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Review Article

Anticancer Properties of Graviola (*Annona muricata* Lin.): A Comprehensive Mechanistic Review

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ABSTRACT

Year after year, there are more cases of cancer, sparking questions about the effectiveness of available treatments. As a result, patients are searching for new therapies to supplement and/or replace radiotherapy, surgery, and chemotherapy. Graviola and other plants have been found to contain phytochemicals compounds that could be employed to cure cancer. This review seeks to highlight the phytochemicals from *A. muricata* as possible anticancer agents, taking into account the increasing inadequacies of cancer treatments provided by healthcare facilities. Graviola's potential to suppress malignant cell proliferation while having minimal to no impact on normal cell survival has been demonstrated *in vitro* and *in vivo* systems against a wide range of human cancers and pathogens. The antioxidant property of bioactive principles in *A. muricata* appears to influence the anticancer potentials of the plant. Graviola extracts made from various plant parts have been found to have a variety of phytochemical components. Phenols, alkaloids, acetogenins and essential oils are the most important phytochemical components isolated. *In vivo* and *in vitro* studies have revealed that *A. muricata* extracts and bioactive compounds have anticancer and antioxidant properties.

Keywords: *Annona muricata*, Traditional medicine, Phytochemicals, Anticancer, Antioxidant

Introduction

The word cancer was coined by Hippocrates, the father of medicine, who used the Greek term *carcinos* to describe tumours.[1] *Carcinos* is the Greek word meaning crab. Hippocrates thought the body of a crab was to be like a cancerous tumour. He also believed that an excess of the black bile in the body caused cancer. Cancer cells proliferate uncontrollably in a different way from normal cell growth and invade normal cell function, and in some cancers, it results in the formation of an abnormal mass of tissue called tumours. [2] Cancer is a disturbed balance between the rate of cell division and cell death. Normal cells in the body undergo growth, division, and death. However, cancer cells are not programmed like normal cells, thus, they continue to grow and divide. This leads to a mass of abnormal cells with uncontrolled growth that can affect other tissues. [3] The main risk factors of cancers are often related to lifestyle choices, while some infections, exposures to harmful chemicals and rays, and some environmental factors can also initiate cancer. [4] Cancer has been regarded as a Western problem, but of late, it is increasingly becoming a public health problem in developing countries. Its occurrence is mainly due to lifestyle - smoking, excess alcohol consumption and diet; [5] exposure to diverse physical, chemical and biological agents also plays a significant role in the occurrence of the disease. [1]

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According to Ferlay,[6] WHO report, in 2008 alone, there were 12.7 million global new cancer cases; and it was suggested that it will increase to 17 million by 2021. This increase will be greater in low- and medium-resource countries. [7] Global cancer mortality is projected to rise continually, with over 18.1 million deaths in 2030.[8] Cancers, particularly breast cancer and prostate cancer, are now major health concerns in low- and middle-income countries (LMICs). [9] The WHO estimated that cancers will contribute to 84 million deaths between 2005 and 2015. [10]

About 18.1 million new cases of cancers were expected to be diagnosed in 2018, with over 9.6 million deaths attributed to cancer globally. [11] It is pertinent to mention that 65–70% of these deaths were predicted to occur in LMIC. The most common cancer among the female population was cervix uteri (24.1%) followed by breast cancer (12.9%), and for the male population, it was prostate cancer (25.1%) and oesophhagus cancer (16.2%) according to the reports by National Cancer Institute. [12] Colon, esophageal, lung, nasopharyngeal, lymphoma, and prostate cancers are the five most prevalent cancers in men, whereas liver, colorectum, lung, breast, ovary and cervix uteri cancers are the most common malignancies in women.[13] At least 80% of cancer patients will require surgery as part of their treatment.[14] The Lancet Oncology Commission proposes prioritizing cancers with a high disease burden and in which surgery plays a critical role. [14]

Despite major advances in the fields of surgery, chemotherapy, and radiotherapy, many people still have reservations about these treatments because of their limitations and, most importantly, their side effects. Although conventional 3D radiation therapy has been demonstrated to be beneficial in the treatment of head and neck cancers, the side effects typically cause discomfort and a decrease in patients' quality of life. Xerostomia, which causes weight loss, and persistent infections in the oral cavity and dental cavities are examples of side effects.[15] Although the invention of intensity-modulated radiotherapy (IMRT) to replace conventional radiation therapy allows for the preservation of the parotid glands and an overall improvement in patient quality of life, large doses of IMRT radiation have been linked to dysphagia in patients. [16]

The most obvious side effect induced by chemotherapy is toxicity, while that for radiotherapy is hypothyroidism. Following ten years of radiation therapy for head and neck cancer, it is expected that 20%–25% of patients will be diagnosed with hypothyroidism. [16] Chemotherapy is also thought to be dangerous when given to elderly persons. According to a study conducted by the Southwest Oncology Group on the induction of neuropathy in patients aged 65 and up, the toxicity of the taxane-based chemotherapy agent caused an increase in the incidence of neuropathy in patients. [17]. Cisplatin is another chemotherapy drug that has been linked to significant side effects in people who have been diagnosed with cancer. [18] Although cisplatin treatment for testicular cancer was proven to improve 5-year survival rates to more than 95%, it was also linked to unfavourable secondary side effects such as heart difficulties, nervous system toxicity, lung toxicity, and the development of secondary malignancies in patients. [19] Furthermore, cisplatin was found to be responsible for the formation of altered red blood cells, with the possibility that this discovery was due to stem cell mutagenesis. [17] These issues, among others, have led to widespread skepticism of hospital-based cancer management procedures, prompting patients to seek alternative treatment, particularly from traditional medications, whether as a complement to conventional medications or to improve their health without relying on hospital-based treatments. Even though traditional drugs have a lot of concerns with toxicity and efficacy due to a lack of high-quality trials, they should not be completely dismissed as therapies. Multiple bodies of data have been presented in the scientific community based on cell cultures and animal studies supporting the potential use of traditional remedies to treat various diseases. The high number of cancer-related deaths has piqued scientists' interest in researching potential anticancer substances. Many researchers have been looking at natural materials as a target test material in recent years because they are abundant in nature and can also reduce adverse effects.

