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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