanial	[40, 55–57]
Seeds	corossolin	AGE	toxicity against oral KB cancer cells and brine shrimp larva	[55]
Seeds, Roots, Leaves	solamin	AGE	toxicity against oral KB cancer and normal kidney VERO cells	[40, 46, 58]
Seeds	corepoxylone	AGE	-	[59]
Seeds, Leaves	annonacin-10-one	AGE	-	[15, 60]
Seeds	isoannonacin	AGE	molluscicidal, anticancer	[52, 60]
Seeds	isoannonacin-10-one	AGE	-	[60]
Seeds, Leaves	goniothalamicin	AGE	Molluscicidal	[15, 52, 60]
Seeds	gigantetrocin	AGE	-	[60]
Seeds, Leaves	gigantetrocin A	AGE	toxicity against colon HT-29 cancer cells	[15, 35, 61]
Seeds	gigantetrocin B	AGE	toxicity against colon HT-29 cancer cells	[15,35,61]
Seeds, Leaves	muricatetrocin A	AGE	toxicity against colon HT-29 cancer cells	[61]
Seeds, Leaves	muricatetrocin B	AGE	toxicity against colon HT-29 cancer cells	[61]
Seeds, Leaves	epomuricenin A	AGE	-	[26, 62]
Seeds, Leaves	epomuricenin B	AGE	-	[26,62]
Seeds	annomuricatin A	CP	-	[63, 64]
Seeds	annocatacin A	AGE	toxicity against human hepatoma cells	[41]
Seeds	annomuricatin C	CP	-	[65]
Seeds	*cis*-annonacin	AGE	crown gall tumor inhibition, toxicity against brine shrimp, lung A549, breast MCF-7 and colon HT-29 cancer cells	[66]
Seeds	*cis*-annonacin-10-one	AGE	crown gall tumor inhibition, toxicity against brine shrimp, lung A549, breast MCF-7 and colon HT-29 cancer cells	[66]
Seeds	*cis*-goniothalamicin	AGE	crown gall tumor inhibition, toxicity against brine shrimp, lung A549, breast MCF-7 and colon HT-29 cancer cells	[66]
Seeds	arianacin	AGE	crown gall tumor inhibition, toxicity against brine shrimp, lung A549, breast MCF-7 and colon HT-29 cancer cells	[66]
Seeds	javoricin	AGE	crown gall tumor inhibition, toxicity against brine shrimp, lung A549, breast MCF-7 and colon HT-29 cancer cells	[66]
Seeds	murihexol	AGE	-	[36]
Seeds	donhexocin	AGE	-	[36]
Seeds	cohibin C	AGE	-	[67]
Seeds	cohibin D	AGE	-	[67]
Seeds	muricatenol	AGE	-	[35, 68]
Seeds	2,4-*cis*-gigantetrocinone	AGE	-	[35]
Seeds	2,4-*trans*-gigantetrocinone	AGE	-	[35]
Seeds	2,4-*trans*-isoannonacin-10-one	AGE	-	[35]
Seeds	annomontacin	AGE	-	[35]
Seeds	longifolicin	AGE	toxicity against human hepatoma cells	[69]
Seeds	muricin A	AGE	toxicity against human hepatoma cells	[69]
Seeds	muricin B	AGE	toxicity against human hepatoma cells	[69]
Seeds	muricin C	AGE	toxicity against human hepatoma cells	[69]
Seeds	muricin D	AGE	toxicity against human hepatoma cells	[69]
Seeds	muricin E	AGE	toxicity against human hepatoma cells	[69]
Seeds	muricin F	AGE	toxicity against human hepatoma cells	[69]
Seeds	muricin G	AGE	toxicity against human hepatoma cells	[69]

Seeds	muricin H	AGE	toxicity against human hepatoma cells	[40]
Seeds	muricin I	AGE	toxicity against human hepatoma cells	[40]
Seeds	*cis*-annomontacin	AGE	toxicity against human hepatoma cells	[40]
Seeds, Leaves	annonacinone	AGE	-	[40]
Seeds	xylomaticin	AGE	-	[40]
Seeds	*N*-fatty acyl tryptamines	ALK	-	[35]
Seeds	annoreticuin-9-one	AGE	-	[27]
Stem barks	epoxymurin A	AGE	-	[70]
Stem barks	epoxymurin B	AGE	-	[70]
Leaves, Roots, Stems, Barks	reticuline	ALK	-	[71]
Leaves, Roots, Stems, Barks	coclaurine	ALK	-	[71]
Leaves, Roots, Stems, Barks	coreximine	ALK	-	[71]
Leaves, Roots, Stems, Barks	atherosperminine	ALK	-	[71]
Leaves, Roots, Stems, Barks	stepharine	ALK	-	[71]
Leaves, Roots, Stems, Barks	anomurine	ALK	-	[71]
Leaves, Roots, Stems, Barks	anomuricine	ALK	-	[71]