About thirty-five thousand plant species have been chosen by the National Cancer Institute for their conceivable anticancer activities. Out of which, only about 8% of the examined species formed an activity that was reproducible. Various reports are available for plants' anticancer properties. Plants like *Abrus precatorius*, [20] *Albizza lebbeck*, [21] *Anacardium occidentale*, [22] *Asparagus racemose*, [23] *Ethyrina suberose*,, [24] *Euphorbia hirta*, [25] *Gynandropis pentaphylla*, [26] *Peaderia foetida*, [27] *Picrorrhiza kurroa*, [28] *Withania somnifera*, [29] *Annona muricata* [33] to name a few, are of great scientific interest. Among these plants, the present review is aimed at integrating the reported phytochemicals constituents of *A. muricata* as a promising antidote against cancers.

Methodology

This review aimed at determining the phytochemicals constituents of *A. muricata* as a promising antidote against cancers. The scientific literature includes published articles that describe in *vitro* and in *vivo* experimental investigations on cells and models of animals that focused on *A. muricate's* anticancer activity. Information on the ethnomedicinal applications, pharmacological characteristics, and bioactive substances of *A. muricate* was retrieved by a thorough search of the literature that included published books and conferences as well as access to online scholarly resources like SciFinder, Scopus, PubMed, and Google Scholar. Consequently, an analysis is conducted of the existing gaps in the research on *A. muricate*, and suggestions are provided for future investigations.

Annona muricata

Botany and plant distribution

Graviola (*A. muricata*) commonly known, belongs to the Annonaceae family, which has over 130 genera and 2300 species.[30] *nnona muricata* is extensively spread throughout tropical and subtropical parts of the world, including Southern east Asia like India, Malaysia and Africa like Uganda and Nigeria whose altitudes are below 1200 m sea level, with temperatures between 25 °C and 29 °C, relative humidity between 65% and 85%, and annual rainfall above 1500 mm and also grown around the warmest tropical areas in South and North America. [30] *Annona muricata* is a land-based, vertical tree reaching 5–8 m in height, evergreen with features of an open, roundish shade with huge, shiny, and dark green leaves. [31] The tree consists of edible fruit which are large heart-shaped, dark green in colour, prickly and with a diameter that varies between 15 and 20 cm. The fruit is commonly referred to as soursop because to its marginally acidic taste when ripe. When dry the fruit changes to light brown and when fresh, each fruit may comprise of 55–170 black seeds [31]. The flesh fruit is a creamy white with a distinctive aroma and flavor. [31] The flower stalks are woody and long with a length of 2 mm (0.079 in) to 5 mm (0.20 in). [31] Figure 1 shows the leaves and fruit of *A. muricata*.

Traditionally medicinal uses

Most parts of *A. muricata* have traditional medicinal properties. These parts are used in the treatment of various diseases including cancer, fever, hypertension, rheumatism, parasitic infestation and inflammation.[37] The seed is removed from the fruit and used in the treatment of parasitic infections and worm. [33] The fruit is being utilized as a natural remedy to treat fever, diarrhea, arthritis, parasitic infections. parasitic infections, neuralgia, rheumatism, worms, skin rushes , dysentery, malaria and it is also consumed to raise a mother's breast milk.[34,33] The fruits are commonly used in the production of ice creams, syrups, drinks, milkshakes and candies in addition to their traditional therapeutic purpose.[34] The leaves are traditionally used to fight against diabetes, headaches, collapse, spasms, hypoglycaemia, inflammation and cystitis. [35,37] The leaves of *A. muricata* have been nicknamed as "the cancer killer" because they are traditionally used to treat breast cancer however there is no medical evidence it is effective for treating cancer and tumors.[30] The leaves of *A. muricata* are deployed in South America and tropical Africa including Nigeria to fight against tumors and cancer. [37] The leaves are also used in the treatment of malaria especially in the tropical regions like Uganda. In Malaysia, an infusion prepared from the crushed leaves of *Annona squamosa*, *Hibiscus rosa-sinensis*, and *A. muricata* is administered topically to prevent off fainting. In tropical Africa, the plant is used as an astringent insecticide and piscicide, as well as for the treatment of discomfort, skin problems and cough. Biopesticides, bioinsecticides, and topical insect repellents are all made from leaves, roots, seeds and unripe fruit. [33] The use of aqueous extract of *A. muricata* to control lepidopteran larvae, aphids, and thrips, among other pests, was advised in the edition of 'Pesticide action and alternatives for Latin America,' which recommended the use of this plant in pest control. Table 1 summarized the traditional medicinal use of different parts of *A muricate*

Phytochemisty

Annona muricata has been to have several bioactive chemicals. Acetogenins followed by alkaloids, and phenols have been reported to be the main compounds. [31,37] The major studied plant parts are seeds and leaves, probably because they are the most traditionally used to treat disease. Most phytochemicals have been discovered in organic extracts, although attention has recently been drawn to aqueous extracts. [31,38] Other substances, such as essential oils, vitamins, carotenoids, amides, have also been described in this review. A brief description of some of the major phytochemicals is however discussed below.

