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Research Review

A Review on *Annona muricata* and its Medicinal Applications

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Abstract

The ongoing rise in cancer diagnoses, there is substantial disagreement regarding the efficacy of the many therapy options currently available. As a result, people are searching for substitutes for conventional cancer therapies like surgery, chemotherapy, and radiotherapy. Universally accepted as the foundation of therapeutic and preventative actions, medicinal plants. A member of the Annonaceae family, *Annona muricata* is well-known for its therapeutic benefits. Promising chemicals from *A. muricata* have been found, and they may one day be used to treat cancer. Alkaloids, phenols, and acetogenins are the most often found phytochemical substances that have been isolated from this plant and identified. This review focuses on the role of *Annona muricata* extract in the prevention of various cancers, the control of cellular proliferation and necrosis, and bioactive metabolites that have a variety of pharmacological functions in addition to their ethnomedicinal applications. Additionally, this review focuses on the molecular mechanisms by which *Annona muricata* extract inhibits the growth of cancer cells by upregulating proapoptotic genes and genes that are involved in the destruction of cancer cells while downregulating anti-apoptotic genes and several genes involved in pro-cancer metabolic pathways. As a result, the A. muricata active phytochemicals have the potential to be used as a promising anti-cancer agent.

***Key words*:** *Annona muricata*, Annonaceae, Biological activity, Bioactive compounds, Fruit tree

Natural products, especially those made from plants, have been utilized to support human health since the beginning of medicine. Plant phytochemicals have played a key role in pharmacological discoveries throughout the past century. The importance of plant active components in both agriculture and medicine has spurred a significant scholarly interest in the biological activities of these compounds [1]. Despite these efforts, only a small number of plant species have been thoroughly examined by science, and our understanding of their potential functions in nature is quite limited. Therefore, thorough research on the biological functions of these plants and their primary phytochemicals is required to achieve a meaningful impression of natural goods [2]. Plants with a long history of ethnomedical usage are a rich source of active phytoconstituents that offer therapeutic or health advantages against a variety of maladies and conditions. *Annona muricata* is one such plant having a wide range of traditional uses. In this study, we outline the phytochemistry, biological activities, and potential mechanisms of *A. muricata* bioactivities as well as the botany, distribution, and ethnomedicinal uses of this plant. *Annona muricata* is one such plant having a wide range of traditional uses.

According to the World Health Organization, caner is the leading cause of mortality and morbidity worldwide [3]. According to global cancer statistics in 2022, nearly 1,918,030 new cancer cases and 609,360 cancer deaths worldwide Siegel *et al*. [4]. The most common cancers worldwide have been lung and breast cancer. It is important to note that the value of a good diet has been demonstrated in the prevention and control of cancer; however, it is still unknown if using dietary supplements during cancer treatment is useful [5]. Chemotherapy, radiation, DNA-interacting drugs, and molecular targeting agents are just a few of the cancer treatments available. They are all meant to kill malignant cells and prevent them from proliferating [6]. Contrarily, because most cytotoxic medications affect both malignant and healthy cells, they have drawbacks that might lead to undesirable side effects include hair loss, bone marrow suppression, drug resistance, gastrointestinal ulcers, neurologic dysfunction, and heart toxicity [7]. Since the invention of medicine, natural compounds, particularly phytochemicals, have been employed to support human health [8]. Recently, phototherapy—also known as herbal medicine or herbalism—has offered treatments for illnesses including cancer [9]. In this review, we examine the possible advantages of complementary and alternative medicines (CAMs), specifically *Annona muricata*, as a breast cancer and other types of cancer treatment [10]. It is important to note that the most important areas of conventional medicine are represented by herbal medicine. To support the appropriate use of herbal medicine and to determine their potential as a

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source of alternative pharmaceuticals, it is crucial to do research on medicinal plants [11]. For the treatment of some diseases, medicinal plants have been employed since the dawn of recorded history. The ancient Vedas, which were written between 3500 and 800 B.C., provide numerous references to the usage of medicinal plants [12].