5. Biological Activities

Anticancer Activity

Plenty of studies report the significant antiproliferative effects of different extracts of the plant and isolated AGEs towards various cancer cell lines [29, 72–85]; however, few of these studies have illustrated the underlying mechanism of action (Table 3). Recent *in vitro* studies to determine the mechanism of action of ethyl acetate extract of *A. muricata* leaves against colon cancer cells (HT-29 and HCT-116) and lung cancer cells (A-549). The leaf extract was able to induce apoptosis in colon and lung cancer cells through the mitochondrial-mediated pathway. This antiproliferative effect was associated with cell cycle arrest in the G1 phase [76, 77]. In addition, the migration and invasion of colon cancer cells were significantly inhibited by the leaf extract. The activation of caspase 3 by the ethanolic extract of the leaves also demonstrated an apoptosis-inducing effect in myelogenous leukemic K562 cells, which was confirmed with a TUNEL assay [78].

Table 3: Anticancer studies on *A. muricata*

Plant Part	Subject of Study	Effect	Reference
ethyl acetate extract of the leaves	lung A549 cancer cells	mitochondrial-mediated apoptosis, cell cycle arrest at G1 phase	[83]
ethyl acetate extract of the leaves	colon HT-29 and HCT-116 cancer cells	mitochondrial-mediated apoptosis, cell cycle arrest at G1 phase, suppression of migration and invasion	[84]
water extract of the leaves	rat's prostate	reduction of prostate size	[86]
ethanolic extract of the leaves	breast tissues of mice	prevention of DMBA-induced DNA damage	[87]
ethanolic extract of the leaves	DMBA/croton oil induced mice skin papillomagenesis	suppression of tumor initiation and promotion	[88]
ethanolic extract of the leaves	DMH induced colon cancer	reduction of ACF formation	[89]
ethanolic extract of the leaves	K562 chronic myeloid leukemia cells	induction of apoptosis	[85]
leaves boiled in water	metastatic breast cancer	stabilization of disease	[90]
ethyl acetate of the leaves	azoxymethane induced colon cancer	reduction of ACF formation	[91]
ethyl acetate of the leaves	colon HT-29 cancer cells	bioassay-guided isolation of annomuricin E and its apoptosis inducing effect	[91]

Recent *in vitro* and *in vivo* studies were performed on the water extract of the *A. muricata* leaves against the benign prostatic hyperplasia (BPH-1) cell line and rats' prostates. The results showed a suppressive effect on BPH-1 cells with an IC50 value of 1.36 mg/mL after 72 h associated with an up-regulation of Bax and a down-regulation of Bcl-2 at the mRNA level. After two months of treatment with the extract (30 and 300 mg/mL doses), the size of the rats' prostates were decreased, which was suggested to occur through apoptosis induction [79]. This promising antitumor effect also reported in an *in vivo* study on 7, 12-dimethylbenzene anthracene (DMBA)-induced cell proliferation in the breast tissues of

mice. The protective effect against DNA damage induced by DMBA showed that oral administration of the *A. muricata* leaves may have protective effects towards the development of breast carcinogenesis [80]. The leaves, even at the low dose of 30 mg/kg suppressed the initiation and promotion stage of skin papillomagenesis in mice that was induced by DMBA and croton oil, respectively [81]. Also examined the *in vivo* chemopreventive potential of the ethyl acetate extract of the *A. muricata* leaves against azoxymethane-induced colonic aberrant crypt foci (ACF) in rats. [84] The oral administration of the extract at two doses (250 and 500 mg/kg) for 60 days significantly reduced ACF formation in rats, as assessed by methylene blue staining of colorectal specimens. The immunohistochemistry analysis showed that this activity was accompanied by the up-regulation of Bax and the down-regulation of Bcl-2. This significant reduction in ACF formation was also reported for the ethanolic extract of the leaves against 1,2-dimethyl hydrazine (DMH)-induced colon cancer [82]. study was followed by an *in vitro* bioassay-guided investigation against HT-29 cells, which led to the isolation of annomuricin E. This AGE showed mitochondrial-dependent apoptosis activity in colon cancer cells with an IC50 value of 1.62±0.24 µg/mL after 48 h [84]. Anticancer studies on *A. muricata* were not only limited to *in vitro* and *in vivo* investigations. A case study of a 66-year old woman with a metastatic breast cancer reported that consumption of the leaves boiled in water and Xeloda resulted in stabilization of the disease [83]. These substantial anticancer and antitumor activities mentioned for *A. muricata* leaves led to tablet formulations of the ethyl acetate-soluble fraction of the leaves, which contains AGEs that can be used as a cancer adjuvant therapy [85].