Figure 1: The leaves and fruit of *Annona muricata*

Table 1: Summary of traditional medicine uses of *Annona muricata.*

S/No	Plant part used	Medicine use	Preparation method	Reference
1	Leaves	Cancer, malaria, inflammatory, hypoglycemic, smooth muscle relaxant hypotensive, antispasmodic, ascariasis, hypertension, diabetes ,cough, stomach acidity, headache, urination difficulty	Decoction/oral	37,38
		menstrual hemorrhage, vaginal infection kidneys, inflammation, abdominal and back pain urinary tract, infection, convulsion, sedative		37
		fainting	Infusion/oral	
		Insecticidal		
			Juice	30
				30
2	seeds	Parasitic infections, insomnia, catarrh, febrifuge and worms	Decoction/oral	38
		Insecticidal		33
3	fruit	Malaria, worms, dysentery, arthritic pain, rheumatism, diarrhea, skin rushes, neuralgia, fever, parasites, stomach pain	Juice/oral	33
		raise a mother's milk after childbirth, Kidney disorders and hypertension.		
		Insecticidal		33
5	Roots	Hypotensive antispasmodic effects, inflammatory, sedative, hypoglycemic, smooth muscle relaxant	Decoction/oral	33
		Insecticidal		33
6	Stem	Bronchitis, asthma, leprae,	Infusion/oral	30
7	Bark	Palpitations, rash, spasms	Decoction/oral	34,36
		skin disease, sedative		
		hypoglycemic, smooth muscle relaxant hypotensive antispasmodic effects, Stomach ulcer		

Acetogenins

In methanolic, ethanolic and other organic extracts of diverse organs and tissues of *A. muricata,* such as seeds, bark, leaves, fruit and pulp, more than 120 acetogenins have been discovered.[39] Acetogenins (AGEs) have a long aliphatic chain of 35–38 carbons connected to a g-lactone ring, which is terminally substituted by b-unsaturated methyl (ketolactone), one or two tetrahydrofurans (THF) along the hydrocarbon chain, and a specific number of oxygen groups (hydroxyl, acetoxyls, ketones, epoxy).[31] Several groups based on the availability of tetrahydrofuran (THF) and hydroxyl groups, factors such as the terminal γ-lactone ring and the characteristics aliphatic chain substituents were used to categorize these metabolites. AGEs can be alienated into ten various kinds using the source of these features which comprise of 1) AGEs with a neighbouring bis-THF α-hydroxylated γ-lactone, 2) AGEs with a mono-THF α-hydroxylated γ-lactone,3) linear AGEs (AGEs without the THF rings), 4) AGEs with a saturated lactone bis-THF, 5) AGEs with mono- THF α,α'-dihydroxylated γ-lactone, 6)) AGEs with a non-adjacent bis-THF γ-lactone, 7) AGEs with mono-THF and several lactone moieties, 8) AGEs with mono- THF α,α'-dihydroxylated γ-lactone and 9) epoxy- AGEs (without THF rings). [39,40] The majority of acetogenins discovered in *A. muricata* have a THF ring, however acetogenins with two adjacent or nonadjacent THF rings have also been observed. Acetogenins have one or two epoxy groups and are linear. According to certain research, its bioactivity is influenced by its structure. [41] Annonacin was the most plentiful acetogenin found in *A. muricata* leaves and fruit, [42] although it was also found in seeds, [43] peels, [44] and roots. [45] ^{1}HNMR measurement of acetogenins in leaf extracts ranged from 3.38 to 15.05 mg/g, while HPLC-MALDI detected 0.299 mg/g. [46] Acetogenins are more cytotoxic than alkaloids and rotenone, a synthetic cytotoxic chemical, according to certain research. [47] Due to their therapeutic potential against neurotoxic effects, acetogenins and alkaloids are intensively explored in a contentious form. Figure 2 shows the general skeleton of Annonaceous Acetogenin.

Alkaloids

Alkaloids are organic molecules with basic nitrogen atoms that exist naturally. Coreximine and reticuline are the most common bioactive compounds found in *Annona muricate.* [48] Although alkaloids have been detected in roots, stems, [48] fruit [50,51]and the leaves [49] have the highest concentration . Isoquinoline, protoberberine and aporphine type are the main alkaloids described in *A. muricata*. [50,51] Previous research have indicated that alkaloids extracted from Annona species bind to 5-HT1A

receptors *in vitro* and play a role in dopamine production. As a result, alkaloids produced from *A. muricata* have been suggested to have antidepressant-like [50,51] as well as cytotoxic activities. [52] Some alkaloids have been shown to have neurotoxic effects, indicating that apoptosis atoms were responsible for neuronal death. [53]

4.3 Phenolic compounds

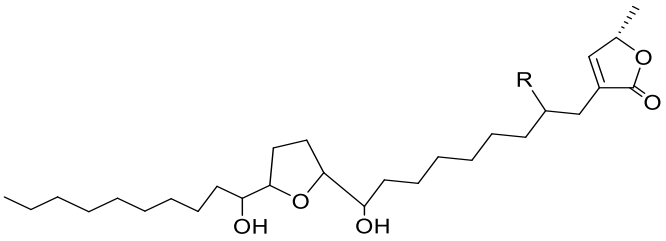
In *Annona muricate*, thirty-seven phenolic compounds were detected. Gallic acid and quercetin are two essential phenolic chemicals found in *A. muricata* leaves. [54,55] The fruit pulp has been reported to have flavonoids and lipophilic antioxidant compounds such as tocotrienols and tocopherols.[55] The amount of extractable total phenols is notably variable in various investigations using organic or aqueous extracts. This is crucial to highlight because aqueous infusion is the most common medical application, and most phenols are water-soluble. The primary phytochemicals accountable for antioxidant action are phenolic compounds.[55] Figure 3 shows some of the phenolic compounds isolated from *A. muricata.*

Essential Oil

The presence of primarily sesquiterpenes in the leaf oil of *A. muricata* gathered in Cameroon was revealed by GC and GC-MS analyses, with the primary component present being *β*-caryophyllene.[37] The volatile oil elements of -pinene (20.6 percent), germacrene D (18.1 percent), -mentha-2,4(8)-diene (9.8 percent), -pinene (9.4 percent), and -elemene (9.1 percent) were found in significant amounts in a second investigation on *A. muricata* gathered from Vietnam. [53] The chemicals epi-α-cadinol , α-cadinol and δ-cadinene appear to be other key components discovered in the leaf oil extracts.[53] It was discovered that the fruit pulp essential oil contains aliphatic acid esters, with the main components being 2-hexenoic acid methyl ester and 2-hexenoic acid ethyl ester. High amounts of mono- and sesquiterpenes, such as -caryophyllene, 1,8-cineole, and linalool, preserved the fruit pulp as well. [53] Figure 4 shows some essential oils isolated from *A. muricata.*