Botanical description and distribution

Taxonomic description

Kingdom	:	Plantae
Phylum	:	Tracheophyta
Class	:	Magnoliopsida
Order	:	Magnoliales
Family	:	Annonaceae
Genus	:	*Annona*
Species	:	*Annona muricata* L.

Annona muricata trees are located in the rainforests of Southeast Asia, South America, and Africa. *A. muricata* has large, glossy, dark green foliage that are also known as soursop, graviola, guanabana, or Brazilian pawpaw has large, glossy, dark green leaves [13] with edible, green heart-shaped fruits [14]. Soft, curved spines cover the leathery skin of the fruits, each of which may contain 55–170 black seeds distributed in a creamy white flesh with a characteristic aroma and flavour. All portions leaves, fruits, seeds and roots of *A. muricata* have been used in traditional medicine but the most widely used in the preparations of traditional medical decoctions are stem barks, roots, seeds, and leaves [15-16]. Nolasco-González *et al*. [17] have reported the ultrasound assisted extraction was more effective in extracting bioactive compounds from *A. muricata* leaves and it is also used to increase the antioxidant activity of extract than decoction.

Traditional medicinal uses

A number of medicinal uses have been reported across the globe ranging from the use of leaves, bark, roots, fruits to seeds of *A. muricata* [18]. The most widely used preparation in traditional medicine is the decoction of bark, root, seed or leaf but applications are varied. In a number of tropical sub-Saharan countries such as Uganda, all parts are used to treat malaria, stomachache, parasitic infections, diabetes [19] and cancer [20-21]. The use of leaves to treat malaria is very important in tropical countries such as Cameroon, Togo, and Vietnam [22-23]. In Ghana, *A. muricata* and some other plants are decocted into a mixture and used in bath for pregnant mothers prior to birth [24]. In Indonesia, the Caribbean islands the leaves are used in bath to treat skin ailments [8] while in Mauritius [25] New Guinea [26] and Ecuador [27]. The ingestion of leaves decoction is used as analgesic in Brazil [28] Mexico and Nicaragua [29] and in Benin [30].

Bioactive compounds of A. muricata and their pharmacological activity

Yathzamiry *et al.* [31] have demonstrated the polyphenols of the total ethanolic extract of the *Annona muricata* leaves at doses of 25 and 50 ppm were cytotoxic against the HeLa cell line according to ISO 10993-5, without affecting the viability of the 3T3 line, so it could be an alternative cancer therapy.

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	[32]
Fruits	nornuciferine	ALK	anti-depressive	[32]
Fruits	asimilobine	ALK	anti-depressive	[32-33]
Fruits	epomusenin-A	AGE	-	[34]
Fruits	epomusenin-B	AGE	-	[35]
Fruits	epomurinin-A	AGE	-	[36]
Fruits	epomurinin-B	AGE	-	[37]
Fruits	muricin J	AGE	toxicity against prostate PC-3 cancer cells	[38]
Fruits	cis-annoreticuin	AGE	-	[39-41]
Fruits	muricin K	AGE	toxicity against prostate PC-3 cancer cells	[42]
Fruits	Muricin L	AGE	Toxicity against prostate PC-3 cancer cells	[43]
Fruits	Cinnamic acid derivative	PL		[44]
Fruits	5-caffeoylquinic acid	PL	-	[45]
Fruits	dihydrokaempferol-hexoside	PL	-	[36]
Fruits	p-coumaric acid	PL	-	[46]
Fruits	caffeic acid derivative	PL	-	[47]
Fruits	dicaffeoylquinic acid	PL	-	[48]
Fruits	feruloyl glucoside	PL	-	[49]
Fruits	4-feruloyl-5-caffeoylquinic acid	PL	-	[50]
Fruits	p-coumaric acid methyl ester	PL	-	[50]
Leaves, Pericarp	annomuricin A	AGE	toxicity against brine shrimp, lung A549, breast MCF-7 and colon HT-29 cancer cells	[51]
Leaves	annomuricin B	AGE	toxicity against brine shrimp, lung A549, breast MCF-7 and colon HT-29 cancer cells	[42]
Leaves	annomuricin C	AGE	toxicity against brine shrimp, lung A549, breast MCF-7 and colon HT-29 cancer cells	[52]
Leaves	annomuricin E	AGE	toxicity against pancreatic MIA PaCa-2 and colon HT-29 cancer cells	[53]
Leaves	annomutacin	AGE	toxicity against lung A549 cancer cells	[42]
Leaves	(2,4-cis)-10R-annonacin-A-one	AGE	toxicity against lung A549 cancer cells	[54]
Leaves	annohexocin	AGE	toxicity against brine shrimp and different cancer cells	[41]