Antioxidant Activity

Immoderate generation of intracellular reactive oxygen species (ROS) is a precursor of oxidative stress which subsequently catalyzes metabolic deficiency and cellular death through biochemical and physiological lesions [95]. The identification of antioxidants from natural products has become a matter of great interest in recent studies for their noteworthy role in nullifying the destructive effects of ROS [96, 97]. DRSA, FRAP and HRSA tests on aqueous and methanolic leaf extracts of *A. muricata* revealed the marked antioxidative activities of both extracts accompanied with DNA protective effects against H_2O_2-induced toxicity [98]. The antioxidant activity of the *A. muricata* leaves was found to be stronger than *A. squamosa* and *A. reticulata* species as shown through different *in vitro* models, such as ABTS, nitric oxide and hydroxyl radicals [99]. The seeds and leaves of the plant are reported to possess enzymatic antioxidants, including catalase and superoxide dismutase, and non-enzymatic antioxidants, including vitamin C and E [100]. Padma and colleagues showed that the ethanolic extract of the *A. muricata* stem bark caused a reduction in lipid peroxidation induced by cold immobilization stress in the brain and liver of rats, indicating the adaptogenic potential of this plant [101, 102]. The stem bark extract (200 mg/kg) also showed protective effects against oxidative stress induced by carbon tetrachloride in rats and significantly increased the oxidant levels and serum enzyme activities to near normal. The DPPH test showed the antioxidant activity of the stem bark [103]. These findings strongly suggest the potential use of *A. muricata* as a natural source of antioxidants.

Antihypertensive Activity

To evaluate the antihypertensive properties of *A. muricata* leaves, aqueous leaf extract (9.17-48.5 mg/kg) was administered to normotensive Sprague–Dawley rats. The results demonstrated that treatments of rats with the leaf extract significantly decreased blood pressure in a dose-dependent manner without affecting heart rates. This effect was suggested to be induced through peripheral mechanisms involving the antagonism of Ca^{2+} [104].

Antiparasitic Activity

Protozoal infections because debilitating diseases, such as leishmaniasis and trypanosomiasis, which have both afflicted a noteworthy proportion of the world population. The development of resistance to empirically discovered drugs represents a major hindrance to treatment of protozoal diseases. Moreover, in case of long-term usage, toxicity and several side effects have made the available treatments more unsatisfactory. As a natural agent, *A. muricata* has been subjected to various pathogenic parasites to determine its cytotoxic effects (Table 4). The ethyl acetate leaf extract of *A. muricata* was assayed against three *Leishmania* species (PH8, M2903 and PP75) and *Trypanosoma cruzi*. Promising activity was reported with IC50 values lower than 25 µg/mL [105]. The same promising antileishmanial effect was reported against *L. braziliensis* and *L. panamensis* species with a toxicity effect higher than Glucantime, which was used as a positive control [29]. A bioassay-guided investigation on the *A. muricata* seeds against three *Leishmania* species, namely *donovani*, *mexicana* and *major*, led to the isolation of two AGEs as the bioactive compounds. Isolated annonacinone and corossolone elicited an EC50 dose of 6.72-8.00 and 16.14-18.73 µg/mL against the tested species, respectively [56]. A bioassay-guided investigation on the seeds of *A. muricata* against two forms of *L. chagasi*, promastigote and amastigote, also led to the isolation of the same bioactive AGE compounds, annonacinone and corossolone [57]. In addition, the methanolic extract of *A. muricata* seeds showed significant antiparasitic activity against the infective larvae of *Molinema dessetae*, and this activity was contributed to its isolated AGEs [106]. A recent *in vitro* investigation on *A. muricata* aqueous leaf extract was performed against *Haemonchus contortus*, a gastrointestinal parasite. The result showed 89.08% and 84.91% toxicity against larvae and eggs as assessed by larval motility and egg hatch tests. The immobilization of adult worms within 6 to 8 h of exposure to different doses of the extract revealed a promising anthelmintic activity in the leaves [107].

Table 4: Antiparasitic studies on *A. muricata*

Plant Part	Subject of Study	Result	Reference
ethyl acetate extract of the leaves	*Leishmania* species (PH8, M2903, PP75), *T. cruzi*	IC50 values lower than 25 µg/mL	[105]
ethyl acetate extract of the pericarp	*L. braziliensis*, *L. panamensis*	toxicity effect higher than Glucantime as a positive control	[29]
methanol extract of the seeds	*L. donovani*, *L. mexicana*, *L. major*	bioassay-guided isolation of annonacinone (EC50: 6.72–8.00 µg/mL) and corossolone (EC50: 16.14–18.73 µg/mL)	[56]
methanol-water extract of the seeds	*L. chagasi* (promastigote amastigote)	bioassay-guided isolation of annonacinone and corossolone	[57]
aqueous extract of the leaves	*H. contortus*	toxicity against larvae (89.08%) and egg (84.91%)	[107]
pentane extract of the leaves	*P. falciparum*	toxicity against chloroquine sensitive and (IC50: 16 µg/mL) and resistant strains (IC50: 8 µg/mL)	[108]