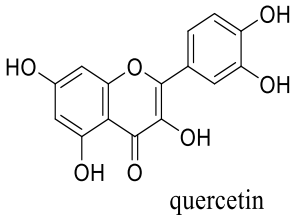
Other compounds

Cyclopeptides, carotenoid, vitamins and amides are some of other compounds that have been found in *Annona muricate.* The leaves, seeds, and fruit pulp were discovered to have carotenoid and vitamins. [56] The seeds contain the amide N-p-coumaroyl tyramine, [56] as well as cyclopeptides [58,59] which have been shown to have anti-inflammatory and anti-tumor properties. The fruit pulp of *A. muricata* have been identified to contain thirty seven volatile compounds , the majority of which are aromatic and aliphatic esters.[60] In addition, leaf of *A. muricata* have been found to contain eighty essential oil, the majority of which are sesquiterpene derivates.[61,62] Because of their bioactivity, the research of *A. muricata* volatiles is promising. Figure 5 shows some of other compounds isolated from *A. muricata.*

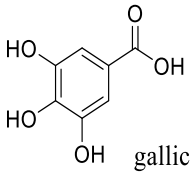


where R=H or OH

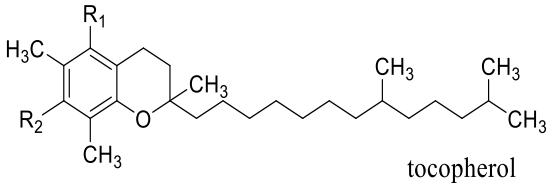
Figure 2: General skeleton of Annonaceous Acetogenin



quercetin



gallic acid

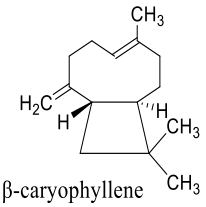


tocopherol

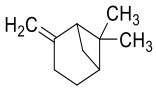
Where

	R_1	R_2
α	CH_3	CH_3
β	CH_3	H
γ	H	CH_3
δ	H	H

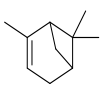
Figure 3: Some of the phenolic compounds isolated from *Annona muricata.*



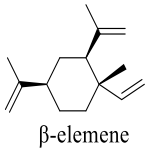
β-caryophyllene



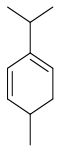
β-pinene



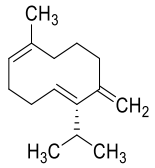
α-pinene



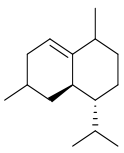
β-elemene



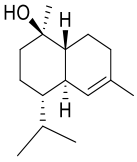
ρ-mentha-2,4(8)-diene



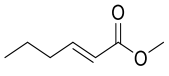
germacrene D



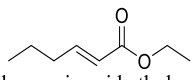
δ-cadinene



α-cadinol



2-hexenoic acid methyl ester



2-hexenoic acid ethyl ester

Figure 4: Some essential oils isolated from *Annona muricata*.

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Anticancer properties of the reported phytochemicals
In vitro studies

Anticancer activity has been reported to be found in *A. muricata*. It has been used for a long time to shrink tumours and has little adverse effects. The phytochemical screening reported by Gavamukulya, [62] revealed that *A. muricata* extract showed the presence of secondary class metabolic components such as acetogenins, flavonoid, anthraquinones saponins, phenols phytosterols, terpenoids, alkaloids coumarines and lactones.The ethanolic leaves extract was proven to be cytotoxic to tumor cell lines *in vitro* (EACC, MDA and SKBR3). Soursop leaf extract has been shown to have anti-breast cancer action in T47D cell lines in previous research.[39] MCF-7 40, HeLa cells, breast cancer cells (MCF-7) [39] and lung cancer cells were all killed by an ethanol extract of Soursop (*A. muricata*) leaves (A549). [37]

In vitro studies, normal human colon epithelial cells; HT-29 and HCT-116,colon cancer cell; Ehrlich ascites carcinoma cells; SKBR3: breast adenocarcinoma cell line; T47D HL-60, human promyelocytic leukemia; Ehrlich ascites carcinoma cells;Capan-1, pancreatic cancer cells; U937, human benign prostate cells; VERO, kidney epithelial cells; Raji cell lines; C-678, stomach cancer cells; HaCat, immortalized human keratinocytes; WRL-68, ECV304, human leukemia carcinoma cells; uterine cervical cancer cell line; MDA-MB-435S , histiocytic lymphoma cell line, HaCat, immortalized human keratinocytes; WRL-68FG/COLO357 and CD18/HPAF are the most the most researched cancer cell lines using *A. muricata* extracts. The ethnobotanically reported usage of *A. muricata* as an anticancer drug may be associated to its selective cytotoxic activity. [62] This bioactivity is regarded to be discriminatory since some of the extracts investigated *in vitro* were found to be more cytotoxic to cancer cell lines than normal cells – despite the fact that the majority of them had no cytotoxic effects on normal human cells. [63] It was discovered that hydroalcoholic extracts of *A. muricata* leaves at concentrations of 1.6 mg/mL and 50 mg/mL enhanced the viability of non-cancerous cells, but 100 mg/mL had no effect.[62] This discriminatory activity has been described as having the ability to cause healing while having minimal side effects. When looking at the bioactivities of other chemicals, the type of extract used has a big impact on the results. The most effective *A. muricata* extracts against cancer cells produced in *vitro* were pentanoic and ethanolic organic solvents. In A-375 cell culture, the activity of these extracts was described as being 10 and 4.5 times greater than that of the aqueous extract.[65]

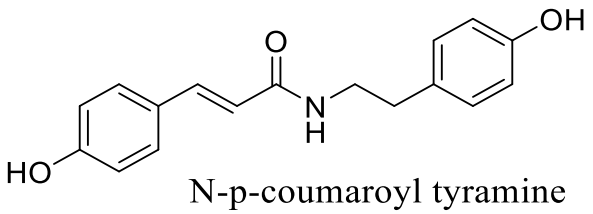

Figure 5: Some other compounds isolated from *Annona muricata*

Table 2: Anticancer compounds isolated from *Annona muricata*.