Leaves	muricapentocin	AGE	toxicity against pancreatic MIA PaCa-2 and colon HT-29 cancer cells	[42]
Leaves	(2,4-cis)-isoannonacin	AGE	-	[54]
Leaves, seeds	(2,4-trans)-isoannonacin	AGE	-	[54]
Leaves	muricatocin C	AGE	toxicity against brine shrimp, lung A549, breast MCF-7 and colon HT-29 cancer cells	[54]
Leaves, Seed Pericarp	annonacin A	AGE	-	[54]
Leaves	annopentocin A	AGE	toxicity against pancreatic MIA PaCa-2 cancer cells	[55]
Leaves	annopentocin B	AGE	toxicity against lung A549 cancer cells	[55]
Leaves	annopentocin C	AGE	toxicity against lung A549 cancer cells	[55]
Leaves	cis-annomuricin-D-one	AGE	toxicity against lung A549, colon HT-29and pancreatic MIA PaCa-2 cancer cells	[55]
Leaves	trans-annomuricin-D-one	AGE	toxicity against lung A549, colon HT-29	[55]
Leaves	murihexocin A	AGE	toxicity against different cancer cells	[55]
Leaves	murihexocin B	AGE	toxicity against different cancer cells	[55]
Leaves	cis-corossolone	AGE	toxicity against human hepatoma cells	[43]
Leaves	annocatalin	AGE	toxicity against human hepatoma cells	[43]
Leaves	annocatacin B	AGE	toxicity against human hepatoma cells	[42]
Leaves	anonaine	ALK	Neurotoxic	[56]
Leaves	isolaureline	ALK	-	[56]
Leaves	xylopine	ALK	-	[56]
Leaves	Quercetin 3-O-α-rhamnosyl-(1→6)-β-sophoroside	FTG	-	[57]
Leaves	gallic acid	FTG	-	[57]
Leaves	epicatechin	FTG	-	[57]
Leaves	quercetin 3-O-rutinosid	FTG	-	[57]
Leaves	quercetin 3-O-neohispredoside	FTG	-	[57]
Leaves	kaempferol 3-O-rutinoside	FTG	-	[57]
Leaves	quercetin 3-O-glucoside	FTG	-	[57]
Leaves	quercetin	FTG	-	[57]
Leaves	kaempferol	FTG	-	[57]
Leaves	annonamine	ALK	-	[56]
Leaves	(S)-norcorydine	ALK	-	[56]
Leaves	turpinionoside A	MG	-	[56]
Leaves	(+)-epiloliolide	MG	-	[56]
Leaves	loliolide	MG	-	[56]
Leaves	(1S,2S,4R)-trans-2-hydroxy-1,8-cineole	MG	-	[56]
Leaves	kaempferol 3-O-β-D-(2″-O-βglucopyranosyl, 6″-O-αL'Rhamnopyranosyl) glucopyranoside	MG	-	[56]
Roots	montecristin	AGE	-	[34]
Roots	cis-solamin	AGE	-	[34]
Roots	coronin	AGE	-	[34]
Seeds	murisolin	AGE	-	[56]
Seeds	muricatacin	AGE	Toxicity against lung A549, breast MCF7, colon HT-29 cancer cells	[56]
Seeds, Leaves, Pericarp	annonacin	AGE	neurotoxic, molluscicidal, inhibitor of mitochondrial complex I	[56]
Seeds	corepoxylone	AGE	-	[34]
Seeds	gigantetrocin	AGE	-	[56]
Seeds	annomuricatin	ACP	-	[34]
Seeds	cis-goniothalamicin	AGE	crown gall tumor inhibition, toxicity against brine shrimp, lung A549, breast MCF-7 and colon HT-29 cancer cells	[56]