Anti-Inflammatory and Anti-Nociceptive Activities

Oral treatment in rats with *A. muricata* ethanolic leaf extracts (10, 30, 100 and 300 mg/kg) significantly reduced carrageenan-induced edema in rat paws by 79% in a dose-dependent manner, exhibiting its anti-inflammatory activities [92]. This anti-inflammatory effect was accompanied by reductions in the leukocyte migration and exudate volume [7]. Oral administration in mice with the same extract showed significant suppression of abdominal contortions induced with acetic acid (0.6% *v*/*v*), exhibiting a powerful anti-nociceptive activity [92, 93]. In addition, the formalin test and paw licking and hot-plate responses also corroborated the marked analgesic effect of the *A. muricata* leaves [7, 92, 93]. The protective effect of the *A. muricata* leaves against Complete Freund's adjuvant (CFA)-induced arthritis in rats and xylene-induced ear edema in mice was associated with an attenuation in the TNF-α and IL-1β protein expression, demonstrating that the leaves could be used against both acute and chronic inflammation [93]. The same assays showed the anti-inflammatory and analgesic activities for the *A. muricata* fruits, which were shown to be induced through the suppression of inflammatory mediators and interactions with the opioidergic pathway, respectively [94]. These findings demonstrated the anti-nociceptive and anti-inflammatory effects of *A. muricata* and substantiated its traditional consumption as pain killer.

6. Contraindications

Graviola has demonstrated uterine stimulant activity in an animal study (rats) and should therefore not be used during pregnancy. Graviola has demonstrated hypotensive, vasodilator, and cardio depressant activities in animal studies and is contraindicated for people with low blood pressure. People taking antihypertensive drugs should check with their doctors before taking graviola and monitor their blood pressure accordingly (as medications may need adjusting). Graviola has demonstrated significant in vitro antimicrobial properties. Chronic, long-term use of this plant may lead to die-off of friendly bacteria in the digestive tract due to its antimicrobial properties. Supplementing the diet with probiotics and digestive enzymes is advisable if this plant is used for longer than 30 days [10].

7. Toxicology

In 1999, a study published in the Lancet Journal discussed the possible relationship between the consumption of tropical fruits and the incidence of atypical Parkinsonism in the French West Indies [109]. In addition, the etiology of a neurodegenerative disease in Guadeloupe Island revealed a close correlation between AGE consumption and the endemic of this disease [53]. Hence, AGEs are suggested to be environmental neurotoxins responsible for neurodegenerative disorders, including Guadeloupean atypical Parkinsonism. A recent study showed that the fruit of *A. muricata* with annonacin as a major AGE may be a potential risk factor for neurode generation due to being a major source of exposure to AGEs [110]. In rat striatal neurons, annonacin depleted the ATP supply and interrupted the transportation of mitochondria to the cell soma, which caused cellular perturbations in the protein tau and led to a number of similar characteristics as neurodegenerative diseases [53]. It is projected that if someone consumes one soursop fruit or its nectar daily, after one year, the total amount of annonacin which was ingested is sufficient to induce brain lesions in rats through intravenous infusion [111]. Hence, excessive consumption of products from Annonaceae species should be precisely considered to prevent any neurotoxic damages.

8. Conclusion

A. muricata is a coveted tropical tree, and a wealth of phytochemical investigations have been conducted for this fruit plant. In addition to being an important source for the food industry and an indigenous medicinal plant, *A. muricata* is proven to possess a wide spectrum of biological activities. Among all former studies on this plant, the most promising activities are found to be its anticancer, antiparasitic and insecticidal activity. Because the majority of the previous studies were focused on the biological activities of the plant extract, further investigations on the biochemical and physiological functions of active compounds and the detailed mechanisms underlying these activities are completely pivotal for the development of pharmaceutical and agricultural products. In addition, clinical trials concerning the rich pharmaceutical potential of *A. muricata* have been markedly neglected in previous studies. Several reports on the neurodegenerative effects of *A. muricata* and its isolated AGEs are completely perplexing, and further research is crucial to distinguish all the compounds contributing to this effect and determine the threshold of these compounds at which this effect is caused. This review is hoped to be a source of enlightenment and motivation for researchers to further

perform *in vitro*, *in vivo* and clinical investigations on the biological activities of *A. muricata* to gain insight into developing new agricultural and pharmaceutical agents. *Annona muricata* thus appears to meet the popular definition of a "Miracle Fruit".

9. References

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