Plant part	Compound	Class	Anticancer property	Reference
leaves	annomuricin A	AEG	toxicity against breast MCF-7, colon HT-29, brine shrimp and lung A549 cancer cells	44,82
leaves	annomuricin B	AEG	toxicity against breast MCF-7, colon HT-29, brine shrimp and lung A549 cancer cells	82
Leaves	annomuricin C	AEG	toxicity against breast MCF-7, colon HT-29, brine shrimp and lung A549 cancer cell	79,82
Leaves	annomuricin E	AEG	toxicity against breast MCF-7, colon HT-29, brine shrimp and lung A549 cancer cell	53,83
Leaves	Annomutacin	AEG	cytotoxic to lung A549 cancer cells	82
Leaves	(2,4-*cis*)-10*R*-annonacin-A-one	AEG	cytotoxic to lung A549 cancer cells	82
Leaves	(2,4-*trans*)-10*R*-annonacin-A-one	AEG	cytotoxic to lung A549 cancer cells	82
Leaves	Muricapentocin	AEG	toxicity against colon HT-29 and pancreatic MIA PaCa-2 cancer cells	85
Leaves	muricatocin A	AEG	cytotoxic to lung A549 cancer cells	86
Leaves	muricatocin B	AEG	cytotoxic to lung A549 cancer cells	86
Leaves	muricatocin C	AEG	toxicity against colon HT-29, breast MCF-7, brine shrimp and lung A549 cancer cells	86
Leaves	annopentocin A	AEG	cytotoxic to pancreatic MIA PaCa-2 cancer cells	87
Leaves	annopentocin B	AEG	cytotoxic to lung A549 cancer cells	87
Leaves	annopentocin C	AEG	cytotoxic to lung A549 cancer cells	87
Leaves	*cis*-annomuricin-D-one	AEG	toxicity against pancreatic MIA PaCa-2, lung A549 and colon HT-29 cancer cells	87
Leaves	*trans*-annomuricin-D-one	AEG	toxicity against pancreatic MIA PaCa-2, lung A549 and colon HT-29 cancer cells	87

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Leaves	murihexocin A	AEG	cytotoxic to different cancer cells	82
Leaves	murihexocin B	AEG	cytotoxic to different cancer cells	82
Leaves	murihexocin C	AEG	cytotoxic to different cancer cells	88
Leaves	Muricoreacin	AEG	cytotoxic to different cancer cells	88
Leaves	*cis*-corossolone	AEG	cytotoxic to human hepatoma cells	89
Leaves	annocatalin A	AEG	cytotoxic to human hepatoma cells	89
Leaves	annocatacin B	AEG	cytotoxic to human hepatoma cells	89
Leaves	Uvaricin	AEG	cytotoxic to HL-60 cells (Human promyelocytic leukaemia cell line)	33
Seeds	muricatacin	AEG	toxicity against colon HT-29, lung A549 and breast MCF7 cancer cells	89
Seeds, Leaves, Pericarp	Corossolone	AEG	toxicity against brine shrimp larva, antileishmanial and oral KB cancer cells	90
Seeds, leaves	Corossolin	AEG	toxicity against brine shrimp larva and oral KB cancer cells	90,91
Seeds, Roots, Leaves	Solamin	AEG	toxicity against normal kidney VERO cells and oral KB cancer	92
Seeds, leaves	gigantetrocin A	AEG	cytotoxic to colon HT-29 cancer cells	93
Leaves	gigantetrocin B	AEG	cytotoxic to colon HT-29 cancer cells	90
Seeds, leaves	muricatetrocin A	AEG	cytotoxic to colon HT-29 cancer cells	90
Seeds	*cis*-annonacin	AEG	toxicity against colon HT-29, breast MCF-7, brine shrimp and lung A549 cancer cells and crown gall tumor inhibition	93
Seeds	*cis*-annonacin-10-one	AEG	toxicity against colon HT-29, breast MCF-7, brine shrimp and lung A549 cancer cells and crown gall tumor inhibition	93
Seeds	*cis*-goniothalamicin	AEG	toxicity against colon HT-29, breast MCF-7, brine shrimp and lung A549 cancer cells and crown gall tumor inhibition	93
Seeds	Arianacin	AEG	toxicity against colon HT-29, breast MCF-7, brine shrimp and lung A549 cancer cells and crown gall tumor inhibition	93
Seeds	Longifolicin	AEG	cytotoxic to human hepatoma cells	94
Seeds	Muricin A	AEG	cytotoxic to human hepatoma cells	94
Seeds	Muricin B	AEG	cytotoxic to human hepatoma cells	94
Seeds	Muricin C	AEG	cytotoxic to human hepatoma cells	94
Seeds	Muricin D	AEG	cytotoxic to human hepatoma cells	94
Seeds	Muricin E	AEG	cytotoxic to human hepatoma cells	94
Seeds	Muricin F	AEG	cytotoxic to human hepatoma cells	94
Seeds	Muricin G	AEG	cytotoxic to human hepatoma cells	94
Seeds	Muricin I	AEG	cytotoxic to human hepatoma cells	94
Seeds	*cis*-annomontacin	AEG	cytotoxic to human hepatoma cells	94
Fruit	muricin J	AEG	cytotoxic to prostate PC-3 cancer cells	95
Fruit	muricin K	AEG	cytotoxic to prostate PC-3 cancer cells	95
Fruit	muricin L	AEG	cytotoxic to prostate PC-3 cancer cells	95
Fruit	Bullatacin	AEG	anti-ovarian and anti-cervical cancer activities	34,80