Pharmacological activities

From the 50 reports of pharmacological studies, we have reviewed for this manuscript, about 66% corresponded to in vitro studies, 32% to in vivo studies in murine models, and 2% to clinical studies. Regarding the type of extracts used, 84% corresponded to maceration of any part of the plant in organic solvents and 16% corresponded to aqueous preparations.

In vitro studies

Most of the in vitro studies correspond to cytotoxic activity (30%) followed by antiprotozoal activity (23%) and insecticidal activity (18%). The remaining 29% was conformed to antioxidant activity and antimicrobial and antiviral activities, among others (Table 3).

Cytotoxic activity

The increasingly popular use of *Annona muricata* as an anticancer treatment reported ethnobotanically may be related to reports of its selective cytotoxic activity [58]. This bioactivity is considered selective as some of the extracts studied in vitro were shown to be more toxic to cancer cell lines than to normal cells [58]. Anticancer activity was investigated using the quantum chemical method via Spartan 14 software, molecular docking via Discovery studio 2017, AutoDock Tool 1.5.6, AutoDock Vina 1.1.2, and PyMol 1.7.4.4 and the molecular dynamic simulation method via AMBER14 molecular dynamics package was studied by the Abel Oyebamiji *et al*. [59]. The study reveals that compound C possesses a greater ability to inhibit than other studied compounds as well as the standard (5FU). Mahmood *et al*. [60] investigated the copper oxide nanoparticles (CuO NPs) using *Annona muricata* L (*A. muricata*) plant extract to test their anti-cancer effects. This study indicates that CuONPs reduced cell proliferation for AMJ-13 and MCF-7. HBL-100 cells were not significantly inhibited for several concentration levels or test periods. *Annona muricata* Linn has been reported to contain valuable bioactive compounds known as *Annonaceous acetogenins*. The study has been done on *Annona muricata* effect in pancreatic cancer cells. In this study, the viability of Capan-1 after treatment with *Annona muricata* extracts was determined by using 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) assay. The results displayed that only hexane and commercialized extract inhibited cell proliferation in a concentration-dependent manner with IC25 varied ~7.8-8µg/ml and ~0.9-1.0µg/ml respectively. The data demonstrate that *A. muricata* hexane and commercialized extracts induced mild cytotoxicity in pancreatic cancer cells (Capan-1) [61]. Nawwar *et al*. [57] reported that 1.6 lg/ml and 50 lg/ml from hydroalcoholic extract of *Annona muricata* leaves increased the viability of non-cancerous cells while 100 lg/ml did not alter their viability. This, selective activity has also been reported to induce healing. Organic solvents, pentanoic and ethanolic, were the most active *Annona muricata* extracts against cancer cells grown *in vitro*. In these extracts, activity has been reported to be 10 and 4.5 times higher, respectively, than the activity of the aqueous extract in the A375 cell culture [62]. According to Osorio *et al*. [64], extracts with LC50 < 10 lg/ml can be classified as highly cytotoxic while the National Cancer Institute [65] suggested that plant extracts with LC50 values 620 lg/ml are suitable for cancer.