AGE: annonaceous acetogenin

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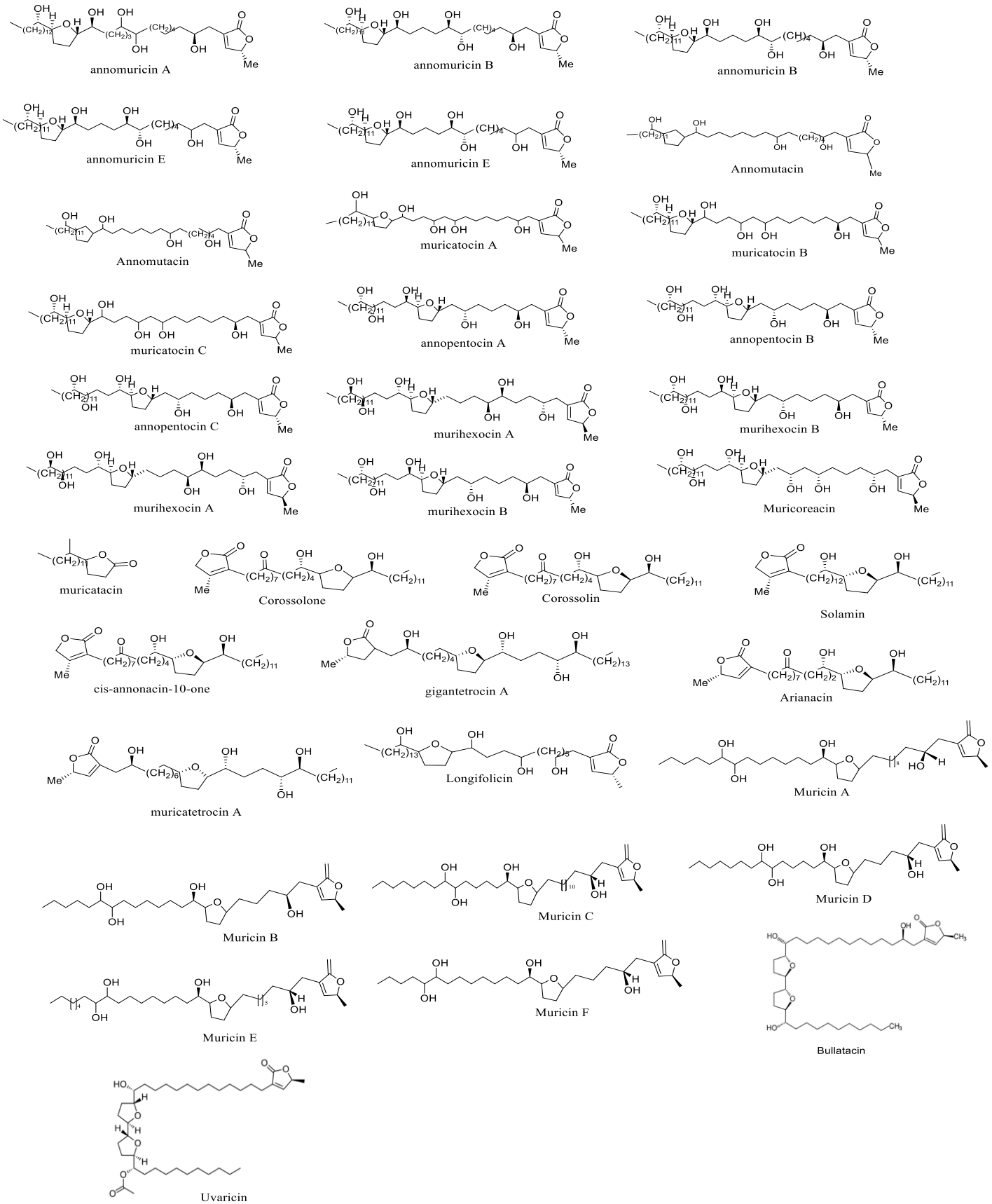

Figure 6: Some of the anticancer compounds isolated from *Annona muricata.*

Extracts with IC_{50} 30 mg/mL can be categorized as extremely cytotoxic [66], however the National Cancer Institute [67] classifies extracts with IC_{50} 10 mg/mL as moderately cytotoxic. Compared to methanol or chloroform extracts, the hexane extract of leaves of *A. muricata* contained the largest amount of flavonoids and the most efficient prevention of cell proliferation. [68] Another analysis revealed that the chloroform fraction extracted from *A. muricata* leaves has a strong cytotoxic effect on Raji and Hela cells. [69] The extract's mode of action is thought to involve breakdown of the mitochondrial membrane, which causes cells to enter the G0/G1 phase and trigger apoptosis, preventing cancer cells from spreading and infiltrating.[53] *Annona muricata* extracts also trigger apoptosis by reactive oxygen species (ROS) and downregulate Bcl-2 proteins, according to Pieme & Ngogang.[67] Studies have shown that Bax proteins facilitate the passage of pro-apoptotic factors such as cytochrome c, Ca2+, and the mitochondrial protein Smac/DIABLO into the cytosol. This however differs from Bax protein Bcl-2 which suppresses apoptosis.[70]

In vitro experiments were used to analyze acetogenins with anti-tumor and anticancer activity, and cytotoxic effects against more than fifteen cancer cell lines were documented, as previously mentioned.[71] Acetogenins have been isolated and shown to have cytotoxic effects on cells. [53] The bioactivity of acetogenins has been associated to their molecular structure.[72] Bullatacin and squamocin are the two neighboring THF rings of acetogenins that have been described mostly in seeds.[72,73] The cytotoxic action of acetogenins is due to the suppression of mitochondrial complex I [74] and ubiquinone-linked NADH oxidase in the plasma membranes of malignant cells, resulting in apoptosis. [62] The phosphorylation of critical components implicated in the extracellular signal-regulated kinase (ERK) and phosphatidylinositol 30 kinase (PI3 K/Akt) pathways, which play a key role in the proliferation and survival of pancreatic cancer cells, was reduced by *A. muricata* extracts.[71] Furthermore, the plant extract suppressed the expression of glucose transporter and glycolytic enzymes, all of which resulted in a decrease in glucose uptake and ATP production by PC cells. [71] Initial apoptosis in cells results in a transverse redistribution of phosphatidylserine (PS) on the outer plasma membrane, which is known as biochemical apoptosis. [53]Annomuricin E was shown to produce mitochondrial membrane potential (MMP) reduction, which resulted in the opening of mitochondrial permeability transition pores and the discharge of proapoptotic proteins including cytochrome c from the mitochondria to the cytoplasm. As a result, the apoptosome is formed, and caspase 9 and caspase 3/7, which have been related to the mitochondrial death pathway, are activated. Bcl-2 proteins were discovered to be downregulated by isolated Annomuricin E, while Bax proteins were shown to be upregulated.

This analysis proves that annonacin E causes apoptosis via a mitochondrial-mediated mechanism.[53] Finally, it has been proposed that *A. muricata's* discriminatory cytotoxicity is owing to cancer cells' higher ATP need than normal cells.[75] A study by Yang,[76] revealed that crude leaf extract inhibited prostate cancer proliferation *in vitro* and had a greater effect on tumor growth inhibition than flavonoid-enriched extract. The efficacy of crude extract is attributed to a synergistic action of flavonoids and acetogenins, according to this report. [76]

In vivo

The ethyl acetate extract of *A. muricata* leaves have demonstrated for its chemopreventive properties in onazoxymethane-induced colonic aberrant crypt foci in rats. [53] As acetogenins, the extract reduces (Targeting Proliferating Cell Nuclear Antigen) PCNA and B-cell leukemia/lymphoma-2 (Bcl-2) protein levels, increases Bax protein levels, and restores antioxidant enzyme levels. Excessive reactive oxygen species (ROS) production occurs in the creation of lipid radicals like malondialdehyde (MDA), and MDA levels have been found to be higher in patients with colorectal cancer. [53] The use of *A. muricata* extract reduced MDA production in colon tissue, indicating that it has anti-oxidant properties. [77] *A. muricata* extracts and isolated acetogenins have been shown to have anti-tumor action. The ethanolic extract of *A. muricata* leaves demonstrated stronger anti-tumor action in mouse models than curcumin, a well-known natural chemopreventive, according to Hamizah. [78] In induced colorectal carcinogenesis, the extract had a protective effect on biochemical processes as well as morphological changes. In animal models of pancreatic cancers, an aqueous extract of commercial powder capsules containing leaf and stem of *A. muricata* using an injection showed anti-tumorigenic and antimetastatic activity. [71] Breast tumor in rats was lowered after treatment with *A. muricata fruit extract* for 5 weeks. [79] The mechanism of action indicates that various signaling pathways regulating metabolism, metastasis, necrosis induction, and cell cycle arrest are inhibited. [71] Two *A. muricata* acetogenin isolates were also found to have antitumor activity. [80] Bullatacin, at 400 mg/kg, decreased a tumor developed in mice 300 times better than the commercial medicine Taxol (paclitaxel), according to Ko. [79] At 10 mg/kg, annonacin reduced tumor size in murine models in a manner that was equivalent to the commercial medicines cisplatin and Adriamycin.[80] Table 2 and Figure 6 show the anticancer compounds isolated from *Annona muricata.*

Antioxidant properties on reported Annona muricata

Excessive production of intracellular reactive oxygen species (ROS) is a forerunner to oxidative stress, which contributes to metabolic insufficiency and cellular death via biochemical and physiological abnormalities.[81,82] *Annona muricata* has been subjected to several other antioxidant investigations. Natural antioxidants derived from plant species have gained significance due to their protective effect against oxygen-derived free radicals, which are implicated in the pathogenesis of a variety of diseases including affections, arthritis, cancer and degenerative diseases like Parkinson's and Alzheimer's.[82,83] A collection of research on the antioxidant activity of *A. muricata* has been carried out using various assays, plant sections, and solvents.[84,85] The overall antioxidant capacity has been determined using a variety of procedures, including (1) DPPH and ABTS+ assays for free radical scavenging activities, (2) carotenes bleaching (3) the ORAC assay for oxygen radicals and (4) the FRAP assay for reduction power.[86,87] The dry or fresh leaves and fresh, frozen and juice pulp have all been evaluated for antioxidant activity. The antioxidant activity of *A. muricata* pulp was tested using ORAC, ABTS and FRAP, and it was discovered that the antioxidant molecules are predominantly lipophilic, with hydrogen donation being the mechanism of action.[88,89,90] The extract's composition varies based on the solvent utilized. The DPPH scavenging assay demonstrated that n-butanolic, aqueous, ethanolic and methanolic leaf extracts all had different antioxidant activities. The aqueous extract of fresh *A. muricata* leaves, for example, was 1000 times less effective than the commercial antioxidant butylated hydroxytoluene.[91,92,93] Padma and colleagues found that an ethanolic extract of *A. muricata* stem bark decreased lipid peroxidation caused by cold immobilization stress in the liver and brain of rats, suggesting that this plant has adaptogenic ability.[94,95] In rats, the stem bark extract (200 mg/kg) revealed therapeutic potential against oxidative stress caused by carbon tetrachloride, massively increasing oxidant levels and serum enzyme activity to near normal levels. The leaf fractions and stem bark's antioxidant activity was demonstrated by the DPPH test. [96,97,98] Sanni, [99] also discovered that different chemical fractions of the ethanolic extract of *A. muricata* leaves might reduce oxidative liver injury by elevating GSH levels, SOD and catalase activity, and suppressing MDA levels, all while suppressing oxidative liver injury. These observations clearly indicated that *Annona muricata* could be used as a natural source of antioxidants. Table 3 and Figure 7 shows antioxidant compounds isolated from *Annona muricata.*

Conclusion

Many people are currently looking for and trying various cancer treatment approaches, owing to the limits of conventional cancer therapy procedures. *Annona muricata* might provide another option for the treatment of cancer besides radiotherapy and chemotherapy, particularly for critically ill patients. The most common preparations are leaf, seed, bark, and root decoctions. Several *in vitro* and *in vivo* studies have validated their efficacy. As a result, conventional claims and usage are given respect. The anticancer activities have been attributed to the reported phytochemicals constituents of the plant, mainly acetogenins, alkaloids and phenols. Although this present review points out the potential of *Annona muricata* and its phytochemicals as an antidote against cancers, there is, however no

records of clinical trials to validate the traditional claims. Studies carried out on the anticancer activities of *A. muricata* also lack reports on the toxicity associated with its use. Consequently, more study should be done on the toxicological, clinical, and preclinical trails to finally ascertain whether *A. muricate* is appropriate for the development of cancer therapies. Also, the structural-biological relationship of the reported phytochemicals will be taken consideration in our future studies.