Table 3 Pharmacological activities of *A. muricata* extract evaluated *in vitro*

Activity	Plant part	Solvent	Test model	Effect	References
Cytotoxic	Lesf	H_2O:EtOH 40%	K562	MIC = 7 mg/ml	[66]
			ECV-304	MIC = 2 mg/ml	
	Peri	MeOH	U-937	MEC > 1 mg/ml	[67]
		Hex		MEC = 1 mg/ml	
		EtOAc		MEC = 0.1 mg/ml	
	Dried leaf	H_2O:Cet 50%	MCF-10A	IC_{50} > 200 µg/ml	[67]
			BC MDA-MB-468	IC_{50} = 4.8 µg/ml	
			MDA-MB-231	IC_{50} > 200 µg/m	
			MCF-7	IC_{50} > 200 µg/m	
	Leaf	EtOAc	U-937	LC_{50} = 7.8 µg/ml	[64]
	Stem	EtOAc		IC_{50} = 10.5 µg/ml	[64]
		MeOH		IC_{50} = 60.9 µg/ml	
		Hex		IC_{50} = 18.2 µg/ml	
		EtOAc		IC_{50} = 28.1 µg/ml	
		MeOH		IC_{50} = 38.5 µg/ml	
		Hex		IC_{50} = 15.7 µg/ml	
	Leaf	EtOH	VERO	IC_{50} < 0.00022 mg/ml	[68]
			H460	IC_{50} < 0.00022 mg/ml	
			C-678	IC_{50} < 0.00022 mg/ml	
	Leaf, Stem	DMSO	PC FG/COLO357	IC50 = 200 µg/ml	[68]
			PC CD18/HPAF	IC50 = 73 µg/ml	
	Leaf	n-But	MDA-MB-435S	IC_{50} = 29.2 µg/ml	[58]
			HaCaT	IC_{50} = 30.1 µg/ml	
			WRL-68	IC_{50} = 52.4 µg	
		H_2O:EtOH	HaCat	1.6 to 50 µg/ml increase cellular activity, 100 µg/ml not change cell behavior	[57]
		H_2O	A375	IC_{50} > 500 µg/ml	[62]
		EtOH		IC_{50} = 320 µg/ml	
		Pen		IC_{50} = 140 µg/ml	
		EtOH	MCF-7	ED_{50} = 6.2 µg/ml	[69]
			H-460	ED_{50} = 4.0 µg/ml	
			SF-268	ED_{50} = 8.5 µg/ml	
	Leaf, seed	EtOH	MDBK	CC50 = 20x10–4 µg/ml	[69]
				CC50 = 24x10–5 µg/ml	
	Leaf	EtOAc	HeLa	15.62 µg/ml = 11.37% inh	[70]
		EtOH + H_2O		15.62 µg/ml = 3.97% inh	
		Chl		15.62 µg/m l = 18.42% inh	
		n-Hex		15.62 µg/ml = 21.41% inh	

n-Hex	HT-29	IC_{50} = 14.93 µg/ml	[8]
EtOAc	HCT-116	IC_{50} = 4.29 µg/ml	
MeOH	CCD841	IC_{50} > 100 µg/ml	
n-Hex		IC_{50} = 12.26 µg/ml	
EtOAc		IC_{50} = 3.91 µg/ml	
MeOH		IC_{50} > 100 µg/ml	
n-Hex		IC_{50} = 42.19 µg/ml	
EtOAc		IC_{50} = 34.24 µg/ml	
MeOH		IC_{50} > 100 µg/ml	

Cell line: ECV304, Human leukemia carcinoma cells; FG/COLO357 and CD18/HPAF, Pancreatic cancer cells; U937, Histiocytic lymphoma cell line; HeLa, Uterine cervical cancer cell line; MDA-MB-435S, Breast carcinoma cells; HaCat, immortalized human keratinocytes; WRL-68, normal human liver cells; MBDK, Bovine cell line; MCF-7, human breast carcinoma; H-460, Human large lung cell carcinoma; S-F-268, glioma; CCD841, normal human colon epithelial cells; HT-29 and HCT-116, colon cancer cell. VERO, kidney epithelial cells; C-678, stomach cancer cells; **Concentration**: MEC: minimum effective concentration; MIC, minimum inhibitory concentration; IC50, medium inhibitory concentration; ED50, medium effective dose; CC50, 50% cytotoxic concentration; inh, inhibitory; **Extract**: n-but, butanol; Chl, chloroform; EtOAc, ethyl acetate; EtOH, ethanol; Hex, hexane; n-hex, n-hexane; H2O, water; MeOH, methanol