Conflict of Interest

The authors declare no conflict 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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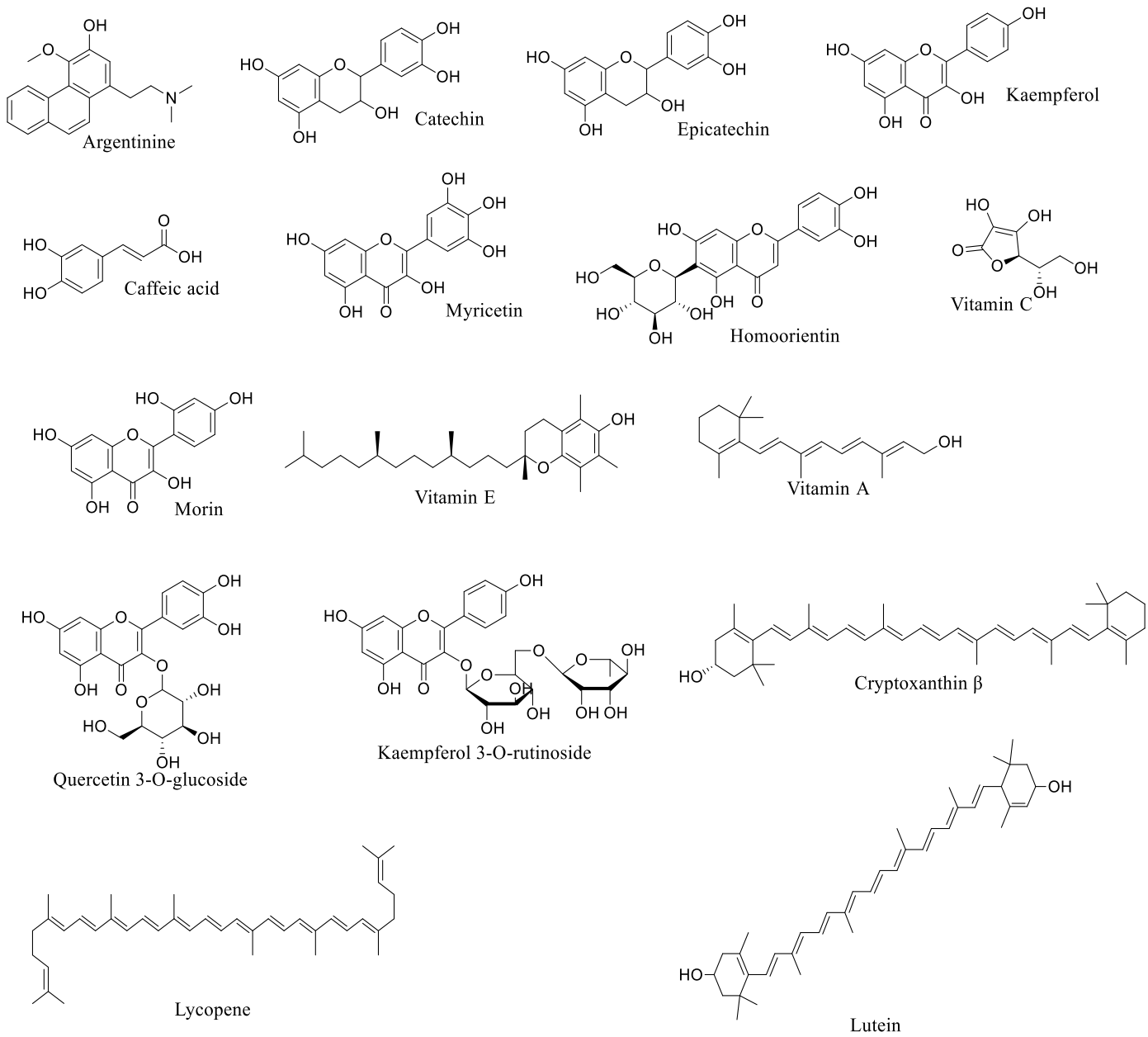

Figure 7: Some of the antioxidant compounds isolated from *Annona muricata*

Table 3: Antioxidant compounds isolated from *Annona muricata*

Part of the plant	Compound	Class	Reference
leaves	Apigenin-6-C-glucoside	phenol	99
leaves	Argentinine	phenol	53
leaves	Catechin	phenol	62
leaves	Epicatechin	phenol	53
leaves	Homoorientin	Flavonoid	62
leaves	Kaempferol	Flavonoid	93
Leaves, pulp	Kaempferol 3-*O*-rutinoside	Flavonoid	63
Leaves, pulp	Luteolin 3´7-di-*O*-glucoside	Flavonoid	99
Leaves,	Quercetin	Flavonoid	53
leaves	Quercetin 3-*O*-glucoside	Flavonoid	53
leaves	Quercetin 3-Oneohesperidoside	Flavonoid	53
leaves	Quercetin 3-*O*-robinoside	Flavonoid	53
leaves	Quercetin –*O*-rutinoside	Flavonoid	53
leaves	Quercetin 3-*O*-α-rhamnosyl	Flavonoid	53
leaves	Caffeic acid	Flavonoid	53
leaves	Gallic acid	phenol	53
leaves	Vitamin A	Vitamin	56
leaves	Vitamin E	Vitamin	55,56
pulp	Morin	Flavonoid	55,56
Pulp	Myricetin	Flavonoid	55
Pulp	Vitamin C	Vitamin C	56
Pulp	Cryptoxanthin β	Carotenoid	55
Pulp	Lycopene	Carotenoid	55
Pulp	Lutein	Carotenoid	55
Pulp	Tocopherol β	Carotenoid	55
Pulp	Tocotrienol α β	Carotenoid	55

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