The increasingly popular use of *A. muricata* as an anticancer treatment reported ethnobotanically may be related to reports of its selective cytotoxic activity [58]. This bioactivity is considered selective as some of the extracts studied in vitro were shown to be more toxic to cancer cell lines than to normal cells [71]. Nawwar *et al*. [57] reported that 1.6 lg/ml and 50 lg/ml from hydroalcoholic extract of *A. muricata* leaves increased the viability of non-cancerous cells while 100 lg/ml did not alter their viability. This selective activity has also been reported to induce healing. In tumor cells, healing time is increased [61]. In tumor cells, healing time is increased [80], whereas in rodents, healing time of induced wound decreases [11]. Organic solvents, pentanoic and ethanolic, were the most active *A. muricata* extracts against cancer cells grown in vitro [11]. In these extracts, activity has been reported to be 10 and 4.5 times higher, respectively, than the activity of the aqueous extract in the A375 cell culture [62]. According to Osorio *et al*. [64], extracts with LC50 < 10 lg/ml can be classified as highly cytotoxic while the National Cancer Institute [65] suggested that plant extracts with LC50 values 620 lg/ml are suitable for cancer drugs from plants. Ethyl acetate *A. muricata* leaf extract showed inhibition of the U-937 cell line with 7.8 lg/ml [64]. Although *A. muricata* extracts exhibit good cytotoxicity, there are plants with more cytotoxic effect, like *Thevetia ahouai* with LC50 < 1 lg/ml. Both plant species are used in Latin American countries to treat cancer [72]. The hexane extract of leaves had the highest content of flavonoids and the most effective inhibition of cell proliferation than the methanol or chloroform extracts [72].

Pieme *et al*. [65] suggested that *A. muricata* extracts induce apoptosis by Reactive Oxygen Species (ROS), and downregulates Bcl2 proteins. Bax protein Bcl-2 are anti-apoptotic proteins that suppress the function of apoptosis, while Bax are proteins that mediate the leakage of pro-apoptotic factors, including cytochrome c, Ca2+ and the mitochondrial protein Smac/DIABLO into the cytosol through dimerization and translocation to the outer mitochondrial membrane; a property that was also observed for acetogenins [72].

Mbuyi *et al*. [73] proposed that the mechanism of action of the extract implies the disruption of mitochondrial membrane to arrest cells in G0/G1 phase, and the induction of apoptosis suppressing the migration and invasion of cancer cells.

The acetogenins with antitumor and anticancer activity have also been studied in vitro assays, and cytotoxic effects against more than 15 cancer cell lines have been used [74-75]. Isolated acetogenins have demonstrated selective cytotoxic effects [8]. The two adjacent THF rings acetogenins are the most active [76], especially bulatacin and squamocin which have been reported mainly in the seeds [77]. The mechanism of the acetogenin cytotoxic action is the inhibition of the mitochondrial complex I [78], and the inhibition of ubiquinone-linked NADH oxidase in the plasma membranes of cancerous cells causing apoptosis [79]. Prasad *et al.* [80] demonstrated that *A. muricata* extracts suppressed phosphorylation of the key molecules involved in the extracellular signal-regulated kinase (ERK) and the phosphatidylinositol 3'kinase (PI3 K/ Akt) pathway which play a crucial role in the proliferation and survival of pancreatic cancer cells. Also, plant extract inhibited the expression of glucose transporter and glycolytic enzymes, all of which leads to the reduction of glucose uptake and ATP production by PC cells [80]. Biochemical apoptosis implied a transverse redistribution of phosphatidylserine (PS) on the outer plasma membrane arises during early apoptosis [8]. Other events in apoptosis are the complex cascade of caspases. Annomuricin E caused depletion of mitochondrial membrane potential (MMP) leading to opening of mitochondrial permeability transition pores and further release of pro-apoptotic proteins, such as cytochrome c from the mitochondria to the cytosol, resulting in the formation of the apoptosome and the activation of caspase 9 and caspase 3/7, which have been linked to the mitochondrial death pathway. *A. muricata* extracts isolated Annomuricin E downregulates Bcl-2 proteins and upregulates Bax protein. This finding confirms that Annonacin E-induced apoptosis was through the mitochondrial mediated pathway [8]. Chang and Wu [42] suggested that selective cytotoxicity of *A. muricata* is due to the enhanced ATP demand of cancer cells with respect to normal cells.

Anti-protozoal activity

A. muricata extracts and some of their isolated compounds have shown effectiveness against protozoans responsible for human diseases (Table 3), as is the case of the genera *Plasmodium* [80], Leishmania [64], Biomphalaria [81], Trypanosoma, and Entamoeba [82], responsible for malaria, leishmaniasis, schistosomiasis, chagas, and amebiasis diseases, respectively. The anti-plasmodic effect has particular interest due to the necessity for antimalarial drugs in tropical areas. Methanol extract of this species has shown inhibition of this parasite in vitro but with less effectivity than the commercial drugs chloroquine and artemisinin [71]. The highest effectiveness was found in seed extracts [71]. It has also been reported that alkaloids [80], acetogenin, anonaine, and gallic acid [80] isolated from *A. muricata* had antiplasmodial activity.

It has been demonstrated that phenolic compounds inhibit the activity of b-ketoacyl-ACP-reductase (FabG), bhydroxyacyl-ACP-dehydratase (FabZ) and enoyl acyl-ACP reductase (FaBI), important enzymes for fatty acid biosynthesis in *P. falciparum* that compromises its growth [83]. In the case

of FabG, phenols like luteolin act as noncompetitive inhibitor of FabG with respect to acetoacetyl-CoA as well as NADPH, while in FabZ, luteolin acts as competitive inhibitor of the substrate crotonyl-CoA [83]. Methanolic and ethyl acetate extracts of *A. muricata* peel showed higher antileishmanial activity than the commercial compound Glucantime [67] used to treat diseases caused by different strains of protozoa.

The trypanocidal activity of *A. muricata* was found in extracts from different plant parts and in different solvents, although its effectiveness was 100 times lower than the commercial trypanocide benznidazole [64]. Extracts of *A. muricata* also have antiparasitic activity against the metazoan or helminth *Haemonchus contortus*, a gastrointestinal parasite of sheep [84]. The extracts of *A. muricata* were active against eggs, infective larvae and adult forms of the parasite, and the effect was comparable to that obtained with using the anthelmintic drug, levamisole [84].

Insecticidal, larvicidal and repellent activity

A. muricata showed insecticidal activity from seed, leaves, barks, stems, roots and flowers [85]. Ethanolic extracts inhibited insect larvae of *Aedes aegypti* [86] *Anopheles albimanus* [87], and insects that affect plants such as *Spodoptera litura* [88], *Callosobruchus maculatus* and *Plutella xylostella* [89]. *A. muricata* seed extracts have shown the most active insecticidal activity probably due to its content of chemical compounds such as alkaloids, fatty acids and acetogenins [90]. The insecticidal action of soursop alkaloids has not been fully studied. Fatty acids are toxic to insects in different manners: by inhalation of volatile compounds, by contact with film at the surface of water, and by penetration due to the amphibolic property of some compounds [91].

CONCLUSION

By providing details on its bioactive chemical components, this review emphasises the anticancer potential and other health benefits of A. muricata. Additionally, a review of the in vitro and in vivo studies conducted to define the molecular mechanisms of action of its ingredients was done. There is potential to fully explore the ability of the plant's acetogenins and other secondary metabolites, such as alkaloids, to suppress the growth of cancer. The appeal of the idea of using these components in a targeted way to boost our toolkit against cancer grows as we get a better understanding of the molecular mechanisms governing the various graviola extract components that control metastasis, proliferation, apoptosis, and cell signalling. The majority of the long-hyped benefits have been supported by in vitro and preclinical in vivo research, but human clinical studies are still required to confirm them. For greater security, it is also necessary to document the toxicological profile. *A. muricata's* enormous pharmacological potential is being studied in clinical studies, which has been disregarded but now needs urgent attention.

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